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A third high dose of inactivated COVID-19 vaccine induces higher neutralizing antibodies in humans against the Delta and Omicron variants: a Randomized, Double-Blinded Clinical Trial

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Dear Editor,

The current pandemic of coronavirus disease 2019 (COVID-19), caused by infection with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has been ongoing for over 2 years. Like other viruses, SARS-CoV-2 continues to develop mutations to improve its adaption and fitness. Compared with other SARS-CoV-2 variants, the Omicron variant (Omicron) has more mutations in the crucial receptor-binding domain, which may mediate vaccine-induced neutralizing antibodies (NAbs) (Cele et al., 2022). Consequently, Omicron has a notably higher immune evasion capability, allowing it to quickly become the dominant SARS-CoV-2 strain worldwide.

Studies have shown that a booster dose given 6–8 months after completion of the original vaccine schedule induces robust NAb levels (Pérez-Then et al., 2021; Zeng et al., 2022). CoronaVac (Sinovac Life Sciences, Beijing, China), an inactivated vaccine against COVID-19, is authorized in China and included in the WHO emergency use list. The recommended schedule was two doses of regular dosage (3 μg) each with an interval of 2–4 weeks. Recent studies indicate that participants who received a third dose (booster dose) of regular dosage (3 μg) of CoronaVac after the two-dose schedule gained elevated levels of NAbs. However, neutralization performance against Omicron was lower than against other SARS-CoV-2 strains (Wang et al., 2022a). Whether a higher dosage of inactivated booster vaccine could lead to a better neutralization performance against Omicron remains unknown. Although studies on the immunogenicity of inactivated vaccines have been conducted, either a pseudovirus assay or non-randomized clinical trials were used to assess the post-booster NAb response against Omicron (Peiris et al., 2022; Wang et al., 2022b). We designed and performed a randomized clinical trial (RCT), to minimize potential bias, for assessing the NAb responses induced by two different booster dosages (3 μg and 6 μg) of CoronaVac against Omicron and other SARS-CoV-2 strains. Additionally, authentic virus cytopathic assays were applied to measure NAb production against different SARS-CoV-2 strains.

Among the 369 screened subjects, 340 healthy adults without history of SARS-CoV-2 infection were eligible and enrolled in this study (Figure S1 in Supporting Information); of the eligible participants, 50 healthy subjects who completed the two-dose schedule of CoronaVac between January and February 2021 continued in the current study (Cao et al., 2021). No significant difference was observed between the two dosage groups regarding age, sex, or time interval be-

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tween receiving the final dose of the original vaccination series and booster doses (Table S1 in Supporting Information). Those who received the high-dose or medium-dose vaccines were aged from 21–67 and 22–64 years, respectively, and had time intervals between the second and third vaccine doses ranging from 161–282 and 151–283 days, respectively.

All 340 participants presented low geometric mean titers (GMTs) of NAbs at 5–9 months after completion of the first two doses of vaccine (baseline). Upon receiving a booster vaccination, the GMTs of all participants increased significantly, regardless of booster dosage or SARS-CoV-2 strains. Regarding the booster dosage difference, higher NAb levels against all SARS-CoV-2 strains over the entire study timeframe were observed in participants who received a high dosage as compared with those who received a medium dosage (Table S2 and S3 in Supporting Information,). Specifically, high-dosage booster vaccination-induced NAb levels against Omicron were 1.5- and 1.4-times higher at 14 and 28 days of post-booster administration (dpb), respectively, compared with medium-dosage booster vaccination (P<0.05 for both). Regarding SARS-CoV-2 strains, the GMTs of NAbs against Delta or Omicron at 14 and 28 dpb were all lower than those against wildtype virus (Table S2 in Supporting information); at 28 dpb with high-dosage CoronaVac, the NAb GMTs for Delta and Omicron were 5.1- and 27.9-fold lower than those against wildtype SARS-CoV-2.

Compared with baseline, the geometric mean increases (GMIs) of NAbs against wildtype at 7, 14, and 28 dpb were 11.7, 22.9, and 17.5, respectively, in the medium-dosage group and 20.4, 40.6, and 31.1, respectively, in the high-dosage group (Figure 1A). The levels of NAbs against Omicron at 7 and 28 dpb were 1.7- to 5.2-fold of baseline levels, respectively, in the medium-dosage group and 2.4- to 7.7-fold of baseline levels, respectively, in the high-dosage group (Figure 1 B and C).

In line with the observed GMT and GMI changes, both booster dosages induced seropositivity rates of >90% for NAbs against wildtype or Delta at 14 and 28 dpb. However, seropositivity rates for NAbs against Omicron peaked at 51.7% for the medium-dosage group and at 70.1% for the high-dosage group at 14 dpb. Higher seropositivity rates were observed among the higher-dosage group participants for all SARS-CoV-2 strains (P<0.05 for all) (Table S4 in Supporting Information).

At days 14 after the original vaccine series, NAb titers were below 1:4 against Omicron (n=50). However, the seropositivity rates and GMTs of NAbs against Omicron were dramatically increased after the administration of the booster dose (Figure S2 in Supporting Information). More remarkably, the GMT was 1:15.3 for participants in the high-dosage group and 1:10.4 for those in the medium-dosage group at 14 days post-second booster.

To our knowledge, this is the first RCT to evaluate the kinetics of NAb levels against Omicron following booster administration with different dosages of CoronaVac. The results

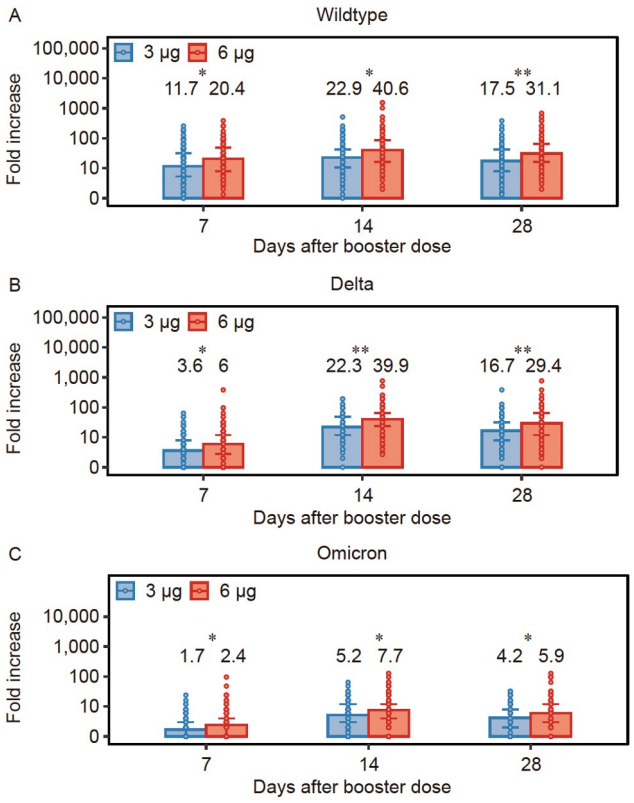

Figure 1 Neutralizing antibody response in GMI before and after the booster vaccination of medium (3 μg) - and high (6 μg) -dosage of CoronaVac against. A, Wuhan-Hu-1 (wildtype). B, B.1.617.2 (Delta) and C) B.1.529 (Omicron) strains. *, P<0.05; **, P<0.01; 3 μg (medium dosage) is the current vaccine regimen for CoronaVac.

of this RCT and our authentic virus cytopathic assays demonstrate that the high-dosage booster vaccine regimen may enhance the potential capability for protection in the real world.

Notably, barely any NAb response against Omicron was observed, even just 14 days after completing two doses of CoronaVac. Additionally, NAbs against Omicron, Delta, and wildtype strains were all at low levels at 5–9 months after receiving the two doses of CoronaVac from the original vaccine series. However, a booster dose quickly augmented the levels of NAbs against all three SARS-CoV-2 strains. In accordance with other studies in different populations and with different vaccine products, a booster vaccine dose generated a lower titer of NAbs against Omicron than its performance against other SARS-CoV-2 strains (Newman et al., 2021; Wang et al., 2022a). Despite lower levels of NAbs against Omicron than against other SARS-CoV-2 strains, the booster dose could still improve these levels up to 7.7-fold, with 70% seropositivity, in the higher-dosage group. The results indicate the importance of recommending and expanding booster dose administration to mitigate global challenge on Omicron.

Regarding the booster dosage difference, subjects who received the high-dosage regimen demonstrated higher seropositivity rates and antibody response against all SARS-CoV-2 variants; thus, the high-dosage booster should be

further tested and considered for administration. Additionally, low NAb responses were observed 5–8 months after the completion of vaccination, suggesting the presentation of a potentially waning immunity, as we observed from baseline data.

NAbs against Omicron had the lowest GMTs and seropositivity rates among the NAbs against all three SARS-CoV-2 strains, which might primarily be caused by immune evasion (Cele et al., 2022). The risk of reinfection with Omicron attests to its ability to evade host immunity as compared with other variants (Pulliam et al., 2021). As a relatively low antibody response was observed against the emerging omicron variant, it is urgent to develop Omicron-specific or multi-valent vaccines.

Notably, immunogenicity does not represent real-world vaccine effectiveness. Despite low levels of NAbs against Omicron, Wang et al. also reported the presence of memory B cells and NAbs with broad neutralizing activities against variants of concern (Wang et al., 2022a), that may benefit future Omicron-specific vaccine development. Despite the reported lower neutralization capability against Omicron (Newman et al., 2021), multi-site real-world vaccine effectiveness studies conducted on the administration of a booster dose found an effectiveness of over 80% and indicated that booster doses provided protection against hospitalization or severe outcomes for multiple vaccine products (Lauring et al., 2022).

Our study has several limitations. First, this study followed up only to 28 days after the administration of the booster dose, and neutralization dynamics remains unknown; thus, further studies on neutralization and real-world vaccine effectiveness for vaccine booster doses against Omicron should be followed up and evaluated in the future. Here, we included humoral immunity responses only, and cellular immunity, which should be included to evaluate the vaccine performance more comprehensively, was not considered. Additionally, as our recruited participants were mostly healthy young-to-middle-aged adults, the results may not be overly generalizable to the entire population. Evaluating vaccine performances on other populations such as the elderly, children, and adolescents as well as people with underlying diseases will also be necessary.

In conclusion, a higher dosage of CoronaVac could be administered as a booster regimen to mitigate the immunological challenge of Omicron.

Compliance and ethics *The author(s) declare that they have no conflict of interest. The study protocol was approved by Beijing Youan Hospital Ethics Committee (No. 2021-77). The trial complies with the Helsinki Declaration for research in human subjects.*

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SUPPORTING INFORMATION

The supporting information is available online at https//doi.org/10.1007/s11427-022-2110-1. The supporting materials are published as submitted, without typesetting or editing. The responsibility for scientific accuracy and content remains entirely with the authors.