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RESEARCH ARTICLE

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Antibody response after two doses of homologous or heterologous SARS-CoV-2 vaccines in healthcare workers at health promotion centers: A prospective observational study

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Abstract

Assaying of anti-spike-protein receptor-binding domain (S-RBD) antibodies are used to aid evaluations of the immune statuses of individuals. The aim of this study was to determine the antibody response after two doses of homologous or heterologous severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines and to identify the factors affecting this response among healthcare workers (HCWs) at health promotion centers. In this prospective observational study, 1095 consenting HCWs were recruited from 16 health checkup centers and were tested at T0 (day of first dose), T1-1 (1 month after first dose), T2-0 (day of second dose), T2-1 (1 month after second dose), and T2-3 (3 months after second dose). SARS-CoV-2 antibodies were measured using a chemiluminescence microparticle immunoassay with SARS-CoV-2 IgG II Quant in the ARCHITECT system (Abbott Diagnostics). At T1-1, anti-SARS-CoV-2 S-RBD IgG levels were significantly higher in participants who received messenger RNA (mRNA) vaccines than in those who received viral vector vaccines ($p < 0.001$). At T2-1, anti-SARS-CoV-2 S-RBD IgG levels were about 10 times higher than at T1-1 in participants who received homologous mRNA vaccines, which decreased to a third of those at T2-3. Anti-SARS-CoV-2 S-RBD IgG levels were highest among those who received homologous mRNA vaccines, followed by heterologous mRNA viral vector vaccines and homologous viral vector vaccines at T2-3 ($p < 0.001$). In a multivariable linear regression analysis, being female, taking at least one mRNA vaccine, and having a history of recovery from coronavirus disease 2019 (COVID-19) were significantly associated with anti-S-RBD levels. Anti-SARS-CoV-2 S-RBD IgG levels were decreased at 3 months after two-dose vaccinations and were associated with sex, vaccine type, and COVID-19 history.

KEYWORDS

anti-spike-protein receptor-binding domain (S-RBD) antibodies, healthcare workers, mRNA vaccines, SARS-CoV-2 IgG, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines, viral vector vaccines

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19) is caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This virus is highly contagious and the resulting disease has led to an ongoing pandemic.[1] Vaccines against SARS-CoV-2 have been rapidly developed to protect people from COVID-19 and provide protective immunity.[2] SARS-CoV-2 vaccines induce cellular and humoral immunity, which lead to the production of antibodies directed against different SARS-CoV-2 antigens. Despite the development of multiple vaccines against the coronavirus SARS-CoV-2, there were vaccine supply shortages and interruptions. Furthermore, adverse events such as thrombosis and thrombocytopenia syndrome associated with adenovirus-based vaccines occurred in Korea. The Korean government recommended various vaccine types and cross-platform mixed-dosing strategies.

SARS-CoV-2 has four major structural proteins: envelope (E), membrane (M), nucleocapsid (N), and spike (S) protein. The S and N proteins are the main immunogens used to detect antibodies specific to anti-SARS-CoV-2.[3–6] The S protein plays an essential role in viral binding, fusion, and replication with the host cell by interacting with angiotensin-converting enzyme 2 (ACE2). The S protein consists of two subunits, the first of which subunit (S1) mediates the virus binding to human cells via a receptor-binding domain (RBD), which interacts directly with the receptors of the host cells.[4] While it is difficult to assess the immunogenicity of vaccines, measuring SARS-CoV-2 antibody levels in vaccinated subjects is accepted as a diagnostic test determining vaccine efficacy.[7] Quantitative determination of anti-SARS-CoV-2 antibodies is crucial to estimate the humoral response of vaccinated individuals.[8] There are different types of serological diagnostic tests for COVID-19 that use different antigenic targets such as N, S, and S1 proteins, and RBD.[9–11] Among them, evaluating S protein receptor-binding domain (S-RBD) IgG antibodies are vital for assessing protection against SARS-CoV-2 infection due to their neutralizing activity.[12]

The magnitude and durability of the humoral immune response have not yet been fully elucidated. A better understanding of the kinetics of SARS-CoV-2 antibodies after vaccination with different vaccine types and schemes is important for developing strategies that maximize the coverage and impact of the vaccine among populations. The aim of this study was to determine the antibody response after two doses of homologous or heterologous SARS-CoV-2 vaccines and to identify the factors that affect this response among healthcare workers (HCWs) at health promotion centers in South Korea.

2 | MATERIALS AND METHODS

2.1 | Study subjects

This prospective observational study recruited 1095 consenting HCWs from 16 health checkup centers, 1 central laboratory, and 1 headquarter between April and August 2021. The inclusion criteria were as follows: HCW with vaccination plan and consented HCW. Subjects who had COVID-19-related symptoms at the time of the study or pregnancy were excluded. Eligible participants received both injections of the ChAdOx1 nCoV-19 (ChAd) vaccine from AstraZeneca, the messenger RNA (mRNA) vaccine BNT162b2 (BNT) from Pfizer-BioNTech, or the mRNA-1273 vaccine from Moderna (Moderna) or Janssen. The first and second injections were administered an approximate interval of 3 months (for virus-vector vaccines) or 1 month (for mRNA vaccines). Participants were asked to complete an online survey of their adverse reactions within 1 week of receiving each vaccination. HCWs were tested for anti-S-RBD IgG antibodies at T0 (day of first dose), T1-1 (1 month after first dose), T2-0 (day of second dose), T2-1 (1 month after second dose), and T2-3 (3 months after second dose).

2.2 | Anti-SARS-CoV-2 S-RBD IgG measurement

Venous blood was collected in 10 ml SST tubes and immediately centrifuged at 1500x*g* for 10 min. Aliquots of serum samples were analyzed. The SARS-CoV-2 IgG II Quant assay (Abbott) is a chemiluminescence microparticle immunoassay used for the qualitative and quantitative determination of IgG SARS-CoV-2 antibodies in human serum on the ARCHITECT i System (Abbott). This is included in the WHO International Standard for anti-SARS-CoV-2 immunoglobulin.[13] This assay was designed to detect SARS-CoV-2 IgG RBD antibodies and neutralizing antibodies in serum. Plaque reduction neutralization (PRNT) are used to quantify the titer of neutralizing antibodies for a virus. A positive percent agreement study was performed with the SARS-CoV-2 IgG II Quant assay that were demonstrated to be positive (≥1:20) using a PRNT by the Broad Institute. The assay utilizes a Four Parameter Logistic Curve data-fit reduction method (4PLC, Y-weighted) to generate calibrations and results. The cutoff value for a positive result was defined as ≥50 AU/ml (values < 50 AU/ml were considered negative).[14] The lower limit of quantification was 21.0 AU/ml, as declared by the manufacturer's. The unit of measurement used is in accordance with the notification received from WHO. The measurement range was 21.0–40 000 AU/ml, and values above this range were recorded as 40 000 AU/ml.[15]

2.3 | Statistical analysis

Statistical analysis were performed using SAS version 9.4 (SAS Institute). Demographic characteristics were presented as number (percentage) values. The normality of a distribution was assessed using the Kolmogorov–Smirnov and Shapiro–Wilk tests. Data were presented as median (25%–75% interquartile range) or frequency (percentage) values. Univariable and multivariable liner regression analyses were performed to verify the associations between immunogenicity and age, sex, vaccine type, region, working place,

history of recovery from COVID-19, and adverse reactions. We used box plots to illustrate anti-S-RBD IgG concentration distributions according to age, sex, region, working place, history of recovery from COVID-19, and adverse reactions. Kruskal–Wallis or Fisher's exact tests were performed to assess differences between groups. Multiple comparisons for age groups were performed using pairwise comparisons of adjacent groups. A $p < 0.05$ was considered statistically significant.

3 | RESULTS

3.1 | Demographic and clinical characteristics of the study subjects

This study analyzed 1095 subjects (372 males and 723 females) with a median age of 39 years (range 21–78 years). The 1095 participants comprised 680 (62.1%) who received heterologous mRNA vaccine and viral vector vaccines and 415 (37.9%) who received homologous vaccines. The 680 heterologous vaccines recipients comprised 673 (61.5%) participants who received ChAd and BNT vaccines, and 7 (0.6%) participants who received Janssen and BNT/Moderna vaccines. The 415 homologous vaccines recipients included 32 (2.9%) participants who received two ChAd vaccines, 303 (27.7%) participants who received two BNT vaccines, and 80 (7.3%) participants who received two Moderna vaccines. Most participants (98.0%) experienced at least one local adverse reaction after the first or second injection, such as muscle pain, tenderness, or redness at the injection site. Systemic adverse reactions such as high fever, lymph node edema, herpes zoster, thrombosis, or vaginal bleeding were reported in 8 (0.7%) participants. The enrolled participants included 6 (0.5%) who had previously recovered from COVID-19 least 3 months before the study (Table 1).

3.2 | Antibody response after vaccinations

Negative serology (<50 AU/ml) was exhibited at 1 month after the first vaccination by 23 (2.1%) participants: 21 who received ChAd, 1 who received BNT, and 1 who received the Moderna vaccine. On the other hand, at the 3 month after the second vaccination, all participants showed a positive serology. At T1-1, anti-SARS-CoV-2 S-RBD IgG levels were significantly higher in participants who received mRNA vaccines than in those who received viral vector vaccines ($p < 0.001$). At T2-1, anti-S-RBD levels were increased about 10 times higher than those at T1-1 in participants who received homologous mRNA vaccines, which decreased to a third of those at T2-3. Anti-SARS-CoV-2 S-RBD IgG levels were highest among those who received homologous mRNA vaccines, followed by heterologous mRNA and viral vector vaccines, and homologous viral vector vaccines at T2-3 ($p < 0.001$) (Table 2, Figure 1).

TABLE 1 Characteristics of the study subjects

	N	%
Total	1095	100
Sex		
Male	372	34
Female	723	66
Age, years		
≤29	165	15.1
30–39	404	36.9
40–49	327	29.9
50–59	177	16.2
60-69	16	1.5
≥70	6	0.6
Vaccinations		
Heterologous vaccinations	**680**	**62.1**
ChAd + BNT	673	61.5
Janssen + BNT/Moderna	7	0.6
Homologous vaccinations	**415**	**37.9**
ChAd + ChAd	32	2.9
BNT + BNT	303	27.7
Moderna + Moderna	80	7.3
Region		
Seoul	291	26.6
Gangwon-do (Gangwon)	19	1.7
Gyeonggi-do (Gyeonggi, Incheon)	151	13.8
Gyeongsangbuk-do (Daegu, Gyeongbuk)	121	11.1
Gyeongsangnam-do (Busan, Ulsan, Gyeongnam)	204	18.6
Jeolla-do (Jeonnam, Jeonbuk)	136	12.4
Chungcheong-do (Chungnam, Chungbuk)	109	10
Jeju-do (Jeju)	64	5.8
Adverse reaction after vaccination		
Local tenderness or muscle pain	1073	98.0
Systemic reaction or local reaction	8	0.7
None	14	1.3
History of recovery from COVID-19		
Yes	6	0.5
No	1089	99.5
Working in patient-facing healthcare		
Yes	898	82
No	197	18

Note: Moderna, mRNA-1273.

Abbreviations: BNT, BNT162b2; ChAd, ChAdOx1 nCoV-19; COVID-19, coronavirus disease 2019.

TABLE 2 Anti-SARS-CoV-2 S-RBD IgG levels after vaccinations

	One month after first vaccination			Three months after second vaccination		
Type of vaccination	Median	(25%–75% IQR)	*p*	Median	(25%–75% IQR)	*p*
Total	591.9	(274.7–1286.9)		1930.9	(1191.6–3105.7)	
Viral vector vaccine			<0.001			<0.001
ChAd + ChAd[a]	406.5	(204.1–797.1)		627.6	(257.0–1638.6)	
ChAd + BNT[b]				1736.2	(1124.0–2787.9)	
Janssen + BNT/Moderna[c]	264.5	(253.5–437.6)		4409	(3862.6–6196.2)	
mRNA vaccine						
BNT + BNT[d]	1072.8	(606.0–1791.6)		2845.6	(1827.5–4279.4)	
Moderna + Moderna[e]	1849.1	(1156.9–3326.2)		3837.9	(2944.1–5261.4)	

Note: Multiple comparisons: a,c < d < e at 1 month after first vaccination; a < b < c,d,e at 3 months after second vaccination.

Abbreviation: BNT, BNT162b2; ChAd, ChAdOx1 nCoV-19; IQR, interquartile range; mRNA vaccine, messenger RNA vaccine; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; S-RBD, anti-spike-protein receptor-binding domain.

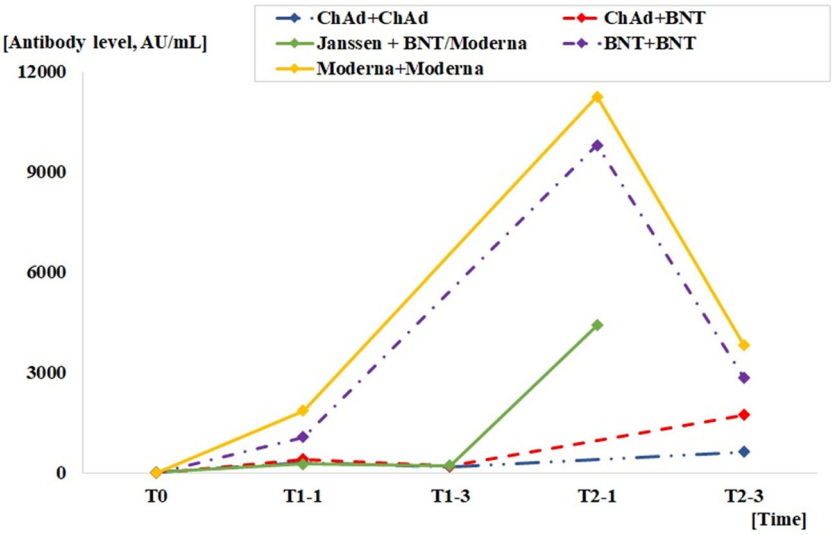

FIGURE 1 Anti-SARS-CoV-2 S-RBD IgG antibodies according to vaccine types. Times of second vaccination: viral vector (T1-3), mRNA (T1-1). BNT, BNT162b2; ChAd, ChAdOx1 nCoV-19; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; S-RBD, anti-spike-protein receptor-binding domain.

3.3 | Association of anti-SARS-CoV-2 S-RBD IgG levels at T2-3 with demographic and clinical characteristics

The median anti-SARS-CoV-2 S-RBD IgG level was higher in females (2098.7 AU/ml) than in males (1591.5 AU/ml, $p < 0.001$). There were significant differences in anti-SARS-CoV-2 S-RBD IgG levels among age groups ($p < 0.001$), regions ($p = 0.004$), and the history of recovery from COVID-19 ($p = 0.033$). However, anti-SARS-CoV-2 S-RBD IgG levels did not differ between participants with and without systemic adverse reactions, or between participants with and without direct contact with recipients of health checkups (Figure 2). Older age was negatively associated with anti-SARS-CoV-2 S-RBD IgG levels in the univariable analyses ($p < 0.001$), but this association disappeared in multivariable linear regression analysis ($p = 0.228$). Multivariable linear regression analysis indicated that anti-SARS-CoV-2 S-RBD IgG levels were significantly associated with being female, receiving at least one mRNA vaccine, and history of recovery from COVID-19 at T2-3 (all $p < 0.05$) (Table 3).

4 | DISCUSSION

This prospective observational study found that anti-SARS-CoV-2 S-RBD IgG levels were highest in the participants who received homologous mRNA vaccines, followed by heterologous mRNA and viral vector vaccines, and homologous viral vector vaccines, which were all decreased at 3 months after the second dose. Moreover, anti-SARS-CoV-2 S-RBD IgG levels were significantly associated with being female, vaccine type, and history of recovery from COVID-19.

Due to vaccine supply shortages and interruptions, and adverse events such as thrombosis and thrombocytopenia syndrome associated with adenovirus-based vaccines, various vaccine types, and schemes have been used in Korea. Several studies have invested the superiority of

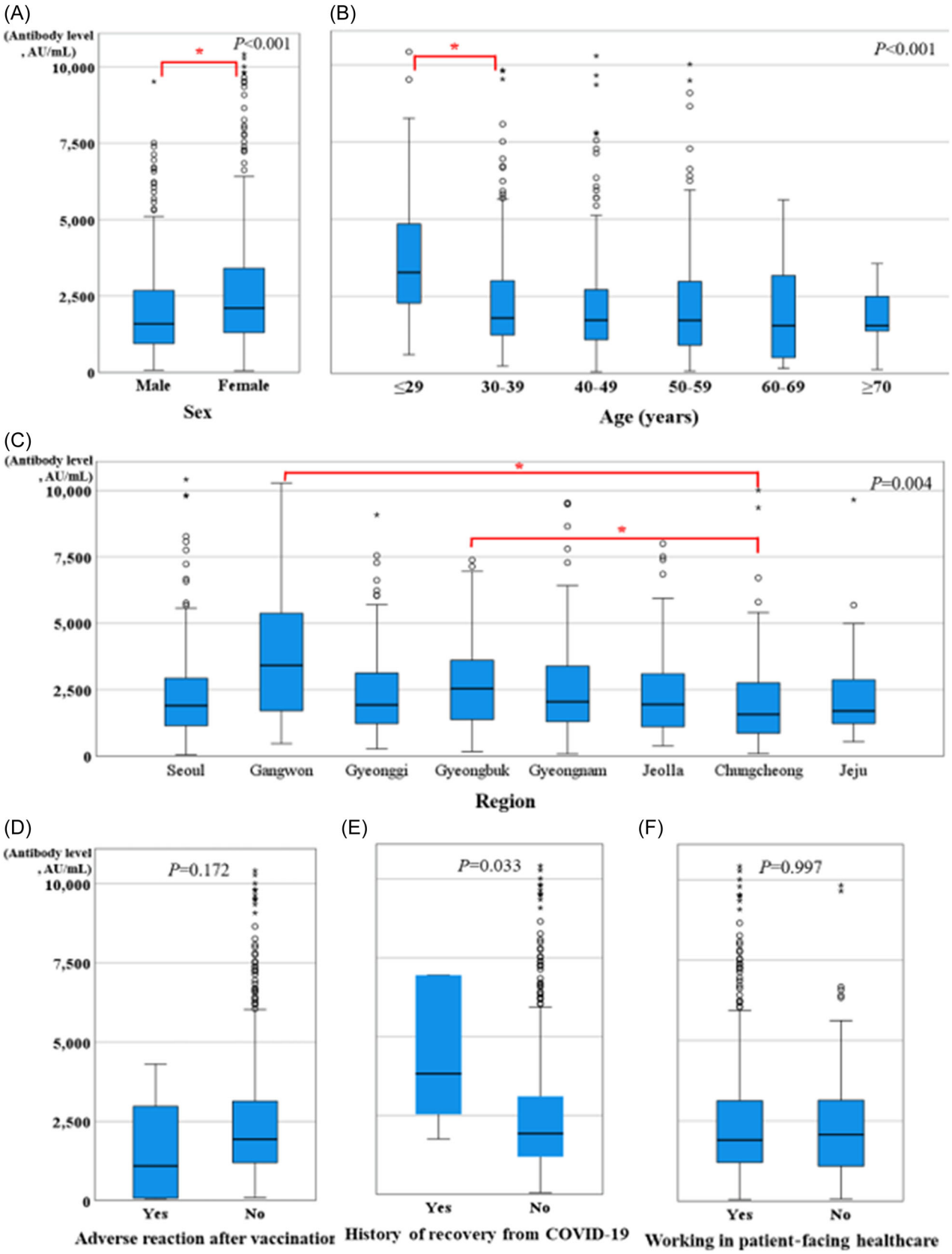

FIGURE 2 Anti-SARS-CoV-2 S-RBD IgG levels according to (A) sex, (B) age, (C) region, (D) adverse reaction after vaccination, (E) history of recovery from COVID-19, and (F) working in patient-facing healthcare. Each box plot shows the median, first and third quartiles, and range, with outliers also indicated.*Significant after Bonferroni correction for multiple testing. COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; S-RBD, anti-spike-protein receptor-binding domain.

TABLE 3 Factors associated with anti-SARS-CoV-2 S-RBD IgG level

	One month after first vaccination[a]						Three months after second vaccination					
	Univariable			Multivariable			Univariable			Multivariable		
	Coeff.	SE	*p*	Coeff.	SE	*p*	Coeff.	SE	*p*	Coeff.	SE	*p*
Sex, (reference: female)	−357.6	129.6	0.006	−239.5	116.1	0.039	−556.6	198	0.005	−386.7	189.6	0.042
Age, years	−21.9	6.2	<0.001	0.6	6.3	0.931	−40.5	9.4	<0.001	−12.6	10.4	0.228
Vaccine type, reference, (ChAd + ChAd)												
ChAd + BNT	-			-			1339.9	506.9	0.008	1063.7	500.7	0.034
Janssen + BNT/Moderna	−448.4	745.1	0.547	−127.9	700.4	0.855	3853.7	1465.8	0.009	3786.7	1444.3	0.009
BNT + BNT	857.8	134.7	<0.001	891	141.7	<0.001	2591.2	536.7	<0.001	2219.8	556.6	<0.001
Moderna + Moderna	1826.7	231.4	<0.001	1878.8	213.9	<0.001	4204.7	741.7	<0.001	3904.1	730.3	<0.001
Working in patient facing healthcare (reference none)	7.5	160.4	0.963	87.1	147.2	0.554	57.6	252.1	0.819	84.3	246.8	0.733
Adverse events after vaccination (reference none)	−490.6	723.1	0.498	−460.9	646.6	0.476	−1008.5	1167.2	0.388	−1151.7	1105.6	0.298
History of recovery from COVID-19 (reference none)	10 358	773.4	<0.001	10 604	737.8	<0.001	8343.6	124	<0.001	8607.2	1204.3	<0.001

Abbreviations: BNT, BNT162b2; ChAd, ChAdOx1 nCoV-19; Coeff, coefficient; COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SE, standard error; S-RBD, anti-spike-protein receptor-binding domain.

[a]ChAd as the reference for vaccine type with results of Janssen, BNT, and Moderna.

heterologous vaccines over homologous vaccines.[16–18] Barros-Martins et al.[16] reported that the IgG and IgA immune responses against the SARS-CoV-2 S protein were significantly larger for heterologous ChAd-BNT doses than for homologous ChAd-ChAd doses, which prompted them to propose superior effectiveness for heterologous vaccines. Incorporating heterologous mRNA vaccines that elicit mostly humoral responses and viral vector vaccines that elicit strong cellular responses may therefore broaden SARS-CoV-2 immunity.[19] Our findings that anti-S-RBD levels were higher in participants who received heterologous ChAd-BNT doses than in those who received homologous ChAd-ChAd doses were consistent with those of Barros-Martins et al. However, anti-S-RBD levels were the highest in participants who received homologous mRNA vaccines, followed by heterologous ChAd-BNT doses in our study. ChAd enables adenovirus-based vaccine platforms to deliver the SARS-CoV-2 S protein in a way that will enhance the immune response. Nevertheless, adenovirus-based vaccine platforms are restricted by them inducing strong T-cell responses while being less effective at inducing a neutralizing antibody response.[20]

Response to vaccines vary according to individual factors such as demographics and the immune status of the vaccinated subjects.[21] The relationship between age and COVID-19 vaccine immunogenicity has been reported to differ with the types of vaccines, study subjects, and the use of a clinical trial or real-world study. Most studies on mRNA COVID-19 vaccines have found weakened antibody responses in older subjects.[22–24] On the other hand, some studies have found no association between age and ChAd immunogenicity.[25–27] In our study, older age was negatively associated with the anti-SARS-CoV-2 S-RBD IgG levels in the univariable analyses but not in the multivariable linear regression analysis. Decreased immunogenicity of the various vaccines in elderly people has been observed, and explained by immunosenescence.[28] However, vaccine immunogenicity was determined by age and other factors, which could explain why an association between age and anti-SARS-CoV-2 S-RBD IgG levels was not found in the multivariable linear regression analysis in our study.

There is some inconsistency in associations between sex and antibody responses to COVID-19 vaccines. While some studies have found sex to be an independent predictor of antibody level, with females having higher anti-SARS-CoV-2 S-RBD IgG antibody levels,[29–31] others found no significant difference between sexes in antibody responses.[25,27,32] Our study found that males had significantly lower antibody levels than females. Most vaccines are likely to have weakened antibody responses in males, which contributes to the higher mortality and worse outcomes of COVID-19 in males.[33]

In addition to sex, an association between antibody response and history of recovery from COVID-19 was found in the present study. This was consistent with the previous finding of anti-S antibody levels being significantly higher in vaccinated HCWs with prior SARS-CoV-2 infection than in their counterparts without prior SARS-CoV-2 infection.[34] Moreover, a prospective study found that those with a history of natural infection had significantly higher antibody levels than those without prior SARS-CoV-2 infection.[35]

This study has some limitations. First, anti-SARS-CoV-2 S-RBD IgG antibodies were used as neutralizing antibody surrogates, even though a correlation between anti-SARS-CoV-2 S-RBD IgG and neutralizing antibodies has been identified previously.[36,37] Second, the study subjects were HCWs, with only a small proportion (2.1%) being older than

60 years, which might not represent the general population. However, the present multicenter nationwide study enrolled subjects who were HCWs that confront apparently healthy individuals at health checkups, which suggest that our subjects could reflect the general population of Korea. Third, we could not measure anti-SARS-CoV-2 S-RBD IgG levels at T1-3 for the mRNA vaccine or at T2-1 for the homologous and heterologous ChAd vaccines due to changes in government vaccination policies. However, we are continuing to prospectively assess the antibody responses after the third vaccination in this cohort, which will help to determine the longevity of the immunity provided by SRS-CoV-2 vaccines in a real-world setting.

In conclusion, this observational study has characterized antibody responses after the administration of various COVID-19 vaccine types and schemes. Anti-SARS-CoV-2 S-RBD IgG levels were found to be significantly associated with being female, receiving at least one mRNA vaccine, and a history of recovery from COVID-19 at 3 months after the second dose.

AUTHOR CONTRIBUTIONS

All of the authors participated in designing this study. Seon Cho, Dongwon Noh, Eunjoo Kwon, and Hyeran Park performed data collection. Suyoung Kim undertook the statistical analysis. Eun-Hee Nah, Suyoung Kim, Han-Ik Cho, and Hyeran Park analyzed and interpreted the data. Eun-Hee Nah wrote the first draft and revision of the manuscript, which was reviewed by all of the other authors, who also provided further contributions and suggestions.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study. The data used to support the findings of this study are included in the article.

ETHICS STATEMENT

This study was approved by the Institutional Review Board of the Korea Association of Health Promotion (approval no. 130750-202104-BR-001). A written informed consent form was signed by each participant.

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