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Antibody responses after BNT162b2 vaccination in Japanese geriatric intermediate care facilities

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ABSTRACT

Background: To evaluate antibody responses against the primary series of vaccination of severe acute respiratory syndrome coronavirus-2 [SARS-CoV-2] vaccines in the staff and residents of Japanese geriatric intermediate care facilities.
Methods: All subjects (159 staff and 96 residents) received two doses of the BNT162b2 mRNA vaccine 3 weeks apart. Baseline data of subject were collected using a structured form. Serum samples were collected three times: before vaccination, 3 weeks after the first dose, and 4 weeks after the second dose, and anti-receptor binding domain of the spike protein of SARS-CoV-2 [anti-RBD] IgG was measured using two immunoassays.
Results: After the second dose, geometric mean titers [GMT] of anti-RBD with both the Abbott and Roche assay were significantly lower in residents than staff (2282 AU/mL vs. 8505 AU/mL, and 258 U/mL vs. 948 U/mL, respectively). Multivariate analysis of characteristics affecting antibody responses ($\geq$1280 AU/mL for Abbott and $>$ 210 U/mL for Roche) showed lower odds ratios [ORs] for older age (adjusted OR per 10 year increase [aOR] = 0.62, 95 % confidence interval [95 %CI]; 0.38–1.02), steroid usage (aOR = 0.09, 95 %CI; 0.01–0.60) and regular nonsteroidal anti-inflammatory drugs [NSAIDs] usage (aOR = 0.16, 95 %CI; 0.03–0.88).
Conclusions: Elderly people and steroid and NSAID users had lower antibody responses following the second vaccine dose.

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Introduction

The coronavirus disease 2019 (COVID-19) had been a pandemic and spreading around the world with unprecedented consequences for previous three years, although in May 2023, WHO declared that COVID-19 was no longer the status of a public health emergency of international concern due to getting of herd immunity by vaccination and infections and lower COVID-19 related hospitalizations and deaths [1]. In Japan, as of the first of October 2023, 33.8 million individuals were infected, with 74,694 deaths [2]. The risk factors for severe illness, including complications, intensive care unit admission and death, are reportedly old age [3–5], hypertension, [6] diabetes [7], and obesity [3,8]. Elderly residents at long-term care facilities, including geriatric intermediate care facilities, often have several of these risk factors for severe illness. Thus, cluster outbreaks and the resulting deaths have been frequently reported in such a population [9,10].

To control the COVID-19 pandemic, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines were rapidly developed, demonstrating ≥ 90 % efficacy for preventing SARS-CoV-2 infection in clinical trials [11]. In terms of post-marketing surveillance, prospective cohort studies reported the effectiveness of two vaccine doses for preventing SARS-CoV-2 infection of 85 % among health care workers [12]. The mRNA vaccine BNT162b2 (Pfizer/BioNTech, NY, USA/Mainz, Germany) was the first vaccine approved for use in Japan. From February 2021, vaccination was first provided in order of priority to health care workers, the elderly, and then to people at high risk of severe illness, as well as people who had frequent interaction with them, such as staff at long-term care facilities [13].

In a Japanese observational study among health care workers, the median titer of antibodies to the spike protein of SARS-CoV-2 was 18,836.9 AU/mL at 7 days after the second vaccine dose [14]. However, no studies have evaluated the institutionalized elderly in Japan, other than a study which reported that antibody titers after the second vaccination among hemodialysis residents was lower than among staff at nursing homes [15]. Other vaccine study, such as on herpes zoster have reported that elderly residents in long-term care facilities have lower immune responses compared to the healthy elderly population [16]. Therefore, elderly residents might not have sufficient antibody responses after SARS-CoV-2 vaccination, which should be clarified to effectively control COVID-19 outbreak at these facilities.

The present study investigated antibody responses to the SARS-CoV-2 vaccine among residents and staff at geriatric intermediate care facilities, and identified the background characteristics that influenced the antibody response. In this study, we used two immunoassays to measure the antibody to the spike protein of SARS-CoV-2 [17]. Most previous studies reported the results using only one immunoassay [12,14,15]. However, since relying on the results of only one immunoassay might lead to misclassification, we decided to use two immunoassays in order to increase the validity of the results and to provide comparability to the study results.

Methods

Study design and subjects

This prospective cohort study was conducted at nine facilities belonging to the Osaka Association of Geriatric Health Service Facilities. Residents and staff at the study facilities were included in the study when they fulfilled the following three eligibility criteria: (1) subject requested SARS-CoV-2 vaccination; (2) could be followed for 1 year; and (3) consented to participation in this study. However, people with contraindications to the SARS-CoV-2 vaccine, such as having a history of anaphylaxis to any of the vaccine components were excluded.

Vaccination

Between March 9, 2021 and July 16, 2021, all subjects received two doses of the BNT162b2 mRNA vaccine. The vaccine dose was 0.3 mL, containing 30 μg of BNT162b2. Following the package insert, the two doses were administrated intramuscularly at an interval of 3 weeks.

Data collection

At the time of study enrollment, we asked the staff to transcribe the following information from the medical records of residents on a structured form: sex, age, height, weight, underlying diseases (hypertension, allergies, heart disease, stroke, diabetes, cancer, collagen diseases, etc.) and prescription drugs (steroids, nonsteroidal anti-inflammatory drugs [NSAIDs], etc.). Similar information regarding the staff was collected using a self-administered questionnaire.

Serological measurement

Serum samples were collected at three time points: within 1 week before the first dose (S0), three weeks after the first dose (S1), and 4 weeks after the second dose (S2). Antibody titers of the anti-receptor binding domain of the spike protein of SARS-CoV-2 [anti-RBD] IgG and SARS-CoV-2 nucleocapsid protein IgG [anti-N] were measured in these serum samples. We used two methods to measure anti-N titers for evaluation of a past history of infection: Alinity I SARS-CoV-2 IgG (Abbott Laboratories, Illinois, USA) and Elecsys Anti-SARS CoV-2 (Roche Diagnostics, Basel, Switzerland). Subjects with antibody titers at or above the cut-off values (value of ≥ 1.40 for Alinity I SARS-CoV-2 IgG and value of ≥ 1.0 for Elecsys Anti-SARS CoV-2) were considered to have been previously infected with SARS-CoV-2 [18,19]. In addition, we also used two assays: AdviseDx SARS-CoV-2 IgG II (ARCHITECT) (Abbott Laboratories, [Abbott assay]) and Elecsys Anti-SARS-CoV-2 S (Roche diagnostics, [Roche assay]) for evaluation of anti-RBD titers. For the Abbott assay, the quantitative range was 0.0–40,000 AU/mL, and the cut-off value for seropositive was 50 AU/mL [20]. For the Roche assay, the quantitative range was 0.4–25,000 U/mL and the cut-off value for seropositive was 0.8 U/mL [21]. Based on the report by the US Food and Drug Administration (FDA), we considered values ≥ 1280 AU/mL for the Abbott assay and > 210 U/mL for the Roche assay as high-titers [22]. These cutoffs were used to represent the second criterion of seropositive in the present study.

Statistical analysis

To assess antibody responses, geometric mean titers (GMT), fold rise, and seropositivity rate at each time point were calculated. For data processing, titers below 0.1 AU/mL titers were treated as 0.1 AU/mL for the Abbott assay, and those below 0.4 U/mL were treated as 0.4 U/mL for the Roche assay. A stratified analysis was conducted to examine the effect of potential confounders, such as roles (staffs or residents), sex, age (10 year categories), BMI (<18.5 kg/m^2, 18.5–24.9 kg/m^2, and ≥ 25.0 kg/m^2), underlying disease, steroid usage, and NSAID usage. The significance of fold rise within a category was assessed by the Wilcoxon signed-rank test. Inter-category comparisons of GMT or fold rise were made by either the Wilcoxon rank-sum test or Kruskal-Wallis test.

Differences of characteristics and seropositively (1. package insert, 2. comparable to convalescent serum) rates between residents and staff were examined using the Fisher's exact test, Chi-square test, Mantel-extension test, or Wilcoxon rank-sum test, as appropriate.

A logistic regression model was used to evaluate the independent effects of potential confounders on seropositivity achieved at 4 weeks after the second vaccine dose. The models were constructed with 'dual seropositivity (i.e. seropositive in both assays)' as the dependent variable and the potential confounders mentioned above as explanatory variables. Since participants' ages and roles are expected to have a

strong association, we conducted multivariate analysis with the following three models. The first model included age, sex, BMI, underlying diseases, steroids and NSAIDs as explanatory variables. The second model, roles were included to replace age in the first model. The third model included both age and roles in the same model. In addition, Variance Inflation Factor (VIF) of age and roles were calculated to check the multicollinearity. If the value of VIF was less than 10, we considered the association between them as low multicollinearity [23]. Odds ratios (ORs) and 95 % confidence intervals (CIs) were used to calculate for estimating the group of lower antibody responses.

SAS version 9.4 software (SAS Institute, Cary, NC, USA) was used for all analyses. Statistical significance was set at $P < 0.05$.

Ethics statement

The present study was performed in accordance with the principles of the Declaration of Helsinki, and was approved by the Certified Review Board of Osaka City University Hospital (OCU011E; first version: March 1, 2021; second version: April 6, 2021; third version: July 7, 2021; fourth version: October 12, 2021). This study was also registered (jRCT1051200148) and published (date of first publication: March 5, 2021; date of registration of the first case: March 8, 2021) in the Japan Registry of Clinical Trials (jRCT). Before participation in the study, written informed consent was obtained from all subjects or their proxies after a thorough explanation of the study.

Results

Subjects

A total of 159 staff and 96 residents received two doses of the vaccine, although one resident left the facility before collecting the S2 blood sample. None of the subjects reported SARS-CoV-2 infection throughout the study, and anti-N titers for all subjects were below the cut-off values indicating previous infection at all time points. Table 1 shows the characteristics of the subjects. Compared with staff, the residents included more females (59 % vs. 77 %). Median age was 46 (range: 20–82) years among staff and 88 (range: 71–106) years among residents. Residents had significantly lower BMI than staff members, and 28 % of the residents were underweight (BMI < 18.0 kg/m^2), while 25 % of the staff were overweight (BMI > 25.0 kg/m^2). Residents were likely to have underlying diseases, including hypertension, heart disease, stroke, diabetes and cancer. However, allergies were more common among staff members.

Antibody responses after the first and second vaccine doses

Table 2 shows the anti-RBD titer by the Abbott assay according to roles, sex, age, BMI, underlying disease, steroid use and NSAID use. In the total cohort, GMT increased from 1.0 AU/mL (S0) to 322 AU/mL after the first dose (S1) and to 5200 AU/mL after the second dose (S2). Compared with staff, residents achieved significantly lower GMT at both S1 (735 AU/mL vs. 82 AU/mL; $P < 0.01$) and S2 (8505 AU/mL vs. 2282 AU/mL; $P < 0.01$). Residents who reached the seropositive (comparable

Table 1
Characteristics of staff and residents in the study facilities.

Characteristics		All (N = 255)		Staff (n = 159)		Residents (n = 96)		P [1]
		n	(%)	n	(%)	n	(%)	
Sex								
	Male	87	(34)	65	(41)	22	(23)	<0.001
	Female	168	(66)	94	(59)	74	(77)	
Age (years)								
	Median (range)	57	(20-106)	46	(20-82)	88	(71-106)	<0.001
	20-29	7	(3)	7	(4)	0	(0)	<0.001
	30-39	34	(13)	34	(21)	0	(0)	
	40-49	63	(25)	63	(40)	0	(0)	
	50-59	35	(14)	35	(22)	0	(0)	
	60-69	14	(5)	14	(9)	0	(0)	
	70-79	19	(7)	5	(3)	14	(15)	
	80-89	41	(16)	1	(1)	40	(42)	
	≥90	42	(16)	0	(0)	42	(44)	
BMI (kg/m^2)								
	Median (range)	21.3	(13.1-38.6)	22.5	(14.8-38.6)	20.2	(13.1-31.3)	<0.001
	Underweight (<18.5)	36	(14)	10	(6)	26	(28)	<0.001
	Normal (18.5-24.9)	167	(67)	107	(68)	60	(65)	
	Overweight (≥25)	47	(19)	40	(25)	7	(8)	
	Data missing	5		2		3		
Underlying disease [2]								
	No	101	(40)	97	(61)	4	(4)	<0.001
	Yes	154	(60)	62	(39)	92	(96)	
	Hypertension	73	(29)	18	(11)	55	(57)	<0.001
	Allergy	68	(27)	61	(38)	7	(7)	<0.001
	Heart disease	27	(11)	3	(2)	24	(25)	<0.001
	Stroke	29	(11)	2	(1)	27	(28)	<0.001
	Diabetes	22	(9)	4	(3)	18	(19)	<0.001
	Cancer	17	(7)	4	(3)	13	(14)	<0.001
	Collagen diseases	4	(2)	3	(2)	1	(1)	1.00
Prescription drugs								
	Steroids	10	(4)	4	(3)	6	(6)	0.18
	NSAIDs	16	(6)	10	(6)	6	(6)	0.99

BMI: body mass index, NSAIDs: nonsteroidal anti-inflammatory drugs.

[1] P-values were calculated using the Fisher's exact test or Chi-square test (variables with two categories), Mantel-extension test (variables with three or more categories), or Wilcoxon rank sum test (continuous variables).

[2] Some people who were in "Yes" (154 people) had two or more underlying diseases listed in Table1. Thus, the total number of people who have each underlying disease shown in Table1 (254 people) did not match the number of people whose "underlying disease" is "Yes".

Table 2
Antibody responses to SARS-CoV-2 vaccination according to selected characteristics (measured by the Abbott assay).

Characteristics	N	GMT (AU/mL)[1]			Fold rise[1]				Seropositivity rate at S1		Seropositivity rate at S2	
		S0	S1	S2	S1/S0	(P)	S2/S1	(P)	≥50 AU/mL (%)[2] (Package insert)	≥1280 AU/mL (%)[2] (Comparable to convalescent sera)	≥50 AU/mL (%)[2] (Package insert)	≥1280 AU/mL (%)[2] (Comparable to convalescent sera)
Total	255	1.0	322	5200	332	(<0.01)	16	(<0.01)	87	19	99.6	87
Roles												
Staff	159	0.9	735	8505	817	(<0.01)	12	(<0.01)	98	28	100	98
Residents	96	1.1	82	2282	74	(<0.01)	28	(<0.01)	68	4	99	67
		P = 0.69	P<0.01	P<0.01	P<0.01		P<0.01		P<0.01	P<0.01	P = 0.37	P<0.01
Sex												
Male	87	1.1	378	5163	339	(<0.01)	14	(<0.01)	87	21	99	86
Female	168	0.9	296	5219	328	(<0.01)	17	(<0.01)	86	18	100	87
		P = 0.39	P = 0.35	P = 0.80	P = 0.68		P = 0.13		P = 0.82	P = 0.67	P = 0.34	P = 0.89
Age (years)												
20-29	7	1.5	1935	13290	1283	(0.02)	7	(<0.01)	100	71	100	100
30-39	34	1.0	1129	12166	1110	(<0.01)	11	(<0.01)	97	56	100	100
40-49	63	0.9	629	8137	736	(<0.01)	13	(<0.01)	98	19	100	98
50-59	35	1.0	673	7797	706	(<0.01)	12	(<0.01)	100	20	100	97
60-69	14	0.6	557	5822	939	(<0.01)	10	(<0.01)	100	14	100	100
70-79	19	0.9	308	4845	348	(<0.01)	16	(<0.01)	95	0	100	95
80-89	41	0.9	64	1920	69	(<0.01)	30	(<0.01)	58	10	98	58
≥90	42	1.4	70	2091	51	(<0.01)	30	(<0.01)	67	0	100	67
		P = 0.85	P<0.01	P<0.01	P<0.01		P<0.01		P<0.01	P<0.01	P = 0.31	P<0.01
BMI (kg/m^2)												
<18.5	36	0.7	150	3049	231	(<0.01)	20	(<0.01)	81	11	97	80
18.5-24.9	167	1.1	327	5397	311	(<0.01)	17	(<0.01)	86	19	100	86
≥25.0	47	1.0	553	7204	579	(<0.01)	13	(<0.01)	91	30	100	91
		P = 0.35	P<0.01	P<0.01	P = 0.28		P = 0.07		P = 0.15	P = 0.03	P = 0.07	P = 0.14
Underlying disease												
No	101	1.0	806	8612	841	(<0.01)	11	(<0.01)	99	32	100	98
Yes	154	1.0	176	3726	180	(<0.01)	21	(<0.01)	79	11	99	79
		P = 0.71	P<0.01	P<0.01	P<0.01		P<0.01		P<0.01	P<0.01	P = 1.00	P<0.01
Steroids												
No	245	1.0	363	5497	374	(<0.01)	15	(<0.01)	88	20	100	88
Yes	10	0.9	16	1339	18	(0.02)	82	(<0.01)	50	0	90	50
		P = 0.79	P<0.01	P<0.01	P<0.01		P<0.01		P<0.01	P = 0.22	P = 0.04	P<0.01
NSAIDs												
No	239	1.0	333	5345	344	(<0.01)	16	(<0.01)	87	20	99.6	87
Yes	16	1.0	190	3454	194	(<0.01)	18	(<0.01)	75	13	100	75
		P = 0.94	P = 0.26	P = 0.07	P = 0.45		P = 0.65		P = 0.24	P = 0.74	P = 1.00	P = 0.24

GMT: geometric mean titer, S0: within 1 week before the first vaccination, S1: 3 weeks after the first vaccination, S2: 4 weeks after the second vaccination, BMI: body mass index, NSAIDs: nonsteroidal anti-inflammatory drugs.

[1] P-values were calculated using the Wilcoxon rank sum test or Kruskal-Wallis test for inter-category comparisons, and Wilcoxon signed-rank test for intra-category comparisons.

[2] P-values were calculated using the Fisher's exact test or Chi-square test (variables with two categories) or Mantel-extension test (variables with three or more categories).

to convalescent serum) of antibody titer also exhibited lower than staff at S1 (4 % vs. 28 %) and S2 (67 %vs. 98 %). No sex-related differences in GMT, fold rise, seropositivity rate were observed. Older people had lower GMTs and seropositivity rate at both S1 and S2 (trend $P < 0.01$). The fold rise of S1/S0 (i.e., antibody response to the first dose) decreased gradually with older age, although that of S2/S1 (i.e., antibody response to the second dose) increased with older age (trend $P < 0.01$). GMT at S1 and S2 were significantly higher in the group with greater BMI (trend $P < 0.01$). Subjects with underlying diseases and steroid users also showed lower antibody responses after both the first and second vaccine doses compared to those without underlying diseases and steroid usage.

A similar trend in antibody responses was observed with the Roche assay (Table 3). Residents, older subjects, lower BMI, subjects with underlying diseases, and steroid users had lower antibody responses after both the first and second vaccine doses.

Association between the characteristics of subjects and seropositivity rate at 4 weeks after the second dose

After consideration of the effects of potential confounders, people using steroids and NSAIDs had significantly decreased ORs for seropositivity rate (comparable to convalescent serum) at S2 (Table 4). Moreover, we checked multicollinearity between age and role by calculating VIF. Since the VIF of age was 5.21 and that of role was 5.01, we decided model 3 as our final model. The adjusted OR (aOR) of steroid usage was 0.09 (95 %CI: 0.01–0.60), and that of NSAID usage was 0.16 (95 %CI: 0.03–0.88). Older age was also associated with a lower OR for achieving seropositivity (comparable to convalescent sera) after the

Table 3
Antibody responses to the SARS-CoV-2 vaccine according to selected characteristics (measured by the Roche assay).

Characteristics	N	GMT (U/mL)[1]			Fold rise[1]				Seropositivity rate at S1		Seropositivity rate at S2	
		S0	S1	S2	S1/S0	(P)	S2/S1	(P)	≥0.8 U/mL (%) [2](Package insert)	>210 U/mL (%) [2](Comparable to convalescent sera)	≥0.8 U/mL (%) [2](Package insert)	>210 U/mL (%) [2](Comparable to convalescent sera)
Total	255	0.4	13	583	32	(<0.01)	45	(<0.01)	82	5	100	83
Roles												
Staff	159	0.4	38	948	94	(<0.01)	25	(<0.01)	99	8	100	97
Residents	96	0.4	2	258	5	(<0.01)	121	(<0.01)	53	2	100	60
		P = 0.44	P<0.01	P<0.01	P<0.01		P<0.01		P<0.01	P = 0.06		P<0.01
Sex												
Male	87	0.4	19	642	47	(<0.01)	34	(<0.01)	87	5	100	85
Female	168	0.4	10	554	26	(<0.01)	52	(<0.01)	79	6	100	83
		P = 0.17	P = 0.03	P = 0.25	P = 0.04		P = 0.02		P = 0.09	P = 0.78		P = 0.62
Age (years)												
20-29	7	0.4	83	1162	207	(0.02)	14	(0.02)	100	14	100	100
30-39	34	0.4	65	1351	162	(<0.01)	21	(<0.01)	97	12	100	97
40-49	63	0.4	34	972	83	(<0.01)	29	(<0.01)	98	5	100	98
50-59	35	0.4	33	837	82	(<0.01)	26	(<0.01)	100	6	100	97
60-69	14	0.4	22	533	56	(<0.01)	24	(<0.01)	100	7	100	93
70-79	19	0.4	9	489	21	(<0.01)	57	(<0.01)	89	5	100	79
80-89	41	0.4	2	229	4	(<0.01)	128	(<0.01)	49	2	100	58
≥90	42	0.4	2	245	5	(<0.01)	134	(<0.01)	48	2	100	60
		P = 0.88	P<0.01	P<0.01	P<0.01		P<0.01		P<0.01	P = 0.07		P<0.01
BMI (kg/m^2)												
<18.5	36	0.4	4	313	11	(<0.01)	66	(<0.01)	67	0	100	71
18.5-24.9	167	0.4	13	602	32	(<0.01)	47	(<0.01)	81	5	100	82
≥25.0	47	0.4	31	869	78	(<0.01)	28	(<0.01)	91	11	100	96
		P = 0.78	P<0.01	P<0.01	P<0.01		P = 0.03		P<0.01	P = 0.04		P<0.01
Underlying disease												
No	101	0.4	40	1055	99	(<0.01)	26	(<0.01)	98	8	100	98
Yes	154	0.4	6	394	15	(<0.01)	64	(<0.01)	71	4	100	74
		P = 0.22	P<0.01	P<0.01	P<0.01		P<0.01		P<0.01	P = 0.17		P<0.01
Steroids												
No	245	0.4	14	636	35	(<0.01)	45	(<0.01)	83	6	100	85
Yes	10	0.4	1	68	3	(0.13)	60	(<0.01)	40	0	100	40
		P = 0.86	P<0.01	P<0.01	P<0.01		P = 0.51		P<0.01	P = 1.00		P<0.01
NSAIDs												
No	239	0.4	13	591	32	(<0.01)	45	(<0.01)	82	6	100	84
Yes	16	0.4	11	470	26	(<0.01)	44	(<0.01)	81	0	100	81
		P = 0.81	P = 0.85	P = 0.31	P = 0.85		P = 0.72		P = 1.00	P = 1.00		P = 0.73

GMT: geometric mean titer, S0: within 1 week before the first vaccination, S1: 3 weeks after the first vaccination, S2: 4 weeks after the second vaccination, BMI: body mass index, NSAIDs: nonsteroidal anti-inflammatory drugs.

[1] P-values were calculated using the Wilcoxon rank sum test or Kruskal-Wallis test for inter-category comparisons, and Wilcoxon signed-rank test for intra-category comparisons.

[2] P-values were calculated using the Fisher's exact test or Chi-square test (variables with two categories) or Mantel-extension test (variables with three or more categories).

second dose with marginal significance (aOR per 10 year increased = 0.62, 95 %CI: 0.38–1.02). However, the decreasing OR of residents did not reach statistical significance when mutually adjusted for the effect of age in multivariate analysis (model 3 in Table 4). There was no significant association between underlying diseases and seropositivity rate. Even with separate examinations for each underlying disease, no significant association was seen for any of the underlying diseases (Supplemental Table).

Discussion

This study shows that residents achieved lower antibody responses than staff even after receiving two doses of SARS-CoV-2 vaccination, and that the negative association could be mainly explained by the effect of older age. Moreover, our final model (model 3), which considering multicollinearity of variables and included both age and role, showed that people using steroids and NSAIDs also achieved a lower seropositivity rate at 4 weeks after the second vaccination.

In the result of model 3, we showed that higher age remained to be associated with a lower seropositivity rate. Thus, we concluded that age was a stronger predictive factor of seropositivity than role (staff or residents). Lower antibody responses among subjects > 80 years [24] and elderly residents without a history of COVID-19 infection [25] have been previously reported. This effect could be the result of a decline in immune response due to immune aging, and a delay in the immune response. As for decline in immune response by immune aging, class switched memory B cells and late memory B cells may contribute. Class switching is a function that allows Immunoglobulin G (IgG) and IgA to be expressed on the surface of B cells. Since class switched memory B cells decline with age [26,27], this could be the reason for lower

Table 4
Relationship between selected characteristics and seropositivity rate comparable to convalescent sera (Abbott: ≥1280 AU/mL, Roche: >210 U/mL) at 4 weeks after the second vaccine dose.

Characteristics		N (%)	Crude						Model 1[1]						Model 2[2]						Model 3[3]					
			OR	(	95 %CI			)	OR	(	95 %CI			)	OR	(	95 %CI			)	OR	(	95 %CI			)
Roles																										
	Staff	154 (97)	1.00												1.00						1.00					
	Residents	50 (53)	**0.04**	**(**	**0.01**	**–**	**0.10**	**)**							**0.04**	**(**	**0.01**	**–**	**0.14**	**)**	0.19	(	0.03	–	1.25	)
Sex																										
	Female	133 (80)	1.00						1.00						1.00						1.00					
	Male	71 (82)	1.13	(	0.59	–	2.20	)	0.46	(	0.19	–	1.14	)	0.52	(	0.21	–	1.27	)	0.45	(	0.18	–	1.12	)
Age (every 10 years)			**0.46**	**(**	**0.36**	**–**	**0.58**	**)**	**0.44**	**(**	**0.32**	**–**	**0.61**	**)**							0.62	(	0.38	–	1.02	)
BMI (kg/m^2)																										
	<18.5	23 (66)	0.49	(	0.22	–	1.08	)	1.19	(	0.44	–	3.23	)	1.30	(	0.49	–	3.46	)	1.30	(	0.48	–	3.52	)
	18.5–24.9	133 (80)	1.00						1.00						1.00						1.00					
	≥25.0	43 (91)	2.75	(	0.92	–	8.18	)	2.44	(	0.56	–	10.51	)	2.02	(	0.48	–	8.51	)	2.10	(	0.48	–	9.14	)
Underlying diseases																										
	No	99 (98)	1.00						1.00						1.00						1.00					
	Yes	105 (69)	**0.04**	**(**	**0.01**	**–**	**0.19**	**)**	0.36	(	0.07	–	1.85	)	0.28	(	0.05	–	1.42	)	0.38	(	0.07	–	2.03	)
Steroids																										
	No	200 (82)	1.00						1.00						1.00						1.00					
	Yes	4 (40)	**0.15**	**(**	**0.04**	**–**	**0.54**	**)**	**0.09**	**(**	**0.01**	**–**	**0.55**	**)**	**0.12**	**(**	**0.02**	**–**	**0.73**	**)**	**0.09**	(	**0.01**	–	**0.60**	)
NSAIDs																										
	No	193 (81)	1.00						1.00						1.00						1.00					
	Yes	11 (69)	0.51	(	0.17	–	1.55	)	**0.16**	**(**	**0.03**	**–**	**0.83**	**)**	0.19	(	0.03	–	1.02	)	**0.16**	**(**	**0.03**	**–**	**0.88**	**)**

OR: odds ratio, CI: confidence interval, BMI: body mass index, NSAIDs: nonsteroidal anti-inflammatory drugs.
[1] Model 1: The model included sex, age, BMI, underlying diseases, steroids and NSAIDs.
[2] Model 2: The model included roles, sex, BMI, underlying diseases, steroids and NSAIDs.
[3] Model 3: The model included all the variables in this table.

antibody titers among elderly than young individuals after the first and second vaccination. Besides, late memory (IgD- CD27-; double negative) B cells increase with older age [27]. A previous study reported that a greater number of late memory B cells correlated with lower SARS-CoV-2 antibody titers after vaccination [28]. Thus, the lower antibody titers among elderly individuals seen in this study could have been due to the effect of late memory B cells.

Steroid usage were associated with decreased antibody acquisition in the subjects of this study. Previous cohort studies among healthcare workers [29] and patients with brain tumors [30] presented that people receiving steroids got lower immuno responses. Our results and those of previous studies can be explained by the following mechanism. Steroid hormones, such as glucocorticoids, inhibit interleukin-2 (IL-2) signaling transduction through suppression of IL-2 receptor expression and its binding [31,32]. This might lead to inhibit T-cell activation, and influence cellular immunity. Since IL-2 might also play a role in B-cell differentiation into antibody-producing cells [33], this would also impair humoral immunity.

Subjects using NSAIDs were also found to get lower anti-RBD titers in the present study. A previous mouse model study of the vaccinia virus showed that production of IgG antibodies decreased when cyclooxygenase 2 (Cox-2), which is the target of NSAIDs, was chronically inhibited [34]. Moreover, another study suggested that inhibition of Cox-2 led to a decrease in the production of IgG antibodies in human [35]. Among infected mice with SARS-CoV-2, NSAID-treated mice did not alter the number of immune cells in their lungs, although their serum levels of anti-spike protein of SARS-CoV-2 IgG and IgM decreased in comparison with mice without NSAID treatment [36]. However, since we only evaluated antibody responses among those regularly taking NSAIDs, the results of the present study might reflect the mechanism mentioned above. Moreover, patients under immunosuppressive therapy including steroids were reported to elicit strong immune response following the booster vaccination even if their antibody titer remained low after the second vaccination [37]. Long-term NSAIDs use among the elderly was also reported to have the higher percent of long-term immunity, such as memory B cell, after influenza vaccination [38]. Thus, even if antibody titers remained low after the second vaccination, booster vaccinations may induce an adequate antibody response and thus should be recommended.

The strength of this study is that we used two measurement assays, the Abbott assay and Roche assay, to quantitatively evaluate antibody titers, which are recognized as being associated with neutralizing antibodies [39]. In our study, the trends measured by using the two different immunoassays were consistent with each other. Moreover, people who obtained lower antibody titers could be identified more robustly, since the outcome was defined as the antibody titer that achieved seropositivity rate (comparable to convalescent serum) in both assays.

There are some limitations to interpretations of the present results. First, the timing of blood sampling might have been inappropriate for observing peak antibody titers. However, we desided this timing based on a previous study which suggested that spike-antibody titers 3–5 weeks after the second vaccine dose reached the peak [40]. A previous study conducted in residential care homes demonstrated that subjects $\geq$ 70 years old achieved the same antibody responses as younger subjects at 6 weeks after the first dose [41], suggesting that we might have evaluated the elderly patients before the peak in this study. Second, a standard cut-off value to define sufficient antibody titers that can protect against infection or developing severe diseases has not yet been established. We used the report by the FDA to determine the level of antibodies, which is equivalent to that in the convalescent sera of infected subjects [22]. However, this value might change depending on future reports. Nevertheless, it is important to suggest the characteristics of people in geriatric intermediate care facilities who acquire lower antibody responses with the currently applicable information, since it provides one of the evidence for staff to consider future preventive measures. Third, we only included the subjects who could be tracked for 1 year in the present study. Thus, the results might represent a source of selection bias toward residents who stay longer in the facility for long-term care.

Conclusion

Among residents and staff in Japanese geriatric intermediate care facilities, aging, steroid usage, and NSAID usage might lead to lower antibody responses after two doses of SARS-CoV-2 vaccination. Considering the lower antibody titers and the extent of antibody increase from the first to the second dose, a booster vaccination to achieve higher antibody titers should be recommended for these groups.

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CRediT authorship contribution statement

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

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