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MAJOR ARTICLE

Bivalent Vaccine Effectiveness Among Adults Aged ≥65 Years During the BA.5-Predominant Period in Japan: The VENUS Study

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Background. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Omicron BA.5 became prevalent in July 2022 in Japan. Bivalent messenger RNA (mRNA) vaccines were approved as booster doses for individuals who received the primary series or booster dose by monovalent vaccines. We aimed to assess the effectiveness of bivalent vaccines in Japanese adults aged ≥65 years.

Methods. We conducted a population-based cohort study using data collected from January 2019 to February 2023 in Japan. We included individuals aged ≥65 years in a municipality who received the first or second booster dose of monovalent mRNA vaccines. We estimated the effectiveness of the second or third booster dose of bivalent mRNA vaccines during the Omicron BA.5–predominant period (July–December 2022), compared with ≥90 days after the booster dose of monovalent vaccines. We used a Cox proportional hazard regression model with vaccination status as a time-dependent covariate.

Results. A total of 81 977 individuals aged ≥65 years (mean [standard deviation] age, 78.3 [7.4] years; 33 487 male [40.8%]) were included in the study cohort. Among them, 57 396 were vaccinated with the second or third dose of bivalent vaccines (BA.1 or BA.4/5). The effectiveness against coronavirus disease 2019 (COVID-19) was estimated to be 57.9% (95% confidence interval, 52.7%–62.5%) for ≥14 days after the second or third bivalent booster dose, compared with 90 days after the first or second monovalent booster dose.

Conclusions. The study showed that the bivalent mRNA vaccines as the second and third doses would provide protection against COVID-19 among adults ≥65 years in Japan.

Keywords. COVID-19; SARS-CoV-2; effectiveness; mRNA vaccine; observational study.

The Omicron subvariant and other recombinant variants of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have dominated the world since their emergence in November 2021. The Omicron BA.1 wave started in January 2022, and its sublineage successively caused a pandemic in Japan. Furthermore, the Omicron BA.2 variant was prevalent starting in April 2022, and the sublineage was replaced by BA.5 from July 2022. The seventh wave caused by BA.5 peaked in August 2022, followed by the eighth wave in November 2022. There were 520 coronavirus disease 2019 (COVID-19) cases per 100 000 per week during 7–13 September 2022 [1], with a peak in 4–10 January 2023 (932 per 100 000) [2].

Monovalent messenger RNA (mRNA) vaccines (BNT162b2 [Pfizer-BioNTech] and mRNA-1273 [Moderna]) have shown high efficacy against COVID-19, substantially reducing COVID-19–related deaths and helping control the pandemic [3, 4]. However, their effectiveness wanes over time and decreases because of immune evasion owing to numerous mutations in SARS-CoV-2 [5]. Notably, the levels of Omicron BA.1 and BA.2 neutralizing antibodies are lower [6], and their effectiveness decreases compared with that against earlier strains [7, 8]. Furthermore, Omicron BA.5 showed higher transmissibility than did BA.2 and escaped humoral immunity induced by previous BA.1 and BA.2 infections [9]. Moreover, the BA.4/5 variant showed reduced neutralization titers compared with those of BA.1 and BA.2 [10]. Thus, to provide a better immune response against these Omicron subvariants, Pfizer-BioNTech and Moderna have developed bivalent BA.1 and BA.4/BA.5 mRNA vaccines. While several studies have reported on the effectiveness of bivalent vaccines against Omicron BA.5 [11–15], data on the effectiveness of bivalent vaccines during BA.5 predominance are limited in Japan [16].

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Vaccination coverage was high in Japan as >90% of people aged ≥65 years received the first dose booster. A national seroepidemiological study showed that the prevalence of anti-spike antibodies was 96.5% between February and March 2022, during a period of BA.1 and BA.2 predominance [17]. In contrast, the proportion of anti-nucleocapsid (infection-induced) antibodies was only 3.5%. Notably, the proportion of the Japanese population with infection-induced immunity was lower than the proportions in the United States and the United Kingdom before the Omicron BA.5 wave. These variations could affect the estimated vaccine effectiveness; thus, every country should monitor the sustained vaccine effectiveness when planning future vaccination strategies to protect a high-risk population aged ≥65 years. Therefore, the current study aimed to estimate bivalent vaccine effectiveness in people aged ≥65 years, compared with monovalent booster doses.

METHODS

Study Design, Setting, and Data Source

We conducted a cohort study in a municipality between 1 January 2019 and 31 December 2022, based on the Vaccine Effectiveness, Networking, and Universal Safety (VENUS) Study [18]. The municipality is located in the Chubu region, at the center of Japan's main island. The VENUS Study has developed a database to assess vaccine effectiveness and safety in Japan, including the Health Center Real-Time Information-Sharing System on COVID-19 (HER-SYS), the Vaccination Record System, and healthcare claims data. HER-SYS data accumulated information on all patients with COVID-19 until 26 September 2022. However, reporting was later relaxed, and the government adjusted the rule to report patients aged ≥65 years, had risk factors for severe COVID-19, needed anti–COVID-19 medication or supplementary oxygen, or were pregnant. The Vaccination Record System data included information on COVID-19 vaccination.

The BA.1 (Pfizer and Moderna), BA.4/5 bivalent (Pfizer), and BA.4/5 bivalent (Moderna) vaccines were approved on 12 September, 5 October, and 1 November 2022, respectively. Furthermore, bivalent vaccination was initiated on 20 September 2022. The approved vaccination schedule was ≥5 months after the last dose, including the first or second booster dose and primary series with monovalent vaccines. However, the indication changed to ≥3 months after the last vaccination on 19 October 2022. Therefore, the inclusion criteria of the study comprised individuals who (1) received the first or second booster doses of monovalent mRNA vaccines before 20 September 2022 and (2) were aged ≥65 years on the cohort entry date (CED).

The CED was set at either (20 September 2022, for those who received their last dose of monovalent mRNA vaccine ≥90 days earlier, or 90 days after the last dose of the first or second booster doses of monovalent mRNA vaccine for those who had received their last dose of vaccine <90 days earlier, as of 20 September 2022. We excluded individuals who (1) died or did not have residency before the CED, (2) had no claims per year before the CED, (3) had been vaccinated with Novavax or bivalent vaccine before the CED, or (4) had confirmed COVID-19 between 1 July 2022 and the CED. We followed up with the individuals until (1) the event date; (2) COVID-19 vaccination, including monovalent mRNA vaccine and another type of vaccine; (3) death; (4) discontinuation of residency for any reason; or (5) the end of the study period (31 December 2022), whichever came first.

Exposure

Exposure was defined as receiving BA.1 or BA.4/5 bivalent mRNA vaccines (Pfizer or Moderna). To estimate vaccine effectiveness, vaccination status was classified as (1) no bivalent vaccine booster dose (≥90 days after the first or second booster dose by monovalent mRNA vaccines) or (2) 0–1 week or ≥2 weeks after bivalent mRNA vaccination. We compared 0–1 week and ≥2 weeks after the bivalent mRNA vaccines with the first or second booster dose without bivalent vaccine booster dose (≥90 days after the first or second booster dose by monovalent mRNA vaccines) to assess the relative vaccine effectiveness.

Outcomes and Covariates

The study outcomes were COVID-19, COVID-19–related hospitalization, or COVID-19–related death. The COVID-19 data were identified on the reporting form, and the specimen submitted date or reported date as the COVID-19 date in the HER-SYS records. The reporting form for COVID-19 was simplified starting on 30 June 2022; information on the symptoms, type of testing for SARS-CoV-2, and testing specimens were removed from the reporting items. Therefore, the outcome of COVID-19 was defined as information, regardless of the symptoms. Using healthcare claims data, COVID-19–related hospitalization was defined as hospitalization between 2 days before and 14 days after the COVID-19 date. Furthermore, COVID-19–related deaths were defined as those that occurred 30 days after the COVID-19 date, which were determined using residence-related information.

Covariates included baseline demographics (age and sex) on the CED and the presence of 9 underlying diseases (cancer, cardiovascular disease, cerebrovascular disease, chronic pulmonary disease, chronic renal disease, chronic liver disease, diabetes, rheumatic disease, and dementia retrieved from healthcare claims) diagnosed using the *International Classification of Diseases, Tenth Revision* codes in the previous year. These codes were summarized in the Supplementary Table 1. The number of outpatient visits to clinics/hospitals was calculated in the previous year. Previous COVID-19 cases were categorized as post-Omicron infection (until December 2021) and pre-Omicron infection (between January and June 2022).

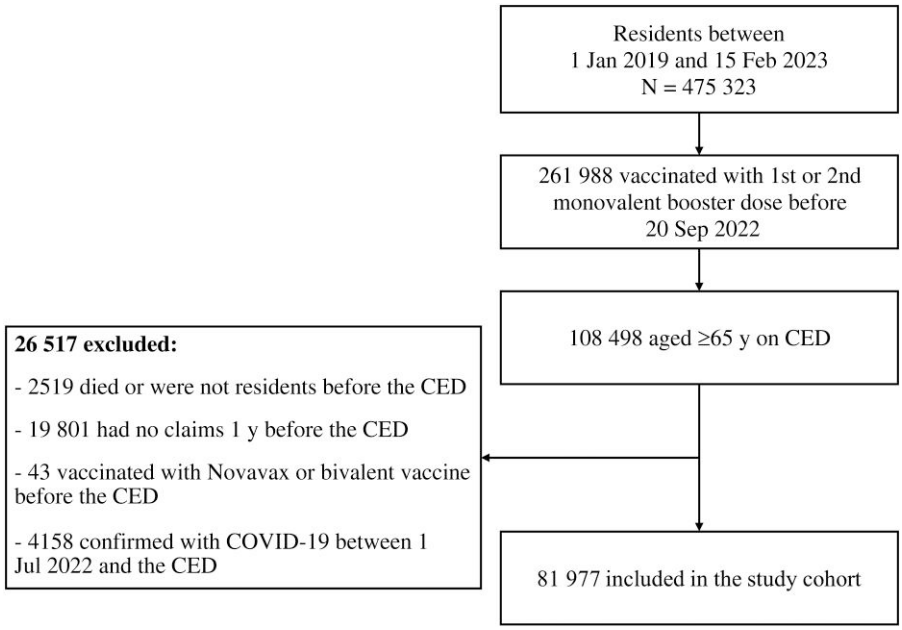

Figure 1. Flow diagram of the study. The cohort entry date (CED) was set at either (1) 20 September 2022, for those who received their last dose of monovalent messenger RNA (mRNA) vaccine ≥90 days earlier, or (2) 90 days after the last dose of the first or second booster doses of monovalent mRNA vaccine, for those who received their last dose of vaccine <90 days earlier, as of 20 September 2022. Abbreviation: COVID-19, coronavirus disease 2019.

Statistical Analyses

Baseline characteristics are described using mean (standard deviation) or median (interquartile range [IQR]) and frequency (percentage) in the overall cohort. We used the Cox regression model with time-dependent exposure as the vaccination status, including the covariates (age, sex, number of vaccination doses at CED, days after the last dose before CED, underlying diseases, number of outpatient visits in the previous year, post-Omicron infection, and pre-Omicron infection), and estimated adjusted hazard ratios (HR) and their confidence intervals (CIs). Vaccine effectiveness was calculated using the following formula: $[(1 - \mathrm{HR}) \times 100]$ (%). In the subgroup analysis, we analyzed the effectiveness of the third bivalent vaccine booster dose compared to the second monovalent vaccine dose. Furthermore, as an additional analysis, we assessed the effectiveness of the second booster dose by mRNA vaccines when compared to the first booster dose by mRNA vaccines, regardless of whether it was bivalent or monovalent. In this analysis, we changed the cohort entry date to 1 July 2022. All analyses were performed using R version 4.1.2 (R Foundation for Statistical Computing).

Patient Consent Statement

This study was approved by the Kyushu University Institutional Review Board for Clinical Research (no. 22114-00). The requirement for individual informed consent was waived based on the Japanese ethical guidelines, as this secondary analysis used routinely collected anonymized data by the municipalities.

RESULTS

Among the 475 323 people identified, we included 81 977 individuals (mean age [standard deviation], 78.3 [7.4] years; 33 487 [40.8%] male) who met the inclusion and exclusion criteria (Figure 1). The numbers of individuals vaccinated with the first, second, and third booster doses by the CED were 11 638 (14.2%), 70 326 (85.8%), and 13 (0.02%), respectively (Table 1). Of these, 81 964 (99.9%) received monovalent vaccines as the first and second booster doses, and 13 (0.02%) received bivalent vaccines as the third booster dose at the CED. During the observation period, 6819 (8.3%), 663 (0.8%), 48 280 (58.9%), and 1621 (2.0%) of the individuals received their second or third booster doses of BA.1 (Pfizer), BA.1 (Moderna), BA.4/5 (Pfizer), and BA.4/5 (Moderna), respectively. A total of 1256 individuals (1.5%) were infected with COVID-19 before the Omicron-predominant period (before 31 December 2021). Moreover, in the Omicron BA.1 and BA.2–predominant period (from 1 January to 30 June 2022), 359 individuals (0.4%) were infected.

The median follow-up period (IQR) was 34 (21–51) days after the first or second monovalent vaccine booster dose and 32 (19–46) days after the second or third bivalent vaccine booster dose. The median time (IQR) after the monovalent booster dose until bivalent vaccination or end of follow-up was 163 (155–177) days. A total of 2775 individuals (3.4%) were confirmed to have COVID-19 during the follow-up period. Furthermore, COVID-19–related hospitalization and death occurred in 55 (0.07%) and 42 (0.05%) of the cases, respectively

Table 1. Characteristics of Patients in Study Cohort

Characteristic	Patients, No. (%)[a] (n = 81 9770)
Age, mean (SD), y	78.3 (7.4)
Sex	
Male	33 487 (40.8)
Female	48 490 (59.2)
Underlying disease	
Cancer	12 940 (15.8)
Chronic pulmonary disease	17 024 (20.8)
Cardiovascular disease	29 307 (35.8)
Cerebrovascular disease	14 756 (18.0)
Renal disease	15 016 (18.3)
Liver disease	5059 (6.2)
Diabetes	33 486 (40.8)
Rheumatologic disease	3909 (4.8)
Dementia	7728 (9.4)
No. of outpatient visits, median (IQR)	21.0 (12.0–33.0)
Post-Omicron infection	1256 (1.5)
Pre-Omicron infection	359 (0.4)
Vaccination status at CED	
1st Booster by Moderna (monovalent)	4958 (6.0)
1st Booster by Pfizer (monovalent)	6680 (8.1)
2nd Booster by Moderna (monovalent)	15 327 (18.7)
2nd Booster by Pfizer (monovalent)	54 999 (67.1)
3rd Booster by Pfizer (BA.1)	2 (0.0)
3rd Booster by Pfizer (BA.4/.5)	11 (0.0)
Cohort entry month in 2022	
September	11 881 (14.5)
October	35 122 (42.8)
November	28 769 (35.1)
December	6205 (7.6)
Vaccinated after CED	
2nd Booster by Moderna (BA.1)	35 (0.0)
2nd Booster by Moderna (BA.4/5)	196 (0.2)
2nd Booster by Pfizer (BA.1)	2259 (2.8)
2nd Booster by Pfizer (BA.4/5)	1780 (2.2)
Third booster by Moderna (BA.1)	628 (0.8)
3rd Booster by Moderna (BA.4/5)	1425 (1.7)
3rd Booster by Pfizer (BA.1)	4560 (5.6)
3rd Booster by Pfizer (BA.4/5)	46 500 (56.7)

Abbreviations: CED, cohort entry date; IQR, interquartile range; SD, standard deviation.

[a]Data represent no. (%) of patients unless otherwise specified.

(Table 2). Among COVID-19 cases, hospitalizations and deaths represented 2.0% and 1.5% of the sample, respectively. Moreover, the adjusted effectiveness of the bivalent vaccine against COVID-19 was 57.9% (95% CI, 52.7%–62.5%), while the unadjusted effectiveness was 77.5% (46.7%–90.5%) against COVID-19–related hospitalization and 77.3% (44.3%–90.7%) against COVID-19–related death at ≥14 days after the second or third bivalent vaccine booster doses relative to that ≥90 days after the first or second monovalent mRNA vaccine booster dose.

The third bivalent vaccine booster dose showed 55.3% (95% CI, 49.1%–60.8%) effectiveness against COVID-19 compared with ≥90 days after the second monovalent vaccine booster dose (Supplementary Table 2). In the additional analysis, compared with the first mRNA vaccine booster dose, the effectiveness of the second mRNA vaccine booster dose against COVID-19 and COVID-19–related hospitalization was 33.0% (95% CI, 28.1%–37.5%) and 53.1% (37.5%–64.8%), respectively (Supplementary Table 3).

DISCUSSION

This cohort study reported the effectiveness of the bivalent mRNA vaccines among the older population (aged ≥65 years) during the Omicron BA.5–predominant period in Japan. The second or third bivalent vaccine booster doses provided additional protection, and their effectiveness against COVID-19 was 57.9% at ≥14 days after the doses. Furthermore, they were highly effective against COVID-19–related hospitalization (77.5%) and death (77.3%), though without adjustment for other factors owing to the low hospitalization and mortality rates. Almost the entire study population was vaccinated with a second monovalent mRNA booster dose. The effectiveness of the third dose of bivalent vaccines was comparable to that of their second or third booster doses. The vaccine effectiveness against COVID-19 was higher than that reported in previous studies; however, the effectiveness against hospitalization and death was consistent with previous findings [13–16, 19].

The National Institute of Infectious Diseases in Japan reported 72% effectiveness of the bivalent vaccine against symptomatic infection at ≥14 days after vaccination, compared with unvaccinated individuals during the predominant period of Omicron BA.5 in the Kanto region. The relative effectiveness was 35% and 46% compared with ≥2 doses of monovalent vaccine during 3–6 and 6 months after monovalent vaccination, respectively [16]. Moreover, the United States reported a 37% effectiveness against symptomatic BA.5-related infection at ≥2 weeks after the bivalent dose compared with 2–4 monovalent doses among adults aged ≥65 years. The effectiveness of the bivalent vaccine against COVID-19 hospitalization was reported to be 73% (vs ≥2 monovalent mRNA vaccine doses ≥2 months after the last dose) among adults aged ≥65 years [14].

Another study showed that the effectiveness of the fourth dose monovalent vaccine at 1 month after vaccination was 57% against BA.4/5 symptomatic infection among ≥65-year-olds [20], while its effectiveness against hospitalization or death was 61.5% [13]. In the United Kingdom, the bivalent vaccine effectiveness against hospitalization was estimated to be 63.6% in persons ≥50 years old compared with ≥2 doses ≥6 months after the last dose [15]. Moreover, the effectiveness against mortality was reported to be about 70% [21]. The HR for medically attended symptomatic SARS-CoV-2 infection and hospitalization in the ≥60-year age group was 0.20–0.24, while that for the ≥18-year age group was 0.10 compared with receiving the fourth dose of the bivalent vaccine after 3 doses in Singapore [22].

Table 2. Vaccine Effectiveness After the Second or Third Booster Doses by Bivalent Vaccine Among Adults Aged ≥65 Years During Omicron BA.5 Predominance

Event Type	No. of Events	No. of Individuals	No. of PD	Event Rate per 1 000 000 PD	HR (95% CI)		VE (95% CI), %	
					Unadjusted	Adjusted	Unadjusted	Adjusted
COVID-19 infection								
≥90 d After 1st or 2nd monovalent booster dose	1923	81 964	3 198 491	601.2	Ref	Ref	Ref	Ref
0–13 d After 2nd or 3rd bivalent booster dose	348	57 405	762 030	456.7	0.635 (.565–.714)	0.565 (.501–.637)	36.5 (28.6–43.5)	43.5 (36.3–49.9)
≥14 d After 2nd or 3rd bivalent booster dose	504	48 749	1 174 012	429.3	0.486 (.436–.542)	0.421 (.375–.473)	51.4 (45.8–56.4)	57.9 (52.7–62.5)
COVID-19–related hospitalization[a]								
≥90 d After 1st or 2nd monovalent booster dose	45	81 964	3 253 770	13.8	Ref	…	Ref	…
0–13 d After 2nd or 3rd bivalent booster dose	4	57 626	766 499	5.2	0.291 (.104–.810)	…	70.9 (19.0–89.6)	…
≥14 d After 2nd or 3rd bivalent booster dose	6	49 148	1 187 522	5.1	0.225 (.095–.533)	…	77.5 (46.7–90.5)	…
COVID-19–related death[a]								
≥90 d After 1st or 2nd monovalent booster dose	34	81 964	3 283 378	10.4	Ref	…	Ref	…
0–13 d After 2nd or 3rd bivalent booster dose	2	57 629	766 711	2.6	0.167 (.040–.702)	…	83.3 (29.8–96.0)	…
≥14 d After 2nd or 3rd bivalent booster dose	6	49 182	1 189 585	5.0	0.227 (.093–.557)	…	77.3 (44.3–90.7)	…

Abbreviations: COVID-19, coronavirus disease 2019; HR, hazard ratio; PD, person-days; Ref, reference; VE, vaccine effectiveness.

[a]Only unadjusted HR and VE are shown for COVID-19–related hospitalization and death, owing to the low event rates.

Notably, our study showed similar or higher vaccine effectiveness compared with previous studies, which could be explained as a short duration after bivalent vaccination. In addition, the variations in effectiveness could be affected by the comparator used and the prevalence of infection-induced immunity. In particular, asymptomatic cases are more prevalent in the Kanto region, which comprises the Tokyo Metropolis and 6 prefectures, and other countries than in our study municipality, which could have caused the variations in the effectiveness of the bivalent vaccine against COVID-19.

Furthermore, infection-induced seroprevalence is lower in Japan than in other countries (Table 3). A report of a study using blood donors showed that 28.6% were positive for anti-nucleocapsid antibodies between 6 and 13 November 2022 (during the Omicron BA.5–predominant period) [23]. Moreover, the prevalence was lower in the older group than in the younger group (17.0% in the 60–69-year age group). The low prevalence would be associated with the difference in household contacts, working, work-related social gatherings, and vaccination coverage. Therefore, compared with other studies, our results would suggest vaccine effectiveness in populations with low hybrid immunity.

The World Health Organization's Strategic Advisory Group of Experts on Immunization revised the road map for prioritizing uses of COVID-19 vaccines to consider high vaccination coverage and infection-induced immunity on 30 March 2023 [27]. Furthermore, the Japanese government announced the COVID-19 vaccination schedule for fiscal year 2023. The priority group between March and August 2023 includes older adults (aged ≥65 years), individuals <65 years old with underlying diseases, medical staff, and long-term care staff. After September 2023, all individuals aged ≥5 years will be eligible for vaccination.

However, the recombinant subvariants XBB and the BA.5 subvariant BQ.1 have gradually become prevalent in Japan after

Table 3. Prevalence of the Infection-Induced Immunity in Japan, the United States, and the United Kingdom

Country	Period in 2022	Age, y	Prevalence of Infection-Induced Immunity, %
Tokyo, Japan	February–March	Overall	3.5 [17]
Japan	6–13 November	16–69	28.6 [23]
	6–13 November	60–69	17.0 [23]
	19–27 February 2023	60–69	27.5 [24]
United States	January–March	≥65	26.0 [25]
	April–June	≥65	32.6 [25]
	July–September	≥65	46.6 [25]
United Kingdom	29 June to 19 August	60–69	62.7 [26]
	29 June to 19 August	70–84	53.9 [26]
	30 August to 18 November	60–69	72.4 [15]
	30 August to 18 November	70–84	62.4 [15]

BA.5, and the effectiveness of the bivalent vaccine against XBB/XBB.1.5-related symptomatic infection was shown to be 49% for those aged 18–49 years, 40% for those aged 50–64 years, and 43% for those aged ≥65 years [11]; although its effectiveness was comparable to that against BA.2, the hybrid immunity from the previous BA.2 infection waned faster against XBB reinfection [28]. Moreover, anti-nucleocapsid antibodies rose significantly to 4.3% in February–March 2022, during the sixth wave due to Omicron BA.1/BA.2 in Japan, although seroprevalence was low before our study period [17]. Thus, evaluating the effectiveness and the decline over time after the Omicron BA.5–dominant phase is crucial for updating the vaccination program.

The current study had a few limitations. First, we could not identify the type of Omicron subvariants based on genome sequencing. However, our study period was dominated by BA.5 subvariants; thus, our results could be interpreted as evidence of vaccine effectiveness against the BA.5 sublineage. Second, we could not evaluate the symptoms because reporting based on the reporting form (which must be submitted according to the Act on the Prevention of Infectious Diseases and Medical Care for Patients with Infectious Diseases in Japan) was relaxed, and the symptoms were removed from the reporting items. Therefore, our COVID-19 outcome might be mixed with asymptomatic and symptomatic cases.

A third limitation was that we used data from a single municipality. Thus, it would be difficult to generalize the results to the entire elderly population (aged ≥65 years) in Japan, as there are regional differences in the seroprevalence of anti-nucleocapsid antibodies. Specifically, our study population showed a low prevalence of previous infections; thus, vaccine effectiveness may differ in areas with high infection rates in Japan. Fourth, residual confounding factors were included in the analysis. In addition, we could not perform adjustments using covariates to estimate the relative vaccine effectiveness against COVID-19–related hospitalization and death owing to the low rates in our study population. Finally, the effectiveness of the vaccine on the outcomes of this study was limited to a short duration. The median follow-up period (IQR) was 32 (19–46) days after the second or third booster dose of the bivalent vaccine. Thus, we could not assess the waning of bivalent vaccine effectiveness over time after the Omicron BA.5–predominant period.

This study provided the bivalent vaccine's effectiveness against COVID-19, hospitalization, and death in Japan for adults aged ≥65 years. Furthermore, our results indicated that the booster dose of bivalent vaccines provided additional protection against COVID-19. Therefore, the bivalent booster dose remains an important measurement for high-risk groups to reduce the disease burden of COVID-19.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Data availability. Data cannot be made available for privacy or ethical reasons.

Potential conflicts of interest. All authors: No reported conflicts.

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