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Active Surveillance for Safety Monitoring of XBB.1.5-Containing COVID-19 mRNA Vaccines in Korea

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ABSTRACT

The emergence of the omicron variant and its sub-lineages has necessitated vaccine updates for coronavirus disease 2019. In September 2023, the U.S. Food and Drug Administration approved an updated BNT162b2 vaccine targeting the omicron XBB.1.5 variant, which was initiated in Korea in October 2024. This study demonstrates the adverse events reported through active nationwide surveillance after XBB.1.5 vaccination in Korea. Since October 19, 2023, the Korea Disease Control and Prevention Agency has conducted daily Short Message Service surveys to collect data on health issues, fever, vaccination site reactions, systemic symptoms, impact on daily life, and healthcare visits. Among 20,180 respondents, 27.9% reported health issues. Adverse reactions peaked on day 1 (28.7%), including pain at the vaccination site, muscle pain, fatigue, and fever. These findings elucidate the short-term safety of the XBB.1.5 vaccine and support its co-administration with the influenza vaccine, reducing vaccine hesitancy and achieving herd immunity.

Keywords: COVID-19; Korea Disease Control and Prevention Agency; Omicron; Safety; Vaccination; XBB.1.5 Variant

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection offers natural immunity against reinfection; however, this immunity wanes gradually, necessitating vaccines against coronavirus disease 2019 (COVID-19) variants.[1] Initially, the development of COVID-19 vaccines targeting the Wuhan-Hu-1 strain was highly effective.[2] However, since late 2021, the omicron variant and its sublineages have gained dominance.[3,4] Additionally, the original vaccines offer reduced protection, with the potential evasion of immunity from prior infections or vaccinations.[5] The emerging novel SARS-CoV-2 variants have become more pronounced.[6] Thus, in September 2023, the U.S. Food and Drug Administration authorized an updated monovalent BNT162b2 vaccine encoding the viral spike protein of the SARS-CoV-2 omicron XBB.1.5 variant.[7] In Korea, on October 19, 2023, the XBB.1.5 vaccine

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Disclosure

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Lee H, Park H. Formal analysis: Kim Y, Kim CH. Funding acquisition: Park H. Investigation: Park H. Methodology: Lee H. Software: Park H. Validation: Lee H. Visualization: Jun S, Lee H. Writing - original draft: Park B, Lee HA. Writing - review & editing: Kwon SL, Heo Y.

was initiated for individuals aged ≥ 65 years and those aged from 12 to 64 years who were immunocompromised or members of facilities vulnerable to infection. Additionally, on November 1, 2023, people aged ≥ 12 years were deemed eligible for this vaccine.

Researchers have evaluated the safety and immunogenicity of boosters, including XBB.1.5, for COVID-19 vaccinations scheduled for 2023 to 2024. Moreover, clinical trials have confirmed the efficacy and safety of the XBB.1.5-adapted mRNA vaccine.[2,8] Post-marketing surveillance to detect unreported adverse events has helped reduce public hesitation.[9-11]

Therefore, we aimed to analyze the results of active vaccine surveillance. Moreover, we intended to report the prevalence and short-term characteristics of adverse events related to the XBB.1.5 mRNA vaccine and its co-administration with the influenza vaccine in Korea. Using the information registered in the COVID-19 Vaccination System, the Korea Disease Control and Prevention Agency sent a daily Short Message Service (SMS) comprising a survey URL for 8 days, beginning from the day of vaccination to 7 days after vaccination. People who received COVID-19 vaccines from October 19, 2023, and consented to the surveillance immediately after vaccination participated in this survey. The goal was to survey 10,000 recipients each for the Pfizer and Moderna vaccines. People who responded to the SMS on at least one of the 8 days were included in the analysis. Text response data were linked with data stored in the Immunization Registry Information System on the vaccination dates, including the co-administration of influenza vaccine, age, sex, and type of vaccine for each respondent.[12] A "yes" response to the question "Were there any new health issues after vaccination?" indicated an adverse event. The respondents were inquired about local symptoms at the vaccination site or systemic symptoms after vaccination. They were instructed to select their response from a list of solicited reactions, with the provision for multiple responses. They described any other unsolicited reactions in free-text format.

A total of 20,180 respondents were analyzed. Of them, the majority were men (71.1%), and 81.8% were aged ≥ 65 years. Approximately 38.6% of the respondents concurrently received the quadrivalent influenza vaccine. The proportion of males was higher among individuals who received the COVID-19 vaccine and the influenza vaccine simultaneously compared to those who received the COVID-19 vaccine alone (74.6% vs. 68.8%). The average age was 67.9 and 68.3 years, respectively. Approximately 18.9% of respondents responded to all eight instances from days 0 to 7 after vaccination, followed by 15.5% and 14.8% who responded one and seven times, respectively. **Table 1** summarizes the characteristics of the study population.

Table 2 summarizes the responses regarding adverse events, disruption of daily life, and medical visits after vaccination. Approximately 27.9% of respondents experienced adverse events at least once after vaccination regardless of concurrently receiving the influenza vaccine. The reasons for visiting medical institutions are listed in the following order: myalgia, pain, fever, and headache. Additionally, 9.3% of respondents reported that the adverse events disrupted their daily lives. Furthermore, 1.4% of respondents cited health issues after vaccination as their reason for visiting.

Fig. 1A displays the distribution of adverse events based on the number of text responses submitted during days 0 to 7 after vaccination. The reporting rate of adverse events was 9.5% for respondents with only one response. The total rate tended to increase with the number of responses, with a 34.6% rate for respondents with six responses. The rate of adverse events was higher in respondents with two or more responses than in those with one response.

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Table 1. Characteristics of study participants

Characteristics	Total	No adverse event	Adverse event[a]	*P* value[b]
Total	20,180	14,555	5,625	
Sex				< 0.000
Male	14,340 (71.1)	10,675 (73.3)	3,665 (65.2)	
Female	5,840 (28.9)	3,880 (26.7)	1,960 (34.8)	
Age, yr				
Mean ± SD	68.1 ± 11.8	69.0 ± 11.1	66.0 ± 13.1	< 0.000
< 19	31 (0.1)	21 (0.2)	10 (0.1)	< 0.000
19–64	3,650 (18.1)	2,330 (16.0)	1,320 (23.5)	
≥ 65	16,499 (81.8)	12,204 (83.8)	4,295 (76.4)	
Simultaneous administration of influenza vaccine				0.924
Yes	7,783 (38.6)	5,617 (38.6)	2,166 (38.5)	
No	12,397 (61.4)	8,938 (61.4)	3,459 (61.5)	
No. of survey response				< 0.000
1	3,122 (15.5)	2,826 (19.4)	296 (5.3)	
2	2,328 (11.5)	1,758 (12.1)	570 (10.1)	
3	2,050 (10.2)	1,424 (9.8)	626 (11.1)	
4	1,841 (9.1)	1,219 (8.4)	622 (11.1)	
5	1,847 (9.2)	1,233 (8.5)	614 (10.9)	
6	2,188 (10.8)	1,432 (9.8)	756 (13.4)	
7	2,985 (14.8)	1,998 (13.7)	987 (17.5)	
8	3,819 (18.9)	2,665 (18.3)	1,154 (20.5)	

Values are presented as number (%) not otherwise specified.
[a]Adverse events reported at least once within 0–7 days after vaccination.
[b]Differences in mean age between individuals who experienced adverse events and those who did not were assessed using Wilcoxon Rank-Sum Test, and differences in other variables were tested using χ^2 tests.

Table 2. Presence of adverse events following COVID-19 vaccination, and subsequent interferes with daily life and healthcare facility visits

Variables	Total (N = 20,180)	SV (n = 7,783)	No-SV (n = 12,397)	*P* value
Adverse event	5,625 (27.9)	2,166 (27.8)	3,459 (27.9)	0.924
Interferes with daily life	1,883 (9.3)	756 (9.7)	1,127 (9.1)	0.146
Healthcare facility visits	283 (1.4)	92 (1.2)	191 (1.5)	0.041

Values are presented as number (%).
COVID-19 = coronavirus disease 2019, SV = simultaneous administration of influenza vaccine.

Fig. 1B illustrates the daily rate of adverse events after vaccination. Approximately 28.7% of adverse events occurred on day 1 after vaccination, followed by 13.0% and 8.1% on days 2 and 3, respectively. Similar trends were observed for respondents who simultaneously received the influenza vaccine and those who did not. The reporting rate of adverse events was significantly higher on days 0 and 5 for respondents who received the COVID-19 vaccine alone, without significant differences on other days.

Fig. 2A illustrates the symptoms reported at the vaccination site. Pain was most reported, with the highest reports on day 1 after vaccination. **Fig. 2B and C** illustrate the distribution of vaccination site symptoms in respondents who received the influenza vaccine concurrently and those who did not. All respondents exhibited similar symptom patterns. **Fig. 3A** illustrates the daily incidence of systemic symptoms after vaccination, with muscle pain, fatigue, and fever being most reported, particularly on day 1 after vaccination. **Fig. 3B and C** illustrate the distribution of systemic symptoms in respondents who received the influenza vaccine concurrently and those who did not. All respondents exhibited similar symptom patterns.

Our findings elucidate the short-term safety of the XBB.1.5 vaccine, supported by a Danish post-marketing study that reported no increased risk of 28 adverse events.[13] We investigated the impact of co-administering influenza and COVID-19 vaccines on the adverse reaction

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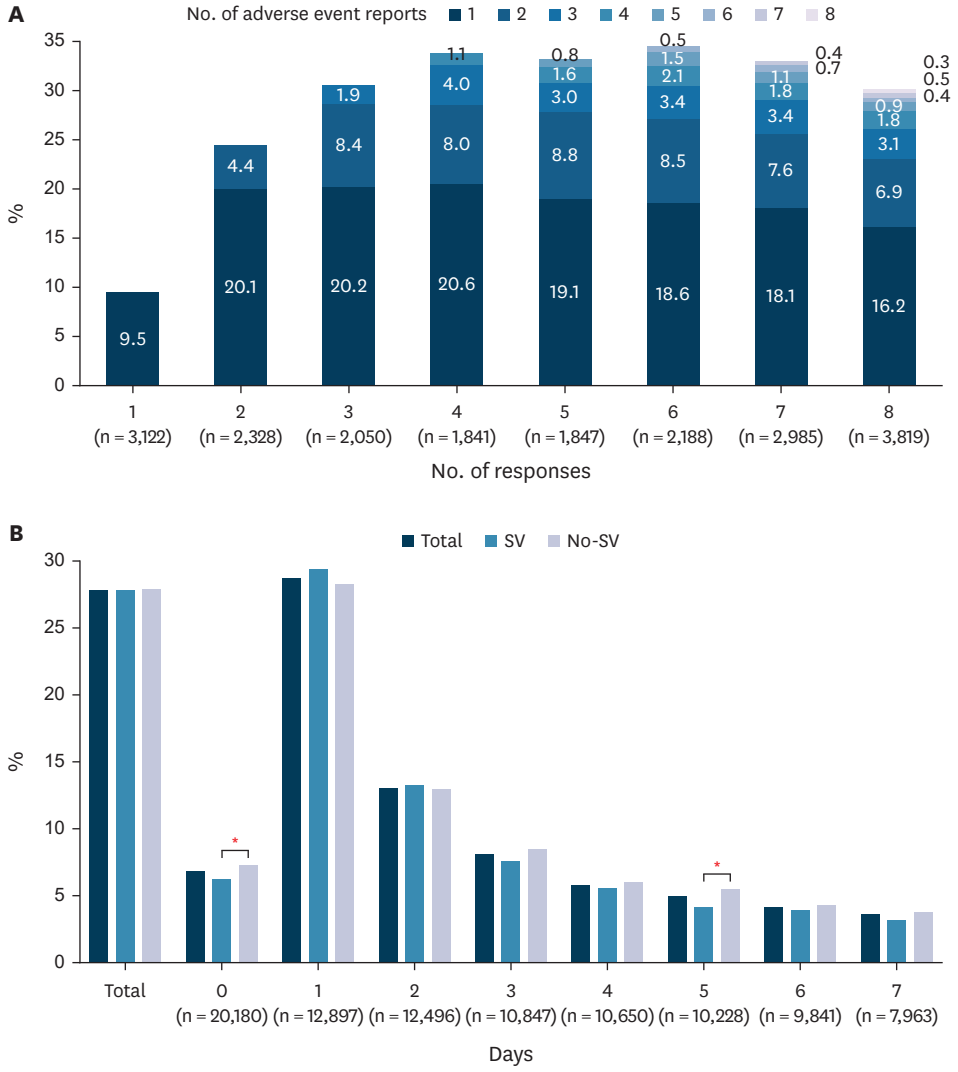

Fig. 1. Adverse event reports. (**A**) The number of responses and adverse event reports, (**B**) Proportion of adverse event reports by date following vaccination. Differences in adverse event reports between SV and No-SV individuals were calculated using a χ^2 test, with days with significant differences marked with *.
SV = simultaneous administration of influenza vaccine.

rates. Coadministration is crucial to address seasonal influenza, respiratory syncytial viruses, and COVID-19.[14] The World Health Organization and more than 20 European countries recommended co-administration during the influenza season from 2021 to 2022. The French health authorities followed suit from 2022 to 2023.[15] Previous reviews have confirmed its safety and effectiveness against immune responses.[15,16] We observed no significant increase in adverse reactions with co-administration, suggesting the benefits of increased vaccination rates and simplified schedules for public health strategies. However, addressing vaccine hesitancy and ensuring safety across populations warrant continued research and communication.

Our study had some limitations. First, we relied on SMS questionnaire responses, raising concerns regarding the representativeness of the sample. Respondents who experienced health issues on the day of vaccination were more likely to respond. Moreover, people who

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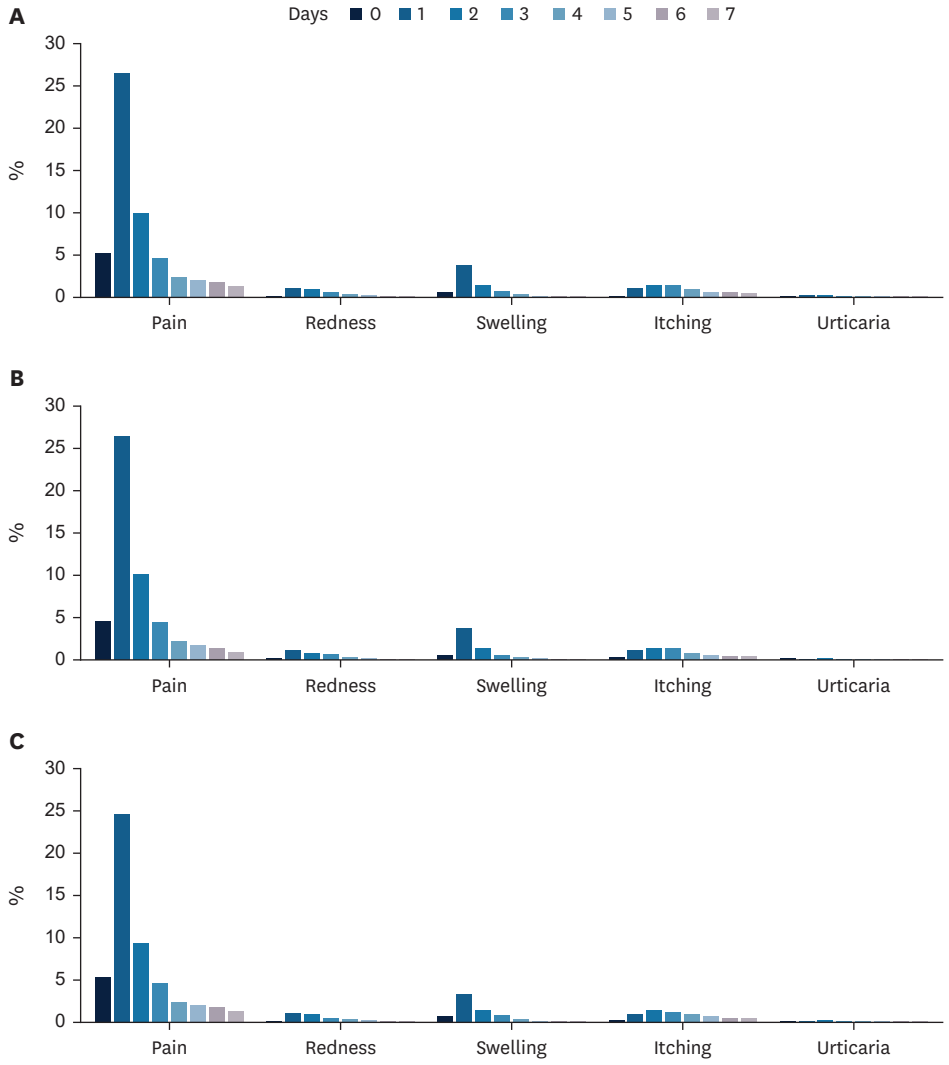

Fig. 2. Reporting of injection site symptoms by simultaneous vaccination status. (**A**) Total, (**B**) SV, and (**C**) No-SV.
SV = simultaneous administration of influenza vaccine.

have experienced adverse effects from previous vaccinations may have been missing from the population.[17] Additionally, non-respondents may have experienced serious health issues after vaccination, hindering their participation and making it difficult to assess their health status. Second, the survey responses were self-reported. Therefore, they may reflect subjective judgments, and the symptoms may not necessarily be related to the vaccine. Finally, we did not collect information on the underlying medical history of the respondents.

Nevertheless, our study provides essential information on the post-launch safety of the XBB.1.5 mRNA vaccine. Real-world data on this post-launch vaccine are scarce; we comprehensively investigated the possible adverse reactions reported immediately after vaccination. Moreover, we assessed the severity of the health issues by examining the health problems reported after vaccination, their impact on daily life, and visits to medical facilities. This approach lays the groundwork for a better understanding of the frequency and impact of vaccine-related adverse reactions.[18]

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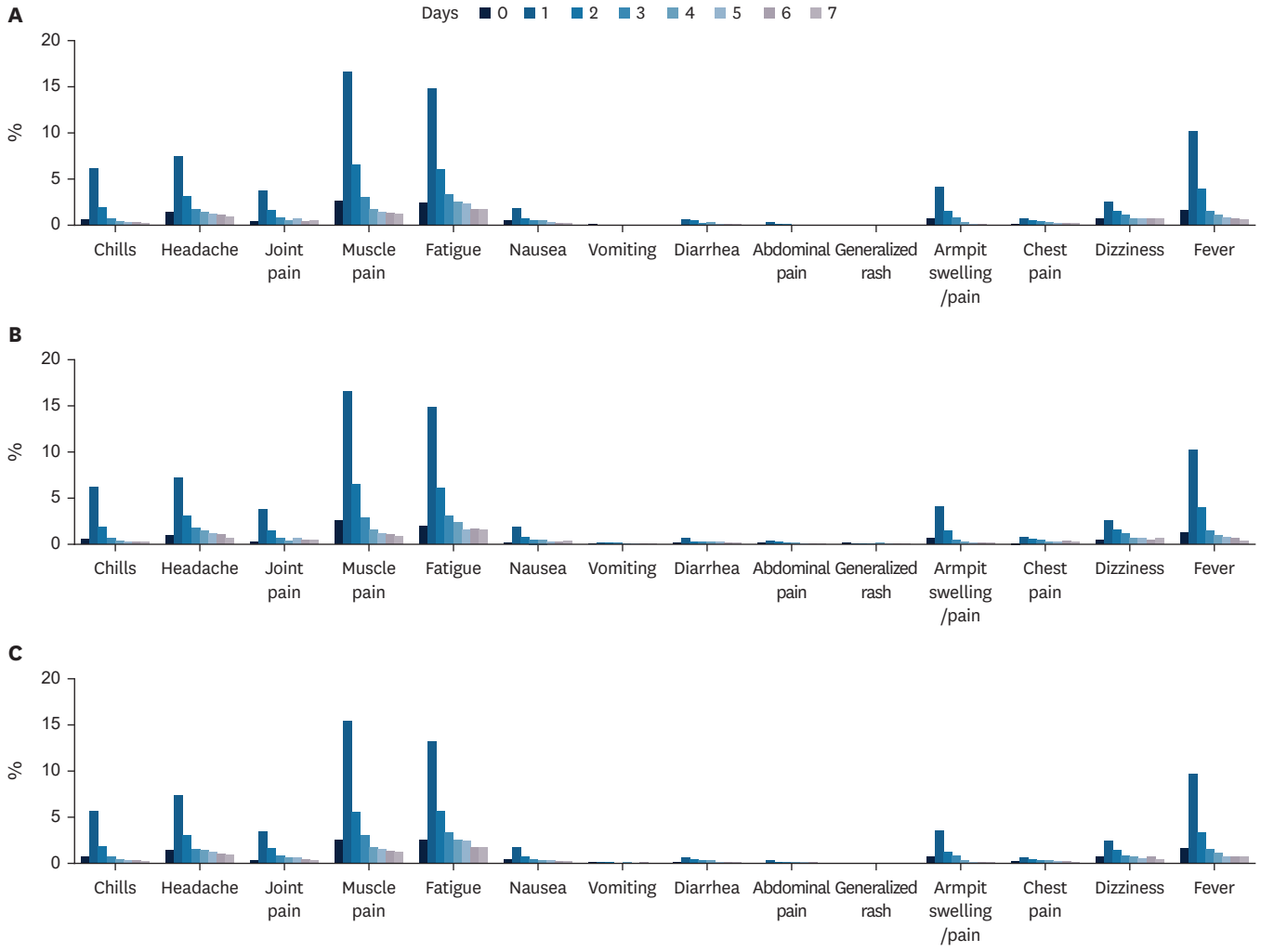

Fig. 3. Reporting of systemic symptoms by simultaneous vaccination status. (**A**) Total, (**B**) SV, and (**C**) No-SV.
SV = simultaneous administration of influenza vaccine.

In conclusion, our study highlights the short-term safety of the XBB.1.5-adapted COVID-19 mRNA vaccine and supports its administration. Additionally, concurrent influenza vaccination does not affect the safety profile, supporting its co-administration with COVID-19 vaccines.

Ethics statement

All respondents provided informed consent for inclusion in the study database. The study protocol was reviewed and approved by the Institutional Review Board of Ewha Woman's University (ewha-202401-0011-01).

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