Enhanced neutralization against SARS-CoV-2 by vaccine booster exhibits reduction of Omicron variant

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Abstract

The Omicron Variant of concern (B.1.1.529) has spread internationally and is raising serious concerns about the reduced vaccine efficacy and the increased risk of reinfection. Here we assessed the serum neutralizing activity using a pseudovirus-based neutralization assay in 292 healthcare workers who had administered a third homologous boosting vaccination 8 to 9 months after completion of the priming two-dose inactivated vaccination to investigate whether the newly identified Omicron variant could escape serum antibody neutralization elicited by the booster vaccination. The third booster dose with BBIBP-CorV could enhance the neutralizing immune response against SARS-CoV-2, and the neutralization GMT on day 28 after the third booster dose was 6.1 times higher than the GMT on day 28 after the second dose. The Omicron variant did cause significantly lower neutralization sensitivity compared to the wild-type strain of the booster elicited serum, with about 20.1-fold reduction. Our study demonstrated that a third booster dose of BBIBP-CorV lead to a significant rebound in neutralizing immune response against SARS-CoV-2, while the Omicron variant showed extensive but incomplete escape of the booster elicited neutralization.

As of December 15, 2021, more than 272 million people have been infected with SARS-CoV-2. Multiple types of vaccines have been used to build herd immunity for the pandemic, however, decreased protective efficacy has been reported, and neutralizing antibody titers induced by the two doses vaccination declined after 6 months to near or below the seropositive threshold[1]. Meanwhile, with the unprecedented transmission of the COVID-19 pandemic, several SARS-CoV-2 variants of concern have emerged, whereby the virus become more contagious. Most recently, the B.1.1.529 variant Omicron has spread internationally, which appears to have arisen in November 2021. Omicron variant is the fifth "variant of concern" as designated by the WHO, primarily due to 32 mutations it has in the Spike gene, especially in the receptor-binding domain and N-terminal domain. As Omicron variant is the most divergent variant so far, it may lead to escape from immunity elicited by the existing COVID-19 vaccines, and cause a large number of breakthrough infection[2].

The waning immunity and viral diversification both create the potential need for further booster vaccination, therefore, we administered a third homologous booster dose 8 to 9 months after completion of the priming two doses vaccination to eligible healthcare workers in Shanghai Ruijin Hospital to investigate whether the newly identified Omicron variant could escape serum antibody neutralization elicited by the BBIBP-CorV vaccine booster. Serum specimens were obtained before and 28 days after the third booster dose. We determined the serum neutralizing activity using a pseudovirus-based neutralization assay, and the SARS-CoV-2 specific antibody levels were assessed using chemiluminescence immunoassay, which was supposed to be a good surrogate for neutralizing antibodies. The details of the methods were described in the Supplementary Methods.

A total of 292 participants were included in this study, among them, 72 were male and 220 were female, the median age was 39.00 (interquartile range (IQR) 32.00-46.00) years. The baseline immune responses at 8 to 9 months after the priming two-dose inactivated vaccination were weak. The specific antibodies against SARS-CoV-2 could still be detected in 229 (78.42%) of 292 participants, but the

median antibody level dropped from 31.96 (10.36-73.66) to 3.63 (1.16-9.93) (Fig 1a). Moreover, the GMT declined rapidly to below the lower limit of detection, and only 53 (18.15%) of 292 participants had quantifiable neutralizing antibodies (Fig. 1b).

A significant enhanced antibody response was observed on day 28 after the third booster dose. Specific antibodies against SARS-CoV-2 against SARS-CoV-2 were detected in 291 (99.66%) participants, with a median antibody level at 486.6 (296.2-681.9), which was also dramatically higher than the baseline antibody level and the lever on day 28 after the second dose (Fig 1a). The seroconversion rate of neutralizing antibodies against the wild-type strain was 287 (98.29%) of 292 individuals, and the GMT increased to 294.9 (95% CI 253.0-343.6), more than 6.1 times of the level on day 28 after the second dose (data from Ruijin Hospital; Ethics Number: RJHKY2021-12) (Fig. 1b). On day 28 after the third booster dose, 228 (78.08%) participants preserved neutralizing activity against the Omicron variant, although the GMT showed a 20.1-fold reduction to 14.66 (12.3-17.48) (Fig. 1b). Sex and age were not factors that associated with the induction of neutralizing antibody and neutralizing titers against SARS-CoV-2 and Omicron variant after the booster dose.

Recent studies reported that a third dose of BNT162b2 mRNA vaccine is effective in preventing severe COVID-19 outcomes[3]. It was demonstrated that a third heterologous booster vaccination of recombinant protein subunit vaccine following the priming two-dose inactivated vaccination could quickly recover immune response, and elicit neutralizing antibodies against variants of concern[4]. This study is organized to answer whether a homologous third booster dose of inactivated vaccine could effectively activate specific immune responses to SARS-CoV-2, especially enhance the neutralizing activity against the newly-emerged Omicron variant. The data revealed that approximately 8 to 9 months after the priming two-doses inactivated vaccination, the neutralizing activity declined rapidly and could hardly be detected, supporting the need for a third booster dose to extend the duration of humoral response against the emerging variants. As expected, a third booster dose following the priming two-dose inactivated vaccination could significantly recall and enhance

antibody responses, indicating that the priming vaccination could induce efficient memory humoral immune responses. The neutralization GMT against the wild-type strain on day 28 after the third booster dose was 6.1 times higher than the GMT on day 28 after the second dose, but the persistency of the enhanced immunity against SARS-CoV-2 and its variants induced by the booster vaccination remains to be evaluated.

It was suggested that achieving a higher neutralizing antibody titer with the booster dose is desirable to increase the breadth of neutralization[5]. However, based on the current data, sera from vaccinated and convalescent individuals neutralized the Omicron variant to a much lesser extent than any other variant of concern[6]. The neutralization capacity of vaccine-elicited sera against Omicron variant was severely reduced, revealed at least 10-fold reduction[7], and 8.4 folds decreased neutralization of convalescent sera suggest that Omicron variant may lead to escape from immune protection elicited by previous SARS-CoV-2 infection and by exiting COVID-19 vaccines[8]. In our findings, although the neutralizing activity could still be detected in 228 (78.08%) participants, the Omicron variant did cause significantly lower neutralization sensitivity compared to the wild-type strain of the booster elicited serum, with about 20.1-fold reduction. Since neutralization is only a part of the humoral immune response, which does not equal to all potentially protective vaccine responses, real-world studies regarding the protection efficacy of the booster vaccination against the Omicron variant are still needed.

In conclusion, a third booster dose of BBIBP-CorV lead to a significant rebound in neutralizing immune response against SARS-CoV-2, while the Omicron variant showed extensive but incomplete escape of the booster elicited neutralization. The data presented here provide a piece of evidence for future establishment of the booster vaccination strategy against COVID-19.

Data availability

The data that support the findings of this study are available from the corresponding authors on reasonable request.

Acknowledgments

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Author contributions

XZ, JQ, ZY, and EC had the idea for and designed the study. XY and WX were responsible for collecting and summarizing the clinical data. DW, WX, YL, and XL performed the experimental studies. XY and DW carried out the analysis. XY and XZ drafted the manuscript. All authors reviewed and approved the final version.

Competing interests

The authors declare no competing interests.

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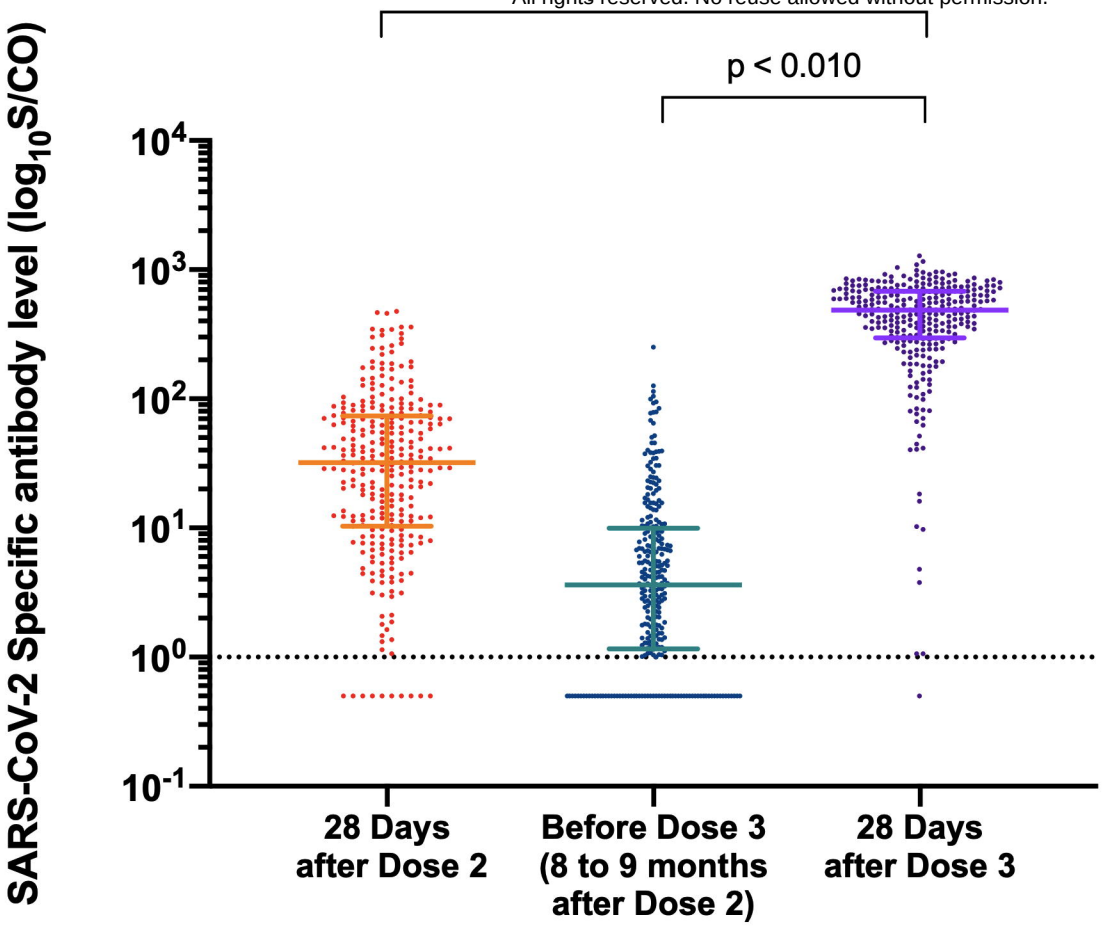
Figure Legends

Figure 1: SARS-CoV-2 specific antibody and neutralizing antibody responses.

a, The specific antibody levels against SARS-CoV-2 are shown for serum specimens obtained at the time points shown on the x axes from 292 participants. The horizontal dashed line represents the lower limit of detection (LLD) of 1; Results below the LLD were set to 0.5 times the LLD. Data points shown on the bar graph represent individual titers. Error bars indicate median and interquartile range (IQR). **b,** The results of 50% pseudovirus neutralization titer (pVNT50) against the wild-type strain and the Omicron variant are shown for serum specimens obtained at the time points shown on the x axes from 292 participants. The horizontal dashed line represents the lower limit of detection (LLD) of 4; Results below the LLD were set to 0.5 times the LLD. Data points shown on the bar graph represent individual titers. Error bars represent the geometric mean with the 95% confidence interval (95% CI). Fold-changes in geometric mean titer are shown above. p values were calculated using the Wilcoxon matched-pairs signed-rank test.

a



b