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Comparison of Anti-Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-COV-2) Antibody Response by Different Vaccine Combinations

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ABSTRACT

Objective: Various types and combinations of vaccines have been utilized at different time intervals due to the variable availability of vaccines in many countries during the Coronavirus Disease 2019 (COVID-19) pandemic. Most current vaccine administrations involve a series of primary doses followed by a homologous booster dose. This study aimed to examine the antibody levels after the BNT162b2 or CoronaVac vaccine was administered as a booster dose to volunteers who received two doses of CoronaVac and to identify the ideal vaccination combination.

Materials and Methods: This cross-sectional study included 254 participants. The groups consisted of volunteers who received two doses of CoronaVac, those who received two doses of BNT162b2, those who received two doses of CoronaVac plus one dose of BNT162b2, and finally, those who received three doses of CoronaVac. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) specific spike (S) Immunoglobulin G (IgG) levels were measured by electrochemiluminescence method on Roche COBAS 8000 series using Anti-SARS-CoV-2 S kit.

Results: Antibody levels after three doses of CoronaVac were found to be lower compared to after two doses of CoronaVac + one dose BNT162b2 ($p<0.001$). IgG responses after three doses of the CoronaVac vaccine (two primary + one booster dose) were lower than those after two doses of BNT162b2 ($p<0.001$).

Conclusion: The use of a heterogeneous booster dose due to problems in vaccine supply may be a good alternative to the homologous approaches applied so far.

Keywords: Coronavirus Disease 2019 (COVID-19), Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), vaccines.

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INTRODUCTION

A novel coronavirus infection, known as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), which originated in Wuhan, China, infected and killed large numbers of people worldwide from 2020 to 2022.[1] After the genetic sequence of SARS-CoV-2 was determined, Research and

Development activities intensified to develop an effective vaccine.[2–5] Coronavirus Disease 2019 (COVID-19) vaccine types include inactivated virus, virtual vector-based, and RNA-based vaccines. In Türkiye, CoronaVac (Sinovac) and the BNT162b2 (Pfizer-BioNTech) vaccines, provided during the pandemic, received approval from the Ministry of Health. CoronaVac, an inactivated whole virion SARS-CoV-2 vaccine, has been shown to have a good safety profile, is well tolerated, and provides a good humoral response.[6] BNT162b2 is a vaccine containing nucleoside-modified messenger RNA (mRNA) encoding the SARS-CoV-2 spike glycoprotein. In healthy adults, two doses elicit high neutralizing antibody titers and antigen-specific T-cell responses. In a randomized controlled study, the BNT162b2 vaccine was found to provide 95% protection from COVID-19 after the second dose.[7,8] Vaccination regimens usually include a series of primary doses one month apart, followed by a homologous booster dose.

Hospital employees were specifically included in this study to ensure their health and increase their motivation for vaccination. It was intended to add a different dimension to the study by evaluating this privileged group. This cross-sectional study aimed to determine the antibody levels after the BNT162b2 or CoronaVac vaccine was administered as a booster (reminder) dose to volunteers vaccinated with two doses of CoronaVac and to reveal the ideal vaccination combination.

KEY MESSAGES

- The study found that a heterologous booster dose (two doses of CoronaVac followed by one dose of BNT162b2) generated significantly higher antibody levels than a homologous booster dose (three doses of CoronaVac), suggesting that mixing vaccine types can lead to a stronger immune response.
- Antibody levels after two doses of the BNT162b2 mRNA vaccine were significantly higher than after two doses of the inactivated CoronaVac vaccine, indicating mRNA vaccines may offer stronger immunity.
- The findings support heterologous vaccination strategies, enhancing vaccine effectiveness and guiding future policies, especially when supply is variable.

MATERIALS AND METHODS

Study Design and Setting

The cross-sectional study included 254 participants aged 18–80 years, consisting of healthcare workers at Erciyes University Hospital and their relatives, from January 2021 to February 2022. In Türkiye, as part of the vaccination program, the inactivated SARS-CoV-2 vaccine, CoronaVac (Sinovac Life Sciences, Beijing, China) was administered to healthcare workers. Two doses of CoronaVac were applied at a 4-week interval in mid-January 2021. Subsequently, the BNT162b2 (Pfizer-BioNTech) vaccine against emerging variants was optionally available.

Ethical Considerations

Following the application made to the Scientific Study Platform of the General Directorate of Health Services of the Ministry of Health, the study was approved by the Erciyes University Clinical Research Ethics Committee (December 12, 2021; no: 2021/808).

Participants

The diagram showing the study design and vaccination groups is shown in Figure 1. Volunteers were divided into four groups, taking into account the vaccination protocol:

Group 1 (n=54): Those who received three doses of CoronaVac vaccines (1st dose January 2021, 2nd dose February 2021, 3rd dose July 2021); homologous booster.

Group 2 (n=89): Those who received two doses of CoronaVac + one dose of BNT162b2 (cross-vaccinated: inactivated + mRNA) (1st dose January 2021, 2nd dose February 2021, 3rd dose July 2021); heterologous booster.

Group 3 (n=33): Those who received two doses of BNT162b2 (1st dose June 2021, 2nd dose July 2021).

Group 4 (n=18): Those who received two doses of CoronaVac (1st dose January 2021, 2nd dose February 2021).

Patients with immunodeficiency, malignant diseases, those undergoing hemodialysis, and participants confirmed to be unvaccinated were excluded from the study. Different vaccine combinations consisting of a small number of volunteers were not included in the vaccination groups. The participants' age, sex, history of SARS-CoV-2 infection, comorbidity (hypertension, diabetes, cardiovascular disease, rheumatoid arthritis, familial Mediterranean fever, thyroiditis), COVID-19 vaccination status, and vaccine type were recorded. In accordance with routine practice, polymerase chain reaction (PCR) tests were performed on those with symptoms suggestive of COVID-19 infection. The occurrence of a PCR test, the timing of the test, and PCR test results were examined.

Measurement

Blood samples were drawn into tubes without anticoagulants in August 2021, 4 weeks after the third dose (booster vaccination) of the SARS-CoV-2 vaccine. Blood samples were centrifuged at 2000 g for 10 minutes and the serum samples obtained were stored at -20 °C. The timing of blood collection is presented in Figure 2.

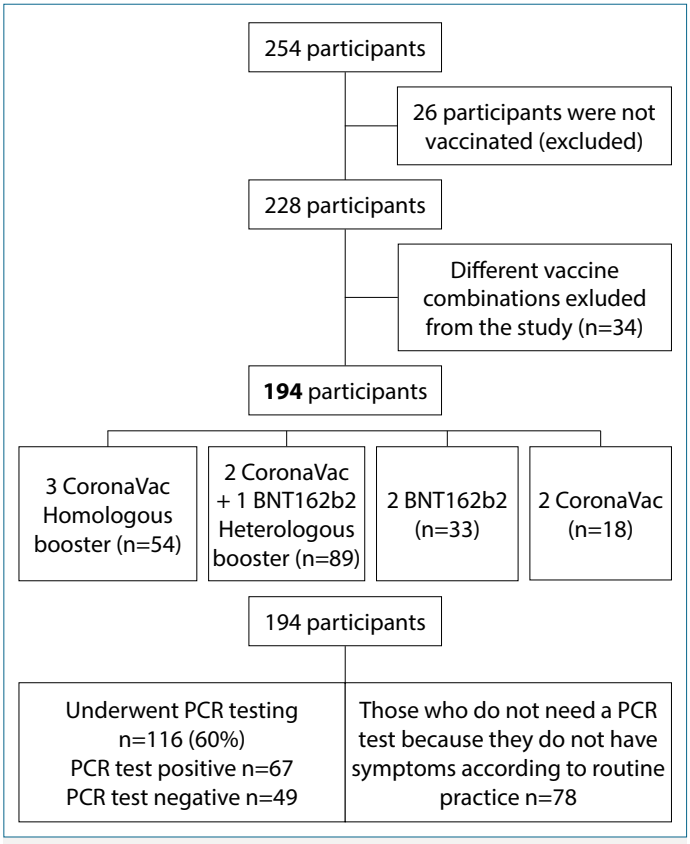

Figure 1. Diagram showing study design and grouping of participants.

SARS-CoV-2 spike (S) Immunoglobulin G (IgG) antibody levels (U/mL) were measured by electrochemiluminescence (ECLIA) on Roche cobas e-801 immunoassay using the Anti-SARS-CoV-2 S kit (Roche Diagnostics GmbH, Mannheim).

Statistical Analysis

Whether the numerical data were normally distributed was evaluated with histograms and the Shapiro-Wilk test. Variables were presented as mean±standard deviation (SD) for normally distributed data, or as median and interquartile range for non-normally distributed data. Summary statistics of categorical variables were expressed as percentages (%), and the exact method of the Chi-square test was used to compare these variables.

Continuous variables were compared using Analysis of Variance (ANOVA) (when the group variances were not homogeneous, Welch ANOVA) or Kruskal-Wallis. Multiple comparisons were tested using Tamhave's T2 test and Dunn-Bonferroni. For comparisons between two groups, the Mann-Whitney U test was used for variables that did not show normal distribution. Power analysis was performed

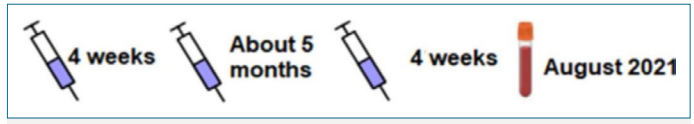

Figure 2. Vaccination plan and blood collection timeline.

using G*Power v.3.1.9.2. The sample size was evaluated based on homologous and heterologous vaccination groups. A total of 102 were determined, 51 in each group (homologous and heterologous) (d=0.5, power=0.80 at α=0.05).

Analyses were conducted using TURCOSA [Turcosa Analytics Ltd. Co., Kayseri, Türkiye] statistical software. A p-value <0.05 was considered statistically significant.

RESULTS

Demographic characteristics and SARS-CoV-2 PCR status of the study groups were shown in Table 1.

The number of participants confirmed to be infected or not infected with SARS-CoV-2 by polymerase chain reaction was 116. Sixty-seven of them were evaluated as positive and 49 volunteers as negative. There was no need to request a PCR test from 78 participants who did not show any signs or symptoms of COVID-19 infection during the study.

Twenty of the 67 participants with a positive PCR test had COVID-19 infection after measuring the SARS-CoV-2 S IgG antibody. Forty-seven of those with a positive PCR test had COVID-19 infection before measuring the SARS-CoV-2 S IgG antibody.

Differences determined between vaccine groups in terms of SARS-CoV-2 PCR status and comorbidities are presented in Table 1.

As seen in Table 2, SARS-COV-2 S Ig G levels were found to be significantly higher in women who received two doses of BNT162b2 compared to men. No difference was detected in the other groups. The comparison of SARS-COV-2 S IgG levels of study groups is shown in Figure 3.

Antibody levels after three doses of CoronaVac administration were found to be statistically significantly lower when compared to two doses of CoronaVac + 1 dose of BNT162b2 [605 (299–2375) and 12798 (7358–24916), p<0.001, respectively]. In addition, IgG levels measured after two doses of mRNA (2BNT162b2) vaccine were higher than after two doses of inactivated vaccine (2 CoronaVac) [4613 (1552–10636) and 298 (119–583), p<0.001, respectively].

Table 1. Demographic characteristics of the groups and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) PCR status

Variables	3 CoronaVac (n=54)	2 CoronaVac + 1 BNT162b2 (n=89)	2 BNT162b2 (n=33)	2 CoronaVac (n=18)	p
Age (years)	45.96±11.87[a]	46.15±11.53[a]	40.33±12.30[a,b]	39.94±4.80[b]	0.001
Sex					0.903
Female	31 (57%)	47 (53%)	18 (54.5%)	11 (61%)	
Male	23 (43%)	42 (47%)	15 (45.5%)	7 (39%)	
SARS-CoV-2 PCR status					<0.001
Positive	17 (32%)[a,b]	40 (45%)[b]	5 (15%)[a]	5 (28%)[a,b]	
Negative	13 (24%)[a,b]	28 (32%)[b]	3 (9%)[a]	5 (28%)[a,b]	
Not routinely tested	24 (44%)[a]	21 (24%)[b]	25 (76%)[c]	8 (44%)[a,b]	
Comorbidity					0.049
Yes	11 (20%)[a]	8 (9%)[a,b]	2 (6%)[a,b]	0 (0%)[b]	
No	43 (80%)[a]	81 (91%)[a,b]	31 (94%)[a,b]	18 (100%)[b]	

PCR: Polymerase chain reaction; Data are shown as Mean±SD or n (%) as median (25%–75%). There is no difference between groups containing the same letters. a,b,c: Different superscripts in the same row indicate a statistically significant difference between groups.

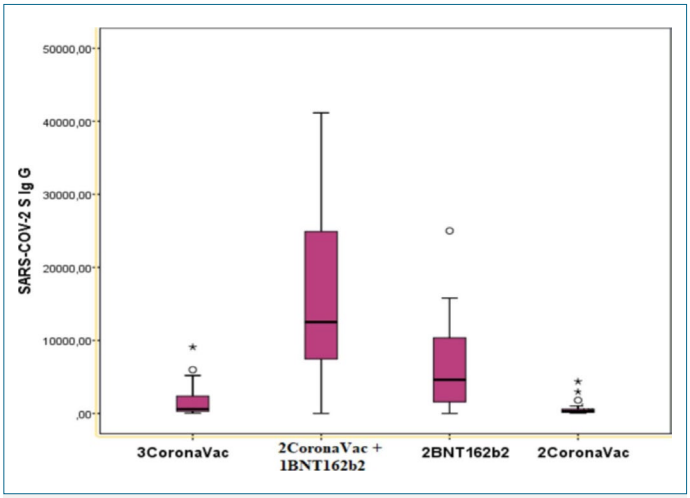

Figure 3. Comparison of antibody levels after different vaccine combinations.

Table 2. Comparison of SARS-CoV-2 S Immunoglobulin G (IgG) levels of groups according to sex

Groups	SARS-CoV-2 S IgG	p
3 CoronaVac		0.463
Male	519 (268–2375)	
Female	11986 (6996–23944)	
2 CoronaVac +1 BNT162b2		0.696
Male	1577 (1157–4613)	
Female	210 (164–364)	
2 BNT162b2		**0.004**
Male	692 (300–2384)	
Female	13644 (7445–24977)	
2 CoronaVac		0.375
Male	8802 (2423–12634)	
Female	367 (118–1800)	

No significant difference was detected in antibody levels between those with positive and negative PCR tests. At the same time, no significant difference was observed between those who had a positive PCR test before and after antibody measurement (Table 3).

DISCUSSION

The SARS-CoV-2 outbreak triggered a global immunization effort. Due to the variable availability of vaccines in many countries during the COVID-19 pandemic, different types and combinations of vaccines have been used at different time intervals. How this condition affects immune responses has been a matter of serious concern. Initially, CoronaVac vaccine was applied in Türkiye, and then the mRNA vaccine was included in the program. This offered the opportunity to compare the antibody response of different combinations created with the third dose after two doses of CoronaVac vaccine.

In this study, antibody responses formed after cross-vaccination (inactivated + mRNA) or two doses of CoronaVac + one dose of BNT162b2 (heterologous) and combinations

Table 3. Comparison of SARS-CoV-2 S IgG levels according to PCR test result

Variable	PCR negative n=49	PCR positive n=67	p
SARS-CoV-2 S IgG	8305 (561–13594) PCR + before measuring antibodies n=47	6689 (713–17521) PCR + after measuring antibodies n=20	0.531
SARS-CoV-2 S IgG	4948 (563–13553)	11866 (3443–23300)	0.053

of three doses of CoronaVac vaccine (homologous) were compared. Heterologous cross-vaccination administration caused higher antibody responses.

In the literature, there are studies on the antibody responses obtained after immunization with different vaccines at varying intervals and combinations according to each country's vaccination protocol. A study reported that anti-spike (S) antibody titers obtained after mRNA vaccines (Moderna and Pfizer) were higher than those from adenovirus vector vaccines and inactivated vaccines in the Bangladeshi population.[9] Another study found the lowest levels of anti-spike IgG with one dose of Ad26.COV2.S (Johnson & Johnson) and the highest levels from two doses of mRNA-1273 or a heterologous vaccination of one dose of ChAdOx1 (viral vector vaccine, Oxford/AstraZeneca) followed by an mRNA vaccine.[10] A cohort study in Catalonia showed that mRNA vaccines, such as Spikevax (previously Moderna), induced higher antibodies after primer doses compared to Vaxzevria (previously AstraZeneca) or Janssen (Johnson & Johnson) vaccines.[11]

Initial studies indicated that the third dose of COVID-19 vaccines stimulated reduced immune responses.[12,13]

A randomized control trial reported that participants who received BNT162b2 approximately four months as a third dose after two doses of CoronaVac showed significantly higher levels of specific antibodies against the spike receptor-binding domain than those who received CoronaVac as a third dose.[14] Additionally, the binding antibody levels post-booster were significantly lower for volunteers originally vaccinated with AZD1222 (Oxford-AstraZeneca) or Ad26.COV2.S compared to those vaccinated with mRNA-1273 or BNT162b2.[15]

Previous studies have reported higher levels of S-specific IgG following heterologous vaccination than homologous vaccination as a prime-boost.[16–19] Again, research has indicated that heterologous vaccinations with ChAdOx1 followed by a mRNA vaccine reveal a more potent immune response than homologous vaccinations with vector-based or mRNA-based vaccines.[20–22]

In addition, two doses of BNT162b2, 3 months apart, caused approximately three times higher neutralizing antibody titers than those administered 3 weeks apart, but a third dose of an mRNA-based booster increased antibody levels four times.[23]

It has also been shown in other studies carried out in our country that the BNT162b2 vaccine as a booster dose after two doses of an inactivated vaccine causes a higher increase in antibody titers.[24–26]

Deng et al.[27] proposed that both the homologous and heterologous booster doses produced a good immune response and that a heterologous booster dose was more effective, which would help make the most appropriate decisions in vaccination.

mRNA-based vaccines were more efficacious than adenovirus vector-based vaccines. Results support these findings by indicating considerable rises in antibody titers after booster doses, particularly with mRNA vaccines.[28]

mRNA-based vaccines produced the highest amount of spike-specific IgG antibodies. Their data also indicated that heterologous vaccination using priming with an adenovirus vector-based vaccine followed by a boost with an mRNA vaccine elicited a more potent antibody expression compared to their homologous counterparts.[29] In other studies, high antibody levels were obtained with mRNA vaccines.[30]

Limitations

One of the most important limitations of this study is that the effect of COVID-19 infection before or after the vaccination protocol on antibody results cannot be excluded. Since the number of participants in each vaccine group was small, an evaluation could not be made by excluding those with COVID-19 infection. However, the fact that some of those with a positive PCR test had COVID-19 infection after antibody measurement, and no significant difference was detected between the antibody levels of those with positive and negative PCR tests can be interpreted as the antibody levels resulting from vaccination not being affected by the COVID-19 infection.

Another limitation of the study is that it is a cross-sectional study with a small sample size of participants.

CONCLUSION

In this study, the results obtained according to the vaccine protocol applied in our country were compatible with the literature. The booster dose with a heterologous vaccine (mRNA) has a higher antibody response compared to homologous vaccination. High immunity after a booster dose with an mRNA vaccine suggests that cross-vaccination may be an ideal combination. Another result of this study was that the antibody responses after the three doses (2 primary + 1 dose booster) of CoronaVac vaccine were lower than those from two doses of BNT162b2. This finding may be related to the initiation of vaccination with CoronaVac in our country, comorbidity, or the inactivated nature of the vaccine.

This study emphasizes that different types of vaccines can be accessed in variable periods under pandemic conditions. The use of heterogeneous booster doses due to deficiencies or delays in vaccine supply may be a good alternative to the homologous approach applied so far. The results obtained from these studies, which were applied with different combinations of vaccines, are of great importance in terms of guiding vaccination policies.

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Ethics Committee Approval: The Erciyes University Clinical Research Ethics Committee granted approval for this study (date: 08.12.2021, number: 2021/808).

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Informed Consent: Written informed consent was obtained from patients who participated in this study.

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