CORRESPONDENCE

Effects of a Prolonged Booster Interval on Neutralization of Omicron Variant

TO THE EDITOR: The coronavirus disease 2019 (Covid-19) pandemic is still ongoing,[1] and the B.1.1.529 (or omicron) variant, first detected in November 2021, has already spread globally. The ability of the omicron variant to escape vaccine-elicited immunity is of great concern. Inactivated vaccines, such as CoronaVac and BBIBP-CorV, and protein subunit vaccines, such as ZF2001, have been widely used in China and several other countries.[2]

We analyzed the binding and neutralizing antibodies elicited by three doses (two priming doses and one booster dose) of an inactivated vaccine or ZF2001, as well as those in persons who had recovered from Covid-19 (the convalescent group). The serum samples from the ZF2001 recipients were grouped according to the interval between the second and third dose; the persons in the short-interval ZF2001 group had received the second priming dose 1 month after the first dose and then the third dose 1 month after the second dose, and those in the prolonged-interval ZF2001 group had received the second priming dose 1 month after the first dose and then the third dose 4 months after the second dose. The decreases in the titers of antibodies binding to the omicron variant were greater in the serum samples from both ZF2001 groups than in those from the inactivated-vaccine group or the convalescent group (Fig. 1A through 1D and Table S1 in the Supplementary Appendix, available with the full text of this letter at NEJM.org).

We used a pseudovirus system to test the serum samples for neutralizing antibodies against the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) prototype strain and variants of concern, including the omicron variant. In the convalescent group, 15 of 16 serum samples were shown to be negative for neutralizing antibodies against the omicron variant, which indicates that the immune escape potential of this variant is high — a finding consistent with those of other recent analyses.[3] However, the antibodies in the serum samples from the inactivated-vaccine and ZF2001 groups remained effective in the neutralization of the omicron variant with relatively high seroconversion. Among the persons who received three doses of either vaccine, 10 of 16 samples (62%) in the inactivated-vaccine group, 9 of 16 samples (56%) in the short-interval ZF2001 group, and 16 of 16 samples (100%) in the prolonged-interval ZF2001 group were shown to be positive for neutralizing antibodies against the omicron variant. In a fifth group of persons who also had a prolonged 4-month interval between the second and third dose of ZF2001 but whose serum samples were collected 4 to 6 months after the third dose, 9 of 13 serum samples (69%) were positive for neutralizing antibodies against the omicron variant. The titer of neutralizing antibodies against the omicron variant was lower than that against the prototype SARS-CoV-2 strain by a factor of 17.4 in the convalescent group, by a factor of 5.1 in the inactivated-vaccine group, by a factor of 10.6 in the short-interval ZF2001 group, and by a factor of 3.1 in the prolonged-interval ZF2001 group (Fig. 1F through 1J). Moreover, as we reported previously,[4] a longer interval between the second priming dose of vaccine and the booster dose appears to result in higher neutralizing antibody titers against all variants tested.

These findings support the use of multiple vaccine boosts and prolonged intervals between vaccine doses to protect against highly mutated variants such as omicron in persons who had previously received two priming doses of vaccine or who had previously recovered from SARS-

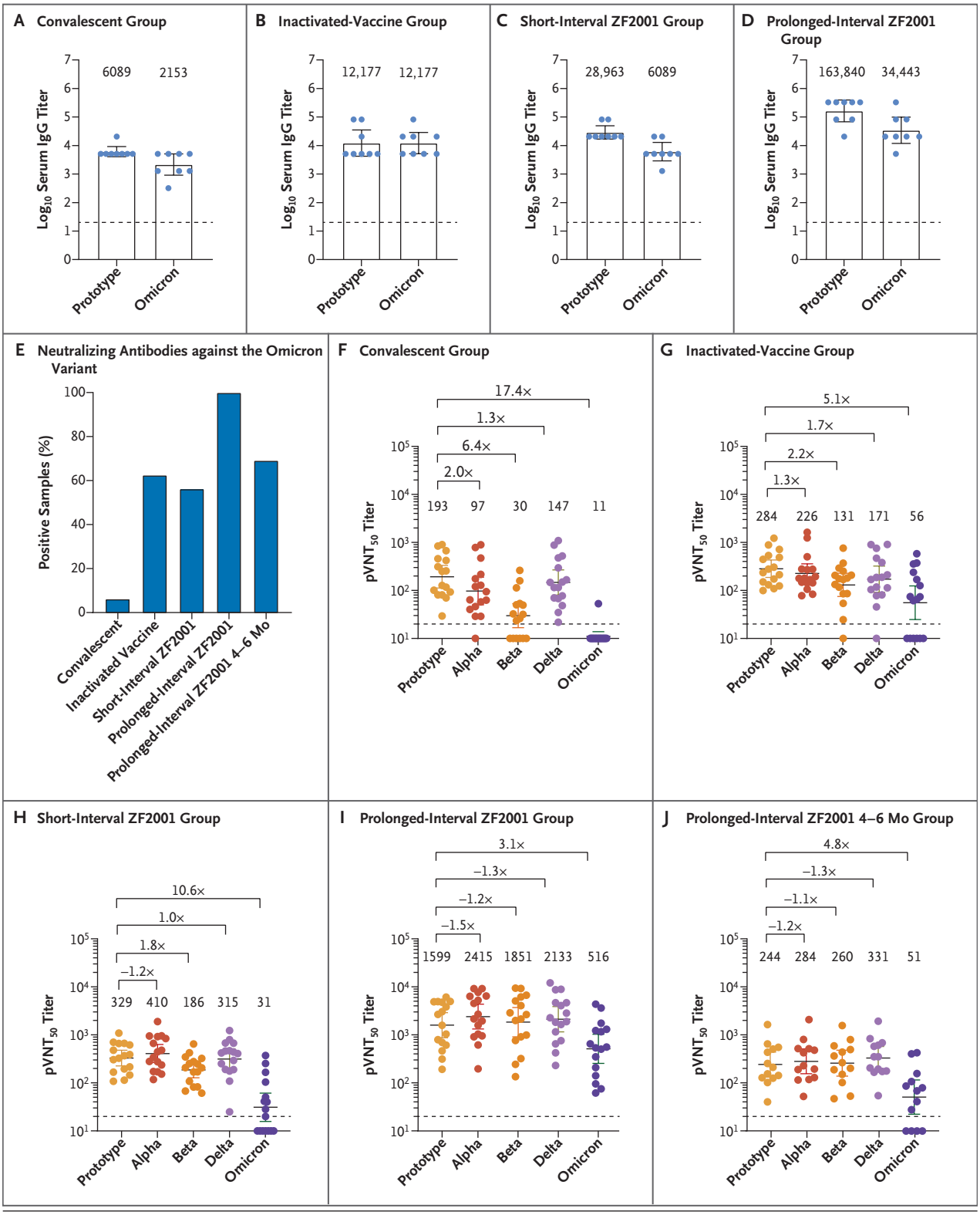
A Convalescent Group
B Inactivated-Vaccine Group
C Short-Interval ZF2001 Group
D Prolonged-Interval ZF2001 Group
Log10 Serum IgG Titer
6089
2153
12,177
12,177
28,963
6089
163,840
34,443
Prototype
Omicron
E Neutralizing Antibodies against the Omicron Variant
Positive Samples (%)
Convalescent
Inactivated Vaccine
Short-Interval ZF2001
Prolonged-Interval ZF2001
Prolonged-Interval ZF2001 4–6 Mo
F Convalescent Group
G Inactivated-Vaccine Group
pVNT50 Titer
17.4×
1.3×
6.4×
2.0×
193
97
30
147
11
5.1×
1.7×
2.2×
1.3×
284
226
131
171
56
Prototype
Alpha
Beta
Delta
Omicron
H Short-Interval ZF2001 Group
I Prolonged-Interval ZF2001 Group
J Prolonged-Interval ZF2001 4–6 Mo Group
10.6×
1.0×
1.8×
–1.2×
329
410
186
315
31
3.1×
–1.3×
–1.2×
–1.5×
1599
2415
1851
2133
516
4.8×
–1.3×
–1.1×
–1.2×
244
284
260
331
51

Figure 1 (facing page). Serum IgG Titers and Pseudovirus Neutralization against the Omicron Variant.

Serum samples were obtained from persons who had recovered from coronavirus disease 2019 (the convalescent group) or persons who had received three doses of an inactivated vaccine or the ZF2001 protein subunit vaccine. These samples were tested for binding and neutralizing antibodies against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) prototype and variants of concern (B.1.1.7 [or alpha], B.1.351 [or beta], B.1.617.2 [or delta], and B.1.1.529 [or omicron]). Panels A through D show the titers of serum IgG antibodies against the SARS-CoV-2 prototype strain or the omicron trimeric spike protein. The persons in the inactivated-vaccine group received the second priming dose 1 month after the first dose and then the third dose more than 6 months after the second dose. The persons in the short-interval ZF2001 group received the second priming dose 1 month after the first dose and then the third dose 1 month after the second dose. The persons in the prolonged-interval ZF2001 group received the second priming dose 1 month after the first dose and then the third dose 4 months after the second dose. A total of 8 samples from 8 persons were tested in each group. Panel E shows the percentage of samples that tested positive (as indicated by a titer of >1:20) for neutralizing antibodies against the omicron variant. "Prolonged-interval ZF2001 4–6 Mo" refers to the 13 serum samples from vaccinees who also had a prolonged interval between the second and third dose but were collected 4 to 6 months after the third dose. Panels F through I show the 50% pseudovirus neutralization titer ($pVNT_{50}$) in serum samples against the SARS-CoV-2 prototype and variants of concern; the $pVNT_{50}$ is the end-point titer of serum dilution that inhibits pseudovirus infection by 50%. A total of 16 samples from 16 persons were tested in each group. Panel J shows the $pVNT_{50}$ in the 13 samples from the prolonged-interval ZF2001 4–6 group. All neutralization assays were repeated twice. In all the panels except Panel E, geometric mean titers (GMTs) with 95% confidence intervals are shown, and the dashed lines indicate the lower limit of detection. In Panels A through D, the values above the bars are the GMT of the end-point titer in the enzyme-linked immunosorbent assay of SARS-CoV-2–binding IgG (see the Supplementary Analysis). In Panels F through J, the values above the bars are the GMT of the $pVNT_{50}$; $pVNT_{50}$ titers lower than 1:20 were considered to indicate that the sample was negative for neutralization antibodies.

CoV-2. Our results are in accordance with those of previous studies involving messenger RNA vaccine recipients.[5] Next-generation vaccines that stimulate broad protection against SARS-CoV-2 variants are also needed.

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