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Estimates of vaccine effectiveness of the updated monovalent XBB.1.5 COVID-19 vaccine against symptomatic SARS-CoV-2 infection, hospitalization, and receipt of oxygen therapy in South Korea - October 26 to December 31, 2023

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ABSTRACT

Objectives: We evaluated the vaccine effectiveness of monovalent XBB.1.5 vaccine against symptomatic COVID-19 infection, hospitalization, and the need for oxygen therapy in South Korea.
Design: This study employed a test-negative case-control design. COVID-19 test results in symptomatic subjects from six university hospitals across South Korea were collected (October 26–December 31, 2023). The adjusted absolute and relative vaccine effectiveness were assessed.
Results: In total, 5516 subjects were enrolled: 4,824 were unvaccinated with XBB.1.5, and 692 were vaccinated with XBB.1.5 COVID-19 mRNA vaccines. The absolute vaccine effectiveness when comparing the odds between XBB.1.5 vaccination and no vaccination against symptomatic COVID-19 infection, hospitalization, and oxygen therapy was 65.2% (95% CI, 36.1-81.0), 77.3% (95% CI, 51.1-89.5), and 85.3% (95% CI, 57.8-94.9), respectively. The relative vaccine effectiveness when comparing the odds between XBB.1.5 vaccination and no XBB.1.5 vaccination against symptomatic COVID-19 infection, hospitalization, and oxygen therapy was 57.7% (95% CI, 34.7-72.6), 64.3% (95% CI, 35.9-80.2), and 65.5% (95% CI, 27.0-83.7), respectively.
Conclusion: The short-term effectiveness of the XBB.1.5 vaccine against symptomatic COVID-19 infection, hospitalization, and receipt of oxygen therapy in South Korea was significant. Long-term vaccine effectiveness warrants evaluation, and these assessments should be conducted regularly.

Introduction

As of September 3, 2023, over 690 million confirmed cases of coronavirus disease 2019 (COVID-19) and nearly seven million COVID-19-related deaths were reported globally [1]. During this period, in South Korea, 34 million COVID-19 cases were confirmed,

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resulting in 35,000 COVID-19-related deaths [2]. Following the development of COVID-19 vaccines, vaccination campaigns were launched in various countries, with the aim of preventing symptomatic COVID-19, severe disease, and mortality, and vaccination has contributed to controlling the COVID-19 pandemic and reducing COVID-19-related mortality [3-5].

Given that COVID-19 vaccines targeting variants have been deployed for clinical use based on a confirmation of antibody response levels [6] rather than on a demonstration of efficacy via well-designed clinical trials, leveraging real-world data to ascertain vaccine effectiveness (VE) is crucial. Therefore, test-negative designs are frequently used to assess COVID-19 VE [7,8]. For example, the US Centers for Disease Control and Prevention (CDC) has been using test-negative design networks to evaluate COVID-19 vaccine effectiveness since 2021 and continues to report the findings [9-11]. While the Korea Disease Control and Prevention Agency (KDCA) regularly analyzes vaccine effectiveness, it has not yet established a system to analyze it in real time using a test-negative design.

In 2023, the XBB.1.5 variant and its sub-lineages became dominant in numerous countries, including South Korea [2,12,13]. Monovalent vaccines targeting the XBB.1.5 antigen were developed by Pfizer and Moderna [14], and vaccination with the XBB.1.5 vaccine commenced in South Korea on October 19, 2023. While studies to evaluate the VE of the XBB.1.5 vaccine have been conducted in several countries [11,15-17], variations in dominant lineages occur by country and over time, necessitating further studies. Therefore, the aim of this study was to assess the effectiveness of the XBB.1.5 vaccine in South Korea. The findings of this study will provide crucial data to inform public health strategies and vaccination policies, aiming to better combat the evolving pandemic in the country.

Methods

Study design

This study was performed using a test-negative case-control design, and data were retrospectively collected from October 26, 2023 to December 31, 2023. The following six university hospitals located in various regions in South Korea participated in the study: Severance Hospital (Seoul), Kyungpook National University Hospital (North Gyeongsang), Chonnam National University Hospital (Gwangju), Wonju Severance Christian Hospital (Wonju, Gangwon), Inha University Hospital (Incheon), and Chungbuk National University Hospital (North Chungcheong). Subjects who underwent diagnostic tests for COVID-19 in the emergency department, outpatient clinics, general wards, and intensive care units of each hospital were included in the study if they presented with symptoms indicative of COVID-19 (fever, cough, sputum, dyspnea, chills, myalgia, headache, sore throat, or loss of smell or taste). Diagnostic tests for COVID-19 included real-time reverse transcription polymerase chain reaction (RT-PCR) and rapid antigen tests conducted in healthcare facilities. Individuals with positive results on a COVID-19 test were considered test-positive cases, whereas those with negative results were considered test-negative controls.

Study population

The inclusion criteria were as follows: 1) adults aged ≥18 years, 2) individuals who underwent PCR testing or rapid antigen testing for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) at the participating healthcare institutions during the study period, and 3) individuals who presented with COVID-19-related symptoms (fever, cough, sputum, dyspnea, chills, myalgia, headache, sore throat, or loss of smell or taste) at the time of testing. In outpatient cases, only tests conducted within 14 days before presentation at the emergency department, outpatient clinics, or screening centers and within 72 hours thereafter were considered. In inpatient cases, only tests conducted within 14 days before admission and within 72 hours thereafter were considered. In intensive care unit cases, only tests conducted within 14 days before admission and within 72 hours thereafter were considered.

The exclusion criteria were as follows: 1) tests conducted for admission screening, 2) tests conducted for caregivers or healthcare workers, or 3) subjects admitted via the emergency department for surgery (oral and maxillofacial surgery, urology, plastic surgery, neurosurgery, ophthalmology, general surgery, otolaryngology, orthopedic surgery, or thoracic surgery).

In cases where multiple tests were conducted for the same subject during the study period, only one test result per subject was retained in accordance with the following criteria: 1) if a "positive" test result was obtained, the earliest positive test was included in the analysis, and the remaining tests were excluded; and 2) if all test results were "negative," the latest test conducted was included in the analysis, and the rest were excluded.

Data collection

Case report forms were created to document information regarding demographics, comorbidities, symptoms, the date of COVID-19 diagnostic testing, and the results of each subject based on hospital medical records. Information regarding hospitalization, oxygen administration, admission to the intensive care unit, and mortality among patients diagnosed with COVID-19 was collected. Each subject's COVID-19 diagnosis- and vaccination-related information (date of vaccination, vaccine type) was obtained from the KDCA data.

A system was constructed to integrate hospital data with KDCA data. For each subject in the extracted dataset from each medical institution, the name, sex, and date of birth were converted into hash values to combine the COVID-19 vaccination information from the KDCA with the COVID-19 confirmation information. Subjects with duplicate hash values (same name, sex, and date of birth) or mismatches (mostly foreigners) were excluded from the analysis because the data could not be combined.

After combining hospital and KDCA data, the following criteria were applied for data processing: 1) individuals with a history of COVID-19 diagnosis within 90 days of undergoing COVID-19 PCR or rapid antigen testing were excluded from the analysis; 2) only COVID-19 vaccination history prior to COVID-19 PCR testing or rapid antigen testing was included in the analysis, excluding vaccinations administered after testing; 3) cases wherein the vaccine type could not be confirmed, such as vaccines administered abroad, were excluded from the analysis; and 4) cases in which COVID-19 PCR or rapid antigen testing was conducted within 7 days of the last vaccine dose were excluded from the analysis.

Definitions

To ensure the consistency of data extraction across hospitals, the definitions of immunocompromised status and underlying comorbidities were established using the Special Cases for Calculation codes (a system designed to lower the cost of the patient's own medical expenses to reduce the financial burden on patients with rare and severe incurable diseases who incur high costs) and International Classification of Diseases, Tenth Revision (ICD-10), codes.

The following conditions were considered indicative of an immunocompromised status: cancer (V027, V193, V081, V082, and

V083) and solid organ transplantation (V005, V013, V015, V085, V087, V088, and V277).

The following comorbidities were considered: chronic lung disease (J44-47) and hematologic malignancy (C81–86, C88, C90–96, D46, D61.0, D61.2, D61.9, D70.0, and D71).

Hospitalization was defined as the admission of a subject to a hospital facility before or after the administration of a diagnostic test for SARS-CoV-2 infection, while oxygen therapy was defined as the requirement for a nasal prong, a high-flow nasal cannula, or ventilator care during hospitalization.

Statistical analysis

The demographic characteristics of the participants are presented using numbers and percentiles for categorical variables and means and standard deviations (SD) for continuous variables.

To evaluate the relative VE, odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using multivariable logistic regression. We compared individuals among both test-positive cases and test-negative controls who received an XBB.1.5 vaccine dose with those who did not, regardless of their history of receiving any monovalent or bivalent COVID-19 vaccine dose. To assess the absolute VE, ORs and 95% CIs were estimated, comparing individuals who had received an XBB.1.5 vaccine dose to those without any history of COVID-19 vaccination. All models were adjusted for age, sex, hospital location, calendar time (in weekly intervals), presentation site, and history of chronic lung disease, hematologic malignancy, and solid organ transplantation. The VE (%) was calculated as $(1 - \text{adjusted OR}) \times 100$.

Further analyses were conducted to estimate the relative and absolute VE against hospitalization or oxygen therapy requirements in COVID-19 patients, using the definitions outlined in the "Definitions" section. Given the potential effects of sex and age, all analyses were stratified by these variables, with age groups defined as 18–64 years and ≥65 years. To better account for the time interval between the vaccination date and COVID-19 test date, we repeated the main analysis, restricting the subjects to those who received the XBB.1.5 vaccine 7-59 days prior.

Sensitivity analyses were conducted to estimate the relative VE by comparing individuals among both the test-positive cases and test-negative controls who had received the XBB.1.5 vaccine dose with those who had not but were previously vaccinated with either a monovalent or bivalent COVID-19 vaccine. Subgroup analyses of relative VE were performed for subgroups with immunocompromised subjects, non-immunocompromised subjects, and COVID-19 testing at the emergency department.

All statistical analyses were performed using SAS software (version 9.4; SAS Institute Inc., Cary, NC, USA).

Results

A total of 5516 individuals from six hospitals were enrolled in this study, with males comprising 55.3% of the population and older subjects aged ≥65 years accounting for 53.0% (Table 1). The number of subjects who did not receive the XBB.1.5 updated COVID-19 vaccine was 4824 (423 tested positive for COVID-19; 4,401 tested negative), while 692 subjects (24 tested positive for COVID-19; 668 tested negative) were vaccinated. Among those vaccinated with the XBB.1.5 vaccine, the median days from XBB.1.5 vaccination to date of the COVID-19 test for all subjects, test-positive cases, and test-negative controls were 33 (IQR 19.5-47), 35.6 (IQR 17-50) and 33 days (IQR 20-47), respectively. The proportion of immunocompromised subjects was 14.5%. The proportion of individuals who had never received a COVID-19 vaccine was 9.3%, while 12.5% had received the XBB.1.5 COVID-19 vaccine during the winter of 2023. Based on the data regarding COVID-19 testing, 87.8% of tests were conducted during emergency room visits. Among the population infected with COVID-19, severe outcomes, such as hospitalization, oxygen therapy administration, and death, occurred in 201, 118, and 18 subjects, respectively.

On comparing the group that received an XBB.1.5 vaccine dose with the group that never received a COVID-19 vaccine, the absolute VE against symptomatic COVID-19 infection was 65.2% (95% CI, 36.1–81.0) in individuals of all ages and 67.2% (95% CI, 34.3-83.6) in those aged ≥65 years (Table 1 and Figure 1). The absolute VE against symptomatic COVID-19 infection was 71.0% (95% CI, 44.6-84.8) in the 7-59 days after the XBB.1.5 vaccine dose group, with a median of 25.5 days from vaccination to COVID-19 test (see Supplementary Fig. 1). On comparing the group that received the XBB.1.5 vaccine during the winter of 2023/2024 with the group that did not (relative VE), the relative VE against symptomatic COVID-19 infection was 57.7% (95% CI, 34.7-72.6) in individuals of all ages and 60.2% (95% CI, 35.6-75.4) in those aged ≥65 years (Fig. 1).

On comparing the group that received the XBB.1.5 vaccine during the winter of 2023/2024 with the group that had a COVID-19 vaccination history but did not receive the vaccine during the winter of 2023/2024, the relative VE against symptomatic COVID-19 infection was 55.6% (95% CI, 31.2-71.3) in individuals of all ages and 57.6% (95% CI, 30.9-74.0) in those aged ≥65 years (see Supplementary Tables 1 and 2).

The absolute VE against hospitalization was 77.3% (95% CI, 51.1-89.5) in individuals of all ages and 72.8% (95% CI, 37.3-88.2) for those aged ≥65 years. The relative VE against hospitalization was 64.3% (95% CI, 35.9-80.2) for all ages and 66.5% (95% CI, 38.1-81.8) for those aged ≥65 years (Table 2). The absolute VE against oxygen therapy requirement was 85.3% (95% CI, 57.8-94.9) for all ages and 78.7% (95% CI, 38.9-92.6) for those aged ≥65 years. The relative VE against oxygen therapy requirement was 65.5% (95% CI, 27.0-83.7) for all ages and 65.7% (95% CI, 27.2-83.8) for those aged ≥65 years.

On comparing the group that received the XBB.1.5 vaccine during the winter of 2023/2024 with the group that had a COVID-19 vaccination history but did not receive the vaccine during the winter of 2023/2024, the relative VE against hospitalization was 61.2% (95% CI, 29.7-78.6) in individuals of all ages and 64.1% (95% CI, 33.2-80.7) in those aged ≥65 years. The relative VE against oxygen therapy requirement was 61.7% (95% CI, 18.2-82.1) in individuals of all ages and 62.2% (95%CI, 18.8-82.4) in those aged ≥65 years (see Supplementary Tables 1 and 2).

Subgroup analyses of relative VE showed comparable patterns for subgroups with immunocompromised subjects, non-immunocompromised subjects, and COVID-19 testing at the emergency department (see Supplementary Table 3).

Discussion

From October 19, 2023, XBB.1.5 updated COVID-19 messenger ribonucleic acid (mRNA) vaccines were offered to individuals of all ages in South Korea, including at-risk groups, such as individuals older than 65 years and those with comorbid conditions. This study corroborates the findings regarding the short-term effectiveness of the XBB.1.5 updated COVID-19 vaccine in preventing infection, hospitalization, and receipt of oxygen therapy. These findings align with those of previous studies on the effectiveness of XBB.1.5 vaccines in other countries [15-17]. We conducted an analysis of the absolute and relative VE according to vaccination history. Estimates for absolute VE were higher than those for relative VE, although the CIs overlapped. Despite this, the effectiveness in preventing hospitalization or receipt of oxygen therapy was >60%.

Table 1
Characteristics of test-positive cases and test-negative controls.

Characteristics	Relative VE		Absolute VE	
	COVID-19 infection (N = 447)	Non-COVID-19 infection (N = 5069)	COVID-19 infection (N = 91)	Non-COVID-19 infection (N = 1115)
Sex [N (%)]				
Male	243 (54.4)	2,805 (55.3)	45 (49.5)	577 (51.8)
Female	204 (45.6)	2,264 (44.7)	46 (50.6)	538 (48.3)
Age, years [N (%)]				
18-64	220 (49.2)	2,373 (46.8)	41 (45.1)	340 (30.5)
≥65	227 (50.8)	2,696 (53.2)	50 (55.0)	775 (69.5)
Vaccine dose received [N (%)]				
Unvaccinated – never or had vaccinated before 23/24 seasons	423 (94.6)	4,401 (86.8)	N/A	N/A
Unvaccinated – never	N/A	N/A	67 (73.6)	447 (40.1)
Vaccinated during 23/24 seasons	24 (5.4)	668 (13.2)	24 (26.4)	668 (59.9)
Interval since the last dose for vaccinated individuals, days [Median (IQR)]				
No updated dose	660.0 (446.0–721.5)	666.0 (456.0–716.0)	N/A	N/A
Received updated dose	36.5 (17.0–50.0)	33.0 (20.0–47.0)	36.5 (17.0–50.0)	33.0 (20.0–47.0)
Hospital locations [N (%)]				
Incheon	123 (27.5)	861 (17.0)	40 (44.0)	303 (27.2)
Gangwon (Wonju)	57 (12.8)	286 (5.6)	12 (13.2)	74 (6.6)
North Gyeongsang	84 (18.8)	892 (17.6)	18 (19.8)	194 (17.4)
North Chungcheong	111 (24.8)	2,041 (40.3)	4 (4.4)	304 (27.3)
Gwangju	42 (9.4)	730 (14.4)	8 (8.8)	184 (16.5)
Seoul	30 (6.7)	259 (5.1)	9 (9.9)	56 (5.0)
Immunocompromised [N (%)]				
Yes	65 (14.5)	731 (14.4)	16 (17.6)	151 (13.5)
No	382 (85.5)	4,338 (85.6)	75 (82.4)	964 (86.5)
Presentation sites [N (%)]				
Outpatient/Triage Room	35 (7.8)	160 (3.2)	7 (7.7)	32 (2.9)
Emergency department	367 (82.1)	4,477 (88.3)	75 (82.4)	996 (89.3)
On admission	45 (10.1)	432 (8.5)	9 (9.9)	87 (7.8)
Underlying diseases, yes [N (%)]				
Chronic lung disease	52 (11.6)	514 (10.1)	12 (13.2)	144 (13.0)
Hematologic malignancy	19 (4.3)	99 (1.9)	3 (3.3)	21 (1.9)
Solid organ transplantation	8 (1.8)	41 (0.8)	5 (5.5)	10 (0.9)
Severe outcomes [N (%)]				
Hospitalization, yes	201 (45.0)	N/A	47 (51.6)	N/A
Oxygen therapy, yes	118 (26.4)	N/A	29 (31.9)	N/A
Death, yes	18 (4.0)	N/A	2 (2.2)	N/A

Abbreviations: VE, vaccine effectiveness; SD, standard deviation; N/A, data not available
Relative VE was estimated by comparing XBB.1.5 vaccine recipients to non-recipients, independent of prior monovalent or bivalent COVID-19 vaccination, among test-positive cases and test-negative controls. Absolute VE was estimated by comparing XBB.1.5 vaccine recipients to individuals with no COVID-19 vaccination history. Death was defined as deceased within 180 days following the last diagnosis.

Table 2
Vaccine effectiveness against hospitalization and receipt of oxygen therapy in patients with COVID-19 stratified by sex and age group.

Characteristics	Against hospitalization		Against requiring oxygen therapy	
	Relative VE, % (95% CI)	Absolute VE, % (95% CI)	Relative VE, % (95% CI)	Absolute VE, % (95% CI)
Total				
Overall	64.3 (35.9–80.2)	77.3 (51.1-89.5)	65.5 (27.0-83.7)	85.3 (57.8-94.9)
Age ≥65 years	66.5 (38.1–81.8)	72.8 (37.3-88.2)	65.7 (27.2-83.8)	78.7 (38.9-92.6)
Male				
Overall	64.0 (23.8–83.0)	77.2 (36.0-91.9)	59.9 (3.9-83.2)	87.6 (52.5-96.7)
Age ≥65 years	69.0 (30.9–86.1)	81.1 (37.9-94.2)	62.2 (9.0-84.3)	84.7 (38.3-96.2)
Female				
Overall	66.7 (13.3–87.2)	74.2 (6.1-92.9)	79.3 (6.2-95.4)	N/A
Age ≥65 years	64.2 (5.6–86.4)	N/A	N/A	N/A

Abbreviations: COVID-19, coronavirus disease; VE, vaccine effectiveness; CI, confidence interval
Relative VE was estimated by comparing XBB.1.5 vaccine recipients to non-recipients, independent of prior monovalent or bivalent COVID-19 vaccination, among test-positive cases and test-negative controls. Absolute VE was estimated by comparing XBB.1.5 vaccine recipients to individuals with no COVID-19 vaccination history. All models were adjusted for age; sex; hospital location; calendar time in weekly intervals; presentation site; and history of pulmonary disease, hematologic malignancy, and solid organ transplantation. N/A referred to the fact that the estimated value and its 95% confidence interval were negative.

These findings suggest that previous vaccinations (original monovalent, BA.1 bivalent, and BA.4/BA.5 bivalent vaccines) still provide some preventive effect against the XBB subvariant, but boosting with the XBB1.5 updated vaccine offers additional benefits. However, the effectiveness in preventing mortality could not be confirmed due to the small number of deaths.

When interpreting the results of this study, it is important to consider the vaccination status and variant trends in South Korea. The KDCA surveyed COVID-19 antibody positivity among 9,798 South Koreans from March 27 to April 15, 2023. The overall antibody positivity rate was 99.2%, with a natural infection antibody positivity rate of 78.6% [18]. As of March 22, 2023, 88.8% of the to-

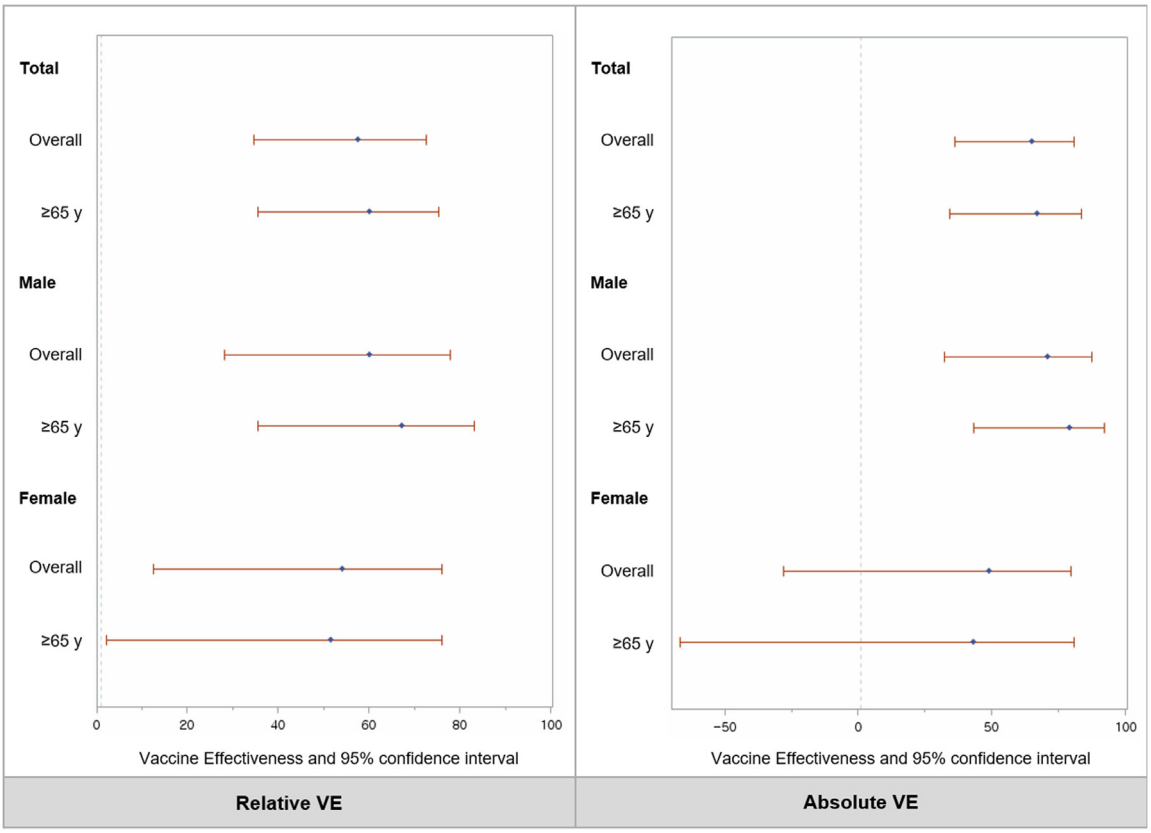

Fig. 1. Vaccine effectiveness against symptomatic COVID-19 infection stratified by sex and age group. *Footnotes*: Relative VE was estimated by comparing XBB.1.5 vaccine recipients to non-recipients, independent of prior monovalent or bivalent COVID-19 vaccination, among test-positive cases and test-negative controls. Absolute VE was estimated by comparing XBB.1.5 vaccine recipients to individuals with no COVID-19 vaccination history. All models were adjusted for age; sex; hospital location; calendar time in weekly intervals; presentation site; and history of pulmonary disease, hematologic malignancy, and solid organ transplantation. *Abbreviations*: COVID-19, coronavirus disease; VE, vaccine effectiveness

tal population had completed the primary vaccination, with 98% of those aged 50–64 years and 96.1% of those aged ≥65 years having completed their primary series. In South Korea, COVID-19 vaccination with the XBB.1.5 updated vaccine began on October 19, 2023, and as of December 31, 2023, the vaccination rate for those aged ≥65 was 40.3% [19]. During the fourth week of December 2023, the most prevalent variant in South Korea was HK.3 at 52.0%, followed by EG.5 at 22.6% and JN.1 at 10.8% [20]. Between October and December 2023, EG.5 and HK.3 were the dominant strains, whereas the prevalence of JN.1 increased from 0.5% in the first week of December to 5.8% in the third week and 10.8% in the fourth week. Considering these factors, the results of this study demonstrate the effectiveness of the XBB.1.5 updated vaccine during the predominant XBB subvariant season in a country with high antibody positivity and past vaccination rates.

Several reports from other countries have demonstrated the short-term effectiveness of the XBB.1.5 updated COVID-19 vaccine. A recent study from the United States reported that the VE of the XBB.1.5 updated vaccine against symptomatic COVID-19 infection was 57% in individuals aged 18-49 years and 46% in those aged ≥50 years [21]. A study from Denmark, which used national health registry data of 1,037,479 people from October 8, 2023 to October 23, 2023, showed that the vaccination was associated with a 76.1% reduced risk of COVID-19 hospitalization [16]. Another study from the Netherlands evaluated the effectiveness of the XBB.1.5 updated vaccine against infections caused by the SARS-CoV-2 Omicron XBB and JN.1 variants from October 2023 to January 2024 [22]. This was a prospective cohort study conducted to estimate the VE of XBB.1.5 vaccination against self-reported SARS-CoV-2 infection between October 9, 2023 and January 9, 2024 among adults aged 18-85 years who had previously received primary vaccination and at least one booster vaccination before October 2, 2023. The researchers determined the variant by sequencing viral genetic material present in positive antigen self-tests. The VE of XBB.1.5 vaccination against self-reported SARS-CoV-2 infection was 41% in 18-59-year-olds and 50% in 60-85-year-olds. The effectiveness seemed slightly lower against BA.2.86 and sub-variant JN.1 infections than against XBB infection. A study from the Netherlands also evaluated the early effectiveness of the XBB.1.5 updated vaccine against hospitalization and admission to the intensive care unit from October 9 to December 5, 2023. In this study, the estimated VE against hospitalization was 70.7% and that against intensive care unit admission was 73.3%. All these studies showed that the VE of the XBB.1.5 updated vaccine against symptomatic COVID-19 infection, hospitalization, and progression to severe disease was significant.

Our study used objective data from medical records and accurate information on each subject's history of COVID-19 diagnosis and vaccination from the KDCA. This reduced the possibility of recall bias, which can occur when subjects are asked to provide information via questionnaires.

The XBB.1.5 vaccine may have been effective in South Korea from late October to late December 2023, as sub-lineages of the XBB family accounted for more than 80% of cases. However, BA.2.86 and JN.1 infections have increased since January 2024; consequently, it is unclear if the vaccine was effective after January

2024. Therefore, it is imperative to implement a systematic approach to assess the ongoing effectiveness of the vaccine.

This study had some limitations. First, the hospitals included in the study employed different criteria for the diagnostic testing of subjects suspected of having COVID-19, which resulted in variations in the number of tests performed at each hospital. Additionally, given that the hospitals included in the study were tertiary hospitals, it can be reasonably assumed that subjects tested for COVID-19 at these hospitals were more likely to have underlying medical conditions than were healthy individuals. When considering the hospitalization of subjects with COVID-19, we included all hospitalizations that occurred after a COVID-19 diagnostic test. Therefore, hospitalizations for reasons other than COVID-19 may have been included. To exclude these cases as much as possible, we included only those with symptoms consistent with COVID-19 and excluded hospitalizations for surgical purposes. Furthermore, combining hospital data with KDCA data through hash value matching led to the exclusion of unmatched data due to duplicate hash values or missing KDCA data. This process resulted in the loss of data. Finally, we were unable to confirm the occurrence of hospitalization or receipt of oxygen therapy if a COVID-19 diagnostic test was performed at a participating hospital, and the subject was subsequently admitted to another hospital.

Nevertheless, to our knowledge, this study is the first to confirm the effectiveness of the updated XBB.1.5 COVID-19 vaccine in South Korea. It also establishes a system for the periodic evaluation of vaccine effectiveness. Furthermore, the data generated can serve as a reference for future national vaccination policies.

In conclusion, this study reveals significant short-term effectiveness of the XBB.1.5 updated COVID-19 vaccine against symptomatic COVID-19 infection, hospitalization, and receipt of oxygen therapy in South Korea. The long-term VE of the XBB.1.5 updated vaccine should be evaluated in future studies, and regular evaluations of COVID-19 VE are necessary.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Ethical approval

The study was approved by the Institutional Review Board (IRB) of the Severance Hospital (IRB authorization number: 4-2023-0395) and was conducted in accordance with the tenets of the Declaration of Helsinki. As the study was retrospective in nature and the study participants were anonymized, the requirement for written consent was waived.

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Author contributions

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2024.107249.

References

[1] World Health Organization *data.who.int, WHO Coronavirus (COVID-19) dashboard >Data [Dashboard]*; 2023. https://data.who.int/dashboards/covid19/data.
[2] Korean Disease Control and Prevention Agency. Coronavirus disease-19 press release. Available from: https://dportal.kdca.go.kr/pot/bbs/BD_selectBbs.do?q_bbsSn=1008&q_bbsDocNo=20230906736900714&q_clsfNo=0. Accessed June 14, 2024.
[3] Watson OJ, Barnsley G, Toor J, Hogan AB, Winskill P, Ghani AC. Global impact of the first year of COVID-19 vaccination: a mathematical modelling study. *Lancet Infect Dis* 2022;**22**(9):1293–302. doi:10.1016/S1473-3099(22)00320-6.
[4] Sohn Y, Choi HK, Yun J, Kim EH, Kim YK. Clinical characteristics and risk of hypoxemia development in women infected with SARS-CoV-2 during pregnancy. *Yonsei Med J* 2024;**65**(1):27–33. doi:10.3349/ymj.2023.0270.
[5] Lee H, Kim S, Jeong M, Choi E, Ahn H, Lee J. Mathematical modeling of COVID-19 transmission and intervention in South Korea: a review of literature. *Yonsei Med J* 2023;**64**(1):1–10. doi:10.3349/ymj.2022.0471.
[6] 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. doi:10.1056/NEJMoa2208343.
[7] Dean NE, Hogan JW, Schnitzer ME. COVID-19 vaccine effectiveness and the test-negative design. *N Engl J Med* 2021;**385**(15):1431–3. doi:10.1056/NEJMe2113151.
[8] Evans SJW, Jewell NP. Vaccine effectiveness studies in the field. *N Engl J Med* 2021;**385**(7):650–1. doi:10.1056/NEJMe2110605.
[9] Grannis SJ, Rowley EA, Ong TC, Stenehjem E, Klein NP, DeSilva MB, et al. Interim estimates of COVID-19 vaccine effectiveness against COVID-19-associated emergency department or urgent care clinic encounters and hospitalizations among adults during SARS-CoV-2 B.1.617.2 (Delta) variant predominance - Nine States, June-August 2021. *MMWR Morb Mortal Wkly Rep* 2021;**70**(37):1291–3. doi:10.15585/mmwr.mm7037e2.
[10] Surie D, Bonnell L, Adams K, Gaglani M, Ginde AA, Douin DJ, et al. Effectiveness of monovalent mRNA vaccines against COVID-19-associated hospitalization among immunocompetent adults during BA.1/BA.2 and BA.4/BA.5 predominant periods of SARS-CoV-2 Omicron Variant in the United States - IVY Network, 18 States, December 26, 2021-August 31, 2022. *MMWR Morb Mortal Wkly Rep* 2022;**71**(42):1327–34. doi:10.15585/mmwr.mm7142a3.
[11] Link-Gelles R, Rowley EAK, DeSilva MB, Dascomb K, Irving SA, Klein NP, et al. Interim Effectiveness of Updated 2023-2024 (Monovalent XBB.1.5) COVID-19 Vaccines Against COVID-19-Associated Hospitalization Among Adults Aged ≥18 Years with Immunocompromising Conditions - VISION Network, September 2023-February 2024. *MMWR Morb Mortal Wkly Rep* 2024;**73**(12):271–6. doi:10.15585/mmwr.mm7312a5.
[12] World Health Organization *XBB.1.5 Updated Risk Assessment*; 2023. https://www.who.int/docs/default-source/coronaviruse/20230620xbb.1.5.pdf?sfvrsn=fff6f686_3. Accessed May 25, 2024.
[13] Shin DH, Smith DM, Choi JY. SARS-CoV-2 Omicron variant of concern: everything you wanted to know about omicron but were afraid to ask. *Yonsei Med J* 2022;**63**(11):977–83. doi:10.3349/ymj.2022.0383.
[14] Rubin R. This fall's COVID-19 vaccines will target Omicron XBB subvariants, but who needs them remains to be seen. *JAMA* 2023;**330**(4):299–301.
[15] van Werkhoven CH, Valk AW, Smagge B, de Melker HE, Knol MJ, Hahne SJ, et al. Early COVID-19 vaccine effectiveness of XBB.1.5 vaccine against hospitalisation and admission to intensive care, the Netherlands, 9 October to 5 December 2023. *Euro Surveill* 2024;**29**(1):2300703. doi:10.2807/1560-7917.ES.2024.29.1.2300703.
[16] Hansen CH, Moustsen-Helms IR, Rasmussen M, Soborg B, Ullum H, Valentiner-Branth P. Short-term effectiveness of the XBB.1.5 updated COVID-19 vaccine against hospitalisation in Denmark: a national cohort study. *Lancet Infect Dis* 2024;**24**(2):e73–4. doi:10.1016/S1473-3099(23)00746-6.
[17] Monge S, Humphreys J, Nicolay N, Braeye T, Van Evercooren I, Holm Hansen C, et al. Effectiveness of XBB.1.5 Monovalent COVID-19 Vaccines During a Period of XBB.1.5 Dominance in EU/EEA Countries, October to November 2023: A VEBIS-EHR Network Study. *Influenza Other Respir Viruses* 2024;**18**(4):e13292. doi:10.1111/irv.13292.
[18] Korean Disease Control and Prevention Agency. Press reference material. Available from: https://dportal.kdca.go.kr/pot/bbs/BD_selectBbs.do?q_bbsSn=1008&q_bbsDocNo=20230906736900714&q_clsfNo=0. Accessed August 25, 2024.

[19] Korean Disease Control and Prevention Agency. Press reference material. Available from: https://www.kdca.go.kr/board/board.es?mid=a20501010000&bid=0015&list_no=724226&cg_code=&act=view&nPage=1&newsField=. Accessed August 25, 2024.
[20] Korean Disease Control and Prevention Agency. Press reference material. Available from: https://dportal.kdca.go.kr/pot/bbs/BD_selectBbs.do?q_bbsSn=1010&q_bbsDocNo=20240104154429126&q_clsfNo=2. Accessed August 25, 2024.
[21] Link-Gelles R, Ciesla AA, Mak J, Miller JD, Silk BJ, Lambrou AS, et al. Early estimates of updated 2023-2024 (Monovalent XBB.1.5) COVID-19 vaccine effectiveness against symptomatic SARS-CoV-2 infection attributable to co-circulating omicron variants among immunocompetent adults - increasing community access to testing program, United States, September 2023-January 2024. *Mmwr-Morbidity Mortality Weekly Rep* 2024;**73**(4):77–83.
[22] Huiberts AJ, Hoeve CE, de Gier B, Cremer J, van der Veer B, de Melker HE, et al. Effectiveness of Omicron XBB.1.5 vaccine against infection with SARS-CoV-2 Omicron XBB and JN.1 variants, prospective cohort study, the Netherlands, October 2023 to January 2024. *Euro Surveill* 2024;**29**(10):2400109. doi:10.2807/1560-7917.ES.2024.29.10.2400109.