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Short Communication

Title

Effectiveness of mRNA vaccines against SARS-CoV-2 infections during the periods of Delta and Omicron variant predominance in Japan: The VENUS Study

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Highlights

- This paper reports the first results of the VENUS Study being conducted in Japan.
- This cohort study assessed COVID-19 mRNA vaccine effectiveness (VE).

- VE of 2 doses against symptomatic infection was 89.8% during the Delta wave.
- VE of 2 doses against symptomatic infection was 21.2% during the Omicron wave.
- VE of 3 doses against symptomatic infection was 71.8% during the Omicron wave.

Abstract

Objective: We aimed to evaluate coronavirus disease 2019 mRNA 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 to December 31, 2021) and the Omicron-predominant period (January 1 to March 29, 2022).

Results: Compared with unvaccinated individuals, the effectiveness of a second dose against symptomatic infection were 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.

Keywords: COVID-19, mRNA vaccine, vaccine effectiveness, population-based cohort study, Japan

Introduction

Vaccination against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in the general population of Japan started on April 12, 2021, and booster vaccination (the third dose) started on December 1, 2021. The Alpha (B.1.1.7) variant was gradually replaced by the Delta (B.1.617.2) variant from 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 from municipalities, including cases of coronavirus disease 2019 (COVID-19) and vaccination records at an individual level 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 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 (HER-SYS) (Ministry of Health, Labour and Welfare., 2021), which included cases of COVID-19, and the Vaccination Record System (VRS), which included COVID-19 vaccination records linked to each resident. The data included information on all residents in the municipality. To account for the circulation of the Delta and Omicron variants, we conducted cohort analyses for two study periods: the Delta-predominant (July 1 to December 31, 2021) and Omicron-predominant periods (January 1 to March 29, 2022). 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 as testing positive for SARS-CoV-2 by a nucleic acid amplification test or antigen test, regardless of symptoms. Symptomatic infection was defined as testing positive for SARS-CoV-2 with COVID-19-related symptoms. Cox proportional hazards models were used to estimate the hazard ratios (HRs) 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−HR)×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 44.0 years (interquartile range: 31.0–53.0 years), and 52.2% of both cohorts were male. Among individuals who received a third dose, 47.9% were vaccinated with a different vaccine from 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 following the BNT162b2 primary series compared with unvaccinated, the VEs were 51.8% (39.0–61.8%) and 73.5% (53.8–84.8%), respectively, against infection; and 67.7% (53.0–77.8%) and 77.9% (50.0–90.2%), respectively, against symptomatic infection.

Discussion

A third dose of a mRNA vaccine increased their effectiveness in the general population. The effectiveness of a second dose was lower during the Omicron-predominant period than that during the Delta-predominant period due to waning immunity and high transmissibility of the Omicron variant, but 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 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 SARS-CoV-2 infections between July and 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 VE of three doses of BNT162b2 and mRNA-1273 vaccines of 67.2% and 73.9%, respectively, against symptomatic Omicron variant infections 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 conducting this study in one local municipality, the results are similar to those of previous studies.

Conflicts of interest

None reported.

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Ethics 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, and 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 being submitted and have approved its submission for publication.

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Table 1. Characteristics of the study cohort during each period

	Delta variant predominant[a] N = 105,618	**Omicron variant predominant[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%)

	Delta variant predominant[a] N = 105,618	Omicron variant predominant[b] N = 105,267
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%)

Abbreviation: IQR, interquartile range

[a]July 1 to December 31, 2021. [b]January 1 to March 29, 2022

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

	No. of events	Person-days	Vaccine effectiveness (95% confidence interval)	
			Unadjusted	Adjusted
Delta-predominant period (July 1, 2021 to December 31, 2021)				
Infection[a]				
Unvaccinated	284	7,259,255	Ref.	Ref.
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	Ref.	Ref.
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, 2022 to March 29, 2022)				
Infection[a]				
Unvaccinated	621	1,587,071	Ref.	Ref.
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)	-	-	54.1 (43.6 to 62.7)	48.3 (36.4 to 57.9)
Symptomatic infection[b]				
Unvaccinated	348	1,598,907	Ref.	Ref.
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)	-	-	68.4 (55.7 to 77.4)	64.2 (49.9 to 74.4)

Abbreviation: 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.