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Breakthrough Infection shapes humoral immunity against SARS-CoV-2 Omicron Variant

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Dear Editor,

The rapid development of safe and effective COVID-19 vaccines was once thought to be the beginning of the end of the pandemic(1). However, with the decline of vaccine efficacy and the emergence of variants of concern (VOCs), massive breakthrough infections have occurred in vaccinated populations(2, 3). Recent articles in this journal mentioned that breakthrough infections caused by VOCs can induce higher immune responses than original infections and simple vaccination(4, 5). The evaluation of neutralization capacity against omicron induced by the "hybrid immunity" elicited by different vaccines and infections is crucial to the future vaccination strategy and the development of new vaccines.

In this study, we recruited 60 participants from 3 locally clustered COVID-19 outbreaks in Rizhao, Jinan, and Weihai, Shandong Province, China in October 2021, May and June 2022. They were all confirmed cases of COVID-19 with positive PCR tests, and the SARS-CoV-2 sequence of most participants has been confirmed by whole genome sequencing on Miseq. We examined neutralising activity against the wild-type SARS-CoV-2 and omicron BA.2.3 sub-variant from convalescent individuals with AY.126, P.1.15 or BA.2 breakthrough infections through live virus neutralization assay. The indirect ELISA kit (Vazyme, China) based on spike protein were used to quantify S-binding IgG antibodies against SARS-CoV-2. The design of this study and the spike protein mutations of the VOCs involved are shown in Figure 1A-B. See supplementary materials for detailed participant characteristics and methods.

Notably, the neutralization ability against BA.2.3 of all breakthrough infection

patients was 3.18-8 times lower than wild-type. In breakthrough infections following two doses of vaccine, the geometric mean titre (GMT) against wild-type and BA.2.3 in the 6 individuals who breakthrough by AY.126 were 3.32-times(from 1952.12 to 587.37) and 2.62-times(from 232.59 to 88.61) higher than individuals with BA.2 breakthrough infections; 3 patients who breakthrough by P.1.15 had 1.58-times(from 930.37 to 587.37) and 3.31-times(from 293.05 to 88.61) higher GMT than individuals who breakthrough by BA.2(Figure 2A). After three doses of the inactivated vaccine, patients with P.1.15 breakthrough infection also had a 1.83-times(from 1254.14 to 686.06) and 1.37-times(from 156.77 to 114.07) higher titre against wild-type and BA.2.3 compared with individuals who breakthrough by BA.2(Figure 2B).

Among the 13 P.1.15-infected patients, 10 patients received three doses of vaccine had 1.35-times(from 1254.14 to 930.37) higher titre against wild-type than patients who received two doses, but no improvement for BA.2.3(Figure 2C). Of the 41 BA.2-infected patients, 5 unvaccinated patients didn't develop high neutralizing antibodies by virtue of only once infection. For individuals with inactivated vaccines, the GMT against wild-type and BA.2.3 increased from 256.00, 41.93 to 686.06, 114.07, respectively, with the increase of pre-infection doses. In patients who vaccinated with three doses, the ZF2001 vaccine induced 1.45-times(from 991.79 to 686.06) and 1.64-times(from 187.04 to 114.07) higher titre against wild-type and BA.2.3 than the inactivated vaccine (Figure 2D).

The change trend of S-binding IgG antibody level in each group was similar to that of neutralizing antibody. The correlation results between neutralizing titers against

wild-type SARS-CoV-2, and BA.2.3, and S-binding IgG titer were R=0.64 ($p < 0.0001$), R=0.54 ($p < 0.0001$), and R=0.54 ($p < 0.0001$), and showing a moderate significant positive correlation between antibodies(Figure S1-2). Similar to a recent study(6), we also found that the ELISA assays could reflect the humoral immune response partly.

Consistent with previous studies(7, 8), the immune evasion ability of the omicron shouldn't be underestimated. Under the same vaccination conditions, the resistance to wild-type and BA.2.3 after BA.2 breakthrough infection was weaker than that of AY.126 and P.1.15 breakthrough infection. It suggests that the heterologous "hybrid immunity" could mediate stronger humoral immunity, whereas the omicron variant is less immunogenic in comparison(9). Although breakthrough infections may still occur after vaccination, vaccinated individuals could trigger stronger immune recall after infection than unvaccinated individuals(10). A limitation of this study is based on a small number of individuals. But this real-world antibody results from breakthrough infections individuals suggest that implementing complete vaccinations, optimizing vaccination and developing new vaccines regimens the key to combating VOCs and reducing the incidence of COVID-19.

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Declaration of competing interest

The authors have declared that no conflicts of interest exist.

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Legend

Figure 1. (A) The details of this study design. (B) The spike protein mutations of SARS-CoV-2 in breakthrough-infected individuals and live virus neutralization assays.

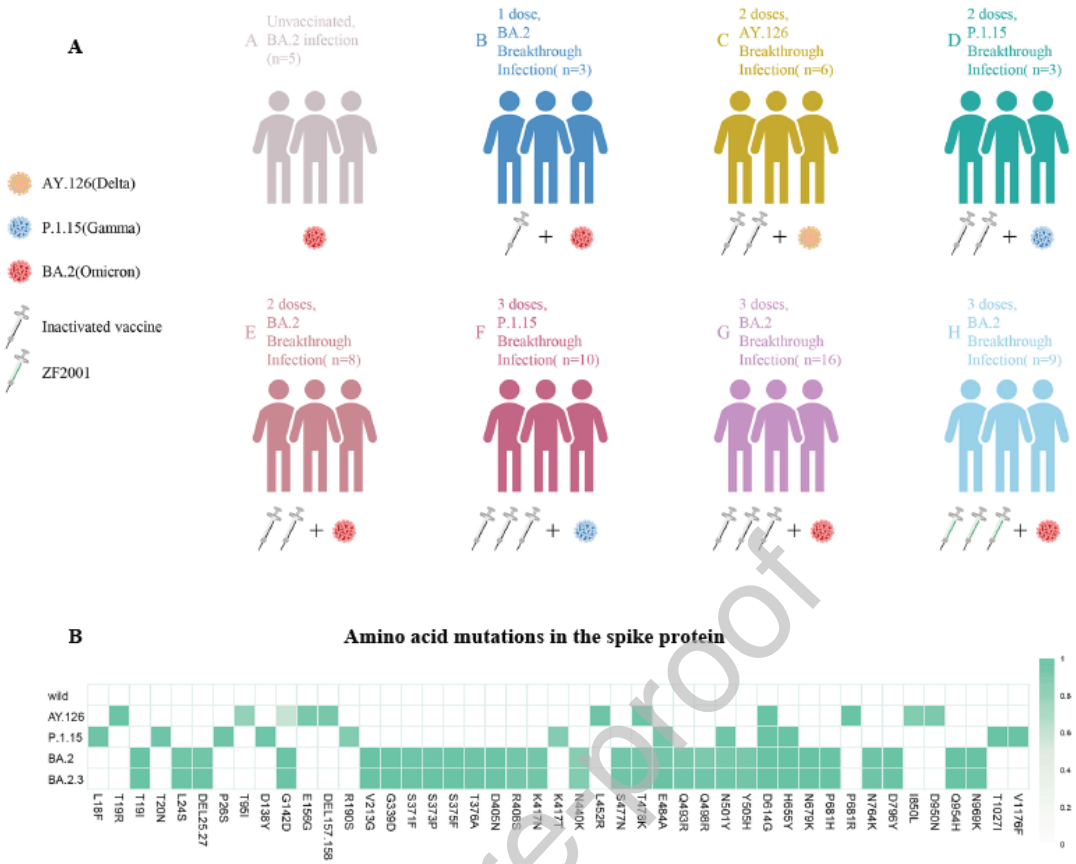

Figure 2. Neutralizing Antibodies against wild-type SARS-CoV-2 and omicron BA.2.3 sub-variant from breakthrough-infected individuals. Box violin plots show differences in neutralizing antibody titers against wild-type SARS-CoV-2 and Omicron BA.2.3 from AY.126, P.1.15 and BA.2 breakthrough-infected individuals after two doses of vaccine(C), P.1.15 and BA.2 breakthrough-infected individuals after three doses of vaccine(D), 13 P.1.15 breakthrough-infected individuals(E), and 41 BA.2 breakthrough-infected individuals(F). The geomatic mean titers (GMTs) are shown above each column.