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Letter to the Editor

Antibody efficacy of inactivated vaccine boosters (CoronaVac) against Omicron variant from a 15-month follow-up study

Dear editor,

In this Journal, Au and colleagues previously compared the potency of CoronaVac in the seroprotection against SARS-CoV-2 Alpha, Beta, Gamma, and Delta variants,[1] we went on to provide an immunoprotection profile of CoronaVac against Omicron variants. As the latest variant of concern (VOC), the immune escape of Omicron poses a severe threat to vaccination effectiveness and immune protection. Earlier studies indicated a substantial decrease in the neutralizing antibody (Nab) response strength and antibody titers against Omicron elicited by mRNA-based vaccines.[2,3] Despite a third vaccination boosting the immune response, it still presents a risk of breakthrough infection. It has been extensively reported on the effects of a booster vaccination with mRNA regimens,[4–6] but a pressing question related to the immune response after three doses of inactivated COVID-19 vaccines is whether the antibody is potent enough to combat the Omicron variant strain after booster vaccination, which is yet to be determined. In this study, we examined the antibody response against the Omicron variant after three doses of the inactivated COVID-19 vaccine, and compared the immune protection efficacy with the ancestral strain, which may assist in optimizing the immune strategy.

The study was a follow-up that lasted for 15 months from 2021.01 to 2022.04, in which 116 healthy adult volunteers were included, with 46 males and 70 females, ranging in age from 19 to 32 years, with a median age of 25 (22, 27). These individuals were students recruited from colleges who had been vaccinated or planned to receive inactivated COVID-19 vaccines (CoronaVac, Sinovac). All volunteers included in the study had no underlying diseases and without a history of exposure or infection with COVID-19. None of them were obese, smokers or alcoholics. To examine the antibody response before and after vaccinations, we collected peripheral blood samples from volunteers at multiple time points before, after the second and the third dose of the inactivated COVID-19 vaccines (CoronaVac, Sinovac). Antibodies were measured in individual subjects up to 10 time points during the observation period until 159 days post the third vaccination (Tables S1 and S2). To evaluate the protective antibody response following vaccination, the iFlash-2019-nCoV Neutralizing Antibody Kit and the iFlash-SARS-CoV-2 IgG S assay (YHLO, Shenzhen, China) were used to quantify neutralizing and IgG S antibodies against SARS-CoV-2 in plasma[7,8] (See the Supplementary Materials for detailed methods).

It was found that an overall protective antibody immune response against both the Omicron variant and the ancestral strain was significantly enhanced after the third dose of the inactivated COVID-19 vaccine compared to two doses alone. Neutralizing and IgG S antibody levels in the plasma peaked approximately 10–14 days after three vaccinations and were relatively stable for 60 days (Fig. 1A). In comparison with the ancestor strain, the ability of most volunteer sera to produce neutralizing and IgG S antibodies against Omicron was considerably impaired. Even when the antibody response peaked 2 weeks after the booster vaccination, a 6.4-fold reduction in the geometric mean titer (GMT) of Nabs and a 2.3-fold decrease in anti-S antibodies against Omicron were observed (Fig. 1B). Analysis of protective antibody positivity rates revealed that the Nab potency against Omicron post two doses of inactivated COVID-19 vaccination was 18.2% in the first month and dropped rapidly to 7.7% at three months, while entirely undetectable six months after the second dose. Comparatively, following the booster doses, 61.9% of volunteers produced detectable Nabs against Omicron within one week, which rocketed to 97.5% within 14 days and declined to 65.2% 150 days after the vaccination (Fig. 1 C). To better visualize the immune escape of antibodies against Omicron after booster vaccination, we plotted the variations in Nab titers against the ancestral and Omicron strains at the same time point and sample. It was observed that Nab titers against Omicron decreased in 97.4% (370/380) of the samples (Fig. 2 A) and were highly correlated with Nab titers against the ancestral Wuhan strain (r=0.9045, p<0.0001) (Fig. 2 B).

During the 15-month follow-up study of healthy young volunteers who received inactivated COVID-19 vaccines, the antibody response and immunoprotective efficacy against the Omicron strain before and after the third dose (booster) were explored, as compared to the ancestral strain. Our results suggest that two doses of inactivated COVID-19 alone struggled to elicit sufficient Nab responses against the new variant of Omicron in the population. In fact, more than 80% of individuals failed to produce detectable Nab throughout. In contrast, following a booster, approximately 98% of individuals were able to produce efficient Nabs against the Omicron strain and maintained effectiveness of over 90% for 60 days and over 60% for 5 months, although falling short of the wild type. Based on our results, the conventional COVID-19 inactivated vaccine booster developed on the ancestral strain provided a favorable protective effect against the Omicron strain, which may be ascribed to two factors: first, the inclusion of intact viral particles provides as many loci associated with the neutralization activity, which allows uniquely beneficial in response to mutant viruses. Second, the included youth in the trial adhered to the standard vaccination routine and provided possibly greater immune protection effectiveness than the general population.

Furthermore, our results reiterated the inevitable impact of Omicron variants on antibody response attenuation and immune escape as indicated previously.[9,10] During our follow-up period, protective antibody levels against Omicron also declined to varying

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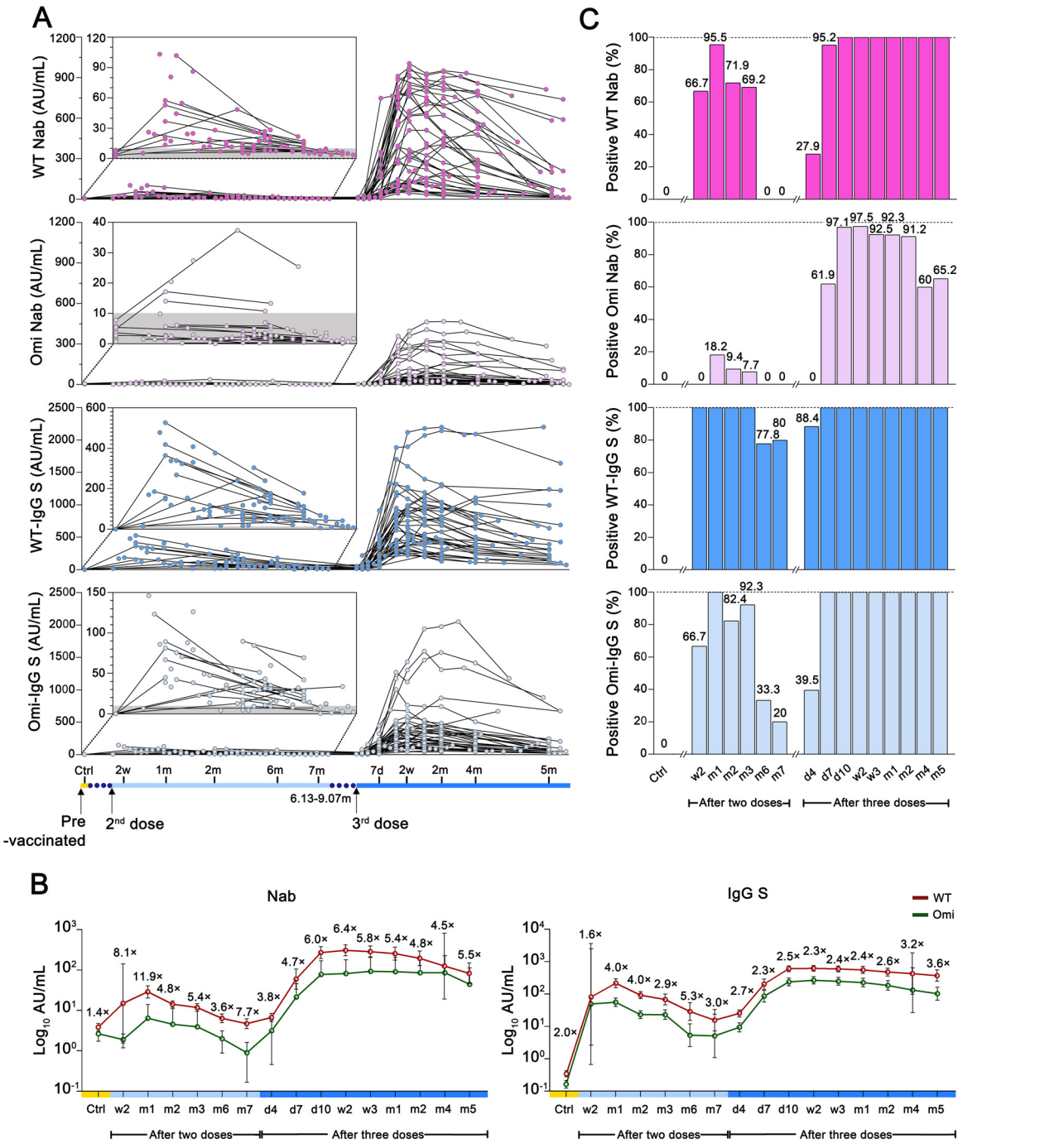

Fig. 1. Protective antibody responses against ancestral Wuhan-Hu-1 and the omicron variant before and after three doses of inactivated COVID-19 vaccines (CoronaVac, Sinovac). (A) Plasma Nab and IgG S antibody responses against Wuhan-Hu-1 (wild type, WT) and Omicron were measured in volunteers after two and three doses of inactivated vaccination, respectively. Antibody titers below 10 AU/mL were considered negative and were shaded in gray. Serum from the same individual was shown by connecting lines. A magnified view of the data was depicted prior to the third vaccination. The dotted line following the second dose on the horizontal axis indicated 6.13–9.07 months after the second vaccination. (B) Summary graph comparing the levels of protective antibodies against Omicron and the ancestral strain (WT). Differences in protective antibody titers against strains were expressed as a geometric mean titer (GMT) with 95% confidence intervals. Antibody concentrations were presented in a logarithmic format, and the time axis showed the main sample collection time points. (C) Varying positive rates of Nab and IgG S antibodies against Omicron and Wuhan-Hu-1 were detected in plasma following vaccination. The length of the bars reflected the percentage share. Omi, Omicron; WT, Wild type; Nab, Neutralizing antibodies.

degrees. Over seven months post-second vaccination, Nabs against Omicron were found to decrease by 3.6–11.9 fold, and five months post-third vaccination by 3.8–6.4 fold. The weakening of the anti S antibody against Omicron is relatively moderate, with a 1.6–5.3-fold drop in antibody potency after two vaccinations and a 2.3–3.6-fold reduction after three vaccinations. By continuously monitoring vaccinated individuals, these data add to a comprehensive picture of the immune response against Omicron.

To our limited knowledge, this is the longest follow-up report available regarding the antibody response of inactivated COVID-19 vaccine boosters against Omicron. An accurate assessment of the change in antibodies against the variant strain after vaccination could aid in the development of optimal immunization regimens.

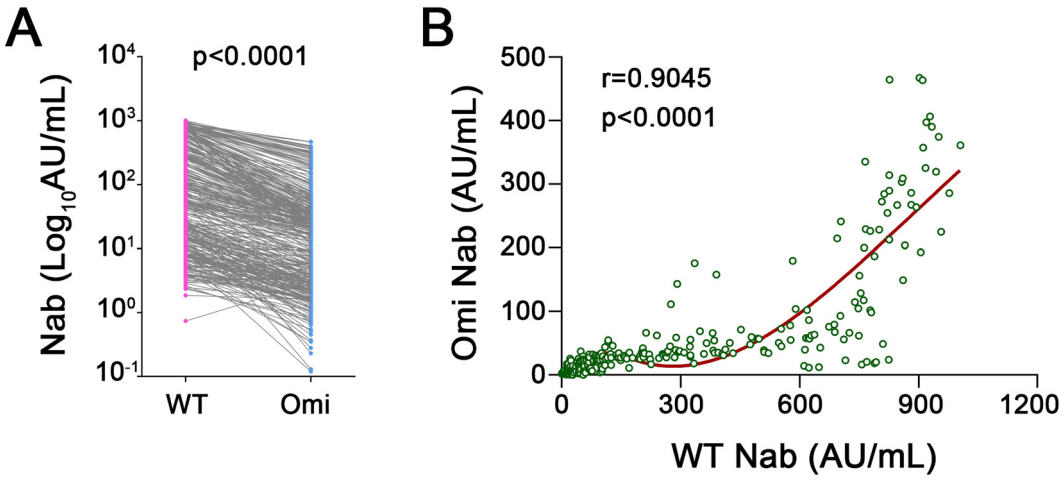

Fig. 2. Nab titer variations against the ancestral and the omicron variant at the same time point and sample. (A) Nab titers against Omicron compared to the ancestral Wuhan strain (Wuhan-Hu-1, WT) in plasma. The connected lines indicate blood samples obtained from the same individual and time point, and the Y-axis is in logarithmic form. A decrease in Nab titers against Omicron was found in 97.4% (370/380) of samples. The Wilcoxon matched-pairs signed rank test was performed to compare the differences between the two groups ($p<0.0001$). (B) The correlation between Nabs titers against Omicron and that against the ancestral Wuhan strain (Wuhan-Hu-1, WT). The horizontal axis represents the Nab levels of the ancestral Wuhan strain at a particular time point, whereas the vertical axis represents the corresponding Omicron-specific Nab titers, respectively. The correlation was examined using a nonparametric Spearman correlation analysis. The Nab titers against Omicron were highly correlated with that against the ancestral strain ($r=0.9045$, $p<0.0001$). Omi, Omicron; WT, Wild type; Nab, Neutralizing antibodies.

In conclusion, despite the disappointing decline in vaccine efficacy resulting from new variants, booster immunizations continue to be an integral part of establishing complete immunological protection among the population.

Declaration of Competing Interest

The authors have declared that no competing interest exists.

Ethics approval

The study was approved by the Peking University Biomedical Ethics Board (PUIRB) (ethics approval number: IRB00001052-22030). The study was conducted in compliance with all International Council for Harmonisation Good Clinical Practice guidelines and the ethical principles of the Declaration of Helsinki.

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Author contributions

T.S., Y.Y., X.L. designed the whole study. X.L. and Y.Y. contributed to the sample collection and isolation. Y.Y. compiled, analyzed, and visualized the data. C.Q., B.C., and F.L. supervised the laboratory testing results and undertook the data management. X.L. wrote and revised the manuscript. All authors reviewed and approved the manuscript for publication.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jinf.2022.06.018.

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