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ORIGINAL ARTICLE

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Durability of antibody titers and associated factors after the booster dose of COVID-19 mRNA vaccination in Japanese SARS-CoV-2 infection-naive residents in geriatric intermediate care facilities

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Aim: Elderly adults are at higher risk for severe COVID-19 infection. This multicenter, prospective cohort study assessed immunogenicity after COVID-19 vaccinations in elderly residents compared with staff in geriatric intermediate care facilities. Predictors of lower antibody titers were also examined.

Methods: Fifty-four residents and 117 staff who had received three doses of the COVID-19 mRNA vaccine between March 2021 and September 2022 were included. Anti-receptor binding domain antibody titers were measured 3–4 weeks and 6 months after the vaccinations. Adjusted geometric mean titers (GMT) were calculated using multivariable linear mixed effects models.

Results: After the first dose, residents had a significantly lower adjusted GMT than did staff (115 vs. 267 AU/mL, $P < 0.01$), whereas the adjusted GMT of residents was comparable to that of staff after the third dose (14 178 vs. 12 159 AU/mL, $P = 0.63$). However, 6 months later, the adjusted GMT of residents was less than half that of staff (1645 vs. 4302 AU/mL, $P < 0.01$). In residents, steroid users had a significantly lower adjusted GMT than did steroid nonusers.

Conclusions: The third dose of mRNA vaccine boosted the immune response of elderly residents. However, their antibody titers, particularly in steroid users, were highly attenuated 6 months after the last vaccination. For this population, attention should be focused on additional vaccinations. **Geriatr Gerontol Int 2025; 25: 588–597**.

Keywords: antibody titer, booster dose, immunogenicity, long-term care facility, mRNA COVID-19 vaccine.

Introduction

During the COVID-19 pandemic, great efforts, including vaccination, were made to prevent infection and severe disease. One of the most vulnerable populations was elderly nursing home residents, who faced a disproportionate risk of severe disease and mortality from COVID-19.[1,2] Therefore, under the vaccination strategy in Japan, vaccination with the primary series (first and second doses) and periodic booster doses, including vaccines with updated strains adjusted for the variants of concern, were recommended for them. In Japan, the mRNA vaccines (BNT162b2 or mRNA-1273) were mainly used, and they had tolerable safety and high efficacy against COVID-19 in randomized, controlled, phase 3 trials.[3,4]

As the pandemic subsides and transitions into the post-pandemic phase,[5,6] the vaccination strategy for COVID-19 has changed. Since April 2024, the vaccination strategy in Japan has been to provide only once-a-year vaccination for high-risk populations such as elderly (65 years and older) persons and those aged 60–64 years with underlying illnesses. However, sentinel surveillance showed a bimodal peak in summer and winter in Japan, and more than 80% of hospitalized patients due to COVID-19 were aged 60 years or older.[7] In addition, several studies have shown that antibody titers wane over time after vaccination,[8,9] and some countries continue to vaccinate high-risk populations twice a year.[10,11] In order to consider future directions, including the frequency and timing of vaccination, information regarding the long-term immunogenicity of COVID-19 vaccines, especially for high-risk populations, should be accumulated.

However, there is a scarcity of reports on longitudinal immunity after vaccinations in residents of elderly care facilities, even though they are a high-risk group for severe infections. Understanding the immunogenicity of booster doses, the extent of waning immunity over time, and how the waning differs according to individuals' characteristics will be crucial for the appropriate scheduling and targeting of future booster vaccinations and when considering COVID-19 management at these facilities. The present study provides immunogenicity data up to 6 months after the first booster dose of vaccination following the primary series of vaccination in elderly residents compared with staff in geriatric intermediate care facilities (GICFs). During the study period, because the infection had not prevailed yet among the study participants at the facilities, it was possible to examine the genuine long-term immunogenicity of the vaccine itself. In addition, further multivariate analysis in the present study using a linear mixed effects model showed predictors of lower antibody titers at each time point, taking into account the longitudinal changes of antibody titers.

Methods

Study design and participants

This prospective cohort study included residents and staff at nine GICFs belonging to the Osaka Association of Geriatric Health Service Facilities between March 2021 and September 2022. The residents at these GICFs are elderly persons who do not require hospitalization but are mentally or physically impaired.[12] The eligibility criteria for this study were as follows: (1) individuals who received both the primary series and the third dose of COVID-19 mRNA vaccination; (2) individuals who could be followed for more than six months; and (3) individuals who consented to participate in this study. Those with a history of contraindications to the COVID-19 mRNA vaccination were excluded.

Data collection

At the time of recruitment, the staff were asked to fill out a questionnaire form using the medical records of residents with the following information: age, sex, height and body weight, underlying diseases (e.g., hypertension, diabetes mellitus, etc.), prescription drugs (steroids, anticancer drugs, etc.), and nursing care level. These underlying diseases are known to increase individual risk of severe illness from COVID-19.[2] As for nursing care level, the following five levels are allowed for admission to GICFs: care levels 1 and 2 (moderate disability), and care levels 3–5 (severe disability). Elderly persons certified as care levels 3–5 require almost complete assistance with activities of daily living.[13,14] Staff themselves also completed a self-administered questionnaire to collect similar information other than nursing care level.

Vaccination

All vaccines used in this study were original strain vaccines. The primary series of vaccinations was performed using BNT162b2 vaccine twice at about a 21-day interval between March 9, 2021 and July 16, 2021. The participants received the booster dose as the third vaccination approximately 7 months after the second vaccination, using either BNT162b2 or mRNA-1273 vaccine according to availability at each facility. The timing of the third dose varied among facilities, but the last vaccination was completed on March 25, 2022.

Serological assessment

Blood samples were collected at six time points: within 1 week before the first vaccination (S0), 3 weeks after the first vaccination (S1), 4 weeks after the second vaccination (S2), 6 months after the second vaccination (S3), 4 weeks after the third vaccination (S4), and 6 months after the third vaccination (S5). Antibody titers of the anti-receptor-binding domain (anti-RBD) of the spike protein of SARS-CoV-2 IgG and anti-SARS-CoV-2 nucleocapsid protein IgG (anti-N) were measured in the collected blood samples. Anti-N titers were used to judge whether the participant had already been infected during the study period by means of two immunoassays for confirmation: Alinity i SARS-CoV-2 IgG (Abbott Laboratories, Chicago, Illinois, USA) and Elecsys Anti-SARS CoV-2 (Roche Diagnostics, Basel, Switzerland). If both anti-N titers of the blood sample were above the cutoff (values of ≥1.40 for Alinity i SARS-CoV-2 IgG and ≥1.0 for Elecsys Anti-SARS CoV-2), the participant was considered to have been previously infected.[15,16] Anti-RBD titers were also measured using two immunoassays for confirmation: AdviseDx SARS-CoV-2 IgG II (ARCHITECT) (Abbott Laboratories [Abbott assay]) and Elecsys Anti-SARS CoV-2 S (Roche Diagnostics [Roche assay]).[17,18] The quantitative range of the Abbott assay was 0.0–40 000 AU/mL, and that of the Roche assay was 0.4–25 000 U/mL in this study.

Statistical analysis

When comparing participants' characteristics, values are presented in summary form as percentages for categorical variables and as medians and ranges for continuous variables. Differences between categories were tested using Fisher's exact test, the chi-squared

test, or the Mantel-extension test for categorical variables and the Wilcoxon rank-sum test for continuous variables.

The geometric mean antibody titer (GMT) and its 95% confidence interval (95% CI) were used at each time point to assess the change in anti-RBD antibody titers using the two assays. For data processing, titers of less than 0.1 AU/mL were treated as 0.1 AU/mL for the Abbott assay, and titers of less than 0.4 U/mL were treated as 0.4 U/mL for the Roche assay, as in the previous study.[19] GMTs were compared between categories using the Wilcoxon rank-sum test or the Kruskal–Wallis test. Sex-stratified analyses were also performed for GMT for each age category.

A linear mixed effects model was used for multivariate analysis to examine the independent effects of the following factors on post-vaccination titers at each point: role in the facilities (staff or resident), age category (<45, 45–59, 60–84, ≥85 years), sex, body mass index (BMI) category (<18.5, 18.5–24.9, ≥25.0 kg/m^2), underlying diseases, and steroid use. Because there is expected to be a strong correlation between the age of the participants and their role, the variance inflation factor (VIF) was checked. Although it is generally accepted that multicollinearity exists when the VIF exceeds 10,[20,21] the VIF calculated in this study was less than 10. Antibody titers are expressed as the adjusted GMT values, and the ratio of antibody titers to the reference category is expressed as the ratio of the mean (RoM) and its 95% CI.

A subgroup analysis limited to residents was also conducted to examine the antibody titers by resident-specific characteristics. The linear mixed effects model included age category (60–84, ≥85 years), sex, BMI category, care level (low 1–2, high 3–5), underlying diseases, and steroid use as explanatory variables.

All statistical analyses were performed using SAS version 9.4 software (SAS Institute Inc., Cary, NC, USA), and significance was set at $P < 0.05$.

Results

Study population and participants' characteristics

A total of 259 individuals, including 172 staff and 87 residents, were initially enrolled in the cohort. Of them, 88 were excluded because one or more of the blood samples from S0 to S5 were not available ($n = 78$), necessary information was missing ($n = 2$), or they were regarded as post-infection with SARS-CoV-2 according to positive anti-N antibody levels ($n = 8$). Finally, the cohort for the analysis included 171 individuals, including 117 staff and 54 residents (Fig. 1).

Table 1 shows the participants' characteristics. The median age of staff was 47 years (range, 20–78 years) and of residents was 89 years (range, 71–101 years), 43% of staff were under the age of 45 years, and 70% of residents were 85 years or older. Both staff (62%) and residents (83%) were predominantly female. One-third of residents were underweight (BMI <18.5 kg/m^2), and one-third of staff were overweight (BMI ≥25.0 kg/m^2). Few staff and residents used steroids (3% of staff, 6% of residents).

Longitudinal changes in anti-RBD antibody titers in all participants

Table 2 shows the change in anti-RBD antibody titers and 95% CIs with the Abbott assay. For total participants, GMT increased after the first and second vaccinations (421 AU/mL at S1 and 6024 AU/mL at S2) and decreased after 6 months (625 AU/mL at S3), but increased considerably after the third vaccination (17 723 AU/mL at S4), then decreased 6 months later (5311 AU/mL at S5), with this latter level similar to that after the second dose (S2). Until receiving the third dose, antibody titers in residents were significantly lower than those in staff, but after the third dose (S4), the difference was no longer significant (18 786 AU/mL in staff vs. 15 623 AU/mL in residents). Six months later, however, GMT was again significantly lower in residents (6525 AU/mL in staff vs. 3400 AU/mL in residents). In addition, GMT was significantly lower with older age, lower BMI, underlying disease, and steroid use before receiving the third dose (S1 to S3), but there was no significant difference in GMT for most categories after the third dose (S4). In the sex-stratified analysis, lower GMTs with older age were observed from S1 to S3 regardless of sex (Table S1).

With the Roche assay, the negative effects of residents, older age, lower BMI, and underlying disease for antibody titers remained at each point (Table S2). The sex-stratified analysis also showed lower GMT trends with older age regardless of sex (Table S3).

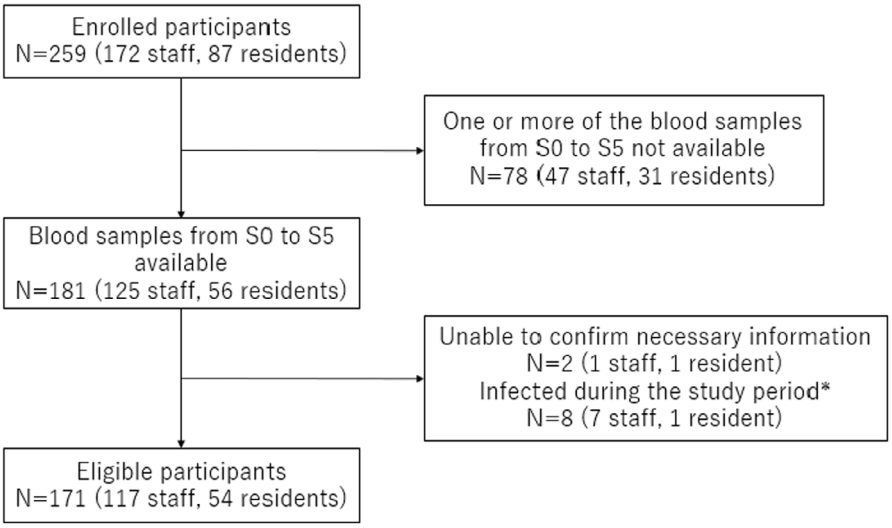

Figure 1 Cohort development flow diagram.

Table 1 Characteristics of participants in the study facilities

Characteristic	Overall ($n = 171$)	Staff ($n = 117$)	Residents ($n = 54$)	*P*-value*
Age (years), median (range)	55 (20–101)	47 (20–78)	89 (71–101)	<0.01
Age category (years)				
<45	50 (29)	50 (43)	0 (0)	
45–59	49 (29)	49 (42)	0 (0)	
60–84	34 (20)	18 (15)	16 (30)	
≥85	38 (22)	0 (0)	38 (70)	<0.01
Sex				
Male	54 (32)	45 (38)	9 (17)	
Female	117 (68)	72 (62)	45 (83)	<0.01
BMI (kg/m^2), median (range)	22.0 (13.1–38.6)	22.8 (14.8–38.6)	20.1 (13.1–31.3)	<0.01
BMI category (kg/m^2)				
<18.5	21 (12)	6 (5)	15 (28)	
18.5–24.9	111 (65)	78 (67)	33 (61)	
≥25.0	39 (23)	33 (28)	6 (11)	<0.01
Type of third vaccine				
BNT162b2	109 (72)	86 (86)	23 (45)	
mRNA-1273	42 (28)	14 (14)	28 (55)	<0.01
Data missing	20	17	3	
Underlying disease†				
No	72 (42)	68 (58)	4 (7)	
Yes	99 (58)	49 (42)	50 (93)	<0.01
Steroid use				
No	165 (97)	114 (97)	51 (94)	
Yes	6 (4)	3 (3)	3 (6)	<0.01

**P*-values were obtained using Fisher's exact test, chi-squared test (variables with two categories), the Mantel-extension test (variables with three or more categories), or the Wilcoxon rank-sum test (continuous variables).

†Hypertension, diabetes mellitus, heart disease, stroke, asthma, chronic obstructive pulmonary disease (COPD), kidney disease, and so on.

BMI, body mass index. Data are expressed as *n* (%) unless otherwise indicated.

Linear mixed effects model analysis to identify predictors for anti-RBD antibody titers at each point

Table 3 shows the adjusted GMT, RoM, and its 95% CI with the Abbott assay. Adjusted GMT was significantly lower for residents, older age (especially ≥60 years age group), lower BMI, and steroid use before receiving the third dose (S1 to S3), but there was no significant difference in GMT after the third dose (S4). However, 6 months later, adjusted GMT was again significantly lower in residents (4302 AU/mL in staff vs. 1645 AU/mL in residents; RoM 0.38) and steroid users (4340 AU/mL in nonusers vs. 1631 AU/mL in users; RoM 0.38).

A similar trend was observed in the analysis with the Roche assay (Table S4).

Immunogenicity after vaccinations only for residents

Table 4 shows the adjusted GMT, RoM, and its 95% CI with the Abbott assay in residents. After the first vaccination (S1), adjusted GMT was significantly lower for those aged 85 years and older compared with those aged less than 84 years (RoM = 0.36), for those in a higher care level compared with those in a lower care level (RoM = 0.52), and for steroid users compared with nonusers (RoM = 0.26). After the second dose, the significant difference disappeared, but 6 months later with the third dose (S5), the adjusted GMT was again significantly lower in steroid users (RoM = 0.25).

A similar trend was observed in the analysis with the Roche assay (Table S5).

Discussion

The present results indicate that the antibody response to the COVID-19 mRNA vaccine was lower in elderly residents than in staff even after receiving the primary series of vaccinations, but the third dose provided them with a similar level of antibody titers to in the staff.

To date, elderly persons have been known to have lower antibody titers and less durability before receiving the third dose.[22] Furthermore, in a study conducted in a Japanese long-term care facility, residents were shown to have significantly lower antibody titers than healthcare workers after the second dose.[23] However, a separate study of healthcare workers in Japan reported that antibody titers in elderly persons reached levels comparable to those in younger adults after the third dose.[24] Furthermore, a Canadian study, which measured both IgG levels and neutralization activities up to one month after the third dose, showed similar findings.[25] The present results are consistent with these previous reports and suggest that third vaccine doses strongly improved vaccine immunogenicity, even in elderly residents.

However, antibody titers did not persist up to 6 months after the third vaccination in elderly residents. Similarly, in a study conducted at long-term care facilities in the UK, the third dose vaccination strongly increased the antibody response of elderly residents, but antibody titers fell 21–78% within 100 days after the third dose, and 27% of participants developed a breakthrough Omicron variant infection.[26] Another study of healthcare workers showed a 25% decrease of antibody titers per 30 days after the

Table 2 Change in GMT across the selected characteristics measured using the Abbott assay

Characteristic	*n*	Estimated anti-RBD antibody titers (AU/mL), GMT (95% CI)					
		Before vaccination (S0)	After the first vaccination (S1)	After the second vaccination (S2)	Six months after the second vaccination (S3)	After the third vaccination (S4)	Six months after the third vaccination (S5)
Overall	171	0.8 (0.6–1.1)	421 (332–533)	6024 (5224–6947)	625 (546–717)	17 723 (15844–19 825)	5311 (4491–6281)
Role							
Staff	117	0.8 (0.6–1.2)	816 (690–967)	8539 (7591–9605)	842 (738–960)	18 786 (16538–21 339)	6525 (5420–7854)
Resident	54	0.8 (0.5–1.2)	100 (63–159)	2829 (2124–3768)	328 (255–423)	15 623 (12466–19 578)	3400 (2456–4706)
		$P = 0.43$	**$P < 0.01$**	**$P < 0.01$**	**$P < 0.01$**	$P = 0.23$	**$P < 0.01$**
Type of third vaccine							
BNT162b2	109					17 539 (15162–20 288)	5969 (4861–7331)
mRNA-1273	42					19 458 (15630–24 225)	4531 (3128–6564)
						$P = 0.42$	$P = 0.17$
Age (years)							
<45	50	1.0 (0.6–1.7)	1049 (800–1411)	9590 (7997–11 501)	902 (728–1117)	19 864 (16704–23 621)	7023 (5200–9486)
45–59	49	0.8 (0.4–1.3)	727 (590–897)	8661 (7353–10 202)	888 (729–1081)	19 726 (16999–22 892)	5788 (4636–7227)
60–84	34	0.6 (0.3–1.2)	349 (240–506)	5063 (3819–6712)	520 (392–690)	15 115 (10610–21 535)	4643 (2968–7263)
≥85	38	0.9 (0.5–1.4)	74 (41–135)	2390 (1674–3414)	290 (216–390)	15 320 (11644–20 156)	3711 (2422–5687)
		$P = 0.44$	**$P < 0.01$**	**$P < 0.01$**	**$P < 0.01$**	$P = 0.50$	$P = 0.12$
Sex							
Male	54	1.0 (0.6–1.5)	535 (372–770)	6395 (4992–8192)	742 (585–942)	19 530 (15645–24 381)	6251 (4757–8214)
Female	117	0.8 (0.6–1.1)	377 (278–509)	5860 (4913–6990)	578 (489–682)	16 946 (14889–19 288)	4926 (3987–6086)
		$P = 0.49$	$P = 0.34$	$P = 0.56$	$P = 0.08$	$P = 0.12$	$P = 0.10$
BMI (kg/m^2)							
<18.5	21	0.5 (0.2–1.0)	125 (58–271)	3197 (1949–5243)	345 (214–557)	14 110 (9157–21 742)	2966 (1834–4798)
18.5–24.9	111	0.9 (0.6–1.2)	443 (334–588)	6250 (5240–7455)	683 (577–807)	17 321 (15375–19 512)	5665 (4603–6972)
≥25.0	39	0.9 (0.6–1.6)	697 (451–1075)	7631 (6015–9681)	671 (531–849)	21 392 (16115–28 396)	6048 (4245–8616)
		$P = 0.35$	**$P < 0.01$**	**$P < 0.01$**	**$P < 0.01$**	**$P = 0.03$**	$P = 0.06$
Underlying disease							
No	72	0.9 (0.6–1.3)	791 (629–995)	7851 (6657–9260)	737 (624–870)	18 038 (15126–21 512)	5950 (4606–7686)
Yes	99	0.8 (0.6–1.1)	266 (188–376)	4969 (4031–6124)	555 (454–679)	17 497 (15094–20 284)	4890 (3907–6120)
		$P = 0.47$	**$P < 0.01$**	**$P < 0.01$**	**$P = 0.03$**	$P = 0.83$	$P = 0.35$
Steroid use							
No	165	0.8 (0.6–1.1)	445 (352–563)	6170 (5352–7113)	637 (557–728)	18 146 (16247–20 267)	5513 (4665–6516)
Yes	6	0.7 (0.1–4.0)	91 (15–563)	3127 (806–12 126)	383 (73–2017)	9262 (2859–30 001)	1898 (447–8059)
		$P = 0.84$	**$P = 0.02$**	$P = 0.17$	$P = 0.35$	$P = 0.14$	$P = 0.054$

P-values were obtained using the Wilcoxon rank-sum test or Kruskal–Wallis test for intercategory comparisons.

BMI, body mass index; CI, confidence interval; GMT, geometric mean antibody titer.

Bold font indicates significance ($P < 0.05$).

Table 3 Adj. GMT and RoM measured using the Abbott assay

Variable	*n*	After the first vaccination (S1)			After the second vaccination (S2)			Six months after the second vaccination (S3)			After the third vaccination (S4)			Six months after the third vaccination (S5)		
		Adj. GMT	RoM (95% CI)	*P*-value	Adj. GMT	RoM (95% CI)	*P*-value	Adj. GMT	RoM (95% CI)	*P*-value	Adj. GMT	RoM (95% CI)	*P*-value	Adj. GMT	RoM (95% CI)	*P*-value
Role																
Staff	117	267	Ref		4510	Ref		500	Ref		12 159	Ref		4302	Ref	
Resident	54	115	0.43 (0.35–0.53)	**<0.01**	3293	0.73 (0.59–0.91)	0.33	367	0.73 (0.59–0.91)	0.34	14 178	1.17 (0.94–1.45)	0.63	1645	0.38 (0.31–0.47)	**<0.01**
Age (years)																
<45	50	339	Ref		6073	Ref		651	Ref		15 845	Ref		2597	Ref	
45–59	49	239	0.71 (0.62–0.80)	0.06	5284	0.87 (0.77–0.99)	0.46	562	0.86 (0.76–0.98)	0.44	15 460	0.98 (0.86–1.11)	0.90	2105	0.81 (0.71–0.92)	0.26
60–84	34	188	0.55 (0.47–0.66)	**0.02**	3578	0.59 (0.50–0.70)	**0.04**	384	0.59 (0.50–0.70)	**0.04**	11 476	0.72 (0.66–0.86)	0.20	2677	1.03 (0.87–1.22)	0.90
≥85	38	62	0.18 (0.14–0.24)	**<0.01**	1921	0.32 (0.25–0.41)	**<0.01**	240	0.37 (0.29–0.47)	**<0.01**	10 568	0.67 (0.52–0.86)	0.27	3423	1.32 (1.03–1.69)	0.46
Sex																
Male	54	156	0.79 (0.71–0.88)	0.12	3428	0.79 (0.71–0.88)	0.13	425	0.98 (0.89–1.09)	0.91	13 499	1.06 (0.95–1.17)	0.72	2780	1.09 (0.98–1.21)	0.57
Female	117	197	Ref		4333	Ref		432	Ref		12 767	Ref		2546	Ref	
BMI (kg/m^2)																
<18.5	21	121	0.55 (0.41–0.58)	**0.02**	3126	0.73 (0.61–0.87)	0.23	363	0.86 (0.72–1.03)	0.56	11 429	0.75 (0.63–0.89)	0.27	2180	0.77 (0.64–0.91)	0.31
18.5–24.9	111	203	0.92 (0.82–1.04)	0.65	4281	1.00 (0.89–1.12)	1.00	514	1.22 (1.09–1.37)	0.25	12 957	0.85 (0.76–0.95)	0.34	3034	1.07 (0.95–1.20)	0.71
≥25.0	39	220	Ref		4277	Ref		422	Ref		15 279	Ref		2846	Ref	
Underlying disease																
No	72	177	Ref		3591	Ref		376	Ref		12 249	Ref		2342	Ref	
Yes	99	174	0.98 (0.88–1.09)	0.90	4135	1.15 (1.03–1.29)	0.39	488	1.30 (1.16–1.45)	0.11	14 070	1.15 (1.03–1.28)	0.40	3022	1.29 (1.15–1.44)	0.12
Steroid use																
No	165	303	Ref		4848	Ref		506	Ref		17 964	Ref		4340	Ref	
Yes	6	101	0.33 (0.26–0.43)	**<0.01**	3063	0.63 (0.49–0.82)	0.23	363	0.72 (0.56–0.93)	0.38	9594	0.53 (0.41–0.69)	0.27	1631	0.38 (0.29–0.49)	**0.01**

adj. GMT, adjusted GMT; BMI, body mass index; CI, confidence interval; GMT, geometric mean antibody titer; RoM, ratio of the mean.

All GMT units are expressed in AU/mL.

Adj. GMT and RoM were estimated using the multivariable linear mixed effects model with adjustment for all variables in the table.

Bold font indicates significance ($P < 0.05$).

Table 4 Adj. GMT and RoM only for residents, measured using the Abbott assay

		After the first vaccination (S1)			After the second vaccination (S2)			Six months after the second vaccination (S3)			After the third vaccination (S4)			Six months after the third vaccination (S5)		
Variable	*n*	Adj. GMT	RoM (95% CI)	*P*-value	Adj. GMT	RoM (95% CI)	*P*-value	Adj. GMT	RoM (95% CI)	*P*-value	Adj. GMT	RoM (95% CI)	*P*-value	Adj. GMT	RoM (95% CI)	*P*-value
Age (years)																
60–84	16	95	Ref		2191	Ref		226	Ref		11 368	Ref		1160	Ref	
≥85	38	34	0.36 (0.29–0.45)	**<0.01**	1284	0.59 (0.47–0.73)	0.10	156	0.69 (0.55–0.86)	0.26	10 952	0.96 (0.77–1.20)	0.91	1594	1.37 (1.10–1.71)	0.33
Sex																
Male	9	59	1.07 (0.81–1.42)	0.86	1608	0.92 (0.70–1.21)	0.84	208	1.22 (0.92–1.61)	0.63	11 590	1.08 (0.82–1.42)	0.85	1491	1.20 (1.10–1.71)	0.66
Female	45	55	Ref		1750	Ref		170	Ref		10 742	Ref		1241	Ref	
BMI (kg/m^2)																
<18.5	15	44	0.72 (0.50–1.03)	0.54	1396	0.70 (0.49–1.01)	0.51	193	1.08 (0.75–1.55)	0.89	9913	0.68 (0.47–0.97)	0.47	1359	1.04 (0.73–1.50)	0.94
18.5–24.9	33	70	1.14 (0.82–1.59)	0.79	1701	0.97 (0.61–1.19)	0.75	193	1.08 (0.77–1.50)	0.88	9609	0.66 (0.47–0.92)	0.40	1421	1.09 (0.98–1.52)	0.86
≥25.0	6	61	Ref		1989	Ref		179	Ref		14 585	Ref		1302	Ref	
Care level																
Low (1–2)	40	79	Ref		2216	Ref		232	Ref		11 989	Ref		1547	Ref	
High (3–5)	14	41	0.52 (0.43–0.64)	**0.04**	1270	0.57 (0.47–0.71)	0.07	152	0.65 (0.53–0.81)	0.17	10 385	0.87 (0.70–1.07)	0.64	1196	0.77 (0.63–0.95)	0.40
Underlying disease																
No	4	47	Ref		1194	Ref		136	Ref		9273	Ref		963	Ref	
Yes	50	71	1.51 (1.03–2.23)	0.47	2357	1.97 (1.34–2.91)	0.24	259	1.90 (1.29–2.80)	0.27	13 428	1.45 (0.98–2.13)	0.52	1919	1.99 (1.35–2.94)	0.23
Steroid use																
No	51	113	Ref		2569	Ref		309	Ref		15 937	Ref		2720	Ref	
Yes	3	29	0.26 (0.16–0.40)	**0.04**	1095	0.37 (0.27–0.67)	0.20	115	0.37 (0.24–0.58)	0.14	7813	0.49 (0.31–0.77)	0.28	680	0.25 (0.16–0.39)	**0.04**

adj. GMT, adjusted GMT; BMI, body mass index; CI, confidence interval; GMT, geometric mean antibody titer; RoM, ratio of the mean.

All GMT units are expressed in AU/mL.

Adj. GMT and RoM were estimated using the multivariable linear mixed effects model with adjustment for all variables in the table.

Bold font indicates significance ($P < 0.05$).

third dose in both younger adults and those aged 40 years or older.[27] In addition, a study of healthcare workers evaluating the antibody titers after the fifth and sixth booster doses reported lower antibody titers more than six months after the last vaccination.[28] These results, along with the present results, suggest that antibody titers decrease over time since the last booster dose, and the decay may be faster in the elderly population. Thus, some vulnerable populations such as elderly residents may need repeated vaccinations to maintain their antibody levels.

In this study, of the characteristics examined other than role in the facilities, steroid use was the only predictor of lower antibody titers at 6 months after the third vaccination, especially for residents. A previous study reported that immunosuppressed healthcare workers had 65% of the antibody titer compared with those without immunosuppression at 6 months after the primary series of vaccinations.[22] Even 6 months after the third dose, another study showed that the antibody titer was about 60% lower with immunosuppression than without.[27] The present findings support the previous reports regarding the lower immunogenicity and shorter durability of steroid users.

In the analysis limited to residents, higher care levels were associated with lower antibody titers after the first vaccination, but the negative association was no longer observed thereafter. Though frailty has been reported to decrease the immune response to pneumococcal or influenza vaccines,[29,30] some studies of the COVID-19 mRNA vaccine have also reported that poor performance status[31] or a higher score on clinical frailty scale[32] is strongly associated with lower antibody titers up to 6 months after the primary series of vaccinations. However, the latter studies, as well as the present study, showed that the booster dose induced an appropriate immune response even in such frail persons, suggesting the benefit of the booster vaccination in these individuals.

Since April 2024, Japan has initiated annual routine vaccination for elderly persons over 65 years old and those at risk of severe COVID-19 infection. However, elderly residents or steroid users may already have decreased antibody titers 6 months after the last booster dose. Although there is no evidence regarding the protective levels of antibody titers against infection or severe illness, this population may need to be vaccinated more frequently than others and should be prioritized for future additional vaccinations. Further research on the disease burden of COVID-19 and trends of seroprevalence after annual vaccination, especially in elderly facility residents or steroid users, is warranted in subsequent years.

This study has the following strengths: first, anti-N antibodies were measured serologically, and potentially infected individuals were excluded. This allowed us to evaluate pure vaccine-induced changes in antibody titers in SARS-CoV-2 infection-naive individuals. Second, the robustness of the results was confirmed by using two different assays, Abbott and Roche,[33,34] and the predictive factors for lower antibody titers were almost the same with the two assessments, which supports the validity of the present study results.

However, there are several limitations in this study. First, the study participants received only the monovalent vaccine with the original strain. Because variant strains of concern have emerged over time, vaccines with updated strains have been developed. Therefore, caution is needed for the generalizability of the present results to vaccines against variant strains. Second, only antibody titers were measured, without assessment of cellular immunity to evaluate the immune response. According to the previous studies, T cell responses were significantly lower in individuals aged ≥80 years than in younger individuals,[35] and steroid treatment was shown to suppress the T cell response to vaccination in patients with systemic autoimmune rheumatic disease.[36] In addition, a recent study reported that booster vaccination in older adults over 65 years of age impaired memory T-cell activation, while the B-cell response was induced at levels comparable to those in younger adults.[37] This suggests that additional vaccination may increase IgG antibody titers, and that even elderly individuals may have an adequate immune response. Third, the small number of residents in this study may have resulted in some significant factors related to the antibody response being missed. The present study also excluded potentially infected participants during the study period, to examine the longitudinal immunity of the vaccine itself, so the clinical effectiveness of vaccination among the study participants could not be assessed. Fourth, the sample size was not sufficient for obtaining adequate data regarding the infection rates or hospitalization rates after vaccinations among the elderly residents, compared with those of the general population.

In Japan, up to seven doses of the vaccine had been available by the end of 2023, whereas the prevalence of infection reached as high as 64.5% in March 2023.[38] Therefore, it may be necessary to consider whether the present study results, which showed the immunogenicity up to 6 months after the third vaccination, could be applied to those who received four or more vaccinations or those who have already been infected. However, considering that antibody titers decreased 6 months after the fifth or sixth vaccination among healthcare workers,[28] antibody titers among elderly residents or steroid users would also likely decrease at 6 months even after the additional vaccination. Moreover, taken together with the present results, the extent of waning immunity at 6 months after the last dose may be larger in elderly residents or steroid users. Because vaccination coverage in Japan decreased after the third dose,[39] it may be important to remind these vulnerable individuals about the need for periodic booster doses to maintain their immunity.

Conclusion

The immune response of elderly residents was boosted by the third COVID-19 mRNA vaccination. However, six months after the last vaccination, antibody titers were significantly lower than those of staff. Additional vaccinations are required for elderly residents, particularly for those who use steroids: this may help to determine the priority for booster dose administration and the appropriate timing of vaccination.

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Disclosure statement

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.

Author contributions

Conceptualization: SO, TKa, YK, HK, WF, YH; Data Curation: AKa, SO, AS, KK; Formal Analysis: AKa, SO, AS, KK; Funding Acquisition: YH, WF; Investigation: AKa, SO, AS, HN, TKi, AD, MF, KIb, HidS, KIw, NS, HikS, YY, YN, AKo, EM, KM, TM; Methodologies: AKa, SO, AS, YN, TM, TKa, WF, YH; Project Administration: SO, YK, HK; Resources: AKa, SO, AS, KK, HN, TKi, AD, MF, KIb, HidS, KIw, NS, HikS, YY, YN; Supervision: SO, WF, YH; Writing – original draft: AKa, SO, WF; Writing – review & editing: AKa, SO, AS, KK, HN, TKi, AD, MF, KIb, HidS, KIw, NS, HikS, YY, YK, YN, AKo, EM, KM, TM, TKa, HK, WF, YH; All authors approved the final version of the manuscript.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Ethics statement

The study protocol was conducted in accordance with the principles of the Declaration of Helsinki, and it was approved by the Certified Review Board of Osaka Metropolitan University Hospital (OCU011E; first version: March 1, 2021; second version: April 6, 2021; third version: July 7, 2021; fourth version: October 12, 2021) and the Ethics Review Board of the Osaka Metropolitan University Graduate School of Medicine (2021–204). This study was also registered in the Japan Registry of Clinical Trials (jRCT1051200148). Informed consent was obtained from participants after adequate explanation of the nature and content of this study. For residents with dementia, consent was obtained from a surrogate such as a family member.

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Supporting Information

Additional supporting information may be found in the online version of this article at the publisher's website:

Data S1

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