Open Forum Infectious Diseases

MAJOR ARTICLE

Effectiveness of a Third Dose of COVID-19 mRNA Vaccine During the Omicron BA.1- and BA.2-Predominant Periods in Japan: The VENUS Study

Wataru Mimura,[1] Chieko Ishiguro,[1] Megumi Maeda,[2] Fumiko Murata,[2] and Haruhisa Fukuda[2]

[1]Section of Clinical Epidemiology, Department of Data Science, Center for Clinical Sciences, National Center for Global Health and Medicine, Tokyo, Japan, and [2]Department of Health Care Administration and Management, Kyushu University Graduate School of Medical Sciences, Fukuoka, Japan

Background. Vaccine effectiveness against the severe acute respiratory syndrome coronavirus 2 Omicron BA.2 sublineage in Japan is unknown. We assessed the effectiveness of a third dose of COVID-19 mRNA vaccine compared with that of 2 doses.

Methods. We performed a population-based cohort study using a municipality database located in the Chubu region of Japan during the Omicron BA.1- and BA.2-predominant periods (January 1–March 31, 2022 and April 1–27, 2022, respectively). We included residents aged ≥16 years who received a second vaccine dose at ≥14 days before the start of each period, regardless of the third dose. We compared the data at 14 days after the second and third dose and at 2-week intervals from 14 days to 10 weeks after the third dose using a Cox regression model. Vaccine effectiveness was defined as (1 – hazard ratio) × 100 (%).

Results. In total, 295 705 and 288 184 individuals were included in the BA.1- and BA.2-predominant periods, respectively. The effectiveness of a third dose against infection was 62.4% and 48.1% in the BA.1- and BA.2-predominant periods, respectively. Vaccine effectiveness at 2–3 weeks and ≥10 weeks after the third dose decreased from 63.6% (95% confidence interval [CI], 56.4–69.5%) to 52.9% (95% CI, 41.1–62.3%) and from 54.5% (95% CI, 3.0–78.7%) to 40.1% (95% CI, 15.1–57.7%) in the BA.1- and BA.2-predominant periods, respectively.

Conclusions. A third dose was moderately effective against BA.1 and BA.2 sublineages, but its effectiveness decreased by approximately 10% age points from 2–3 weeks to ≥10 weeks after the third vaccination.

Keywords. COVID-19; Japan; mRNA vaccine; SARS-COV-2; vaccine effectiveness.

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Omicron variant (B.1.1.529) rapidly spread worldwide after first being reported in South Africa [1–3]. The Omicron variant was first detected in late November 2021 in Japan, and the Omicron BA.1. sublineage replaced the Delta variant, as the predominant variant in Japan in late December 2021 [4]. The wave of infection caused by the Omicron variant was larger than past waves caused by the Alpha and Delta variants. The daily coronavirus disease 2019 (COVID-19) reporting rate increased from approximately 5 cases per 100 000 individuals in January 2022 to 505 cases per 100 000 individuals in February 2022 [4, 5]. Moreover, the Omicron BA.2 sublineage replaced the BA.1 sublineage in April 2022 [6]. Despite the higher transmissibility of the Omicron variant, the risk of severe COVID-19 was lower than that with the Delta variant [7, 8]. In addition, the Omicron sublineage BA.2 had a higher effective reproduction number than that of the BA.1 sublineage [9, 10].

By April 2022, the BNT162b2 (Pfizer, New York, NY; BioNTech, Mainz, Germany), mRNA-1273 (Moderna, Cambridge, MA), ChAdOx1 nCoV-19 (Oxford-AstraZeneca, Cambridge, UK), and NVX-CoV2373 (Novavax, Gaithersburg, MD) COVID-19 vaccines were approved in Japan [11]. In Japan, vaccinations of the general population began on 12 April 2021, and administration of a third (booster) dose started on December 1, 2021. The vaccination campaign for the third dose initially prioritized healthcare workers and older adults. As of April 25, 2022, vaccination coverage of the second dose and third dose of vaccine in the older adult population, was 80.0% and 50.8%, respectively [12].

The effectiveness of the primary 2-dose mRNA series against the Omicron variant was lower than that against the Delta and Alpha variants because of its high transmissibility and immune evasion [13–16]. The effectiveness of a primary series against the symptomatic Omicron variant infection waned rapidly. In a recent study, researchers found that the effectiveness of a

Received 26 August 2022; editorial decision 17 November 2022; accepted 23 November 2022; published online 24 November 2022

Correspondence: Chieko Ishiguro, MPH, PhD, Section of Clinical Epidemiology, Department of Data Science, Center for Clinical Sciences, National Center for Global Health and Medicine, 1-21-1 Toyama, Shinjuku-ku, Tokyo 162-8655, Japan (chishiguro@hosp.ncgm.go.jp).

Open Forum Infectious Diseases®2022

https://doi.org/10.1093/ofid/ofac636

primary series 20–24 weeks after the second vaccination was 11.5% (95% confidence interval [CI], 10.1–12.9%) and 15.0% (95% CI, 11.6–18.2%) by BNT162b2 and mRNA-1273, respectively [16]. In addition, in a study conducted in Qatar, researchers found no effect 7 months after a second mRNA vaccine dose [17]. However, the administration of 3 doses of vaccine was moderately effective at preventing infection and highly effective against hospitalization or death compared to individuals who were unvaccinated and individuals who had completed the primary vaccination series [16–26]. In addition, the immunogenicity and effectiveness of a third dose, against sublineage BA.2 and BA.1, were comparable [27, 28]. A few studies have reported more rapid waning of vaccine effectiveness with the Omicron BA.1 and BA.2 sublineages than with earlier variants [17–21]. In Japan, some studies have estimated the effectiveness of 3 doses of vaccine against the Delta and Omicron BA.1 variants; however, no study has estimated the effectiveness of 3 doses of vaccine against the BA.2 variant [26, 29–31]. Therefore, this study aimed to evaluate mRNA vaccine effectiveness and duration during the periods of Omicron BA.1 and BA.2 predominance in Japan from the Vaccine Effectiveness, Networking, and Universal Safety (VENUS) Study.

METHODS

Study Design, Data Source, and Setting

In this population-based cohort study, we identified the residents between January 1, 2019 and April 13, 2022, using the VENUS Study data from 1 municipality in the Chubu region of Japan [32]. The Chubu region is located in the middle of the main island. The VENUS Study constructed 2 municipality-based databases: the Health Center Real-Time Information-Sharing System on COVID-19 (HER-SYS) and the Vaccination Record System (VRS) [33]. Records in the 2 databases were linked individually. The HER-SYS included information on COVID-19 cases (date of testing, type of specimens, type of testing, results of testing, and symptoms), and the VRS included COVID-19 vaccination records (vaccine type and date of vaccination). The data were anonymized, and the Kyushu University Institutional Review Board for Clinical Research approved the study (No. 2021-399) and waived the requirement for informed consent.

This study comprised 2 cohorts to assess the effectiveness against the Omicron BA.1 and BA.2 sublineages. The study cohorts were the BA.1- (January 1–March 31, 2022) and BA.2- (April 1–27, 2022) predominant periods [34, 35]. Several vaccines for COVID-19 were approved in Japan before the start of the study period, with mRNA vaccines being the predominant type. Thus, we aimed to assess the effectiveness of mRNA vaccines. We included individuals who met the following 2 criteria: (1) individuals aged ≥16 years at the start of the 2 study periods (January 1, 2022 and April 1, 2022, for the BA.1 and BA.2 cohorts, respectively) and (2) individuals who had received at least 2 doses of mRNA vaccine ≥14 days before the start of each study period, regardless of the third dose. We excluded the following individuals: (1) those with a history of COVID-19 before the start of each study period; (2) those with missing data on the first dose of vaccine; (3) those vaccinated before 12 April 2021; (4) those vaccinated with the ChAdOx1 nCoV-19 (Oxford-AstraZeneca) vaccine; (5) those with first and second doses <19 days apart before the start of each period; or (6) those with second and third doses <150 days apart before the start of each period.

The vaccination status changed during the follow-up period; for example, some individuals received a third dose of vaccine after the cohort entry. In the primary analysis, the vaccination status was categorized as that at ≥14 days after the second dose to 13 days after the third dose and that at ≥14 days after the third dose. In the secondary analysis, to evaluate the change in immunity over time since the third dose, vaccination status was categorized as follows: 14 days after the second dose to 13 days after the third dose, 2–3 weeks after the third dose, 4–5 weeks after the third dose, 6–7 weeks after the third dose, 8–9 weeks after the third dose, and ≥10 weeks after the third dose.

Infection was defined as a positive SARS-CoV-2 nucleic acid amplification test or antigen test result, regardless of symptoms. Symptomatic infection was defined as a positive SARS-CoV-2 nucleic acid amplification test or antigen test, with symptoms related to COVID-19.

Statistical Analysis

We described the characteristics of the individuals in the 2 cohorts (sex, age at the entry, the vaccination series through the study period, and the month of the second dose). In this cohort study, we followed up the individuals from the start of each cohort (January 1, 2022 and April 1, 2022). Follow up was censored at the end of the study period, death, moving to a different locale, or no longer being a resident for other reasons. In the primary analysis, for assessing the vaccine effectiveness of the third dose in each cohort, effectiveness at ≥14 days after the third dose was compared with that at ≥14 days after the second dose to 13 days after the third dose. In the secondary analysis, for assessing the waning immunity after the third dose, effectiveness at 2–3 weeks after the third dose, 4–5 weeks after the third dose, 6–7 weeks after the third dose, 8–9 weeks after the third dose, and ≥10 weeks after the third dose were compared with that at ≥14 days after the second dose to 13 days after the third dose. We used a Cox proportional hazards model considering a time-varying vaccination status to estimate the hazard ratios and 95% confidence intervals. To estimate the adjusted hazard ratios, age at the cohort entry date, sex, and the month of the second dose were added as fixed covariates in

the model. Vaccine effectiveness was calculated as follows: 1 − hazard ratio (×100%). In addition, we conducted a subgroup analysis with the stratified by age (<65 and ≥65 years) to assess the effect of age as a potential effect modifier. All statistical analyses were performed using R version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria).

Patient Consent Statement

The Kyushu University Institutional Review Board for Clinical Research approved this study (No. 2021-399) and allowed the researchers to waive the requirement for obtaining informed consent because of the retrospective nature of the study and the use of anonymized data.

RESULTS

During the study period, 462 864 residents were identified in the municipality's VENUS data system (Figure 1). Of these, 295 705 and 288 184 individuals were included in the study during the BA.1- and BA.2-predominant periods, respectively. The median age was 56.0 years and 46.5% were male (Table 1) in both cohorts. The median follow-up periods were 89 days and 26 days in BA.1 cohort and BA.2 cohort, respectively; thus, almost all individuals were followed through the study period. In the BA.1 cohort, 2720 (0.92%) residents moved out; 1095 (0.37%) died during the study period. In the BA.2 cohort, 335 (0.12%) moved out; 118 (0.04%) died during the study period. The period from June to October 2021 was a common timing of the second dose. In the 2 cohorts, 57.9% and 69.7% of individuals had received a third dose by the end of the follow-up period. In the BA.1-predominant cohort, almost all individuals (295 695 of 295 705) had received only 2 doses of vaccine on cohort entry (January 1, 2022). They received the second dose of vaccine a median of 144 days (interquartile range [IQR], 95–181 days) before cohort entry. In contrast, 145 942 (44.2%) of individuals in the BA.2-predominant cohort had received only 2 doses of vaccine on cohort entry (April 1, 2022). They received the second dose of vaccine a median of 185 days (IQR, 161–212 days) before cohort entry. Heterologous booster vaccinations were common. Of the BA.2-predominant cohort members who received the third dose after a 2-dose BNT162b2 primary series, 44.3% received the mRNA-1273 vaccine as the third dose. Of the BA.2-predominant cohort members who received the third dose after a 2-dose mRNA-1273 primary series, 12.5% received the BNT162b2 vaccine as the third dose.

In the primary analysis, the effectiveness of mRNA vaccine against infection at 14 days after the third dose during the BA.1- and BA.2-predominant periods was 62.4% (95% CI, 56.9–67.2%) and 48.1% (95% CI, 39.2–55.7%), respectively (Table 2). In the secondary analysis, the effectiveness decreased from 63.6% (56.4–69.5%) at 2–3 weeks to 54.5% (95% CI, 3.0–78.7%) at ≥10 weeks after the third dose during the BA.1-predominant period (Figure 2A and Supplementary Table 1). The effectiveness decreased from 52.9% (95% CI, 41.1–62.3%) at 2–3 weeks to 40.1% (95% CI, 15.1–57.7%) at ≥10 weeks after the third dose during the BA.2-predominant period (Figure 2B and Supplementary Table 1). In the population aged 16–64 years, the effectiveness against infection was 46.2% (95% CI, 37.4–53.8%) and 42.9% (95% CI, 33.1–51.3%) during the BA.1- and BA.2-predominant periods, respectively) (Supplementary Table 2). In the population aged ≥65 years, the effectiveness against infection was 61.3% (95% CI, 50.7–69.6%) and 58.4% (95% CI, 39.3–71.5%) during the BA.1- and BA.2-predominant periods, respectively.

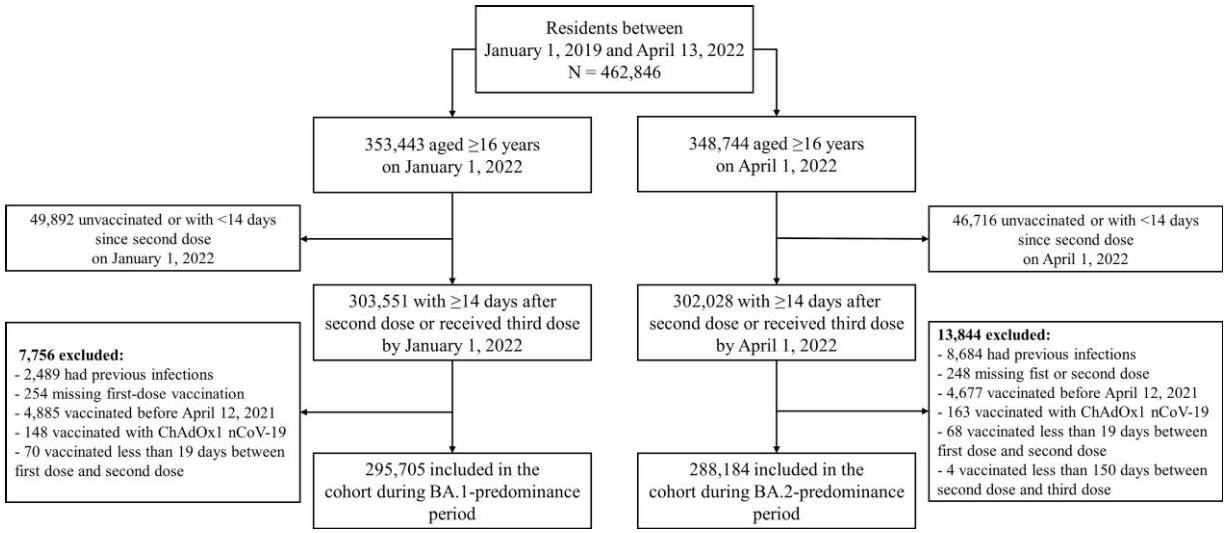

Figure 1. Study flow chart.

DISCUSSION

This population-based cohort study showed vaccine effectiveness and waning effectiveness against the Omicron BA.1 and BA.2 sublineages in the VENUS Study. The effectiveness of a third dose of mRNA vaccine compared to only 2 doses against infection and symptomatic infection during the BA.2-predominant period was slightly lower than that during the BA.1-predominant period. Although the 95% CIs for the vaccine effectiveness during the BA.1- and BA.2-predominant periods overlapped considerably in the analysis of the effectiveness every 2 weeks after the third dose, the third dose maintained moderate effectiveness during both periods. The effectiveness against infection and symptomatic infection gradually decreased by approximately 10% age points from 2–3 weeks to ≥10 weeks after the third dose in the BA.2-predominant period.

According to our results, the effectiveness of a third dose of mRNA vaccine was lower in BA.2- than that in BA.1-predominate period. The US VISION Network study found that effectiveness of a third dose of vaccine at preventing symptomatic COVID-19 and hospitalization during the BA.2/BA.2.12.2 period was lower than that during the BA.1 period [20]. In contrast, in previous studies, researchers have found no significant differences in neutralizing antibody titers against BA.1 and BA.2 after the third dose [27, 28]. In addition, several observational studies have not found any clinically significant difference in the effectiveness of a third dose of mRNA vaccine against BA.1 and BA.2 [17–19]. The wave caused by BA.1 in Japan was the largest of all the waves to date. Therefore, untested individuals with infection might have been included in the groups of individuals with 2 or 3 doses of infection. Moreover, the rates of testing (and hence diagnosis of infection) may have varied according to the study period (cohort) or the number of doses of vaccine received. For example, hospitals and clinics for diagnosis of COVID-19 could have been overwhelmed owing to the drastic increase in COVID-19 cases during the BA.1-predominant period, even though the healthcare setting had been reinforced, like free COVID-19 testing in pharmacies. Although the municipality in the study did not adopt the COVID-19 diagnosis based on the symptoms without testing, the Japanese government announced the statement to mitigate the burden of the healthcare system [36]. Those changes during the study period may have caused bias in the estimates of the effectiveness of a third dose of vaccine. In addition, in the BA.1-predominant cohort, more individuals were in the early period of 14 days after the third dose on cohort entry than in the BA.2-predominant cohort. This may have resulted in a higher estimated effectiveness during the BA.1-predominant period than during the BA.2-predominant period.

In this study, the rate of decline in the effectiveness after the third vaccination was similar during the BA.1- and BA.2-predominant periods. The effectiveness of a third dose of BNT162b2 vaccine against symptomatic infection in Qatar was 59.9% at <1 month after the third dose and 40.5% (30.8–48.8%) at ≥1 month after the third dose against BA.1, whereas it was 43.7% at <1 month after the third dose and 40.2% at

Table 1. Characteristics of the Study Cohort in Each Period

Characteristic	Predominant SARS-CoV-2 variant	
	Omicron BA.1[a] N = 295 705	Omicron BA.2[b] N = 288 184
Sex, n (%)		
Male	137 548 (46.5%)	133 971 (46.5%)
Female	158 157 (53.5%)	154 213 (53.5%)
Age, median (IQR)	56.0 (40.0–72.0)	56.0 (41.0–72.0)
Age group, n (%)		
16–24	27 625 (9.3%)	26 072 (9.0%)
25–34	27 868 (9.4%)	26 340 (9.1%)
35–44	36 442 (12.3%)	34 913 (12.1%)
45–54	52 159 (17.6%)	50 564 (17.5%)
55–64	43 070 (14.6%)	42 827 (14.9%)
65–74	49 941 (16.9%)	48 892 (17.0%)
75–84	39 609 (13.4%)	39 421 (13.7%)
85–94	17 335 (5.9%)	17 464 (6.1%)
≥95	1656 (0.6%)	1691 (0.6%)
Vaccination series, n (%)		
BNT162b2/BNT162b2/No vaccination	99 602 (33.7%)	70 538 (24.5%)
BNT162b2/mRNA-1273/No vaccination	0 (0.0%)	7 (0.0%)
BNT162b2/BNT162b2/BNT162b2	82 835 (28.0%)	99 769 (34.6%)
BNT162b2/BNT162b2/mRNA-1273	72 634 (24.6%)	79 319 (27.5%)
mRNA-1273/BNT162b2/No vaccination	79 (0.0%)	79 (0.0%)
mRNA-1273/mRNA-1273/No vaccination	24 694 (8.4%)	16 636 (5.8%)
mRNA-1273/BNT162b2/BNT162b2	0 (0.0%)	1 (0.0%)
mRNA-1273/BNT162b2/mRNA-1273	0 (0.0%)	1 (0.0%)
mRNA-1273/mRNA-1273/BNT162b2	1493 (0.5%)	2729 (0.9%)
mRNA-1273/mRNA-1273/mRNA-1273	14 368 (4.9%)	19 105 (6.6%)
Month of second dose, n (%)		
2021–05	7835 (2.6%)	7535 (2.6%)
2021–06	54 138 (18.3%)	52 692 (18.3%)
2021–07	67 017 (22.7%)	65 525 (22.7%)
2021–08	51 374 (17.4%)	49 416 (17.1%)
2021–09	45 032 (15.2%)	43 439 (15.1%)
2021–10	47 452 (16.0%)	45 570 (15.8%)
2021–11	22 226 (7.5%)	21 375 (7.4%)
2021–12	631 (0.2%)	1055 (0.4%)
2022–01	-	630 (0.2%)
2022–02	-	663 (0.2%)
2022–03	-	284 (0.1%)

Abbreviations: IQR, interquartile range; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a]January 1, 2022 to March 31, 2022.

[b]April 1, 2022 to April 27, 2022.

Table 2. Vaccine Effectiveness Against SARS-CoV-2 Infection and Symptomatic Infection During the Omicron BA.1- and BA.2-predominant Periods

	No. of Events	Person-Days	Vaccine Effectiveness (95% Confidence Interval)	
			Unadjusted	Adjusted
BA.1-predominant period (January 1, 2022 to March 31, 2022)				
Infection[a]				
14 d after the second dose to 13 d after the third dose	5638	22 619 192	Ref.	Ref.
14 d after the third dose	294	3 331 548	66.9 (62.6 to 70.7)	62.4 (56.9 to 67.2)
Symptomatic Infection[b]				
14 d after the second dose to 13 d after the third dose	4887	22 646 508	Ref.	Ref.
14 d after the third dose	216	3 337 182	72.3 (68.1 to 75.9)	65.4 (59.6 to 70.4)
BA.2-predominant period (April 1, 2022 to April 27, 2022)				
Infection[a]				
14 d after the second dose to 13 d after the third dose	1143	3 132 999	Ref.	Ref.
14 d after the third dose	513	4 329 470	67.7 (64.1 to 70.9)	48.1 (39.2 to 55.7)
Symptomatic Infection[b]				
14 d after the second dose to 13 d after the third dose	1036	3 134 386	Ref.	Ref.
14 d after the third dose	400	4 330 984	72.3 (68.9 to 75.3)	52.9 (43.9 to 60.4)

Abbreviation: d, days; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a]Tested positive for SARS-CoV-2 by nucleic acid amplification tests or antigen tests regardless of symptoms.

[b]Tested positive for SARS-CoV-2 with any symptoms related to COVID-19.

≥1 month after the third dose against BA.2 [17]. In a test-negative case-control study in England, researchers found that effectiveness against symptomatic disease with BA.1 and BA.2 was 70.6% and 74.0%, respectively, 1 week after the booster dose, and that the effectiveness decreased to 37.4% and 43.7%, respectively, at >15 weeks after the third dose compared to unvaccinated individuals [18]. Whereas there was no difference in waning effectiveness against symptomatic infection, the effectiveness of a third dose of vaccine against hospitalization appeared to decrease more rapidly during the BA.2-predominant period than during the BA.1-predominant period. It is difficult to compare the results from these previous studies because not only the time since the third dose, but also the time since the second dose, which is used as a comparator, as well as regional differences in the COVID-19 pandemic all affect the results. However, it is worth determining the rate of waning effectiveness of a third dose of vaccine in each setting to determine the timing of subsequent booster vaccinations.

The effectiveness of a third dose of mRNA vaccine compared with 2 doses of vaccine during the BA.1-predominant period was higher than that in previous studies with a test-negative design conducted in Japan; however, the effectiveness after subgroup analyses stratified by age was comparable to that of previous studies. In a previous study (median age, 35 years), researchers found that the effectiveness of a third dose compared to 2 doses was 51% during the Omicron period [26]. Moreover, in another study, researchers showed that the effectiveness of a third dose of vaccine in individuals aged 16–64 years was 51.0%, while the corresponding effectiveness in individuals aged ≥65 years was 80.5% [29]. Our subgroup analyses according to age (<65 and ≥65 years) during the BA.1-predominant period indicated that the effectiveness of a third dose against symptomatic infection was 53.6% and 64.8%, respectively. Higher vaccine effectiveness in the older than in the younger population would be affected by the time since the second dose vaccination. The older population tend to have a longer time since the second vaccination dose than the younger population due to high priority in the third-dose vaccination program.

Vaccination with 3 doses of vaccine among younger adults in Japan did not proceed as smoothly as for older adults. In April 2022, the vaccination coverage was approximately 90% among older adults, but among younger adults, the overall coverage plateaued at approximately 50%–60% from April until July 2022 [37, 38]. The prevalence of hesitancy against a third dose of vaccine was higher in young adults, especially among young men [39]. The most common reasons were concerns regarding the adverse reactions; however, some participants expressed the opinion that 2 doses were enough and that there was a lack of information on the effectiveness of vaccination [40]. The effectiveness at 20–24 weeks after the second dose was approximately 10%, and it waned progressively over time [16, 17, 20]. In our study cohort, the median time since the second vaccination among participants who had not received a third dose of vaccine by April 1, 2022 was 185.0 days. This study provides information concerning the effectiveness of a third dose of mRNA vaccine in Japan. Thus, the results can be used to promote uptake of a third dose of vaccine in young adults.

There were some limitations to this study. First, we did not have information on the Omicron sublineage that infected the individuals in the study. However, we set study periods of

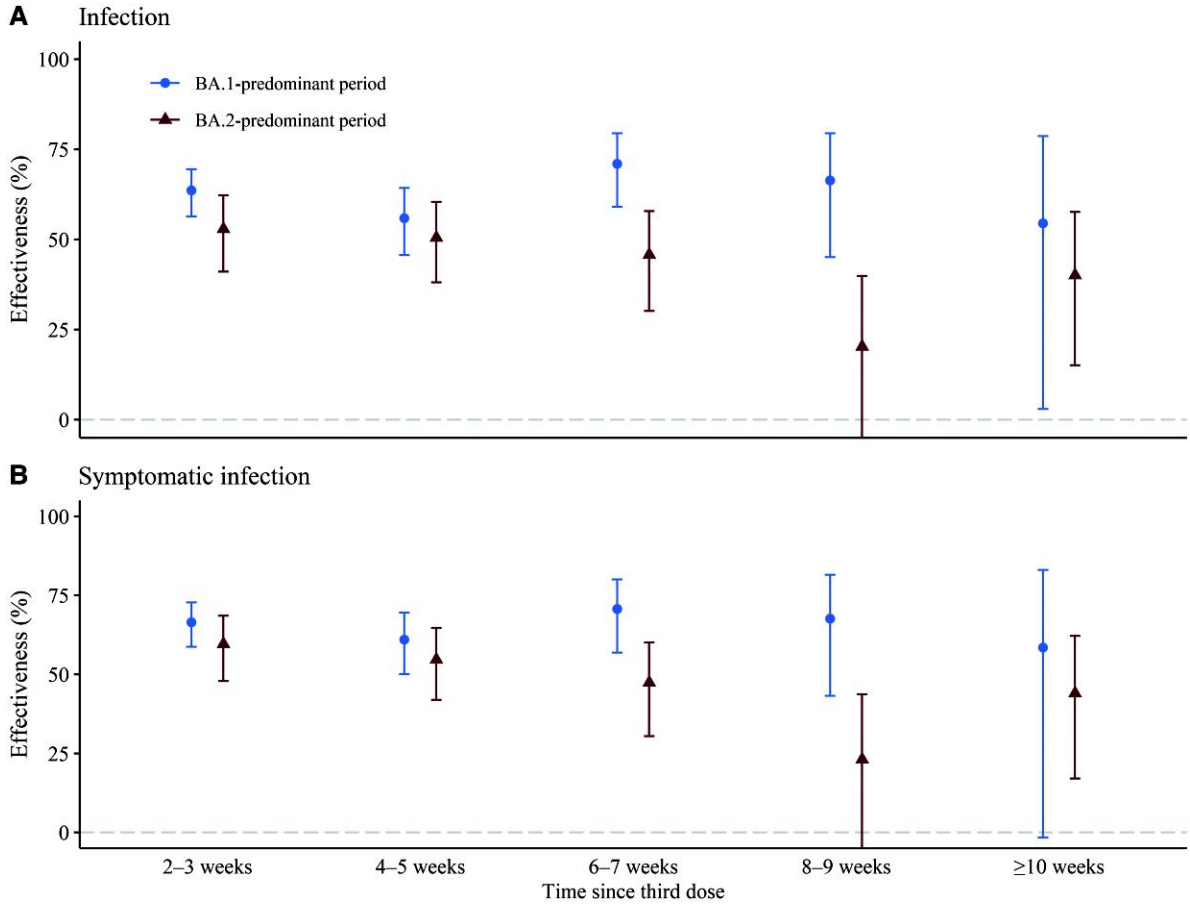

Figure 2. Waning vaccine effectiveness against infection and symptomatic infection during BA.1- and BA.2-predominant period. (A) BA.1-predominant period: January 1, 2022 to March 31, 2022; (B) BA.2-predominant period: April 1, 2022 to April 27, 2022.

BA.1 and BA.2 predominance, based on national reports. Second, there are potential confounding factors, although we used the data from one municipality and controlled for age and sex. For example, it was possible that there were testing propensity differences depending on the number of vaccines. However, the study population consisted of individuals who had received at least 2 doses of mRNA vaccine; therefore, the healthcare-seeking behavior in our study population was likely to be more similar between individuals who have received 3 or 2 doses of vaccine than among individuals who have received 3 doses of vaccine and unvaccinated individuals. Third, we could not assess the effectiveness during the BA.5 sublineage-predominant period because we only had data up to the end of April 2022, and the BA.5 sublineage became predominant in July 2022 [41]. We plan to assess the vaccine effectiveness of further doses of vaccine during the period of BA.5 predominance as soon as the data become available.

CONCLUSIONS

In conclusion, we showed waning vaccine effectiveness during the BA.1- and BA.2-predominant periods. The effectiveness of a third dose of mRNA vaccine against the BA.1 and BA.2 sublineages decreased over time since the third dose. However, this study confirmed that 3 doses of mRNA vaccine have moderate effectiveness compared to only 2 doses of vaccine. A BA.5 sublineage has emerged and rapidly replaced the BA.2 sublineage. Further lineages are likely to follow. Timely assessments are needed to determine the effectiveness of a third dose of vaccine against severe COVID-19 and death and to determine the rate of waning of immunity. More importantly, the results show the importance of a third dose of vaccine. These results will contribute toward decision making on public health policies and vaccination campaigns in the Japanese setting.

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.

Acknowledgments

Author contributions. WM, CI, FM, and HF contributed to study concept and design. MM, FM, and HF contributed to acquisition of data. All

authors contributed to analysis and interpretation of data. WM contributed to statistical analysis. HF obtained funding and supervised the study. WM drafted the manuscript, and all authors contributed to critical revision of the manuscript for important intellectual content.

Financial support. This research was funded by AMED under Grant Number JP21nf0101635.

Potential conflicts of interest. All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

References

1. World Health Organization. Classification of Omicron (B.1.1.529): SARS-CoV-2 Variant of Concern. 2021. Available at: https://www.who.int/news/item/26-11-2021-classification-of-omicron-(b.1.1.529)-sars-cov-2-variant-of-concern. Accessed 1 August 2022.
2. National Center for Immunization and Respiratory Diseases (NCIRD), Division of Viral Diseases. Science Brief: Omicron (B.1.1.529) Variant. In: CDC COVID-19 Science Briefs. Atlanta (GA): Centers for Disease Control and Prevention (US); December 2, 2021. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34932278. Accessed 22 August 2022.
3. Tegally H, Wilkinson E, Giovanetti M, et al. Detection of a SARS-CoV-2 variant of concern in South Africa. Nature **2021**; 592:438–43.
4. National Institute of Infectious Diseases. Current Situation of Infection, January 6, 2022. Available at: https://www.niid.go.jp/niid/en/2019-ncov-e/10908-covid19-ab66th-en.html. Accessed 7 July 2022.
5. National Institute of Infectious Diseases. Current Situation of Infection, February 9, 2022. Available at: https://www.niid.go.jp/niid/en/2019-ncov-e/10974-covid19-ab71th-en.html. Accessed 7 July 2022.
6. Hirotsu Y, Maejima M, Shibusawa M, et al. SARS-CoV-2 Omicron sublineage BA.2 replaces BA.1.1: genomic surveillance in Japan from September 2021 to March 2022. J Infect **2022**; 85:174–211.
7. Lewnard JA, Hong VX, Patel MM, Kahn R, Lipsitch M, Tartof SY. Clinical outcomes associated with SARS-CoV-2 Omicron (B.1.1.529) variant and BA.1/BA.1.1 or BA.2 subvariant infection in southern California. Nat Med **2022**; 28: 1933–43.
8. World Health Organization. Enhancing response to Omicron SARS-CoV-2 variant. 2022. Available at: https://www.who.int/publications/m/item/enhancing-readiness-for-omicron-(b.1.1.529)-technical-brief-and-priority-actions-for-member-states. Accessed 2 August 2022.
9. Yamasoba D, Kimura I, Nasser H, et al. Virological characteristics of the SARS-CoV-2 Omicron BA.2 spike. Cell **2022**; 185:2103–15.e19.
10. Ito K, Piantham C, Nishiura H. Estimating relative generation times and reproduction numbers of Omicron BA.1 and BA.2 with respect to Delta variant in Denmark. Math Biosci Eng **2022**; 19:9005–17.
11. Ministry of Health, Labour and Welfare. COVID-19 Vaccines. Available at: https://www.mhlw.go.jp/stf/covid-19/vaccine.html. Accessed 26 July 2022.
12. Song P, Mitsuya H, Kokudo N. COVID-19 in Japan: an update on national policy, research, clinical practice, and vaccination campaign. Glob Health Med **2022**; 4: 64–6.
13. Planas D, Saunders N, Maes P, et al. Considerable escape of SARS-CoV-2 omicron to antibody neutralization. Nature **2022**; 602:671–5.
14. Zeng B, Gao L, Zhou Q, Yu K, Sun F. Effectiveness of COVID-19 vaccines against SARS-CoV-2 variants of concern: a systematic review and meta-analysis. BMC Med **2022**; 20:200.
15. Lauring AS, Tenforde MW, Chappell JD, et al. Clinical severity of, and effectiveness of mRNA vaccines against, COVID-19 from omicron, delta, and alpha SARS-CoV-2 variants in the United States: prospective observational study. BMJ **2022**; 376:e069761.
16. Andrews N, Stowe J, Kirsebom F, et al. COVID-19 vaccine effectiveness against the Omicron (B.1.1.529) variant. N Engl J Med **2022**; 386:1532–46.
17. Chemaitelly H, Ayoub HH, AlMukdad S, et al. Duration of mRNA vaccine protection against SARS-CoV-2 Omicron BA.1 and BA.2 subvariants in Qatar. Nat Commun **2022**; 13:3082.
18. Kirsebom FCM, Andrews N, Stowe J, et al. COVID-19 vaccine effectiveness against the Omicron (BA.2) variant in England. Lancet Infect Dis **2022**; 22:931–3.
19. Andeweg SP, de Gier B, Eggink D, et al. Protection of COVID-19 vaccination and previous infection against omicron BA.1, BA.2 and Delta SARS-CoV-2 infections. Nat Commun **2022**; 13:4738.
20. Link-Gelles R. Effectiveness of 2, 3, and 4 COVID-19 mRNA vaccine doses among immunocompetent adults during periods when SARS-CoV-2 Omicron BA.1 and BA.2/BA.2.12.1 sublineages predominated—VISION Network, 10 states, December 2021–June 2022. MMWR Morb Mortal Wkly Rep **2022**; 71:931–9.
21. Björk J, Bonander C, Moghaddassi M, et al. COVID-19 vaccine effectiveness against severe disease from SARS-CoV-2 Omicron BA.1 and BA.2 subvariants—surveillance results from southern Sweden, December 2021 to March 2022. Eurosurveillance **2022**; 27:2200322.
22. Tartof SY, Slezak JM, Puzniak L, et al. Durability of BNT162b2 vaccine against hospital and emergency department admissions due to the Omicron and Delta variants in a large health system in the USA: a test-negative case-control study. Lancet Respir Med **2022**; 10:689–99.
23. Tseng HF, Ackerson BK, Luo Y, et al. Effectiveness of mRNA-1273 against SARS-CoV-2 omicron and Delta variants. Nat Med **2022**; 28:1063–71.
24. Nyberg T, Ferguson NM, Nash SG, et al. Comparative analysis of the risks of hospitalisation and death associated with SARS-CoV-2 Omicron (B.1.1.529) and Delta (B.1.617.2) variants in England: a cohort study. Lancet **2022**; 399:1303–12.
25. Feikin DR, Abu-Raddad LJ, Andrews N, et al. Assessing vaccine effectiveness against severe COVID-19 disease caused by Omicron variant. Report from a meeting of the World Health Organization. Vaccine **2022**; 40:3516–27.
26. Arashiro T, Arima Y, Muraoka H, et al. COVID-19 vaccine effectiveness against symptomatic SARS-CoV-2 infection during Delta-dominant and Omicron-dominant periods in Japan: a multi-center prospective case-control study (FASCINATE study). Clin Infect Dis **2022**; ciac635. doi: 10.1093/cid/ciac635.
27. Evans JP, Zeng C, Qu P, et al. Neutralization of SARS-CoV-2 Omicron sublineages BA.1, BA.1.1, and BA.2. Cell Host Microbe **2022**; 30:1093–102.e3.
28. Seki Y, Yoshihara Y, Nojima K, et al. Safety and immunogenicity of the Pfizer/BioNTech SARS-CoV-2 mRNA third booster vaccine dose against the BA.1 and BA.2 Omicron variants. Med (NY) **2022**; 3:406–21.e4.
29. Institute of Tropical Medicine, Nagasaki University. [Vaccine Effectiveness Real-Time Surveillance for SARS-CoV-2 (VERSUS) Study: Fifth report]. Available at: http://www.tm.nagasaki-u.ac.jp/versus/results/20220608.html. Accessed 17 August 2022.
30. Maeda H, Saito N, Igarashi A, et al. Effectiveness of messenger RNA coronavirus disease 2019 vaccines against symptomatic severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections during the Delta variant epidemic in Japan: vaccine effectiveness real-time surveillance for SARS-CoV-2 (VERSUS). Clin Infect Dis **2022**; 75:1971–79.
31. Hara M, Furue T, Fukuoka M, et al. Real-world effectiveness of the mRNA COVID-19 vaccines in Japan: a case-control study. Vaccines (Basel) **2022**; 10:779.
32. Cabinet Public Affairs Office, Cabinet Secretariat. Chubu. Available at: https://www.japan.go.jp/regions/chubu.html. Accessed 1 August 2022.
33. Ministry of Health, Labour and Welfare. Health Center Real-time Information-sharing System on COVID-19 (HER-SYS). Available at: https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/0000121431_00181.html. Accessed 16 June 2022.
34. Ode H, Nakata Y, Nagashima M, et al. Molecular epidemiological features of SARS-CoV-2 in Japan, 2020-1. Virus Evol **2022**; 8:veac034.
35. National Institute of Infectious Diseases. Current Situation of Infection, January 13, 2022. Available at: https://www.niid.go.jp/niid/en/2019-ncov-e/10914-covid19-ab67th-en.html. Accessed 16 June 2022.
36. The Mainichi Newspapers Co. [Japan gov't to allow COVID diagnoses without testing as omicron cases surge]. January 25, 2022. Available at: https://mainichi.jp/english/articles/20220125/p2a/00 m/0na/008000c. Accessed 2 November 2022.
37. National Institute of Infectious Diseases. Current Situation of Infection, April 20, 2022. Available at: https://www.niid.go.jp/niid/en/2019-ncov-e/11122-covid19-ab81th-en.html. Accessed 21 July 2022.
38. National Institute of Infectious Diseases. Current Situation of Infection, June 30, 2022. Available at: https://www.niid.go.jp/niid/en/2019-ncov-e/11275-covid19-ab89th-en.html. Accessed 21 July 2022.
39. Khan MSR, Nguyen TXT, Lal S, Watanapongvanich S, Kadoya Y. Hesitancy towards the third dose of COVID-19 vaccine among the younger generation in Japan. Int J Environ Res Public Health **2022**; 19:7041.
40. Yoshida M, Kobashi Y, Kawamura T, et al. Factors associated with COVID-19 vaccine booster hesitancy: a retrospective cohort study, Fukushima Vaccination Community Survey. Vaccines (Basel) **2022**; 10:515.
41. National Institute of Infectious Diseases. Current Situation of Infection, July 27, 2022. Available at: https://www.niid.go.jp/niid/en/2019-ncov-e/11367-covid19-ab92th-en.html. Accessed 10 August 2022.