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# Reported Adverse Events and Associated Factors in Korean Coronavirus Disease 2019 Vaccinations

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## ABSTRACT

**Background:** Despite their effectiveness, coronavirus disease 2019 (COVID-19) vaccines have been associated with adverse effects, underscoring the importance of continuous surveillance to ensure vaccine safety and effective management of public health. Herein, the characteristics and risk factors of vaccine-related adverse events (AEs) were identified to gain an in-depth understanding of vaccine safety by investigating the impact of the vaccination dose on changes in post-vaccination AEs.
**Methods:** Herein, a linked database of COVID-19 vaccination records from the Korea Disease Control and Prevention Agency, AE reports from the COVID-19 Vaccination Management System, and healthcare claims from the National Health Insurance Service, targeting ≥ 5-year-old individuals, was utilized (study duration = February 26, 2021, to January 31, 2023). The frequency and severity of reported post-vaccination AEs were evaluated. Furthermore, we specifically explored AEs in relation to the cumulative dosage of vaccines administered while evaluating associated risk factors.
**Results:** During the observation period, 42,804,523 individuals completed the COVID-19 vaccination series, with 365,900 reporting AEs, with headache, muscle pain, and fever being the most frequently reported. Notably, the AE reports were approximately twice as high for women than for men, which was further exacerbated following both doses. Analysis by age group revealed that AE reports were lower among children, adolescents, and older adults than in the middle-aged cohort (age = 50–64 years), with higher reports observed for 18–49-year-old individuals. Additionally, a higher risk of reporting was identified among individuals with lower socioeconomic status compared with those of middle socioeconomic status. Excluding dementia, the risk of reporting AEs was high in individuals with underlying diseases compared with those without, for instance, the risk of reporting AEs following two-dose vaccinations was approximately twice as high in individuals with chronic obstructive pulmonary disease and asthma.
**Conclusion:** These findings indicate that women, younger people, those with a lower socioeconomic status, and those with underlying health conditions reported a higher incidence of AEs following COVID-19 vaccinations. This emphasizes the need for continued

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**Disclosure**

The authors have no potential conflicts of interest to disclose.

**Data Availability Statement**

The protocol for this study can be obtained upon request from the corresponding author. This research utilized secondary data, safeguarded under stringent confidentiality measures as mandated by the Personal Information Protection Act. Access to personal data for research purposes may be granted by the Korea Disease Control and Prevention Agency and the National Health Insurance Service, subject to a formal application for data access.

**Author Contributions**

Conceptualization: Park H, Lim E, Lee HA, Park H, Choi NC, Park B; Data curation: Park H, Lim E, Lee HA, Park H, Choi NC, Park B; Formal analysis: Lim E, Park H; Investigation: Park H, Lim E, Jun S, Lee H.; Methodology: Lee HA, Park H, Choi NC, Park B; Project administration: Park H, Choi NC, Park B; Software: Lim E, Park H, Jun S, Lee H; Supervision: Park H, Choi NC, Park B; Validation: Lee HA, Park H, Choi NC, Park B; Visualization: Lee HA, Park H, Lim E, Jun S, Lee H.; Writing - original draft: Park B, Park H, Lim E, Lee HA, Park H, Choi NC; Writing - review & editing: Park H, Lim E, Jun S, Lee H, Lee HA, Park H, Choi NC, Park B.

monitoring to ensure safe vaccination and address vaccine-related anxiety and fear, especially within the aforementioned groups.

**Keywords:** COVID-19; COVID-19 Vaccines; Vaccination; Adverse Effects; Safety

## INTRODUCTION

In December 2019, the novel coronavirus disease 2019 (COVID-19) was first identified in China, from where it rapidly spread worldwide.[1] During the initial stages, before the development of vaccines and therapeutics, emphasis was on non-pharmacological interventions, such as hand hygiene, mask usage, sanitization practice, and maintaining social distancing, which served as primary management strategies.[2,3] Considerable resources and efforts have been dedicated to the rapid development of a COVID-19 vaccine, leading to its rapid creation and worldwide distribution. In response to the pandemic, health authorities across various nations expedited the Emergency Use Authorization (Biological License Application) for COVID-19 vaccines, advocating widespread vaccination.[4] The initial phase of global COVID-19 vaccinations began between December 2020, and February 2021. By November 2023, approximately 70% of the global population had administered at least one dose of the COVID-19 vaccine, amounting to 135.3 million doses worldwide.[5]

In South Korea, COVID-19 vaccination began on February 26, 2021, with free vaccination administered sequentially based on priorities.[6] Initially, the focus of vaccination was on individuals aged ≥ 65 years in care facilities, healthcare professionals, and frontline responders. This was progressively expanded to encompass the entire population as part of a broader vaccination strategy. The country introduced the following six vaccines: two each of viral vector (ChAdOx1 and Ad26.COV2.S), mRNA (BNT162b2 and mRNA-1273), and synthetic antigen (NVX-CoV2373 and GBP 510) vaccines. By December 31, 2023, approximately 88% and 87% of the total population received the first and second doses, respectively.[7]

COVID-19 vaccines can effectively establish herd immunity and combat the COVID-19 pandemic,[8,9] along with reducing the severity of symptoms in severe COVID-19 cases.[10] However, post-vaccination incidents of thrombosis, Bell's palsy, myocarditis, and death have been reported,[11,12] raising the importance of post-vaccination monitoring of adverse events (AEs). Owing to limited cohorts and short observation periods, unexpected AEs and severe, rare side effects may have been overlooked during vaccine development and clinical trials. Therefore, monitoring, evaluating, and analyzing AEs following immunization (AEFIs) are crucial. Furthermore, the transition of COVID-19 to an endemic phase warrants the need for a long-term management system, which highlights the importance of continuous monitoring of post-vaccination AEs to identify new, unexpected, or rare AEs.[13] Additionally, it can provide accurate and reliable information regarding vaccine-related AEs, alleviating vaccination-related concerns and positively influencing attitudes towards vaccines, thereby potentially increasing booster vaccination rates.[14,15]

Therefore, this study aimed to examine the AEs reported following the first and second doses of COVID-19 vaccination, administered between February 26, 2021, and January 31, 2023, while focusing on if AEs varied depending on the vaccination dose. Additionally, we aimed to identify the key factors associated with reported post-vaccination AEs to further deepen our understanding of vaccine safety and improve vaccination strategies.

# METHODS

## Data source

Herein, we utilized an extensive linked database that combines COVID-19 vaccination data, AE report data from the COVID-19 Vaccination Management System (CVMS) and the healthcare claims database from the National Health Insurance Service (NHIS). The Korea Disease Control and Prevention Agency (KDCA) has been collecting COVID-19 vaccination data, including vaccination status, dates, dosages, and administered vaccine types, since the initiation of the vaccination program in South Korea on February 26, 2021.

The CVMS, a web-based passive vaccine safety surveillance system, is operated by the KDCA and aimed at detecting AEFIs and supporting further analysis. Physicians and forensic pathologists must report all AEFIs to the CVMS, according to the Infectious Disease Control and Prevention Act, regardless of the suspected causal link to the vaccine.[16] The CVMS includes information on AEs, including their characteristics, onset dates, and severity. The COVID-19 infection status was retrieved using the COVID-19 infection registry data from the KDCA, ensuring comprehensive tracking and analysis of infection and vaccination data.

Data on socio-demographic characteristics and healthcare utilization were extracted from the NHIS healthcare claims database, covering the entire South Korean population.[17]

## Study population

This study included individuals (age ≥ 5 years) who received both doses of the monovalent COVID-19 vaccine between February 26, 2021, and January 31, 2023. Individuals who received a single dose of the Ad26.COV2.S (Janssen) vaccines were included in the study. The exclusion criteria were as follows: 1) non-South Korean citizens, 2) participants in clinical trials for COVID-19 vaccines or treatment, 3) individuals already infected with COVID-19 before their first vaccination dose, as identified from COVID-19 infection registry, 4) individuals who received either their first or second vaccination dose outside South Korea, 5) individuals who did not receive their second vaccination dose per the recommended minimum interval after the first dose, and 6) cases with errors in their records (**Fig. 1**). The types of COVID-19 vaccines and the intervals between doses were defined according to the guidelines provided by the KDCA. Detailed information on these criteria is provided in **Supplementary Table 1**.

## Variables

AE reports among the vaccine recipients were analyzed following the categories defined by the CVMS (**Supplementary Table 2**), and uncategorized reports were excluded. In accordance with the Guidelines for Adverse Events Following COVID-19 Immunization,[18] the AEs in this study were systematically classified into two distinct categories: non-serious and serious. AEs classified with progress status codes as life-threatening, permanent disability, intensive care unit admission, and death in CVMS, as well as AEs included in adverse events of special interest (AESI), were categorized as serious AEs. Other conditions were classified as non-serious AEs.

The sex, age, type of insurance, income level, comorbidities, and history of COVID-19 infection regarding the participants, which have been previously associated with vaccine-related adverse reactions, were taken into consideration.[19-22] Age was determined based on the date of the administration of the second COVID-19 vaccine dose. The insurance types were categorized as medical aid and health insurance. Additionally, income levels were categorized based on health insurance costs: medical aid and five tiers of health insurance (lowest, lower, middle, upper,

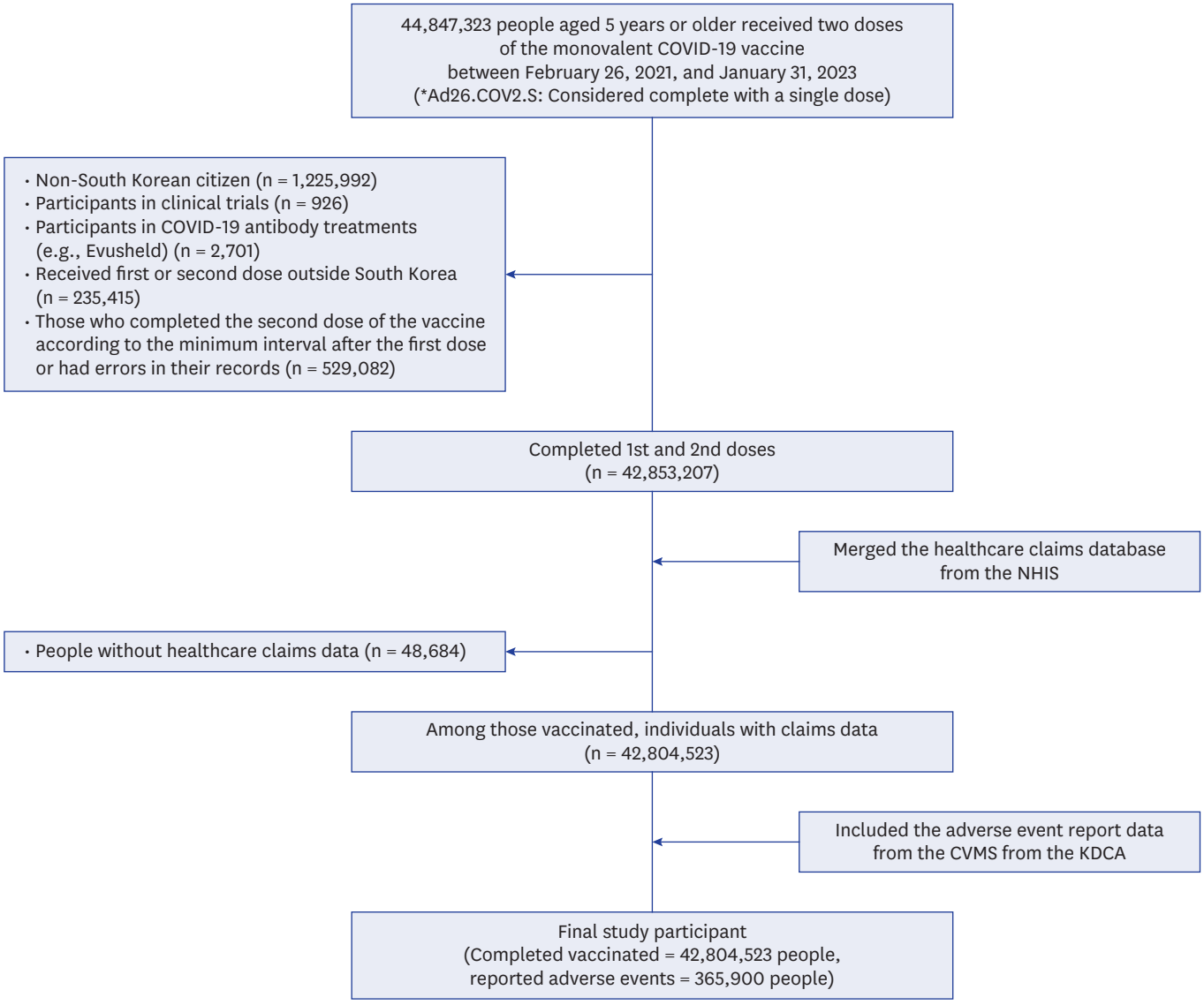


**Fig. 1.** Flow chart of the selection procedure of study participants.
COVID-19 = coronavirus disease 2019, NHIS = National Health Insurance Service, CVMS = Coronavirus Disease 2019 Vaccination Management System, KDCA = Korea Disease Control and Prevention Agency.

and highest), as well as an "unknown" category. The presence of underlying comorbidities, including diabetes, hypertension, dyslipidemia, chronic kidney disease, myocardial infarction, dementia, cancer, atopic dermatitis, chronic obstructive pulmonary disease (COPD), and asthma, was determined based on the presence of healthcare utilization records with the International Classification of Diseases, 10th Revision codes for the specified conditions documented at least once in the past year (**Supplementary Table 3**).

## Statistical analysis

The characteristics of people who received both doses of the COVID-19 vaccine and those who did report AEs were analyzed. The timing of AE reports was categorized based on when the reports were made, as follows: after the first dose, after the second dose, and after both doses. Additionally, the number of AE reports was analyzed based on the types of vaccine combinations administered for the first and second doses and the severity of the reported AEs.


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The number of reports per 100,000 vaccinations for each type of AE was also determined. We calculated the reporting rate per 1,000 vaccine doses based on the type of vaccine combination administered and the severity of AEs for each dose. Participant characteristics, including sex, age, insurance type, income level, comorbidities, and history of COVID-19 infection, were associated with AE reports through logistic regression analyses. The probabilities of reporting an AE, reporting an AE after the first dose, reporting an AE after the second dose, and reporting two AEs were compared with that of not reporting an AE. Age, sex, and insurance type were adjusted for, except when they were the independent variables.

### Ethics statement

The linked database, with personal identification information removed, was provided by KDCA. This study was exempted from review by the Public Institutional Review Board designated by the Ministry of Health and Welfare of the Republic of Korea (Approval Number: P01-202203-01-005).

## RESULTS

### AE reports by population characteristics

From February 26, 2021, to January 31, 2023, 42,804,523 individuals received both doses of the COVID-19 vaccine. Among them, 365,900 reported AEs. Of them, 355,949 (0.83% of fully vaccinated individuals) reported AEs once, while 9,951 (0.02% of fully vaccinated individuals) reported AEs after both doses. The reporting rate was higher among women (1.10%) than among men (0.61%), regardless of the number or timing of the reports. Regarding the reporting rate by age group, the 18–29 years age group had the highest reporting rate (1.02%), followed by the 30–49 and 65–74 years age groups. The reporting rates after the first and second dose were the highest in the 65–74 and 18–29 years age groups, respectively. Among those who reported AEs twice, the difference in reporting rates between the age groups was minimal. Regarding the insurance type and income level, medical aid recipients had a higher AE reporting rate (0.91%) than insured individuals. Additionally, individuals with underlying conditions such as asthma (1.24%), atopic dermatitis (1.18%), and COPD (1.02%) had a higher reporting rate of AEs compared with those without underlying conditions. The reporting rate of AEs after the second dose was slightly higher for those who contracted COVID-19 after the first dose (0.90%) than for those who did not (0.85%) (**Table 1**).

### AE reports by administered vaccine

**Table 2** summarizes the characteristics of AE reports according to the combination of vaccines received for the first and second doses. The reporting rate of adverse reactions after the first dose was the highest for the viral vector vaccine platform (6.82 reports per 1,000 doses). Based on the vaccine type, the highest reporting rate occurred following the administration of ChAdOx1 (6.82 reports per 1,000 doses). Among those who reported AEs one time, the mRNA combination was associated with the highest reporting rate of adverse reactions after the second dose (4.33 reports per 1,000 doses), with the mRNA-1273–mRNA-1273 combination showing the highest rate (7.44 reports per 1,000 doses). Among those who reported AEs after both the first and second doses, the highest reporting rate was observed for the viral vector–synthetic antigen combination, with ChAdOx1–NVX-CoV2373 showing the highest rate (3.44 reports per 1,000 doses). For a meaningful comparison, the comparison was conducted only among combinations with more than 1,000 recipients.


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**Table 1.** Characteristics of study participants by the number of adverse event reports

| Characteristics | Completed vaccinated | Reported adverse events | | | | |
|---|---|---|---|---|---|---|
| | | Total | Report 1 time | | | Report 2 times |
| | | | Total | After 1st dose | After 2nd dose | |
| Total | 42,804,523 | 365,900 (0.85) | 355,949 (0.83) | 192,598 (0.45) | 163,351 (0.38) | 9,951 (0.02) |
| Sex | | | | | | |
| Male | 21,351,110 | 129,842 (0.61) | 127,111 (0.60) | 67,778 (0.32) | 59,333 (0.28) | 2,731 (0.01) |
| Female | 21,453,413 | 236,058 (1.10) | 228,838 (1.07) | 124,820 (0.58) | 104,018 (0.48) | 7,220 (0.03) |
| Age group, yr | | | | | | |
| 5–11 | 41,359 | 38 (0.09) | 38 (0.09) | 18 (0.04) | 20 (0.05) | NA |
| 12–17 | 2,180,449 | 11,147 (0.51) | 10,910 (0.50) | 4,469 (0.20) | 6,441 (0.30) | 237 (0.01) |
| 18–29 | 7,054,397 | 72,053 (1.02) | 70,446 (1.00) | 34,943 (0.50) | 35,503 (0.50) | 1,607 (0.02) |
| 30–49 | 13,282,226 | 122,720 (0.92) | 119,241 (0.90) | 65,351 (0.49) | 53,890 (0.41) | 3,479 (0.03) |
| 50–64 | 11,959,342 | 98,484 (0.82) | 95,465 (0.80) | 53,173 (0.44) | 42,292 (0.35) | 3,019 (0.03) |
| 65–74 | 4,851,031 | 44,408 (0.92) | 43,174 (0.89) | 28,910 (0.60) | 14,264 (0.29) | 1,234 (0.03) |
| ≥ 75 | 3,435,719 | 17,050 (0.50) | 16,675 (0.49) | 5,734 (0.17) | 10,941 (0.32) | 375 (0.01) |
| Insurance type | | | | | | |
| Standard | 41,552,400 | 354,516 (0.85) | 344,930 (0.83) | 186,754 (0.45) | 158,176 (0.38) | 9,586 (0.02) |
| Medical aid | 1,252,133 | 11,384 (0.91) | 11,019 (0.88) | 5,844 (0.47) | 5,175 (0.41) | 365 (0.03) |
| Income level | | | | | | |
| Medical aid | 1,281,768 | 11,646 (0.91) | 11,268 (0.88) | 5,989 (0.47) | 5,279 (0.41) | 378 (0.03) |
| Lowest | 8,001,250 | 69,094 (0.86) | 67,101 (0.84) | 35,538 (0.44) | 31,563 (0.39) | 1,993 (0.02) |
| Low | 7,953,604 | 70,656 (0.89) | 68,633 (0.86) | 36,804 (0.46) | 31,829 (0.40) | 2,023 (0.03) |
| Middle | 7,982,640 | 71,600 (0.90) | 69,679 (0.87) | 37,644 (0.47) | 32,035 (0.40) | 1,921 (0.02) |
| High | 7,940,154 | 67,914 (0.86) | 66,184 (0.83) | 36,281 (0.46) | 29,903 (0.38) | 1,730 (0.02) |
| Highest | 8,512,598 | 66,078 (0.78) | 64,417 (0.76) | 35,652 (0.42) | 28,765 (0.34) | 1,661 (0.02) |
| Unknown | 1,132,509 | 8,912 (0.79) | 8,667 (0.77) | 4,690 (0.41) | 3,977 (0.35) | 245 (0.02) |
| Comorbidities | | | | | | |
| Diabetes mellitus | | | | | | |
| Yes | 5,837,846 | 50,654 (0.87) | 49,128 (0.84) | 27,475 (0.47) | 21,653 (0.37) | 1,526 (0.03) |
| No | 36,966,677 | 315,246 (0.85) | 306,821 (0.83) | 165,123 (0.45) | 141,698 (0.38) | 8,425 (0.02) |
| Hypertension | | | | | | |
| Yes | 10,145,953 | 80,048 (0.79) | 77,789 (0.77) | 43,809 (0.43) | 33,980 (0.33) | 2,259 (0.02) |
| No | 32,658,570 | 285,852 (0.88) | 278,160 (0.85) | 148,789 (0.46) | 129,371 (0.40) | 7,692 (0.02) |
| Hyperlipidemia | | | | | | |
| Yes | 12,701,239 | 121,530 (0.96) | 117,794 (0.93) | 66,424 (0.52) | 51,370 (0.40) | 3,736 (0.03) |
| No | 30,103,284 | 244,370 (0.81) | 238,155 (0.79) | 126,174 (0.42) | 111,981 (0.37) | 6,215 (0.02) |
| Chronic kidney disease | | | | | | |
| Yes | 632,269 | 5,878 (0.93) | 5,710 (0.9) | 3,027 (0.48) | 2,683 (0.42) | 168 (0.03) |
| No | 42,172,254 | 360,022 (0.85) | 350,239 (0.83) | 189,571 (0.45) | 160,668 (0.38) | 9,783 (0.02) |
| Myocardial infarction | | | | | | |
| Yes | 265,378 | 2,250 (0.85) | 2,184 (0.82) | 1,176 (0.44) | 1,008 (0.38) | 66 (0.02) |
| No | 42,539,145 | 363,650 (0.85) | 353,765 (0.83) | 191,422 (0.45) | 162,343 (0.38) | 9,885 (0.02) |
| Dementia | | | | | | |
| Yes | 1,381,331 | 10,093 (0.73) | 9,817 (0.71) | 5,072 (0.37) | 4,745 (0.34) | 276 (0.02) |
| No | 41,423,192 | 355,807 (0.86) | 346,132 (0.84) | 187,526 (0.45) | 158,606 (0.38) | 9,675 (0.02) |
| Cancer | | | | | | |
| Yes | 1,578,593 | 15,523 (0.98) | 15,085 (0.96) | 8,343 (0.53) | 6,742 (0.43) | 438 (0.03) |
| No | 41,225,930 | 350,377 (0.85) | 340,864 (0.83) | 184,255 (0.45) | 156,609 (0.38) | 9,513 (0.02) |
| Atopy dermatitis | | | | | | |
| Yes | 1,714,040 | 20,238 (1.18) | 19,561 (1.14) | 10,492 (0.61) | 9,069 (0.53) | 677 (0.04) |
| No | 41,090,483 | 345,662 (0.84) | 336,388 (0.82) | 182,106 (0.44) | 154,282 (0.38) | 9,274 (0.02) |
| COPD | | | | | | |
| Yes | 439,047 | 4,490 (1.02) | 4,340 (0.99) | 2,289 (0.52) | 2,051 (0.47) | 150 (0.03) |
| No | 42,365,476 | 361,410 (0.85) | 351,609 (0.83) | 190,309 (0.45) | 161,300 (0.38) | 9,801 (0.02) |
| Asthma | | | | | | |
| Yes | 2,137,620 | 26,400 (1.24) | 25,458 (1.19) | 13,807 (0.65) | 11,651 (0.55) | 942 (0.04) |
| No | 40,666,903 | 339,500 (0.83) | 330,491 (0.81) | 178,791 (0.44) | 151,700 (0.37) | 9,009 (0.02) |
| History of COVID-19 infection[a] | | | | | | |
| Yes | 302,163 | 2,716 (0.90) | NA | NA | 2,716 (0.90) | NA |
| No | 42,502,360 | 363,184 (0.85) | NA | NA | 363,184 (0.85) | NA |

The values are presented as number or number (%). These were classified according to income level.
COVID-19 = coronavirus disease 2019, COPD = chronic obstructive pulmonary disease, NA = not applicable.
[a]A history of COVID-19 infection between the first and second vaccination doses.


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**Table 2.** Number of adverse event reports by types of vaccine combination received

| 1st–2nd vaccine | No. | Reported adverse events | | | | | |
|---|---|---|---|---|---|---|---|
| | | Report 1 time | | | | Report 2 times | |
| | | After 1st dose | | After 2nd dose | | | |
| | | No. | Reporting rate[a] | No. | Reporting rate[a] | No. | Reporting rate[a] |
| Platform | | | | | | | |
| mRNA–mRNA | 30,583,436 | 108,618 | 3.55 | 132,355 | 4.33 | 7,106 | 0.23 |
| mRNA–Viral vector | 151 | | | 2 | 13.25 | NA | NA |
| mRNA–Synthetic antigen | 7,447 | | | 23 | 3.09 | 9 | 1.21 |
| Viral vector–mRNA | 1,748,626 | 82,558 | 6.82 | 6,816 | 3.90 | 736 | 0.42 |
| Viral vector–Viral vector | 10,360,265 | | | 23,892 | 2.31 | 2,088 | 0.20 |
| Viral vector–Synthetic antigen | 1,163 | | | 4 | 3.44 | 4 | 3.44 |
| Synthetic antigen–mRNA | 130 | 95 | 0.92 | NA | NA | NA | NA |
| Synthetic antigen–Synthetic antigen | 103,305 | | | 259 | 2.51 | 8 | 0.08 |
| Vaccine name | | | | | | | |
| BNT162b2–BNT162b2 | 24,145,259 | 77,690 | 3.22 | 84,851 | 3.51 | 4,257 | 0.18 |
| BNT162b2–mRNA-1273 | 355 | | | 10 | 28.17 | 1 | 2.82 |
| BNT162b2–ChAdOx1 | 116 | | | NA | NA | NA | NA |
| BNT162b2–NVX-CoV2373 | 5,429 | | | 17 | 3.13 | 6 | 1.11 |
| BNT162b2–GBP510 | 5 | | | NA | NA | NA | NA |
| mRNA-1273–mRNA-1273 | 6,338,401 | 32,255 | 5.01 | 47,168 | 7.44 | 2,814 | 0.44 |
| mRNA-1273–BNT162b2 | 99,421 | | | 326 | 3.28 | 34 | 0.34 |
| mRNA-1273–ChAdOx1 | 35 | | | 2 | 57.14 | NA | NA |
| mRNA-1273–NVX-CoV2373 | 2,012 | | | 6 | 2.98 | 3 | 1.49 |
| mRNA-1273–GBP510 | 1 | | | NA | NA | NA | NA |
| ChAdOx1–ChAdOx1 | 9,090,869 | 73,943 | 6.82 | 23,892 | 2.63 | 2,088 | 0.23 |
| ChAdOx1–BNT162b2 | 1,748,082 | | | 6,810 | 3.90 | 734 | 0.42 |
| ChAdOx1–mRNA-1273 | 544 | | | 6 | 11.03 | 2 | 3.68 |
| ChAdOx1–NVX-CoV2373 | 1,163 | | | 4 | 3.44 | 4 | 3.44 |
| Ad26.COV2.S[b] | 1,269,396 | 8,615 | 6.79 | NA | NA | NA | NA |
| NVX-CoV2373–NVX-CoV2373 | 103,107 | 95 | 0.92 | 259 | 2.51 | 8 | 0.08 |
| NVX-CoV2373–BNT162b2 | 122 | | | NA | NA | NA | NA |
| NVX-CoV2373–mRNA-1273 | 7 | | | NA | NA | NA | NA |
| GBP510–GBP510 | 197 | NA | NA | NA | 0 | NA | NA |
| GBP510–BNT162b2 | 1 | | | NA | NA | NA | NA |
| GBP510-NVX–CoV2373 | 1 | | | NA | 0 | NA | NA |

There was no synthetic antigen-viral vector vaccine platform combination. mRNA vaccines include the BNT162b2 (Pfizer/BioNTech) and mRNA-1273 (Moderna) vaccines. Viral vector vaccines include the ChAdOx1 (AstraZeneca) and Ad26.COV2.S (Janssen) vaccines. Protein subunit vaccines, referred to here as synthetic antigen vaccines, include the NVX-CoV2373 (Novavax) and GBP510 (SKYCovione) vaccines.
NA = not applicable.
[a]The reporting rate is per 1,000 vaccinations.
[b]The primary regimen for the Ad26.COV2.S (Janssen) coronavirus disease 2019 vaccine is a single administration; therefore, recipients are only considered in the analysis of adverse events following the first dose.

## AE reporters and cases categorized by severity of AEs and timing of reports

Among the 365,900 individuals who reported AEs, 364,111 (0.85%) reported non-serious AEs and 6,028 (0.01%) reported severe AEs. Notably, 211 individuals reported serious AEs after both first and second doses (**Table 3**). Among the 365,900 individuals who reported AEs, 796,709 reports were made (reports per person = 1–20, average = 2.18; standard deviation [SD], 1.42). Regarding the severity of AEs, non-serious and serious AEs were reported at an average of 2.16 (SD, 1.41) and 1.31 (SD, 0.86) reports per person. The number of AE reporters was higher after the second dose (0.008%) compared with that after the first dose. When categorized by vaccine combinations, the mRNA–mRNA combination exhibited the highest number of reports for both the severity of AEs and the timing of reports, followed by the viral vector–viral vector combination (**Supplementary Table 4**).


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**Table 3.** Number of adverse event reporters and cases categorized by severity of adverse events and the timing of reports

| Severity of adverse events × Timing of reports | No. of reporting adverse event reporters | No. of reported adverse events[a] |
|---|---|---|
| | No. (%) | No. (per 1,000 vaccinations) |
| Total | 365,900 (0.85) | 796,709 (9.45) |
| Either after 1st dose or 2nd dose | 355,949 (0.83) | 752,634 (8.92) |
| Both after 1st and 2nd dose | 9,951 (0.02) | 44,075 (0.52) |
| Non-serious adverse events[a,b] | 364,111 (0.85) | 788,249 (9.35) |
| After 1st dose only | 192,246 (0.45) | 398,243 (9.30) |
| After 2nd dose only | 161,925 (0.39) | 346,343 (8.34) |
| Both after 1st and 2nd dose | 9,940 (0.02) | 43,663 (0.52) |
| Serious adverse events[a,c] | 6,028 (0.01) | 8,460 (0.10) |
| After 1st dose only | 2,568 (0.01) | 3,001 (0.07) |
| After 2nd dose only | 3,221 (0.01) | 5,047 (0.12) |
| Both after 1st and 2nd dose | 211 (< 0.00) | 412 (< 0.00) |

The percentage (%) was calculated based on the number of people who completed vaccination (42,804,523 people). The number of reported adverse events was calculated per 1,000 doses for only the first dose (42,804,523), only the second dose (41,535,127), and for both the first and second doses combined (84,339,650). The primary regimen for the Ad26.COV2.S (Janssen) coronavirus disease 2019 vaccine is a single administration, thus recipients are excluded from the analysis of adverse events following the second dose.
[a]In each report, the number of reported adverse event symptoms may include more than one simultaneously.
[b]Non-serious adverse events include common symptoms such as redness, pain, and swelling at the injection site, myalgia, fever, headache, chills, and others.
[c]Serious adverse events include those classified in Coronavirus Disease 2019 Vaccination Management System as life-threatening, permanent disability, intensive care unit admission, death, and those listed as adverse events of special interest (adverse events following immunization).

## Ranking of AEs

The rankings of AEs following COVID-19 vaccination are presented in **Table 4**. The most commonly reported adverse reactions after the first or second dose included headaches, muscle pain, dizziness, nausea, allergic reactions, fever, and chills. These AEs were frequently reported regardless of vaccine combinations (**Supplementary Table 5**). Those who reported AEs twice presented a very low rate of reporting the same AEs after the first and second vaccinations, but the top 10 AE types remained consistent. Notably, despite not being within the top 20 AEs after either the first or second dose individually, uterine bleeding emerged as the seventh most common condition among those who reported the same AE after both doses. Additionally, thrombocytopenic purpura (TTP), vaccine-associated enhanced disease, Bell's palsy, and anaphylactoid reactions, which are included in AESI, were seen ranked between 18th and 20th. Additionally, death after the second dose (1.31 per 100,000 doses) was ranked 19th (**Table 4**).

## Factors associated with reported post-vaccination AEs

The results of the logistic regression analysis, adjusted for sex, age, and insurance type (**Table 5**), indicated that women were approximately twice as likely to experience AEs following COVID-19 vaccination than men (odds ratio [OR], 1.86, 95% confidence interval [CI], 1.84–1.87 for AE report). Increasing cumulative number of reports revealed the increased risk of experiencing AEs for females (OR, 1.89, 95% CI, 1.87–1.90 for one-time reports after the first dose; OR, 1.78, 95% CI, 1.76–1.80 for one-time reports after the second dose; OR, 2.70, 95% CI, 2.59–2.83 for two-time reports). Based on age, the 18–49 and 65–74 years age groups were more likely to report AEs than the middle-aged group (50–64 years), while the 5–17 and over 75 years age groups were less likely to report AEs. When reporting twice, adolescents (12–17 years) and older adults (over 75 years) had lower risks of reporting AEs twice compared to the middle-aged group, with ORs of 0.43 and 0.38, respectively. Medical aid recipients were more likely to report AEs once (OR, 1.14, 95% CI, 1.11–1.17 after the first dose; OR, 1.17, 95% CI, 1.13–1.20 after the second dose) and twice (OR, 1.38, 95% CI, 1.29–1.49) than those with health insurance. Additionally, the highest-income group (OR, 0.96, 95% CI,

**Table 4.** Ranking of adverse events based on the number of reports per 100,000 vaccinations

| Rank | Individuals reporting adverse events | | | | | |
|---|---|---|---|---|---|---|
| | Only after the 1st dose | | Only after the 2nd dose | | After both the 1st and 2nd doses | |
| | Adverse event[a] | Reporting rate[b] | Adverse event[a] | Reporting rate[b] | Adverse event[a] | Reporting rate[b] |
| 1 | Headache | 110.34 | Headache | 107.76 | Headache | 2.70 |
| 2 | Myalgia | 102.67 | Myalgia | 107.34 | Myalgia | 2.70 |
| 3 | Dizziness | 70.90 | Dizziness | 57.69 | Dizziness | 1.54 |
| 4 | Allergic reaction | 53.73 | Fever | 50.96 | Allergic reaction | 1.47 |
| 5 | Nausea | 50.38 | Nausea | 48.66 | Nausea | 0.91 |
| 6 | Fever | 40.03 | Chills | 41.67 | Pain at the injection[c] | 0.60 |
| 7 | Chills | 36.82 | Allergic reaction | 31.38 | Abnormal uterine bleeding | 0.45 |
| 8 | Pain at the injection[c] | 28.87 | Chest pain | 27.17 | Chest pain | 0.37 |
| 9 | Vomiting | 22.10 | Pain at the injection[c] | 21.29 | Chills | 0.35 |
| 10 | Abdominal pain | 18.41 | Vomiting | 21.29 | Fever | 0.32 |
| 11 | Diarrhea | 14.83 | Abdominal pain | 16.93 | Vomiting | 0.30 |
| 12 | Chest pain | 10.11 | Diarrhea | 11.65 | Lymphadenitis | 0.23 |
| 13 | Cellulitis[d] | 8.95 | Lymphadenitis | 6.65 | Abdominal pain | 0.20 |
| 14 | Severe local adverse reaction | 6.66 | Abnormal uterine bleeding | 4.92 | Cellulitis[d] | 0.20 |
| 15 | Arthritis | 4.95 | Arthritis | 4.35 | Diarrhea | 0.14 |
| 16 | Lymphadenitis | 4.86 | Cellulitis[d] | 3.90 | Arthritis | 0.09 |
| 17 | Abnormal uterine bleeding | 2.45 | Severe local adverse reaction | 2.01 | Severe local adverse reaction | 0.06 |
| 18 | Thrombocytopenic purpura | 2.34 | Vaccine-associated enhanced disease | 1.80 | Thrombocytopenic purpura | 0.02 |
| 19 | Vaccine-associated enhanced disease | 2.26 | Death | 1.31 | Dyspnea | 0.02 |
| 20 | Bell's palsy | 1.15 | Bell's palsy | 1.16 | Anaphylactoid reactions | 0.02 |

Only the top 20 of the total reporting rates are presented. Only individuals who completed both doses were included in the analysis; therefore, deaths were only confirmed after the second dose. The diseases included in adverse events following immunization and death are highlighted in red.
[a]One report may include multiple types of symptoms.
[b]Number of adverse events per 100,000 doses administered.
[c]Pain, redness, or swelling at the injection site within 3 days after.
[d]Inflammation rather than an abscess at the vaccination site.

0.94–0.97 after the first dose; OR, 0.90, 95% CI, 0.89–0.91 after the second dose; OR, 0.88, 95% CI, 0.83–0.94 after both doses) was less likely to report AEs than the middle-income group. Excluding dementia, the risk of reporting AEs was significantly higher in patients with comorbidities than in those without those diseases. Among the comorbidities, COPD (OR, 2.21, 95% CI, 1.88–2.61) and asthma (OR, 2.06, 95% CI, 1.93–2.21) presented the highest risk. Patients with a history of COVID-19 between the first and second doses were found to be less likely to report AEs after the second dose (OR, 0.73, 95% CI, 0.68–0.78).

## DISCUSSION

Given the rapid development of COVID-19 vaccines, safety remains a primary concern and can act as a barrier to subsequent booster vaccinations. Therefore, assessing the safety of vaccines and providing accurate information about them is crucial. This study aimed to determine the number of individuals experiencing AEs after completing both doses of the COVID-19 vaccine and to understand the characteristics of those who reported such events. Notably, utilizing linked data on vaccinations and AE reports enabled the analysis of AE reports after the first and second doses in the same individuals, which was further linked with the NHIS National Health Information Database to analyze the relationship between socioeconomic status, presence of comorbidities, other participant characteristics, and AEs. Between February 26, 2021, and January 31, 2023, 42,804,523 individuals completed two doses of monovalent vaccine, of whom 0.85% reported AEs.

**Table 5.** Logistic regression analysis on the association between participant characteristics and the number of adverse event reports

| Characteristics | Adverse event report | | | Adverse event reports after 1st dose | | | Adverse event reports after 2nd dose | | | 2 Adverse event reports | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | OR | 95% CI | *P* value | OR | 95% CI | *P* value | OR | 95% CI | *P* value | OR | 95% CI | *P* value |
| Sex[a] | | | | | | | | | | | | |
| Male | 1.00 | | | 1.00 | | | 1.00 | | | 1.00 | | |
| Female | 1.86 | 1.84–1.87 | < 0.001 | 1.89 | 1.87–1.90 | < 0.001 | 1.78 | 1.76–1.80 | < 0.001 | 2.70 | 2.59–2.83 | < 0.001 |
| Age group, yr[b] | | | | | | | | | | | | |
| 5–11 | 0.11 | 0.08–0.15 | < 0.001 | 0.10 | 0.06–0.15 | < 0.001 | 0.14 | 0.09–0.21 | < 0.001 | NA | NA | |
| 12–17 | 0.62 | 0.61–0.64 | < 0.001 | 0.46 | 0.45–0.48 | < 0.001 | 0.84 | 0.82–0.86 | < 0.001 | 0.43 | 0.38–0.50 | < 0.001 |
| 18–29 | 1.26 | 1.25–1.27 | < 0.001 | 1.13 | 1.12–1.15 | < 0.001 | 1.45 | 1.43–1.47 | < 0.001 | 0.93 | 0.87–0.99 | 0.010 |
| 30–49 | 1.14 | 1.13–1.15 | < 0.001 | 1.12 | 1.11–1.13 | < 0.001 | 1.16 | 1.15–1.18 | < 0.001 | 1.06 | 1.01–1.11 | 0.020 |
| 50–64 | 1.00 | | | 1.00 | | | 1.00 | | | 1.00 | | |
| 65–74 | 1.09 | 1.08–1.11 | < 0.001 | 1.32 | 1.30–1.34 | < 0.001 | 0.82 | 0.80–0.84 | < 0.001 | 0.98 | 0.92–1.05 | 0.550 |
| ≥ 75 | 0.56 | 0.55–0.57 | < 0.001 | 0.35 | 0.34–0.36 | < 0.001 | 0.84 | 0.82–0.85 | < 0.001 | 0.38 | 0.34–0.42 | < 0.001 |
| Insurance type[c] | | | | | | | | | | | | |
| Standard | 1.00 | | | 1.00 | | | 1.00 | | | 1.00 | | |
| Medical aid | 1.16 | 1.14–1.18 | < 0.001 | 1.14 | 1.11–1.17 | < 0.001 | 1.17 | 1.13–1.20 | < 0.001 | 1.38 | 1.29–1.49 | < 0.001 |
| Income level[c] | | | | | | | | | | | | |
| Medical aid | 1.13 | 1.11–1.16 | < 0.001 | 1.08 | 1.01–1.16 | < 0.034 | 1.13 | 1.05–1.22 | < 0.001 | 1.39 | 1.24–1.55 | < 0.001 |
| Lowest | 0.98 | 0.97–0.99 | < 0.001 | 0.96 | 0.95–0.97 | < 0.001 | 1.00 | 0.98–1.01 | 0.800 | 1.05 | 0.98–1.11 | 0.160 |
| Low | 0.99 | 0.98–1.00 | 0.010 | 0.97 | 0.96–0.99 | < 0.001 | 1.00 | 0.98–1.02 | 0.940 | 1.04 | 0.98–1.11 | 0.240 |
| Middle | 1.00 | | | 1.00 | | | 1.00 | | | 1.00 | | |
| High | 1.00 | 0.98–1.01 | 0.320 | 1.01 | 1.00–1.03 | 0.060 | 0.97 | 0.96–0.99 | 0.001 | 0.96 | 0.90–1.02 | 0.190 |
| Highest | 0.93 | 0.92–0.94 | < 0.001 | 0.96 | 0.94–0.97 | < 0.001 | 0.90 | 0.89–0.91 | < 0.001 | 0.88 | 0.83–0.94 | < 0.001 |
| Unknown | 0.88 | 0.86–0.90 | < 0.001 | 0.89 | 0.86–0.92 | < 0.001 | 0.87 | 0.84–0.90 | < 0.001 | 0.92 | 0.81–1.05 | 0.220 |
| Comorbidities (ref. without these specific comorbidity) | | | | | | | | | | | | |
| Diabetes mellitus | 1.16 | 1.15–1.17 | < 0.001 | 1.16 | 1.15–1.17 | < 0.001 | 1.12 | 1.03–1.06 | < 0.001 | 1.30 | 1.22–1.38 | < 0.001 |
| Hypertension | 1.08 | 1.07–1.09 | < 0.001 | 1.11 | 1.10–1.12 | < 0.001 | 1.05 | 1.03–1.06 | < 0.001 | 1.13 | 1.07–1.20 | < 0.001 |
| Hyperlipidemia | 1.36 | 1.35–1.37 | < 0.001 | 1.37 | 1.36–1.39 | < 0.001 | 1.33 | 1.31–1.34 | < 0.001 | 1.61 | 1.54–1.69 | < 0.001 |
| Chronic kidney disease | 1.31 | 1.28–1.34 | < 0.001 | 1.28 | 1.23–1.33 | < 0.001 | 1.34 | 1.29–1.39 | < 0.001 | 1.40 | 1.20–1.63 | < 0.001 |
| Myocardial infarction | 1.33 | 1.28–1.39 | < 0.001 | 1.32 | 1.24–1.40 | < 0.001 | 1.34 | 1.26–1.43 | < 0.001 | 1.58 | 1.24–2.02 | < 0.001 |
| Dementia | 1.07 | 1.05–1.10 | < 0.001 | 1.13 | 1.09–1.16 | < 0.001 | 1.02 | 0.98–1.05 | 0.370 | 1.11 | 0.97–1.26 | 0.120 |
| Cancer | 1.19 | 1.17–1.20 | < 0.001 | 1.16 | 1.14–1.19 | < 0.001 | 1.22 | 1.19–1.25 | < 0.001 | 1.15 | 1.04–1.26 | 0.010 |
| Atopy dermatitis | 1.35 | 1.33–1.37 | < 0.001 | 1.35 | 1.32–1.37 | < 0.001 | 1.34 | 1.31–1.37 | < 0.001 | 1.68 | 1.55–1.82 | < 0.001 |
| COPD | 1.64 | 1.59–1.69 | < 0.001 | 1.59 | 1.53–1.66 | < 0.001 | 1.67 | 1.60–1.75 | < 0.001 | 2.21 | 1.88–2.61 | < 0.001 |
| Asthma | 1.55 | 1.53–1.57 | < 0.001 | 1.54 | 1.52–1.57 | < 0.001 | 1.53 | 1.50–1.56 | < 0.001 | 2.06 | 1.93–2.21 | < 0.001 |
| History of COVID-19 infection[d] | | | | | | | | | | | | |
| Yes | NA | NA | NA | NA | NA | NA | 0.73 | 0.68–0.78 | < 0.001 | NA | NA | NA |
| No | NA | NA | NA | NA | NA | NA | 1.00 | | | NA | NA | NA |

These were classified according to income level. For comorbidities, the reference group is the absence of the disease. A history of coronavirus disease 2019 infection between 1st and 2nd vaccination dose.
OR = odds ratio, 95% CI = 95% confidence interval, COPD = chronic obstructive pulmonary disease, NA = not applicable.
[a]Adjusted for age and insurance type.
[b]Adjusted for sex and insurance type.
[c]Adjusted for sex and age.
[d]Adjusted for sex, age, and insurance type.

The World Health Organization lifted the Public Health Emergency of International Concern (PHEIC) declaration for COVID-19 on May 5, 2023, which had been in place since January 2020 for approximately 3 years and 4 months. South Korea also declared an effective endemic by downgrading the COVID-19 infectious disease crisis alert from "serious" to "alert" on May 11, 2023, after considering both the domestic and international situations of COVID-19.[23] However, the risk of COVID-19 particularly remains for vulnerable groups (high-risk populations). Vaccination still remains the most effective method to prevent severe disease progression, hospitalizations, and deaths related to COVID-19 and reduces the impact of long COVID, occurring during or after acute infections, that last for a long time.[24] Considering that COVID-19 continues to evolve through mutations, a new vaccine targeting the currently circulating omicron subvariant XBB 1.5 has been introduced as a booster shot. This new XBB

1.5 monovalent vaccine is effective against the current circulating variants as long as there are no significant genetic changes in the virus.[25,26] Therefore, administering the XBB 1.5 COVID-19 vaccine as an additional shot is important to maintain immunity and protect against subvariant viruses in an endemic situation, preventing a resurgence of the pandemic situation.

Experiencing adverse reactions from initial COVID-19 vaccinations negatively affects the intention and attitude toward receiving booster vaccinations.[14,27,28] Despite the general side effects of the COVID-19 vaccine being mild, the experience of adverse effects, especially the number and intensity, can substantially reduce the willingness to receive additional vaccinations.[29] Moreover, experiencing post-vaccination adverse reactions has been linked to an increased likelihood of adverse reactions after subsequent vaccinations.[30] This study analyzed whether the systemic side effects experienced by individuals receiving their second dose of the COVID-19 vaccine were related to their expectations of vaccine efficacy and side effects. The findings indicated that individuals who expected more side effects from the vaccine and those who experienced more side effects after the first dose reported an increased severity of systemic side effects, even after adjusting for pre-vaccination symptom levels. Possibly because of the post-vaccination nocebo effects arising through mechanisms such as learning, expectations, and misattribution. Additionally, some individuals may have specific immunological predispositions that cause them to experience similar side effects from both vaccine doses. Previously reported findings suggest that for individuals who experienced AEs after both doses, more efforts are needed to increase booster vaccination rates and monitoring for safety. Therefore, the findings of this study, presenting post-vaccination surveillance results, may help address these needs.

Herein, the most frequently reported adverse reactions were headaches, myalgia, dizziness, allergic reactions, nausea, fever, chills, and pain at the injection site, similar to those previously reported.[11,12,31-33] Generally, the rate of reporting the same AEs after the first and second vaccine doses was very low. However, some AEs, such as abnormal uterine bleeding, recurred in the same individual, suggesting the need for attention to such cases. The low rate of reporting the same AEs after both doses could be attributed to various factors, including the development of immunity or tolerance to the vaccine components following initial exposure,[34,35] differences in individual health conditions during vaccination,[36] affecting the response of the body, or psychological factors such as reduced anxiety following the first dose.[37] Therefore, while most individuals do not experience the same AEs after subsequent doses, monitoring and investigation of recurrent or severe cases is important to ensure a comprehensive understanding and management of vaccine safety.

Myocarditis and pericarditis are rare AEs associated with COVID-19 mRNA vaccine administration.[38,39] In our study, chest pain was reported in 10.11 per 100,000 individuals after the first dose and in 27.17 per 100,000 individuals after the second dose. The rate of reporting chest pain after both doses was 0.37 per 100,000 individuals. When analyzed by vaccine type, chest pain ranked within the top 10 AEs for all vaccination combinations, except for the viral vector-mRNA and viral vector-viral vector combinations (**Supplementary Table 5**). In addition, TTP and Bell's palsy were among the top 20 AEs reported in this study. In the general population, the global incidence of TTP is approximately 1 new case per million people annually,[40] and the incidence of Bell's palsy in Korea is 23.0 to 30.8 per 100,000 individuals annually.[41] Previous studies reported that the incidence of TTP and Bell's palsy following COVID-19 vaccination was 0.80 per million doses[42] and 25.3 per million individuals,[43] respectively. In our study, the rates were approximately 1–2 per 100,000 doses,


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which is lower than those reported either in the general population or vaccinated population. However, since they are within the top 20 AEs, it is necessary to evaluate the causal relationship to determine if these occurrences are vaccine-related.

After the second dose, the death rate was 1.31 per 100,000 doses; we analyzed the characteristics of these cases in detail (**Supplementary Table 6**). Deaths post-vaccination were more prevalent among males, older adults, and individuals with underlying conditions. This indicates that the deaths may have been due to pre-existing conditions rather than the vaccine itself, or that these individuals may be more susceptible to adverse vaccine reactions. To determine whether the deaths in this study were causally related to the vaccine, further research on causality at the individual level is necessary.

Previous studies have suggested that women may experience higher rates of adverse reactions to vaccinations.[44] Our data also indicated that women reported AEs at a higher rate than men. This could be because most women elicit stronger immune responses to vaccinations than men and experience more pronounced symptoms after vaccination. Such phenomena could be attributed to biological mechanisms, including differences in sex hormone levels and chromosomal variations.[44-46] However, higher anxiety levels and health awareness in women may also lead to more frequent reporting of AEs. Reportedly, anxiety-related AEs are more common in women, contributing to increased reporting of vaccine side effects.[47] These factors suggest that both biological and psychological mechanisms contribute to the higher incidence of reported adverse reactions in women. Moreover, AEs exclusively associated with women, such as abnormal uterine bleeding, further increase the reporting rates in this group.[48]

Herein, the reporting rates of AEs were higher in the 18–49 and 65–74 years age groups than in the 50–64 years age group. However, lower rates were observed in the 12–17 and over 75 years age groups. Similar to other studies, there was a general decrease in the frequency of reported AEs with increasing age, with a notably higher incidence rate of AEs among individuals in their 30s.[12,49,50] This could be attributed to the presence of more active thymus cells and immune response substances in younger individuals, leading to stronger immune responses.[12,50] However, the higher incidence of AEs among younger individuals may be because of a higher reporting rate rather than the actual occurrence of AEs.

Additionally, our findings revealed a higher incidence of post-vaccination AEs among individuals receiving basic livelihood security benefits compared to those covered by health insurance. To the best of our knowledge, no previous study has investigated the relationship between income level and the reporting rate of adverse reactions following vaccination. The mechanism underlying the correlation between income level and the reporting rate of AEs related to the COVID-19 vaccine is not yet clearly understood. However, examining this is important because AEs that lead to decreased productivity or job loss can impose a greater economic burden on lower-income populations, warranting greater attention. Given the passive surveillance nature of the reporting system, a higher reporting rate of AEs in lower socioeconomic groups may not necessarily mean that the actual incidence of AEs is high. Lower-income individuals might have poorer baseline health characteristics and behavioral factors that may affect AE reporting. Alternately, they may also report AEs more frequently to seek compensation through the national vaccine injury compensation program for vaccine-related adverse effects.

Individuals with underlying conditions, such as diabetes, hypertension, hyperlipidemia, chronic kidney disease, myocardial infarction, dementia, cancer, atopic dermatitis, COPD,

and asthma, reported a higher incidence of AEs than those without these comorbidities. These findings align with previous studies.[11,51] Notably, individuals with underlying conditions may report AEs more frequently because of regular healthcare visits or the worsening of their existing conditions. This study does not establish causality, and caution is needed in the interpretation of these results. Further research is needed to explore the link between comorbidities and severe AEs to develop customized vaccination guidelines and minimize risks.

Since AE reporting could be influenced by the timing of vaccination, the vaccination period was divided as follows: February 26, 2021, to January 31, 2022, and February 1, 2022, to January 31, 2023. Additional analysis of AE reporting rates for each period showed no significant difference between the overall reporting rates and those in period 1, regardless of the recipient characteristics. Furthermore, the reporting rates during the initial vaccination period were notably higher than those during the later period, suggesting that vaccination timing considerably affected the reporting rates (**Supplementary Table 7**). The higher reporting rates in the initial vaccination period could be due to the increased degree of anxiety regarding vaccine side effects during the early stages of vaccination,[52] leading to increased reporting rates; during the subsequent periods, the reporting rates were lower, probably as the degree of anxiety decreased. Women reported AEs at much higher rates than men. However, when analyzed by period, the gender difference in reporting rates decreased significantly in period 2; this may support the hypothesis regarding the influence of anxiety over time. Additionally, the notably low AE reporting rates among the 5–11 age group, compared with those in the other age groups, became less pronounced during the analysis of AE reporting rates by period. In period 2, the difference in reporting rates between the 5–11 age group and other age groups diminished. Since vaccination for the 5–11 age group started later than that for other age groups, it is likely that the vaccination timing influenced the AE reporting rates.

This study has several limitations. First, owing to passive surveillance method-based data collection, the reporting rate of AEs may not accurately reflect the actual incidence rate, especially regarding less serious AEs that may have been underreported and severe or delayed AEs with low reporting rates. Some symptoms reported post-vaccination might have been exaggerated or caused by underlying conditions, rather than being directly related to the vaccine. Therefore, further epidemiological research is needed to establish the causality of observed AEs for a deeper understanding of vaccine safety. Moreover, the small number of administered doses may have resulted in a higher reporting rate, necessitating cautious interpretation. Additionally, only individuals who received both doses were included in the analysis, excluding those who could not receive the second dose due to severe AEs or death after the first dose. Consequently, the information regarding those individuals is not available. Lastly, our study utilized information on COVID-19 infection history between the first and second doses to compare the AEs experienced after the first dose with those experienced after the second dose, if the individual was infected between doses. However, due to the possibility of undetected infections, there may be limitations associated with the accuracy of the COVID-19 infection history.

Despite these limitations, our study has the strength of utilizing national system data to analyze the entire population of COVID-19 vaccine completers and AE reporters in the country, and by linking individual healthcare utilization data, it enabled in-depth analysis using demographic, socioeconomic, and clinical information. Through this, it was possible to identify that women, younger age groups, individuals from lower socioeconomic status groups, and those with underlying conditions have a higher risk of reporting AEs post-

vaccination. Our research identifies groups that may be more susceptible to vaccine safety concerns and delivers insights for individuals hesitant to get the XBB 1.5 booster due to AEs from the monovalent vaccine.

In conclusion, the overall reporting rate of AEs following either the first or second doses of the COVID-19 vaccine was 0.85%, and the reporting rate after both the first and second doses was 0.02%, which was lower than the rate reported only once (0.83%). In most cases, non-serious adverse reactions were reported. However, serious AEs, though rare (at 0.01%; 6,028 individuals), were also reported, including deaths. Furthermore, women, younger age groups, individuals with lower socioeconomic status, and those with underlying conditions were significantly more likely to report AEs. Additional clinical research based on medical data is needed to establish a causal relationship between the reported AEs and the COVID-19 vaccine.

Although the PHEIC has been lifted, maintaining immunization levels in an endemic situation to avoid reaching a tipping point requires reducing hesitancy and refusal to vaccinate and increasing vaccination rates. Therefore, the continuous management of vaccine AEs and safety and providing clear explanations to the public about the safety and benefits of vaccination are necessary. Altogether, this study identifies groups with higher reporting rates of AEs following COVID-19 vaccination, emphasizing the importance of monitoring post-vaccination AEs for promoting safe vaccination, alleviating vaccine-related anxiety and fear, and achieving optimal vaccination rates.

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## SUPPLEMENTARY MATERIALS

**Supplementary Table 1**
Coronavirus disease 2019 vaccination criteria by vaccine type

**Supplementary Table 2**
List of adverse events defined by Coronavirus Disease 2019 Vaccination Management System

**Supplementary Table 3**
ICD-10 codes for ten comorbid diseases

**Supplementary Table 4**
Number of adverse event reporters and cases by severity and timing of reports for different vaccine combinations

**Supplementary Table 5**
Ranking of adverse events by vaccine combinations (based on the number of reports per 100,000 vaccinations)

**Supplementary Table 6**

Characteristics of deaths reported after 2nd doses

**Supplementary Table 7**

Characteristics of reported adverse events according to vaccination period

## REFERENCES

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