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COVID-19 vaccine effectiveness against severe COVID-19 requiring oxygen therapy, invasive mechanical ventilation, and death in Japan: A multicenter case-control study (MOTIVATE study)

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ABSTRACT

Introduction: Since the SARS-CoV-2 Omicron variant became dominant, assessing COVID-19 vaccine effectiveness (VE) against severe disease using hospitalization as an outcome became more challenging due to incidental infections via admission screening and variable admission criteria, resulting in a wide range of estimates. To address this, the World Health Organization (WHO) guidance recommends the use of outcomes that are more specific to severe pneumonia such as oxygen use and mechanical ventilation.
Methods: A case-control study was conducted in 24 hospitals in Japan for the Delta-dominant period (August-November 2021; "Delta") and early Omicron (BA.1/BA.2)-dominant period (January-June 2022; "Omicron"). Detailed chart review/interviews were conducted in January-May 2023. VE was measured using various outcomes including disease requiring oxygen therapy, disease requiring invasive mechanical ventilation (IMV), death, outcome restricting to "true" severe COVID-19 (where oxygen requirement is due to COVID-19 rather than another condition(s)), and progression from oxygen use to IMV or death among COVID-19 patients.
Results: The analysis included 2125 individuals with respiratory failure (1608 cases [75.7%]; 99.2% of vaccinees received mRNA vaccines). During Delta, 2 doses provided high protection for up to 6 months (oxygen requirement: 95.2% [95% CI:88.7–98.0%] [restricted to "true" severe COVID-19: 95.5% {89.3–98.1%}]; IMV: 99.6% [97.3–99.9%]; fatal: 98.6% [92.3–99.7%]). During Omicron, 3 doses provided high protection for up to 6 months (oxygen requirement: 85.5% [68.8–93.3%] ["true" severe COVID-19: 88.1% {73.6–94.7%}]; IMV: 97.9% [85.9–99.7%]; fatal: 99.6% [95.2–99.97]). There was a trend towards higher VE for more severe and specific outcomes.
Conclusion: Multiple outcomes pointed towards high protection of 2 doses during Delta and 3 doses during Omicron. These results demonstrate the importance of using severe and specific outcomes to accurately measure VE against severe COVID-19, as recommended in WHO guidance in settings of intense transmission as seen during Omicron.

1. Introduction

Several vaccines against coronavirus disease (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), initially showed high efficacy and effectiveness [1–8]. However, concerns have arisen due to waning immunity and the emergence of variants with immune escape capacity [9–16]. Further, since the Omicron variant became dominant globally in early 2022, assessing vaccine effectiveness (VE) against severe disease using hospitalization as a surrogate for severe outcomes has become more challenging [17,18]. Although hospitalization is the most widely used outcome to measure VE against severe disease owing to its ease and clarity in classification, this definition would include hospitalizations unrelated to COVID-19 due to Omicron's high prevalence in the community with an incidental diagnosis of SARS-CoV-2 infection during routine admission screening. Since VE is lower against infection than against severe diseases (i.e. a decoupling of VE against infection and VE against severe disease) [15,17,18], VE against severe disease via hospitalization outcome would be underestimated. Furthermore, criteria for hospitalization have varied over time and by local context. For example, in Japan, all Omicron cases were hospitalized regardless of disease severity when Omicron was initially introduced into the country, and less-burdened prefectures had lower thresholds for hospitalization to ensure case isolation until hospital bed capacities were overwhelmed [19]. These concerns are evident from past studies showing a wide range of VE estimates (30–100% for 2 doses and 50–100% for 3 doses) against severe disease [18]. To address these issues, guidance from the World Health Organization (WHO) proposed the use of outcomes that are more specific to severe pneumonia such as oxygen use and mechanical ventilation [20]. The guidance also recommends using VE against disease progression. However, no study has examined multiple outcomes related to severe pneumonia at the hospital level with detailed medical chart reviews, as such studies are resource-intensive. Therefore, we conducted a hospital-based multicenter case-control study in Japan to measure VE using various outcomes including disease requiring oxygen therapy, disease requiring invasive mechanical ventilation, death, outcome restricting to "true" severe COVID-19 (where oxygen requirement is due to COVID-19 rather than another condition(s)), and progression from oxygen use to mechanical ventilation or death among COVID-19 patients. We examined these outcomes during the Delta-dominant period and the early Omicron-dominant period (BA.1/BA.2-dominant period).

2. Methods

2.1. COVID-19 vaccination rollout in Japan

In Japan, the primary series (doses 1 and 2) rollout started in mid-February 2021, the first booster dose (dose 3) in December 2021, and the second booster dose (dose 4) in late May 2022 [21]. For the first

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booster dose, individuals became eligible 5 months after their last dose. The second booster dose was administered exclusively to individuals who were ≥ 60 years old, had any comorbidities, or were healthcare/long-term care workers and excluded from this report. Vaccines from multiple manufacturers are approved in Japan, but a great majority of those used were BNT162b2 (Pfizer/BioNTech) and mRNA-1273 (Moderna) (99.9% for primary series; no published data for the third dose) [22]. The primary series followed manufacturer-recommended intervals (21 days for BNT162b2, 28 days for mRNA-1273).

2.2. Study design and setting

Our study, Moderate-to-severe disease requiring Oxygen Therapy, Intubation, and Ventilation And The Effectiveness of COVID-19 vaccines (MOTIVATE study), is a multicenter case-control study in acute care hospitals in Japan to estimate the real-world effectiveness of COVID-19 vaccines against severe disease. Participating healthcare facilities screened all routinely admitted patients with COVID-19 and other causes of respiratory failure. Although this study was mainly a retrospective chart review, when data were missing from the chart, patients or their family members were contacted by phone to fill in the information. This report includes patients hospitalized in 24 hospitals in 9 of Japan's 47 prefectures between 1 August 2021 and 30 June 2022.

2.3. Inclusion and exclusion criteria

The inclusion criterion was patients aged ≥ 16 years who were hospitalized with respiratory failure (i.e. requiring oxygen therapy). Patients were excluded for the following reasons: unknown symptom onset date; admission ≥ 15 days after onset; onset during hospitalization; tested either ≥ 8 days before or ≥ 15 days after onset; tested ≥ 15 days before or ≥ 15 days after admission; currently on home oxygen therapy or home mechanical ventilation; started oxygen therapy ≥ 15 days before or ≥ 15 days after admission; started invasive mechanical ventilation ≥ 15 days before or ≥ 20 days after admission; past SARS-CoV-2 infection ≥ 3 months before admission; and immunodeficiency or current use of immunosuppressants. The rationale for including patients tested up to 7 days before onset and excluding those tested earlier is that patients may have been tested on routine asymptomatic screening, but the likelihood of testing positive is lower ≥ 8 days before onset. Also, the rationale for including patients who were tested up to 14 days before admission and excluding those who were tested ≥ 15 days before admission is that it takes from a few days to 2 weeks from symptom onset for patients to develop severe disease, and these patients may be tested right after onset and later hospitalized. Finally, the rationale for including patients tested up to 14 days after the onset of illness is that viral load as measured by PCR continues to be high for severe cases in the second week of illness and would likely continue to be positive if the cases are true COVID-19 cases.

2.4. Classification of exposures and outcome

Vaccination status (number of doses, date of last vaccination, and [if available] vaccine manufacturer) was recorded from the medical charts and checked for plausibility. If unavailable, patients or their family members were contacted by phone and asked to refer to their vaccine records/certificates. Vaccination status was classified into 8 categories: (1) not vaccinated, (2) ≤ 13 days after dose 1, (3) ≥ 14 days after dose 1 or ≤ 13 days after dose 2 (partially vaccinated), (4) 14 days–6 months (14–180 days) after dose 2, (5) > 6 months (181 days) after dose 2, (6) ≤ 13 days after dose 3 (booster dose), (7) 14 days–6 months (14–180 days) after dose 3, and (8) > 6 months (181 days) after dose 3.

Regardless of test type, patients who tested positive before or after admission based on the above inclusion and exclusion criteria were defined as cases; patients who tested negative before or after admission based on the above criteria were defined as controls.

To measure VE, we used various severe outcomes including disease requiring oxygen therapy, disease requiring invasive mechanical ventilation, death, outcome restricting to "true" severe COVID-19 (where oxygen requirement is due to COVID-19 rather than other differential diagnoses), and progression from oxygen use to mechanical ventilation or death. "True" severe COVID-19 outcome was based on the judgment of the treating physicians (record on the chart), trained nurse or pharmacist responsible for chart review, as well as the primary investigator (final judgment). For controls, we included all patients who required oxygen for the measurement of VE against all severe outcomes (thus, it is not strictly a test-negative design).

The chart review was conducted between January and May 2023 to ensure that at least 6 months had passed since participants were hospitalized to allow for sufficient time to reach the final discharge outcome for participants.

2.5. 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 [23]. Therefore, we defined 1 August to 30 November 2021 as the Delta-dominant period. By the beginning of December 2021, the number of hospitalized cases decreased substantially. This low level lasted until the end of December 2021 [24]. Therefore, we defined 1–31 December 2021 as the non-epidemic period. Based on data from SARS-CoV-2 genomic surveillance with systematic sampling, in early January 2022, the case counts rose rapidly owing to the introduction of BA.1, with BA.1 estimated to be responsible for over 80% of SARS-CoV-2 infections [25]. In mid-March, BA.2 overtook BA.1 and became dominant. BA.2 was estimated to be responsible for 80% of SARS-CoV-2 infections in the Kanto region during the week of 20–26 June (epidemiologic week 25), but was rapidly replaced by BA.5 [26]. Therefore, we defined 1 January to 30 June 2022 as the early Omicron-dominant period (BA.1/BA.2-dominant period). Since the sample size was limited with previous reports suggesting similar VE estimates against BA.1 and BA.2 [27], we did not stratify these periods.

2.6. Sample size

The sample size was determined by the number of patients admitted to participating hospitals during the study period. However, based on *a priori* sample size calculations (assuming a 1:1 ratio between cases and controls, expected COVID-19 vaccine coverage of 80%, and 90% VE, 89 patients are needed in each group for the precision of a lower CI boundary of 10%), we considered that our design would allow for adequately precise VE estimates.

2.7. Data analysis

Patient characteristics were described overall and by case/control status. A severe disease risk score was developed to be incorporated as a covariate. Based on published reports [28,29], we assigned 2 points for the presence of either diabetes mellitus, chronic kidney disease, dementia, Down syndrome, or obesity and assigned 1 point for the presence of cardiovascular disease (including hypertension), dyslipidemia, chronic liver disease, chronic obstructive pulmonary disease, cancer, depression/schizophrenia, stroke, pregnancy while hospitalized, or overweight; the points were added up to calculate the risk score for each patient.

Logistic regression was used to estimate the odds of being vaccinated among cases relative to controls. The model was adjusted for age group (categorical), sex, risk score categories (0, 1, 2, 3–4, 5+; categorical), hospitalization in the past year (either the admitting hospital or another

Table 1
Diagnoses of control group patients during the respective Delta- and early Omicron (BA.1/BA.2)-dominant periods.[a]

Diagnosis	Delta-dominant period, n (%)	Early Omicron (BA.1/BA.2)-dominant period, n (%)
Pneumonia[b]	74 (40.7)	107 (38.4)
Heart failure	51 (28.0)	76 (27.2)
Aspiration pneumonia	27 (14.8)	65 (23.3)
Interstitial pneumonia exacerbation	18 (9.9)	28 (10.0)
Chronic obstructive pulmonary disease exacerbation	4 (2.2)	9 (3.2)
Pneumonia (due to *Streptococcus pneumoniae*)	2 (1.1)	8 (2.9)
Lung cancer	1 (0.6)	2 (0.7)
Influenza[c]	0 (0.0)	0 (0.0)
Other	17 (9.3)	21 (7.5)

[a] Multiple diagnoses are possible for each patient.
[b] Not due to COVID-19, aspiration, or *Streptococcus pneumoniae*.
[c] Tested positive since onset.

hospital), smoking history, prefecture of the admitting hospital, and calendar week of hospitalization (biweekly).

To estimate VE against progression from oxygen use to mechanical ventilation or death among COVID-19 patients, additional adjustments were made for use of antivirals, monoclonal antibody therapy, steroids, anti-inflammatory drugs (tocilizumab or baricitinib), anticoagulation, and proning. These potential confounders were determined *a priori* based on published reports [8,9,15,17]. VE was estimated using the following equation: VE = (1 – adjusted odds ratio [aOR]) × 100%, including VE against disease progression [30]. Data analyses were performed using STATA version 17.0.

2.8. Consideration of bias due to co-circulation of influenza/influenza vaccination and Streptococcus pneumoniae pneumonia/pneumococcal vaccination

Co-circulation of influenza and COVID-19 can result in biased VE estimates as propensity to get vaccinated may be similar for COVID-19 vaccines and influenza vaccines [31]. In theory, the same concern applies to *Streptococcus pneumoniae* pneumonia and pneumococcal vaccination. However, no influenza was diagnosed since symptom onset for any of the study participants (Table 1). Indeed, unlike in much of Europe and the U.S., which experienced epidemics in the 2021–2022 season at a level similar to the pre-pandemic era, influenza circulation was extremely low since the beginning of the pandemic until the end of the study period (end of June 2022) in Japan [32]. Also, invasive pneumococcal disease was less common during COVID-19 [33], suggesting that the circulation of *Streptococcus pneumoniae* was low. Therefore, we assumed that this potential bias was negligible.

2.9. Ethics statement

The ethics committee of the National Institute of Infectious Diseases approved our study (approval numbers 1454, 1527). Ethics approval was also sought from medical facilities that required review from on-site committees. Although the main design of this study was a retrospective chart review with a waiver of informed consent, patients or their family members were contacted by phone to fill in any missing data on the chart. In this case, their consent was obtained verbally.

3. Results

3.1. Characteristics of the study participants

A total of 2417 individuals were enrolled from 24 hospitals in 9 prefectures. After excluding 292 patients based on exclusion criteria, the final analysis included 2125 patients (1608 cases [75.7%]): 1116 for the

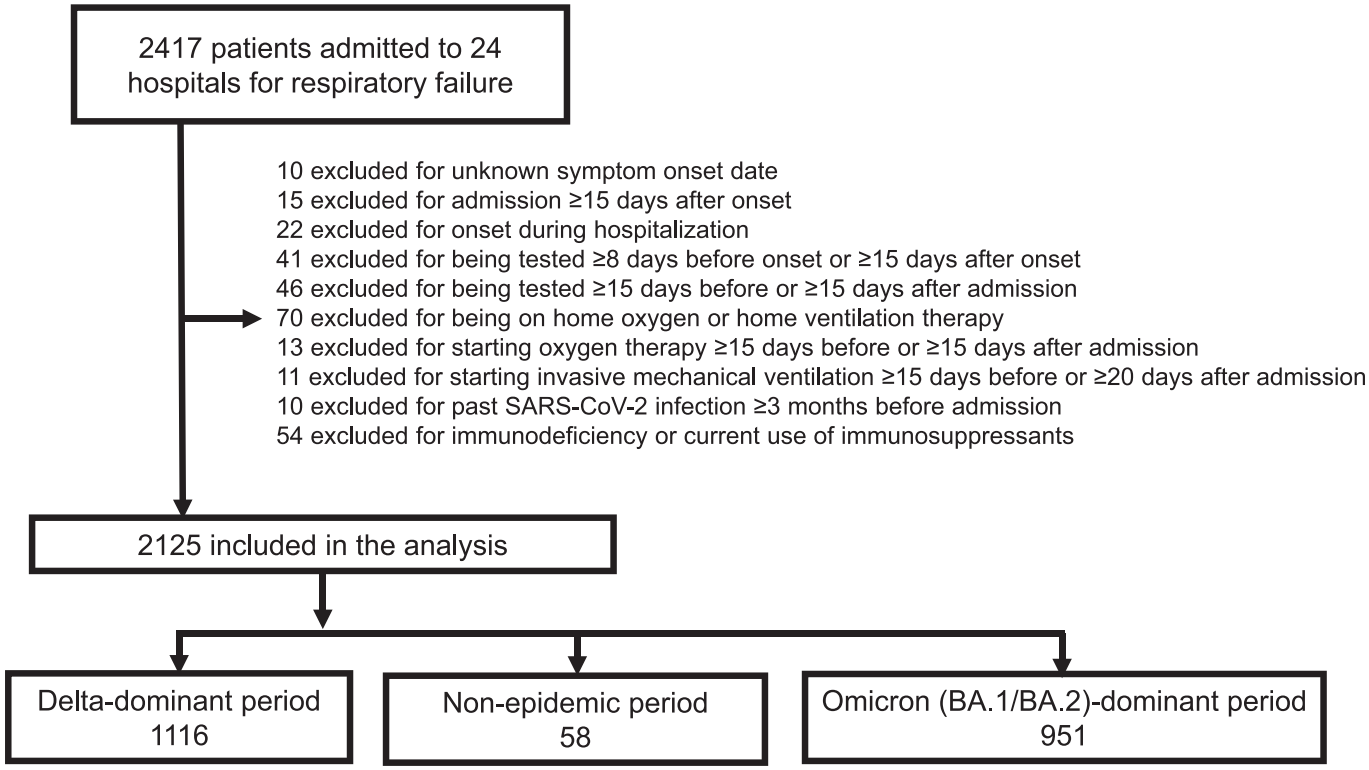

Fig. 1. Flow diagram of the study participants.

Table 2
Demographic and clinical characteristics of the study participants during the Delta- and early Omicron (BA.1/BA.2)-dominant periods.

(A) Delta-dominant period			
	All(n = 1116)	Test positive (n = 934)	Test negative (n = 182)
Median age in years[a]	55 (45–69)	52 (43–61)	79 (71–86)
Age in years, n (%)			
16–19	0 (0.0)	0 (0.0)	0 (0.0)
20–29	49 (4.4)	46 (4.9)	3 (1.7)
30–39	118 (10.6)	117 (12.5)	1 (0.6)
40–49	227 (20.3)	219 (43.5)	8 (4.4)
50–59	309 (27.7)	302 (32.3)	7 (3.9)
60–69	139 (12.5)	117 (12.5)	22 (12.1)
70–79	139 (12.5)	85 (9.1)	54 (29.7)
80–89	101 (9.1)	31 (3.3)	70 (38.5)
≥90	34 (3.1)	17 (1.8)	17 (9.3)
Sex, n (%)			
Male	787 (70.5)	672 (72.0)	115 (63.2)
Female	329 (29.5)	262 (28.1)	67 (36.8)
Pregnancy at hospitalization, n (%)			
No	1111 (99.6)	929 (99.5)	182 (100.0)
Yes	5 (0.5)	5 (0.5)	0 (0.0)
Comorbidities, n (%)			
Cardiovascular disease	381 (34.1)	269 (28.8)	112 (61.5)
Diabetes mellitus	231 (20.7)	184 (19.7)	47 (25.8)
Dyslipidemia	148 (13.3)	112 (12.0)	36 (19.8)
Chronic kidney disease	64 (5.7)	39 (4.2)	25 (13.7)
Chronic liver disease	28 (2.5)	17 (1.8)	11 (6.0)
Chronic obstructive pulmonary disease	43 (3.9)	28 (3.0)	15 (8.2)
Cancer	98 (8.8)	56 (6.0)	42 (23.1)
Dementia	47 (4.2)	12 (1.3)	35 (19.2)
Depression/schizophrenia	66 (5.9)	55 (5.9)	11 (6.0)
Stroke	48 (4.3)	21 (2.3)	27 (14.8)
Down syndrome	1 (0.1)	0 (0.0)	1 (0.0)
Body mass index			
<25	734 (65.8)	562 (60.2)	172 (94.5)
25–29 (overweight)	219 (19.6)	213 (22.8)	6 (3.3)
≥30 (obese)	163 (14.6)	159 (17.0)	4 (2.2)
Severe disease risk score[b]			
0	316 (28.3)	294 (31.5)	22 (12.1)
1	245 (21.9)	213 (22.8)	32 (17.6)
2	221 (19.8)	177 (19.0)	44 (24.2)
3	144 (12.9)	112 (12.0)	32 (17.6)
4	90 (8.1)	70 (7.5)	20 (11.0)
5	50 (4.5)	36 (3.9)	14 (7.7)
≥6	50 (4.5)	32 (3.4)	18 (9.9)
Hospitalization in the past year, n (%)			
No	1017 (91.1)	890 (95.3)	127 (69.8)
Yes	99 (8.9)	44 (4.7)	55 (30.2)
Smoking, n (%)			
Never-smoker	481 (43.1)	415 (44.4)	66 (36.3)
Past smoker	328 (29.4)	261 (27.9)	67 (36.8)
Current smoker	191 (17.1)	166 (17.8)	25 (13.7)
Unknown	116 (10.4)	92 (9.9)	24 (13.2)
Number of COVID-19 vaccinations received, n (%)			
None	808 (72.4)	770 (82.4)	38 (20.9)
One	129 (11.6)	116 (12.4)	13 (7.1)
Two	179 (16.0)	48 (5.1)	131 (72.0)
Three	0 (0.0)	0 (0.0)	0 (0.0)
Vaccine type, n (%)[c]			
BNT162b2	144 (82.3)	90 (78.9)	54 (88.5)
mRNA-1273	27 (15.4)	21 (18.4)	6 (9.8)
AZD1222	2 (1.1)	2 (1.8)	0 (0.0)
mRNA heterologous	1 (0.6)	0 (0.0)	1 (1.6)
Other	1 (0.6)	1 (0.9)	0 (0.0)
Interval from symptom onset to hospitalization (days)	7 (3–9)	7 (5–9)	0 (0–3)
SARS-CoV-2 testing type			
Nucleic acid amplification test	867 (77.7)	734 (78.6)	133 (73.1)
Rapid antigen detection kit	79 (7.1)	74 (7.9)	5 (2.8)
Quantitative antigen test	91 (8.2)	66 (7.1)	25 (13.7)
Unknown	79 (7.1)	60 (6.4)	19 (10.4)

(B) Early Omicron-dominant period			
	All(n = 951)	Test positive (n = 672)	Test negative (n = 279)
Median age in years[a]	79 (69–86)	77 (65–85)	81 (74–87)
Age in years, n (%)			
16–19	4 (0.4)	2 (0.3)	2 (0.7)
20–29	6 (0.6)	4 (0.6)	2 (0.7)
30–39	10 (1.1)	9 (1.3)	1 (0.4)
40–49	26 (2.7)	22 (3.3)	4 (1.4)
50–59	89 (9.4)	73 (10.9)	16 (5.7)
60–69	113 (11.9)	92 (13.7)	21 (7.5)
70–79	257 (27.0)	176 (26.2)	81 (29.0)
80–89	304 (32.0)	201 (29.9)	103 (36.9)
≥90	142 (14.9)	93 (13.8)	49 (17.6)
Sex, n (%)			
Male	598 (62.9)	430 (64.0)	168 (60.2)
Female	353 (37.1)	242 (36.0)	111 (39.8)
Pregnancy at hospitalization, n (%)			
No	951 (100.0)	672 (100.0)	279 (100.0)
Yes	0 (0.0)	0 (0.0)	0 (0.0)
Comorbidities, n (%)			
Cardiovascular disease	596 (62.7)	418 (62.2)	178 (63.8)
Diabetes mellitus	293 (30.8)	215 (32.0)	78 (28.0)
Dyslipidemia	166 (17.5)	109 (16.2)	57 (20.4)
Chronic kidney disease	128 (13.5)	88 (13.1)	40 (14.3)
Chronic liver disease	36 (3.8)	22 (3.3)	14 (5.0)
Chronic obstructive pulmonary disease	90 (9.5)	63 (9.4)	27 (9.7)
Cancer	165 (17.4)	111 (16.5)	54 (19.4)
Dementia	184 (19.4)	116 (17.3)	68 (24.4)
Depression/schizophrenia	50 (5.3)	36 (5.4)	14 (5.0)
Stroke	160 (16.8)	103 (15.3)	57 (20.4)
Down syndrome	1 (0.1)	1 (0.2)	0 (0.0)
Body mass index			
<25	793 (83.4)	528 (78.6)	265 (95.0)
25–29 (overweight)	98 (10.3)	90 (13.4)	8 (2.9)
≥30 (obese)	60 (6.3)	54 (8.0)	6 (2.2)
Severe disease risk score[b]			
0	104 (10.9)	74 (11.0)	30 (10.8)
1	168 (17.7)	113 (16.8)	55 (19.7)

(*continued on next page*)

Table 2 (*continued*)

(A) Delta-dominant period	All(n = 1116)	Test positive (n = 934)	Test negative (n = 182)
2	180 (18.9)	131 (19.5)	49 (17.6)
3	162 (17.0)	118 (17.6)	44 (15.8)
4	135 (14.2)	94 (14.0)	41 (14.7)
5	120 (12.6)	89 (13.2)	31 (11.1)
≥6	82 (8.6)	53 (7.9)	29 (10.4)
Hospitalization in the past year, n (%)			
No	816 (85.8)	590 (87.8)	226 (81.0)
Yes	135 (14.2)	82 (12.2)	53 (19.0)
Smoking, n (%)			
Never-smoker	395 (41.5)	252 (37.5)	143 (51.3)
Past smoker	318 (33.4)	233 (34.7)	85 (30.5)
Current smoker	90 (9.5)	61 (9.1)	29 (10.4)
Unknown	148 (15.6)	126 (18.8)	22 (7.9)
Number of COVID-19 vaccinations received, n (%)			
None	227 (23.9)	202 (30.1)	25 (9.0)
One	11 (1.2)	9 (1.3)	2 (0.7)
Two	471 (49.5)	357 (53.1)	114 (40.9)
Three	242 (25.5)	104 (15.5)	138 (49.5)
Vaccine type, n (%)[c]			
BNT162b2	321 (87.5)	237 (89.1)	84 (83.2)
mRNA-1273	19 (5.2)	14 (5.3)	5 (5.0)
AZD1222	1 (0.3)	1 (0.4)	0 (0.0)
mRNA heterologous	26 (7.1)	14 (5.3)	12 (11.9)
Other	0 (0.0)	0 (0.0)	0 (0.0)
Interval from symptom onset to hospitalization (days)	2 (0–6)	3 (1–7)	0 (0–2)
SARS-CoV-2 testing type			
Nucleic acid amplification test	633 (66.6)	410 (61.0)	223 (79.9)
Rapid antigen detection kit	111 (11.7)	106 (15.8)	5 (1.8)
Quantitative antigen test	79 (8.3)	65 (9.7)	14 (5.0)
Unknown	128 (13.5)	91 (13.5)	37 (13.3)

[a] Median (interquartile range).

[b] The following points were added up for each patient: assigned 2 points for the presence of either diabetes mellitus, chronic kidney disease, dementia, Down syndrome, or obesity and assigned 1 point for the presence of cardiovascular disease (including hypertension), dyslipidemia, chronic liver disease, chronic obstructive pulmonary disease, cancer, depression/schizophrenia, stroke, pregnancy while hospitalized, or overweight.

[c] Among individuals with known vaccine type.

Delta-dominant period, 58 for the non-epidemic period, and 951 for the early Omicron-dominant period (Fig. 1). The data from the non-epidemic period are excluded from the further analyses. The median age (interquartile range [IQR]) was 55 (45–69) for the Delta-dominant period and 79 (69–86) for the early Omicron-dominant period. Eight hundred (71.7%) for the Delta-dominant period and 847 (89.1%) for the Omicron-dominant period had at least one risk factor for severe COVID-19 (Table 2). The diagnoses of control groups are described in Table 1. Among vaccinees with known vaccine type, 538/542 (99.2%) received mRNA vaccines (BNT162b2, mRNA-1273, or mRNA heterologous) and 465/542 (85.8%) received BNT162b2 as it was approved first and mainly used for healthcare workers, the elderly, and individuals with comorbidities (Table 2). The number of patients included in estimating each VE is shown in Table 3.

3.2. Vaccine effectiveness against COVID-19 requiring oxygen therapy, COVID-19 requiring mechanical ventilation, and fatal COVID-19

During the Delta-dominant period, VE estimates for 14 days–6 months after dose 2 were 95.2% (95% confidence interval [CI]: 88.7–98.0%) against COVID-19 requiring oxygen therapy (Table 4**A**, Fig. 2), 99.6% (95% CI: 97.3–99.9%) against COVID-19 requiring invasive mechanical ventilation (Table 5**A**), and 98.6% (95% CI: 92.3–99.7%) against fatal COVID-19 (Table 6**A**).

During the early Omicron-dominant period, VE estimates for > 6 months after dose 2 were 47.9% (95% CI: −2.1–73.4%) against COVID-19 requiring oxygen therapy (Table 4**B**), 82.7% (95% CI: 37.1–95.3%) against COVID-19 requiring invasive mechanical ventilation (Table 5**B**), and 59.5% (95% CI: −41.9–88.4%) against fatal COVID-19 (Table 6**B**). VE estimates for 14 days–6 months after dose 3 (first booster dose) were 85.5% (95% CI: 68.8–93.3%) against COVID-19 requiring oxygen therapy (Table 4**B**), 97.9% (95% CI: 85.9–99.7%) against COVID-19 requiring invasive mechanical ventilation (Table 5**B**), and 99.6% (95% CI: 95.2–99.97%) against fatal COVID-19 (Table 6**B**).

Table 3
Number of patients included in each vaccine effectiveness (VE) estimate.[a]

Diagnosis	Case-patients,n	Control patients,n
VE against severe COVID-19 requiring oxygen therapy		
Delta	911	157
Omicron	574	205
VE against severe COVID-19 requiring invasive mechanical ventilation		
Delta	293	157
Omicron	138	205
VE against fatal COVID-19		
Delta	94	157
Omicron	90	205
VE against severe COVID-19 restricting to patients with respiratory failure due to COVID-19		
Delta	900	157
Omicron	516	205

[a] Note that for controls, all patients who required oxygen were included for the measurement of VE against all severe outcomes (thus the number of patients are the same for Delta and Omicron, respectively).

3.3. Vaccine effectiveness against "true" severe COVID-19 where oxygen requirement was due to COVID-19 rather than another differential diagnosis(es)

We estimated VE by excluding COVID-19 patients whose oxygen requirement was not due to COVID-19 or who likely had oxygen requirements from COVID-19 as well as another condition(s) (i.e. when it was difficult to distinguish whether oxygen requirement was due to one or the other). Such cases were present for 13/934 (1.4%) cases during the Delta-dominant period and 69/672 (10.3%) during the early Omicron-dominant period (Table 7).

During the Delta-dominant period, the resulting VE estimate for 14 days–6 months after dose 2 was 95.5% (95% CI: 89.3–98.1%) (Table 8**A**). During the early Omicron-dominant period, VE estimates were 50.2% (95% CI: 1.1–75.0%) for > 6 months after dose 2 and 88.1% (95% CI: 73.6–94.7%) for 14 days–6 months after dose 3 (Table 8**B**).

3.4. Vaccine effectiveness against progression from oxygen use to mechanical ventilation or death among COVID-19 patients

We finally estimated VE against progression from oxygen use to mechanical ventilation or death among COVID-19 patients. During the Delta-dominant period, the resulting VE estimate for 14 days–6 months after dose 2 was 90.5% (95% CI: 65.4–97.4%) (Table 9**A**). During the early Omicron-dominant period, VE estimates were 45.9% (95% CI: −4.0–71.9%) for > 6 months after dose 2 and 65.5% (95% CI: −73.3–93.1%) for 14 days–6 months after dose 3 (Table 9**B**).

Table 4
Vaccine effectiveness against severe COVID-19 requiring oxygen therapy during the Delta- and early Omicron (BA.1/BA.2)-dominant periods by time since vaccination.

(A) Delta-dominant period

Vaccination status	Case-patients,n	Control patients,n	Last vaccination to admission, days[a]	Adjusted odds ratios (95% CI)[b]	Vaccine effectiveness, % (95% CI)
Unvaccinated	770	38	N/A	1	N/A
Within 13 days of dose 1	67	4	9 (7–11)	0.430 (0.104–1.786)	57.0 (-78.6–89.6)
14 days after dose 1 or within 13 days of dose 2	41	27	15 (10–21)	0.044 (0.017–0.110)	95.6 (89.0–98.3)
14 days to 6 months after dose 2	33	87	76 (47–117)	0.048 (0.020–0.113)	95.2 (88.7–98.0)
>6 months after dose 2	0	1	222 (222–222)	N/A	N/A

(B) Early Omicron-dominant period

Vaccination status	Case-patients,n	Control patients,n	Last vaccination to admission, days[a]	Adjusted odds ratios (95% CI)[b]	Vaccine effectiveness, % (95% CI)
Unvaccinated	202	25	N/A	1	N/A
Within 13 days of dose 1	1	0	7 (7–7)	N/A	N/A
14 days after dose 1 or within 13 days of dose 2	6	2	220 (100–243)	0.213 (0.032–1.409)	78.7 (-40.9–96.8)
14 days to 6 months after dose 2	76	22	155 (123–172)	0.630 (0.263–1.509)	37.0 (-50.9–73.7)
>6 months after dose 2	202	47	218 (204–235)	0.521 (0.266–1.021)	47.9 (-2.1–73.4)
Within 13 days of dose 3	36	16	6 (3–9)	0.271 (0.104–0.706)	72.9 (29.4–89.6)
14 days to 6 months after dose 3	51	93	67 (34–104)	0.145 (0.067–0.312)	85.5 (68.8–93.3)
>6 months after dose 3	0	0	N/A	N/A	N/A

Abbreviations: CI, confidence interval; N/A, not applicable.
[a] Median (interquartile range).
[b] Adjusted for age group, sex, risk score category (0, 1, 2, 3–4, 5 +), hospitalization in the past year (either the admitting hospital or another hospital), smoking history, prefecture of admitting hospital, and calendar week of hospitalization (biweekly).

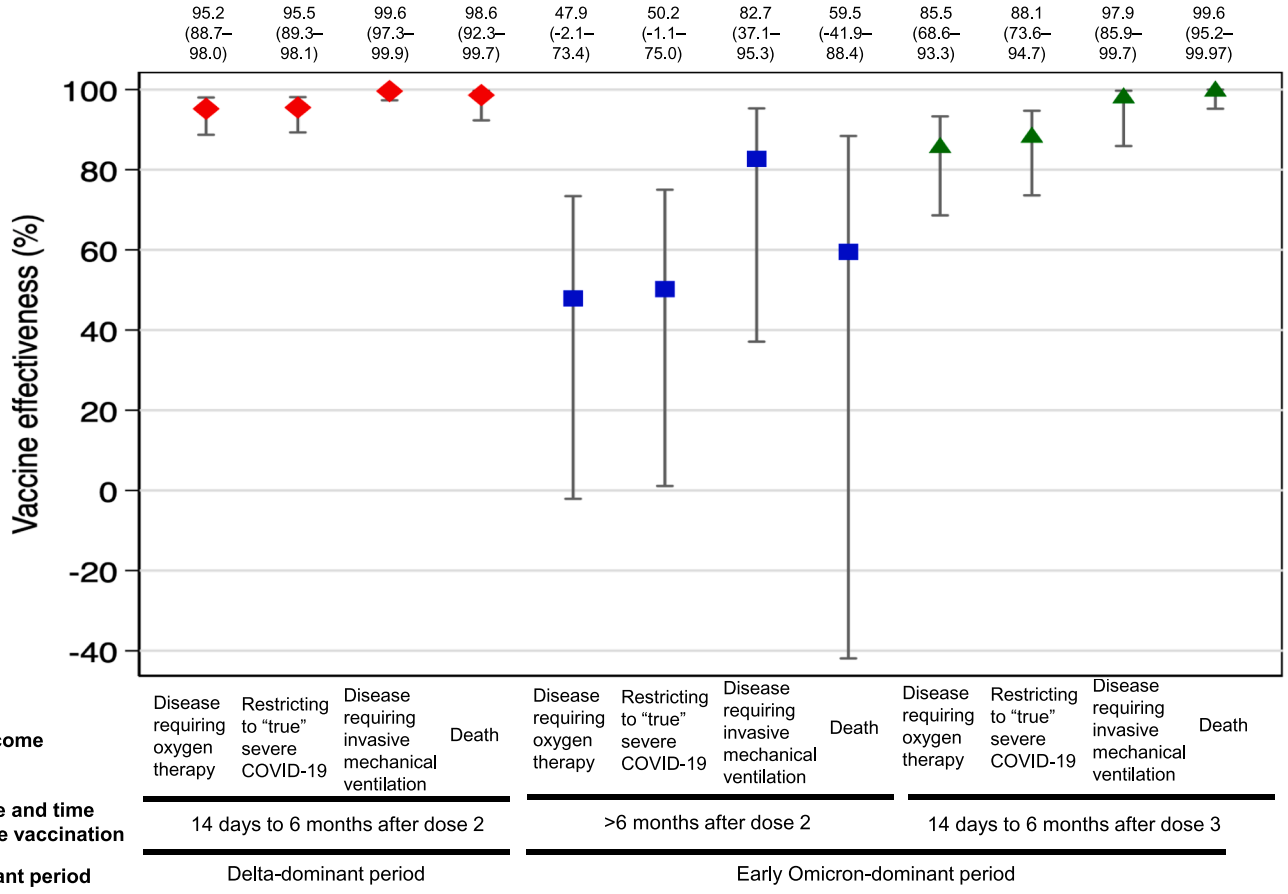

Fig. 2. Vaccine effectiveness against various severe outcomes during the Delta-dominant period (red diamonds) and early Omicron (BA.1/BA.2)-dominant periods (blue squares for 2 doses and green triangles for 3 doses), all compared to unvaccinated individuals. Red diamonds, blue squares, and green triangles indicate point estimates and error bars indicate 95% confidence intervals. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 5
Vaccine effectiveness against severe COVID-19 requiring invasive mechanical ventilation during the Delta- and early Omicron (BA.1/BA.2)-dominant periods by time since vaccination.

(A) Delta-dominant period

Vaccination status	Case-patients,n	Control patients,n	Last vaccination to admission, days[a]	Adjusted odds ratios (95% CI)[b]	Vaccine effectiveness, % (95% CI)
Unvaccinated	257	38	N/A	1	N/A
Within 13 days of dose 1	22	4	9 (7–10)	0.810 (0.093–7.048)	19.0 (-604.8–90.7)
14 days after dose 1 or within 13 days of dose 2	9	27	11 (7–24)	0.009 (0.002–0.055)	99.1 (94.5–99.8)
14 days to 6 months after dose 2	5	87	83 (49–123)	0.004 (0.001–0.027)	99.6 (97.3–99.9)
>6 months after dose 2	0	1	222 (222–222)	N/A	N/A

(B) Early Omicron-dominant period

Vaccination status	Case-patients,n	Control patients,n	Last vaccination to admission, days[a]	Adjusted odds ratios (95% CI)[b]	Vaccine effectiveness, % (95% CI)
Unvaccinated	63	25	N/A	1	N/A
Within 13 days of dose 1	1	0	7 (7–7)	N/A	N/A
14 days after dose 1 or within 13 days of dose 2	1	2	53 (12–146)	0.065 (0.004–1.161)	93.5 (-16.1–99.6)
14 days to 6 months after dose 2	20	22	149 (123–168)	0.263 (0.053–1.306)	73.7 (-30.6–94.7)
>6 months after dose 2	37	47	215 (201–237)	0.173 (0.047–0.629)	82.7 (37.1–95.3)
Within 13 days of dose 3	11	16	5 (3–9)	0.315 (0.067–1.471)	68.5 (-47.1–93.3)
14 days to 6 months after dose 3	5	93	64 (27–102)	0.021 (0.003–0.141)	97.9 (85.9–99.7)
>6 months after dose 3	0	0	N/A	N/A	N/A

[a] Median (interquartile range).
[b] Adjusted for age group, sex, risk score categories (0, 1, 2, 3–4, 5 +), hospitalization in the past year (either the admitting hospital or another hospital), smoking history, prefecture of admitting hospital, and calendar week of hospitalization (biweekly).
Abbreviations: CI, confidence interval; N/A, not applicable.

Table 6
Vaccine effectiveness against fatal COVID-19 during the Delta- and early Omicron (BA.1/BA.2)-dominant periods by time since vaccination.

(A) Delta-dominant period

Vaccination status	Case-patients,n	Control patients,n	Last vaccination to admission, days[a]	Adjusted odds ratios (95% CI)[b]	Vaccine effectiveness, % (95% CI)
Unvaccinated	77	38	N/A	1	N/A
Within 13 days of dose 1	9	4	9 (7–11)	0.712 (0.069–7.358)	28.8 (-635.8–93.1)
14 days after dose 1 or within 13 days of dose 2	3	27	10 (7–38)	0.006 (0.000–0.073)	99.4 (92.7–99.96)
14 days to 6 months after dose 2	5	87	83 (47–123)	0.014 (0.003–0.077)	98.6 (92.3–99.7)
>6 months after dose 2	0	1	222 (222–222)	N/A	N/A

(B) Early Omicron-dominant period

Vaccination status	Case-patients,n	Control patients,n	Last vaccination to admission, days[a]	Adjusted odds ratios (95% CI)[b]	Vaccine effectiveness, % (95% CI)
Unvaccinated	37	25	N/A	1	N/A
Within 13 days of dose 1	0	0	N/A	N/A	N/A
14 days after dose 1 or within 13 days of dose 2	1	2	53 (12–218)	0.343 (0.001–1.409)	65.7 (-40.9–99.9)
14 days to 6 months after dose 2	10	22	139 (99–164)	0.569 (0.103–3.134)	43.1 (-213.4–89.7)
>6 months after dose 2	30	47	216 (205–244)	0.405 (0.116–1.419)	59.5 (-41.9–88.4)
Within 13 days of dose 3	10	16	4 (2–8)	0.142 (0.027–0.747)	85.8 (25.3–97.3)
14 days to 6 months after dose 3	2	93	64 (28–104)	0.004 (0.000–0.048)	99.6 (95.2–99.97)
>6 months after dose 3	0	0	N/A	N/A	N/A

[a] Median (interquartile range).
[b] Adjusted for age group, sex, risk score categories (0, 1, 2, 3–4, 5 +), hospitalization in the past year (either the admitting hospital or another hospital), smoking history, prefecture of admitting hospital, and calendar week of hospitalization (biweekly).
Abbreviations: CI, confidence interval; N/A, not applicable.

4. Discussion

In this multicenter case-control study in Japan, we evaluated COVID-19 VE against various severe outcomes for 2 doses during the Delta-dominant period and 2 or 3 doses during the Omicron-dominant period. During the Delta-dominant period, in agreement with other observational studies [9,15,17], 2 doses provided very high (over 95%) protection for up to 6 months (oxygen requirement: 95.2% [restricted to "true" severe COVID-19: 95.5%]; invasive mechanical ventilation: 99.6%; fatal: 98.6%). During the Omicron-dominant period, 2 doses provided variable moderate-to-high (50–85%) protection after 6 months depending on outcome severity (oxygen requirement: 47.9% [restricted to "true" severe COVID-19: 50.2%]; invasive mechanical ventilation: 82.7%; fatal: 59.5% [some with wide CI]). However, the first booster (3

Table 7
Differential diagnosis in patients whose oxygen requirement was not or not solely due to COVID-19[a].

Diagnosis	Delta-dominant period, n (%)	Early Omicron (BA.1/BA.2)-dominant period, n (%)
Aspiration pneumonia	3 (23.1)	18 (26.1)
Heart failure[b]	4 (30.8)	12 (17.4)
Pneumonia (etiology other than COVID-19)	0 (0.0)	10 (14.5)
Cancer [c]	1 (7.7)	2 (2.9)
Other respiratory disease	3 (23.1)	4 (5.8)
Other[d]	2 (15.4)	23 (33.3)

[a] Primary diagnosis for oxygen requirement ascertained based on disease course and test results including CT scan.
[b] Includes pulmonary edema due to acute kidney injury on chronic kidney disease.
[c] Includes non-lung cancer resulting in pulmonary effusion.
[d] Includes non-pulmonary causes of oxygen requirement including altered mental status due to stroke.

doses total) again provided very high protection for up to 6 months (oxygen requirement: 85.5% [restricted to "true" severe COVID-19: 88.1%]; invasive mechanical ventilation: 97.9%; fatal: 99.6%). There was a consistent trend towards higher VE for more severe and specific outcomes during the Delta-dominant period for 2 doses and during the Omicron-dominant period for 2 or 3 doses (Fig. 2). This concurs with a study in the U.K., which is the only study, to our knowledge, that looked at varying severity in detail [17]. However, the study used hospital-coded data, which can still result in contamination of incidental SARS-CoV-2 infection. The authors noted that "a study where data are collected prospectively on cases using reporting forms or detailed case note review could avoid this misclassification bias, but is much more challenging to do". We addressed their concern by conducting a detailed chart review. Since our first outcome was on COVID-19 requiring oxygen therapy, which is already a specific outcome for severe pneumonia, we did not see a large difference when restricting to "true" severe COVID-19. The difference may have been larger if we had used hospital admission (regardless of oxygen use) as the main outcome. Notably, 2 doses provided high (85%) protection after 6 months against invasive mechanical ventilation use even against Omicron, which may explain the relatively low incidence of COVID-19 requiring mechanical ventilation despite high case counts during the Omicron-dominant period [24,34,35]. Overall, our report supports previous reports where VE against severe disease is sustained for at least 6 months despite lower/waning effectiveness against symptomatic infection during Omicron [18].

Finally, we examined VE against progression from oxygen use to mechanical ventilation; the estimates were high (90.5% after 2 doses) during the Delta-dominant period, but moderate (45.9% for > 6 months after dose 2; 65.5% for 14 days–6 months after dose 3) during the Omicron-dominant period, with wide confidence intervals. Although WHO guidance recommends measuring VE against disease progression [20] and VE can be estimated through analysis of COVID-19 cases only (i.e. non-COVID-19 controls are not required), the concept may be harder to interpret or communicate.

5. Limitations

This study has several limitations. First, biases, confounding, and misclassifications inherent in observational studies are possible. However, using specific and severe outcomes, we aimed to minimize the inclusion of incidental SARS-CoV-2 positive cases. Second, the current hospital-based case-control study was not strictly a test-negative design as controls include all patients who required oxygen even for severe outcomes such as mechanical ventilation use and death. However, individuals who require oxygen therapy are likely to seek care regardless of SARS-CoV-2 infection or vaccination status due to shortness of breath and other manifestations, resulting in the same advantage of control for healthcare-seeking behavior. Third, wide CIs for some estimates warrant careful interpretation of point estimates and the small sample size in some multivariable models resulted in possible sparse data bias. However, even when the VE was very high (e.g. two doses against severe COVID-19 requiring invasive mechanical ventilation during the Delta-

Table 8
Vaccine effectiveness against severe COVID-19 requiring oxygen therapy during the Delta- and early Omicron (BA.1/BA.2)-dominant periods by time since vaccination, restricting to patients with respiratory failure due to COVID-19.

(A) Delta-dominant period

Vaccination status	Case-patients,n	Control patients,n	Last vaccination to admission, days[a]	Adjusted odds ratios (95% CI)[b]	Vaccine effectiveness, % (95% CI)
Unvaccinated	764	38	N/A	1	N/A
Within 13 days of dose 1	67	4	9 (7–11)	0.436 (0.107–1.784)	56.4 (-78.4–89.3)
14 days after dose 1 or within 13 days of dose 2	40	27	15 (10–21)	0.045 (0.018–0.113)	95.5 (88.7–98.2)
14 days to 6 months after dose 2	29	87	79 (46–118)	0.045 (0.019–0.107)	95.5 (89.3–98.1)
>6 months after dose 2	0	1	222 (222–222)	N/A	N/A

(B) Early Omicron-dominant period

Vaccination status	Case-patients,n	Control patients,n	Last vaccination to admission, days[a]	Adjusted odds ratios (95% CI)[b]	Vaccine effectiveness, % (95% CI)
Unvaccinated	189	25	N/A	1	N/A
Within 13 days of dose 1	0	0	N/A	N/A	N/A
14 days after dose 1 or within 13 days of dose 2	4	2	220 (53–242)	0.088 (0.012–0.639)	91.2 (36.1–98.8)
14 days to 6 months after dose 2	67	22	155 (125–171)	0.589 (0.241–1.439)	41.1 (-43.9–75.9)
>6 months after dose 2	185	47	218 (204–235)	0.498 (0.250–0.989)	50.2 (1.1–75.0)
Within 13 days of dose 3	30	16	6 (4–9)	0.259 (0.098–0.688)	74.1 (31.2–90.2)
14 days to 6 months after dose 3	41	93	67 (34–104)	0.119 (0.053–0.264)	88.1 (73.6–94.7)
>6 months after dose 3	0	0	N/A	N/A	N/A

[a] Median (interquartile range).
[b] Adjusted for age group, sex, risk score categories (0, 1, 2, 3–4, 5 +), hospitalization in the past year (either the admitting hospital or another hospital), smoking history, prefecture of admitting hospital, and calendar week of hospitalization (biweekly).
Abbreviations: CI, confidence interval; N/A, not applicable.

Table 9
Vaccine effectiveness against disease progression to intubation and/or death during the Delta- and early Omicron (BA.1/BA.2)-dominant periods by time since vaccination among individuals with severe COVID-19 requiring oxygen therapy.

(A) Delta-dominant period

Vaccination status	Case-patients,n	Control patients,n	Last vaccination to admission, days[a]	Adjusted odds ratios (95% CI)[b]	Vaccine effectiveness, % (95% CI)
Unvaccinated	280	488	N/A	1	N/A
Within 13 days of dose 1	24	42	9 (7–11)	0.676 (0.318–1.437)	32.4 (-43.7–68.2)
14 days after dose 1 or within 13 days of dose 2	9	32	18 (15–21)	0.364 (0.124–1.066)	63.6 (-6.6–87.6)
14 days to 6 months after dose 2	7	26	58 (47–85)	0.095 (0.026–0.346)	90.5 (65.4–97.4)
>6 months after dose 2	0	0	N/A	N/A	N/A

(B) Early Omicron-dominant period

Vaccination status	Case-patients,n	Control patients,n	Last vaccination to admission, days[a]	Adjusted odds ratios (95% CI)[b]	Vaccine effectiveness, % (95% CI)
Unvaccinated	82	119	N/A	1	N/A
Within 13 days of dose 1	1	0	7 (7–7)	N/A	N/A
14 days after dose 1 or within 13 days of dose 2	2	4	232 (218–244)	0.445 (0.060–3.295)	55.5 (-229.5–94.0)
14 days to 6 months after dose 2	25	51	157 (130–173)	0.791 (0.338–1.852)	20.9 (-85.2–66.2)
>6 months after dose 2	52	148	219 (204–234)	0.541 (0.281–1.040)	45.9 (-4.0–71.9)
Within 13 days of dose 3	18	17	7 (3–9)	1.321 (0.441–3.956)	−32.1 (-295.6–55.9)
14 days to 6 months after dose 3	5	45	71 (40–104)	0.345 (0.069–1.733)	65.5 (-73.3–93.1)
>6 months after dose 3	0	0	N/A	N/A	N/A

[a] Median (interquartile range).
[b] Adjusted for age group, sex, risk score categories (0, 1, 2, 3–4, 5 +), hospitalization in the past year (either the admitting hospital or another hospital), smoking history, prefecture of admitting hospital, and calendar week of hospitalization (biweekly).
Abbreviations: CI, confidence interval; N/A, not applicable.

dominant period), adjusted OR and crude OR were fairly similar (crude OR: 0.008 [95% CI: 0.003–0.022]; adjusted OR: 0.004 [95% CI: 0.006–0.027]) and the qualitative conclusion remains similar. Fourth, our analysis was a complete case analysis in relation to vaccination history; 220/2067 (10.6%) had no record of the last vaccination date and thus were excluded from the VE estimates although VE by vaccine dose yielded similar estimates (data not shown), and this missing proportion is less than observed in data-linkage studies [9]. Another variable with missing data was smoking status, in which unknown smoking status was included as one category. There were no other variables with missing data included in the model. Fifth, vaccine type was not always recorded in the charts, though almost all individuals with known vaccine type (99.2%) received mRNA vaccines. Sixth, we could not classify individual COVID-19 cases as infected with the Omicron or Delta variant. However, since there was a non-epidemic period between these two periods, misclassification was likely minimal. Finally, our VE estimates were short- to mid-term and we did not assess the effectiveness of Omicron-containing bivalent vaccines.

6. Conclusions

In this multicenter case-control study in Japan, VE of 2 doses of COVID-19 was high against Delta and moderate to high against Omicron for multiple severe outcomes. With a booster (third) dose, VE recovered to a high level against Omicron for multiple severe outcomes. There was a consistent trend towards higher VE for more severe and specific outcomes during the Delta-dominant period for 2 doses and during the Omicron-dominant period for 2 or 3 doses. These results demonstrate the usefulness of severe and specific outcomes to accurately measure VE, as recommended in WHO guidance in the setting of intense transmission as seen during Omicron.

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Takeshi Arashiro is an unpaid consultant for the World Health Organization. The other authors declare no conflicts of interest.

Data availability

Individual-level data of patients included in this manuscript after de-identification are considered sensitive and will not be shared. The study methods and statistical analyses are all described in detail in the Methods and throughout the manuscript.

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References

[1] Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N Engl J Med 2020;383 (27):2603–15. https://doi.org/10.1056/NEJMoa2034577.

[2] Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. N Engl J Med 2021;384(5):403–16. https://doi.org/10.1056/NEJMoa2035389.

[3] Thomas SJ, Moreira Jr ED, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine through 6 months. N Engl J Med 2021;385(19):1761–73. https://doi.org/10.1056/NEJMoa2110345.

[4] El Sahly HM, Baden LR, Essink B, Doblecki-Lewis S, Martin JM, Adnerson EJ, et al. Efficacy of the mRNA-1273 SARS-CoV-2 vaccine at completion of blinded phase. N Engl J Med 2021;385(19):1774–85. https://doi.org/10.1056/NEJMoa2113017.

[5] Dagan N, Barda N, Kepten E, Miron O, Perchik S, Katz MA, et al. BNT162b2 mRNA Covid-19 vaccine in a nationwide mass vaccination setting. N Engl J Med 2021;384 (15):1412–3. https://doi.org/10.1056/NEJMoa2101765.

[6] Thompson MG, Burgess JL, Naleway AL, Tyner HL, Yoon SK, Meece J, et al. Interim estimates of vaccine effectiveness of BNT162b2 and mRNA-1273 COVID-19 vaccines in preventing SARS-CoV-2 infection among health care personnel, first responders, and other essential and frontline workers - eight U.S. locations, December 2020-March 2021. MMWR Morb Mortal Wkly Rep 2021; 70(13): 495–500. 10.15585/mmwr.mm7013e3.

[7] Pilishvili T, Fleming-Dutra KE, Farrar JL, Gierke R, Mohr NM, Talan DA, et al. Interim estimates of vaccine effectiveness of Pfizer-BioNTech and Moderna COVID-19 vaccines among health care personnel - 33 U.S. sites, January-March 2021. MMWR Morb Mortal Wkly Rep 2021; 70(20): 753–8. 10.15585/mmwr.mm7020e2.

[8] Chung H, He S, Nasreen S, Sundaram ME, Buchan SA, Wilson SE, et al. Effectiveness of BNT162b2 and mRNA-1273 covid-19 vaccines against symptomatic SARS-CoV-2 infection and severe covid-19 outcomes in Ontario, Canada: test negative design study. BMJ 2021;374:n1943. https://doi.org/10.1136/bmj.n1943.

[9] Andrews N, Tessier E, Stowe J, Gower C, Kirsebom F, Simmons R, et al. Duration of protection against mild and severe disease by Covid-19 vaccines. N Engl J Med 2022;386(4):340–50. https://doi.org/10.1056/NEJMoa2115481.

[10] Chemaitelly H, Tang P, Hasan MR, AlMukdad S, Yassine HM, Benslimane FM, et al. Waning of BNT162b2 vaccine protection against SARS-CoV-2 infection in Qatar. N Engl J Med 2021;385(24):e83.

[11] Goldberg Y, Mandel M, Bar-On YM, Bodenheimer O, Freedman L, Haas EJ, et al. Waning immunity after the BNT162b2 vaccine in Israel. N Engl J Med 2021;385 (24):e85.

[12] Tartof SY, Slezak JM, Fischer H, Hong V, Ackerson BK, Ranasinghe ON, et al. Effectiveness of mRNA BNT162b2 COVID-19 vaccine up to 6 months in a large integrated health system in the USA: a retrospective cohort study. Lancet 2021;398 (10309):1407–16. https://doi.org/10.1016/S0140-6736(21)02183-8.

[13] Andrews N, Stowe J, Kirsebom F, Toffa S, Rickeard T, Gallagher E, et al. Covid-19 vaccine effectiveness against the omicron (B.1.1.529) variant. N Engl J Med 2022; 386(16):1532–46. https://doi.org/10.1056/NEJMoa2119451.

[14] Accorsi EK, Britton A, Fleming-Dutra KE, Smith ZR, Shang N, Derado G, et al. Association between 3 doses of mRNA COVID-19 vaccine and symptomatic infection caused by the SARS-CoV-2 omicron and delta variants. JAMA 2022;327 (7):639–51. https://doi.org/10.1001/jama.2022.0470.

[15] Tseng HF, Ackerson BK, Luo Y, Sy LS, Talarico CA, Tian Y, et al. Effectiveness of mRNA-1273 against SARS-CoV-2 Omicron and Delta variants. Nat Med 2022;28 (5):1063–71. https://doi.org/10.1038/s41591-022-01753-y.

[16] Arashiro T, Arima Y, Muraoka H, Sato A, Oba K, Uehara Y, et al. Coronavirus disease 19 (COVID-19) vaccine effectiveness against symptomatic severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection during Delta-dominant and Omicron-dominant periods in Japan: a multicenter prospective case-control study (Factors Associated with SARS-CoV-2 Infection and the Effectiveness of COVID-19 Vaccines Study). Clin Infect Dis 2023;76(3):e108–15. https://doi.org/10.1093/cid/ciac635.

[17] Stowe J, Andrews N, Kirsebom F, Ramsay M, Bernal JL. Effectiveness of COVID-19 vaccines against Omicron and Delta hospitalisation, a test negative case-control study. Nat Commun 2022;13(1):5736. https://doi.org/10.1038/s41467-022-33378-7.

[18] International Vaccine Access Center (IVAC), Johns Hopkins Bloomberg School of Public Health; World Health Organization; Coalition for Epidemic Preparedness Innovations. Results of COVID-19 vaccine effectiveness studies: an ongoing systematic review. [cited 10 October 2023]. Available from: https://view-hub.org/sites/default/files/2023-06/COVID19%20VE%20Studies_Forest%20Plots_Omicron.pdf.

[19] Ministry of Health, Labour and Welfare, Japan. Hospitalization, discharge, and handling of close contacts on aircraft for cases infected with B.1.1.529 (Omicron) [in Japanese]. [cited 10 October 2023]. Available from: https://www.mhlw.go.jp/content/000860731.pdf.

[20] World Health Organization. Evaluation of COVID-19 vaccine effectiveness in a changing landscape of COVID-19 epidemiology and vaccination: second addendum to Evaluation of COVID-19 vaccine effectiveness: interim guidance. [cited 10 October 2023]. Available from: https://apps.who.int/iris/handle/10665/363344.

[21] Ministry of Health, Labour and Welfare, Japan. About COVID-19 vaccines [in Japanese]. [cited 10 October 2023]. Available from: https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/vaccine_00184.html.

[22] Cabinet Public Affairs Office, Cabinet Secretariat. COVID-19 vaccines [in Japanese]. [cited 10 October 2023]. Available from: https://www.kantei.go.jp/jp/headline/kansensho/vaccine.html.

[23] Kobayashi Y, Arashiro T, Otsuka M, Tsuchihashi Y, Takahashi T, Arima Y, et al. Replacement of SARS-CoV-2 strains with variants carrying N501Y and L452R mutations in Japan: an epidemiological surveillance assessment. Western Pac Surveill Response J 2022;13(3):1–10. https://doi.org/10.5365/wpsar.2022.13.3.943.

[24] National Institute of Infectious Diseases, Japan. COVID-19 surveillance weekly report [in Japanese]. [cited 10 October 2023]. Available from: https://www.niid.go.jp/niid/ja/2019-ncov/2484-idsc/10754-2021-41-10-11-10-17-10-19.html.

[25] Ministry of Health, Labour and Welfare, Japan. Variant-specific PCR results [in Japanese]. [cited 10 October 2023]. Available from: https://www.mhlw.go.jp/content/10900000/000892298.pdf.

[26] Ministry of Health, Labour and Welfare, Japan. Estimated subvariant prevalence via SARS-CoV-2 genomic surveillance using specimen from commercial company [in Japanese]. [cited 10 October 2023]. Available from: https://www.mhlw.go.jp/content/10900000/001039363.pdf.

[27] UK Health Security Agency. COVID-19 vaccine surveillance report: 4 August 2022 (week 31). [cited 10 October 2023]. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1096327/Vaccine_surveillance_report_week_31_2022.pdf.

[28] Williamson EJ, Walker AJ, Bhaskaran K, Bacon S, Bates C, Morton CE, et al. Factors associated with COVID-19-related death using OpenSAFELY. Nature 2020;584 (7821):430–6. https://doi.org/10.1038/s41586-020-2521-4.

[29] Clift AK, Coupland CAC, Keogh RH, Diaz-Ordaz K, Williamson E, Harrison EM, et al. Living risk prediction algorithm (QCOVID) for risk of hospital admission and mortality from coronavirus 19 in adults: national derivation and validation cohort study. BMJ 2020;371:m3731. https://doi.org/10.1136/bmj.m3731.

[30] Lauring AS, Tenforde MW, Chappell JD, Gaglani M, Ginde AA, McNeal T, 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.

[31] Doll MK, Pettigrew SM, Ma J, Verma A. Effects of confounding bias in coronavirus disease 2019 (COVID-19) and influenza vaccine effectiveness test-negative designs due to correlated influenza and COVID-19 vaccination behaviors. Clin Infect Dis 2022;75(1):e564–71. https://doi.org/10.1093/cid/ciac234.

[32] National Institute of Infectious Diseases, Japan. Influenza activity compared to past 10 years [in Japanese]. [cited 10 October 2023]. Available from: https://www.niid.go.jp/niid/ja/flu-m/813-idsc/map/130-flu-10year.html.

[33] National Institute of Infectious Diseases, Japan. Notifications of invasive pneumococcal disease, 2014 week 1 to 2021 week 35 [in Japanese]. [cited 10 October 2023]. Available from: https://www.niid.go.jp/niid/ja/pneumococcal-m/pneumococcal-idwrs/10779-ipd-211126.html.

[34] NPO Japan ECMOnet. Summary situation of COVID-19 severe cases. [cited 10 October 2023]. Available from: https://crisis.ecmonet.jp.

[35] Ministry of Health, Labour and Welfare, Japan. Visualizing the data: information on COVID-19 infections [in Japanese]. [cited 10 October 2023]. Available from: https://covid19.mhlw.go.jp/en/.