International Journal of Infectious Diseases 162 (2026) 108194

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Incidence of respiratory infections after the COVID-19 pandemic (2023-2024) and its association of vaccination among entire populations in Korea

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ARTICLE INFO

Article history:
Received 11 September 2025
Revised 3 November 2025
Accepted 5 November 2025

Keywords:
Post-COVID
COVID-19 vaccine
Respiratory infectious diseases

ABSTRACT

Objectives: We aimed to investigate nationwide trends in respiratory infections during and after the COVID-19 pandemic and to evaluate the risk according to the COVID-19 vaccine dose.
Methods: Using the database, which integrates the insurance claims and vaccination records for the entire Korean population (N = 51,645,564), trends were assessed using SARIMAX models. We assessed associations between the doses that have been received until June 1, 2023, and the onset of respiratory infections, using Cox hazard and Fine-Gray models.
Results: Compared with pre-pandemic levels (2017-2019), influenza like illness (ILI) and pneumonia incidences dropped by over 90% during 2020-2021, followed by a resurgence of upper respiratory tract infection (URI) and common cold in 2023-2024. Pertussis incidence rose 46-fold above expected levels in late 2023. Individuals ($\geq 4^{th}$ dose) had lower risks of ILI (adjusted hazard ratio: 0.55 [95% CI: 0.54-0.57]) and pertussis (0.06 [0.04-0.08]), but higher risks of URI (1.32 [1.32-1.33]) and common cold (1.63 [1.62-1.64]), compared with unvaccinated or partially vaccinated.
Conclusion: With changes in respiratory infection patterns, COVID-19 vaccination may be differentially associated with respiratory infections in the post-pandemic era, reflecting shifts in population-level immunity and highlighting the need for adaptive public health strategies.

1. Introduction

Since the COVID-19 pandemic waves (2020-2022), numerous countries have witnessed substantial alterations of public health infrastructure, individual hygiene practices, healthcare accessibility, and patterns of diseases [1–4]. As our society has gradually transitioned into the end of the pandemic, often referred to as the "Post-COVID," "New Normal," or 'With-COVID' (2023-2024), total change has lasting implications not only on the healthcare system but also on the epidemiology of respiratory infectious diseases.

During the start and height of the pandemic, non-pharmaceutical interventions (NPIs) such as mask-wearing, social distancing, remote work, and school closures may reduce the transmission of various respiratory pathogens such as *influenza virus, human rhinovirus, human adenovirus, human respiratory syncytial virus*, and *SARS-CoV-2* [5–7]. Additionally, restrictions on healthcare services and reduced diagnostic tests for non-SARS-CoV-2 respiratory infections [8] contributed to an underreporting of cases, resulting in an unprecedented decline in the incidence of flu, *etc.* during 2020 and 2021 [9–11]. Nevertheless, as public vigilance against several infections waned in Mid-2022, a notable resurgence of respiratory infections was expected. For instance, the re-emergence of non-SARS-CoV-2 respiratory infections after Mid-2022 has alarmed potential rebound effects following prolonged

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https://doi.org/10.1016/j.ijid.2025.108194

suppression of pathogen circulation [12,13]. Immune responses and pulmonary tissue damage following SARS-CoV-2 infection may render individuals more susceptible to other respiratory infections [14]. Furthermore, structural and behavioral changes in the Post-COVID era, including improved indoor ventilation standards, early surveillance systems, adjustments in border controls, and updated governmental policies for infectious disease preparedness, have continued to change the pattern and seasonal trend of respiratory diseases after the pandemic. Amid these changes, concerns regarding unidentified viral interference and increased population susceptibility emerged. An immunity debt, referring to reduced population immunity due to decreased exposure to common pathogens during the pandemic, is especially relevant to children and older adults who may face increased risk of infection or more severe clinical outcomes [15]. Moreover, the administration of COVID-19 vaccines may also have altered the seasonality of infection outbreaks and modulated population-level susceptibility to other pathogens than *SARS-CoV-2*. Therefore, it is time for studies to be carried out to analyze new trends and evaluate the impact of vaccines on other respiratory diseases. Understanding this new epidemiology of respiratory infectious diseases is essential for informing future public health strategies, resource allocation, and clinical preparedness against ongoing respiratory disease threats.

Here, with the entire national cohort (N = 51,645,564), our study aims to analyze the trends and characteristics of major respiratory infections in the Republic of Korea during the Pandemic (2020-2022) and the Post-pandemic (2023-2024) and to assess the association between the dose of the COVID-19 vaccine and the onset of major respiratory infections.

2. Methods

2.1. Data source and study population

This retrospective cohort study included the entire Korean population, utilizing national health insurance data provided by the National Health Insurance Service (NHIS; database number: NHIS-2024-10-1-045). To facilitate COVID-19 research, the Korea Disease Control and Prevention Agency (KDCA), in collaboration with the NHIS, developed the K-CoV-N database. Nationwide polymerase chain reaction testing for *SARS-CoV-2* was conducted across hospitals and medical centers under KDCA supervision between January 2020 and May 2023, establishing comprehensive epidemiological data, including daily SARS-CoV-2-infected cases [16]. The K-CoV-N database integrates epidemiological surveillance data, complete vaccination records, and health insurance claims data, enabling longitudinal monitoring of clinical outcomes, including respiratory infections, alongside detailed sociodemographic information such as age, sex, and household income [17].

To investigate the incidence of seven major respiratory infections, this study analyzed insurance claims for the entire Korean population (N = 51,645,564) from the K-CoV-N database, with approval from the Institutional Review Board (IRB exemption number: E-2405-013-1534). Additionally, to assess the association between total received dose of COVID-19 vaccine and respiratory infectious diseases, an analytic cohort (N = 39,447,030) was constructed, excluding individuals with events of infection within 3 months prior to the start of observation (June 1, 2023).

2.2. COVID-19 pandemic and inoculation of COVID-19 vaccine (exposure)

The COVID-19 pandemic was categorized into distinct phases based on dominant SARS-CoV-2 variants and corresponding epidemic waves: Origin (January 2020-December 2020), Alpha/Beta (January 2020-June 2021), Delta (July 2021-December 2021), and Omicron and Sub-variant (January 2022-December 2022) [18,19]. The Post-pandemic phase was defined as the years of 2023 and 2024, coinciding with the termination of national quarantine policies and formal COVID-19 patient management programs (June 2023; Post-COVID). Severity of COVID-19 was operationally defined by incorporating indicators such as admission to the intensive care unit, oxygen supplementation, cardiopulmonary resuscitation, and use of extracorporeal membrane oxygenation, based on the World Health Organization (WHO) criteria [20,21]. The prescription of COVID-19-specific therapeutics, including regdanvimab, nirmatrelvir, and Paxlovid, along with comorbidities known to impact disease severity, was also considered to determine the severity.

COVID-19 Vaccines included ChAdOx1 nCov-19, BNT162b2, mRNA-1273, Ad26.COV2.S, Novavax, and SKYCovione, as well as updated formulations (BNT162b2-BA.1, BNT162b5, and mRNA-1273.214). Based on the history of the vaccine in the K-COV-N database, all participants were classified by the final received dose of COVID-19 vaccine status on June 1, 2023: no and first dose, second dose, third dose (first boost shot), and ≥fourth dose. Participants were followed up from June 1, 2023, to the end of observation (September 30, 2024) or the date of death or events.

2.3. Outcome: major respiratory infectious diseases

Outcome was operationally defined with the International Classification of Diseases, Tenth Revision (ICD-10) codes: I. upper respiratory tract infection (URI, "J00-J06") [22], II. hospitalized pneumonia ("J10-J18," requiring more than 2 days of hospitalization; accuracy=∼96%) [23], III. influenza like illness (ILI, "J09-J11") [24], IV. acute nasopharyngitis (common cold, "J00") [25], V. scarlet fever ("A38") [26], VI. pertussis ("A37") [27], VII. tuberculosis ("A15-A19," "B90," "U84.3," and "U88") [28], and VIII. COVID-19 ("U07.1" and "U07.2" with the KDCA's reports) [29]. Based on the operational definition, claims for the above infection from hospitals were extracted from insurance claim data between January 2016 and September 2024. If 91 days had elapsed from the previous infection (URI, pneumonia, ILI, common cold, scarlet fever, pertussis, and COVID-19), it was determined as the new infection (re-infection), and if not, the existing infection would continue. The time gap to determine a new onset of tuberculosis was used as a standard of 182 days.

2.4. Statistical analysis

Variables that were considered and included in the regression models were selected based on their clinical relevance and statistical significance: age (continuous), sex (male or female), income level (quartiles), Charlson comorbidity index (continuous), severity of COVID-19 (mild or severe among patients with COVID-19), phase of initial SARS-CoV-2 infection (origin, alpha/beta, delta, or omicron), and intervals between date of last inoculation and start date of observation (year, continuous). All citizens in Korea were stratified into four age groups for subgroup analyses: children and adolescents (0-19 years), young adults (20-39 years), middle-aged adults (40-64 years), and older adults (≥65 years).

All statistical analyses were performed using SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA). Statistics were reported as frequencies with percentages for categorical variables and means with standard deviations for continuous variables. The chi-square test and one-way analysis of variance (ANOVA) were employed to evaluate differences between groups for categorical and continuous variables, respectively. To estimate the pattern or seasonal trend during the Pandemic or Post-pandemic, autoregressive integrated moving average exogenous (ARIMAX) models for pertussis and tuberculosis or seasonal ARIMAX (SARIMAX) models

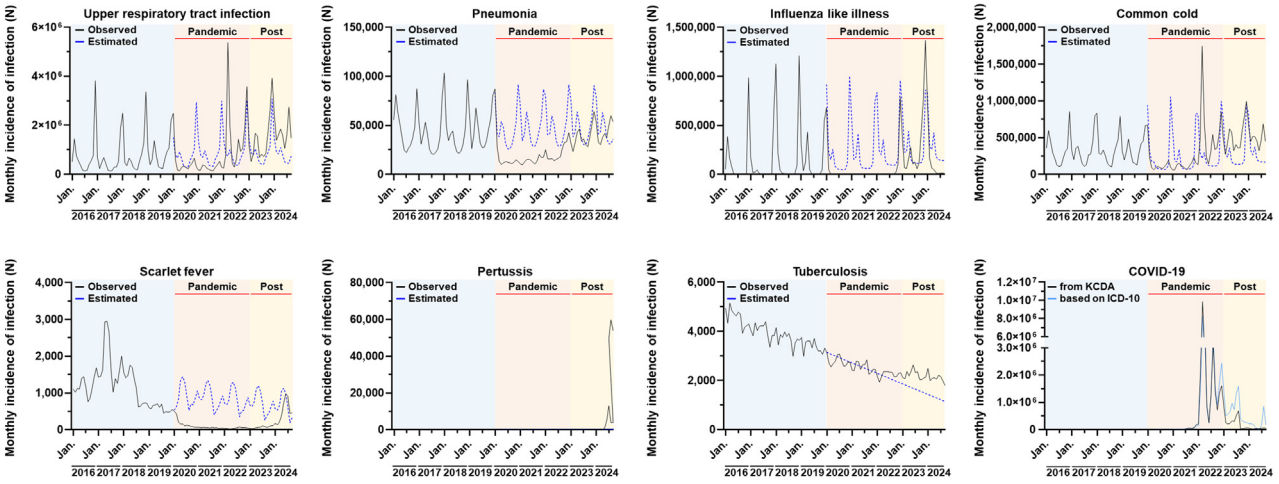

Figure 1. Monthly incidence of respiratory infectious diseases in Korea. From January 2016 to September 2024, monthly incidence of respiratory infectious diseases (ICD-10 codes): upper respiratory tract infection (URI, J00-J06), pneumonia (J10-J18), influenza like illness (J09-J11), acute nasopharyngitis (common cold, J00), scarlet fever (A38), pertussis (A37), tuberculosis (A15-A19, B90, U84.3, and U88), and COVID-19 (U07.1 and U07.2). While the black solid line is the observed incidence, the blue dashed line indicates an estimated incidence using autoregressive integrated moving average exogenous (ARIMAX) or seasonal autoregressive integrated moving average exogenous (SRIMAX) models with a trend of 2017-2019 and inputs of age, sex, income levels, and Charlson comorbidity index.

for URI, pneumonia, ILI, common cold, and scarlet fever calculated an estimated or expected monthly incidence of each infectious diseases, based on the previous incidence (2017-2019) and inputs (age, sex, income level, and Charlson comorbidity index). Then, comparisons between the monthly observed and estimated incidence during the periods or phases were performed. Furthermore, multivariable Cox proportional hazard regression or Fine-Gray sub-distribution hazards model (competing events: all-cause mortality) was used to estimate adjusted hazard ratio (aHR) or adjusted sub-distribution hazard ratio (aSHR) with corresponding 95% confidence intervals (CIs) and to evaluate the association between the dose of vaccine and major respiratory infectious diseases. Statistical significance thresholds (*P*-value, two-tailed) were set at $^{*}<0.05$, $^{**}<0.01$, and #<0.001. As one of the solutions for the error of multiple comparisons, the Benjamini-Hochberg method was used to calculate the adjusted *P*-value.

3. Results

3.1. New trends of respiratory infectious diseases during and after the COVID-19 pandemic

Figure 1 illustrates the monthly observed (black solid line) and estimated (blue dashed line) incidence of major respiratory infectious diseases during the Pandemic (2020-2022) and Post-pandemic periods (2023-2024). During the early COVID-19 pandemic (2020-2021), the monthly incidence of pneumonia, ILI, and scarlet fever markedly declined compared to the pre-pandemic periods (2017-2019). Especially, the monthly incidence of ILI decreased by more than 90% during the winter season of 2020-2021, relative to the expected level that was estimated from SARIMAX models (Table 1). During the Post-pandemic period, a resurgence of respiratory infections was observed. Notably, infectious cases of URI and common cold increased during the winter season of 2023 and 2024; the ratio of observed and estimated values of common cold between January 2023 and September 2024 was approximately 2.2-fold. While tuberculosis incidence remained stably decreasing throughout the overall period, that of pertussis, initially low (N of monthly cases < 100), began rising notably after mid-2023. ARIMAX models estimated a 46.1-fold (95% CIs, 2.04-90.2) increase in the incidence of pertussis, compared to the expected values. Similarly, stratified time series by age groups show that the dynamics and seasonality of major respiratory infections such as URI, hospitalized pneumonia, and common cold in Korea have substantially changed, with lower incidence and re-emerging (Supplementary Figure 1). Notably, the proportion of the middle-aged (orange) and older (red) adults increased in pneumonia and ILI during the Pandemic (Supplementary Figure 2). Conversely, the proportion of children (sky blue) and adolescents (blue) in the ILI increased after the COVID-19 pandemic (2023-2024). Supplementary Figure 3 illustrates the monthly sex ratio of infected cases.

3.2. Association of the dose of the vaccine and major respiratory infections after the pandemic

Among 39,447,030 individuals included in the analytic cohort, the association between the total dose of COVID-19 vaccine on June 1, 2023, and the onset of subsequent major respiratory infections was evaluated (Table 2). The mean of age ± SD in those who were unvaccinated or received only the first dose (No and 1st dose; N = 7,933,859), those who have received with two doses (2nd dose; N = 7,551,773), those who have inoculated with the first boost shoot (3rd dose; N = 16,662,259), and those who have received four and more doses (≥4th dose; N = 7,299,139) were 37.0 ± 24.2, 38.0 ± 15.0, 47.3 ± 15.9, and 67.1 ± 13.2 years, respectively, with substantial differences in age distribution across the groups (Supplementary Table 1). The number (%) of patients with COVID-19 was 3,824,829 (48.2%) in No and 1st, 4,423,939 (58.6%) in 2nd dose, 8,723,256 (52.4%) in 3rd dose, and 3,169,059 (43.4%) in 4th dose. Sex ratio (male to female) in No and 1st, 2nd dose, 3rd dose, and ≥4th dose was 1.18, 1.13, 0.99, and 0.99, in order. Individuals who received the four or more doses of COVID-19 vaccine (≥4th dose) showed a significantly lower risk of ILI, compared to those who were unvaccinated or only partially vaccinated (no and 1st): the aHR in Model 3 = 0.55 (0.54-0.57, adjusted P < 0.001) and aSHR for ILI was 0.56 (0.54-0.97, P < 0.001). Similarly, an inverse association was observed for pertussis. Participants in ≥4th dose had a 94% lower risk of pertussis (aHR in Model 3 = 0.06 (0.04-0.08, adjusted P < 0.001) and aSHR= 0.06 (0.04-0.08, P < 0.001) compared to those in No and 1$^{st\ dose}$. Conversely, the aHRs for URI and common cold in the ≥4th dose were higher than those in the 2nd dose; after adjustment (Model 3), the aHRs for URI and common cold were 1.32 (1.32-1.33, P < 0.001) and 1.63 (1.62-1.64, P < 0.001) in the ≥4th group, respectively. The aHRs for pneumo-

Table 1
Ratio of observed to estimated incidence of respiratory infections.

	Obs.	Est.	Difference (Obs. - Est.)	Ratio (Obs. per Est.)
Upper respiratory tract infection				
COVID-19 pandemic (January 2020-December 2022)	28,318,005	33,243,495	−4,925,490	0.98 (0.55, 1.42)
In Delta phase (July 2021-December 2021)	1,797,941	6124,186	−4,326,245	0.41 (0.25, 0.57)
In Omicron/sub-variant phase (January-December 2022)	18,669,363	11510,037	7,159,326	1.90 (0.68, 3.11)
Post-pandemic (January 2023-September 2024)	32,908,366	19319,903	13,588,463	1.92 (1.42, 2.43)
Pneumonia				
COVID-19 pandemic (January 2020-December 2022)	682,927	1730,273	−1,047,346	0.41 (0.34, 0.47)
In Delta phase (July 2021-December 2021)	92,064	280,976	−188,912	0.36 (0.26, 0.46)
In Omicron/sub-variant phase (January-December 2022)	272,136	589,805	−317,669	0.49 (0.38, 0.60)
Post-Pandemic (January 2023-September 2024)	857,140	1019,019	−161,879	0.92 (0.75, 1.08)
Influenza Like Illness				
COVID-19 pandemic (January 2020-December 2022)	1,692,345	9019,560	−7,327,215	0.08 (0.01, 0.15)
In Delta phase (July 2021-December 2021)	5367	1117,027	−1,111,660	0.01 (0.00, 0.01)
In Omicron/sub-variant phase (January-December 2022)	931,294	3387,157	−2,455,863	0.15 (0.03, 0.33)
Post-Pandemic (January 2023-September 2024)	4,970,983	5928,136	−957,153	0.88 (0.36, 1.41)
Common cold				
COVID-19 pandemic (January 2020-December 2022)	9,778,720	9534,016	244,704	1.54 (1.03, 2.05)
In Delta phase (July 2021-December 2021)	811,241	1274,436	−463,195	1.23 (0.54, 1.92)
In Omicron/sub-variant phase (January-December 2022)	6,379,630	3531,585	2,848,045	2.68 (1.34, 4.01)
Post-Pandemic (January 2023-September 2024)	10,721,067	6327,289	4,393,778	2.24 (1.76, 2.72)
Pertussis				
COVID-19 pandemic (January 2020-December 2022)	227	4835	−4608	0.05 (0.01, 0.09)
In Delta phase (July 2021-December 2021)	23	827	−804	0.03 (0.01, 0.04)
In Omicron/sub-variant phase (January-December 2022)	45	1847	−1802	0.02 (0.02, 0.03)
Post-pandemic (January 2023-September 2024)	191,591	3847	187,744	46.1 (2.04, 90.2)
Tuberculosis				
COVID-19 pandemic (January 2020-December 2022)	90,843	90,744	99	1.01 (0.98, 1.04)
In Delta phase (July 2021-December 2021)	14,975	14,482	493	1.03 (0.95, 1.11)
In Omicron/sub-variant phase (January-December 2022)	26,924	25,115	1809	1.08 (1.01, 1.14)
Post-pandemic (January 2023-September 2024)	45,682	31,606	14,076	1.47 (1.38, 1.55)

Estimated (or expected) values were calculated using ARIMAX or SRIMAX models, based on monthly incidences before the COVID-19 pandemic (2017-2019; 3-year.
Ratio >1: excess events occurred.
Abbreviation: Observed (Obs.); Estimate (Est.); Autoregressive integrated moving average exogenous (ARIMAX); Seasonal autoregressive integrated moving average exogenous (SRIMAX).

nia among children and adolescents (0-19 years) and older adults (≥65 years) were 0.46 (0.44-0.49, $P < 0.001$) and 0.75 (0.73-0.76, $P < 0.001$) in ≥4th dose, respectively, compared to those in 2nd dose (Supplementary Table 3) Additionally, the risk of tuberculosis was reduced by 12% in ≥4th dose; the aHR was 0.88 (0.79-0.98, $P < 0.05$) compared in 2nd dose. Among patients with COVID-19, the risk of common cold gradually increased according to more dose of vaccine; the aHRs in 2nd, 3rd, and ≥4th dose were 1.05 (1.03-1.06, $P < 0.001$), 1.12 (1.10-1.14, $P < 0.001$), and 1.36 (1.34-1.39, $P < 0.001$), in order, compared to that in No and 1st (Supplementary Table 2). Notably, regardless of the history of SARS-CoV-2 infection, the risk of ILI and pertussis gradually reduced when individuals received more doses of the vaccine.

4. Discussion

Through the retrospective cohort study, a temporary decline followed by a resurgence of URI and common cold was observed during and after the COVID-19 pandemic. In the Post-pandemic period (January 2023-September 2024), the risk of URI and common cold increased with higher COVID-19 vaccine doses, while ILI and pertussis showed an inverse association, indicating a protective effect. These key findings highlight the divergent trajectories of respiratory infections and their varying associations with vaccination status.

Our findings reveal the distinct pattern of respiratory infection incidence, including the short-term suppression of URI, pneumonia, ILI, and pertussis (2020-2022) and the following rise of URI, common cold, pertussis, and tuberculosis (2023-2024). The initial sharp decline in respiratory infections observed during the early phase of the COVID-19 pandemic is consistent with previous international reports [30,31]. Previous studies documented significant reductions in *influenza virus* and other common respiratory viruses during the Pandemic, due to strict NPIs and an abnormal monitoring system [32,33]. Hidden and undetected infection cases may be one of the reasons to decline due to the restrictions on hospital visits and the allocation of medical resources for COVID-19 management [34]. Another important distinction lies in the timing and magnitude of resurgence after the Pandemic. While some countries would experience immediate rebounds of respiratory infections following the relaxation (early 2022), our study shows a more gradual increase, with pronounced peaks emerging during late 2023 and early 2024, potentially reflecting differences in public health policies, healthcare access, population immunity, and spread of SARS-CoV-2 infection. This difference could be partially explained by Korea's own national health programs, including mandatory reporting and a national-level vaccination system, which persisted despite pandemic disruptions. The relaxation of NPIs and immunity debt (reduced population immunity) has created conditions favorable for other respiratory infections [35,36], such as damage to mucous membranes and lung tissues caused by SARS-CoV-2 infection, the prognosis of excess antibiotic prescription to prevent other infections during treatment for COVID-19, and disturbance of or exhaustion of the immune system. Especially, disruption of immune homeostasis due to prior SARS-CoV-2 infection may increase vulnerability to secondary infections [37,38]. Thus, these socio- and biological factors together contribute to altered transmission dynamics of the pathogens and heightened infection risk during the Post-pandemic era.

In terms of varying vaccine-associated outcomes, some studies have suggested that COVID-19 vaccines may exert indirect protective effects against some respiratory pathogens [39,40] by modulating the host immune response or through behavioral changes such as refraining from outdoor activities after the inoculation. Our

Table 2
Association of vaccine history of SARS-CoV-2 with respiratory infections during the post-pandemic periods (2023-2024).

	Vaccine status on June 01, 2023, [dose]				$P_{for\ trend}$
	No and 1st	2nd	3rd	≥4th	
Study population, N	7,933,859	7,551,773	16,662,259	7,299,139	
Upper respiratory tract infection					
Events, N (%)	3,678,488 (46.4)	3,692,666 (48.9)	7,830,605 (47.0)	3,145,640 (43.1)	
PY [Year]	7,367,938.0	7,014,610.8	15,824,024.5	7,131,273.0	
Crude HR (95% CIs)	1.00 (Reference)	1.05 (1.05, 1.05)***	0.99 (0.99, 0.99)***	0.88 (0.88, 0.89)***	
aHR (95% CIs)					
Model 1	1.00 (Reference)	1.09 (1.09, 1.09)***	1.16 (1.15, 1.16)***	1.32 (1.32, 1.33)***	
Model 2	1.00 (Reference)	1.04 (1.03, 1.04)***	1.11 (1.10, 1.11)***	1.28 (1.27, 1.28)***	
Model 3	1.00 (Reference)	1.25 (1.24, 1.26)***	1.36 (1.35, 1.37)***	1.65 (1.64, 1.67)***	<0.001
		1.00 (Reference)	1.09 (1.09, 1.09)***	1.32 (1.32, 1.33)***	
Adjusted *P*-value	Reference	<0.001	<0.001	<0.001	
aSHR (95% CIs) in Model 3	1.00 (Reference)	1.26 (1.25, 1.27)***	1.38 (1.37, 1.38)***	1.68 (1.66, 1.69)***	
Pneumonia					
Events, N (%)	996,832 (12.6)	573,188 (7.6)	883,776 (5.3)	342,199 (4.7)	
PY [Year]	9,778,049.3	9,604,102.3	21,496,359.6	9,417,705.1	
Crude HR (95% CIs)	1.00 (Reference)	0.59 (0.58, 0.59)***	0.40 (0.40, 0.41)***	0.36 (0.36, 0.36)***	
aHR (95% CIs)					
Model 1	1.00 (Reference)	0.71 (0.71, 0.71)***	0.62 (0.61, 0.62)***	0.85 (0.84, 0.85)***	
Model 2	1.00 (Reference)	0.66 (0.65, 0.66)***	0.58 (0.58, 0.58)***	0.82 (0.81, 0.82)***	
Model 3	1.00 (Reference)	0.85 (0.84, 0.87)***	0.78 (0.77, 0.79)***	1.18 (1.16, 1.21)***	<0.001
		1.00 (Reference)	0.92 (0.91, 0.92)***	1.39 (1.38, 1.40)***	
Adjusted *P*-value	Reference	<0.001	<0.001	<0.001	
aSHR (95% CIs) in Model 3	1.00 (Reference)	0.86 (0.84, 0.87)***	0.79 (0.77, 0.80)***	1.20 (1.17, 1.22)***	
Influenza Like Illness					
Events, N (%)	777,053 (9.8)	535,361 (7.1)	743,054 (4.5)	141,548 (1.9)	
PY [Year]	9,876,113.4	9,612,599.6	21,562,774.8	9,533,754.3	
Crude HR (95% CIs)	1.00 (Reference)	0.71 (0.70, 0.71)***	0.44 (0.44, 0.44)***	0.19 (0.19, 0.19)***	
aHR (95% CIs)					
Model 1	1.00 (Reference)	0.96 (0.96, 0.96)***	0.83 (0.83, 0.83)***	0.76 (0.75, 0.76)***	
Model 2	1.00 (Reference)	0.87 (0.87, 0.87)***	0.77 (0.77, 0.77)***	0.72 (0.72, 0.73)***	
Model 3	1.00 (Reference)	0.72 (0.71, 0.73)***	0.62 (0.61, 0.63)***	0.55 (0.54, 0.57)***	<0.001
		1.00 (Reference)	0.86 (0.86, 0.87)***	0.77 (0.76, 0.78)***	
Adjusted *P*-value	Reference	<0.001	<0.001	<0.001	
aSHR (95% CIs) in Model 3	1.00 (Reference)	0.72 (0.71, 0.73)***	0.62 (0.61, 0.63)***	0.56 (0.54, 0.57)***	
Common cold					
Events, N (%)	993,934 (12.5)	819,428 (10.8)	1,735,891 (10.4)	750,674 (10.3)	
PY [Year]	9,780,153.2	9,445,667.6	20,884,470.7	9,092,919.1	
Crude HR (95% CIs)	1.00 (Reference)	0.85 (0.85, 0.86)***	0.82 (0.82, 0.82)***	0.81 (0.81, 0.82)***	
aHR (95% CIs)					
Model 1	1.00 (Reference)	0.91 (0.91, 0.92)***	0.99 (0.98, 0.99)***	1.25 (1.24, 1.25)***	
Model 2	1.00 (Reference)	0.89 (0.89, 0.89)***	0.97 (0.96, 0.97)***	1.23 (1.22, 1.23)***	
Model 3	1.00 (Reference)	1.36 (1.34, 1.38)***	1.55 (1.53, 1.57)***	2.22 (2.18, 2.25)***	<0.001
		1.00 (Reference)	1.14 (1.14, 1.15)***	1.63 (1.62, 1.64)***	
Adjusted *P*-value	Reference	<0.001	<0.001	<0.001	
aSHR (95% CIs) in Model 3	1.00 (Reference)	1.37 (1.35, 1.38)***	1.57 (1.55, 1.59)***	2.24 (2.20, 2.28)***	
Pertussis					
Events, N (%)	7,296 (0.09)	3,007 (0.04)	1,759 (0.01)	428 (0.01)	
PY [Year]	10,542,860.5	10,053,110.8	22,167,825.7	9,648,262.7	
Crude HR (95% CIs)	1.00 (Reference)	0.43 (0.41, 0.45)***	0.12 (0.11, 0.12)***	0.06 (0.06, 0.07)***	
aHR (95% CIs)					
Model 1	1.00 (Reference)	0.91 (0.87, 0.95)***	0.42 (0.40, 0.45)***	0.84 (0.75, 0.94)***	
Model 2	1.00 (Reference)	0.81 (0.77, 0.85)***	0.40 (0.37, 0.42)***	0.85 (0.76, 0.95)***	
Model 3	1.00 (Reference)	0.12 (0.10, 0.16)***	0.05 (0.04, 0.06)***	0.06 (0.04, 0.08)***	<0.001
		1.00 (Reference)	0.39 (0.36, 0.41)***	0.46 (0.40, 0.53)***	
Adjusted *P*-value	Reference	<0.001	<0.001	<0.001	
aSHR (95% CIs) in Model 3	1.00 (Reference)	0.12 (0.11, 0.15)***	0.05 (0.04, 0.06)***	0.06 (0.04, 0.08)***	
Tuberculosis					
Events, N (%)	4,368 (0.06)	3,067 (0.04)	9,736 (0.06)	11,100 (0.15)	
PY [Year]	10,541,496.4	10,051,637.6	22,161,372.4	9,640,946.1	
Crude HR (95% CIs)	1.00 (Reference)	0.74 (0.70, 0.77)***	1.06 (1.02, 1.10)**	2.78 (2.68, 2.88)***	
aHR (95% CIs)					
Model 1	1.00 (Reference)	1.07 (1.02, 1.13)**	1.00 (0.96, 1.03)	1.01 (0.97, 1.05)	
Model 2	1.00 (Reference)	1.08 (1.03, 1.13)**	1.00 (0.96, 1.03)	1.01 (0.97, 1.05)	
Model 3	1.00 (Reference)	1.12 (0.97, 1.29)	1.04 (0.89, 1.21)	1.06 (0.88, 1.28)	0.049
		1.00 (Reference)	0.93 (0.89, 0.97)**	0.95 (0.89, 1.02)	
Adjusted *P*-value	Reference	0.190	0.668	0.650	
aSHR (95% CIs) in Model 3	1.00 (Reference)	1.16 (1.01, 1.33)*	1.09 (0.93, 1.27)	1.14 (0.94, 1.37)	

HRs (95% CIs) and *P*-value were calculated, using the Cox proportional hazards model, with the following adjustments.
Model 1: age, sex, income level, and Charlson comorbidity index.
Model 2: Model 1 + COVID-19.
Model 3: Model 2 + severity, phase of infection, interval between last inoculation and May 31, 2023.
SHRs (95% CIs) and *P*-value were calculated, using the Fine-Gray sub-distribution hazards model (mortality as competing event), with the adjustments (Model 3).
Abbreviation: number (N); Person year (PY); hazard ratio (HR); adjusted hazard ratio (aHR); confidence intervals (CIs); adjusted sub-distribution hazard ratio (aSHR).
* Unadjusted *P*-value: <0.05/Adjusted *P*-value, using Benjamini-Hochberg method.
** Unadjusted *P*-value: <0.01/Adjusted *P*-value, using Benjamini-Hochberg method.
*** Unadjusted *P*-value: <0.001/Adjusted *P*-value, using Benjamini-Hochberg method.

results align with these observations, potentially showing an inverse association between the number of COVID-19 vaccine doses and the onset of ILI and pertussis. The inverse association of COVID-19 vaccination with ILI and pertussis might be explained by immune system priming. COVID-19 vaccines, particularly platforms of mRNA, virus-driven materials, or adjuvants, have been shown to stimulate innate immune responses, potentially enhancing antiviral and antibacterial defenses [41]. Additionally, individuals who adhere to vaccination schedules may also engage more rigorously in other protective health behaviors, such as inoculation for seasonal influenza vaccination [42–44]. Despite these similarities, however, our study also revealed notable deviations from prior findings. Interestingly, we observed that the risk of URI and common cold increased in proportion to the number of COVID-19 vaccine doses received. This finding contrasts with earlier hypotheses proposing that COVID-19 vaccination might confer broad nonspecific protection against other respiratory viruses. Since the demographic nature of vaccinated individuals, such as age and the interests of individual health care, greatly differed, the positive relationship between higher vaccine doses and increased risk of URI and common cold may reflect age-related confounding. Older adults, who were more likely to receive booster doses, are inherently at higher risk for respiratory infections due to immune-senescence and underlying comorbidities. Although multivariable adjustments and stratified analysis were done, residual confounding cannot be completely solved. Nevertheless, several biological mechanisms may underlie the observed associations between COVID-19 vaccination status and respiratory infection risk. Pandemic-driven changes in pathogen circulation patterns and viral interference may have contributed. Suppression of one respiratory virus can sometimes facilitate the spread of others through the ecological niche model. For example, suppression of the *influenza virus* during the pandemic may have altered competitive dynamics among respiratory pathogens. Furthermore, alterations in mucosal immunity due to prolonged periods of reduced pathogen exposure may have rendered populations more susceptible to certain infections once public health restrictions were lifted [45]. This mechanism likely contributed to the observed rebound in URI and common cold incidence, particularly among younger individuals who had limited exposure to common pathogens during the pandemic.

This study has several limitations. First, although this retrospective cohort study provides novel evidence on the potential associations of COVID-19 vaccine doses with the onset of several respiratory infections, our findings should be interpreted as associative in the absence of immunologic and clinical biomarkers. Since the mechanisms underlying these heterogeneous results remain unclear, further immunologic, epidemiologic, and laboratory-based investigations are warranted to clarify and confirm these associations among different populations. Next, as we utilized a nationwide cohort encompassing all insurance claims data in Korea, diagnostic accuracy may be affected by potential miscoding or limitations inherent to claims-based operational definitions. Notably, young and middle-aged adults may be less likely to visit the hospitals for mild symptoms of common cold or ILI, which could lead to an underestimation of the incidence of URI, common cold, and ILI due to unrecorded claims. Moreover, despite adjusting for multiple covariates, residual confounding effects, particularly related to age and behavioral factors, may persist. While both crude and adjusted risks were presented across population groups, further methods to solve the heterogeneity, such as matching or weighting, could not be feasibly implemented due to substantial differences in demographic and clinical characteristics between vaccination groups. Additionally, vaccination status was classified solely based on the number of doses received, without accounting for vaccine type, intervals between doses, or episodes of inoculation and SARS-CoV-2 infection, all of which may influence susceptibility to other infections. Finally, as this was an observational study, causal inferences between COVID-19 vaccination and the risk of subsequent respiratory infections cannot be definitively established.

In conclusion, this retrospective cohort study provides robust evidence of dynamic changes in respiratory infection patterns during and after the COVID-19 pandemic in Korea. While COVID-19 vaccination appears to confer partial protection against certain respiratory infections, such as ILI and pertussis, a paradoxical increase in the risk of URI and common cold with higher vaccine doses was noted. These findings identify the complex interplay between vaccination, immunity, and pathogen ecology in the post-COVID era and highlight the need for tailored public health strategies to manage respiratory infections in a transitioning global health landscape.

Generative AI and AI-assisted technologies

Generative AI (ChatGPT) was used exclusively to clarify sentences and to check grammar. All research processes, including data analysis, presentation of results (tables, figures, and supplementary materials), and manuscript writing, were entirely conducted by the authors and authored under the full responsibility of the authors.

Data sharing statement

The original and processed data in this cohort study are only accessible to qualified researchers in permitted security facilities for a certain period since the used database was based on records of national insurance. Thus, the raw data cannot be shared openly. However, access to the code used in this study can be shared for noncommercial and academic purposes.

Declaration of competing interest

The authors declared that no conflict of interest exists.

Funding

This study was supported by a grant of the National Research Foundation of Korea funded by the Korean government (NRF-2022R1A2C2092076 and RS-2023-00227944).

Ethical approval

The Institutional Review Board of Seoul National University Hospital approved this study (Notice of Ethics Review and Results (Exemption): *E-2405-013-1534*), which complies with the principles of the Declaration of Helsinki: the encrypted information and no informed consent. Individuals cannot be identified through de-identified data of authorized institutions, raw data can only be accessed at security centers, and finally, processed results (tables and graphs) can only be taken out with approval. This retrospective cohort and observation study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines and checklist.

Acknowledgments

None.

Author contributions

J. Song and SM. Park had full access to all of the data. Study concept and design: J. Song, A.Y. Chun, and SM. Park. Analysis of data: J. Song. Validation: J. Jung, S. Jeong, and SJ. Park. Interpretation of data: All authors. Writing the manuscript: All authors. Revision of the manuscript: All authors.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2025.108194.

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