

RESEARCH ARTICLE

SARS-CoV-2 specific antibody responses in healthcare workers after a third booster dose of CoronaVac or BNT162b2 vaccine

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Abstract

The first SARS-CoV-2 vaccination campaign in Turkey has started in mid-January for the healthcare workers (HCWs) with the inactive virus vaccine CoronaVac (Sinovac). After four and a half months, the Turkish Ministry of Health rolled out a booster-dose vaccination campaign for HCWs and all people over 50 years old beginning in July 2021. The individuals eligible were given the choice of either CoronaVac or mRNA vaccine BNT162b2 for the third booster-dose vaccination. This study aimed to evaluate SARS-CoV-2 IgG antibody titers against the S1 subunit of the spike protein as a marker of the humoral response in 179 HCWs who received a third booster dose of either CoronaVac or BNT162b2. A total of 136 HCWs, 71 female (52.2%) and 65 male (47.8%), completed both serum collections on Days 0 and 28. The median SARS-CoV-2 IgG S Protein (SP) titer in all participants before the vaccination was 175.7 AU/ml. Of 136 HCWs, 103 (75.73%) chose BNT162b2 vaccine and 33 (24.26%) chose CoronaVac as the third booster dose. There was a significant difference between the BNT162b2 group and the CoronaVac group in terms of SARS-CoV-2 IgG SP titers ($p < 0.001$). The median SARS-CoV-2 IgG SP titers in BNT162b2 group ($n = 103$) and in CoronaVac group ($n = 33$) were 17619.3 AU/ml and 1153.0 AU/ml, respectively. The third booster dose with BNT162b2 and CoronaVac increased antibody titers in each participant a mean of 162-fold and 9-fold, respectively. HCWs in the BNT162b2 group reported more frequent adverse events than HCWs in the CoronaVac group ($p < 0.001$).

KEYWORDS

BNT162b2, CoronaVac, immunoglobulin G, SARS-CoV-2

1 | INTRODUCTION

In the current situation where there is no definitive treatment option against SARS-CoV-2, vaccines are considered the most promising intervention to end the pandemic by promoting “herd immunity” and protecting lives.¹ A massive vaccination campaign has begun worldwide, starting with the United Kingdom in December 2020 with the availability of various COVID-19 vaccines. With the arrival of spring

2021 and increasing vaccination rates worldwide, a steady decline in cases, hospitalizations, and deaths, particularly among individuals at high risk for severe infection and complications, was observed.² However, since mid-June, COVID-19 cases began to increase rapidly in many countries.³ It was suggested that this current wave of infections had been strongly associated with the emergence of a new variant of SARS-CoV-2, the Delta variant (B.1.617.2).² The Centers for Disease Control and Prevention (CDC) currently classifies Delta as

a variant of concern, a variant with one or more mutations that allow the virus to infect people more easily or spread from person to person more easily, making the virus less responsive to treatments or affect how well vaccines work against the virus.⁴ The Delta variant is highly transmissible, estimated to be about 60%–100% more transmissible than the previous dominant Alpha variant.^{4,5} The CDC has suggested its basic reproduction rate (R0, i.e., the estimated number of secondary cases of infections that are transmitted from an infected person to a susceptible population) was 5–8.⁴ Currently, the Delta variant (B.1.617.2) dominates COVID-19 infections in most parts of the world. SARS-CoV-2 vaccines, however, still were based on the original Wuhan virus.⁶ A recent study suggested that the effectiveness of one dose of vaccine BNT162b2 or ChAdOx1 nCoV-19 was notably lower among people with the delta variant compared with those with the alpha variant (30.7% vs. 48.7%). With the BNT162b2 vaccine, the effectiveness of two doses decreased to 88% from 93.7% with the delta variant. Similarly, the effectiveness of the two doses of the ChAdOx1 nCoV-19 vaccine decreased from 74.5% to 67% with the delta variant.⁷ A recent study from Thailand reported that CoronaVac, an inactivated whole virus vaccine (Sinovac) used in some countries such as Turkey, Chile, Thailand, Brazil, and Indonesia, provided a low degree of neutralization-afforded protection when compared with natural infection. The researchers concluded that further booster doses, heterologous or otherwise, might be needed for recipients of CoronaVac to maintain a long-term anamnestic response.⁸ Another explanation suggested for the Delta variant surge was the waning immunity of both natural infection and SARS-CoV-2 vaccines.⁶

It was shown that neutralizing antibody responses after natural infection declines over time.⁹ Recently, a preliminary study from Israel assessed the correlation between the time from the BNT162b2 (Pfizer-BioNTech) vaccine and the incidence of breakthrough infections and found that the risk for infection was significantly higher for early vaccinees compared to those vaccinated later.¹⁰

Due to the emergence of the Delta variant and preliminary evidence of waning immunity both after natural infection and vaccination, decision-makers in different countries have developed various policy recommendations.² CDC distinguishes a “third dose” from a “booster dose”. An additional (third) dose of an mRNA COVID-19 vaccine (Pfizer-BioNTech or Moderna) at least 28 days after completing the initial 2-dose mRNA COVID-19 vaccine series was recommended to moderately to severely immunocompromised individuals who failed to build immunity after the two initial doses. On the other hand, CDC defines a “booster dose” as another dose of a vaccine that is given to someone who built enough protection initially after vaccination, but then that protection decreased over time due to waning immunity.¹¹ Recently, the US Food and Drug Administration (FDA) modified the current Emergency Use Authorization (EUA) for additional third doses of mRNA COVID-19 vaccines on August 12, 2021.¹² CDC expanded eligibility for COVID-19 booster shots to all adults at least 6 months after the primary vaccination series on November 19, 2021. The officials stated that

the recent emergence of the Omicron variant (B.1.1.529) further emphasized the importance of a booster dose.¹³

United States, Israel, United Arab Emirates, Indonesia, Hungary, Lithuania, Luxembourg, Slovenia, Serbia, and Turkey rolled out booster dose vaccination campaigns, particularly for high-risk individuals such as the elderly, those with a chronic illness, or those who are immunocompromised.^{14–16} The first SARS-CoV-2 vaccination campaign in Turkey has started in mid-January for the healthcare workers (HCW) and the elderly with the inactive virus vaccine CoronaVac (Sinovac). Second doses were given at a 21-day interval. Gradually the population for the vaccine was offered has been widened. Currently, all individuals over 15 years old and people with chronic diseases over 12 years old can have two doses of either the inactive virus vaccine CoronaVac or the now available mRNA vaccine, BNT162b2 (Pfizer-BioNTech). After four and a half months, the Turkish Ministry of Health rolled out a booster-dose vaccination campaign for HCWs and all people over 50 years old on July 1, 2021. Eligible individuals were offered vaccination with CoronaVac (Sinovac) or BNT162b2 (Pfizer-BioNTech) for a third booster dose. This study aimed to evaluate the changes in SARS-CoV-2 IgG antibody titers against the S1 subunit of the spike protein as a marker of the humoral response in 179 HCWs who received a third booster dose of either CoronaVac or BNT162b2 after initially vaccinated with two doses of CoronaVac.

2 | MATERIALS AND METHODS

2.1 | Study population

This study was performed at Samsun Training and Research Hospital, a tertiary reference medical center for COVID-19 patients with more than 1200 HCWs. The participants were recruited after an internal announcement. HCWs, 18 years of age or older previously vaccinated with two doses of SARS-CoV-2 inactive vaccine CoronaVac (Sinovac) with a 28-day interval between January 14, 2021, and February 21, 2021, who agreed to be vaccinated with a third booster dose with either CoronaVac (Sinovac) or BNT162b2 (Pfizer-BioNTech) as their choice were included. A total of 179 HCW responded and volunteered to participate.

The study was approved by the Ministry of Health Scientific Research Platform, and Ethics approval was obtained from Institutional Clinical Research Ethics Committee (approval number: 2021/05/02). All participants signed the Informed Consent Form. HCWs who then refused vaccination or failed to finish sample collection were excluded.

2.2 | Sample collection and assay

Two venous blood samples from the participants were collected: before the vaccination with the third booster dose on the day of

vaccination and 28 days later. These samples were centrifuged shortly after collection and stored at -20°C .

The SARS-CoV-2 IgG II Quant assay (Abbott), an automated, two-step immunoassay developed for the quantitative determination of IgG antibodies against the spike receptor-binding domain (RBD) of SARS-CoV-2 in human serum and plasma using chemiluminescent microparticle immunoassay (CMIA) technology was used for analysis on Abbott' "Alinity i" platform following the manufacturer's package insert. In this assay, the SARS-CoV-2 antigen-coated paramagnetic microparticles bind to the IgG antibodies attached to the spike protein in serum and plasma samples. The resulting chemiluminescence in relative light units (RLU) following the addition of anti-human IgG-labeled compared to the IgG II calibrator or standard indicates the strength of the response, which reflects the quantity of IgG S Protein (SP) present. Antibody levels of 50 AU/ml and above in this test are considered positive. This assay has an analytical measuring interval of 21–40 000 AU/ml (up to 80 000 AU/ml with on-board 1:2 dilution). The assay presented a positive predictive agreement of 99.4% (95% confidence interval [95% CI]: 96.50%–99.97%) and a negative predictive agreement of 99.6% (95% CI: 99.15%–99.37%), and was in agreement with a neutralization method (positive agreement, 100.0%; 95% CI: 95.72%–100.00%)¹⁷

2.3 | Statistical analysis

SPSS 20.0 (Statistical Package for the Social Sciences, SPSS Inc.) was used for analysis. Data were evaluated for normal distribution using the Kolmogorov–Smirnov test. When comparing the groups, the Student's *t* test (independent-sample *t* test) was used for the analysis of variables with normal distribution, and the Mann–Whitney *U* test was used for the analysis of variables that did not show normal distribution, and variables for the two groups were shown as mean \pm standard deviation or (median [min to max]). The two test was used for categorical variables, and it was shown as the number of patients with percentages. Analysis of independent variables within the group was performed by repeated-measures *t* test. A *p* value of 0.05 or less was considered statistically significant. Since the distributions were not normal, the Spearman's correlation test was used to analyze whether independent variables such as body mass index, presence of chronic disease, regular Vitamin D use, smoking, and previous COVID-19 infection influenced antibody titer values.

3 | RESULTS

Serum collections before and 28-days after the third booster dose vaccination were completed by 136 HCWs, 71 female (52.2%) and 65 male (47.8%). The mean age of the participants was 42.14 ± 8.97 years (min: 21, max: 63 years). A previous PCR confirmed SARS-CoV-2 infection was documented in 46 (33.8%) participants. Seven (5.14%) of them were infected at least 2 weeks after the initial two-dose vaccination with the inactive virus vaccine,

CoronaVac/Sinovac. Three (2.2%) HCWs reported two PCR-confirmed episodes of SARS-CoV-2 infection. The demographic characteristics of HCWs are presented in Table 1.

The median SARS-CoV-2 IgG SP titer in all participants before the vaccination with the third booster dose was 175.7 AU/ml (min: 10.90 AU/ml, max: 5201.60 AU/ml). Antibody titers were below the threshold (50 AU/ml) in 11 (8%) HCWs. In HCWs who currently smoke, antibody titers were found to be lower compared to nonsmokers ($p = 0.034$), and antibody titers in HCWs with a previous COVID 19 history were found to be higher compared to COVID-naïve HCWs ($p < 0.001$). No correlations were found between demographic characteristics, body mass index, underlying conditions, and regular use of Vitamin D and SARS-CoV-2 IgG SP titer before the vaccination with the third dose.

Of 136 HCWs, 103 (75.73%) chose BNT162b2 (Pfizer-BioNTech) vaccine and 33 (24.26%) chose the inactive virus vaccine, CoronaVac (Sinovac) as the third booster dose. These two groups did not differ in terms of age, sex, body mass index, underlying conditions, previous SARS-CoV-2 infection, regular use of Vitamin D and SARS-CoV-2 IgG SP titers before the third booster dose. Smoking was more frequent among HCWs who chose CoronaVac/Sinovac ($p = 0.007$).

After vaccination with the third dose, the median SARS-CoV-2 IgG SP titer in BNT162b2 group ($n = 103$) was 17619.3 AU/ml (Min: 2329.4 AU/ml, max: 40 000 AU/ml). This increase was statistically significant. (Table 1) All HCWs were seropositive. The third booster dose with BNT162b2 increased antibody titers in each participant, a mean of 162-fold (min: 4-fold, max: 966-fold). In 11 (10.6%) HCWs in the BNT162b2 group, SARS-CoV-2 IgG SP titers were measured as 40 000 AU/ml, which was the maximum value of the assay's analytical measuring interval. Previous SARS-CoV-2 infection and SARS-CoV-2 IgG SP antibody titers before vaccination positively correlated with postvaccination antibody titers in the BNT162b2 group ($p = 0.016$ and 0.001, respectively). No correlations between other characteristics such as age, sex, body mass index, underlying conditions, smoking, regular use of Vitamin D, adverse events, and postvaccination antibody titers were found in this group. Of 103 HCWs, 91 (88.3%) reported an adverse reaction. The most frequent adverse events were pain in the injection site, pain in the arm, fatigue, myalgia, headache, and fever. No serious adverse reactions were reported.

After vaccination with the third dose, the median SARS-CoV-2 IgG SP titer in CoronaVac group ($n = 33$) was 1153.0 AU/ml (min: 225.2 AU/ml, max: 5542.5 AU/ml). This increase was statistically significant (Table 1). The third booster dose with CoronaVac increased antibody titers in each participant a mean of 9-fold (min: 1.13-fold, max 55-fold). No correlations between demographic characteristics, body mass index, underlying conditions, smoking, previous SARS-CoV-2 infection, and regular use of Vitamin D and IgG SP titers was found in this group. Interestingly, only three (9.09%) of 33 HCWs reported an adverse reaction as being only pain in the injection site.

There was a significant difference between the BNT162b2 group and the CoronaVac group in terms of SARS-CoV-2 IgG SP titers

TABLE 1 Demographic and clinical characteristics of HCWs and comparison of two vaccine groups

	Total (n = 136)	Pfizer/Biontec (n = 103)	CoronaVac/Sinovac (n = 33)	p
Age ^a	42.15 ± 8.979	42.31 ± 9.099	41.64 ± 8.706	0.709 ^a
Age groups ^b				
<50 year	109 (80.1%)	81 (78.6%)	28 (84.8%)	0.598 ^b
≥50 year	27 (19.9%)	22 (21.4%)	5 (15.2%)	
BMI kg/m ^{2b}	25.309 ± 3.696	25.231 ± 3.741	25.55 ± 3.597	0.668 ^a
BMI groups ^a				
<25	67 (49.3%)	52 (50.5%)	15 (45.5%)	0.762 ^b
≥25	69 (50.7%)	51 (49.5%)	18 (54.5%)	
Sex ^b				
Female	71 (52.2%)	59 (57.3%)	12 (36.4%)	0.058 ^b
Male	65 (47.8%)	44 (42.7%)	21 (63.6%)	
Chronic disease ^b	49 (36%)	37 (35.9%)	12 (36.4%)	1.000 ^b
Medication ^b	38 (27.9%)	29 (28.2%)	9 (27.3%)	1.000 ^b
Vitamin D ^b	7 (5.1%)	6 (5.8%)	1 (3.0%)	1.000 ^b
Smoking ^b	32 (23.5%)	18 (17.5%)	14 (42.4%)	0.007^b
COVID 19 history ^b	46 (33.8%)	36 (35.0%)	10 (30.3%)	0.780 ^b
Before vaccination SARS-CoV-2 IgG SP antibody titers (AU/ml) ^c	175.7 (10.90–5201.60)	166.30 (16.20–5201.60)	219.30 (10.90–4593.10)	0.257 ^c

Note: p values were obtained using the ^a Independent samples t test; ^b Pearson χ^2 , Fisher's exact test; ^c Mann-Whitney U test. Before Vaccine SARS-CoV-2 IgG Ab titers: SARS-CoV-2 IgG SP antibody titers before the vaccination with the third dose, after vaccine SARS-CoV-2 IgG Ab titers: SARS-CoV-2 IgG SP antibody titers after the vaccination with the third dose. Vitamin D: Regular use of Vitamin D, COVID 19 history: COVID 19 infection before vaccination with third dose.

Abbreviation: BMI, body mass index.

^aMean ± standard deviation.

^bn (%).

^cMedian (min–max).

($p < 0.001$). The difference between the groups in terms of antibody titers was so marked that the mean SARS-CoV-2 IgG SP titer in the BNT162b2 group was 13.5 times more than the mean SARS-CoV-2 IgG SP titer in the CoronaVac group (Figure 1). Only six HCWs' antibody titers in the BNT162b2 group were below the maximum antibody titer calculated in the CoronaVac group. HCWs in the BNT162b2 group reported more frequent adverse events after the third booster dose compared to HCWs in the CoronaVac group ($p < 0.001$) (Table 2).

The data that support the findings of this study are available in the Supporting Information material of this article (Supporting Information: Appendix).

4 | DISCUSSION

This study aimed to measure the level of antibodies directed against the spike protein of SARS-CoV-2 following vaccination of HCWs with a third booster dose of either BNT162b2 or CoronaVac. All HCWs were previously vaccinated with two

consecutive doses of CoronaVac. The results of this study suggested three main outcomes:

- Four and a half months after a two-dose vaccination regime with an inactive vaccine CoronaVac, anti-SARS-CoV-2 IgG SP antibody responses were relatively low compared with previously reported levels.
- BNT162b2 (Pfizer-BioNTech) vaccine as a third booster dose in HCWs previously vaccinated with CoronaVac was much stronger than CoronaVac (Sinovac) as a third booster dose in eliciting anti-SARS-CoV-2 IgG SP antibody responses.
- CoronaVac (Sinovac) as a third booster dose was related to much less frequent adverse reactions compared with BNT162b2 (Pfizer-BioNTech).

Bayram et al. investigated SARS-CoV-2 anti-spike antibodies in 1012 Turkish HCWs after two doses of CoronaVac (Sinovac) using the same assay (SARS-CoV-2 IgG II Quant; Abbott). They found that antibodies were detected in 1008 of 1012 (99.6%) HCWs 21 days after the second dose, and the median antibody titer of HCWs was

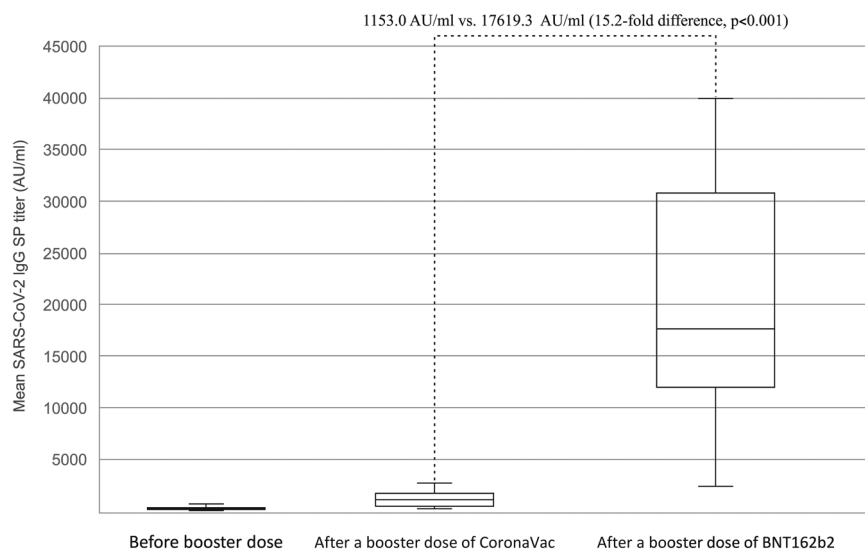


FIGURE 1 Anti-SARS-CoV-2 IgG S Protein antibody responses before and after the booster dose of either BNT162b2 ($n = 103$) or CoronaVac ($n = 33$) in healthcare workers all previously vaccinated with inactivated virus vaccine (CoronaVac).

TABLE 2 Comparison of the two groups in terms of median SARS-CoV-2 IgG SP antibody titers analyzed after the third dose vaccine and adverse events

	BNT162b2 (Pfizer/Biontec) ($n = 103$)	CoronaVac/Sinovac ($n = 33$)	p value
After vaccine SARS-CoV-2 IgG antibody titers (AU/ml)	17619.3 (2329.0–40000)	1153.0 (225.2–5542.0)	<0.001
Adverse events, n (%)	91 (96.8)	3 (3.2)	<0.001

Abbreviation: SP, S Protein.

calculated as 1022.40 AU/ml (range: 10.10–66 923.70 AU/ml).¹⁸ Soysal et al. analyzed immunogenicity and reactogenicity of inactivated SARS-CoV-2 vaccine (CoronaVac) in both previously SARS-CoV-2 infected and uninfected Turkish HCWs and reported median SARS-CoV-2 IgG antibody levels of 1220 AU/ml (range: 202–10 328 AU/ml) and 913 AU/ml (range: 2.8–15 547 AU/ml) 28 days after the second vaccination in infected and uninfected HCWs, respectively.¹⁹ Yigit et al. investigated 678 Turkish HCWs 2 months after the second dose of CoronaVac using a semiquantitative method deployed a recombinant protein to represent the nucleocapsid (N) antigen of the virus (Elecys Anti-SARS-CoV-2; Roche) and found titer in all participants after approximately four and a half months after the vaccination with a two-dose regime of CoronaVac before the vaccination with the third booster dose was 175.7 AU/ml (min: 10.90 AU/ml, max: 5201.60 AU/ml) and 11% of the participants were seronegative supporting the idea that antibody titers decrease over time sometimes in the degree of patients being seronegative.²⁰ In a recent study, Yue et al. reported antibody titers fading after inoculation with two doses of an inactivated SARS-CoV-2 vaccine in a cohort of 355 volunteers participating in the development and production of inactivated vaccines. At 8 months after the second dose, the serum neutralizing antibody titers in this cohort decreased significantly, and the positive conversion rate decreased to 48.5%. Their results suggested that a third booster dose was necessary to maintain the effectiveness of inactivated vaccines regardless of sex and two-dose immunization procedure.²¹

Keskin et al. recently compared SARS-CoV-2 specific antibody responses 1 month after a third CoronaVac or BNT162b2 vaccine

following a two-dose CoronaVac vaccine regimen in a small cohort of Turkish HCWs. Using the same assay (Abbott Laboratories), they found that the mean SARS-CoV-2 IgG SP titer was 1215.8 AU/ml (min: 242 AU/ml, max: 2900.9 AU/ml) in 18 healthy HCWs who chose to have a third CoronaVac vaccine as a booster dose. This result is very similar to the mean IgG SP titer of 1187.90 AU/ml (range: 149.9–9682.0) in the three-dose CoronaVac group in the present study. In 27 HCWs who had BNT162b2 (Pfizer/Biontec) vaccine as the booster dose, they found that the mean SARS-CoV-2 IgG SP titer was significantly higher with a mean titer of 31277.9 AU/ml (min: 5999 AU/ml, max: 102290 AU/ml) ($p < 0.001$). The mean IgG SP titer in the BNT162b2 (Pfizer/Biontec) vaccine group of the present study was 17619 AU/ml (range: 2329.0–40 000 AU/ml), but it should be kept in mind that we did not proceed with dilutions to quantify the titers over 40 000 AU/ml which was the maximum antibody titer level that the test could report in default.²²

There are a few studies that used the same testing method the present study used to evaluate the immunogenicity of recommended two-dose mRNA vaccinations. Narasimhan et al. evaluated Abbott Alinity SARS-CoV-2 spike-specific quantitative IgG and IgM assays among infected, recovered, and vaccinated groups and reported that a median of 18 272 AU/ml IgG SP titer after 27 days of the second dose in 145 previously uninfected cases vaccinated with two doses of either BNT162b2 ($n = 132$) or Moderna ($n = 13$) mRNA vaccines. They measured the mean IgG SP as 20 760 AU/ml in patients who were previously infected ($n = 8$) and then vaccinated with two doses of mRNA vaccines.²³ These median titers of IgG SP are close to the

result of a median of 17 619 AU/ml in HCWs who were vaccinated with BNT162b2 as a third dose in the present study.

Using the same assay, Grupper et al. included a control group consisting of HCWs ($n = 95$) in their study evaluating humoral response to BNT162b2 vaccine in patients undergoing hemodialysis. They reported a mean IgG SP titer of 10144 AU/ml a median of 30 days (26–34 days) after the second dose of BNT162b2.²⁴ Maneikis et al. analyzed the immunogenicity of the BNT162b2 in patients with hematological malignancies with the same laboratory method we used and reported a mean IgG SP titer of 21395 AU/ml (14831–33553) in 67 healthy HCWs used as the control group. The higher median titer in this study may be attributed to the early timing of the analysis reported as 7–21 days after the second dose.²⁵

A recent study investigated quantitative SARS-CoV-2 anti-spike responses to two doses of BNT162b2 using Abbott's assay and reported median IgG SP titers of 10 058 (6408–15 582) AU/mL in cases without evidence of previous infection and 18 047 (10 884–22 413) AU/ml in cases with known previous infection.²⁶

Antibody response to the third dose of a COVID-19 vaccine has been investigated primarily with mRNA vaccines and in immunocompromised patients such as organ transplants, undergoing hemodialysis, hematological malignancies, solid tumors, receiving monoclonal antibody treatment.^{25,27–34} The only exception we could find was the study from the United Kingdom performed in healthy volunteers investigated a different vaccine, ChAdOx1nCoV-19's reactogenicity, and immunogenicity after a third dose. Flaxman et al. concluded that a third dose of ChAdOx1nCoV-19 induced antibodies to a level that correlated with high efficacy after the second dose and boosted T-cell responses.³⁵

Recent evidence supports the idea that neutralizing antibodies and protection gained by mRNA vaccines wane over time.^{36–38} As a result, combined with high levels of transmission of the delta variant, a decrease in vaccine efficacy has been observed in countries such as Israel. In an effort to address this problem, Israeli authorities approved the administration of a booster dose to those who received two doses of the BNT162b2 vaccine at least 5 months earlier, starting with high-risk populations and then to the elderly who were 60 years of age or older and subsequently to the general population. Bar-On et al. analyzed the real-world effectiveness of a third booster dose of BNT162b2 vaccine in the Israeli population and reported that the rate of confirmed infection was lower in the booster group than in the nonbooster group by a factor of 11.3, and the rate of severe illness was lower by a factor of 19.5.³⁹

Interestingly, very few HCWs vaccinated with the third dose of CoronaVac reported an adverse event in this present study. Only three participants (9.09%) in this group reported one adverse event: injection site pain. We failed to find any data regarding the adverse events from a third booster inactive virus COVID-19 vaccine. Tanriover et al. reported that 18.9% of two-dose CoronaVac vaccine recipients experienced adverse events in the phase 3 trial conducted in Turkey with 6,646 vaccinated participants. Fatigue (8.22%), headache (5.91%), myalgia (4.02%), chills (2.47%), and site pain

(2.36%) were the most common adverse events.⁴⁰ The small number of HCWs vaccinated with CoronaVac in the present study may have resulted in fewer adverse events.

Recently a safety monitoring report was published in the United States after FDA authorization of an additional dose of Pfizer-BioNTech vaccine ≥ 6 months after completion of the primary series among persons aged ≥ 65 years, at high risk for severe COVID-19, or whose occupational or institutional exposure puts them at high risk for COVID-19 on 22 September 2021. Of 11 209 participants, 69.4% reported injection site reactions, and 65.1% reported systemic reactions such as fatigue (51%), headache (38.4%), myalgia (36.3), and fever (22%), similar to the findings of the present study.⁴¹

The present study had some limitations. It was conducted in a single center, and the sample size was relatively small. The participants with asymptomatic infection could not be detected in the time between vaccination and sampling, so the antibodies elicited from a silent natural infection may have altered antibody levels. Additionally, the assay we used was not a direct measurement of neutralizing antibody levels which were suggested to be highly predictive of immune protection from symptomatic SARS-CoV-2 infection.⁴² However, it was reported that it was in agreement with a neutralization method (positive agreement, 100.0%; 95% CI, 95.72%–100.00%).¹⁷

5 | CONCLUSION

In this era of delta variant and surge of vaccine breakthrough cases, a booster dose for inactive COVID-19 vaccine CoronaVac should be considered in light of the recent evidence. Heterologous vaccination with an mRNA vaccine elicited a much more robust immune response than vaccination with inactive virus vaccine in HCWs who were previously vaccinated with a two-dose regime of inactive COVID-19 vaccine.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data presented in this study are available as Supporting Information: [Appendix](#) file.

ETHICS STATEMENT

Ethical approval was obtained from the Ethics Committee of Samsun Training and Research Hospital, Health Sciences University. Written consent was obtained from all participants.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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