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Short communication

Effectiveness of messenger RNA vaccines against infection with SARS-CoV-2 during the periods of Delta and Omicron variant predominance in Japan: the Vaccine Effectiveness, Networking, and Universal Safety (VENUS) study

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ABSTRACT

Objectives: We aimed to evaluate COVID-19 messenger RNA vaccine effectiveness during the Delta- and Omicron-predominant periods in Japan.
Methods: We conducted a population-based cohort study among individuals aged 16–64 years during two periods: the Delta-predominant period (July 1–December 31, 2021) and the Omicron-predominant period (January 1–March 29, 2022).
Results: When comparing individuals who were vaccinated with those who were unvaccinated, the effectiveness of a second dose against symptomatic infection was 89.8% (95% confidence interval [CI]: 80.5–94.7%) during the Delta-predominant period and 21.2% (95% CI: 11.0–30.3%) during the Omicron-predominant period. The effectiveness of a third dose against symptomatic infection was 71.8% (95% CI: 60.1–80.1%) during the Omicron-predominant period.
Conclusion: Vaccine effectiveness against symptomatic infection decreased during the Omicron-predominant period but was maintained by a third dose.

Introduction

Vaccination against infection with SARS-CoV-2 in the general population of Japan began on April 12, 2021, and booster vaccination (the third dose) began on December 1, 2021. The Alpha (B.1.1.7) variant was gradually replaced by the Delta (B.1.617.2) variant beginning in June 2021, and the Delta variant accounted for approximately 80% of infections in Japan in August 2021 (National Institute of Infectious Diseases, 2021). The Delta variant predominated until the Omicron (B.1.1.529) variant surged in January 2022 (National Institute of Infectious Diseases, 2022; Ode *et al.*, 2022). Although several case-control studies have been conducted to assess vaccine effectiveness (VE) in hospital settings, no population-based cohort studies have been conducted in Japan to date (Arashiro *et al.*, 2022; Hara *et al.*, 2022; Maeda *et al.*, 2022). We launched the Vaccine Effectiveness, Networking, and Universal Safety (VENUS) study to utilize data, including cases of COVID-19 and vaccination records at an individual level, from municipalities in Japan. This is the first report of COVID-19 VE based on an analysis of the VENUS study data.

Methods

We conducted this population-based cohort study to assess the effectiveness of messenger RNA (mRNA) vaccines (BNT162b2 or mRNA-1273) in the population aged 16–64 years in a municipality in the Chugoku region. We used data from the Health Center Real-time Information-sharing System on COVID-19 (Ministry of Health, Labour and Welfare, 2021), which included cases of COVID-19, and from the Vaccination Record System, which included COVID-19 vaccination records linked to each resident. The data included information on all residents in the municipality. To ac-

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Table 1
Characteristics of the study cohort during each period

	Delta-predominant period[a] N = 105,618	Omicron-predominant period[b] N = 105,267
Sex, n (%)		
Male	55,153 (52.2%)	54,971 (52.2%)
Female	50,465 (47.8%)	50,296 (47.8%)
Age, years, median (IQR)	44 (31–53)	44 (31–53)
Age group, n (%)		
16–24 years	16,454 (15.6%)	16,366 (15.5%)
25–34 years	16,167 (15.3%)	16,101 (15.3%)
35–44 years	20,987 (19.9%)	20,908 (19.9%)
45–54 years	29,373 (27.8%)	29,302 (27.8%)
55–64 years	22,637 (21.4%)	22,590 (21.5%)
Vaccine series (first/second/third), n (%)		
No vaccination/No vaccination/No vaccination	19,508 (18.5%)	18,057 (17.2%)
BNT162b2/No vaccination/No vaccination	439 (0.4%)	346 (0.3%)
BNT162b2/BNT162b2/No vaccination	71,743 (67.9%)	36,967 (35.1%)
BNT162b2/mRNA-1273/No vaccination	0 (0.0%)	20 (0.0%)
BNT162b2/BNT162b2/BNT162b2	53 (0.1%)	17,291 (16.4%)
BNT162b2/BNT162b2/mRNA-1273	0 (0.0%)	18,550 (17.6%)
mRNA-1273/No vaccination/No vaccination	44 (0.0%)	153 (0.1%)
mRNA-1273/BNT162b2/No vaccination	7 (0.0%)	8 (0.0%)
mRNA-1273/mRNA-1273/No vaccination	13,824 (13.1%)	9,999 (9.5%)
mRNA-1273/mRNA-1273/BNT162b2	0 (0.0%)	464 (0.4%)
mRNA-1273/mRNA-1273/mRNA-1273	0 (0.0%)	3,412 (3.2%)

IQR, interquartile range; mRNA, messenger RNA.
[a] July 1–December 31, 2021.
[b] January 1–March 29, 2022.

count for the circulation of the Delta and Omicron variants, we conducted analyses for two study periods: the Delta-predominant (July 1–December 31, 2021) and Omicron-predominant (January 1–March 29, 2022) periods. We included individuals aged 16–64 years without previous COVID-19 at the start of each period. Vaccination status of each individual was categorized according to the number of doses (unvaccinated; 14 days after the first dose to 13 days after the second dose; 14 days after the second dose to 13 days after the third dose; and 14 days after the third dose). Infection was defined by a positive SARS-CoV-2 nucleic acid amplification or antigen test result, regardless of symptoms. Symptomatic infection was defined by a positive SARS-CoV-2 test result along with COVID-19-related symptoms. Cox proportional hazards models were used to estimate the hazard ratios with 95% confidence intervals (CIs) of the outcomes. Vaccination status was included as a time-dependent covariate, and age and sex were included as covariates. VE was calculated as (1−hazard ratio) × 100%. We performed additional analyses to assess the effectiveness of the third dose of BNT162b2 or mRNA-1273 after the BNT162b2 primary series. All statistical analyses were performed using R version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Overall, 105,618 and 105,267 individuals aged 16–64 years were included for the Delta- and Omicron-predominant periods, respectively (Table 1). The median age was 44 years (interquartile range 31–53 years), and 52.2% of both cohorts were male. Among individuals who received a third dose, 47.9% were vaccinated with a vaccine different from that received in their primary series. The VEs against infection and symptomatic infection 14 days after the second dose were 83.8% (95% CI: 75.3–89.3%) and 89.8% (95% CI: 80.5–94.7%), respectively, during the Delta-predominant period and 15.8% (95% CI: 7.9–23.1%) and 21.2% (95% CI: 11.0–30.3%), respectively, during the Omicron-predominant period (Table 2). During the Omicron-predominant period, the VEs against infection and symptomatic infection 14 days after the third dose were 56.5% (95% CI: 46.0–65.0%) and 71.8% (95% CI: 60.1–80.1%), respectively, compared with unvaccinated and 48.3% (95% CI: 36.4–57.9%) and 64.2% (95% CI: 49.9–74.4%), respectively, compared with 14 days after the second dose. At ≥14 days after a third dose of BNT162b2 or mRNA-1273 (after the BNT162b2 primary series) compared with unvaccinated, the VEs were 51.8% (95% CI: 39.0–61.8%) and 73.5% (95% CI: 53.8–84.8%), respectively, against infection; and 67.7% (95% CI: 53.0–77.8%) and 77.9% (95% CI: 50.0–90.2%), respectively, against symptomatic infection.

Discussion

A third dose of an mRNA vaccine increased VE in the general population. The effectiveness of a second dose was lower during the Omicron-predominant period than during the Delta-predominant period due to waning immunity and high transmissibility of the Omicron variant; however, a third dose provided adequate effectiveness against infection and symptomatic infection. Specifically, after the BNT162 primary series, the effectiveness of a third dose of mRNA-1273 was higher than that of a third dose of BNT162b2. Our results are consistent with those of previous studies. In a previous study in Japan with a test-negative case-control design, the VE of the second dose was 88.7% against symptomatic infection with SARS-CoV-2 from July-September 2021 (Maeda *et al.*, 2022). Test-negative case-control studies found a VE of two doses of mRNA-1273 vaccine of 13.9% (95% CI: 10.5–17.1%) against the Omicron variant in the United States (Tseng *et al.*, 2022) and a VE of three doses of BNT162b2 and mRNA-1273 vaccines of 67.2% and 73.9%, respectively, against symptomatic infections with the Omicron variant in England (Andrews *et al.*, 2022). Although our population-based study has a potential for residual confounding, and the generalizability of the results may be limited due to the fact that the study was conducted in one local municipality, the results are similar to those of previous studies.

Table 2
Vaccine effectiveness against infection and symptomatic infection with SARS-CoV-2 during the periods of Delta and Omicron predominance

	No. of events	Person-days	Vaccine effectiveness (95% CI)	
			Unadjusted	Adjusted
Delta-predominant period (July 1-December 31, 2021)				
Infection[a]				
Unvaccinated	284	7,259,255	Reference	Reference
14 days after the first dose to 13 days after the second dose	12	1,788,207	84.1 (71.6 to 91.1)	82.9 (69.4 to 90.4)
14 days after the second dose to 13 days after the second dose	25	9,194,506	84.9 (77.1 to 90.0)	83.8 (75.3 to 89.3)
Symptomatic infection[b]				
Unvaccinated	188	7,268,685	Reference	Reference
14 days after the first dose to 13 days after the second dose	2	1,789,823	96.0 (83.9 to 99.0)	95.7 (82.5 to 98.9)
14 days after the second dose to 13 days after the second dose	10	9,199,315	90.7 (82.3 to 95.1)	89.8 (80.5 to 94.7)
Omicron-predominant period (January 1-March 29, 2022)				
Infection[a]				
Unvaccinated	621	1,587,071	Reference	Reference
14 days after the first dose to 13 days after the second dose	29	51,507	−52.3 (−121.0 to 4.9)	−45.6 (−111.4 to 0.3)
14 days after the second dose to 13 days after the second dose	1,997	6,632,782	23.1 (15.8 to 29.7)	15.8 (7.9 to 23.1)
14 days after the third dose	102	746,240	64.7 (56.2 to 71.5)	56.5 (46.0 to 65.0)
14 days after the third dose (vs 14 days after the second dose to 13 days after the third dose)	-	-	54.1 (43.6 to 62.7)	48.3 (36.4 to 57.9)
Symptomatic infection[b]				
Unvaccinated	348	1,598,907	Reference	Reference
14 days after the first dose to 13 days after the second dose	14	52,187	−30.3 (−122.4 to 23.6)	−24.4 (−112.3 to 27.1)
14 days after the second dose to 13 days after the second dose	1,038	6,675,052	28.5 (19.2 to 36.7)	21.2 (11.0 to 30.3)
14 days after the third dose	37	750,527	77.4 (68.0 to 84.0)	71.8 (60.1 to 80.1)
14 days after the third dose (vs 14 days after the second dose to 13 days after the third dose)	-	-	68.4 (55.7 to 77.4)	64.2 (49.9 to 74.4)

CI, confidence interval.
[a] Positive SARS-CoV-2 nucleic acid amplification or antigen test results, regardless of symptoms.
[b] Positive SARS-CoV-2 test results, along with any symptoms related to COVID-19.

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Ethical approval

The study was approved by the Kyushu University Institutional Review Board for Clinical Research (No. 2021-399).

Author contributions

WM, CI, FM, and HF designed the study. MM, FM, and HF collected the data. WM performed analysis; the data was interpreted by all authors. WM drafted the original manuscript. All authors reviewed and edited the manuscript. The study was supervised by CI and HF. All authors have read the manuscript and have approved its submission for publication.

Declarations of competing interest

The authors have no competing interests to declare.

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