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CORRESPONDENCE

Restoration of Neutralization Activity Against Omicron BA.2 and BA.5 in Older Adults and Individuals With Risk Factors Following the Fourth Dose of Severe Acute Respiratory Syndrome Coronavirus 2 BNT162b2 Vaccine

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 1*A*) 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 [NT_{50}]) 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 NT_{50} of the same sera using VeroE6^{TMPRSS} 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 1*A*, mean $NT_{50} = 307$), 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 NT_{50} of 2238 (Figure 1*A*). On day 470 (1 week pre–fourth dose), the mean NT_{50} decreased to 541, 24% of the peak value on day 300 (2 weeks post–third dose) (Figure 1*A*). However, by day 490, 2 weeks post–fourth dose, neutralization activity was restored to 2096 (Figure 1*A*). 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 1*B*).

On the other hand, mean NT_{50} 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 1*B*). By contrast, mean NT_{50} of sera on day 300 (2 weeks post–third dose) against BA.2 and BA.5 increased to 223 and 191, respectively (Figure 1*B*). By day 470, 1 week pre–fourth dose, the mean NT_{50} had decreased to 28% and 25% of those observed on day 300 sera against BA.2 and BA.5, respectively (Figure 1*B*, mean $NT_{50} = 62$ and 47, respectively); however, the mean NT_{50} 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 1*B*).

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 naive 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

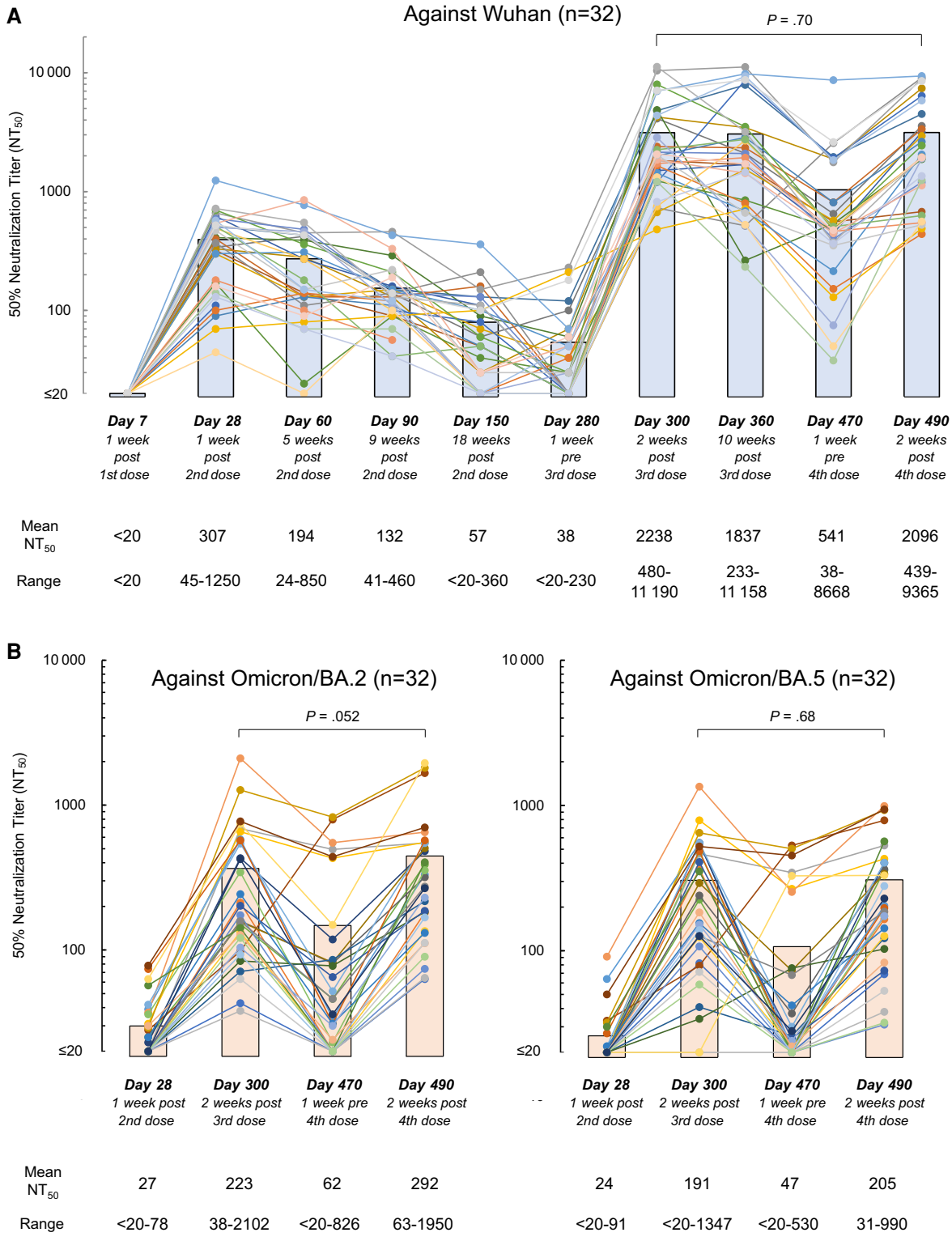

Figure 1. Neutralizing activity of post–second, third, and fourth dose sera against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Wuhan strain, Omicron BA.2, and Omicron BA.5. Temporal changes of neutralizing activity of participants' sera over 490 days post–first dose are shown. BNT162b2 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^{05-2N} strain were determined on days 7, 28, 60, 90, 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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Masayuki Amano,[1] Sachiko Otsu,[1] Yasuko Ichikawa,[2] Nobuyo Higashi-Kuwata,[3] Shuzo Matsushita,[1] Shinya Shimada,[2] and Hiroaki Mitsuya[3]

[1]Department of Clinical Retrovirology, Joint Research Center for Human Retrovirus Infection, Kumamoto University, Kumamoto, Japan; [2]Kumamoto Ganeral Hospital, Japan Community Health Care Organization, Kumamoto, Japan; and [3]Department of Refractory Viral Infections, National Center for Global Health and Medicine Research Institute, Tokyo, Japan

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Correspondence: Hiroaki Mitsuya, MD, PhD, Department of Refractory Viral Infections, National Center for Global Health and Medicine Research Institute, 1-21-1 Toyama, Shinjuku, Tokyo 162-8655, Japan (hmitsuya@hosp.ncgm.go.jp).

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