

# SARS-CoV-2 Infectivity and Antibody Titer Reduction for 6 Months After Second Dose of BNT162b2 mRNA Vaccine in Health Care Workers: A Prospective Cohort Study

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Several studies reported that severe acute respiratory syndrome coronavirus-2 antibody levels change over 6 months in participants receiving the vaccination. From the enrolled 272 health care workers (HCWs), blood samples were obtained at 2, 16, and 24 weeks after the second vaccination dose. In the 267 noninfected HCWs, the neutralizing antibodies decreased by 23.9%, and the anti-spike/receptor binding domain antibody decreased by 53.8% at 24 weeks. We observed no significant difference in antibody reduction between the sexes; however, in younger individuals, there was higher antibody formation and lower reduction rates of the neutralizing antibody. In 3 HCWs with breakthrough infections, the antibody levels were relatively low just before the coronavirus disease 2019 infection. In conclusion, as antibody titers decrease over time after the second vaccination dose and HCWs with low antibody titers tend to have a high probability of breakthrough infection, an additional dose should be considered after several months.

Blood samples were obtained from health care workers at 2, 16, and 24 weeks after a second vaccination dose. Antibody titers decreased over time and the participants with low antibody titers tended to have a high probability of breakthrough infection.

**Keywords.** antibody titer dynamics; health care workers; mRNA vaccination; SARS-CoV-2.

In adults who have received the second dose of BNT162b2 mRNA vaccine (Tozinameran, Pfizer-BioNTech) against severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), the antibody titer increases significantly 1 week following vaccination, and the initially reported efficacy reaches approximately 95% [1–4]. However, the number of breakthrough infection cases has recently increased, and the expectations for prophylactic and preventive effects have gradually decreased. This is because (1) existing vaccines do not exhibit effective protection against novel mutant variants such as the delta and omicron types, and (2) several months have elapsed after vaccination, leading to antibody decay and reduction in immune effect. Several large-scale studies have been published as long-term data on the coronavirus disease 2019 (COVID-19) vaccination effect have become available. Antibody titers remain high until 3 months after complete vaccination; however, after 6 months, it decreased significantly, and the prevention effect was poorer [5–7].

This is a follow-up to the study reported by Kim et al [4]. In this study, we review the history of COVID-19 breakthrough infection and antibody titer dynamics in participants during 6 months after the second dose of the BNT162b2 mRNA vaccination and discuss the need for a booster shot (third dose).

## METHODS

### Participants

This was an observational, single-center, prospective cohort study. Health care workers (HCWs) of the Seoul Metropolitan Government-Seoul National University Boramae Medical Center who had received the second dose of the BNT162b2 mRNA vaccine (the interval between the first and second doses was 3 weeks) were recruited. All participants underwent complete blood count (hemoglobin, white blood cells, and platelets) and chemistry panel (blood urea nitrogen, creatinine, cholesterol, protein, albumin, bilirubin, alkaline phosphatase, aspartate transaminase, and alanine aminotransferase), and inflammation markers (C-reactive protein and procalcitonin). Moreover, hepatitis B surface antigen/hepatitis B surface antibody were assessed. Blood sampling for antibody titer testing was performed at 2 weeks, 16 weeks (4 months), and 24 weeks (6 months) after vaccination. In addition, COVID-19 infection history and vaccine administration dates were confirmed through a survey.

A total of 292 HCWs were recruited in this study; however, 20 were excluded due to confusion of the vaccine type, resignation

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of the hospital, and/or intention to withdraw. Thus, 272 HCWs were finally enrolled. Among them, 5 had a history of COVID-19 infection, while 267 had no history of COVID-19 infection 8 months after vaccination (Figure 1).

### Antibody Tests

Four types of antibody tests were performed.

#### Antibody test 1:

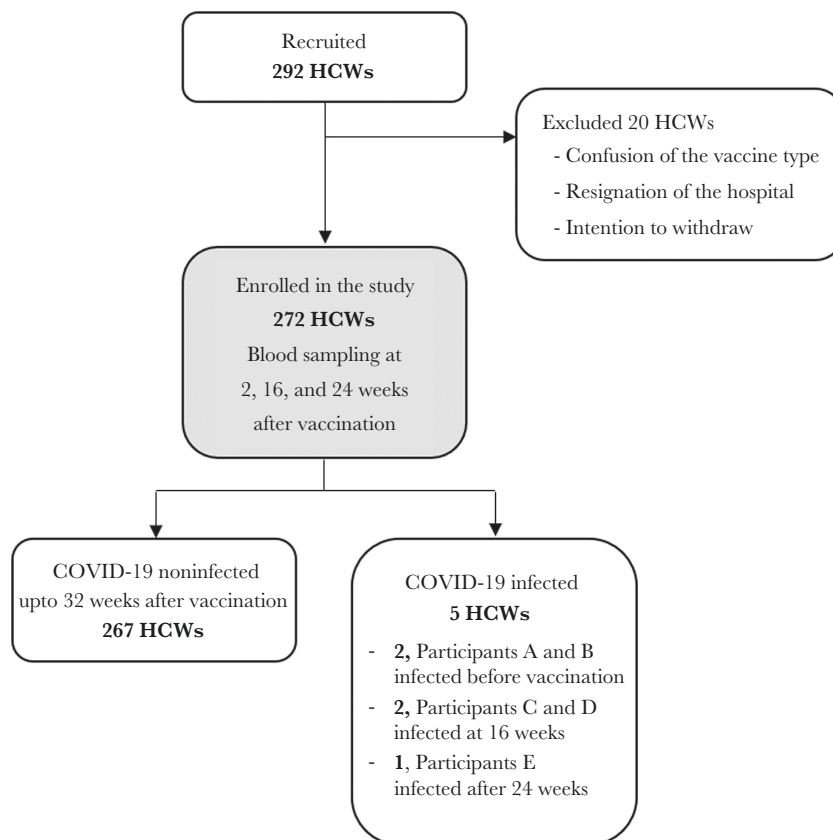
To identify neutralizing antibodies, the cPass SARS-CoV-2 Neutralization Antibody Detection Kit version RUO 3.0 (cPass Neutralizing Antibody; GenScript Biotech), which is an enzyme-linked immunosorbent assay (ELISA)-based surrogate virus neutralization test (sVNT), was used. The results are based on the interpretation of the percent inhibition rate, and the percent inhibition rate exhibited a good correlation with the plaque reduction neutralization test [8–10]. According to the manufacturer’s instructions, the cutoff value was 30%; therefore, if neutralizing antibodies of  $\geq 30\%$  were detected, it was considered positive, while values  $< 30\%$  were negative (no detectable SARS-CoV-2 neutralizing antibody). This cutoff value is based on validation with COVID-19 patient sera and healthy control sera [11].

#### Antibody test 2:

To investigate changes in antibody titer due to vaccination and/or infection, an automated electrochemiluminescence immunoassay (ECLIA)-based quantitative Elecsys Anti-SARS-CoV-2 S assay (Elecsys Anti-S/RBD; Roche Diagnostics) using a Cobas 800 e801 unit (Roche Diagnostics) was performed. The Elecsys Anti-S/RBD assay uses a recombinant protein representing the receptor binding domain (RBD) of the spike (S) antigen, which favors the quantitative determination of high-affinity antibodies against SARS-CoV-2. According to the manufacturer’s instructions, titer values  $\geq 0.8$  U/mL were considered positive (reactive), while those  $< 0.8$  U/mL were negative [12].

#### Antibody test 3:

To double-check the infection history of the participants, and ensure conformance with the survey results, an automated ECLIA-based Elecsys Anti-SARS-CoV-2 assay (Elecsys Anti-N; Roche Diagnostics) using a Cobas 800 e801 unit was undertaken. The Elecsys Anti-N assay uses a recombinant protein representing the nucleocapsid (N) antigen for the determination of antibodies against SARS-CoV-2 [13]. The N antigen is not a target of the BNT162b2 mRNA vaccine; therefore, its



**Figure 1.** Study profile depicting recruitment of HCWs fully vaccinated with the BNT162b2 mRNA vaccine. Abbreviations: COVID-19, coronavirus disease 2019; HCW, health care worker.

antibody is not affected by vaccination, theoretically. A coefficient of variation  $\geq 1.0$  (reactive) indicates past SARS-CoV-2 infection history.

#### Antibody test 4:

To confirm the humoral immunity status of the participants, the level of total immunoglobulin (Ig) was assessed using the ECLIA-based Tina-quant Gen.2 IgG, IgA, IgM assay (Roche Diagnostics) with a Cobas 8000 c702 unit (Roche Diagnostic). The expected (reference) values were IgG, 300–5000 mg/dL; IgA, 70–400 mg/dL; and IgM, 40–230 mg/dL.

#### Ethics

This study was reviewed and approved by the Institutional Review Board at the Boramae Medical Center (IRB number 30-2021-31). All participants provided written informed consent.

## RESULTS

### Demographic Characteristics and Baseline Laboratory Data

The participants in our study had similar demographic characteristics and baseline laboratory data (Supplementary Table 1) as those in the preceding study [4], in which the participant group was near identical. The total IgG, IgA, and IgM values of the 267 noninfected COVID-19 participants at 2, 16, and 24 weeks were maintained above the reference lower limit level without any significant change, and there was no evidence of immunosuppression. In addition, it was confirmed that none of the 267 participants had a COVID-19

infection history because Elecsys Anti-N was nonreactive throughout the entire blood sampling period (2, 16, and 24 weeks) (data not shown).

### Neutralizing Antibody and Anti-S/RBD Antibody Titer Waning

The neutralizing antibody levels of the 267 noninfected COVID-19 participants showed a significant decreasing trend from a mean of 95.4% (95% confidence interval [CI], 94.7%–96.1%) at 2 weeks to 85.5% (95% CI, 84.1%–86.8%) at 16 weeks, and to 72.6% (95% CI, 70.6%–74.7%) at 24 weeks ( $P < .001$ ). The reduction rates were 10.4% (95% CI, 9.2%–11.6%) at 16 weeks and 23.9% (95% CI, 21.9%–26.0%) at 24 weeks, with the neutralizing antibody titers at 2 weeks taken as the baseline. There was no significant difference in neutralizing antibody levels between men and women. Furthermore, when analyzed by age group, those who were younger were found to have higher titers of neutralizing antibody and lower rate of reduction of the neutralizing antibodies. The results of the neutralizing antibody tests are shown in Table 1 and Figure 2A.

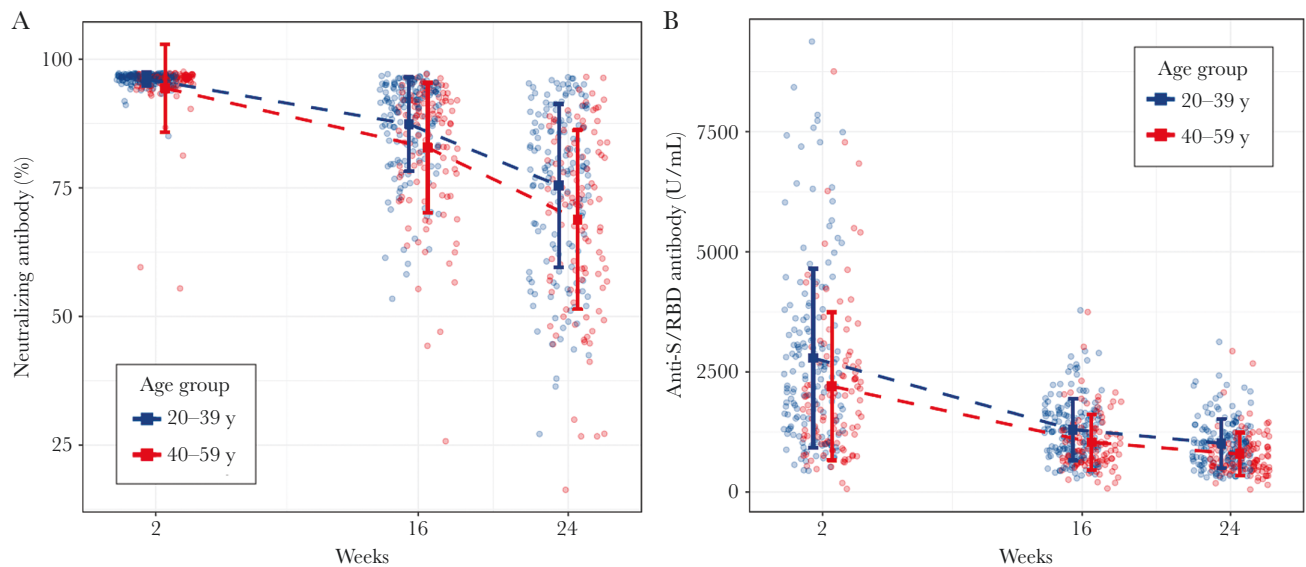
The anti-S/RBD antibody among the 267 non-COVID-19-infected participants showed a significant decreasing trend from 2545 U/mL (95% CI, 2334–2756 U/mL) at 2 weeks to 1190 U/mL (95% CI, 1115–1266 U/mL) at 16 weeks and 919 U/mL (95% CI, 859–980 U/mL) at 24 weeks ( $P < .001$ ). The reduction rates were 42.2% (95% CI, 38.4%–46.1%) at 16 weeks and 53.8% (95% CI, 50.3%–57.2%) at 24 weeks, considering the anti-S/RBD antibodies at 2 weeks as the baseline. There was no significant difference in the anti-S/RBD antibody between men and

**Table 1. Neutralizing Antibody and Anti-S/RBD Antibody Titers of 267 Noninfected COVID-19 Participants Following Vaccination**

Characteristic	Neutralizing Antibody, %, Mean (95% CI)			S/RBD Antibody, U/mL, Mean (95% CI)		
	2 wk	16 wk	24 wk	2 wk	16 wk	24 wk
All, n = 267	95.4 (94.7–96.1)	85.5 (84.1–86.8)	72.6 (70.6–74.7)	2545 (2333–2757)	1190 (1114–1266)	919 (858–980)
Sex						
Male, n = 25	94.5 (91.5–97.5)	83.2 (78.4–88.0)	70.6 (63.6–77.6)	2275 (1612–2937)	985 (767–1203)	808 (628–987)
	†NS	†NS	†NS	†NS	†NS	†NS
Female, n = 242	95.5 (94.8–96.2)	85.7 (84.1–86.8)	72.8 (70.7–75.0)	2573 (2349–2797)	1212 (1131–1292)	930 (865–995)
Age group 1, y						
20–39, n = 156	96.1 (95.9–96.3)	87.4 (85.9–88.8)	75.4 (72.9–78.0)	2789 (2494–3083)	1301 (1199–1402)	1013 (930–1096)
	‡	‡*	‡*	‡*	‡*	‡**
40–59, n = 111	94.4 (92.8–96.0)	82.8 (80.4–85.2)	68.8 (65.5–72.1)	2202 (1913–2492)	1037 (928–1145)	791 (705–876)
Age group 2, y						
20–29, n = 61	96.3 (96.1–96.5)	88.7 (86.5–91.0)	75.9 (71.6–80.2)	2815 (2398–3231)	1363 (1184–1541)	1058 (910–1206)
	†NS	†NS	†NS	†NS	†NS	†NS
30–39, n = 95	96.0 (95.7–96.3)	86.5 (84.6–88.4)	75.1 (71.9–78.4)	2772 (2364–3181)	1260 (1137–1384)	984 (885–1083)
	†NS	†NS	‡	†NS	†NS	†NS
40–49, n = 77	94.7 (93.2–96.1)	82.8 (80.2–85.4)	68.0 (64.0–72.0)	2455 (2074–2835)	1055 (915–1194)	799 (687–912)
	†NS	†NS	†NS	†NS	†NS	†NS
50–59, n = 34	93.7 (89.5–97.9)	82.8 (77.6–88.0)	70.7 (64.5–76.9)	1631 (1294–1967)	997 (826–1167)	771 (649–893)

Student *t* test was used to compare mean values. \* $P < .05$ , \*\* $P < .01$ , \*\*\* $P < .001$ .

Abbreviations: NS, not significantly different; RBD, receptor binding domain; S, spike protein.

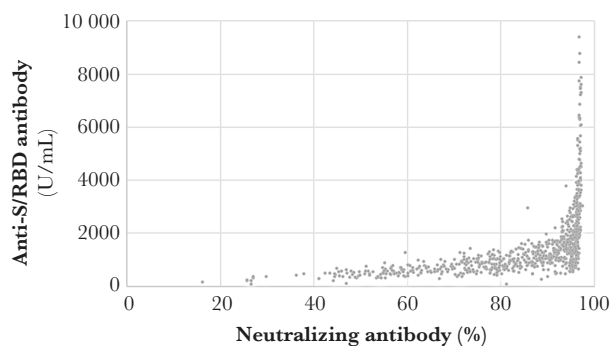


**Figure 2.** Comparison of antibody titer changes between vaccinated and uninfected patients aged 20–39 years (blue) and those aged 40–59 years (red): (A) neutralizing antibody, and (B) anti-S/RBD antibody. Bars indicate standard deviation of the mean. Abbreviations: RBD, receptor binding domain; S, spike protein.

women. Furthermore, younger age was associated with higher anti-S/RBD antibody levels. These results are shown in Table 1 and Figure 2B.

#### Relationship Between Neutralizing Antibody and Anti-S/RBD Antibody

The neutralizing antibody of the cPass SARS-CoV-2 Neutralization Antibody Detection Kit (ELISA-based sVNT method) and the anti-S/RBD antibody of the Elecsys Anti-SARS-CoV-2 S assay were significantly positively correlated ( $r = 0.514$ ,  $P < .001$ ). The cPass Neutralizing Antibody Kit cutoff value of 30.0%, suggested by GenScript, was equivalent to approximately 340 U/mL by the Elecsys Anti-SARS-CoV-2 S assay (Figure 3).



**Figure 3.** Correlation analysis between neutralizing antibody levels (ELISA-based sVNT) and anti-S/RBD antibody levels (ECLIA method). Abbreviations: ECLIA, electrochemiluminescence immunoassay; ELISA, enzyme-linked immunosorbent assay; RBD, receptor binding domain; S, spike protein; sVNT, surrogate virus neutralization test.

#### Results in the 5 COVID-19-Infected Participants

Five participants had a history of COVID-19 infection. Two participants (participants A and B) were infected before vaccination (before study participation), 2 (participants C and D) were infected at 16 weeks after vaccination (diagnosed at 1 day and 2 days after the 16-week blood sampling, respectively), and 1 (participant E) was infected at 27 weeks after vaccination. Participants A, B, C, and D had laboratory-test-confirmed history of infection; the Elecsys Anti-N values were continuously reactive (coefficient of variation  $\geq 1.0$ ) since the time of infection mentioned in the survey. Participant E became infected following the last blood sampling time point (24 weeks after vaccination), making it difficult to confirm with laboratory data. Table 2 shows the changes in neutralizing antibody and anti-S/RBD antibody titers in these 5 participants.

The neutralizing antibody titers of participants A and B (infected before vaccination) were 97.4% and 97.3% at 2 weeks after vaccination, respectively, which were higher than those in the noninfected group (95.4%). The antibody reduction rates of participants A and B were 0.2% and 0.4% at 16 weeks and  $-0.1\%$  and  $1.3\%$  at 24 weeks, respectively, with that at 2 weeks considered the baseline. That is, the infected participants who underwent vaccination had a much higher antibody titer and maintained an effective neutralizing antibody titer for a longer duration than the noninfected participants who underwent vaccination.

Participants C and D, who were infected at 16 weeks after vaccination, showed low neutralizing antibody and anti-S/RBD antibody titers just before COVID-19 infection confirmation (1–2 days before diagnosis); however, the titer increased significantly at 6 weeks after infection (24 weeks after vaccination).

**Table 2. Baseline Characteristics and Dynamics of Antibody Titers of the 5 COVID-19–Infected Participants Following Vaccination**

Participant	Age, y	Sex	Time of COVID-19 Diagnosis	Neutralizing Antibody, %			S/RBD Antibody, U/mL		
				2 wk	16 wk	24 wk	2 wk	16 wk	24 wk
A	29	F	Dec 2020, before vaccination	97.4	97.2	97.5	31 870	7380	6541
B	34	F	Jan 2021, before vaccination	97.3	96.9	96.0	17 624	2126	1595
C	39	F	Jul 2021, 16 wk after vaccination	76.3	27.6	96.4	127	254	13 998
D	33	F	Jul 2021, 16 wk after vaccination	96.2	85.1	97.2	1707	1073	23 332
E	44	M	Sep 2021, 27 wk after vaccination	91.6	60.0	24.5	376	290	249

Participant C, D, and E had breakthrough infections and were all infected with the delta variants.

Abbreviations: COVID-19, coronavirus disease 2019; RBD, receptor binding domain; S, spike protein.

The neutralizing antibody titers increased from 27.6% and 85.1% to 96.4% and 97.2%, and the anti-S/RBD antibody titers from 254 U/mL and 1073 U/mL to 13 998 U/mL and 23 332 U/mL. Participant E, infected after the last blood sampling (24 weeks after vaccination), had 24.5% neutralizing antibodies and 249 U/mL anti-S/RBD antibody at 24 weeks after vaccination.

## DISCUSSION

Of the 272 participants in this study, 8 (2.9%) had less than 30% neutralizing antibodies at least once during the study period; 2 of these 8 participants (25.0%) had breakthrough infection events. This 25.0% is a very high probability because only 1 of the 264 participants (0.4%) had a breakthrough infection event in the group of individuals who had neutralizing antibodies  $\geq$  30%.

In recent studies, the correlation between ECLIA-based SARS-CoV-2 S/RBD antibody and protective immunity with virus neutralization assay was analyzed, and positive correlations were seen in many results, including those of this study [14–17]. It has also been noted that anti-S/RBD titers or neutralizing antibodies do not represent actual immunity because the immune response is very complex and there have been cases of infection even with high antibody titers [18, 19]. Because many studies have shown a positive correlation, various attempts have been made in central laboratories to predict the neutralizing antibody titers of infected or vaccinated recipients by using the easier and more convenient method, ECLIA-based anti-S/RBD antibody assay. However, there is still a need for further discussion about the extent to which the anti-S/RBD antibody titer is a measure of effective defense against SARS-CoV-2 in the real world. Some European medical institutions suggest that higher than 200–300 U/mL in the Elecsys Anti-S/RBD assay is an indication of effective protection against SARS-CoV-2, and this is the target often used for vaccine booster shots [20–22]. In our study, the 30.0% cutoff of the neutralizing antibody titer of the cPass Neutralizing Antibody kit was equal to approximately 350 U/mL using the Elecsys Anti-S/RBD kit (Figure 3).

The Korean Central Disease Control Headquarters announced on 24 October 2021 that the breakthrough infection rate of the BNT162b2 mRNA vaccine was 0.04%; however, the

breakthrough infection rate in our study was 1.10 % (3/272) [23]. In this study, the breakthrough infection rate among HCWs was relatively higher than that in the general population, which is believed to be due to the high frequency of direct exposure to COVID-19 patients [24, 25]. Like hepatitis B virus, it is necessary to consider recommending booster vaccination for high-risk HCWs if there is no evidence of immunity, as assessed using antibody tests.

In conclusion, neutralizing antibody titers and anti-S/RBD antibody levels decrease with time after vaccination. Furthermore, older age was associated with lower titers. However, as there are only a few studies on the long-term effect of vaccination, additional research is needed on clinically effective targets of antibody titer and booster shot efficacy. Because active studies are ongoing globally, it is expected that the antibody test results will aid in the identification of the appropriate time and participants in need of booster vaccinations.

## Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

## Notes

**Author contributions.** N. K., S. S., and H. P. contributed study concept and design. D. M., S. P., D. A., and E. Y. R. performed experiments. N. K., D. M., S. P., and D. A. acquired data. N. K. and H. P. analyzed and interpreted data, and drafted the manuscript. N. H. and J. H. P. contributed visualization. E. Y. R., J. H. Y., H. P., and S. S. critically reviewed the manuscript for important intellectual content. H. P. and S. S. supervised the study. S. S. acquired funding. All authors read and approved the final manuscript.

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