

TO THE EDITOR—We read with interest the article by Mwimanzi et al about humoral responses after second and third doses of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) messenger RNA vaccination in older adults [1]. Here, we determined the effects of consecutive 4 BNT162b2 doses on neutralizing activity in sera from participants aged ≥60 years and those with risk factors against SARS-CoV-2 Wuhan and 2 Omicron sublineages, and analyzed longitudinal changes of neutralization activity pre- and post-second through fourth BNT162b2 doses in a prospective study over 490 days.

In the present prospective clinical study, 32 of 225 healthcare workers in Kumamoto General Hospital, Japan (225 were initially recruited in the primary clinical study [2]), who were either ≥60 years of age and/or had preexisting diseases/risk factors (see demographic characteristics in Supplementary Table 1A) were enrolled. These 32 participants received a fourth BNT162b2 dose as they had risk of developing severe coronavirus disease 2019. The SARS-CoV-2 neutralizing activity (50% neutralization titer [NT50]) of their sera against the Wuhan strain of SARS-CoV-2 was determined over 490 days using sera collected consecutively on (i) 1 week post-second dose, (ii) 2 weeks post-third dose, (iii) 1 week pre-fourth dose, and (iv) 2 weeks post-fourth dose (Supplementary Methods), representing a continuation of our previous studies [2-4]. We also evaluated the profile of S1-binding immunoglobulin G (IgG) levels following pre-/post-fourth dose (on days 300/490). In addition, we determined NT50 of the same sera using VeroE6TRMPRSS cells against infectious Omicron BA.2 and BA.5 variant sublineages, whose emergence has been associated with the present explosive increases globally [5].

Against SARS-CoV-2 Wuhan, moderate neutralizing activity was seen on day 28, 1 week after second-dose samples (Figure 1A, mean NT50 = 307), whereas there was a remarkable rise in neutralizing activity of the same participants’ sera of 2 weeks after third-dose administration (day 300), achieving a mean NT50 of 2238 (Figure 1A). On day 470 (1 week pre-fourth dose), the mean NT50 decreased to 541, 24% of the peak value on day 300 (2 weeks post-third dose) (Figure 1A). However, by day 490, 2 weeks post-fourth dose, neutralization activity was restored to 2096 (Figure 1A). The mean S1-binding IgG levels in pre-/post-fourth dose sera also showed an increase, from 247 on day 470 (1 week pre-fourth dose) to 1152 on day 490 (2 weeks post-fourth dose) (Supplementary Table 1B).

On the other hand, mean NT50 values against BA.2 and BA.5 on day 28, 1 week post-second dose were only 27 and 24, respectively, close to the cutoff value (20) (Figure 1B). By contrast, mean NT50 of sera on day 300 (2 weeks post-third dose) against BA.2 and BA.5 increased to 223 and 191, respectively (Figure 1B). By day 470, 1 week pre-fourth dose, the mean NT50 had decreased to 28% and 25% of those observed on day 300 sera against BA.2 and BA.5, respectively (Figure 1B, mean NT50 = 62 and 47, respectively); however, the mean NT50 against BA.2 and BA.5 was restored to 292 and 205, respectively, on day 490, to the extent seen after the third dose (Figure 1B).

Compared to the significantly boosted response elicited by the third dose, the magnitudes of neutralizing activity against SARS-CoV-2 Wuhan following the fourth dose were only comparable to and not greater than those following the third dose (Figure 1). The magnitudes of neutralizing activity against 2 Omicron variants following the fourth dose were also comparable to and not greater than those following the third dose. The present data, that a fourth vaccine dose restores protection but does not further enhance the humoral response, may be related to “original antigenic sin” [6], wherein high-affinity memory B cells inhibit the recruitment of naïve B cells against subsequent antigenic stimuli, in particular, against new stimuli. Thus, it is likely that despite the fourth dose, breakthrough infections continue to occur. It remains to be determined whether the upcoming Omicron-specific booster vaccines strengthen or attenuate the Omicron-specific protection already acquired through 4 regular doses in older individuals and those with other risks.

Supplementary Data

Supplementary materials are available at The Journal of Infectious Diseases online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. M. A. and H. M. had access to all data in this study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: M. A. and H. M. Acquisition, analysis, or interpretation of data: M. A. and S. O. Obtained funding: H. M. Administrative and material support: Y. I., N. H.-K., and S. S. Supervision: S. M. and

Reference

[1] Mwimanzi M, et al. Human response to the SARS-CoV-2 BNT162b2 vaccine in a prospective study over 490 days. The Journal of Infectious Diseases; 2022. https://doi.org/10.1093/infdis/jit113

Supplementary materials
Figure 1. Neutralizing activity of post–second, third, and fourth dose sera against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Wuhan strain, Omicron BA.2, and Omicron BA.5. Temporal changes of neutralizing activity of participants’ sera over 490 days post–first dose are shown. BNT162b2 doses were administered on days 0, 21, 287, and 477. A, The 50% neutralization titers (NT$_{50}$) of participants’ sera against infection by SARS-CoV-2 Wuhan strain were determined on days 7, 28, 60, 150, 280, 300, 360, 470, and 490 post–first dose using VeroE6-TMPRSS2 cell-based neutralization assay. Solid circles denote NT$_{50}$ titers of each participant’s serum and filled bars denote average NT$_{50}$ titers of 32 participants’ sera at each time point. Geometric mean NT$_{50}$ titers and ranges of NT$_{50}$ at each time point are shown at the bottom. B, Temporal changes of neutralizing activity of participants’ sera at day 28, 300, 470, and 490 post–first dose against Omicron BA.2 and BA.5 variants are shown. Solid circles denote NT$_{50}$ titers of each participant’s serum and filled bars denote average NT$_{50}$ titers of 32 participants’ sera at each time point. The NT$_{50}$ values were found to be normally distributed following conversion to the log$_{10}$ values and the differences between day 300 and day 490 values were calculated using paired $t$ test.
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Data availability. The data sets generated during this study are available from the corresponding author upon request.

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Potential conflicts of interest. All authors: No reported conflicts of interest.

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References

1. Mwimanzi F, Lapointe HR, Cheung PK, et al. Older adults mount less durable humoral responses to two doses of COVID-19 mRNA vaccine but strong initial responses to a third dose. J Infect Dis 2022; 226:983–94.

2. Maeda K, Amano M, Uemura Y, et al. Correlates of neutralizing/SARS-CoV-2-S1-binding antibody response with adverse effects and immune kinetics in BNT162b2-vaccinated individuals. Sci Rep 2021; 11:22848.

3. Amano M, Maeda K, Tsuchiya K, et al. Third-dose BNT162b2 vaccination elicits markedly high-level SARS-CoV-2-neutralizing antibodies in vaccinees who responded poorly to a second dose in Japan. J Infect Dis 2022; 226:2038–9.

4. Amano M, Otsu S, Maeda K, et al. Neutralization activity of sera/IgG preparations from fully BNT162b2 vaccinated individuals against SARS-CoV-2 Alpha, Beta, Gamma, Delta, and Kappa variants. Sci Rep 2022; 12:13524.

5. World Health Organization. COVID-19 weekly epidemiological update. 2022. https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19. Accessed 3 August 2022.

6. Brown EL, Essigmann HT. Original antigenic sin: the downside of immunological memory and implications for COVID-19. mSphere 2021; 6: e00056-21.