

## CORRESPONDENCE

## Immunologic Effect of Bivalent mRNA Booster in Patients Undergoing Hemodialysis

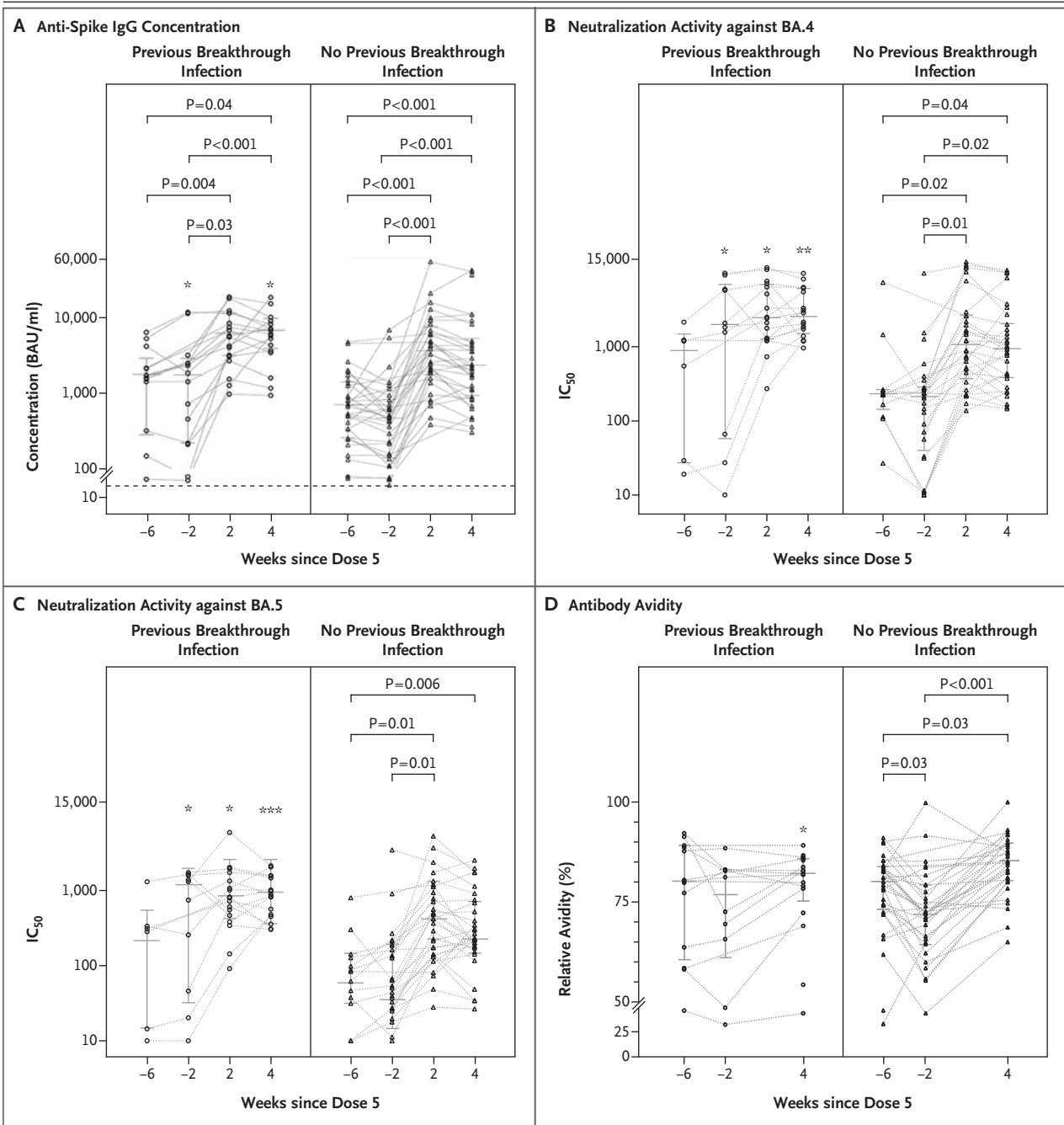
**TO THE EDITOR:** Booster doses of bivalent messenger RNA (mRNA) vaccines containing the ancestral severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the omicron B.1.1.529 (BA.4 and BA.5) variant spike sequences have been strongly recommended for persons at risk for severe sequelae of coronavirus disease 2019 (Covid-19). Patients undergoing hemodialysis have shown inferior humoral immunity against variants despite the receipt of four monovalent vaccine doses.<sup>1,2</sup>

In this case series, 55 patients undergoing hemodialysis who had received four previous SARS-CoV-2 vaccinations were monitored 6 and 2 weeks before and 2 and 4 weeks after a fifth vaccination with a bivalent mRNA vaccine (see the Supplementary Appendix, available with the full text of this letter at NEJM.org). Before the fifth vaccination, 18 patients had had previous omicron breakthrough infection that had been confirmed by polymerase-chain-reaction testing, whereas 37 had not had previous omicron breakthrough infection.

From 2 weeks before to 2 weeks after the fifth vaccination, a significant increase by a factor of 2.5 in anti-spike IgG concentrations was stimulated in the patients who had had previous omicron breakthrough infection, and an increase by a factor of 7.3 was stimulated in those who had not had previous omicron breakthrough infection (Fig. 1A). Patients with previous breakthrough infection had significantly higher anti-spike IgG concentrations and neutralization activities (expressed as 50% inhibitory concentrations)<sup>3,4</sup> against BA.4 (Fig. 1B) and BA.5 (Fig. 1C) than those without previous breakthrough infection, both before and after the fifth vaccination. Patients without previous breakthrough infection had significantly increased infection-neutralizing

capacity by a factor of 4.9 against BA.4 and by a factor of 3.3 against BA.5 at 2 weeks after vaccination and increased anti-spike IgG avidity by 17% at 4 weeks after vaccination (Fig. 1D). After the fifth vaccination, neutralization activities against both omicron BA.4 and BA.5 in both groups — those with and those without previous breakthrough infection — positively correlated with anti-spike IgG concentrations, antibody avidity, and neutralization activity before the fifth vaccination (Figs. S2 and S3 in the Supplementary Appendix), whereas age did not significantly influence the results. A regression analysis that included all study patients showed that the anti-spike IgG concentration after booster vaccination was the most important indicator of high neutralization activity against BA.4 ( $P=0.008$ ) and BA.5 ( $P=0.005$ ).

The findings are in accordance with results from clinical studies of bivalent mRNA vaccines in healthy persons that showed a significant rise in anti-spike IgG concentrations.<sup>5</sup> In particular, patients who did not have previous breakthrough infection immunologically benefited from a bivalent mRNA booster: despite having lower anti-spike IgG concentrations before the fifth vaccination, they had a significant increase after the fifth vaccination, such that their concentrations matched those in persons with hybrid immunity due to omicron breakthrough infection. The high dependency of neutralization activity against omicron BA.4 and BA.5 on baseline anti-spike IgG concentrations and binding activity before booster vaccination corroborates the concept that antibodies should be maintained at high levels by means of periodic vaccinations. The results may be of particular importance for persons at risk for severe disease such as patients undergoing hemodialysis and support recommendations that



**Figure 1 (facing page). Anti-Spike IgG Responses against Omicron BA.4 and BA.5 Subvariants before and after Bivalent mRNA Booster in Patients Undergoing Hemodialysis.**

Anti-spike IgG concentrations 6 and 2 weeks before, as well as 2 and 4 weeks after, fifth messenger RNA (mRNA) vaccination in patients with previous B.1.1.529 (omicron) breakthrough infection (open circles) and those with no previous omicron breakthrough infection (triangles) are shown (Panel A). Connecting lines between the time points indicate matched serum samples. The dashed horizontal line indicates the lower limit of detection (31 binding antibody units [BAU] per milliliter) in the detection system. Neutralizing activities are presented as serum dilutions for half-maximal infection-neutralization capacities normalized to  $10^7$  viral RNA copies (50% inhibitory concentration [ $IC_{50}$ ]) for omicron BA.4 (Panel B) and BA.5 (Panel C). The anti-spike IgG antibody avidities are shown as relative percentages for three time points (Panel D). The median value (horizontal line) and interquartile range (whiskers) are shown. P values are given for comparison of the dependent variables between different time points for each group. For comparison between patients with previous omicron breakthrough infection and those with no previous omicron breakthrough infection at each time point, one asterisk denotes  $P < 0.05$ , two asterisks  $P < 0.01$ , and three asterisks  $P < 0.001$ .

these patients should receive booster doses of bivalent mRNA vaccines, particularly if they have no hybrid immunity from an omicron breakthrough infection.

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