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Comparison of the Results of Five SARS-CoV-2 Antibody Assays before and after the First and Second ChAdOx1 nCoV-19 Vaccinations among Health Care Workers: a Prospective Multicenter Study

Seri Jeong,[a] Nuri Lee,[a] Su Kyung Lee,[b] Eun-Jung Cho,[b] Jungwon Hyun,[b] Min-Jeong Park,[a] Wonkeun Song,[a] Eun Ju Jung,[c] Heungjeong Woo,[c] Yu Bin Seo,[d] Jin Ju Park,[d] Hyun Soo Kim[b]

[a]Department of Laboratory Medicine, Kangnam Sacred Heart Hospital, Hallym University College of Medicine, Seoul, South Korea
[b]Department of Laboratory Medicine, Dongtan Sacred Heart Hospital, Hallym University College of Medicine, Hwaseong, South Korea
[c]Division of Infectious Diseases, Department of Internal Medicine, Dongtan Sacred Heart Hospital, Hallym University College of Medicine, Hwaseong, South Korea
[d]Division of Infectious Diseases, Department of Internal Medicine, Kangnam Sacred Heart Hospital, Hallym University College of Medicine, Seoul, South Korea

Seri Jeong and Nuri Lee contributed equally to this work. Author order was determined by type of contribution.

ABSTRACT Reliable results for serological positivity to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antibody after the second dose of AstraZeneca (AZ) vaccination are important to estimate the real efficacy of vaccination. We evaluated positivity rates and changes in semiquantitative antibody titers before and after the first and second ChAdOx1 nCoV-19 vaccinations using five SARS-CoV-2 antibody assays, including two surrogate virus neutralization tests. A total of 674 serum samples were obtained from 228 participants during three blood sampling periods. A questionnaire on symptoms, severity, and adverse reaction duration was completed by participants after the second vaccination. The overall positive rates for all assays were 0.0 to 0.9% before vaccination, 66.2 to 92.5% after the first vaccination, and 98.2 to 100.0% after the second vaccination. Median antibody titers in five assays after the second dose of vaccination were increased compared to those after the first dose (106.4-fold increase for Roche total antibody, 3.6-fold for Abbott IgG, 3.6-fold for Siemens, 1.2-fold for SD Biosensor V1 neutralizing antibody, and 2.2-fold for GenScript neutralizing antibody). Adverse reactions were reduced after the second dose in 89.9% of participants compared to after the first dose. Overall, the second vaccination led to almost 100% positivity rates based on these SARS-CoV-2 antibody assays. The results should be interpreted with caution, considering the characteristics of the applied assays. Our findings could inform decisions regarding vaccination and the use of immunoassays, thus contributing to SARS-CoV-2 pandemic control.

KEYWORDS SARS-CoV-2, antibody, assay, vaccine, titer, adverse reaction

INTRODUCTION

Since its emergence in December 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused a pandemic that has progressed at tremendous speed. Coronavirus disease 2019 (COVID-19) was considered a global public health crisis beginning in 2020. To date, several vaccines have been authorized for use, and their efficacy has been reported in an increasing number of vaccinated populations (1–3). However, there is still a lack of data on the vaccination efficacy that may be reliably achieved following the second dose and how long the antibodies last, depending on the type of vaccine, the type of antibody, and the antibody detection reagents. As only several months have passed since the vaccination initiation, few studies have been conducted to follow up on antibody titers after the second vaccination dose. Moreover, more clinical data on

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Address correspondence to Hyun Soo Kim, hskim0901@empas.com.

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antibody titers and symptom severity concerning the adverse effects of vaccination are required.

Previously, our group investigated the antibody responses to a single dose of the AstraZeneca (AZ) (ChAdOx1 nCoV-19) vaccine (AstraZeneca, Lund, Sweden) using five SARS-CoV-2 antibody assays (4). That study showed a seroconversion rate ranging from 66.2% to 92.5% after first-dose vaccination, consistent with the rates in previous studies (5, 6). The five assays used in the study showed strong agreement and correlation with each other, but also some discrepancies. Therefore, we emphasized the importance of understanding the differences in the detailed detection principles of anti-SARS-CoV-2 immunoassays according to the various detection reagents and cutoff values (4). Furthermore, it has been reported that the AZ vaccine raises greater concerns about adverse effects compared to other vaccines (7, 8). In-depth analyses of the relationship between serological responses and the severity of symptoms associated with AZ vaccination or with patient groups prone to adverse effects are necessary.

Therefore, in this study, following the previous study that analyzed antibodies after the first AZ vaccination, serologic responses after the second vaccination were determined using five semiquantitative immunoassays, including surrogate virus neutralization tests, among health care workers. In particular, the fluctuation of antibody titers between the first and second vaccinations was more intensively analyzed according to the type of assay. Furthermore, the relevance of symptom severity after the second vaccination and the changes in symptoms compared to the first vaccination with the serologic responses were analyzed. Moreover, the agreement and correlation of the results of the included SARS-CoV-2 antibody assays were also investigated to provide useful information about the assays available in laboratory settings.

MATERIALS AND METHODS

Study population and sample collection. A total of 218 health care workers from two university hospitals (Hallym University Dongtan Sacred Heart Hospital and Hallym University Kangnam Sacred Heart Hospital) were enrolled in this study. All participants were Asian and >20 years old. They received the first dose of the AZ vaccine between 4 and 12 March 2021 and the second dose between 20 May and 15 June 2021. Serum samples were obtained from the participants to measure the presence of SARS-CoV-2 antibodies at baseline. The second sampling was performed between 11 and 28 days after the first vaccination to observe the serological response. The third sampling was executed between 10 and 38 days after the second dose, corresponding to 101 to 117 days after the first vaccination. After the second sampling, three health care workers resigned from their job, and two workers did not receive the second dose and were thus excluded. Four participants who did not submit samples and one worker who received the Pfizer-BioNTech vaccine were also excluded. Finally, 218 samples were collected, aliquoted, and stored at −70°C until further use. The results for the baseline (n = 228) and second samples (n = 228) used in our previous study (4) were deposited in a public database (Harvard Dataverse) (9) and extracted for this study.

This study was approved by the Institutional Review Board of Hallym University Kangnam Sacred Heart Hospital (HKS 2021-02-030-003) and the Institutional Review Board of Hallym University Dongtan Sacred Heart Hospital (HDT 2021-02-007). Informed consent was obtained from all participants.

Questionnaire on adverse reactions after AZ vaccination. All workers received the questionnaire on adverse reactions after the second dose of the AZ vaccine. The questionnaire comprised five questions regarding the presence, severity, and duration of adverse reactions after the second AZ vaccination and the use of antipyretic drugs. Differences in the severity of adverse reactions between the first and second vaccinations were also included.

SARS-CoV-2 antibody assays. Serum samples were assessed using the following five SARS-CoV-2 antibody assays: (i) Elecsys anti-SARS-CoV-2 S total antibody assay on the Cobas e801 platform (Roche Diagnostics, Mannheim, Germany); (ii) SARS-CoV-2 IgG II Quant on the Alinity i platform (Abbott Laboratories Abbott Park, IL, USA); (iii) SARS-CoV-2 IgG assay on the Atellica platform (Siemens, Munich, Germany); (iv) STANDARD E SARS-CoV-2 neutralizing antibody (nAb) enzyme-linked immunosorbent assay (ELISA) kit (SD Biosensor, Suwon, South Korea); and (v) cPass SARS-CoV-2 neutralization antibody detection kit (GenScript, NJ, USA). SD Biosensor ELISA and GenScript ELISA were conducted using the Epoch microplate spectrophotometer (BioTek Instruments, Winooski, VT, USA) and ELx50 filter microplate washer (BioTek Instruments), similar to a previous study (4). Briefly, both the GenScript cPass SARS-CoV-2 neutralization antibody detection kit and the SD Biosensor STANDARD E SARS-CoV-2 nAb ELISA kit are surrogate virus neutralization tests. The SD Biosensor STANDARD E SARS-CoV-2 nAb ELISA kit comprises the V1 and V2 assays. The V1 assay was developed for the receptor-binding domain (RBD) of the Wuhan/UK variant and the V2 assay for the RBD of the South Africa/Brazil variant. At least one positive result in the V1 or V2 assay was designated a positive result for SARS-CoV-2 neutralizing antibody using the SD Biosensor assay. The detection principle, instrument, targeting antibody, utilized reagents, sample volume, cutoff value, and time to the first result of each assay are listed in Table 1. All experiments were conducted according to the manufacturers' instructions.

TABLE 1 Characteristics of the five SARS-CoV-2 antibody assays[a]

Variable	Roche_total antibody	Abbott_IgG	Siemens_IgG	SD biosensor_nAb[b]	GenScript_nAb
Product name	Elecsys Anti-SARS-CoV-2 S	SARS-CoV-2 IgG II Quant	SARS-CoV-2 IgG	STANDARD E SARS-CoV-2 nAb ELISA	cPass SARS-CoV-2 neutralization antibody detection kit
Analyzer	Elecsys Cobas e801	Alinity i	Atellica IM	ELISA	ELISA
Principle	ECLIA (double-antigen sandwich principle)	CMIA	CLIA	ELISA, sVNT	Competitive ELISA, sVNT
Target antibody	Anti-RBD, total	Anti-RBD, IgG	Anti-RBD, IgG	RBD binding nAb	RBD binding nAb
Reagent antigen(s) used	1. Biotinylated RBD 2. RBD labeled with a ruthenium complex	RBD coated microparticle	RBD coated microparticle	1. HRP-labeled RBD 2. ACE2	1. HRP-labeled RBD 2. ACE2 coated in ELISA plate
Sample type	Serum, plasma	Serum, plasma	Serum, plasma	Serum, plasma	Serum, plasma
Sample vol	12 μl	25 μl	40 μl	60 μl $\times$ 2	10 μl
Cutoff value (unit)	0.8 (U/ml)	50 (AU/ml)	1.0 index	30 (%, PI)	30 (%, PI)
Time to first result (min)	18	29	15	95	80

[a]ECLIA, electrochemiluminescence immunoassay; CMIA, chemiluminescence microparticle immunoassay; CLIA, chemiluminescence immunoassay; ELISA, enzyme-linked immunosorbent assay; sVNT, surrogate virus neutralization test; nAb, neutralizing antibody; HRP, horseradish peroxidase; RBD, receptor-binding domain; AU, arbitrary unit; PI, percent inhibition.
[b]SD Biosensor is composed of the V1 and V2 assays. The SD Biosensor V1 assay measures neutralization antibody against the Wuhan/UK variant. The SD Biosensor V2 assay measures neutralization antibody against the South Africa/Brazil variant.

Statistical analysis. Positive responses were counted using different subgroups based on the participants' characteristics. The chi-square test, Mann-Whitney *U* test, and Kruskal-Wallis test were applied to assess comparisons of nominal and continuous variables. Positive, negative, and total agreements between assays were examined using Cohen's kappa statistics, using the following categories: poor (below 0.00), slight (0.00 to 0.20), fair (0.21 to 0.40), moderate (0.41 to 0.60), substantial (0.61 to 0.80), and almost perfect (0.81 to 1.00). Spearman's rank correlation coefficients for the correlations among the five SARS-CoV-2 antibody assays were calculated and presented in correlation graphs. They were interpreted as negligible (<0.1), weak (0.1 to 0.39), moderate (0.40 to 0.69), strong (0.70 to 0.89), or very strong (≥ 0.9). Statistical analysis was conducted using Analyse-it Method Evaluation Edition software version 2.26 (Analyse-it Software Ltd., Leeds, UK) and MedCalc software version 19.8 (MedCalc Software Ltd., Ostend, Belgium).

Data availability. The data from this study and our previous study (4) were deposited at https://dataverse.harvard.edu/ (9).

RESULTS

Characteristics of participants and samples. A total of 218 serum samples from participants who received the second vaccination were collected. The participants' demographic data and serological positivity are shown in Table 2. The median age of the participants was 34.0 years (first to third quartile range, 27.0 to 44.0 years). The median number of days elapsed after the second vaccination until sampling occurred was 29.0 days, and the first to third quartile range was 26.0 to 32.0 days. This corresponded to a median number of days before sampling after the first vaccination of 107.0 days, with a range of 101.0 to 117.0 days. In our cohort, nurses, laboratory technicians, and doctors accounted for 66.5%, 26.1%, and 6.4% of the participants, respectively. About half of the participants experienced no adverse reactions after the second vaccination (n = 108, 49.5%), which was in contrast with the findings of our previous study that most participants experienced adverse reactions after the first vaccination (n = 220, 96.5%) (4). Among the participants with adverse reactions after the second dose, most experienced mild symptoms (n = 108, 98.2%) that had a duration of less than 1 day (n = 55, 53.9%), which was also in contrast with the finding that after the first dose, many participants experienced severe symptoms (n = 68, 30.9%) for which the duration was more than 2 days (n = 161, 73.2%). Most participants (89.9% for participants with adverse reactions and 89.8% for participants without prophylactic antipyretics) experienced less severe adverse reactions after the second dose compared to those after the first dose. Antipyretics were administered to 47.2% of participants after the second dose of vaccination, representing a decrease compared to the 89.9% of participants who received antipyretics after the first vaccination. Similar to that after the first vaccination, after the second vaccination, all participants were given two Tylenol tablets and instructed to take them if adverse reactions occurred. Some participants took them prophylactically before the adverse reactions occurred, and they were analyzed separately.

Positivity of SARS-CoV-2 antibody assays after vaccination. The overall positive rates for SARS-CoV-2 antibody before vaccination and after the first and second vaccine doses are summarized in Table 2. The positive rates after the second vaccination for all assays were increased (100.0% for Roche, 100.0% for Abbott IgG, 98.2% for Siemens, 100.0% for SD Biosensor, and 98.2% for GenScript assay) compared to the rates after the first vaccination. A total of six samples showed discrepant results among the SARS-CoV-2 antibody assays (2 samples had negative results for both Abbott IgG and GenScript nAb, 2 samples only for Abbott IgG, and 2 samples only for GenScript nAb), all of which had concentrations near the cutoff of Siemens IgG (index, 0.76 to 1.2). The SD Biosensor V2 assay, targeting antibodies to the South Africa/Brazil variant of SARS-CoV-2, as well as the SD Biosensor V1 assay, targeting antibodies to the original Wuhan SARS-CoV-2 and the UK variant, revealed 100.0% positivity. The presence and duration of adverse reactions after vaccination were not significantly associated with the positivity rates of SARS-CoV-2 antibody assays, in contrast with the results after the first vaccination.

TABLE 2 Positivity rates of SARS-CoV-2 antibody assays after a second dose of AstraZeneca vaccine according to the characteristics of the participants

Characteristic	*n*	Data for:[a] Roche	Abbott IgG	Siemens Rate	Siemens *P* value	SD Biosensor	GenScript Rate	GenScript *P* value
Positivity rate								
Before vaccination	228	0 (0.0)	1 (0.4)	0 (0.0)		2 (0.9)	0 (0.0)	
After first vaccination	228	193 (84.6)	211 (92.5)	172 (75.4)		206 (90.7)	151 (66.2)	
After second vaccination	218	218 (100.0)	218 (100.0)	214 (98.2)		218 (100.0)	214 (98.2)	
Sex					0.601			0.386
Male	34	34 (100.0)	34 (100.0)	33 (97.1)		34 (100.0)	34 (100.0)	
Female	184	184 (100.0)	184 (100.0)	181 (98.4)		184 (100.0)	180 (97.8)	
Age					0.494			0.869
21–30	95	95 (100.0)	95 (100.0)	94 (98.9)		95 (100.0)	94 (98.9)	
31–40	48	48 (100.0)	48 (100.0)	46 (95.8)		48 (100.0)	47 (97.9)	
41–50	44	44 (100.0)	44 (100.0)	43 (97.7)		44 (100.0)	43 (97.7)	
51–60	31	31 (100.0)	31 (100.0)	31 (100.0)		31 (100.0)	30 (96.8)	
Occupation					0.909			0.682
Doctor	14	14 (100.0)	14 (100.0)	14 (100.0)		14 (100.0)	14 (100.0)	
Nurse in operating room	3	3 (100.0)	3 (100.0)	3 (100.0)		3 (100.0)	3 (100.0)	
Nurse in emergency room	31	31 (100.0)	31 (100.0)	31 (100.0)		31 (100.0)	31 (100.0)	
Nurse in intensive care unit	52	52 (100.0)	52 (100.0)	50 (96.2)		52 (100.0)	50 (96.2)	
Nurse in general ward	59	59 (100.0)	59 (100.0)	58 (98.3)		59 (100.0)	57 (96.6)	
Laboratory technician	57	57 (100.0)	57 (100.0)	56 (98.2)		57 (100.0)	57 (100.0)	
Other	2	2 (100.0)	2 (100.0)	2 (100.0)		2 (100.0)	2 (100.0)	
Hospital					0.331			0.331
Dongtan	177	177 (100.0)	177 (100.0)	173 (97.7)		177 (100.0)	173 (97.7)	
Kangnam	41	41 (100.0)	41 (100.0)	41 (100.0)		41 (100.0)	41 (100.0)	
Adverse reactions after second vaccination					0.318			0.939
Absent without antipyretics	80	80 (100.0)	80 (100.0)	76 (95.0)		80 (100.0)	78 (97.5)	
Absent with prophylactic antipyretics	28	28 (100.0)	28 (100.0)	28 (100.0)		28 (100.0)	28 (100.0)	
Mild without antipyretics	34	34 (100.0)	34 (100.0)	34 (100.0)		34 (100.0)	34 (100.0)	
Mild with prophylactic antipyretics	31	31 (100.0)	31 (100.0)	31 (100.0)		31 (100.0)	30 (96.8)	
Mild with antipyretics due to symptoms	43	43 (100.0)	43 (100.0)	43 (100.0)		43 (100.0)	42 (97.7)	
Severe without antipyretics	1	1 (100.0)	1 (100.0)	1 (100.0)		1 (100.0)	1 (100.0)	
Severe with prophylactic antipyretics	1	1 (100.0)	1 (100.0)	1 (100.0)		1 (100.0)	1 (100.0)	
Duration of adverse reactions after second vaccination								0.650
<1 day	55	55 (100.0)	55 (100.0)	55 (100.0)		55 (100.0)	54 (98.2)	
2 to 3 days	39	39 (100.0)	39 (100.0)	39 (100.0)		39 (100.0)	39 (100.0)	
>4 days	8	8 (100.0)	8 (100.0)	8 (100.0)		8 (100.0)	8 (100.0)	
Severity of adverse reaction compared to that of first vaccination					0.923			0.923
Less	195	195 (100.0)	195 (100.0)	191 (97.9)		195 (100.0)	191 (97.9)	
Similar	14	14 (100.0)	14 (100.0)	14 (100.0)		14 (100.0)	14 (100.0)	
More	8	8 (100.0)	8 (100.0)	8 (100.0)		8 (100.0)	8 (100.0)	
Antipyretics after second vaccination					0.161			0.964
Taken with symptoms	43	43 (100.0)	43 (100.0)	43 (100.0)		43 (100.0)	42 (97.7)	
Prophylactically taken	60	60 (100.0)	60 (100.0)	60 (100.0)		60 (100.0)	59 (98.3)	
Not taken	115	115 (100.0)	115 (100.0)	111 (96.5)		115 (100.0)	113 (98.3)	

[a]All positivity rates are expressed as *n* (%). *P* values for the Roche total, Abbott IgG, and SD Biosensor nAb assays could not be calculated because of 100.0% positivity.

Semiquantitative antibody titers of SARS-CoV-2 antibody assays between the first and second vaccination. After the second vaccination, the semiquantitative titers increased significantly for all assays ($P < 0.001$) (Fig. 1 and Table 3). Figure 1 depicts the results of the SARS-CoV-2 antibody assays before and after the first and second vaccination using box and whisker plots. This figure includes data for all participants, regardless of increased or decreased antibody titers. The median values of the Roche, Abbott IgG, Siemens IgG, SD Biosensor V1, SD Biosensor V2, and GenScript assay results in the samples after the second dose were 830.0 U/ml, 1,003.7 AU/ml, 10.8 index, 99.5%, 97.4%, and 88.0%, respectively, which showed that the second dose of vaccination led to a significant increase of 106.4-fold for Roche total antibody, 3.6-fold for

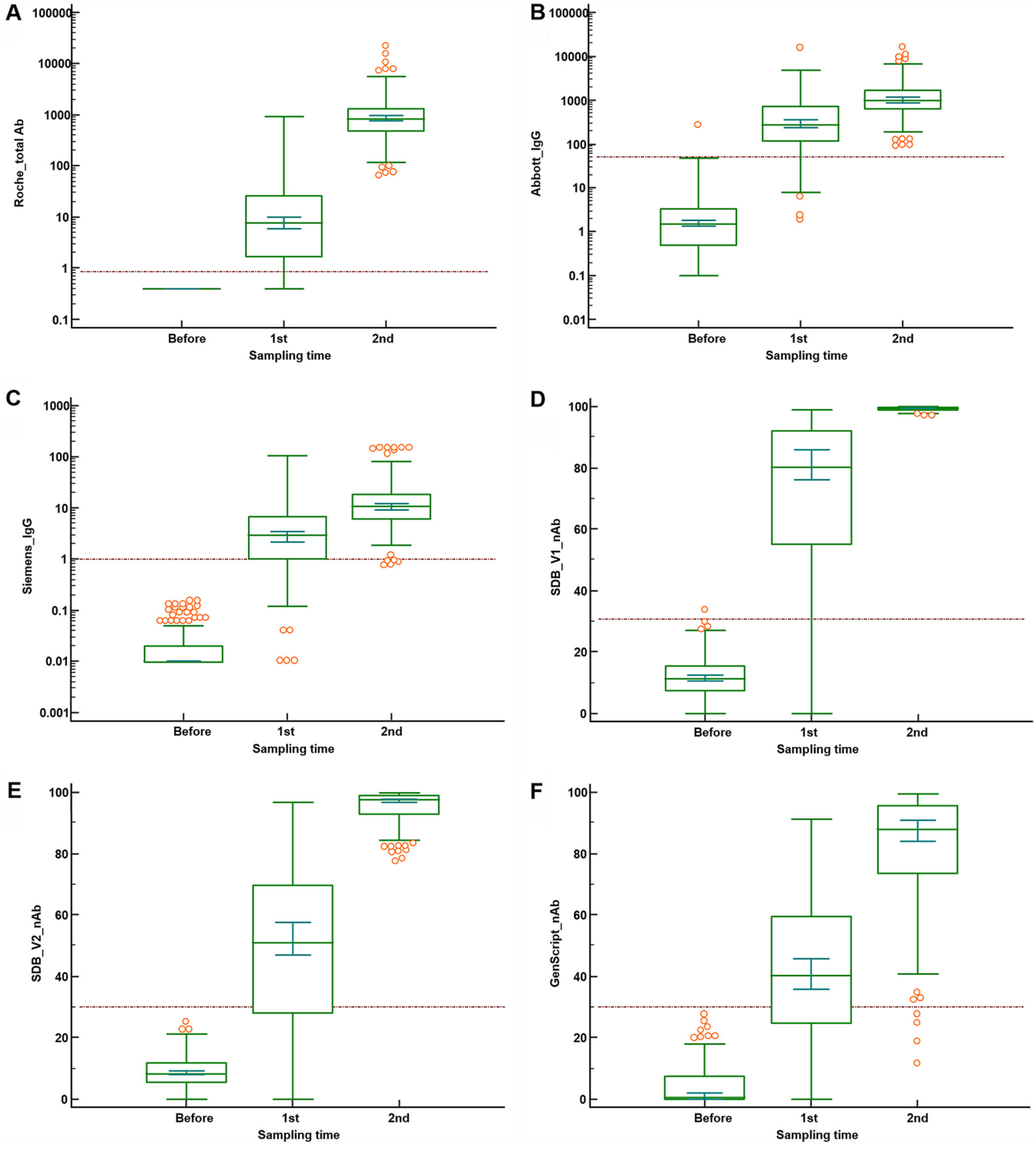

FIG 1 Quantitative serological responses before and after the first and second doses of the AstraZeneca vaccine according to the Roche total Ab (A), Abbott IgG (B), Siemens IgG (C), SD Biosensor V1 neutralizing antibody (D), SD Biosensor V2 neutralizing antibody (E), and GenScript neutralizing antibody (F) assays. *P* values were calculated using the Kruskal-Wallis test for the quantitative differences between before and after the first and second vaccinations. The differences among the results at baseline and after the first and second vaccinations for all included assays were significant ($P < 0.001$). The cutoff for each assay is shown as a dashed line.

Abbott IgG, 3.6-fold for Siemens, 1.2-fold for SD Biosensor V1 neutralizing antibody, 1.9-fold for SD Biosensor V2 neutralizing antibody, and 2.2-fold for GenScript neutralizing antibody compared to the first dose (Table 3). More than 90% of participants showed elevated antibody titers with Roche (99.1%), SD Biosensor V1 (99.1%), SD

TABLE 3 Quantitative serological responses after the first and second dose of AstraZeneca vaccine according to the changes in antibody titer[a]

Change in antibody titer by assay	*n*	Antibody titer after the first vaccination	Antibody titer after the second vaccination	Increase in titer (fold change)	*P* value
Roche total antibody (U/ml)					
Total	218	7.8 (1.7–25.6)	830.0 (484.0–1,289.4)	106.4	<0.001
Increase	216	7.6 (1.7–24.2)	837.0 (489.9–1,291.9)		<0.001
Decrease	2	808.0 (703.0–913.0)	361.5 (311.0–412.0)		0.333
Abbott IgG (AU/ml)					
Total	218	278.4 (115.3–716.0)	1,003.7 (629.1–1,677.8)	3.6	<0.001
Increase	184	240.8 (93.4–484.7)	1,156.4 (709.2–1,729.5)		<0.001
Decrease	34	910.0 (627.9–1371.2)	510.7 (323.5–949.1)		0.008
Siemens IgG (index)					
Total	218	3.0 (1.0–6.7)	10.8 (6.2–18.1)	3.6	<0.001
Increase	188	2.3 (0.8–5.6)	11.7 (7.4–18.7)		<0.001
Decrease	30	9.8 (5.0–15.4)	4.3 (2.6–6.3)		0.005
SD Biosensor V1 nAb (%)					
Total	218	80.3 (54.8–91.6)	99.5 (98.9–99.6)	1.24	<0.001
Increase	216	80.3 (54.7–91.6)	99.5 (98.9–99.6)		<0.001
Decrease	2	85.9 (78.2–93.7)	83.9 (77.3–90.6)		0.667
SD Biosensor V2 nAb (%)					
Total	218	50.4 (28.0–69.5)	97.4 (92.9–99.0)	1.93	<0.001
Increase	216	50.4 (27.8–69.4)	97.4 (93.0–99.0)		<0.001
Decrease	2	64.6 (47.4–81.9)	53.4 (43.3–63.4)		0.667
GenScript nAb (%)					
Total	218	40.3 (24.6–59.1)	88.0 (73.4–95.6)	2.18	<0.001
Increase	203	38.8 (24.1–58.3)	90.1 (77.0–95.8)		<0.001
Decrease	15	57.3 (51.4–77.4)	47.8 (35.9–65.5)		0.174

[a]Data are expressed as median (first to third quartile).

Biosensor V2 (99.1%), and GenScript (93.1%) after the second dose. Meanwhile, more than 10% of participants showed lowered antibody titers with Abbott IgG (n = 34, 15.6%) and Siemens IgG (n = 30, 13.8%) after the second dose compared to the results after the first dose. We classified the participants into two subgroups: the increased antibody titer group and the decreased antibody titer group. The median quantitative values of the two groups are presented in Table 3. The median antibody titer after the first dose in the decreased antibody titer group was significantly higher than that after the first dose in the increased antibody titer group ($P = 0.015$ for the Roche, $P < 0.001$ for the Abbott IgG, $P < 0.001$ for the Siemens IgG). In fact, their median titer after the first dose in the decreased antibody titer group is within the quartiles of those after the second dose in the increased titer group, which means that these participants had a significantly increased antibody titer only after the first dose. Twenty-six participants showed a decreased IgG antibody titer after the second dose using both the Abbott IgG and Siemens IgG assays but increased Roche total antibody titers, compared to those after the first dose.

Agreement and correlation between SARS-CoV-2 assays. The agreement rates between the results obtained from the five assays are presented in Table 4. Data on 674 samples from before and after the first and second vaccinations were included for these analyses. The total agreement rates ranged from 90.3% (95% confidence interval [CI] = 87.8% to 92.5%) to 98.4% (95% CI = 97.1% to 99.1%). Consistent with the results after the first vaccination, the rate between the Abbott and SD Biosensor showed the highest agreement. There were also no significant differences in agreements between the neutralizing and non-neutralizing antibody assays. There was almost perfect agreement among all the assays based on kappa values ranging from 0.80 to 0.96. The Abbott and SD Biosensor showed the highest kappa value (0.96; 95% CI = 0.94 to 0.99) among the assays. Conversely, correlations among the assays were somewhat different according to the type of antibody (Table 5). The Abbott IgG and Siemens IgG showed the highest correlation (rho value for correlation, 0.973) among the assays. Correlation

TABLE 4 Agreement rates between the five SARS-CoV-2 assays[a]

Compared assays (A/B)	P/P (*n*)	P/N (*n*)	N/P (*n*)	N/N (*n*)	Positive agreement of A to B	Negative agreement of A to B	Positive agreement of B to A	Negative agreement of B to A	Total agreement	Kappa value
Roche/Abbott IgG	408	22	3	239	99.3 (97.9–99.8)	91.6 (87.5–94.6)	94.9 (92.4–96.8)	98.8 (96.4–99.7)	96.3 (94.6–97.5)	0.92 (0.89–0.95)
Roche/Siemens	381	30	5	256	98.7 (97.0–99.6)	89.5 (85.4–92.8)	92.7 (89.7–95.0)	98.1 (95.6–99.4)	94.8 (92.8–96.3)	0.89 (0.86–0.93)
Roche/SD Biosensor	407	4	20	241	95.3 (92.9–97.1)	98.4 (95.9–99.6)	99.0 (97.5–99.7)	92.3 (88.4–95.3)	96.4 (94.7–97.6)	0.92 (0.89–0.95)
Roche/GenScript	362	49	3	258	99.2 (97.6–99.8)	84.0 (79.5–88.0)	88.1 (84.5–91.0)	98.9 (96.7–99.8)	92.3 (90.0–94.1)	0.84 (0.80–0.88)
Abbott IgG/Siemens	385	45	1	241	99.7 (98.6–100.0)	75.5 (70.5–80.2)	85.2 (79.4–86.5)	99.6 (97.7–100.0)	93.2 (91.0–94.8)	0.86 (0.82–0.90)
Abbott IgG/SD Biosensor	423	7	4	238	99.1 (97.6–99.7)	97.1 (94.2–98.8)	98.4 (96.7–99.3)	98.3 (95.8–99.5)	98.4 (97.1–99.1)	0.96 (0.94–0.99)
Abbott IgG/GenScript	365	65	0	242	100.0 (99.0–100.0)	78.8 (73.8–83.3)	84.9 (81.1–88.1)	100.0 (98.5–100.0)	90.3 (87.8–92.5)	0.80 (0.76–0.85)
Siemens/SD Biosensor	385	1	42	244	90.2 (86.9–92.8)	99.6 (97.7–100.0)	99.7 (98.6–100.0)	85.3 (80.7–89.2)	93.6 (91.5–95.2)	0.87 (0.83–0.90)
Siemens/GenScript	356	30	9	277	97.5 (95.4–98.9)	90.2 (86.3–93.3)	92.2 (89.1–94.7)	96.9 (94.1–98.6)	94.2 (92.2–95.8)	0.88 (0.85–0.92)
SD Biosensor/GenScript	365	62	0	245	100.0 (99.0–100.0)	79.8 (74.9–84.2)	85.5 (81.8–88.7)	100.0 (98.5–100.0)	90.8 (88.3–92.7)	0.81 (0.77–0.86)

[a]Agreement rates are expressed as percent (95% confidence interval). N, negative; P, positive.

TABLE 5 Correlations among five SARS-CoV-2 antibody assays

Compared assays	ρ	*P* value
Roche total/Abbott IgG	0.824	<0.001
Roche total/Abbott IgG after first dose	0.808	<0.001
Roche total/Abbott IgG after second dose	0.919	<0.001
Roche total/Siemens IgG	0.829	<0.001
Roche total/Siemens IgG after first dose	0.803	<0.001
Roche total/Siemens IgG after second dose	0.933	<0.001
Roche total/SD Biosensor V1 nAb	0.899	<0.001
Roche total/SD Biosensor V1 nAb after first dose	0.781	<0.001
Roche total/SD Biosensor V1 nAb after second dose	0.568	<0.001
Roche total/GenScript nAb	0.899	<0.001
Roche total/GenScript nAb after first dose	0.803	<0.001
Roche total/GenScript nAb after second dose	0.840	<0.001
Abbott IgG/Siemens IgG	0.973	<0.001
Abbott IgG/SD Biosensor V1 nAb	0.796	<0.001
Abbott IgG/SD Biosensor V2 nAb	0.908	<0.001
Abbott IgG/GenScript nAb	0.885	<0.001
Siemens IgG/SD Biosensor V1 nAb	0.797	<0.001
Siemens IgG/SD Biosensor V2 nAb	0.911	<0.001
Siemens IgG/GenScript nAb	0.886	<0.001
SD Biosensor V1 nAb/SD Biosensor V2 nAb	0.933	<0.001
SD Biosensor V1 nAb/GenScript nAb	0.904	<0.001
SD Biosensor V2 nAb/GenScript nAb	0.932	<0.001

graphs between the Roche total antibody and the other assays, including the Abbott IgG, Siemens IgG, GenScript nAb, and SD Biosensor nAb, showed two linear correlation patterns distinguishing the results after the first vaccination from those after the second vaccination (Fig. S1). These two trend lines in Fig. S1 are derived from different correlations between samples after the first and second vaccinations. The correlation of samples after the second vaccination showed stronger correlation (rho = 0.840 to 0.933) than those after the first vaccination (rho = 0.781 to 0.808).

DISCUSSION

In this study, we investigated participants' antibody responses to the second dose of the AZ vaccine using five SARS-CoV-2 assays, composed of two assays for IgG, one assay for total antibody, and two surrogate virus-neutralizing antibody assays. The seroconversion rates after the second vaccination ranged from 98.2% to 100.0%, indicating that the second dose of vaccination led to almost 100% positivity for the SARS-CoV-2 antibody based on the five SARS-CoV-2 antibody assays. Median antibody titers in all five assays after the second dose of vaccination were found to be increased compared to those after the first dose of vaccination, but some patients showed decreased antibody titers after the second dose. Most participants experienced lessened adverse reactions after the second dose compared to the first dose.

These findings are consistent with the results of a previous report on the safety and immunogenicity of the booster dose of the ChAdOx1 nCoV-19 vaccine, in which the second vaccination led to an increase in anti-spike antibody responses as well as neutralizing antibody titers (10). A previous study on immune responses after homologous AZ vaccination demonstrated a 2.9-fold increased titer for anti-spike IgG antibody (11), which is similar to our result of 3.6-fold increased titers in Abbott IgG and Siemens IgG antibody assays. Another study (6) measured a vaccine efficacy of 81.3% (95% CI = 60.3% to 91.2%) more than 14 days after the booster dose in participants who received two standard doses with a prime-booster interval of more than 12 weeks. A study analyzing four randomized controlled trials presented a pooled efficacy of 70.4% after two-dose vaccination (12), which was lower than the seroconversion rate (98.2% to 100.0%) found in our study. The number of days elapsed before sampling, the size

of the study population, and the antibody measurement platform may influence the positivity rates.

The representative immunoassays included in this study showed almost perfect agreement and strong correlation with each other (kappa values, 0.80 to 0.96; Spearman's correlation coefficients, 0.781 to 0.973), concordant with previous studies (13, 14). However, only one correlation between the Roche total and SD Biosensor V1 assays after the second dose showed a moderate (rho = 0.568) coefficient. Although these two assays presented almost perfect agreement in the qualitative agreement analysis, the high values of nearly 100% of the SD Biosensor V1 after the second dose regardless of the titers of the Roche total (Fig. S1) may have caused the relatively decreased correlation coefficient in the quantitative analysis. After the second dose, six samples showed discrepancies among the five SARS-CoV-2 antibody assays, and the quantitative values of these samples were near the cutoff of the Siemens IgG assay (index, 0.76 to 1.2). Detecting high-affinity antibody with the Roche assay uses the double-antigen sandwich method (15–17), which in addition to the cutoff values could influence these discrepant results.

In terms of the neutralizing antibodies, a previous clinical trial showed that the response rates after the booster dose of the AZ vaccine were 100.0%, both using a microneutralization assay at day 42 (9/9) and a plaque reduction neutralization test at day 56 (10/10) (5). Consistent with this study, the results from our surrogate virus neutralization tests showed 100.0% (218/218) positivity using the SD Biosensor assay and 98.2% (214/218) positivity using the GenScript assay. The median elapsed time before sampling in our study was approximately 107 days from the first vaccination and 29 days from the second vaccination. In this study, we revealed the positivity of neutralization antibodies for longer follow-up periods in a larger study population.

Most participants (89.9%) experienced less severe adverse reactions after the second dose of vaccination compared to those after the first dose, and about half of the participants (49.5%) experienced no adverse reactions. Local and systemic adverse reactions, such as injection site pain, chills, and headache, were lessened in most participants (93.5%), demonstrating the safety and better tolerance of the booster dose (10, 18). Furthermore, there were no significant associations of adverse reactions with serologic responses after booster vaccination, in contrast to the results after the first vaccination. In other studies, postvaccination symptoms after the second dose of the BNT162b2 vaccine were not associated with the magnitude of vaccine-induced IgG antibody titers (19), consistent with our results. However, two patients with severe adverse reactions only showed seroconversion after the second vaccination. The appropriate injection of the first vaccine dose was questionable in these two cases.

Older age was reported to be related to lower seroconversion rates in some previous reports (20–22). These studies included health care workers, comprising predominantly healthy working-age adults, similar to our study. However, Eyre et al. (20) found that the 95% CIs of quantitative levels of 30, 45, and 60 years were overlapped for participants receiving the AZ vaccine without any evidence of prior infection. Singh et al. (22) enrolled 15.9% (88/552) participants aged more than 60 years. In our study, age was not associated with the positive rates of SARS-CoV-2 antibodies after either the first or second doses of vaccine in all the included assays. According to a previous clinical trial for the AZ vaccine, the median IgG responses and neutralizing antibody titers after the boost dose were similar across age groups (21), concordant with our results. Study population characteristics such as the number of included participants, their age distribution, ethnicity, and the types of vaccine received may influence these results. In particular, further studies, including sufficient numbers of patients of the age group $>$60 years, are required for demonstrating the serologic responses of these age groups.

In conclusion, the second dose of AZ vaccination induced high positivity based on five representative SARS-CoV-2 antibody assays. The median antibody titers of these assays were found to be significantly increased after the second dose of vaccination compared with those conducted after the first dose of vaccination, but the degree of

increase in antibody titers varied from assay to assay, and some participants showed decreased antibody titers. The agreement and correlation among nearly all the included assays were almost perfect and strong. However, the results should be interpreted cautiously, considering the characteristics of each assay and its cutoff values. To the best of our knowledge, this is the first report to provide reliable serological responses after the second AZ vaccination based on five representative SARS-CoV-2 antibody assays, including neutralization antibody assays. Furthermore, this study includes information about serological responses in an East Asian population. The results should facilitate precise decision-making for vaccination, give further insight into anti-SARS-CoV-2 immunoassays, and contribute to controlling the spread of SARS-CoV-2 infection.

SUPPLEMENTAL MATERIAL

Supplemental material is available online only.

SUPPLEMENTAL FILE 1, PDF file, 1.4 MB.

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