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BRIEF REPORT

Effectiveness of BA.1- and BA.4/BA.5-Containing Bivalent COVID-19 mRNA Vaccines Against Symptomatic SARS-CoV-2 Infection During the BA.5-Dominant Period in Japan

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In this multicenter, prospective, test-negative, case-control study in Japan, the effectiveness of both BA.1-containing and BA.4/BA.5-containing bivalent coronavirus disease 2019 mRNA vaccines against symptomatic infection during the BA.5-dominant period was high compared with no vaccination (65% and 76%) and moderate compared with monovalent vaccines administered over half a year earlier (46% combined).

Keywords. COVID-19; SARS-CoV-2; SARS-CoV-2 variants; test-negative design; vaccine effectiveness.

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Although mRNA vaccines against coronavirus disease 2019 (COVID-19) initially showed high efficacy and effectiveness, waning immunity and the repeated emergence of variants with immune escape capacity caused concern [1]. To combat this, bivalent vaccines containing mRNA coding for the ancestral strain and either omicron subvariant BA.1 or BA.4/BA.5 were developed by both Pfizer/BioNTech and Moderna. In Japan, both BA.1-containing and BA.4/BA.5-containing bivalent vaccines were approved for use on September 20 and October 13, 2022, respectively. Because these bivalent vaccines were approved based on in vitro and animal model data, quality real-world epidemiological data are urgently needed to assess their real-world vaccine effectiveness (VE). Japan provides a uniquely suited population to estimate VE, because over two thirds of the population are considered infection-naive based on a nationwide seroprevalence study among blood donors with infection-induced seroprevalence of 26.5% in mid-November 2022 and with a relatively stable testing strategy [2, 3]. In this study, we report the results of a multicenter prospective, test-negative design, case-control study conducted in Japan to evaluate the effectiveness of bivalent vaccines against symptomatic severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection during the BA.5-dominant period.

METHODS

Patient Consent Statement

The ethics committee of the National Institute of Infectious Diseases approved our study (approval numbers 1332 and 1392). The study is conducted with a waiver of informed consent granted by the ethics committee.

Study Design and Setting

The COVID-19 vaccination rollout in Japan is detailed in the Supplementary Methods. Our study, Factors Associated with SARS-CoV-2 Infection And The Effectiveness of COVID-19 vaccines (FASCINATE study), is a multicenter, prospective, case-control study in healthcare facilities in Japan [4]. This report includes individuals who visited 1 of 10 healthcare facilities in an outpatient setting due to COVID-19-like symptom(s) in the Kanto region (Tokyo and 3 surrounding metropolitan prefectures) between September 20 and December 31, 2022. During this period, BA.5 was estimated to be responsible for 75%–100% of SARS-CoV-2 infections in the Kanto region [5].

Inclusion and Exclusion Criteria

The inclusion criterion was all individuals aged ≥16 years. Individuals who did not or could not consent to participate in the study, required immediate lifesaving treatment, or had

Table 1. Demographic and Clinical Characteristics of the Study Participants

Characteristics	All (n = 6191)	Test Positive (n = 3498)	Test Negative (n = 2693)
Age in Years, n (%)			
16–19	300 (4.9)	181 (5.2)	119 (4.4)
20–29	1719 (27.8)	900 (25.7)	819 (30.4)
30–39	1505 (24.3)	793 (22.7)	712 (26.4)
40–49	1243 (20.1)	743 (21.2)	500 (18.6)
50–59	897 (14.5)	591 (16.9)	306 (11.4)
60–69	347 (5.6)	200 (5.7)	147 (5.5)
70+	180 (2.9)	90 (2.6)	90 (3.3)
Sex, n (%); missing = 18 (0.3%)			
Male	3404 (55.1)	1976 (56.7)	1428 (53.2)
Female	2769 (44.9)	1512 (43.4)	1257 (46.8)
Comorbidity,[a] n (%)			
Yes	1525 (24.6)	824 (23.6)	701 (26.0)
No	4666 (75.4)	2674 (76.4)	1992 (74.0)
Occupation, n (%)			
Healthcare/long-term care worker	427 (6.9)	203 (5.8)	224 (8.3)
Other	5764 (93.1)	3295 (94.2)	2469 (91.7)
Days from onset to SARS-CoV-2 Test; Exact Onset Date Missing = 7 (0.1%)[b]	1 (1–2)	1 (1–2)	1 (1–2)
History of Close Contact, n (%)			
Yes	658 (10.6)	425 (12.2)	233 (8.7)
No/unknown	5533 (89.4)	3073 (87.9)	2460 (91.4)
SARS-CoV-2 Diagnostic Test in the Past Month, n (%); Missing = 200 (3.2%)			
Yes	898 (15.0)	446 (13.2)	452 (17.4)
No	5093 (85.0)	2945 (86.9)	2148 (82.6)
Past SARS-CoV-2 Infection, n (%); Missing = 74 (1.2%)			
Yes	647 (10.6)	94 (2.7)	553 (20.8)
Ancestral strain-dominant period (2020–February 2021)	37 (0.6)	14 (0.4)	23 (0.9)
Ancestral-to-alpha replacement period (March–May 2021)	12 (0.2)	6 (0.2)	6 (0.2)
Alpha-to-delta replacement period (June–July 2021)	24 (0.4)	9 (0.3)	15 (0.6)
Delta-dominant period (August–December 2021)	42 (0.7)	16 (0.5)	26 (1.0)
BA.1/BA.2-dominant period (January–June 2022)	294 (4.8)	35 (1.0)	259 (9.7)
BA.5-dominant period (July 2022)	202 (3.3)	8 (0.2)	194 (7.3)
Multiple infections	6 (0.1)	1 (0.0)	5 (0.2)
Period of infection missing	30 (0.5)	5 (0.1)	25 (0.9)
No	5471 (89.4)	3364 (97.3)	2107 (79.2)
Number of Vaccinations Received, n (%); Missing = 66 (1.1%)			
0	668 (10.9)	442 (12.8)	226 (8.5)
1	63 (1.0)	33 (1.0)	30 (1.1)
2	1380 (22.5)	811 (23.5)	569 (21.3)
3	2945 (48.1)	1617 (46.8)	1328 (49.8)
4	947 (15.5)	492 (14.2)	455 (17.1)
5	122 (2.0)	62 (1.8)	60 (2.3)
Vaccine Type for All Doses Received, n (%)			
BNT162b2 (Pfizer/BioNTech)	2349 (43.1)	1325 (44.0)	1024 (41.9)
mRNA-1273 (Moderna)	1127 (20.7)	633 (21.0)	494 (20.2)
Heterologous mRNA	1410 (25.8)	761 (25.2)	649 (26.6)
BA.1-containing bivalent	227 (4.2)	121 (4.0)	106 (4.3)
BA.4/BA.5-containing bivalent	344 (6.3)	175 (5.8)	169 (6.9)
Interval between ba.1-containing bivalent vaccine and SARS-CoV-2 Testing,[b] days	37 (17–54)	39 (20–57)	34 (15–54)
Interval between BA.4/BA.5-containing bivalent vaccine and SARS-CoV-2 testing,[b] days	21 (9–33)	22 (8–33)	21 (11–33)
Interval between BA.1-containing bivalent vaccine and SARS-CoV-2 testing among individuals who received the bivalent vaccine ≥14 days before,[b] days	42 (28–57)	42 (31–59)	43 (28–54)
Interval between BA.4/BA.5-containing bivalent vaccine and SARS-CoV-2 testing among individuals who received the bivalent vaccine ≥14 days before,[b] days	30 (23–44)	30 (24–45)	29 (22–44)
Doses of Monovalent Vaccines Received Before Bivalent Vaccine (Among Individuals Who Received Bivalent Vaccine)			

Table 1. Continued

Characteristics	All (n = 6191)	Test Positive (n = 3498)	Test Negative (n = 2693)
2	51 (8.9)	22 (7.4)	29 (10.6)
3	399 (69.9)	213 (72.0)	186 (67.6)
4	121 (21.2)	61 (20.6)	60 (21.8)
Mask Wearing in the Past 2 Weeks; Missing = 132 (2.1%)			
Wore at home and outside	414 (6.8)	235 (6.9)	179 (6.8)
Wore outside at all times	5263 (86.9)	2987 (87.2)	2276 (86.5)
Wore only when having conversation	349 (5.8)	189 (5.5)	160 (6.1)
Almost never wore masks	33 (0.5)	16 (0.5)	17 (0.7)
High-Risk Behaviors in the Past 2 Weeks (Went to Restaurant/Bar at Night With Alcohol Present), n (%); Missing = 195 (3.1%)			
Yes	2081 (34.7)	1183 (34.8)	898 (34.6)
No	3915 (65.3)	2216 (65.2)	1699 (65.4)

Abbreviation: mRNA, messenger ribonucleic acid; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[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).

previously participated in this study were excluded. In the analysis, we also excluded individuals who had unknown symptom onset time, were tested ≥15 days after symptom onset, received vaccine types other than mRNA vaccines, or received unknown vaccine types.

Classification of Exposures and Outcome

A questionnaire was administered before the test results were available to minimize social desirability bias. Vaccination status was recorded based on the questionnaire via a copy of the vaccine record/certificate and checked for plausibility. Vaccination status was classified into 17 categories: (1) not vaccinated, (2) dose 1 or ≤13 days after dose 2, (3) 14 days–3 months (14–90 days) after dose 2, (4) 3–6 months (91–180 days) after dose 2, (5) >6 months (181 days) after dose 2, (6) ≤13 days after dose 3 (first booster dose), (7) 14 days–3 months (14–90 days) after dose 3, (8) 3–6 months (91–180 days) after dose 3, (9) >6 months (181 days) after dose 3, (10) ≤13 days after dose 4 (second booster dose), (11) 14 days–3 months (14–90 days) after dose 4, (12) 3–6 months (91–180 days) after dose 4, (13) >6 months (181 days) after dose 4, (14) ≤13 days after BA.1-containing bivalent vaccine, (15) ≥14 days after BA.1-containing bivalent vaccine, (16) ≤13 days after BA.4/BA.5-containing bivalent vaccine, and (17) ≥14 days after BA.4/BA.5-containing bivalent vaccine (categories 1–13 include monovalent recipients only). Severe acute respiratory syndrome coronavirus 2 polymerase chain reaction (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 the following a priori determined covariates: age group, sex, presence of any comorbidity, occupation (healthcare/long-term care worker or not), SARS-CoV-2 diagnostic test in the past month, self-reported past SARS-CoV-2 infection (categorized by the period of infection), history of close contact, healthcare facility that the participant visited, calendar week, mask wearing, high-risk behavior (dining at a restaurant/bar at night with alcohol consumption in a group as a proxy [6, 7]), and influenza vaccination status for the 2022–2023 season. The VE against symptomatic SARS-CoV-2 infection was estimated using the following equation: VE = (1 − adjusted odds ratio [aOR]) × 100%. In addition to absolute VE ([aVE] VE comparing the vaccinated and unvaccinated), we calculated relative VE ([rVE] VE comparing individuals who received the bivalent vaccine vs individuals who only received monovalent doses 3–6 months earlier/6+ months earlier) to evaluate the added effect of the bivalent vaccine. Based on a priori knowledge that time since vaccination contributes more to VE compared to doses received [8] and due to sample size restrictions, we did not categorize by the number of monovalent vaccines received. Finally, we calculated the aOR of SARS-CoV-2 infection comparing ≥14 days after the bivalent vaccine against 14 days–3 months after the third or fourth dose of monovalent vaccines for a head-to-head comparison of monovalent versus bivalent vaccines. We also calculated the aOR of SARS-CoV-2 infection by influenza vaccination status to assess the risk of bias. During the study period, influenza activity was extremely low in Japan [9]. Data analyses were performed using STATA version 17.0.

RESULTS

A total of 6955 individuals were enrolled from 10 medical facilities; 170 were excluded for unknown symptom onset date, 33 for being tested ≥15 days after symptom onset, and 561 for

Table 2. Absolute and Relative Effectiveness of BA.1- or BA.4/BA.5-Containing Bivalent Vaccine Against Symptomatic SARS-CoV-2 by Dose Number and Time Since Vaccination During the BA.5-Dominant Period

Vaccination Status	Test Positive, n	Test Negative, n	Adjusted Odds Ratios (95% CI)[a]	Vaccine Effectiveness, % (95% CI)
Comparison Between Vaccinated Versus Unvaccinated				
Unvaccinated	442	226	1	NA
Dose 1 or ≤13 days after dose 2	36	31	0.54 (.29–1.00)	46 (0–71)
14 days–3 months after dose 2	52	38	0.68 (.40–1.16)	32 (−16–60)
3–6 months after dose 2	34	24	0.58 (.31–1.07)	42 (−7–69)
>6 months after dose 2	571	436	0.58 (.46–.74)	42 (26–54)
≤13 days after dose 3	0	1	NA	NA
14 days–3 months after dose 3	70	115	0.24 (.16–.35)	76 (65–84)
3–6 months after dose 3	364	373	0.45 (.35–.58)	55 (42–65)
>6 months after dose 3	987	664	0.50 (.40–.63)	50 (37–60)
≤13 days after dose 4	9	3	1.27 (.25–6.45)	NA
14 days–3 months after dose 4	119	150	0.33 (.23–.47)	67 (53–77)
3–6 months after dose 4	120	99	0.39 (.26–.59)	61 (41–74)
>6 months after dose 4	6	1	1.78 (.21–15.30)	NA
≤13 days after BA.1-containing bivalent	21	24	0.29 (.14–.51)	71 (49–86)
≤13 days after BA.4/BA.5-containing bivalent	65	57	0.32 (.20–.51)	68 (49–80)
≥14 days after BA.1-containing bivalent	95	76	0.35 (.23–.53)	65 (47–77)
≥14 days after BA.4/BA.5-containing bivalent	112	116	0.24 (.17–.35)	76 (65–83)
Comparison Between Bivalent Vaccine Versus 3–6 Months After Monovalent Dose[b]				
Unvaccinated	442	226	NA	NA
Dose 1 or ≤13 days after monovalent dose[b]	45	35	NA	NA
14 days–3 months after monovalent dose[b]	241	303	NA	NA
3–6 months after monovalent dose[b]	518	496	1	NA
>6 months after monovalent dose[b]	1564	1101	NA	NA
≤13 days after bivalent dose	86	81	0.72 (.49–1.04)	28 (−4–51)
≥14 days after bivalent dose	207	192	0.65 (.49–.85)	35 (15–51)
Comparison Between Bivalent Vaccine Versus >6 Months After Monovalent Dose[b]				
Unvaccinated	442	226	NA	NA
Dose 1 or ≤13 days after monovalent dose[b]	45	35	NA	NA
14 days–3 months after monovalent dose[b]	241	303	NA	NA
3–6 months after monovalent dose[b]	518	496	NA	NA
>6 months after monovalent dose[b]	1564	1101	1	NA
≤13 days after bivalent dose	86	81	0.60 (.42–.86)	40 (14–58)
≥14 days after bivalent dose	207	192	0.54 (.42–.70)	46 (30–58)
Comparison Between Bivalent Vaccine Versus 14 Days–3 Months After 3 or 4 Doses of Monovalent Vaccines				
Unvaccinated	442	226	NA	NA
Dose 1 or dose 2	703	533	NA	NA
14 days–3 months after 3rd or 4th monovalent dose	189	265	1	NA
3–6 months after 3rd or 4th monovalent dose	484	472	1.52 (1.18–1.96)	NA
>6 months after 3rd or 4th monovalent dose	993	665	1.77 (1.38–2.28)	NA
≤13 days after bivalent dose	86	81	1.09 (.73–1.63)	−9 (−63 to 27)
≥14 days after bivalent dose	207	192	0.99 (.72–1.36)	1 (−36 to 28)

Abbreviations: CI, confidence interval; NA, not available (includes categories with small sample size or irrelevant comparisons); SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a]Adjusted for age group, sex, presence of comorbidities, 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, high-risk behavior, and influenza vaccination status for the 2022–2023 season.

[b]Regardless of doses received.

receiving vaccine types other than monovalent mRNA vaccines or receiving an unknown vaccine type. The final analysis included 6191 individuals with 3498 (56.5%) positive cases. The median age was 36 (interquartile range [IQR], 27–48) years (other demographic and clinical characteristics are in Table 1 and the Supplementary Table). The aVE of bivalent vaccine (regardless of subvariant coded) was 72% (95% confidence interval [CI], 61–80). When stratified by subvariant coded in the bivalent vaccine, the aVE of BA.1-containing bivalent vaccine was 65% (95% CI, 47–77), and the aVE of BA.4/BA.5-containing bivalent vaccine was 76% (95% CI, 65–83) (Table 2). The rVE comparing bivalent vaccine (regardless of

subvariant coded) versus monovalent vaccines post-3–6 months was 35% (95% CI, 15–51), whereas rVE comparing bivalent vaccine versus monovalent vaccines post-6 months was 46% (95% CI, 30–58). The aOR of SARS-CoV-2 infection comparing bivalent vaccine ≥14 days versus 14 days–3 months after 3 or 4 doses of monovalent vaccine was 0.99 (95% CI, .72–1.36) (median interval between the bivalent vaccine and SARS-CoV-2 testing 34 days [IQR, 24–49]; median interval between the monovalent vaccine and testing 66 days [IQR, 49–80]). The aOR of SARS-CoV-2 infection by influenza vaccination status was 0.95 (95% CI, .79–1.13).

DISCUSSION

In this multicenter, test-negative study in Japan, we found that aVE of BA.1-containing bivalent COVID-19 vaccines was 65% and that of BA.4/BA.5-containing bivalent vaccines was 76% during the BA.5-dominant period, both against symptomatic infection. Only a few published studies have assessed the effectiveness of BA.4/BA.5-containing bivalent VE, mostly against severe COVID-19 [10–12]. Our estimate of aVE against symptomatic infection was higher than that observed in a US study on BA.4/BA.5-containing bivalent vaccines [10]. This may be due to substantial differences in the proportion of previously infected individuals as well as public health and social measures (eg, high frequency of mask wearing in Japan regardless of vaccination status). We also included a number of factors to adjust for potential differences between vaccinated and unvaccinated individuals. Similar to the US study, rVE was moderate (46%) with more added benefit with a longer period since the last monovalent vaccine. The head-to-head comparison soon after monovalent and bivalent vaccines did not result in the superiority of the bivalent vaccine during the BA.5-dominant period (aOR, 0.99). However, there are some important limitations in this comparison because monovalent booster vaccines became unavailable after introduction of the bivalent vaccine. Overall, although aVE was high in our study, the bivalent vaccine was not superior to the monovalent vaccine, and aVE was lower than that observed for the monovalent primary series against the ancestral strain, alpha, and delta variants (85%–95%) [4, 13]. This is in line with immune imprinting against the ancestral strain as suggested in other studies [14, 15].

This study has several limitations. First, biases and confounding inherent in observational studies are possible. We attempted to minimize these by adjusting for various factors, and there was no association between influenza vaccination and SARS-CoV-2 testing. Second, because we did not have a system to link test results with vaccination history, we asked participants to refer to their vaccine records/certificates and (if not in possession) diary/calendar for accuracy. Third, wide CIs for some estimates warrant careful interpretation of point estimates. Fourth, our analysis was a complete case analysis. Finally, our VE estimates were short term and require continued assessment to monitor mid- to long-term effectiveness.

CONCLUSIONS

In conclusion, we found that bivalent COVID-19 VE was high compared with no vaccination and moderate compared with monovalent vaccines administered over half a year earlier. Although there was evidence suggestive of immune imprinting, our results support the continued rollout of bivalent vaccines.

Supplementary Data

Supplementary materials are available at *Open Forum 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.

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Author contributions. TA, YA, and MS conceived of and designed the study. All authors contributed to the acquisition, analysis, and/or interpretation of the data. TA wrote the first draft of the manuscript. All authors provided critical input to the manuscript for important intellectual content.

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