J Korean Med Sci. 2024 Jan 22;39(3):e15
https://doi.org/10.3346/jkms.2024.39.e15
eISSN 1598-6357·pISSN 1011-8934

JKMS

Original Article
Infectious Diseases

Effectiveness of Bivalent mRNA Booster Vaccine Against COVID-19 in Korea

Jin Gu Yoon [1,2] **Jang Wook Sohn** [3] **Won Suk Choi** [4] **Seong-Heon Wie** [5] **Jacob Lee** [6] **Jin-Soo Lee** [7] **Hye Won Jeong** [8] **Joong Sik Eom** [9] **Hye Seong** [1,2] **Eliel Nham** [1,2] **Yu Jung Choi** [1,2] **Ji Yun Noh** [1,2] **Joon Young Song** [1,2] **Hee Jin Cheong** [1,2] **and Woo Joo Kim** [1,2]

[1]Division of Infectious Diseases, Department of Internal Medicine, Korea University Guro Hospital, Korea University College of Medicine, Seoul, Korea
[2]Vaccine Innovation Center-KU Medicine (VIC-K), Seoul, Korea
[3]Division of Infectious Diseases, Department of Internal Medicine, Korea University Anam Hospital, Korea University College of Medicine, Seoul, Korea
[4]Division of Infectious Diseases, Department of Internal Medicine, Korea University Ansan Hospital, Korea University College of Medicine, Ansan, Korea
[5]Division of Infectious Diseases, Department of Internal Medicine, St. Vincent's Hospital, College of Medicine, The Catholic University of Korea, Suwon, Korea
[6]Division of Infectious Diseases, Department of Internal Medicine, Kangnam Sacred Heart Hospital, Hallym University College of Medicine, Seoul, Korea
[7]Division of Infectious Diseases, Department of Internal Medicine, Inha University School of Medicine, Incheon, Korea
[8]Department of Internal Medicine, Chungbuk National University College of Medicine, Cheongju, Korea
[9]Division of Infectious Diseases, Department of Internal Medicine, Gil Medical Center, Gachon University College of Medicine, Incheon, Korea

Received: Aug 30, 2023
Accepted: Oct 26, 2023
Published online: Dec 26, 2023

Address for Correspondence:
Woo Joo Kim, MD, PhD
Division of Infectious Diseases, Department of Internal Medicine, Korea University Guro Hospital, Korea University College of Medicine, 148 Gurodong-ro, Guro-gu, Seoul 08308, Korea.
Email: wjkim@korea.ac.kr

ORCID iDs
Jin Gu Yoon
https://orcid.org/0000-0003-3283-1880
Jang Wook Sohn
https://orcid.org/0000-0003-4792-0456
Won Suk Choi
https://orcid.org/0000-0001-5874-4764
Seong-Heon Wie
https://orcid.org/0000-0002-7603-5520
Jacob Lee
https://orcid.org/0000-0002-7041-065X
Jin-Soo Lee
https://orcid.org/0000-0001-7862-5519
Hye Won Jeong
https://orcid.org/0000-0002-1063-8476
Joong Sik Eom
https://orcid.org/0000-0003-2744-1159

ABSTRACT

Background: Bivalent booster mRNA vaccines containing the omicron-variant strains have been introduced worldwide in the autumn of 2022. Nevertheless, the omicron subvariants evoked another large coronavirus disease 2019 (COVID-19) pandemic wave in late 2022 and early 2023.
Methods: A retrospective, test-negative, case-control study was conducted to estimate the vaccine effectiveness (VE) of bivalent COVID-19 vaccines in 8 university hospitals between January and February 2023. The case and control groups were divided based on nasopharyngeal COVID-19 real-time polymerase chain reaction results and matched based on age, sex, hospital, and date (week) of the test performed. The VE of the BA.1- or BA.4/BA.5-based mRNA vaccines were estimated. VE was calculated using the 1–adjusted odds ratio from multivariable logistic regression.
Results: In total, 949 patients and 947 controls were enrolled in this study. VE for the BA.4/BA.5-based bivalent mRNA vaccine was 43% (95% confidence interval [CI], 17, 61%). In subgroup analysis based on age and underlying medical conditions, BA.4/BA.5-based bivalent mRNA vaccine was effective against old adults aged ≥ 65-years (VE, 55%; 95% CI, 23, 73%) and individuals with comorbidities (VE, 54%; 95% CI, 23, 73%). In comparison, the BA.1-based bivalent mRNA vaccine did not demonstrate statistically significant effectiveness (VE, 25%; 95% CI, −8, 49%).
Conclusion: The BA.4/BA.5-based bivalent mRNA booster vaccine provided significant protection against COVID-19 in the Korean adults, especially in the older adults aged ≥ 65 years and in individuals with underlying medical conditions.

Keywords: COVID-19; mRNA Vaccine; Vaccine Efficacy; SARS-CoV-2 Omicron Variant

Hye Seong
https://orcid.org/0000-0002-5633-7214
Eliel Nham
https://orcid.org/0000-0001-7509-4863
Yu Jung Choi
https://orcid.org/0009-0008-1933-5843
Ji Yun Noh
https://orcid.org/0000-0001-8541-5704
Joon Young Song
https://orcid.org/0000-0002-0148-7194
Hee Jin Cheong
https://orcid.org/0000-0002-2532-1463
Woo Joo Kim
https://orcid.org/0000-0002-4546-3880

Funding

This work was supported by a grant of Korea University College of Medicine (Q2204881) that was underwritten by SK Bioscience CO., Ltd.

Disclosure

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Kim WJ, Song JY. Data curation: Yoon JG, Sohn JW, Choi WS, Wie SH, Lee J, Lee JS, Jeong HW, Eom JS. Investigation: Sohn JW, Choi WS, Wie SH, Lee J, Lee JS, Jeong HW, Eom JS, Song JY, Kim WJ. Writing - original draft: Yoon JG. Writing - review & editing: Yoon JG, Sohn JW, Choi WS, Wie SH, Lee J, Lee JS, Jeong HW, Eom JS, Seong H, Nham Eliel, Choi YJ, Noh JY, Song JY, Cheong HJ, Kim WJ.

INTRODUCTION

In the era of coronavirus disease 2019 (COVID-19) pandemic, numerous vaccine platforms, including mRNA, have been developed against the severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2). Vaccination is effective in preventing viral infections, hospitalization, and severe diseases. However, the need for a booster dose was emphasized because the neutralizing antibodies produced by vaccination decreases over time, especially in the older adults and high-risk groups.[1-3] In addition, by the end of 2021, the emergence of the omicron subvariants, first reported in South Africa, raised concerns about the decline in the efficacy of existing vaccines due to immune evasion.[4] The monovalent mRNA booster vaccine containing the ancestral SARS-CoV-2 strain also reduces omicron-related hospitalization and severity; however, it exhibits lower effectiveness and neutralizing activity than those of previous variant strains.[5] Therefore, vaccine manufacturers developed bivalent booster vaccines, which include the omicron-variant strain together with the ancestral strain.[6] In August 2022, the U.S. Food and Drug Administration approved the mRNA bivalent vaccines (Pfizer-BioNTech Comirnaty® and Moderna Spikevax®), which additionally contains the omicron BA.1 component or BA.4/BA.5 component. Subsequently, these were introduced to Korea starting from November 2022.

However, the effectiveness of the bivalent COVID-19 vaccines in Korea remains insufficient. In this study, we aimed to investigate the real-world effectiveness of the bivalent booster vaccination against COVID-19 in Korean adults aged ≥ 18 years.

METHODS

Study population and design

Between January 1, 2023, and February 28, 2023, adult patients who were tested for COVID-19 were recruited from 8 university hospitals. This study was conducted using a retrospective, test-negative, case-control design. In order to detect a vaccine effectiveness (VE) of 60% with a vaccine coverage of 30%, the target sample size was calculated to be 801 for both unmatched case and control groups when the desired precision width was 20% and a type 1 error rate was 0.05.[7] Thus, we targeted number of enrollments was 240 patients from each hospital (120 cases and controls), stratified based on age groups (19–49, 50–64, and ≥ 65 years old). If possible, we enrolled the same number of patients by age group, but if that was not possible, we prioritized to fill the target sample size for each hospital. The case group was defined as patients diagnosed with COVID-19 based on positive results obtained from nasopharyngeal real-time polymerase chain reaction (RT-PCR), whereas the control group was defined as patients who tested negative during the same period. Individuals who underwent COVID-19 testing for prehospital screening were excluded. In addition, individuals who were screened after immigration and healthcare workers (HCWs) who underwent regular repetitive testing were excluded from the study. The case and control groups were matched based on age and sex within the same hospital and in the same week as that of the test date, in a 1:1 ratio. Demographic and clinical data were collected based on their medical records, which included reason for polymerase chain reaction (PCR) test, HCW status, COVID-19 related symptoms (fever, cough, sputum, sore throat, rhinorrhea/nasal congestion, dyspnea, chest discomfort, and loss of smell and taste), previous COVID-19 history, underlying medical conditions (diabetes mellitus, solid cancer treated within one year, hematologic malignancy, use of immunosuppressants, human immunodeficiency virus infection and pregnancy, as well as

chronic heart, lung, kidney, liver, and neurological diseases), and clinical outcomes. The vaccination status was verified using immunization registry data from the Korean Disease Control and Prevention Agency. The study followed the guideline of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statements.[8]

Study vaccine and vaccination status

During the study period, four bivalent vaccines (Ancestral/omicron BA.1 manufactured by Pfizer-BioNTech and Moderna; Ancestral/omicron BA.4/BA.5 manufactured by Pfizer-BioNTech and Moderna) were introduced and used in Korea. The vaccine was considered effective if administered within ≥ 7 days before the RT-PCR test. The vaccination history of the study participants was confirmed using a questionnaire regarding whether they had completed the two-doses primary vaccination series and received a monovalent booster vaccination.

Statistical analysis

The statistical significance of the 2 × 2 data in terms of baseline characteristics was assessed using the chi-square and Fisher's exact tests. To estimate the VE for BA.1 or BA.4/BA.5-based bivalent vaccines, we employed a multivariate logistic regression model, and VE was derived as 1–adjusted odds ratio. In the model, age, sex, underlying medical conditions, baseline vaccination status, history of COVID-19, and HCW status, were chosen as independent variables, and multicollinearity of the variables was assessed using the variance inflation factor. In order to fit the model, we employed backward stepwise regression and checked the overdispersion. In addition, a subgroup analysis of each variable was conducted to reveal the differences in the effectiveness of each vaccine within specific groups. Statistical significance was set at $P < 0.05$. All statistical analyses were performed using R software (version 4.2.2; R Foundation, Vienna, Austria).

Ethics statement

This study was approved by the Institutional Review Board (IRB) of Korea University Guro Hospital (approval No. 2022GR0360) and each IRB of the other 7 university hospitals (Korea University Anam Hospital, 2022AN0449; Korea University Ansan Hospital, 2022AS0226; St. Vincent's Hospital, VC22TIDI0150; Kangnam Sacred Heart Hospital, HKS 2022-07-016; Inha University Hospital, 2022-07-036; Chungbuk National University Hospital, 2022-08-022; and Gil Medical Center GAIRB2022-306). Informed consent was submitted by all subjects when they were enrolled. This study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

RESULTS

A total of 1,896 adult participants (949 cases and 947 controls) were enrolled and matched for age and sex between the case and control groups (**Table 1**). The process of enrollment and matching is shown in **Fig. 1**. All hospitals met the target sample size except for Gil hospital (109 cases and 107 controls enrolled). Among them, 541 patients (28.5%) were hospitalized, and 63 (4.2%) died. More than 90% of the participants had been previously vaccinated, and no difference was observed in the ratio of two-doses primary vaccination series (15.8% [n = 150] vs. 15.3% [n = 145]; $P = 0.812$) or the ratio of monovalent booster administration (72.2% [n = 685] vs. 75.5% [n = 715]; $P = 0.812$). BA.1-based bivalent vaccination was performed using both manufacturers' vaccines (Pfizer-BioNTech: 1.5% [n = 29], Moderna: 5.3% [n = 101]), whereas BA.4/BA.5-based bivalent vaccination was mostly performed using the Pfizer-BioNTech vaccine

https://doi.org/10.3346/jkms.2024.39.e15

(6.6% [n = 126]). History of prior SARS-CoV-2 infection (27.7% [n = 263] vs. 26.0% [n = 236]; *P* = 0.441) and presence of underlying medical conditions (46.7% [n = 443] vs. 50.4% [n = 477]; *P* = 0.119) were not significantly different between the groups. Proportions of covariates and characteristics between case and control groups were similar within aged ≥ 65-years and underlying medical conditions subgroups (**Supplementary Tables 1** and **2**).

Table 1. Baseline characteristics of case and control groups

Characteristics	Total (N = 1,896)	COVID-19 test-positive (n = 949)	COVID-19 test-negative (n = 947)	*P* value
Age group				0.998
19–49 yr	616 (32.5)	308 (32.5)	308 (32.5)	
50–64 yr	614 (32.4)	307 (32.3)	307 (32.4)	
≥ 65 yr	666 (35.1)	334 (35.2)	332 (35.1)	
Sex				0.383
Male	919 (48.5)	450 (47.4)	469 (49.5)	
Female	977 (51.5)	499 (52.6)	478 (50.5)	
Health care worker	158 (8.3)	96 (10.1)	62 (6.5)	0.006
Clinical outcome				
Hospitalization	541 (28.5)	233 (24.6)	308 (32.5)	< 0.001
ICU admission	110 (7.9)	62 (9.2)	48 (6.7)	0.097
In-hospital death	63 (4.2)	39 (5.2)	24 (3.2)	0.001
Reason for PCR test				< 0.001
Related symptoms	1,472 (77.6)	560 (59.0)	912 (96.3)	
Close contact with patients	424 (22.4)	389 (41.0)	35 (3.7)	
Symptoms				
Fever	675 (35.6)	260 (27.4)	415 (43.8)	< 0.001
Cough	560 (29.5)	247 (26.0)	313 (33.1)	0.001
Sputum	418 (22.0)	177 (18.7)	241 (25.4)	< 0.001
Sore throat	337 (17.8)	173 (18.2)	164 (17.3)	0.646
Rhinorrhea/nasal congestion	185 (9.8)	82 (8.6)	103 (10.9)	0.118
Dyspnea	481 (25.4)	147 (15.5)	334 (35.3)	< 0.001
Chest discomfort	130 (6.9)	35 (3.7)	95 (10.0)	< 0.001
Loss of smell	3 (0.2)	2 (0.2)	1 (0.1)	1.000
Loss of taste	5 (0.3)	3 (0.3)	2 (0.2)	1.000
Baseline vaccination				
Yes	1,713 (90.3)	843 (88.8)	870 (91.9)	0.031
1 dose	18 (0.9)	8 (0.8)	10 (1.1)	0.812
2 doses	295 (15.5)	150 (15.8)	145 (15.3)	
3 doses or more	1,400 (73.8)	685 (72.2)	715 (75.5)	
Bivalent booster vaccine				
Pfizer BA.1	29 (1.5)	12 (1.3)	17 (1.8)	0.451
Pfizer BA.4/BA.5	126 (6.6)	50 (5.3)	76 (8.0)	0.020
Moderna BA.1	101 (5.3)	46 (4.8)	55 (5.8)	0.395
Moderna BA.4/BA.5	1 (0.1)	1 (0.1)	0	-
Prior SARS-CoV-2 infection	499 (26.9)	263 (27.7)	236 (26.0)	0.441
Underlying medical conditions				
One or more	920 (48.5)	443 (46.7)	477 (50.4)	0.119
DM	351 (18.5)	178 (18.8)	173 (18.3)	0.830
Chronic heart disease	289 (15.2)	138 (14.5)	151 (15.9)	0.432
Chronic lung disease	125 (6.6)	44 (4.6)	81 (8.6)	0.001
Chronic kidney disease	98 (5.2)	53 (5.6)	45 (4.8)	0.471
Chronic liver disease	57 (3.0)	20 (2.1)	37 (3.9)	0.031
Chronic neurologic disease	183 (9.7)	101 (10.6)	82 (8.7)	0.166
Solid cancer	228 (12.0)	103 (10.9)	125 (13.2)	0.134
Hematologic malignancy	20 (1.1)	11 (1.2)	9 (1.0)	0.826
Immunosuppressant user	26 (1.4)	10 (1.1)	16 (1.7)	0.321
HIV	3 (0.2)	0 (0.0)	3 (0.3)	0.247
Pregnancy	12 (0.6)	7 (0.7)	5 (0.5)	0.775

Values are presented as number (%).
COVID-19 = coronavirus disease 2019, ICU = intensive care unit, PCR = polymerase chain reaction, SARS-CoV-2 = severe acute respiratory syndrome-coronavirus-2, DM = diabetes mellitus, HIV = human immunodeficiency virus.

https://doi.org/10.3346/jkms.2024.39.e15

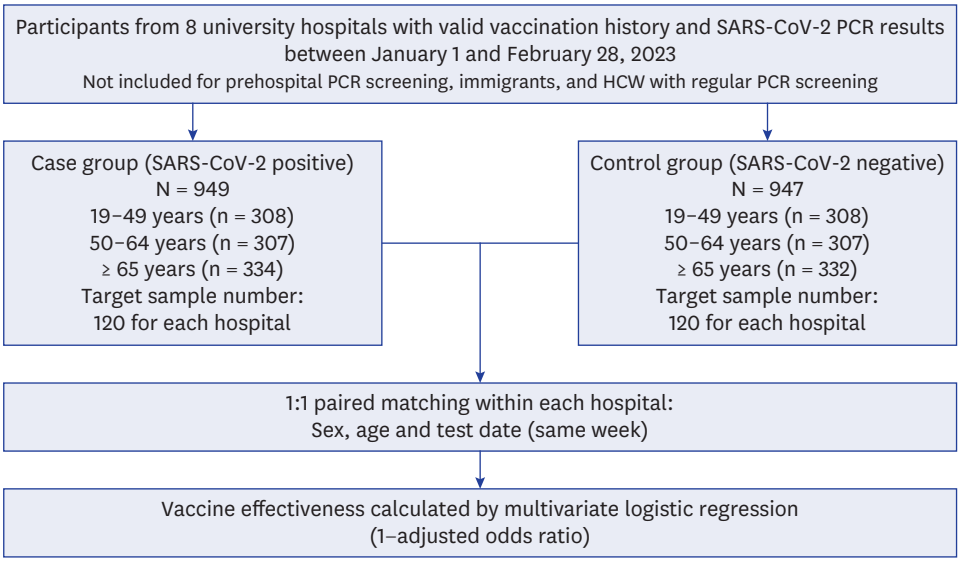

Fig. 1. Matching process and study protocol of case and control groups from 8 university hospitals.
SARS-CoV-2 = severe acute respiratory syndrome-coronavirus-2, PCR = polymerase chain reaction, HCW = healthcare worker.

VE against COVID-19 was estimated to be 34% (95% CI, 13, 50%; $P = 0.003$) for all bivalent booster vaccinations and 43% (95% CI, 17, 61%; $P = 0.004$) for the BA.4/BA.5-based bivalent booster vaccination (**Table 2**). The BA.1-based bivalent booster vaccination was not significantly effective (VE, 25% [95% CI, −8, 49%]; $P = 0.126$). In the subgroup analysis by age, only the BA.4/BA.5-based bivalent vaccine was effective in the older adults aged ≥ 65-years (VE, 55% [95% CI, 23, 73%]; $P = 0.003$). The BA.4/BA.5-based bivalent vaccine was effective in patients who received a monovalent booster vaccination (VE, 39% [95% CI, 10, 59%]; $P = 0.012$). Because very few patients received two or fewer doses, no statistically significant results were observed in these individuals. When further analyzed based on the subgroups, the BA.4/BA.5-based bivalent vaccine demonstrated a significant VE for the non-HCW group (VE, 50% [95% CI, 23, 67%]; $P = 0.002$), individuals with prior SARS-CoV-2 infection (VE, 59% [95% CI, 11, 81%]; $P = 0.023$) and individuals with underlying medical conditions (VE, 54% [95% CI, 23, 73%]; $P = 0.002$). The BA.1-based bivalent vaccine was effective only in individuals without prior SARS-CoV-2 infection (VE, 35% [95% CI, 1, 57%]; $P = 0.045$). VE against symptomatic COVID-19 and hospitalized COVID-19 were also calculated and presented in **Supplementary Tables 3** and **4**. The BA.4/BA.5 based bivalent booster vaccine was effective for symptomatic COVID-19 (VE, 42% [95% CI, 8, 63%]; $P = 0.020$) but showed no statistically significant effectiveness in hospitalized COVID-19 (VE, 49% [95% CI, 0, 74%]; $P = 0.051$).

DISCUSSION

Since the bivalent booster vaccination campaign has begun in the Republic of Korea, the necessity for evaluating the real-world effectiveness data has emerged. In our study, the BA.4/BA.5-based bivalent booster vaccination rather than BA.1-based vaccination was effective in preventing COVID-19, demonstrating a comprehensive VE of 43%. In particular, since VE was significantly effective in the older adults aged ≥ 65 years and in individuals with underlying medical conditions, bivalent booster COVID-19 vaccination should be strongly recommended for these risk groups.

https://doi.org/10.3346/jkms.2024.39.e15

Table 2. VE of bivalent mRNA booster vaccination by subgroups

Characteristics	COVID-19 test positive cases/ total (%)	Unadjusted VE (%) with 95% CI	Adjusted VE (%) with 95% CI	*P* value for adjusted VE
Types of bivalent booster				
All bivalent booster	108/256 (42.2)	31 (10, 47)	34* (13, 50)	0.003
BA.4/BA.5	50/126 (39.7)	36 (8, 56)	43* (17, 61)	0.004
BA.1	58/130 (44.6)	21 (−13, 45)	25 (−8, 49)	0.126
Sex				
Male				
BA.4/BA.5	22/60 (36.7)	42 (0, 66)	44* (2, 68)	0.042
BA.1	36/77 (46.8)	9 (−45, 43)	11 (−46, 45)	0.655
Female				
BA.4/BA.5	28/66 (42.4)	31 (−14, 58)	41* (0, 65)	0.048
BA.1	22/53 (41.5)	30 (−21, 60)	43 (−2, 68)	0.058
Age group				
19–49 yr				
BA.4/BA.5	11/21 (52.4)	−10 (−164, 54)	4 (−134, 60)	0.935
BA.1	1/4 (25.0)	67 (−220, 97)	67 (−227, 97)	0.347
50–64 yr				
BA.4/BA.5	16/37 (43.2)	25 (−46, 62)	42 (−19, 72)	0.140
BA.1	12/29 (41.4)	25 (−58, 64)	30 (−49, 67)	0.350
≥ 65 yr				
BA.4/BA.5	23/68 (33.8)	53 (20, 72)	55* (23, 73)	0.003
BA.1	45/97 (46.4)	16 (−29, 46)	16 (−31, 46)	0.433
Baseline vaccination				
≥ 3 doses				
BA.4/BA.5	49/122 (40.2)	32 (1, 54)	39* (10, 59)	0.012
BA.1	57/127 (44.9)	15 (−23, 41)	21 (−16, 46)	0.228
2 doses				
BA.4/BA.5	1/4 (25.0)	68 (−209, 17)	73 (−164, 97)	0.257
BA.1	1/3 (33.3)	52 (−435, 96)	50 (−461, 96)	0.570
Prior SARS-CoV-2 infection				
Yes				
BA.4/BA.5	12/33 (36.4)	51 (−2, 76)	59* (11, 81)	0.023
BA.1	14/20 (70.0)	−116 (−470, 19)	−77 (−375, 34)	0.256
No				
BA.4/BA.5	38/93 (40.9)	30 (−7, 54)	34 (−2, 58)	0.062
BA.1	44/110 (40.0)	31 (−2, 54)	35* (1, 57)	0.045
Healthcare worker				
Yes				
BA.4/BA.5	13/20 (65.0)	−23 (−228, 54)	−61 (−366, 44)	0.375
BA.1	0/1	NA	NA	
No				
BA.4/BA.5	37/106 (34.9)	46 (19, 64)	50* (23, 67)	0.002
BA.1	58/129 (45.0)	15 (−22, 40)	24 (−10, 48)	0.148
Underlying medical conditions				
Yes				
BA.4/BA.5	23/70 (32.9)	50 (16, 70)	54* (23, 73)	0.003
BA.1	36/87 (41.4)	24 (−19, 51)	35 (−4, 59)	0.071
No				
BA.4/BA.5	27/56 (48.2)	14 (−47, 50)	23 (−34, 56)	0.348
BA.1	22/43 (51.2)	3 (−79, 47)	9 (−72, 52)	0.769

VE = vaccine effectiveness, COVID-19 = coronavirus disease 2019, CI = confidence interval, SARS-CoV-2 = severe acute respiratory syndrome-coronavirus-2, NA = not applicable.
*P value < 0.05.

Although several studies have already reported low effectiveness of booster vaccine with monovalent ancestral strain against the omicron subvariants, VE is much more reduced and the duration of protective immunity is shortened after the emergence and spread of BA.1, followed by other the omicron subvariants.[6,9] To respond to this situation, a bivalent mRNA vaccine combining the ancestral type and a new omicron subvariant had been rapidly

https://doi.org/10.3346/jkms.2024.39.e15

developed and approved for use. The early estimation of bivalent mRNA vaccines from the U.S. Centers for Disease Control and Prevention (CDC) reported 56% absolute VE for urgent care encounters, and another study demonstrated the superior ability of bivalent vaccines to produce neutralizing antibodies against the omicron subvariants.[10,11] One study presented 29% VE during the BA.4/BA.5 epidemic.[12]

In the Republic of Korea, the rate of primary series/monovalent booster vaccinations and the epidemic pattern of the omicron subvariants are different from those of the United States and other countries. For instance, BA.5, BA.2 and XBB and its subvariants were serially dominant in the United States. However, BN.1, a subvariant of BA.2.75, was the most dominant type (50.4%), followed by BA.5 (18.3%) and BA.2.75 (11.2%) during the study period (January 2023 to February 2023) in the Republic of Korea.[13] Both BA.2.75 and BA.5 exhibit reduced neutralizing antibody ability; however, the immune evasion of BA.2.75 is greater than that of BA.5.[14,15] Therefore, it was necessary to verify the real-world effectiveness of bivalent booster in the Republic of Korea, and this study demonstrated similar VE as those of previous studies from other countries.

Notably, the preventive effect of the bivalent vaccine was significant against SARS-CoV-2 infection in the older adults and patients with underlying medical conditions. In a CDC report, the VE of the bivalent booster vaccine demonstrated no significant difference across different age groups, although a slight decrease was observed in the older adult population.[16] The relatively high VE in the older adult group in our study was probably due to differences in PCR testing practices, viral exposure risks, and low underlying immunity in the relevant group. Studies on high-risk groups have already revealed that after bivalent vaccination, VE against severe disease is reported in up to 53% of immunocompromised patients.[16,17]

Additionally, our study revealed that a history of prior SARS-CoV-2 infection and vaccination could also affect the effectiveness of bivalent booster vaccines. Three doses of vaccination are known to improve the protection against the omicron subvariants compared to two doses.[18] One study reported that the production of neutralizing antibodies against BA.2.75.2 increases significantly following the administration of BA.5-based bivalent booster vaccine in individuals with a history of COVID-19 infection.[19] In Italy, prior COVID-19 exposure did not reduce the VE of the bivalent second booster vaccination beyond 26 weeks.[20] This implies that prior SARS-CoV-2 infection and vaccination history over a certain period did not affect or increase the antibody production. These findings are supported by our study results.

Our study had several limitations. First, since most patients had a history of monovalent booster vaccination, VE could not be properly evaluated and compared with unvaccinated individuals. In addition, we were unable to confirm the exact timing of the monovalent booster vaccination and prior SARS-CoV-2 infection. Second, vaccine manufacturers were not considered in the VE analysis. The Pfizer-BioNTech vaccine contains 15 μg of both the ancestral and omicron subvariant mRNAs, whereas the Moderna vaccine contains 25 μg of each of these components. However, because the VE of each manufacturer was relatively the same as in the previous study, we classified and analyzed only the omicron subvariant strain.[21] Third, further analysis is required to determine the longevity of protective effectiveness by bivalent vaccines. Most patients in our study were analyzed within 3 months of vaccination, while the protective effect of vaccination lasted for up to 6 months. Fourth, we did not analyze variant strain sequencing of individual infections or immune responses, such as antibody titers. Finally, due to the low coverage rate of the bivalent vaccine than expected

https://doi.org/10.3346/jkms.2024.39.e15

(ranging from 6.6 to 6.8% for each bivalent vaccine), a larger target sample size would have been required for the study. However, because we matched case and control groups during the study process, the detection power for VE would be higher than originally anticipated.

In conclusion, vaccination with bivalent booster mRNA vaccine containing the BA.4/BA.5 omicron subvariant strains could effectively protect against COVID-19, particularly in the adult population ≥ 65 years age and the individuals with underlying medical conditions. The use of circulating strain-targeted booster vaccines should be encouraged, especially within these vulnerable groups.

SUPPLEMENTARY MATERIALS

Supplementary Table 1

Comparison of covariates and characteristics between case and control groups within subgroup of ≥ 65 years age group

Supplementary Table 2

Comparison of covariates and characteristics between case and control groups within subgroup of ≥ 1 underlying medical condition

Supplementary Table 3

Vaccine effectiveness of bivalent mRNA booster vaccination against symptomatic COVID-19 calculated by subgroups

Supplementary Table 4

Vaccine effectiveness of bivalent mRNA booster vaccination against COVID-19 associated hospitalization calculated by subgroups

REFERENCES

1. 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. PUBMED | CROSSREF
2. 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. PUBMED | CROSSREF
3. Feikin DR, Higdon MM, Abu-Raddad LJ, Andrews N, Araos R, Goldberg Y, et al. Duration of effectiveness of vaccines against SARS-CoV-2 infection and COVID-19 disease: results of a systematic review and meta-regression. *Lancet* 2022;399(10328):924-44. PUBMED | CROSSREF
4. World Health Organization. Classification of Omicron (B.1.1.529): SARS-CoV-2 variant of concern. https://www.who.int/news/item/26-11-2021-classification-of-omicron-(b.1.1.529)-sars-cov-2-variant-of-concern. Updated 2021. Accessed August 30, 2023.
5. Ai J, Zhang H, Zhang Y, Lin K, Zhang Y, Wu J, et al. Omicron variant showed lower neutralizing sensitivity than other SARS-CoV-2 variants to immune sera elicited by vaccines after boost. *Emerg Microbes Infect* 2022;11(1):337-43. PUBMED | CROSSREF
6. 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. PUBMED | CROSSREF
7. World Health Organization. Evaluation of COVID-19 vaccine effectiveness: interim guidance, 17 March 2021. https://apps.who.int/iris/handle/10665/340301. Updated 2021. Accessed August 30, 2023.
8. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet* 2007;370(9596):1453-7. PUBMED | CROSSREF

9. Tseng HF, Ackerson BK, Bruxvoort KJ, Sy LS, Tubert JE, Lee GS, et al. Effectiveness of mRNA-1273 vaccination against SARS-CoV-2 Omicron subvariants BA.1, BA.2, BA.2.12.1, BA.4, and BA.5. *Nat Commun* 2023;14(1):189. PUBMED | CROSSREF
10. Tenforde MW, Weber ZA, Natarajan K, Klein NP, Kharbanda AB, Stenehjem E, et al. Early estimates of bivalent mRNA vaccine effectiveness in preventing COVID-19-associated emergency department or urgent care encounters and hospitalizations among immunocompetent adults - vision network, nine states, September–November 2022. *MMWR Morb Mortal Wkly Rep* 2022;71(5152):1616-24. PUBMED | CROSSREF
11. Chalkias S, Harper C, Vrbicky K, Walsh SR, Essink B, Brosz A, et al. A bivalent omicron-containing booster vaccine against COVID-19. *N Engl J Med* 2022;387(14):1279-91. PUBMED | CROSSREF
12. Shrestha NK, Burke PC, Nowacki AS, Simon JF, Hagen A, Gordon SM. Effectiveness of the coronavirus disease 2019 bivalent vaccine. *Open Forum Infect Dis* 2023;10(6):ofad209. PUBMED | CROSSREF
13. Korea Disease Control and Prevention Agency. *Public Health Weekly Report for COVID-19, February 1, 2023.* Cheongju, Korea: Korea Disease Control and Prevention Agency; 2023.
14. Qu P, Evans JP, Faraone JN, Zheng YM, Carlin C, Anghelina M, et al. Enhanced neutralization resistance of SARS-CoV-2 Omicron subvariants BQ.1, BQ.1.1, BA.4.6, BF.7, and BA.2.75.2. *Cell Host Microbe* 2023;31(1):9-17.e3. PUBMED | CROSSREF
15. Cao Y, Jian F, Wang J, Yu Y, Song W, Yisimayi A, et al. Imprinted SARS-CoV-2 humoral immunity induces convergent Omicron RBD evolution. *Nature* 2023;614(7948):521-9. PUBMED | CROSSREF
16. Link-Gelles R, Ciesla AA, Roper LE, Scobie HM, Ali AR, Miller JD, et al. Early estimates of bivalent mRNA booster dose vaccine effectiveness in preventing symptomatic SARS-CoV-2 infection attributable to Omicron BA.5- and XBB/XBB.1.5-related sublineages among immunocompetent adults - increasing community access to testing program, United States, December 2022–January 2023. *MMWR Morb Mortal Wkly Rep* 2023;72(5):119-24. PUBMED | CROSSREF
17. Link-Gelles R, Weber ZA, Reese SE, Payne AB, Gaglani M, Adams K, et al. Estimates of bivalent mRNA vaccine durability in preventing COVID-19-associated hospitalization and critical illness among adults with and without immunocompromising conditions - vision network, September 2022–April 2023. *MMWR Morb Mortal Wkly Rep* 2023;72(21):579-88. PUBMED | CROSSREF
18. Xia H, Zou J, Kurhade C, Cai H, Yang Q, Cutler M, et al. Neutralization and durability of 2 or 3 doses of the BNT162b2 vaccine against Omicron SARS-CoV-2. *Cell Host Microbe* 2022;30(4):485-488.e3. PUBMED | CROSSREF
19. Kurhade C, Zou J, Xia H, Liu M, Chang HC, Ren P, et al. Low neutralization of SARS-CoV-2 Omicron BA.2.75.2, BQ.1.1 and XBB.1 by parental mRNA vaccine or a BA.5 bivalent booster. *Nat Med* 2023;29(2):344-7. PUBMED | CROSSREF
20. Fabiani M, Mateo-Urdiales A, Sacco C, Fotakis EA, Rota MC, Petrone D, et al. Protection against severe COVID-19 after second booster dose of adapted bivalent (original/Omicron BA.4-5) mRNA vaccine in persons ≥60 years, by time since infection, Italy, 12 September to 11 December 2022. *Euro Surveill* 2023;28(8):2300105. PUBMED | CROSSREF
21. Kirsebom FCM, Andrews N, Stowe J, Ramsay M, Lopez Bernal J. Duration of protection of ancestral-strain monovalent vaccines and effectiveness of bivalent BA.1 boosters against COVID-19 hospitalisation in England: a test-negative case-control study. *Lancet Infect Dis* 2023;23(11):1235-43. PUBMED | CROSSREF