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CORRESPONDENCE

Antibody responses and correlates after two and three doses of BNT162b2 COVID-19 vaccine

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To the editor,

While the mRNA COVID-19 vaccines are highly effective in decreasing the risk of infection, hospitalization, and death [1], a significant variation in the immune response among vaccine recipients has been identified. Specifically, male sex, older age, and chronic diseases have been associated with lower anti-spike antibody levels after two vaccine doses [2, 3]. It remains elusive, however, whether such a difference in humoral immune response persists after the third vaccine dose, which is currently administered in many countries. Here, we report immunogenicity after the third dose of the BNT162b2 vaccine in relation to the correlates of that after the second dose.

We analyzed data of a repeat serological study among the staff of the National Center for Global Health and Medicine, Japan [4]. In the Toyama ward of the center in Tokyo, 1949 staff attended a survey at least 14 days after the second vaccine (baseline survey); of these, 1446 attended the follow-up survey at least 14 days after the third vaccine. Then, we excluded 180 participants who had a history of COVID-19 (n = 55), were seropositive on anti-N antibodies at either or both surveys ($n = 65$), or lacked information on covariates ($n = 60$), leaving 1266 participants for analysis (Section S1). These participants had their anti-spike antibodies measured with both Roche (mature antibodies including IgG) and Abbott (IgG) assays at both baseline and follow-up surveys (Section S2). We used multivariable linear mixed models to examine the spike antibody titers in relation to potential determinants after the second and third doses (Section S3). Written informed consent was obtained from all participants, and the study procedure was approved by the NCGM ethics committee (approved number: NCGM-G-003598).

The interval from the second vaccine dose to the baseline survey was 68 (interquartile range [IQR]: 62–70) days, and that from the third vaccine dose to the follow-up survey was 74 (IQR: 68–81) days. The spike antibody titers with Roche assay after the third dose were increased 11.7-fold from the titers after the second dose (geometric mean titers, 12,765 vs. 1,091), and all subgroups showed substantial elevation in antibody levels (Table 1). Male sex, older age, coexisting diseases, and immunosuppression were associated with lower antibody levels after the second vaccine dose. After the third vaccine dose, the associations with age and coexisting diseases disappeared, while the significant association with immunosuppression remained. Unexpectedly, males had significantly higher antibody levels than females after the third vaccine dose. The antibody correlates with the Abbott assay were materially the same except for obesity (defined as body mass index ≥ 27.5 kg/m^2), which was associated with lower antibody titer after the second dose and not after the third dose (Table S2).

After the third vaccine, we observed a substantial increase in anti-SARS-CoV-2 spike antibody levels, which appears to be larger among subgroups with lower antibody titers after the second dose, eliminating the difference in post-vaccine immune response across the population. The third dose may not only enhance post-vaccine immunogenicity but also minimize the discrepancy observed after the second dose across groups with a different background in terms of age, comorbidity, and obesity.

Members of the study group are listed in the Supplementary Appendix.

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Table 1 Anti-SARS-CoV-2 spike antibody titers (Roche) and their correlates after receipt of the second and third vaccine doses

Variables	*N* (%)	After the second dose (*N* = 1266)[a]		After the third dose (*N* = 1266)[a]		Change from the second dose to the third dose	*P* for interaction by time*group
		Adjusted GMT (95% CI)[b]	Adjusted RoM (95% CI)[b]	Adjusted GMT (95% CI)[b]	Adjusted RoM (95% CI)[b]	Adjusted RoM (95% CI)[b,e]	
Overall	1266	1091 (1050–1133)	–	12,765 (12,287–13,262)	–	**11.7 (11.2–12.2)**	
Sex							**< 0.001**
Male	346 (27)	952 (884–1025)	Reference	14,367 (13,343–15,469)	Reference	**15.1 (14.0–16.3)**	
Female	920 (73)	1150 (1100–1203)	**1.21 (1.11–1.32)**	12,154 (11,622–12,711)	**0.85 (0.78–0.92)**	**10.6 (10.1–11.1)**	
Age							**< 0.001**
< 30 yr	354 (28)	1407 (1304–1518)	Reference	12,988 (12,074–13,972)	Reference	**9.2 (8.6–10.0)**	
30 to < 40 yr	318 (25)	1219 (1132–1312)	**0.88 (0.78–0.99)**	12,878 (11,950–13,879)	1.00 (0.90–1.14)	**10.6 (9.8–11.4)**	
40 to < 50 yr	311 (25)	926 (859–998)	**0.68 (0.60–0.77)**	11,325 (10,498–12,218)	0.90 (0.80–1.02)	**12.2 (11.3–13.2)**	
≥ 50 yr	283 (22)	847 (781–919)	**0.59 (0.52–0.68)**	13,851 (12,770–15,025)	1.04 (0.92–1.18)	**16.4 (15.1–17.7)**	
P for trend[d]			**< 0.001**		0.97		
Interactions between sex and age							
Male							**< 0.001**
< 30 yr	56 (16)	1215 (1019–1448)	Reference	14,158 (11,889–16,861)	Reference	**11.7 (9.8–13.9)**	
30 to < 40 yr	91 (26)	1140 (994–1308)	0.94 (0.75–1.17)	14,452 (12,592–16,588)	1.02 (0.82–1.28)	**12.7 (11.0–14.6)**	
40 to < 50 yr	103 (30)	917 (806–1044)	**0.76 (0.61–0.94)**	13,491 (11,855–15,354)	0.95 (0.77–1.18)	**14.7 (12.9–16.8)**	
≥ 50 yr	96 (28)	667 (581–766)	**0.55 (0.44–0.69)**	14,015 (12,202–16,097)	0.99 (0.79–1.24)	**21.0 (18.4–24.0)**	
P for trend[d]			**< 0.001**		0.78		
Female							**< 0.001**
< 30 yr	298 (32)	1463 (1352–1584)	Reference	12,857 (11,912–13,877)	Reference	**8.8 (8.1–9.5)**	
30 to < 40 yr	227 (25)	1254 (1149–1368)	**0.86 (0.76–0.96)**	12,263 (11,233–13,387)	0.95 (0.85–1.07)	**9.8 (8.9–10.7)**	
40 to < 50 yr	208 (23)	940 (858–1028)	**0.64 (0.57–0.72)**	10,446 (9530–11,450)	**0.81 (0.72–0.92)**	**11.1 (10.1–12.2)**	
≥ 50 yr	187 (20)	944 (857–1040)	**0.65 (0.57–0.73)**	13,516 (12,271–14,889)	1.05 (0.93–1.19)	**14.3 (13.0–15.8)**	
P for trend[d]			**< 0.001**		0.96		
Body mass index							0.08
< 27.5 kg/m^2	1204 (95)	1096 (1054–1140)	Reference	12,691 (12,204–13,197)	Reference	**11.6 (11.1–12.1)**	
≥ 27.5 kg/m^2	62 (5)	997 (839–1184)	0.91 (0.76–1.09)	14,236 (11,978–16,921)	1.12 (0.94–1.34)	**14.3 (11.9–17.1)**	
Specific coexisting diseases[c]							**< 0.001**
No	1147 (91)	1119 (1075–1164)	Reference	12,656 (12,164–13,167)	Reference	**11.1 (10.6–11.6)**	
Yes	119 (9)	899 (788–1025)	**0.80 (0.70–0.92)**	13,172 (11,550–15,020)	1.04 (0.91–1.20)	**18.9 (16.7–21.5)**	

Table 1 (continued)

Variables	*N* (%)	After the second dose (*N* = 1266)[a]		After the third dose (*N* = 1266)[a]		Change from the second dose to the third dose	*P* for interaction by time*group
		Adjusted GMT (95% CI)[b]	Adjusted RoM (95% CI)[b]	Adjusted GMT (95% CI)[b]	Adjusted RoM (95% CI)[b]	Adjusted RoM (95% CI)[b,e]	
Use of immunosuppressive drug							0.34
No	1242 (98)	1111 (1069–1154)	Reference	12,964 (12,474–13,473)	Reference	**11.7 (11.2–12.2)**	
Yes	24 (2)	426 (324–558)	**0.38 (0.29–0.50)**	5715 (4356–7498)	**0.44 (0.34–0.58)**	**13.4 (10.1–17.9)**	

Bold font indicates statistical significance ($P < 0.05$)

[a]The median (interquartile range) intervals from the second or third dose to blood sampling were 68 (62–70) days or 74 (68–81) days, respectively.

[b]The geometric mean titer (GMT) with its 95% confidence intervals (CI) and the ratio of means with its 95% CI were estimated by the multivariable mixed model with adjustment for all variables in the table and the interval between vaccine doses and surveys.

[c]Specific coexisting diseases included hypertension, diabetes, dyslipidemia, cardiovascular disease, and cancer.

[d]*P* for trend was calculated using a post-estimation orthogonal polynomial contrast of marginal linear trends (i.e., "contrast" command in Stata).

[e]Reference category is each corresponding group at baseline survey (i.e., after the second dose) *CI* confidence interval, *GMT* geometric mean titer, *RoM* ratio of mean

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Declarations

Conflict of interest All authors reported that they have no conflict of interest.

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