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)

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Running title: Vaccine effectiveness vs. Delta/Omicron

Abstract

Background

Although several COVID-19 vaccines initially showed high efficacy, there have been concerns due to waning immunity and the emergence of variants with immune escape capacity.

Methods

A test-negative design case-control study was conducted in 16 healthcare facilities in Japan during the Delta-dominant period (August-September 2021) and the Omicron-dominant period (January-March 2022). Vaccine effectiveness (VE) against symptomatic SARS-CoV-2 infection was calculated for 2 doses for the Delta-dominant period and 2 or 3 doses for the Omicron-dominant period, compared to unvaccinated individuals.

Results

The analysis included 5795 individuals with 2595 (44.8%) cases. Among vaccinees, 2242 (55.8%) received BNT162b2 and 1624 (40.4%) received mRNA-1273 at manufacturer-recommended intervals. During the Delta-dominant period, VE was 88% (95% CI: 82-93) 14 days-3 months after dose 2 and 87% (95% CI: 38-97) 3-6 months after dose 2. During the Omicron-dominant period, VE was 56% (95% CI: 37-70) 14 days-3 months since dose 2, 52% (95% CI: 40-62) 3-6 months after dose 2, 49% (95% CI: 34-61) 6+ months after dose 2, and 74% (95% CI: 62-83) 14+ days after dose 3. Restricting to individuals at high risk of severe COVID-19 and additional adjustment for preventive measures (i.e. mask-wearing/high-risk behaviors) yielded similar estimates, respectively.

Conclusions

In Japan where most are infection-naïve and strict prevention measures are maintained regardless of vaccination status, 2-dose mRNA vaccines provided high protection against symptomatic infection during the Delta-dominant period and moderate protection during the

Omicron-dominant period. Among individuals who received an mRNA booster dose, VE recovered to a high level.

Keywords: severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); coronavirus disease 2019 (COVID-19); test-negative design; vaccine effectiveness; SARS-CoV-2 variants

Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has resulted in substantial morbidity and mortality globally [1]. The speed of vaccine development has been unprecedented, with randomized controlled studies [2-5] and several real-world vaccine effectiveness (VE) studies early after the vaccine rollout [6-9] demonstrating high efficacy/effectiveness for two mRNA vaccines (BNT162b2 [Pfizer/BioNTech] and mRNA-1273 [Moderna]) and a viral vector vaccine (AZD1222 [AstraZeneca]). However, subsequent observational studies evaluating mid- to long-term effectiveness against symptomatic infection suggested waning immunity [10-13]. Further complicating the situation, in November 2021, a new variant, B.1.1.529 (Omicron variant), which harbors numerous mutations in the spike protein was detected in South Africa. Initial *in vitro* neutralization studies suggested substantial immune escape capacity [14-16]. Early epidemiological studies from the United Kingdom (U.K.) and the United States (U.S.) retrospectively analyzing surveillance or clinical data suggested low to no VE against symptomatic disease caused by the Omicron variant [17-19]. However, evidence from elsewhere has been limited, and VE studies in mostly infection-naïve populations would provide additional evidence to inform policies and risk communication. In Japan, a national seroprevalance study was conducted by the Ministry of Health, Labour and Welfare in December 2021, prior to the Omicron wave in Japan. Even in Tokyo where the COVID-19 case notification rate has been one of the highest in Japan throughout the pandemic, only 2.8% were seropositive for nucleocapsid protein, which is considered to be the marker for past infection, but not for COVID-19 vaccination as the vaccines rolled out in Japan only code for spike protein (the aforementioned 3 vaccines) [20]. Here we report the results of a multi-center test-negative design case-control study conducted in Japan to evaluate VE against symptomatic SARS-CoV-2 infection during the Delta- and Omicron-dominant

periods. We evaluated VE against 2 doses for the Delta-dominant period and 2 or 3 doses for the Omicron-dominant period.

Methods

COVID-19 vaccination rollout in Japan

In Japan, BNT162b2, mRNA-1273, and AZD1222 have been approved for use since February 2021. The use of AZD1222 has been extremely limited and the majority of individuals received either BNT162b2 or mRNA-1273 (**Supplementary Methods**) [21].

Study design and setting

Our study, Factors Associated with SARS-CoV-2 INfection And The Effectiveness of COVID-19 vaccines (FASCINATE study), is a multi-center case-control study in healthcare facilities in Japan with two objectives: (1) to elucidate behavioral and demographic risk factors associated with SARS-CoV-2 infection and (2) to estimate the real-world effectiveness of COVID-19 vaccines. Participating healthcare facilities have fever clinics that routinely test individuals using polymerase chain reaction (PCR) for diagnostic purposes. This report includes data from 16 healthcare facilities in the Kanto region (Tokyo and 4 surrounding metropolitan prefectures), where the reported COVID-19 case counts and rate per population have been one of the highest throughout the pandemic relative to other regions in Japan. For this report, individuals who were tested between 1 August 2021 and 31 March 2022 were included.

Definition of Delta- and Omicron-dominant periods and non-epidemic period

Based on data from variant-specific PCR that can detect the L452R mutation, which is present in the Delta variant but absent in the Alpha and Omicron variants, by 1 August 2021,

the Delta variant was estimated to be responsible for over 90% of SARS-CoV-2 infections in Japan, replacing the Alpha variant [22]. Therefore, we defined 1 August to 30 September 2021 as the Delta-dominant period (**Figure 1**). By the beginning of October, the number of reported COVID-19 cases decreased rapidly and reached <1 case per 100 000 population. This low level lasted until the end of December 2021. Therefore, we defined 1 October to 31 December 2021 as the non-epidemic period. In early January 2022, the number of cases rose rapidly owing to introduction of the Omicron variant, with Omicron estimated to be responsible for over 90% of SARS-CoV-2 infections [23]. Therefore, we defined 1 January to 31 March 2022 as the Omicron-dominant period.

Inclusion and exclusion criteria

The inclusion criterion was all symptomatic individuals aged ≥20 years (**Supplementary Methods**). Individuals who did not or could not consent to participate in the study, individuals who required immediate lifesaving treatment, and individuals who had previously participated in this study were excluded. At the analysis stage, we also excluded individuals who had unknown symptom onset, were tested ≥15 days after symptom onset, or were tested during the non-epidemic period.

Classification of exposures and outcome

A paper or web-based (according to the subject's preference) questionnaire was administered before the test results were available to avoid social desirability bias. Vaccination status (number of doses, vaccine manufacturer, and date of each dose) was recorded based on the questionnaire (via a copy of the vaccine record/certificate) and checked for plausibility. Vaccination status was classified into 7 categories: (1) not vaccinated, (2) dose 1 or ≤13 days after dose 2 (partially vaccinated), (3) 14 days-3 months (14-90 days) after dose 2, (4) 3-6

months (90-180 days) after dose 2, (5) >6 months (181 days) after dose 2, (6) ≤13 days after dose 3 (booster dose), and (7) ≥14 days after dose 3. SARS-CoV-2 PCR was done at each medical facility or commercial company for diagnostic purposes; PCR-positive individuals were considered cases and PCR-negative individuals were controls.

Data analysis

Logistic regression was used to estimate the odds of being vaccinated among cases relative to controls. The model was adjusted for age group, sex, presence of any comorbidity (**Supplementary Methods**), educational attainment, place of residence, occupation (healthcare worker or not), SARS-CoV-2 diagnostic test in the past month, past SARS-CoV-2 infection, history of close contact, healthcare facility in which SARS-CoV-2 testing was done, and calendar week. These potential confounders were determined *a priori* based on published reports [7-13]. VE against symptomatic SARS-CoV-2 infection was estimated using the following equation: VE = (1 - adjusted odds ratio [aOR]) × 100%. In secondary exploratory analysis, we further adjusted the odds ratios for preventive measures, including mask-wearing (4 categories: wore at home and outside, wore outside at all times, wore only when having conversations, almost never wore masks) and high-risk behavior (dining at a restaurant/bar at night with alcohol consumption in a group was used as a proxy; this provides occasion to talk face-to-face for a prolonged period without masks in an intoxicated state and was identified as a major risk factors associated with SARS-CoV-2 infection [24]) in an attempt to control for differential exposures between vaccinated and unvaccinated individuals. We also performed sub-analysis by restricting the analysis to individuals who either were ≥65 years or had any comorbidities, who have higher risk of developing severe COVID-19. Furthermore, although complete case analysis was done in primary analyses, multiple imputation by chained equations was performed as a sensitivity analysis. We used

the same variables used in the primary analyses to impute missing data and to further calculate aOR and VE. Data analyses were performed using STATA version 17.0.

Ethics statement

The ethics committee of the National Institute of Infectious Diseases approved our study (approval number 1332). Ethics approval was also sought from medical facilities that required review from on-site committees.

Results

Characteristics of the study participants

A total of 7157 individuals were enrolled from 16 medical facilities during the study period; 339 were excluded due to unknown symptom onset and 87 were excluded due to being tested ≥15 days after symptom onset (**Figure 2**). Individuals tested during the non-epidemic period were also excluded. The final analysis included 5795 individuals with 2595 (44.8%) positive cases. The median age (interquartile range [IQR]) was 35 (27-46) years, 2896 (50.0%) were males, and 1491 (25.7%) had comorbidities (**Table 1**). Although data on race/ethnicity were not collected, 5684 (98.5%; 25 missing) were Japanese nationals and most foreigners were from East Asia, so we expect most study participants to be Asians. Almost all (5589, 97.5%) lived in a home, rather than a hospital/care facility or dormitory, and 953 (16.8%) reported having undergone SARS-CoV-2 diagnostic testing in the past month. Median (IQR) time from onset to SARS-CoV-2 testing was 1 (1-3) days; 1256 (21.7%) had history of close contact. Among those vaccinated at least once, 2242 (55.8%) received BNT162b2, 1624 (40.4%) received mRNA-1273, 94 (2.3%) received other types/heterologous regimen, and 60 (1.5%) were of unknown vaccine type. The median interval between the first 2 doses was 21

days for BNT162b2 and 28 days for mRNA-1273, as per manufacturer instructions. The median interval between the primary series and the booster dose was 214 days (7.1 months). Characteristics of participants during the Delta- and Omicron-dominant periods are in **Supplementary Table 1**. Compared to participants in the Delta-dominant period, those in the Omicron-dominant period were more likely to be vaccinated (due to the rollout timeline), slightly less likely to have history of close contact, slightly more likely to have past SARS-CoV-2 infection, slightly more likely to have been vaccinated with BNT162b2, and more likely to be engaged in high-risk behaviors (possibly since a state of emergency was in effect during the Delta-dominant period). Otherwise, the participants' characteristics were similar between the two periods.

Vaccine effectiveness by period since COVID-19 vaccination during the Delta-dominant period

During the Delta-dominant period, VE estimates were 65% (95% confidence interval [CI]: 54-74) for participants who received dose 1 only or were ≤13 days since dose 2 (partially vaccinated), 88% (95% CI: 82-93) for 14 days-3 months after dose 2, and 87% (95% CI: 38-97) for 3-6 months after dose 2, all compared to unvaccinated individuals (**Figure 3, Supplementary Table 2**). Since the Delta-dominant period was during the early rollout phase of the 2-dose regimen, there were no individuals who had received 2 doses over 6 months ago or a booster dose (**Figure 1**).

Vaccine effectiveness by 2 or 3 doses and period since COVID-19 vaccination during the Omicron-dominant period

During the Omicron-dominant period, VE estimates were 34% (95% CI: -20-64) for individuals who received dose 1 or were ≤13 days since dose 2 (partially vaccinated), 56%

(95% CI: 37-70) for 14 days-3 months after dose 2, 52% (95% CI: 40-62) for 3-6 months after dose 2, and 49% (95% CI: 34-61) for >6 months after dose 2, all compared to unvaccinated individuals (**Figure 3, Supplementary Table 2**). VE estimates after dose 3 were 67% (95% CI: 47-79) for ≤13 days after dose 3 and 74% (95% CI: 62-83) for ≥14 days after dose 3. When comparing 3 doses versus 2 doses post-6 months, aOR was 0.49 (0.34-0.71), which translated to a relative VE of 51% (95% CI: 29-66).

Secondary analysis accounting for preventive measures, sub-analysis among individuals with higher risk of developing severe COVID-19, and sensitivity analysis using multiple imputation

Secondary analysis with additional adjustments for preventive measures including mask wearing and high-risk behaviors was performed. These VE estimates were similar to those in the primary analysis during both the Delta-dominant period (86-88% vs. 87-88% after 2 doses, respectively) and the Omicron-dominant period (52-55% vs. 49-56% after 2 doses and 78% vs. 74% after 3 doses, respectively) (**Table 2**). A sub-analysis of individuals who were at higher risk of developing severe COVID-19 was done; this yielded results similar to or slightly higher than those observed for the entire study population (**Table 3**). There were 96 (1.7%) participants who did not report the number of COVID-19 vaccinations received, and among those who did report, 238 (4.1%) did not report the vaccination date. Multiple imputation of missing data yielded similar VE estimates for both the Delta- and Omicron-dominant periods (**Supplementary Table 3**).

Discussion

In this multi-center test-negative case-control study in Japan, we evaluated VE for 2 doses of COVID-19 vaccine during the Delta-dominant period and 2 or 3 doses of COVID-19 vaccine during the Omicron-dominant period. In agreement with many other observational studies [18-19, 25], 2 doses provided high (VE of 80-90%) protection during the Delta-dominant period for up to 6 months. Since the Delta-dominant period abruptly ended in Japan, likely partly owing to the rollout of 2-dose regimens, we could not assess the long-term effectiveness against the Delta variant.

On the other hand, during the Omicron-dominant period, VE estimates were approximately 50% after two doses up to and beyond 6 months in our study. Although these VE estimates against the Omicron variant were substantially lower than those against the Delta variant, they were higher than what was observed in the U.K. and the U.S., where VE estimates against the Omicron variant were reported to be 0-10% after 3 months [17-19]. Several factors may have contributed to VE estimates being higher in Japan than in other countries. First, in Japan, the government has not actively implemented policies to relax social and public health measures specifically for vaccinated individuals using vaccine certificates/passports. Rather, the government has been continuously communicating to the public to continue practicing infection prevention measures such as mask-wearing and physical distancing even after vaccination. VE estimates would be underestimated if vaccinated individuals are more likely to engage in high-risk behaviors due to perceived protection from infection or by relaxation of mask-wearing and physical distancing mandates/policies only among vaccinees or utilization of vaccine certificates/passports to allow vaccinees to engage in high-risk behaviors. In fact, some countries reported negative VE estimates during the Omicron wave, possibly due to biases arising from different levels of risk between vaccinees and non-vaccinees [26-27]. In contrast, the baseline risk of infection

among vaccinees and non-vaccinees may have been more similar in Japan, resulting in estimates less affected by this bias. This is partly supported by the results of the secondary analysis that adjusted for prevention measures including mask wearing and high-risk behaviors. Indeed, among the study participants, only 10 out of 5705 (0.2%) reported not wearing masks, and 9 of the 10 individuals who reported not wearing masks were not vaccinated. Furthermore, differential propensity for vaccination by past infection status can be a concern in estimating VE. For example, if individuals with past infection choose not to be vaccinated due to perceived protection, as observed in the U.K. [28], VE would be underestimated. Moreover, in Japan, only 2.8% of individuals in Tokyo (which is in the Kanto region) were anti-nucleocapsid antibody positive before the Omicron-dominant period, indicating that most of the population was infection-naïve, in stark contrast to the U.K. (approximately 30%) and the U.S. (33.5%) [20, 29-30]. This allowed us to calculate VE estimates in a mostly infection-naïve population. Our study also had a low proportion of individuals with past SARS-CoV-2 infection (4.4%), for which we were also able to account for in our analysis. Finally, Japan followed manufacturer-recommended intervals between the first and second doses, similar to the U.S. but different from the U.K. where the interval was up to 12 weeks, including for mRNA vaccines with a recommended dose interval of 3-4 weeks for the primary series. Some *in vitro* studies have suggested that a longer interval provides better protection against variants [31], so careful interpretation is warranted in extrapolating findings from countries with different intervals especially in the setting of emerging variants. The immune profile against SARS-CoV-2 is becoming increasingly diversified due to a complex combination of exposure to vaccines and infection with various lineages/variants, likely generating heterogeneity in protective immunity. It would be challenging but valuable to tease apart various immune histories in future studies.

Lastly, we found that the VE after 3 doses of COVID-19 vaccine was high (74%) in this study. This was consistent with previous studies done in countries that are rolling out a booster dose [17-19]. Continued monitoring will be necessary to evaluate mid- to long-term effectiveness against the Omicron variant, as early reports from the U.K. and Israel indicate waning effectiveness several months after dose 3 [17, 32].

Limitations

This study has several limitations. First, biases inherent in observational studies are possible. Using a detailed questionnaire, we attempted to minimize confounding that is not necessarily accounted for in studies that retrospectively evaluate routine surveillance data, but unmeasured and residual confounding could have occurred. Individuals who are SARS-CoV-2 negative may be less likely to make an effort to recall exposures such as vaccination history. To avoid these sources of bias, we administered the questionnaires before the test results were available. As we did not have a system to link test results with vaccination history, we asked participants to refer to their vaccine records/certificates. Approximately 39% of individuals reported carrying their vaccine record; others were asked to refer to their diary/calendar for accuracy. Second, although the test-negative design is widely used to estimate VE as it is efficient and can control for some healthcare-seeking behavior, it has some potential shortcomings as well [33]. Third, as the vaccine rollout progresses and vaccination rates stabilize, vaccinated and unvaccinated individuals may differ in characteristics other than vaccination status. However, as noted above, such biases may be less of an issue in Japan. Also, booster vaccination was restricted to individuals who had their second dose ≥6 months before, meaning those who were eligible during the Omicron-dominant period would have consisted mostly of the earliest recipients of the vaccine, such as healthcare workers and those aged ≥65 years, which we accounted for in our analysis. Fourth,

some VE estimates were calculated based on very low numbers, resulting in wide confidence intervals. Fifth, our primary analyses were complete case analyses. However, in this study, missing data on vaccination status were minimal and sensitivity analysis with multiple imputation of missing data resulted in similar estimates. Sixth, we did not assess VE against asymptomatic infection, severe cases, or death. Finally, we were not able to classify individual COVID-19 cases as infected with the Omicron or Delta variant. However, since there was a 3-month non-epidemic period with very few cases between these two periods, misclassification was likely minimal.

Conclusions

In Japan, where most of the population is infection-naïve and strict prevention measures at the government and individual levels are maintained regardless of vaccination status, 2-dose mRNA vaccines provided high protection against symptomatic infection during the Delta-dominant period and moderate protection during the Omicron-dominant period several months after the second dose. Among individuals who received an mRNA booster dose, VE recovered to a high level in the short-term.

NOTES

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Conflicts of interest

Takeshi Arashiro is an unpaid consultant for the World Health Organization. The other authors declare no conflicts of interest.

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FIGURE LEGENDS

Figure 1. Number of reported COVID-19 cases since the beginning of the pandemic and proportion of individuals vaccinated in Japan by dose number. (Data sources: Ministry of Health, Labour and Welfare, Japan [https://www.mhlw.go.jp/stf/covid-19/open-data.html] and Digital Agency, Japan [https://info.vrs.digital.go.jp/dashboard])

Figure 2. Flow diagram of the study participants.

Figure 3. Vaccine effectiveness against symptomatic SARS-CoV-2 infection by period since COVID-19 vaccination during the Delta-dominant period (blue diamonds) and Omicron-dominant periods (red squares), all compared to unvaccinated individuals. Blue diamonds and red squares indicate point estimates and error bars indicate 95% confidence intervals.

Table 1. Demographic and clinical characteristics of the study participants

	All (n =5795)	Test positive (n =2595)	Test negative (n =3200)
Age in years, n (%)			
20-29	1960 (33.8)	924 (35.6)	1036 (32.4)
30-39	1601 (27.6)	666 (25.7)	935 (29.2)
40-49	1145 (19.8)	566 (21.8)	579 (18.1)
50-59	677 (11.7)	295 (11.4)	382 (11.9)
60-69	272 (4.7)	107 (4.1)	165 (5.2)
70-79	107 (1.9)	32 (1.2)	75 (2.3)
80+	33 (0.6)	5 (0.2)	28 (0.9)
Sex, n (%); missing = 6 (0.1%)			
Male	2896 (50.0)	1352 (52.1)	1544 (48.3)
Female	2893 (50.0)	1241 (47.9)	1652 (51.7)
Educational attainment, n (%); missing = 74 (1.3%)			
Middle school or less	160 (2.8)	86 (3.4)	74 (2.3)
High school	1317 (23.0)	623 (24.4)	694 (21.9)
Junior college/technical college	1261 (22.0)	576 (22.5)	685 (21.7)
Undergraduate or graduate school	2983 (52.1)	1273 (49.8)	1710 (54.1)
Place of residence, n (%); missing = 59 (1.0%)			
Home	5589 (97.5)	2488 (97.1)	3101 (97.7)
Hospital or long-term care facility	16 (0.3)	7 (0.3)	9 (0.3)
Dormitory or other	131 (2.3)	67 (2.6)	64 (2.0)
Comorbidity,[a] n (%)			
Yes	1491 (25.7)	588 (22.7)	903 (28.2)
No	4304 (74.3)	2007 (77.3)	2297 (71.8)
Occupation, n (%)			
Healthcare worker	300 (5.2)	107 (4.1)	193 (6.0)
Other	5495 (94.8)	2488 (95.9)	3007 (94.0)
Smoking, n (%); missing = 32 (0.6%)			
Never-smoker	3185 (55.3)	1401 (54.3)	1784 (56.0)
Past smoker	1350 (23.4)	619 (24.0)	731 (23.0)
Current smoker	1228 (21.3)	559 (21.7)	669 (21.0)
Days from onset to SARS-CoV-2 test; exact onset date missing = 7 (0.1%)[b]	1 (1-3)	2 (1-3)	1 (1-3)
History of close contact, n (%)			
Yes	1256 (21.7)	714 (27.5)	542 (16.9)
No/unknown	4539 (78.3)	1881 (72.5)	2658 (83.1)
SARS-CoV-2 diagnostic test in the past month, n (%); missing = 104 (1.8%)			
Yes	953 (16.8)	406 (16.0)	547 (17.4)
No	4738 (83.3)	2140 (84.1)	2598 (82.6)
Past SARS-CoV-2 infection, n (%); missing = 134 (2.3%)			
Yes	250 (4.4)	74 (2.9)	176 (5.7)
Ancestral strain-dominant period (2020 to February 2021)	108 (1.9)	35 (1.4)	73 (2.3)
Ancestral-to-Alpha replacement period (March-May 2021)	43 (0.8)	12 (0.5)	31 (1.0)
Alpha-to-Delta replacement period (June-July 2021)	17 (0.3)	8 (0.3)	9 (0.3)

Delta-dominant period (August-December 2021)	47 (0.8)	9 (0.4)	38 (1.2)
Multiple infections	1 (0.0)	0 (0.0)	1 (0.0)
Period of infection missing	34 (0.6)	10 (0.4)	24 (0.8)
No	5411 (95.6)	2472 (97.1)	2939 (94.4)
Number of COVID-19 vaccinations received, n (%); missing = 96 (1.7%)			
None	1617 (28.4)	922 (36.2)	695 (22.1)
One	323 (5.7)	126 (4.9)	197 (6.3)
Two	3430 (60.2)	1382 (54.2)	2048 (65.0)
Three	329 (5.8)	119 (4.7)	210 (6.7)
Vaccine type, n (%); missing among those vaccinated = 62/4082 (1.5%)			
BNT162b2	2242 (55.8)	905 (56.5)	1337 (55.3)
mRNA-1273	1624 (40.4)	629 (39.3)	995 (41.2)
Others/heterologous	94 (2.3)	39 (2.4)	55 (2.3)
Unknown	60 (1.5)	29 (1.8)	31 (1.3)
Interval between dose 1 and 2 for Pfizer/BioNTech (days)[b,c]	21 (21-22)	21 (21-22)	21 (21-22)
Interval between dose 1 and 2 for Moderna (days)[b,c]	28 (28-31)	28 (28-31)	28 (28-31)
Interval between dose 2 and 3 (days)[b,c]	214 (197-226)	215 (196-226)	213 (198-225)
Interval between dose 3 and SARS-CoV-2 testing [d]	17 (0-108)	15 (1-108)	18 (0-93)
Mask-wearing in the past 2 weeks; missing = 90 (1.6%)			
Wore at home and outside	456 (8.0)	215 (8.4)	241 (7.6)
Wore outside at all times	5108 (89.5)	2261 (88.6)	2847 (90.3)
Wore only when having conversations	131 (2.3)	70 (2.7)	61 (1.9)
Almost never wore masks	10 (0.2)	6 (0.2)	4 (0.1)
High-risk behaviors in the past 2 weeks (went to restaurant/bar at night with alcohol consumption), n (%); missing = 344 (6.3%)			
Yes	1578 (29.0)	776 (32.1)	802 (26.5)
No	3873 (71.1)	1644 (67.9)	2229 (73.5)

[a] Comorbidities include hypertension, heart disease, diabetes mellitus, obesity, kidney disease, asthma, chronic obstructive pulmonary disease, cancer, immunodeficiency, and immunosuppressant use.
[b] Median (interquartile range).
[c] Among individuals with exact dates for both doses.
[d] Median (range).

Table 2. Vaccine effectiveness against symptomatic SARS-CoV-2 during the Delta- and Omicron-dominant period by time since vaccination with additional adjustment for preventive measures

(a) Delta-dominant period

Vaccination status	Adjusted odds ratios (95% CI)[a]	Vaccine effectiveness, % (95% CI)
Unvaccinated	1	N/A
Dose 1 or within 13 days of dose 2	0.36 (0.27-0.48)	64 (52-73)
14 days to 3 months after dose 2	0.12 (0.08-0.20)	88 (80-92)
3-6 months after dose 2	0.14 (0.03-0.65)	86 (35-97)

(b) Omicron-dominant period

Vaccination status	Adjusted odds ratios (95% CI)[a]	Vaccine effectiveness, % (95% CI)
Unvaccinated	1	N/A
Dose 1 or within 13 days of dose 2	0.71 (0.38-1.32)	29 (-32-62)
14 days to 3 months after dose 2	0.45 (0.31-0.66)	55 (34-69)
3-6 months after dose 2	0.46 (0.37-0.58)	54 (42-63)
> 6 months after dose 2	0.48 (0.37-0.63)	52 (37-63)
Within 13 days of dose 3	0.31 (0.19-0.50)	69 (50-81)
≥ 14 days after dose 3	0.22 (0.14-0.33)	78 (67-86)

[a] Adjusted for age group, sex, presence of comorbidities, educational attainment, place of residence, occupation (healthcare worker or not), SARS-CoV-2 diagnostic test in the past month, past SARS-CoV-2 infection, history of close contact, healthcare facility, calendar week, mask-wearing, and high-risk behaviors in the past two weeks

Table 3. Vaccine effectiveness against symptomatic SARS-CoV-2 during the Delta- and Omicron-dominant period by time since vaccination among individuals with higher risk of developing severe COVID-19 (≥65 years of age or having at least one comorbidity)

(a) Delta-dominant period

Vaccination status	Test positive, n (%)	Test negative, n (%)	Adjusted odds ratios (95% CI)[a]	Vaccine effectiveness, % (95% CI)
Unvaccinated	111 (72.6)	113 (36.0)	1	N/A
Dose 1 or within 13 days of dose 2	29 (19.0)	81 (25.8)	0.24 (0.13-0.45)	76 (65-87)
14 days to 3 months after dose 2	13 (8.5)	116 (36.9)	0.10 (0.04-0.23)	90 (77-96)
3-6 months after dose 2	0 (0.0)	4 (1.3)	N/A	N/A

(b) Omicron-dominant period

Vaccination status	Test positive, n	Test negative, n	Adjusted odds ratios (95% CI)[a]	Vaccine effectiveness, % (95% CI)
Unvaccinated	78 (18.4)	45 (7.8)	1	N/A
Dose 1 or within 13 days of dose 2	4 (1.0)	9 (1.6)	0.37 (0.09-1.41)	63 (-41-91)
14 days to 3 months after dose 2	19 (4.5)	38 (6.5)	0.50 (0.23-1.09)	50 (-9-77)
3-6 months after dose 2	162 (38.3)	258 (44.4)	0.34 (0.20-0.57)	66 (43-80)
> 6 months after dose 2	122 (28.8)	145 (25.0)	0.36 (0.20-0.62)	64 (38-80)
Within 13 days of dose 3	15 (3.6)	27 (4.7)	0.19 (0.08-0.48)	81 (52-92)
≥ 14 days after dose 3	23 (5.4)	59 (10.2)	0.18 (0.08-0.38)	82 (62-92)

[a] Adjusted for age group, sex, presence of comorbidities, educational attainment, place of residence, occupation (healthcare worker or not), SARS-CoV-2 diagnostic test in the past month, past SARS-CoV-2 infection, history of close contact, healthcare facility, and calendar week.

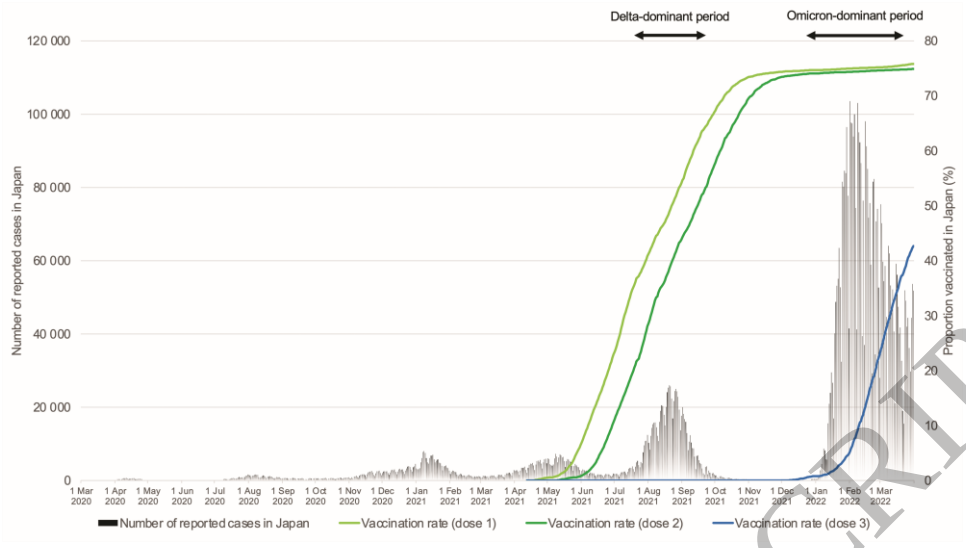

Figure 1
127x71 mm (x DPI)

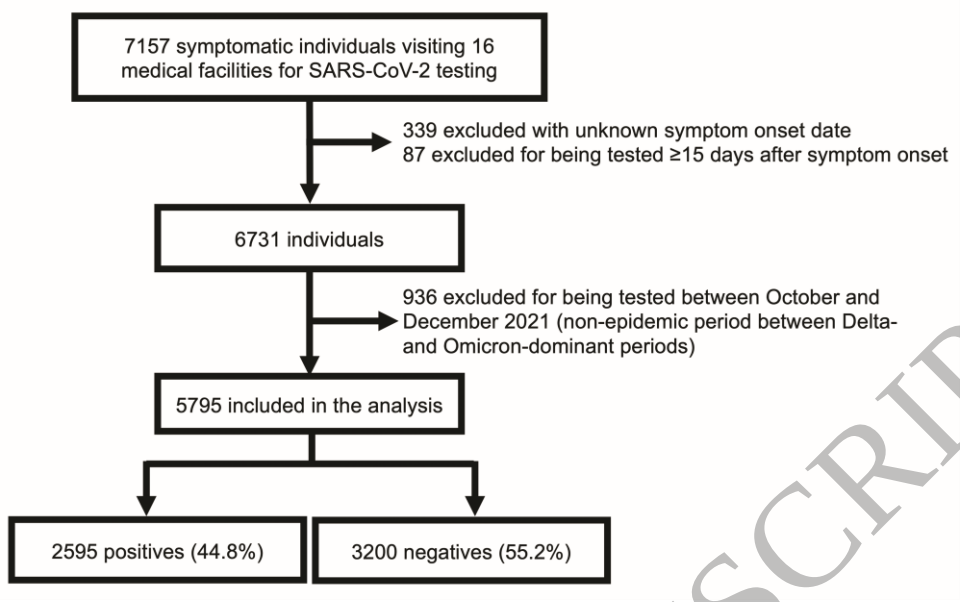

Figure 2
127x79 mm (x DPI)

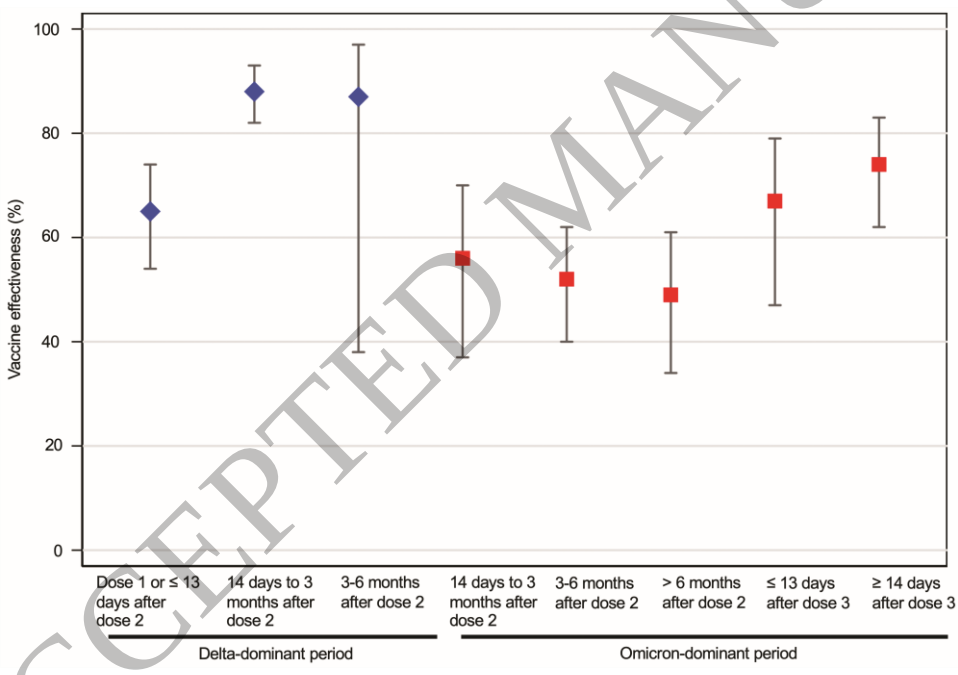

Figure 3
127x87 mm (x DPI)