Antibody response assessment of immediate breakthrough infections after zero-COVID policy adjustment in China

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Dear Editor:

Vaccines previously designed based on the prototype (PT) sequence of SARS-CoV-2 are currently not effective against SARS-CoV-2 infection due to the continued emergence and spread of SARS-CoV-2 Omicron sub-lineages. The proportion of individuals with breakthrough infections (BTI) is increasing, generating much concern. In China, the inactivated vaccine, the adenovirus type 5 (Ad5)-vectored vaccine developed using the SARS-CoV-2 spike protein as an antigen, and the protein-subunit vaccine designed based on the spike protein dimeric receptor-binding domain (RBD) have been administered to most of the population.[1] From November 2022 to early January 2023, the Chinese population encountered a large wave of SARS-CoV-2 infections primarily attributed to Omicron BA.5.2 and BF.7.[2] Therefore, the current neutralising antibody (NAb) levels in the population after BTI are of serious concern, particularly whether protection can be provided against potentially upcoming sub-variants, such as BQ.1.1, XBB.1.5, XBB.1.16, or CH.1.1. Moreover, in China, most individuals have not been infected with any SARS-CoV-2 variants. Thus, the data provided an appropriate model for analysing Omicron BA.5/BF.7 BTI after vaccination with an inactivated vaccine, protein-subunit, or Ad5-vectored vaccine.

This study reports the test results of serum samples collected from convalescents who were infected during the COVID-19 wave from November 2022 to January 2023 in China after the adjustment of the zero-COVID policy. The samples were tested for the neutralisation of SARS-CoV-2 PT, and Omicron sub-variants, including BQ.1, BQ.1.1, BM.1.1.1, BJ.1, XBB, XBB.1.5, XBB.1.16, and CH.1.1, using a pseudovirus neutralisation assay (Fig. 1A and Supplementary Fig. S2). The samples were categorised based on vaccine type and approach, encompassing the following groups: those who received no COVID-19 vaccine (group 1), two or three shots of inactivated vaccines (CoronaVac or BBIBP-CorV, groups 2, 3, and 4), two or three shots of the Ad5-vectored vaccine (Convidecia, groups 5, and 6), and three shots of protein-subunit vaccines with short or long intervals between the second, and third doses (ZF2001, groups 7, and 8). In seven of the eight groups, samples were collected from Beijing, China, where according to the China CDC, over 70% of people were infected with BF.7[2] in this wave. In Group 4 (three doses of inactivated vaccine administered before BTI), samples were collected from convalescents in Hunan and Jiangxi provinces in China, where 70–80% of individuals were reported to be infected with BA.5.2[2] (Supplementary Fig. S1 and Table S1).

Generally, in the serum samples from the unvaccinated group, the NAb levels against SARS-CoV-2 PT and all Omicron sub-variants were lower than those in the samples from the vaccinated groups (Fig. 1 and Supplementary Table S2). In the sera from the unvaccinated group, the NAb levels against BA.4/5 (sharing the same representative amino acid sequence with BA.5.2 in its spike protein) and BF.7 (with an additional R346T mutation in its spike protein) were the highest among all the variants detected. The NAb levels against CH.1.1 (34.8 times lower than BA.4/5), BM.1.1.1 (31.9 times lower than BA.4/5), and PT (23.3 times lower than BA.4/5) were the lowest among all variants detected, specifically lower than XBB, XBB.1.5, and XBB.1.16 (8.6–16.5 times lower than BA.4/5). This indicates that limited NAb levels against PT and BA.2.75 sub-lineages and BA.2.75-related recombinant strains were observed after infection (Supplementary Fig. S3–S6 and Table S2).

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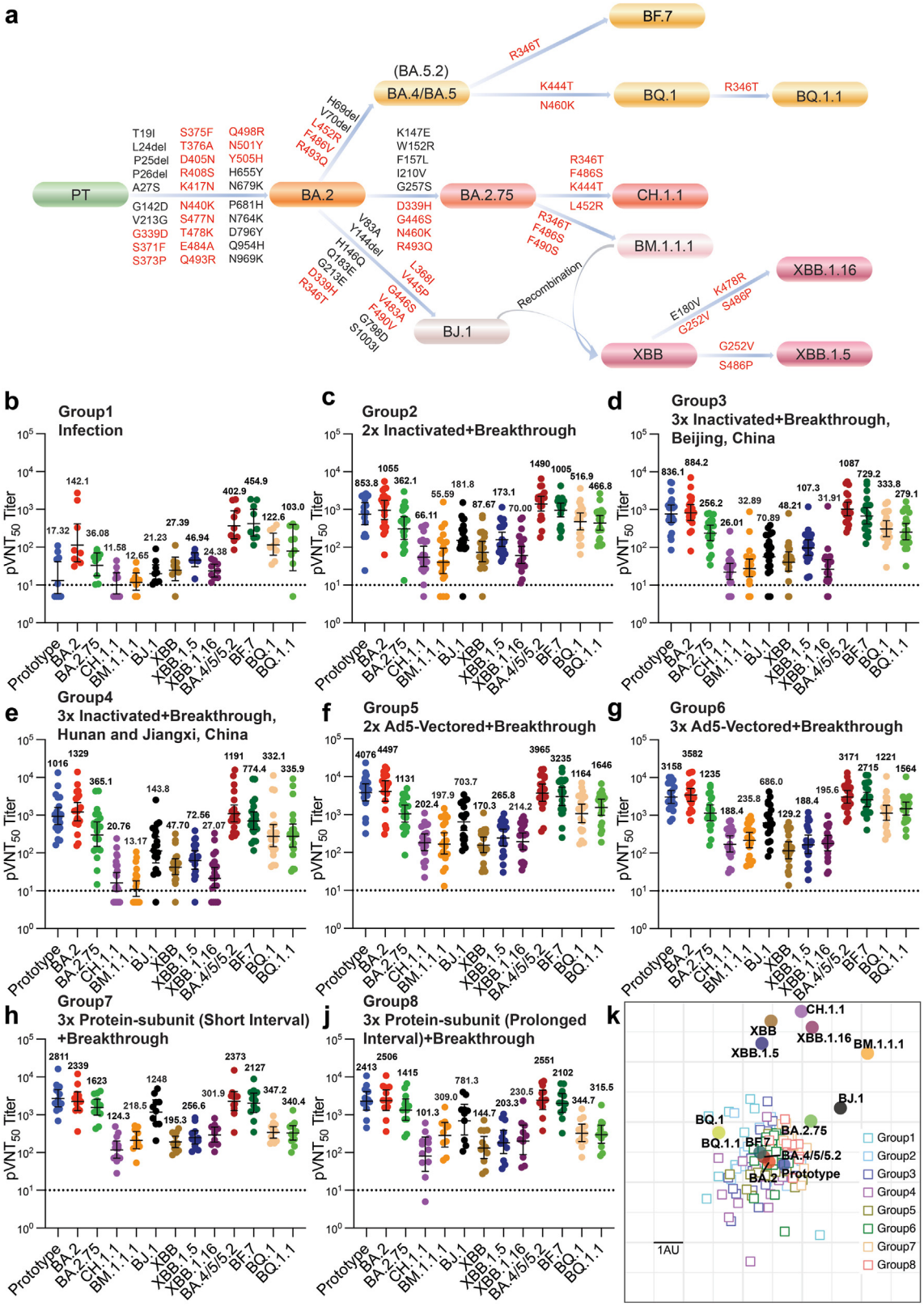
a
PT
BA.2
BA.4/BA.5
(BA.5.2)
BA.2.75
BF.7
BQ.1
BQ.1.1
CH.1.1
BM.1.1.1
BJ.1
XBB
XBB.1.16
XBB.1.5
T19I L24del P25del P26del A27S G142D V213G G339D S371F S373P
S375F T376A D405N R408S K417N N440K S477N T478K E484A Q493R
Q498R N501Y Y505H H655Y N679K P681H N764K D796Y Q954H N969K
H69del V70del L452R F486V R493Q
K147E W152R F157L I210V G257S D339H G446S N460K R493Q
R346T F486S K444T L452R
R346T K444T N460K
R346T
V83A Y144del H146Q Q183E G213E D339H R346T
L368I V445P G446S V483A F490V G798D S1003I
R346T F486S F490S
Recombination
E180V G252V K478R S486P
G252V S486P
b
Group1
Infection
c
Group2
2x Inactivated+Breakthrough
d
Group3
3x Inactivated+Breakthrough,
Beijing, China
e
Group4
3x Inactivated+Breakthrough,
Hunan and Jiangxi, China
f
Group5
2x Ad5-Vectored+Breakthrough
g
Group6
3x Ad5-Vectored+Breakthrough
h
Group7
3x Protein-subunit (Short Interval)
+Breakthrough
j
Group8
3x Protein-subunit (Prolonged
Interval)+Breakthrough
pVNT50 Titer
Prototype BA.2 BA.2.75 CH.1.1 BM.1.1.1 BJ.1 XBB XBB.1.5 XBB.1.16 BA.4/5/5.2 BF.7 BQ.1 BQ.1.1
k
1AU
Group1
Group2
Group3
Group4
Group5
Group6
Group7
Group8

In all BTI groups, the NAbs against PT, BA.2, BA.4/5, and BF.7 were higher (with the NAb titres 1.3 times lower to 1.7 times higher than that of PT). BM.1.1.1, CH.1.1, XBB, XBB.1.5, and XBB.1.16 were the sub-variants with the lowest NAb titres (4.9–48.8 times lower than PT). In China, more than 90% of the population had been vaccinated with these three types of vaccines. Therefore, it can be expected that the potential threat of the next epidemic in China may arise from strains CH.1.1, XBB, or their descendants. As a recombinant of BM.1.1.1, and BJ.1, XBB presented an immune escape potency similar to that of BM.1.1.1, but higher than that of BJ.1. The mutations in XBBs derived from BM.1.1.1, such as N460K, F486S/P, and F490S may play essential roles in immune escape (Fig. 1A and Supplementary Fig. S2b). Among XBBs, XBB.1.5 showed less resistance, which may be due to the close antigenicity between XBB and XBB.1.16.[3] Generally, individuals who received the Ad5-vectored and protein-subunit vaccines had higher NAb titres against the PT and Omicron sub-variants than those who received the inactivated vaccine (Fig. 1 and Supplementary Fig. S3). For inactivated or Ad5-vectored vaccines, 1.7–3.5 times lower NAb titres against BQ.1 and BQ.1.1 were observed than those against PT and 2.0–3.9 times lower than those against BA.4/5. However, for the protein-subunit vaccine ZF2001 developed using RBD as antigen, the NAb titres against BQ.1 and BQ.1.1 were 7.0–8.3 times lower than those against PT and 6.8–8.1 times lower than those against BA.4/5 (Fig. 1, Supplementary Figs. S3 and S4). This indicates that the two additional mutation sites on the RBD of BQ.1 and BQ.1.1; K444T, and N460K, play important roles in mediating immune escape (Fig. 1A and Supplementary Fig. S2).

A booster shot of both inactivated and Ad5-vectored vaccines can induce higher NAb titres against the SARS-CoV-2 PT and variants.[4] However, after BTI in both the inactivated and Ad5-vectored vaccine groups, individuals who received two shots of the vaccine before BTI had similar, if not higher, NAb levels against the PT and Omicron sub-variants (Fig. 1 and Supplementary Fig. S5). This is consistent with previous reports on mRNA and inactivated vaccines after the BTI.[5–7]

Furthermore, our previous study showed that the long-interval strategy of the protein-subunit vaccine ZF2001 resulted in a much higher NAb titre against all SARS-CoV-2 variants, particularly Omicron sub-variants.[8,9] Here, the data revealed that after BTI, the two groups shared similar NAb levels against PT and all detected Omicron sub-variants (the NAb levels of the short-interval group were, –1.1 to –1.6 times that of the long-interval group, Fig. 1 and Supplementary Fig. S5). It may be because that BTI was equivalent to another boost of the immune system, and the time interval between the last shot and BTI was so long that the impact of the length of the gap between the second and third shots was not as influential.

Furthermore, a comparison was conducted between the two groups with identical vaccination backgrounds, with three doses of the inactivated vaccine were compared. However, these groups originated from different regions of China, with the major epidemic strains during the wave being BF.7 in Group 3 and BA.5.2 for Group 4. No significant differences were detected between the variants (Fig. 1 and Supplementary Fig. S6). This may be due to the original antigenic sin provided by the vaccination, as well as the similarity in the spike proteins of BA.5.2 and BF.7.

Fig. 1: **Neutralisation of sera of convalescents infected with SARS-CoV-2 against the pseudoviruses of SARS-CoV-2 variants.** (**a**) Schematic representation of the phylogenetic relationship between spike proteins of the SARS-CoV-2 prototype (PT) and current Omicron sub-variants, BA.2, BA.2.75, CH.1.1, BM.1.1.1, BJ.1, XBB, XBB.1.5, XBB.1.16, BA.4, BA.5, BA.5.2, BF.7, BQ.1, and BQ.1.1. As the sequences of the spike proteins of BA.4, BA.5, and BA.5.2 are the same, they are grouped as BA.4/5/5.2. Mutations (including substitutions, deletions, and insertions) in amino acids (AA) from PT to sub-variant sequences are shown along with arrows, and alterations in RBDs are coloured red. (**b–j**) Show 50% pseudovirus neutralisation titres ($pVNT_{50}$) of human sera against the SARS-CoV-2 PT strain and the Omicron sub-variants BA.2, BA.2.75, CH.1.1, BM.1.1.1, BJ.1, XBB, XBB.1.5, XBB.1.16, BA.4, BA.5, BA.5.2, BF.7, BQ.1, and BQ.1.1. Human sera were collected from convalescents infected during the recent wave, which was caused by the Omicron sub-variants BF.7 and BA.5.2 in China. Convalescent were grouped based on COVID-19 vaccination backgrounds. In Group 1, named infection group, participants received no COVID-19 vaccine before infection (**b**); Groups 2 through 4 represented participants who received two and three doses of COVID-19 inactivated vaccine before breakthrough infection (BTI) (**c–e**); Groups 5 and 6 represent individuals who were double- and triple-vaccinated with Ad5-Vectored COVID-19 vaccine before BTI (**f, g**); Groups 7 and 8 represented participants who received three shots of COVID-19 protein-subunit vaccine with short (less than two months) and long (longer than four months) intervals between the second and the third doses before BTI (**h, j**). The $pVNT_{50}$ in each group are shown as geometric mean titres (GMTs) with 95% confidence intervals (CI). The GMT numbers are indicated at the top of each column. The lowest limit of the pseudovirus neutralisation assay (1:10) is indicated by dashed lines. (**k**) Antigenic maps based on serum pseudovirus neutralisation ($pVNT_{50}$) in groups one–eight (shown in panels **b–j**). The distance between the dots in the figure represents the antigen (SARS-CoV-2 variants) distance measured by the $pVNT_{50}$, and the distance between the antigen and antiserum is inversely proportional to the $\log_2$ titre. The positions of the SARS-CoV-2 variants are represented by solid circles, and the serum positions are shown as empty squares. Pseudoviruses are coloured by variants. Sera are coloured by group. Both axes represent the antigenic distance, with one antigenic distance unit (AU) in any direction corresponding to a two-fold change in $pVNT_{50}$.

In summary, the serological NAb background was tested in individuals infected with Omicron in a wave following the zero-COVID policy adjustment in China. The tests covered all three major types of vaccines authorised in mainland China: inactivated, protein-subunit, and Ad5-vectored. The results illustrated that CH.1.1, XBB, and their sublineages were the strains with the highest immune escape potential and posed major threats to future reinfections. The NAb levels in convalescent patients with BTI varied according to the type of vaccine they received. However, a booster shot or the interval between the second and third shots, which have been proven to have a notable effect on NAb production, did not remarkably influence NAb levels after BTI. These results indicate that the original antigenic sin should be considered when designing future immunisation strategies.

Contributors

G.F.G., X.Z., Y.M., and Y.L. conceptualized the study. X.Z. wrote the original draft. Y.L., and S.Q. did data analysis, and figure making with the assistant of R.Z. S.Q., and Y.L. wrote the methodology. Y.L. drafted, figured, and tabled the supplementary with the assistant of S.Q., R.Z., and Shijie Q. G.F.G., X.Z., and Y.M. supervised the study. G.F.G., X.Z., Y.M., Y.L., S.Q., and R.Z. curated the data. S.Q., Y.L., R.Z., and R.L. did the pseudovirus neutralization assays. L.D., X.L., D.Y., Ying L., and Y.L. were responsible for sample collection. Shijie Q. generated drafts of antigenic maps, and wrote the corresponding method, and figure legends (Antigenic cartography). G.F.G., X.Z., and Y.M. are responsible for resources. All authors reviewed, and edited the manuscript. All authors had full access to all the data in the study, and had final responsibility for the decision to submit for publication.

Data sharing statement

The data used in this article are available in the article and its online supplementary materials. The individual-level data underlying this study cannot be shared publicly. All proposals for the data will be reviewed by the relevant data custodian to ensure that the proposed use complies with participant consent. To initiate a data request, please contact the corresponding author.

Patients and other consents

This study was approved by the Ethics Committees of the Institute of Microbiology, Chinese Academy of Sciences (SQIMCAS2021149), the Second Affiliated Hospital of Nanhua University (2022k120201), and the Second Affiliated Hospital of Nanchang University ([2022] No. 115). All participants provided written informed consent.

Declaration of interests

G.F.G. are listed in the patent as the inventors of the RBD-dimer as a betacoronavirus vaccine (ZF2001). All other authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanwpc.2023.100945.

References

1 Gao GF. Science-based COVID-19 vaccine development. *Natl Sci Rev*. 2021;8:nwab193.
2 COVID-19 clinical and surveillance data, 2022 to Jan 23, 2023. China https://en.chinacdc.cn/news/latest/202301/t20230126_263523.html.
3 Yamasoba D, Uriu K, Plianchaisuk A, et al. Virological characteristics of the SARS-CoV-2 Omicron XBB. 1.16 variant. *Lancet Infect Dis*. 2023;23:655–656.
4 Li JX, Wu SP, Guo XL, et al. Safety and immunogenicity of heterologous boost immunisation with an orally administered aerosolised Ad5-nCoV after two-dose priming with an inactivated SARS-CoV-2 vaccine in Chinese adults: a randomised, open-label, single-centre trial. *Lancet Respir Med*. 2022;10:739–748.
5 Collier A-RY, Brown CM, McMahan KA, et al. Characterization of immune responses in fully vaccinated individuals after breakthrough infection with the SARS-CoV-2 delta variant. *Sci Transl Med*. 2022;14:eabn6150.
6 Suntronwong N, Yorsaeng R, Puenpa J, et al. COVID-19 breakthrough infection after inactivated vaccine induced robust antibody responses and cross-neutralization of SARS-CoV-2 variants, but less immunity against omicron. *Vaccines (Basel)*. 2022;10:391. https://doi.org/10.3390/vaccines10030391.
7 Varese A, Mazzitelli B, Erra Díaz F, et al. Omicron breakthrough infection after heterologous prime-boost vaccination induces a vigorous antibody response. *J Infect Dis*. 2022;226:1717–1720.
8 Zhao X, Li D, Ruan W, et al. Effects of a prolonged booster interval on neutralization of omicron variant. *N Engl J Med*. 2022;386:894–896.
9 Zhao X, Zhang R, Qiao S, et al. Omicron SARS-CoV-2 neutralization from inactivated and ZF2001 vaccines. *N Engl J Med*. 2022;387:277–280.