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MAJOR ARTICLE

Effectiveness of Messenger RNA Coronavirus Disease 2019 Vaccines Against Symptomatic Severe Acute Respiratory Syndrome Coronavirus 2 Infections During the Delta Variant Epidemic in Japan: Vaccine Effectiveness Real-time Surveillance for SARS-CoV-2 (VERSUS)

Haruka Maeda,[1,2] Nobuo Saito,[3] Ataru Igarashi,[4,5] Masayuki Ishida,[6] Kazuya Suami,[7] Ai Yagiuchi,[7] Yuya Kimura,[8] Masaru Komino,[8] Hiromi Arai,[8] Toru Morikawa,[9] Iori Motohashi,[10] Rei Miyazawa,[10] Tetsu Moriyama,[11] Hiroshi Kamura,[12] Mayumi Terada,[13] Osamu Kuwamitsu,[14] Tomoichiro Hayakawa,[15] Eiichiro Sando,[16,17] Yasuji Ohara,[18] Osamu Teshigahara,[19] Motoi Suzuki,[20] and Konosuke Morimoto[1]

[1]Department of Respiratory Infections, Institute of Tropical Medicine, Nagasaki University, Nagasaki, Japan; [2]Department of Clinical Tropical Medicine, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan; [3]Department of Microbiology, Faculty of Medicine, Oita University, Oita, Japan; [4]Unit of Public Health and Preventive Medicine, Yokohama City University School of Medicine, Kanagawa, Japan; [5]Department of Health Economics and Outcomes Research, Graduate School of Pharmaceutical Sciences, The University of Tokyo, Tokyo, Japan; [6]Chikamori Hospital, Kochi, Japan; [7]Nagoya Ekisaikai Hospital, Aichi, Japan; [8]Saiseikai Kurihashi Hospital, Saitama, Japan; [9]Nara City Hospital, Nara, Japan; [10]Kawasaki Municipal Tama Hospital, Kanagawa, Japan; [11]Moriyama Memorial Hospital, Tokyo, Japan; [12]Loco Clinic Nakameguro, Tokyo, Japan; [13]Nijigaoka Hospital, Nagasaki, Japan; [14]Gohongi Clinic, Tokyo, Japan; [15]Hayakawa Internal Medicine Clinic, Fukuoka, Japan; [16]Kita-Fukushima Medical Center, Fukushima, Japan; [17]Fukushima Medical University, Fukushima, Japan; [18]Takagi Hospital, Aichi, Japan; [19]Mizuho Street Clinic, Aichi, Japan; and [20]Infectious Disease Surveillance Center, National Institute of Infectious Diseases, Tokyo, Japan

Background. Although high vaccine effectiveness of messenger RNA (mRNA) coronavirus disease 2019 (COVID-19) vaccines has been reported in studies in several countries, data are limited from Asian countries, especially against the Delta (B.1.617.2) variant.

Methods. We conducted a multicenter test-negative case-control study in patients aged ≥16 years visiting hospitals or clinics with signs or symptoms consistent with COVID-19 from 1 July to 30 September 2021, when the Delta variant was dominant (≥90% of SARS-CoV-2 infections) nationwide in Japan. Vaccine effectiveness of BNT162b2 or mRNA-1273 against symptomatic SARS-CoV-2 infections was evaluated. Waning immunity among patients aged 16–64 years was also assessed.

Results. We enrolled 1936 patients, including 396 test-positive cases and 1540 test-negative controls for SARS-CoV-2. The median age was 49 years, 53.4% were male, and 34.0% had underlying medical conditions. Full vaccination (receiving 2 doses ≥14 days before symptom onset) was received by 6.6% of cases and 38.8% of controls. Vaccine effectiveness of full vaccination against symptomatic SARS-CoV-2 infections was 88.7% (95% confidence interval [CI], 78.8%–93.9%) among patients aged 16–64 years and 90.3% (95% CI, 73.6%–96.4%) among patients aged ≥65 years. Among patients aged 16–64 years, vaccine effectiveness was 91.8% (95% CI, 80.3%–96.6%) within 1–3 months after full vaccination, and 86.4% (95% CI, 56.9%–95.7%) within 4–6 months.

Conclusions. mRNA COVID-19 vaccines had high effectiveness against symptomatic SARS-CoV-2 infections in Japan during July–September 2021, when the Delta variant was dominant nationwide.

Keywords. SARS-CoV-2; COVID-19; vaccine effectiveness; Delta; Japan.

Since December 2019, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread globally, including in Japan, and has significantly impacted health, livelihoods, and economies. To counter the coronavirus disease 2019 (COVID-19) pandemic, COVID-19 vaccines were developed and distributed globally. Clinical trials of COVID-19 vaccines found high vaccine efficacy [1–3], and observational studies evaluated vaccine effectiveness (VE) in several countries [4–6]. However, data on VE of messenger RNA (mRNA) COVID-19 vaccines, especially against the Delta (B.1.617.2) variant, from Asian countries are limited.

In February 2021, the Japanese government initiated a national COVID-19 vaccination campaign (Supplementary Figure 1). It is crucial to assess COVID-19 VE domestically when evaluating the national policy and, going forward, determining the optimal vaccination policy. Vaccine effectiveness has been estimated to attenuate due to the emergence of new variants [7]. Accordingly, we started surveillance activity

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Correspondence: K. Morimoto, Department of Respiratory Infections, Institute of Tropical Medicine, Nagasaki University, 1-12-4 Sakamoto, Nagasaki 852-8523, Japan (komorimo@nagasaki-u.ac.jp).

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from 1 July 2021 to monitor VE of COVID-19 vaccines in Japan, named Vaccine Effectiveness Real-time Surveillance for SARS-CoV-2 (VERSUS). In this study, we evaluated VE of the mRNA COVID-19 vaccines BNT165b2 and mRNA-1273 against symptomatic SARS-CoV-2 infections during the Delta variant epidemic in Japan using data registered for our surveillance.

METHODS

Design

We conducted a prospective, test-negative, case-control study [8, 9]. The case group included individuals having signs or symptoms and positive test results for SARS-CoV-2, and the control group included individuals having signs or symptoms but negative test results for SARS-CoV-2. All SARS-CoV-2 tests were performed in medical institutions in clinical practice. The following test methods were included, which are commonly used for diagnosis in Japan [10, 11]: nucleic acid amplification tests (NAATs) including polymerase chain reaction (PCR), loop-mediated isothermal amplification (LAMP) [12], nicking endonuclease amplification reaction (NEAR) [13], and transcription-mediated amplification (TMA) [14]; and antigen quantification test [15, 16]. A rapid antigen test was not included in this study.

Setting

This study enrolled individuals visiting medical institutions from 1 July through 30 September 2021, at 9 hospitals and 4 clinics in 9 prefectures on 3 main islands in Japan. During this study period, Japan experienced a fifth epidemic wave due to the Delta variant, starting late in June 2021 (Supplementary Figure 2) [17, 18].

Before the fifth wave in Japan, the Japanese government approved and introduced COVID-19 vaccines [19] (Supplementary Figure 1). The market approval of BNT162b2 was done on 14 February 2021 for individuals aged ≥16 years and expanded on 31 May 2021 to those aged 12–15 years. Two additional vaccines, mRNA-1273 and AZD1222, were approved for person aged ≥18 years on 21 May 2021. For mRNA-1273, approval was expanded to persons aged 12–17 years on 26 July 2021. The government decided to publicly fund COVID vaccinations and set up a prioritization strategy, with a design based in part on procurement issues. Healthcare workers were the first to be vaccinated, beginning on 17 February 2021, followed by priority vaccination of older adults aged ≥65 years started on 12 April 2021. For younger citizens, 12–64 years of age, a vaccination program was started from June 2021, with priority given to those with underlying medical conditions. All were vaccinated with BNT162b2 until 24 May 2021. The first administration of mRNA-1273 for older adults aged ≥65 years began on 24 May 2021, followed by vaccination of adults aged ≥18 years on 17 June 2021 and persons aged ≥12 years on 2 August 2021. Administration of AZD1222 became optional for persons aged ≥40 years from late August. By 30 September 2021, 66% of the Japan population had received at least 1 dose and 57% 2 doses; among people aged ≥65 years, >90% had received 2 doses (Supplementary Figure 2) [20].

Participants

This study included individuals aged ≥16 years visiting participating hospitals or clinics with 1 or more of the following signs or symptoms: fever (≥37.5°C), cough, fatigue, shortness of breath, myalgia, sore throat, nasal congestion, headache, diarrhea, taste disorder, or olfactory dysfunction [21, 22] and tested for SARS-CoV-2. We excluded episodes tested 15 days or more after symptom onset or episodes with undocumented symptom onset dates, because of the inaccuracy of test results [23]. When individuals had multiple episodes, we used the following rules for exclusion: (1) episodes with negative test results within 7 days after a previous negative result; (2) episodes with multiple negative test results and identical symptom onset date; (3) episodes with negative test results within 3 weeks prior to a positive test result, or episodes occurring after a positive test result, due to the possibility of false-negatives; (4) for multiple positive episodes during the study period, we included only the first episode; and (5) we included a maximum of 3 negative test results for each individual.

Data Collection

All data included in this study were obtained from clinical practice. Medical professionals engaged in the study in each medical institution identified eligible patients. Demographic and clinical information was collected from medical records and recorded on an electronic database using REDCap [24].

We collected demographic and clinical information, including age, sex, place of residence, presence of underlying medical conditions (ie, chronic heart disease, chronic respiratory disease, obesity [body mass index ≥30 kg/m^2], malignancy [including solid or hematological malignancy], diabetes mellitus, chronic kidney disease, receiving dialysis, liver cirrhosis, use of immunosuppressive medicines, or pregnancy), smoking history, history of contact with COVID-19 patients, healthcare employment status, clinical symptoms, and COVID-19 vaccination histories.

Classification of Vaccination Status

We obtained vaccination histories (ie, vaccination date of administration, type of vaccine product, and vaccination frequency) from medical records, from vaccination cards, or through interviews with the patient or family members. COVID-19 vaccines are administered as a 2-dose series. Vaccination status was classified into 6 categories based on the number of vaccine doses

received before symptom onset and the number of days between the last vaccination and symptom onset date, specifically (1) no vaccination where individuals had received no vaccine dose before symptom onset; (2) first vaccine dose within 13 days before symptom onset; (3) partially vaccinated where individuals received 1 dose ≥14 days before symptom onset; (4) second vaccine dose within 13 days before symptom onset; (5) fully vaccinated where individuals received 2 doses ≥14 days before symptom onset; and (6) unknown vaccination status where information of vaccination histories was not documented. For patients whose precise vaccination date was not documented (eg, only the month of the vaccination was documented), the midpoint between the 2 possible dates was assumed to be the vaccination date. Additionally, those for whom only the number of vaccine doses were recorded were included in either the partially or fully vaccinated groups depending on the number of vaccine doses.

Statistical Analysis

The odds ratio (OR) was calculated by comparing the odds of antecedent COVID-19 vaccination in test-positive vs test-negative patients. A mixed-effects logistic regression model was used to calculate adjusted ORs. Age, sex, presence of underlying medical conditions, calendar weeks, and history of contact with COVID-19 patients were applied as the fixed effects, and study sites as the random effect to the logistic model. VE was defined as 1 minus adjusted ORs, expressed as a percentage [8, 9].

Vaccine effectiveness estimates were calculated for full vaccinated vs no vaccination and for partially vaccinated vs no vaccination. Those with unknown vaccination status were not included in fully vaccinated, partially vaccinated, or no vaccination groups in the primary analysis. We analyzed VE separately in patients aged 16–64 years and in patients aged ≥65 years, taking into consideration the possibility of confounders due to the priority vaccination strategy for patients aged ≥65 years. For BNT162b2 or mRNA-1273 analysis, we pooled patients who received either BNT162b2 or mRNA-1273 COVID-19 vaccines. We also performed analyses on each vaccine product separately. We excluded the episodes with undocumented vaccine products from the analysis of each vaccine product. Additionally, to assess the extent of waning immunity of mRNA COVID-19 vaccines against the Delta variant in Japan, we evaluated VE separately between 2 groups: episodes within 1–3 months and episodes within 4–6 months after full vaccination status (14 days after the second vaccine receipt) among patients aged 16–64 years. We also conducted subgroup analyses by sex or presence of underlying medical conditions. Several sensitivity analyses were performed to strengthen our results. Methods and results of sensitivity analyses are described in Supplementary Section 1, Supplementary Table 1, and Supplementary Table 2. All analysis was performed using Stata version 16.0 (StataCorp, College Station, Texas)

Ethical Considerations

This study was approved by the Institutional Review Board (IRB) at the Institute of Tropical Medicine, Nagasaki University (approval number 210225257) and the study sites. For the study sites without IRBs, this study was collectively reviewed by the Institute of Tropical Medicine IRB, Nagasaki University.

RESULTS

Participants

Between 1 July 2021 and 30 September 2021, 2082 episodes with signs or symptoms consistent with COVID-19 and evidence of tests for SARS-CoV-2 were registered in our surveillance. After excluding 75 episodes with tests ≥15 days after symptom onset, 43 episodes with undocumented symptom onset dates, and 28 episodes with multiple test occasions, we included 1936 patients (396 test-positive cases, 1540 test-negative controls) (Figure 1) enrolled from 13 medical facilities (Supplementary Figure 3 and Supplementary Table 3). Overall, the median age was 49 years (interquartile range, 30–72 years); 1033 (53.4%) patients were male, 659 (34.0%) had 1 or more underlying medical conditions (Table 1), and 6 had previous COVID-19 histories. Test-positive cases were more likely to be male, to be younger, and to have histories of contact with COVID-19 patients, and less likely to have underlying medical conditions ($P < .001$). Thirteen (3.3%) cases and 89 (5.8%) controls had received partial COVID-19 vaccination, 26 (6.6%) cases and 597 (38.8%) controls had received full COVID-19 vaccination, and 290 (73.2%) cases and 523 (34.0%) controls had not been vaccinated. Among vaccinated patients, 676 (69.6%) received BNT162b2 and 140 (14.4%) mRNA-1273 but the vaccine products of 155 (16.0%) individuals were unknown. No one had received AZD1222, and 86.9% of fully vaccinated individuals had completed full vaccination within 1–3 months before symptom onset.

Vaccine Effectiveness

Vaccine effectiveness of mRNA COVID-19 vaccines against symptomatic SARS-CoV-2 infections is shown in Figure 2. For BNT162b2 or mRNA-1273 analysis among patients aged 16–64 years, VE was 88.7% (95% confidence interval [CI], 78.8%–93.9%) for full vaccination and 54.3% (95% CI, 8.4%–77.2%) for partial vaccination. Point estimates were higher for mRNA-1273 (96.6% [95% CI, 72.8%–99.6%]) than for BNT162b2 (86.7% [95% CI, 73.5%–93.3%]); however, there was no statistically significant difference ($P = .877$). Among patients aged ≥65 years, VE for full vaccination was similar to that of patient aged 16–64 years: 90.3% (95% CI, 73.6%–96.4%) for BNT162b2 or mRNA-1273 analysis, and 85.8% (95% CI, 59.4%–95.0%) for BNT162b2 analysis. VE for partial

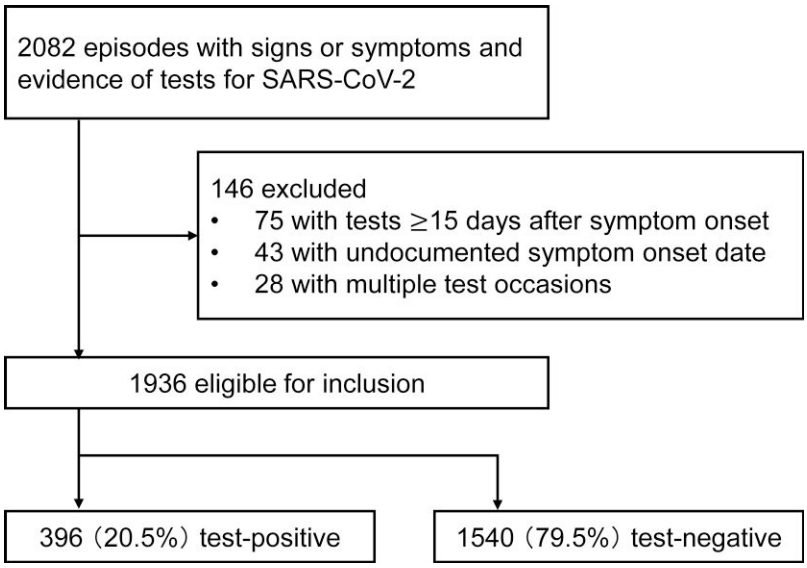

Figure 1. This study included individuals aged ≥16 years visiting participating hospitals or clinics with 1 or more of the following signs or symptoms: fever (≥37.5°C), cough, fatigue, shortness of breath, myalgia, sore throat, nasal congestion, headache, diarrhea, taste disorder, or olfactory dysfunction; and tested for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Japan between 1 July 2021 and 30 September 2021.

vaccination or mRNA-1273 among patients aged ≥65 years was not evaluated due to the small sample size.

The extent of waning immunity of mRNA COVID-19 vaccines against symptomatic SARS-CoV-2 infections was analyzed among patients aged 16–64 years. Vaccine effectiveness after full vaccination was 91.8% (95% CI, 80.3%–96.6%) for patients within 1–3 months and 86.4% (95% CI, 56.9%–95.7%) for patients within 4–6 months (Figure 2).

In a subgroup analysis by sex, a point estimate was higher for women (92.9% [95% CI, 81.0%–97.4%]) than for men (83.5% [95% CI, 62.3%–92.8%]) among patients aged 16–64 years, and higher for men (94.1% [95% CI, 72.5%–98.8%]) than women (88.7% [95% CI, 49.2%–97.5%]) among patients aged ≥65 years, while the 95% CI overlapped in both age groups (Figure 3). In a subgroup analysis by the presence of underlying medical conditions, VE was similar for both age groups. The results of sensitivity analysis are shown in Supplementary Table 1 and Supplementary Table 2 and are similar to the primary analysis.

DISCUSSION

In this prospective test-negative case-control study, we confirmed high mRNA COVID-19 VE against symptomatic SARS-CoV-2 infections in Japan. We estimated that the VE of 2 doses of BNT162b2 or mRNA-1273 against symptomatic SARS-CoV-2 infections was 88.7% (95% CI, 78.8%–93.9%) among patients aged 16–64 years and 90.3% (95% CI, 73.6%–96.4%) among patients aged ≥65 years. This study adds to real-world evaluations that demonstrated the high VE of mRNA COVID-19 vaccines against symptomatic SARS-CoV-2 infections in Japan.

The patients included in this study were those examined for SARS-CoV-2 tests between 1 July 2021 and 30 September 2021. During this period, the Delta variant was dominant within Japan, and >90% of COVID-19 cases nationwide were estimated to be caused by the Delta variant since late August 2021 [25, 26]. Therefore, both mRNA COVID-19 vaccines are effective against symptomatic SARS-CoV-2 infections caused by the Delta variant. Our VE estimates after 2 doses of vaccines were similar to estimates reported from the United Kingdom (88% [95% CI, 85.3%–90.1%] for BNT162b2) [27] and Canada (92% [95% CI, 89%–94%] for BNT162b2 and 92% [95% CI, 90%–97%] for mRNA-1273) [28], but higher than those in Israel (40.5% [95% CI, 8.7%–61.2%] for BNT162b2) [29, 30], the United States (42% [95% CI, 13%–62%] for BNT162b2 and 76% [95% CI, 58%–87%] for mRNA-1273) [31], and Qatar (44.4% [95% CI, 37.0%–50.9%] for BNT162b2 and 73.9 [95% CI, 65.9%–79.9%] for mRNA-1273) [32]. The Japanese national COVID-19 vaccination campaign started >2 months after these countries' campaigns [33], and the symptom onset date for approximately 87% of the fully vaccinated patients in our study was 1–3 months after full vaccination. One reason for the difference between our estimates of VE and those in Israel, the United States, and Qatar could be due to waning immunity [29, 34, 35]. On the other hand, the study in the United Kingdom included SARS-CoV-2 test results in late April to May 2021 [27], whereas in Canada, the vaccination coverage rate started increasing since June 2021 [31] as in Japan (Supplementary Figure 2), which could make waning immunity less than in Israel, the United States,

Table 1. Demographics and Characteristics of Test-Positive Cases and Test-Negative Controls: Vaccine Effectiveness Real-time Surveillance for SARS-CoV-2 (VERSUS) Study, Japan, 1 July to 30 September 2021

Characteristic	Total (n= 1936)	Test-Positive Case (n = 396)	Test-Negative Control (n = 1540)
Age, y, median (IQR)	49 (30–72)	35 (26–50)	55 (32–76)
Age category, y			
16–29	475 (24.5)	148 (37.4)	327 (21.2)
30–39	278 (14.4)	78 (19.7)	200 (13.0)
40–49	239 (12.4)	68 (17.2)	171 (11.1)
50–59	201 (10.4)	64 (16.2)	137 (8.9)
60–69	195 (10.1)	12 (3.0)	183 (11.9)
70–79	220 (11.4)	12 (3.0)	208 (13.5)
80–89	242 (12.5)	11 (2.8)	231 (15.0)
≥90	86 (4.4)	3 (0.8)	83 (5.4)
Male sex	1033 (53.4)	246 (62.1)	787 (51.1)
Living at home	1767 (91.3)	385 (97.2)	1382 (89.7)
Living at a long-term care facility	121 (6.3)	1 (0.3)	120 (7.8)
Underlying medical condition			
Any	659 (34.0)	71 (17.9)	588 (38.2)
Chronic heart disease	166 (8.6)	13 (3.3)	153 (9.9)
Chronic respiratory disease	182 (9.4)	11 (2.8)	171 (11.1)
Obesity	92 (4.7)	24 (6.1)	68 (4.4)
Malignancy	148 (7.6)	8 (2.0)	140 (9.1)
Diabetes mellitus	181 (9.3)	20 (5.1)	161 (10.4)
Chronic kidney disease	76 (3.9)	3 (0.8)	73 (4.7)
Dialysis	21 (1.1)	1 (0.3)	20 (1.3)
Liver cirrhosis	6 (0.3)	0	6 (0.4)
Immunocompromising therapy	46 (2.4)	4 (1.0)	43 (2.7)
Pregnancy	5 (0.3)	2 (0.5)	3 (0.2)
Smoking history	624 (32.2)	143 (36.1)	481 (31.2)
Healthcare worker	108 (5.6)	7 (1.8)	101 (6.6)
History of contact with a COVID-19 patient			
Yes	217 (11.2)	131 (33.1)	86 (5.6)
No	1600 (82.6)	250 (63.1)	1350 (87.7)
Unknown	119 (6.1)	15 (3.8)	104 (6.8)
Test method			
PCR	573 (29.6)	191 (48.2)	382 (24.8)
LAMP	600 (31.0)	112 (28.3)	488 (31.7)
Antigen quantification test	745 (38.5)	91 (23.0)	654 (42.5)
Other NAAT[a]	18 (0.9)	2 (0.5)	16 (1.0)
COVID-19 vaccination status[b]			
No vaccination	813 (42.0)	290 (73.2)	523 (34.0)
First vaccine dose within 0–13 d	125 (6.4)	29 (7.3)	96 (6.2)
Partially vaccinated (first vaccine dose after ≥14 d)	102 (5.3)	13 (3.3)	89 (5.8)
Second vaccine doses within 0–13 d	121 (6.3)	2 (0.5)	119 (7.7)
Fully vaccinated (second vaccine doses after ≥14 d)	623 (32.2)	26 (6.6)	597 (38.8)
Unknown vaccination status	152 (7.9)	36 (9.1)	116 (7.5)
Among vaccinated patients, vaccine product received			
BNT162b2	676 (69.6)	42 (60.0)	634 (71.4)
mRNA-1273	140 (14.4)	14 (20.0)	126 (14.2)
Unknown	155 (16.0)	14 (20.0)	141 (15.9)
Among fully vaccinated patients with documented vaccination date, months after full vaccination[c]			
1–3 mo	458 (86.9)	19 (82.6)	439 (87.1)
4–6 mo	69 (13.1)	4 (17.4)	65 (12.9)

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: COVID-19, coronavirus disease 2019; IQR, interquartile range; LAMP, loop-mediated isothermal amplification; mRNA, messenger RNA; NAAT, nucleic acid amplification test; PCR, polymerase chain reaction.

[a]Other NAATs included nicking endonuclease amplification reaction and transcription-mediated amplification.

[b]Vaccination status was classified based on the number of COVID-19 vaccine doses received before symptom onset. No vaccination was where individuals had received no COVID-19 vaccine dose before symptom onset. Partially vaccinated individuals received 1 dose of COVID-19 vaccine dose ≥14 days before symptom onset. Fully vaccinated individuals received 2 doses of COVID-19 vaccines ≥14 days before symptom onset.

[c]Excluded those with no information of vaccination date: 3 test-positive cases and 93 test-negative controls were excluded.

or Qatar [27, 28]. We also evaluated the VE of each mRNA COVID-19 vaccine among people aged 16–64 years. VE of mRNA-1273 was higher than that of BNT162b2 in the point estimates, consistent with previous studies [31, 32]; however, there was no statistically significant difference ($P = .877$).

As mentioned above, COVID-19 vaccinations were publicly funded in Japan, just after the market approval. This policy would be reasonable under the first phase of the pandemic situation. However, when we reconsider the national COVID-19 vaccination policy, such as a resetting of priority-based booster vaccinations, subgroup analyses (eg, stratified by age group) are needed. Older adults were reported to have lower antibody titers after COVID-19 vaccination compared to younger people [36–38]. On the other hand, COVID-19 VE in older adults compared to younger people varied by studies. For example, in our study, the VE of 2 doses of mRNA COVID-19 vaccines against symptomatic SARS-CoV-2 infections among patients aged ≥65 years was similar to that among patients aged 16–64 years, consistent with studies from Canada and Israel [28, 29], whereas a study from the United Kingdom reported that VE of BNT162b2 against symptomatic SARS-CoV-2 infections caused by the Delta variant was lower in patients aged ≥65 years than in patients aged 16–64 years [39]. Because COVID-19 VE by age group differs by studies, continued assessment is crucial.

To evaluate the waning immunity of mRNA COVID-19 vaccines against symptomatic COVID-19, we assessed VE by dividing the interval between full vaccination date and symptom onset date into 2 groups. Although the 95% CI was wide due to the small sample size, the point estimates were slightly lower in patients with a longer interval after vaccination. This result was consistent with studies in Israel, the United States, and the United Kingdom [29, 34, 39].

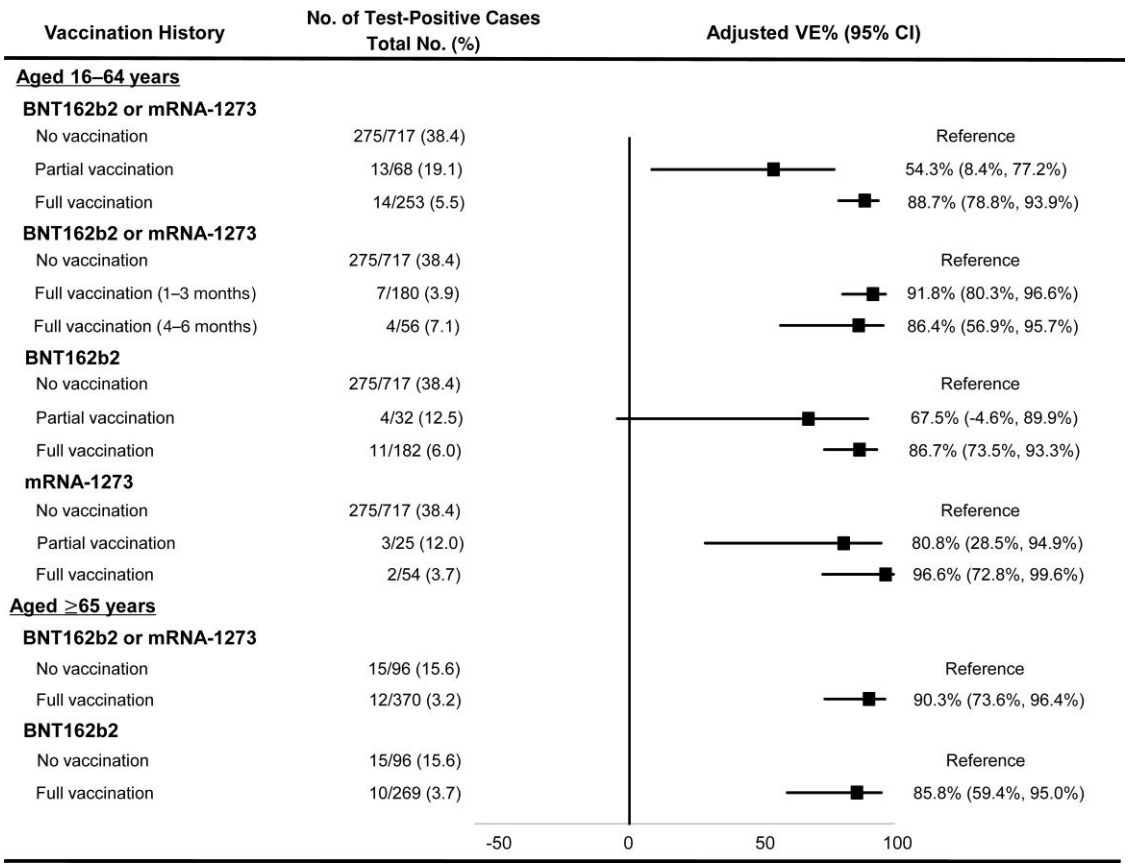

Figure 2. Vaccine effectiveness (VE) of messenger RNA (mRNA) coronavirus disease 2019 (COVID-19) vaccines against symptomatic severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections among individuals aged 16–64 years and aged ≥65 years, Vaccine Effectiveness Real-time Surveillance for SARS-CoV-2 (VERSUS) study, Japan, 1 July–30 September 2021. The analysis included test-positive cases who had signs or symptoms and tested positive for SARS-CoV-2, and test-negative controls who had signs or symptoms and tested negative for SARS-CoV-2. VE (shown with 95% confidence intervals [CIs]) was adjusted for age, sex, presence of underlying medical conditions, calendar week, history of contact with COVID-19 patients, and study site. Vaccination status was classified into 3 statuses based on the number of vaccine doses received before symptom onset and the number of days between the last vaccination date and symptom onset: no vaccination where individuals had received no vaccine dose before symptom onset; partial vaccination where individuals received 1 dose ≥14 days before symptom onset; and full vaccination where individuals who received 2 doses ≥14 days before symptom onset.

This study has several limitations. First, the sample size was small and limited to 13 study sites in 9 prefectures between 1 July 2021 and 30 September 2021. Second, recall bias could occur in vaccination histories. In Japan, there is no system that integrates electronic medical records and vaccination records, since medical care is covered by health insurance system, whereas vaccination is covered by a separate system under the Immunization Act. Additionally, neither medical professionals working at medical institutions nor researchers are allowed to access governmental vaccination records. Therefore, some of the vaccination histories included in this study were obtained through interviews with the patient or family members. To strengthen our results, we conducted several sensitivity analyses (Supplementary Table 1). VE obtained from sensitivity analyses was similar to the primary analysis, and we considered our results robust. Third, since we did not conduct SARS-CoV-2 genome sequencing for test-positive patients, it was impossible to obtain an accurate estimation of VE of mRNA COVID-19 vaccines against the Delta variant. Fourth, the possibility of misclassification in test results cannot be ruled out. This study incorporated the results testing with the following methods clinically used in Japan: NAATs, including PCR, LAMP, NEAR, and TMA, and antigen quantification test. The results of rapid antigen tests were not included. LAMP or antigen quantification tests, which are less sensitive than PCR, could have affected the estimates of VE as shown in the Supplementary Section 1 and Supplementary Table 1.

In conclusion, mRNA COVID-19 vaccines were highly effective for preventing symptomatic SARS-CoV-2 infections in Japan from July to September 2021, when the Delta variant circulated nationwide. Thus, VE of mRNA COVID-19 vaccines remained high in Japan despite the dominancy of a variant virus. As we only evaluated the waning immunity up to 6 months after the full vaccination, and the sample size within 3–6 months after the full vaccination was limited, further follow-up research is needed. Vaccination is one of the essential strategies

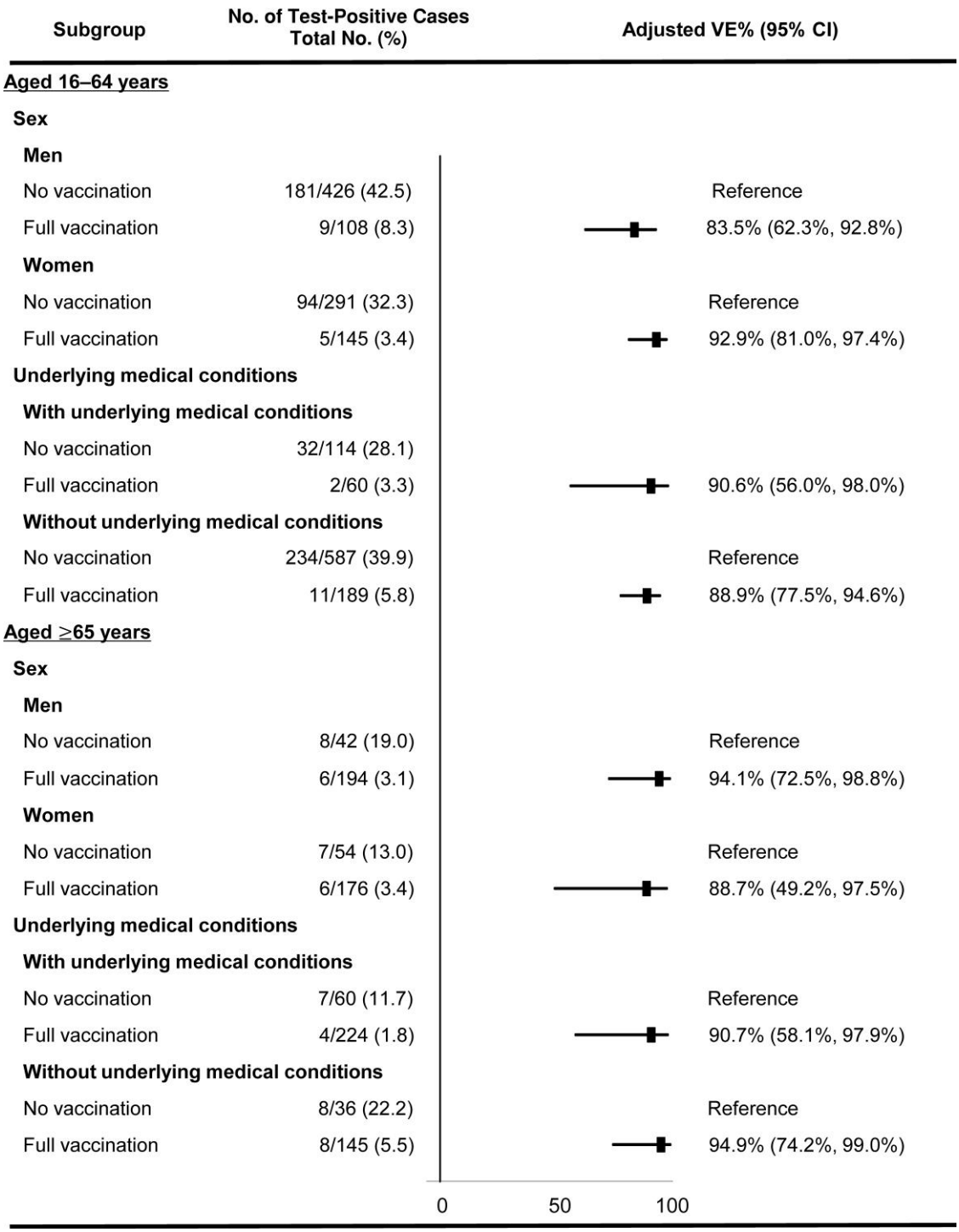

Figure 3. Vaccine effectiveness (VE) of messenger RNA coronavirus disease 2019 (COVID-19) vaccines against symptomatic severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections by subgroups among individuals aged 16–64 years and aged ≥65 years, Vaccine Effectiveness Real-time Surveillance for SARS-CoV-2 (VERSUS) study, Japan, 1 July–30 September 2021. The analysis included test-positive cases who had signs or symptoms and tested positive for SARS-CoV-2, and test-negative controls who had signs or symptoms and tested negative for SARS-CoV-2. VE (shown with 95% confidence intervals [CIs]) was adjusted for age, sex, presence of underlying medical conditions, calendar week, history of contact with COVID-19 patients, and study site. Vaccination status was classified into 3 statuses based on the number of vaccine doses received before symptom onset and the number of days between the last vaccination date and symptom onset: no vaccination where individuals had received no vaccine dose before symptom onset; partial vaccination where individuals received 1 dose ≥14 days before symptom onset; and full vaccination where individuals who received 2 doses ≥14 days before symptom onset. Underlying medical conditions included chronic heart disease, chronic respiratory disease, obesity (body mass index ≥30 kg/m^2), malignancy (including solid or hematological malignancy), diabetes, chronic kidney disease, receiving dialysis, liver cirrhosis, use of immunosuppressive medicines, or pregnancy.

to tackle the COVID-19 pandemic, and it is crucial to continue this surveillance activity, including the evaluation of VE against the Omicron variant, to assess the optimal domestic COVID-19 vaccination strategy.

Supplementary Data

Supplementary materials are available at *Clinical 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.

Notes

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