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Serious adverse events following immunization and predictors of mortality associated with COVID-19 vaccination in India: a secondary data analysis of nationwide causality assessments

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Abstract

Background: Vaccines against COVID-19 were viewed as a way out to the ongoing pandemic and were given the emergency use authorization in India to initiate mass vaccination in January 2021. This study aimed to investigate the serious adverse events following immunizations (AEFIs) reported for COVID-19 vaccines and to identify predictors of mortality among these cases from India.

Methods: A secondary data analysis was conducted on the causality assessment reports for the 2708 serious AEFIs published by the National AEFI Committee under the Immunization Division, Ministry of Health and Family Welfare, Government of India. The analysis included all 21 reports published up until May 2023. The primary outcome variable analyzed was the survival/death status of each AEFI case, with various covariates from the published documents considered in the analysis.

Results: The majority of the serious AEFIs assessed were either coincidental (1220, 45%) or undetermined/unclassifiable (781, 28.8%). The majority of the serious AEFIs were reported among recipients of Covishield (1891, 69.8%) followed by Covaxin (347, 12.8%). Among these, 1114 (42.1%) died while the remaining 1594 (58.9%) were hospitalized and recovered. Systematically, AEFIs involving the cardiovascular system (696, 31.3%) were the most common, followed by those affecting the respiratory system (288, 13%) and neuropsychiatric system (295, 13.3%) which had a significant association with age ($p < 0.001$) and gender ($p < 0.001$). On multivariable analysis, females ($p = 0.001$), younger age groups ($p < 0.001$), AEFIs whose causality was determined and classified ($p < 0.001$), AEFI involving gastrointestinal and neuropsychiatric system ($p < 0.001$), AEFIs reported from North and Western India ($p = 0.001$) and those occurring during the winter season ($p < 0.05$) had significantly lower odds of mortality.

Conclusion: Among the cohort of serious AEFIs reported, older age, male sex, undetermined or unclassifiable causality classification, and involvement of the cardiovascular system were associated with significantly higher odds of mortality and require close monitoring following vaccination.

Plain language summary

Understanding serious side effects from COVID-19 vaccines in India: key findings and risks

COVID-19 vaccines were introduced in India in January 2021 to help control the pandemic. This study looked at serious side effects reported from these vaccines to see which were

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most common and what factors might predict serious outcomes, including death. The research analyzed data from 2708 serious side effect reports reviewed by the National AEFI Committee in India up to May 2023. The study found that many serious side effects were either coincidental (45%) or unclassifiable (29%). Most of these reports came from people who had received the Covishield vaccine (70%), with fewer from those who got Covaxin (13%). Out of the serious side effects reported, 42% resulted in death, while 59% led to hospitalization but recovery. The most frequent side effects affected the heart (31%), followed by the respiratory system (13%) and the nervous system (13%). Age and gender were important factors, with older adults and males showing higher risks of severe outcomes. The study also found that females, younger people, and those with certain types of side effects had lower odds of dying. Additionally, serious side effects reported in northern and western India and during winter had different patterns compared to other regions and times. Overall, the study highlights that older age, male sex, unclassified side effects, and those involving the cardiovascular system are associated with higher mortality rates. It underscores the need for careful monitoring of individuals who experience serious side effects after vaccination, especially those at higher risk.

Keywords: adverse events following immunization, causality assessment, COVID-19 vaccine, mortality, predictors

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Introduction

The COVID-19 pandemic began in December 2019 in Wuhan, China, spreading globally by early 2020 and was declared a public health emergency by the World Health Organization (WHO) in January 2020. By October 2024, the pandemic had resulted in approximately 776 million cases and over 7 million deaths worldwide. Despite evolving strains, WHO ended its Public Health Emergency of International Concern status in May 2023, marking a significant transition in global response efforts.[1,2]

COVID-19 mitigation efforts heavily relied on vaccine rollout, initially utilizing FDA-approved mRNA vaccines such as Pfizer BNT162b2 and Moderna mRNA-1273, alongside adenoviral vector vaccines like Janssen Biotech Ad26.COV2.S and AstraZeneca SkBio AZD1222. In India, vaccination commenced on January 16, 2021, starting with healthcare and frontline workers before expanding to seniors, high-risk individuals, and the general population primarily using Covishield and indigenous Covaxin. Sputnik-V was also made available at private hospitals.[3–7] By December 2023, approximately 67% of the global population had completed their primary vaccine series, with about 32% having received at least one booster dose.[2]

Since the introduction of COVID-19 vaccines, numerous reports globally have documented adverse events following immunization (AEFI). AEFI encompasses any unintended medical occurrence after vaccination that may not be directly linked to the vaccine itself. These events are categorized according to guidelines revised by WHO and the Council for International Organizations of Medical Sciences (CIOMS), which were updated in 2005, 2010, and 2015.[8] In India, AEFIs are classified into five categories for causality assessment: vaccine product-related reactions, vaccine quality defect-related reactions, immunization error-related reactions, immunization anxiety-related reactions, and coincidental events. This framework assists health authorities in evaluating and managing the safety of COVID-19 vaccination programs effectively.[9]

Observational studies have highlighted several factors influencing AEFI following COVID-19 vaccination, including age, gender, and comorbidities such as autoimmune diseases like rheumatoid arthritis and neuropsychiatric disorders

like seizures; de novo cases can be more severe than flare-ups. Notably, females aged 18–45 years often exhibit a higher likelihood of AEFI compared to males and other age groups. Although rare, events like Bacillus Calmette Guerin (BCG) reactivation, Bell's Palsy, Guillain-Barre syndrome, and immune-mediated demyelination have also been reported post-vaccination.[10–12] Moreover, mortality associated with COVID-19 vaccines has been reported from various parts of the globe; however, findings have been inconclusive as most studies failed to establish a causal relationship between deaths and COVID-19 vaccine reception status.[13–18] In India, the National AEFI Committee oversees causality assessments after AEFI reporting, ensuring transparency and ongoing safety monitoring alongside routine vaccination efforts.[19] This committee evaluates reported AEFIs based on various factors such as vaccine type, timing of vaccination, age, gender, comorbidities of recipients, and other relevant information and assigns a causality classification for each AEFI case.

The present study conducts a secondary data analysis of AEFI causality assessment reports published by the National AEFI Committee up to May 2023. Our aim was to explore survival factors associated with serious AEFIs following COVID-19 vaccination in India. By identifying patterns and predictors related to mortality among these cases, we seek to enhance understanding of AEFIs and inform public health policies aimed at improving vaccine safety monitoring.

Methodology

A secondary data analysis was conducted in May 2024 using data from published documents on causality assessment of serious AEFI cases, as compiled by the National AEFI Committee under the Immunization Division, Ministry of Health and Family Welfare, Government of India (GoI), adhering to the WHO/CIOMS guidelines for causality assessment of AEFIs.[8,9] The National AEFI Committee, composed of independent experts, including epidemiologists, clinicians, and public health specialists, is responsible for determining the causality of serious AEFIs reported across the country. Apart from this, we have also ensured that our study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist for the reporting of our findings. For this analysis, a total of 21 documents, published between February 2021 and May 2023, were included, all of which met the inclusion criteria. These documents provided detailed information for each serious AEFI case, including (i) unique ID, (ii) age, (iii) gender, (iv) month and year of vaccination, (v) type of vaccine administered, (vi) outcome status (recovered/death), (vii) diagnosis, (viii) AEFI classification, and (ix) date of report approval by the AEFI committee.[19] Documents that did not meet the serious AEFI classification were excluded. Missing data were handled by coding them separately and specifying this approach during the data analysis. Since this was a secondary data analysis, no specific sampling technique or formal sample size calculation was required, given the objective of the study was to provide a comprehensive overview of the patterns and distribution of all reported AEFI cases and their association with mortality.

Serious AEFIs are those that fulfills at least one among the following criteria after vaccination, including (i) *Life-threatening*: the event poses a significant risk to the life of the individual, (ii) *Hospitalization*: the event results in hospitalization or prolongation of an existing hospitalization, (iii) *Persistent disability*: the event leads to persistent or significant disability or incapacity, (iv) *Congenital anomaly/birth defect*: the event results in a congenital anomaly or birth defect, (v) *Fatal outcome*: the event results in death, (vi) *Intervention required*: any medical event that requires intervention to prevent one of the outcomes listed above may also be considered serious.

The unique ID of each case included information regarding the state and district from which the AEFI case was reported. This information was used to develop a new variable, indicating the state from which the AEFI case was reported. The states were then categorized into six different geographic locations namely, North, North-east, East, West, South, and Central India, following methodologies used in similar studies.[20]

Age groups were categorized as <25, 26–40, 41–59, and $\geqslant 60$ years. The rationale for these age group categories is based on common demographic trends observed in vaccine responses and adverse events. The sex categories included male

and female. Types of vaccines administered included Covishield, Covaxin, and others—where "others" refers to vaccines such as Sputnik-V and Corbevax.

The month and year during which AEFI was reported were used to categorize occurrences into four weather categories; winter, pre-monsoon, monsoon, and post-monsoon as per categorization provided by the Indian Meteorological Department, Ministry of Earth Sciences, GoI.[21]

The individual diagnosis was categorized based on the organ system involved namely, cardiovascular system, respiratory system, central or peripheral nervous system and psychiatric diagnosis, gastrointestinal system, infectious diseases, acute organ injuries, and others.

After causality assessment, the National AEFI Committee classifies serious AEFIs into the following categories; A1—vaccine product-related reaction, A2—vaccine quality defect-related reaction, A3—immunization error-related reaction, A4—immunization anxiety-related reaction, B1—temporal relationship is consistent but there is insufficient definitive evidence for vaccine causing event, B2—reviewing factors result in conflicting trends of consistency and inconsistency with causal association to immunization, C—coincidental—underlying or emerging condition(s), or conditions caused by exposure to something other than vaccine, D—unclassifiable. In our analysis, we have clubbed those cases that were classified as B1, B2, and D as unclassifiable/undetermined and the rest were reported as it is.

The data accessed from the reports were first converted to MS Excel, coded, and later extracted to SPSS software version 22 of IBM for analysis. After checking for duplicate cases, descriptive analysis of all the variables was performed and were expressed as frequencies and proportions. The association of age, gender, and vaccine type with AEFI classification and organ system involved was assessed using a chi-squared test/Fischer's exact test. Stratified analysis of AEFI classification with organ system involved was done among age groups, gender, and type of vaccine administered to address any confounders. The primary outcome variables analyzed were death or recovery after reporting a serious AEFI episode. Independent predictors for outcomes were evaluated using univariate logistic regression; those variables found significant in univariate analysis were included for multivariable logistic regression. All estimates were represented as odds ratios with 95% confidence intervals.

Since this was a secondary data analysis of reports available in the public domain, ethical permission was waived by the Institute Human Ethics Committee, All India Institute of Medical Sciences (AIIMS), Gorakhpur, India.

Results

Causality assessment of a total of 2708 serious AEFIs following COVID-19 vaccination published by the National AEFI Committee of India, was included in the current analysis (Figure 1).

Sociodemographic and clinical characteristics

The majority (1592, 58.8%) of serious AEFI cases were reported in individuals aged 41 years and above. The incidence of serious AEFI cases was equally distributed among both sexes. When averaging the incidence of AEFI cases for the years 2021 and 2022 by season, the highest number of serious AEFIs was reported during the summer months, followed by the monsoon. Geographic location wise, the highest incidence of AEFIs was reported from southern India (33.8%), followed by eastern India (19.3%). With respect to the type of vaccine administered, the highest number of serious AEFIs was reported among the recipients of Covishield (1891 cases, 69.8%), followed by Covaxin (347 cases, 12.8%) and other vaccines (147 cases, 5.1%), while data on the type of vaccine administered were unavailable for 322 serious AEFI cases. In the causality assessment, 1927 (71.2%) serious AEFIs were classified, while the remaining cases could not be determined or classified. Among the total reported cases, 1114 (41.1%) died, while the remaining 1594 (58.9%) were hospitalized and subsequently recovered (Table 1).

Stratified analysis of AEFI classification and diagnosis by age group

On stratified analysis of the causality assessment with age categories (<25, 26–40, 41–59, and

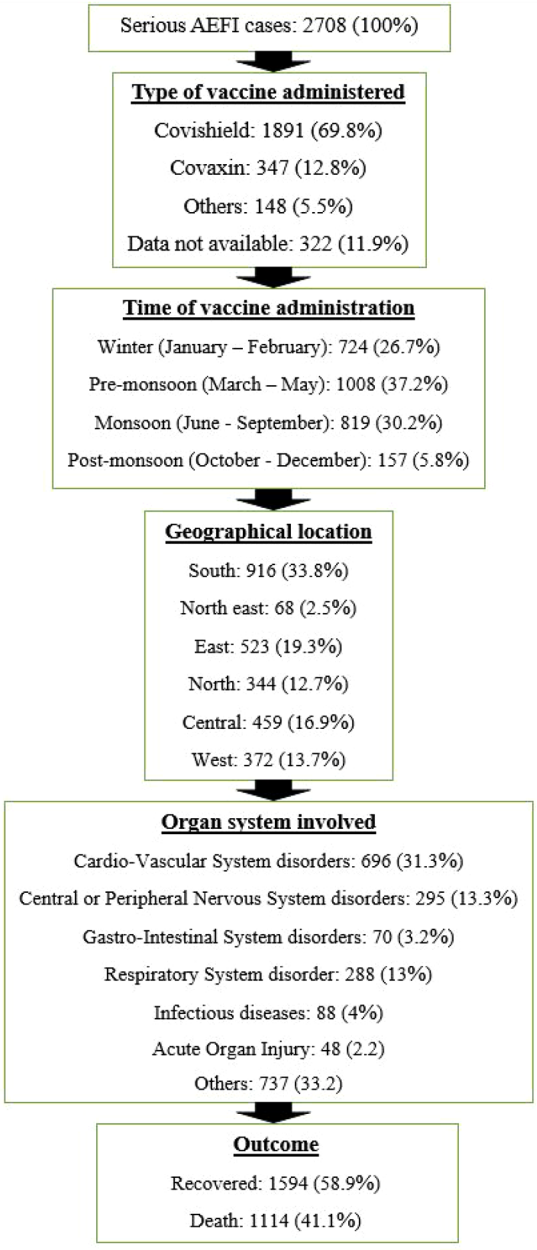

Figure 1. Flow chart shows patterns of serious adverse events following immunization in India.

⩾60 years), it was found that the contribution of vaccine product-related reactions was proportionately higher in the 26–40-year age group (22.7%), followed by <25-year age group (19.9%). by contrast, immunization error-related reactions were higher in the <25-year age group (8.6%), compared to the combined total of the other age groups (1.9%). Immunization anxiety-related reactions were again higher in the <25-year age group (19.9%) followed by the 26- to 40-year age group (14.5%), while coincidental reactions were higher in the ⩾60-year age group (73.7%) and followed by a decreasing trend as age decreased. These findings were expected as a weak immune system of the elderly would be anticipated to react less strongly to the foreign antigens due to immunosenescence,[22] which likely resulted in fewer occurrences of vaccine product-related reactions in this age group. Conversely, comorbidities associated with older adults may have led to a higher proportion of coincidental reactions. Those serious AEFIs that could not be determined and classified were almost equally distributed among the first three age categories (34.2%, 33.7%, and 31%), while 20% of AEFIs among those aged ⩾60 years were unclassifiable. These findings were statistically significant during a chi-squared test, with $p < 0.001$ (Table 2).

Regarding the organ systems involved or the diagnosis of serious AEFI cases, the cardiovascular system (54.3%) and respiratory system (17.2%) were most affected in older age groups (⩾60 years), while nervous system involvement (28.5%) and infectious disease etiologies (4.6%) were more common in younger age groups (<25 years). The former association is expected, as cardiovascular and respiratory morbidities are prevalent among the elderly population, while the involvement of the nervous system and infectious diseases associated with AEFI cases reported among younger populations should be given proper consideration, as insults to the nervous system earlier in life can have serious implications later on, such as cognitive impairment or other neuropsychiatric illnesses. These findings were also statistically significant using a chi-squared test, with $p < 0.001$ (Table 2).

In a 2×2 table analysis of AEFI classifications with organ systems involved, stratified by age, it was found that there was virtually no association between vaccine product-related reactions and either cardiovascular or nervous system involvement across any age categories, while gastrointestinal system involvement was associated with vaccine product-related reactions in all age groups, with proportional contributions increasing with age. Another notable observation under coincidental reactions was that the proportion of individuals presenting with cardiovascular

Table 1. Distribution of sociodemographic and clinical characteristics of serious AEFI cases ($n = 2708$).

Variables	Categories	Frequency, *n* (%) (*N* = 2708)
Age groups (in years)	<25 years	573 (21.2)
	26–40 years	543 (20.1)
	41–59 years	758 (28)
	⩾60 years	834 (30.8)
Sex	Male	1354 (50)
	Female	1354 (50)
Seasons of vaccination	Winter (January–February)	724 (26.7)
	Pre-monsoon (March–May)	1008 (37.2)
	Monsoon (June–September)	819 (30.2)
	Post-monsoon (October–December)	157 (5.8)
Geographic location[a]	South	916 (33.8)
	North east	68 (2.5)
	East	523 (19.3)
	North	344 (12.7)
	Central	459 (16.9)
	West	372 (13.7)
Type of vaccine[b]	Covishield	1891 (69.8)
	Covaxin	347 (12.8)
	Others	148 (5.5)
Causality assessment classification	Causality determined and classified	1927 (71.2)
	Causality undetermined/unclassified	781 (28.8)
Outcome	Recovered	1594 (58.9)
	Death	1114 (41.1)

[a]Data available for 2682 cases.
[b]Data available for 2386 cases.
AEFI, adverse events following immunization.

manifestations increased with age (3.6%, 23.7%, 45.9%, and 65.3%), while the association for nervous system involvement reversed (26.2%, 14.5%, 6.4%, and 1.2%). Immunization error-related reactions were mostly associated with infectious disease manifestations and this association was evenly distributed across all the age groups (Supplemental Table 1).

Table 2. Distribution of causality assessment and organ system involved by age ($N = 2708$).

Variables	Age group (in years)					*p*-Value
	<25 (*N* = 573), *n* (%)	26–40 (*N* = 543), *n* (%)	41–59 (*N* = 758), *n* (%)	⩾60 (*N* = 83,4) *n* (%)	Total (*N* = 2708), *n* (%)	
Causality assessment classification						
Vaccine product-related reaction	114 (19.9)	123 (22.7)	95 (12.5)	34 (4.1)	366 (13.5)	
Immunization error-related reaction	49 (8.6)	4 (0.7)	5 (0.7)	4 (0.5)	62 (2.3)	<0.001
Immunization anxiety-related reaction	114 (19.9)	79 (14.5)	72 (9.5)	14 (1.7)	279 (10.3)	
Coincidental reaction	100 (17.5)	154 (28.4)	351 (46.3)	615 (73.7)	1220 (45.1)	
Unclassifiable	196 (34.2)	183 (33.7)	235 (31)	167 (20)	781 (28.8)	
Organ system involved[a]						
Cardiovascular system disorders	12 (3.1)	60 (14.2)	205 (32.2)	419 (54.3)	696 (31.3)	
Central or peripheral nervous system disorders	111 (28.5)	76 (17.9)	78 (12.2)	30 (3.9)	295 (13.3)	
Gastrointestinal system disorders	12 (3.1)	22 (5.2)	13 (2)	23 (3)	70 (3.2)	
Respiratory system disorder	30 (7.7)	28 (6.6)	97 (15.2)	133 (17.2)	288 (13)	<0.001
Infectious diseases	18 (4.6)	16 (3.8)	29 (4.6)	25 (3.2)	88 (4)	
Acute organ injury	7 (1.8)	14 (3.3)	17 (2.47)	10 (1.3)	48 (2.2)	
Others	199 (51.2)	208 (49.1)	198 (31.1)	132 (17.1)	737 (33.2)	

[a]Data was available for only 2222 cases (<25 years = 389, 26–40 years = 424, 41–59 years = 637, ⩾60 years = 772).

Stratified analysis of AEFI classification and diagnosis by sex

Stratified analysis of causality assessment among females and males revealed a proportionately higher incidence of vaccine product-related reactions (17.9% vs 9.1%) and immunization anxiety-related reactions (15.6% vs 5%) in females compared to males, while coincidental reactions were more prevalent in the males (53% vs 37.1%) and immunization error-related reactions, as well as unclassified serious AEFI reactions, were almost equally distributed between both genders. These findings were statistically significant, with $p < 0.001$ (Table 3).

Among the organ system involved/diagnosis categories of serious AEFIs stratified among males and females, it was found that the cardiovascular system (38.7% vs 23%) and respiratory system (15.5% vs 10.1%) were more affected among males while the gastrointestinal system (2% vs 4.5%) and the nervous system (12.9% vs 13.7%) were more involved among the females. These findings were statistically significant, with $p < 0.001$ (Table 3).

On 2×2 table analysis of AEFI classification and organ system involved stratified by sex also revealed a higher proportion of cardiovascular

Table 3. Distribution of causality assessment and organ system involved by gender ($N = 2708$).

Variables	Male ($N = 1354$), *n* (%)	Female ($N = 1354$), *n* (%)	Total ($N = 2708$), *n* (%)	*p*-Value
Causality assessment classification				
Vaccine product-related reaction	123 (9.1)	243 (17.9)	366 (13.5)	
Immunization error-related reaction	31 (2.3)	31 (2.3)	62 (2.3)	<0.001
Immunization anxiety-related reaction	68 (5)	211 (15.6)	279 (10.3)	
Coincidental reaction	717 (53)	503 (37.1)	1220 (45.1)	
Unclassifiable	415 (30.6)	366 (27)	781 (28.8)	
Organ system involved[a]				
Cardiovascular system disorders	454 (38.7)	242 (23)	696 (31.3)	
Central or peripheral nervous system disorders	151 (12.9)	144 (13.7)	295 (13.3)	
Gastrointestinal system disorders	23 (2)	47 (4.5)	70 (3.2)	
Respiratory system disorder	182 (15.5)	106 (10.1)	288 (13)	<0.001
Infectious diseases	39 (3.3)	49 (4.7)	88 (4)	
Acute organ injury	25 (2.1)	23 (2.2)	48 (2.2)	
Others	298 (25.4)	439 (41.8)	737 (33.2)	

[a]Data available for only 2222 cases (male = 1172, female = 1050).

system and respiratory system involvement with coincidental reactions in both males and females, while immunization error-related reactions were maximally associated with infectious disease manifestations (Supplemental Table 2).

Stratified analysis of AEFI classification and diagnosis by type of vaccine administered

Causality assessment stratified by type of vaccine administered (Covishield, Covaxin, and others) revealed that vaccine product-related reactions (14.2%, 7.5%, and 6.8%) and coincidental reactions (47.6%, 33.7%, and 10.8%) were more common with Covishield followed by Covaxin and others, while immunization error-related reactions (0.6%, 2.3%, and 27.7%) and immunization anxiety-related reactions (8.1%, 15%, and 33.1%) were higher among the vaccines belonging to the other category (Sputnik and Corbevax), followed by Covaxin and Covishield. These findings were statistically significant, with $p < 0.001$ (Table 4).

Nervous system involvement (10.9%, 21%, and 42.6%) and infectious disease etiologies (3.6%, 5.5%, and 8.2%) were more frequent with Corbevax and Sputnik vaccines followed by Covaxin and Covishield, while the cardiovascular system was more involved with Covishield vaccine (34.4%, 21.7%, and 1.6%) and the respiratory system (11.9%, 12.9%, and 1.6%) was more involved with Covaxin. These findings, after excluding the cases of acute organ injury, were statistically significant with $p < 0.001$ (Table 4).

The association between the cardiovascular system and respiratory system with coincidental reactions was similar across all the vaccine categories, while nervous system involvement and infectious disease manifestations were almost exclusively associated with immunization anxiety-related

Table 4. Distribution of causality assessment and organ system involved by vaccine type ($N = 2386$).

Variables	Covishield ($N = 1891$), *n* (%)	Covaxin ($N = 347$), *n* (%)	Others ($N = 148$), *n* (%)	Total ($N = 2386$), *n* (%)	*p*-Value
AEFI causality classification					
Vaccine product-related reaction	269 (14.2)	26 (7.5)	10 (6.8)	305 (12.8)	
Immunization error-related reaction	11 (0.6)	8 (2.3)	41 (27.7)	60 (2.5)	
Immunization anxiety-related reaction	154 (8.1)	52 (15)	49 (33.1)	255 (10.7)	<0.001
Coincidental reaction	900 (47.6)	117 (33.7)	16 (10.8)	1033 (43.3)	
Unclassifiable	557 (29.5)	144 (41.5)	32 (21.6)	733 (30.7)	
Organ system involved[a]					
Cardiovascular system disorders	551 (34.4)	59 (21.7)	1 (1.6)	611 (31.6)	
Central or peripheral nervous system disorders	174 (10.9)	57 (21)	26 (42.6)	257 (13.3)	
Gastrointestinal system disorders	48 (3)	7 (2.6)	2 (3.3)	57 (2.9)	
Respiratory system disorder	191 (11.9)	35 (12.9)	1 (1.6)	227 (11.7)	—
Infectious diseases	57 (3.6)	15 (5.5)	5 (8.2)	77 (4)	
Acute organ injury	33 (2.1)	7 (2.6)	0 (0.0)	40 (2.1)	
Others	546 (34.1)	92 (33.8)	26 (42.6)	664 (34.4)	

[a]Data was available for 1933 cases (Covishield = 1600, Covaxin = 272, Others = 61).
AEFI, adverse events following immunization.

reactions and immunization error-related reactions, respectively, in all vaccine types.

Independent predictors of mortality among serious AEFI cases

On applying logistic regression to find the independent predictors of death associated with serious AEFI reported due to COVID-19 vaccines, it was found that age groups belonging to 41–59 years and more than 60 years, male sex, Covishield vaccine, undetermined and unclassified AEFI cases, cardiovascular system involvement, cases reported from southern India and those occurring during the pre-monsoon and monsoon seasons were significantly associated with death due to serious AEFI (Table 5 and Figure 2).

Out of the total 2708 cases, 1114 (41.2%) unfortunately succumbed to the illness, while 1594 (58.8%) recovered. Age emerged as a significant factor influencing mortality ($p < 0.001$). The risk of death increased with age, with individuals aged 60 years and above facing the highest odds of mortality, with an adjusted odds ratio (aOR) of 4.29 (95% CI: 2.72–6.78) compared to those below 25 years. Gender disparity was evident in mortality outcomes ($p < 0.001$). Females exhibited lower odds of death compared to males, with an adjusted odds ratio of 0.66 (95% CI: 0.52–0.83) after controlling for other variables. Compared to Covishield, the odds of death associated with Covaxin and other vaccines (Sputnik, Corbevax) were lower; however, this finding was not significant for Covaxin while it was significant for the other two vaccines at $p = 0.003$. This

Table 5. Independent predictors of mortality among serious AEFI cases ($n = 2708$).

Variables	Recovered ($n = 1594$), *n* (%)	Died ($n = 1114$), *n* (%)	Total ($n = 2708$), *n* (%)	cOR (95% CI)	aOR (95% CI)	Adjusted *p*-value
Age						
<25 years	488 (30.6)	85 (7.6)	573 (21.2)	Ref	Ref	—
26–40 years	407 (25.5)	136 (12.2)	543 (20.1)	1.92 (1.42–2.59)	1.20 (0.78–1.87)	0.398
41–59 years	417 (26.2)	341 (30.6)	758 (28.0)	4.69 (3.58–6.15)	2.82 (1.85–4.30)	<0.001
⩾60 years	282 (17.7)	552 (49.6)	834 (30.8)	11.23(8.56–14.74)	4.29 (2.72–6.78)	<0.001
Sex						
Male	671 (42.1)	683 (61.3)	1354 (50)	Ref	Ref	—
Female	923 (57.9)	431 (38.7)	1354 (50)	0.458 (0.39–0.54)	0.66 (0.52–0.83)	0.001
Type of vaccine[a]						
Covishield	1001 (72.6)	890 (88.3)	1891 (79.3)	Ref	Ref	—
Covaxin	234 (17)	113 (11.2)	347 (14.5)	0.54 (0.42–0.69)	0.89 (0.62–1.28)	0.556
Others	143 (10.4)	5 (0.5)	148 (6.2)	0.03 (0.01–0.09)	0.16 (0.05–0.53)	0.003
AEFI causality assessment						
Causality determined and classified	1207 (75.7)	720 (64.6)	1927 (71.2)	Ref	Ref	—
Causality undetermined/ unclassifiable	387 (24.3)	394 (35.4)	781 (28.8)	1.707 (1.44–2.01)	5.15 (3.82–6.94)	<0.001
Organ system involved[b]						
Cardiovascular system disorders	192 (16.4)	504 (48)	696 (31.3)	Ref	Ref	—
Central or peripheral nervous system disorders	281 (24)	14 (1.3)	295 (13.3)	0.01 (0.01–0.03)	0.01 (0.00–0.02)	<0.001
Gastrointestinal system disorders	55 (4.7)	15 (1.4)	70 (3.2)	0.10 (0.05–0.18)	0.18 (0.09–0.38)	<0.001
Respiratory system disorders	109 (9.3)	179 (17.1)	288 (13)	0.62 (0.46–0.83)	1.04 (0.73–1.49)	0.827
Infectious diseases	36 (3.1)	52 (5)	88 (4)	0.55 (0.34–0.86)	1.23 (0.69–2.19)	0.484
Acute organ injury	37 (3.2)	11 (1)	48 (2.2)	0.11 (0.05–0.22)	0.16 (0.07–0.36)	<0.001
Others	463 (39.5)	274 (26.1)	737 (33.2)	0.22 (0.18–0.28)	0.26 (0.19–0.36)	<0.001

(Continued)

Table 5. (Continued)

Variables	Recovered (*n* = 1594), *n* (%)	Died (*n* = 1114), *n* (%)	Total (*n* = 2708), *n* (%)	cOR (95% CI)	aOR (95% CI)	Adjusted *p*-value
Geographic zones						
South	497 (31.5)	419 (38)	916 (34.2)	Ref	Ref	—
North east	45 (2.9)	23(2.1)	68 (2.5)	0.60 (0.36–1.01)	0.96 (0.44–2.09)	0.918
East	324 (20.5)	199 (18)	523 (19.5)	0.72 (0.58–0.90)	0.89 (0.64–1.25)	0.528
North	227 (14.4)	117 (10.6)	344 (12.8)	0.61 (0.47–0.79)	0.52 (0.36–0.76)	0.001
Central	244 (15.5)	215 (19.5)	459 (17.1)	1.04 (0.83–1.30)	1.54 (1.08–2.19)	0.018
West	241 (15.3)	131 (11.9)	372 (13.9)	0.64 (0.50–0.82)	0.53 (0.38–0.77)	0.001
Seasons of vaccination						
Winter	142 (12.7)	582 (36.5)	724 (26.7)	Ref	Ref	—
Pre-monsoon	536 (48.1)	472 (29.6)	1008 (37.2)	4.65 (3.7–5.80)	1.76 (1.24–2.49)	0.001
Monsoon	357 (32)	462 (29)	819 (30.2)	3.16 (2.5–3.98)	2.53 (1.81–3.51)	<0.001
Post-monsoon	79 (7.1)	78 (4.9)	157 (5.8)	4.15(2.88–5.96)	1.62 (0.99–2.64)	0.054

[a]Data for 2386 cases available.
[b]Data for 2222 cases available.
AEFI, adverse events following immunization; aOR, adjusted odds ratio; cOR, crude odds ratio.

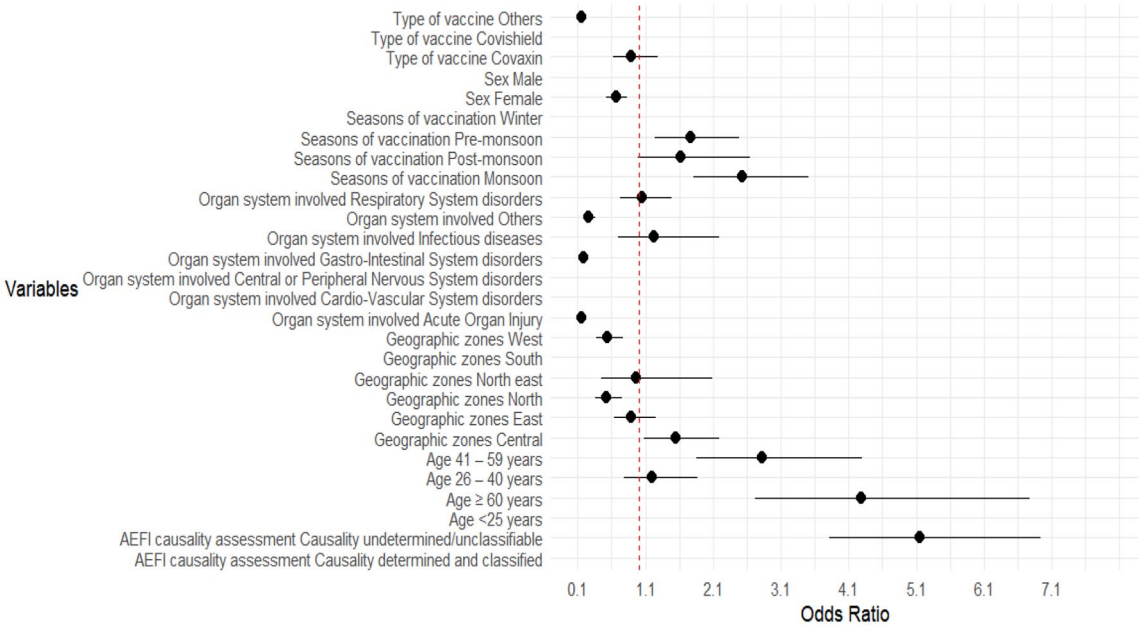

Figure 2. Forest plot of adjusted odds ratio for independent variables.

indicates that the safety profiles of Covishield and Covaxin were more or less similar; however, the safest option was Corbevax or Sputnik. However, this finding should be taken with caution as Sputnik and Corbevax contributed only 6.2% of the total reported AEFI cases. The assessment of AEFI causality demonstrated a strong association with mortality ($p < 0.001$). Cases where causality could not be determined had significantly higher odds of death compared to cases where causality was determined and classified, with an adjusted odds ratio of 5.15 (95% CI: 3.82–6.94). The involvement of different organ systems in adverse events was significantly associated with mortality ($p < 0.001$). Only those cases diagnosed as infectious diseases had higher odds of mortality (aOR = 1.25, 95% CI: 0.70–2.29) after adjustment compared to cardiovascular system manifestations; however, this finding was not significant. Geographic zones also demonstrated varying trends with mortality ($p < 0.001$). The proportionate higher odds of death due serious AEFI in southern region compared to Northern and Western part of India were statistically significant at $p = 0.001$. This may be attributed to the higher number of vaccine recipients from southern India (34.2%). The season of vaccination exhibited significant predictability with mortality ($p < 0.001$). Notably, individuals vaccinated in the monsoon season had the highest odds of mortality compared to other quarters, with an adjusted odds ratio of 2.53 (95% CI: 1.81–3.51) after adjustment. This may also be attributed to the proportionately higher occurrence of AEFI cases during the pre-monsoon and monsoon seasons (Table 5).

Discussion

The major findings of the study are (i) out of the total serious AEFI cases reported, 60% of the cases recovered while the rest succumbed. (ii) Causality assessment and classification of nearly 30% of the reported serious AEFI cases could not be completed by the National AEFI Committee. (iii) Vaccine product-related reaction was more in the younger age group and among females while coincidental reaction was more common in the elderly sample and males. Also, the cardiovascular system and nervous system were the most common organ systems involved during the AEFI episode in older and younger populations, respectively. (iv) Cardiovascular system involvement was mostly associated with coincidental reactions among different age groups, sex categories, and types of vaccine received which indicates other than AEFI, some other etiology such as preexisting comorbidities must have some role in it. (v) Age groups belonging to 41–59 years and more than 60 years, male sex, Covishield vaccine, undetermined and unclassified AEFI cases, cardiovascular system involvement, cases reported from southern India and during pre-monsoon and monsoon seasons were significantly associated with death after the serious AEFI episode.

Multiple studies done locally and internationally have provided proof of the increased probability of death in the elderly population after COVID-19 vaccination and AEFI occurrence.[23] Observational studies done in South Korea, by taking into account the number of deaths before vaccination and conducting an Autoregressive Integrated Moving Average (ARIMA) modeling to predict the expected number of deaths after the initiation of vaccination drive found that the observed deaths were less compared to expected deaths among total study participants, but higher odds of observed deaths in the elderly population.[24] This is in part due to the presence of multimorbidity status in the older population and the association with weakened status of the immune system, making them more vulnerable to the stress associated with vaccination or AEFI occurrence. In our study, even though equal participation of serious AEFI cases was reported from different age categories, the odds of death after a serious AEFI were more associated with the older age group after adjusting for covariates. Multiple studies[23,25,26] have indicated that the odds of any AEFI with the COVID-19 vaccine were higher in females, but reports of death after vaccination were higher in males compared to females after AEFI, similar to findings in our study. An equal number of males and females were reported as AEFI cases and adjusting for variables significant in univariate analysis gives credibility to the findings observed in our study. Another study conducted in the USA based on the data available from the Centers for Disease Control also revealed a higher incidence of mortality associated with the older population and male sex.[27]

Our study found no increased risk of death due to serious AEFI associated with Covishield (a viral vector vaccine) compared to Covaxin (an

inactivated virus vaccine). This finding suggests that both vaccines have a comparable safety profile concerning serious adverse events, which is an important consideration for public health recommendations. By contrast, various systematic reviews and meta-analyses have reported differing safety profiles among COVID-19 vaccine types. For instance, a systematic review indicated that mRNA vaccines were associated with a higher incidence of serious adverse events compared to both viral vector and inactivated vaccines. Specifically, it highlighted that serious metabolic, musculoskeletal, immune system, and renal disorders were more frequently observed among recipients of inactivated vaccines, while mRNA vaccines were linked to increased occurrences of myocarditis and other cardiovascular events following vaccination. Furthermore, a network meta-analysis assessing the safety of COVID-19 vaccines concluded that inactivated virus vaccines might be the safest option overall, with lower rates of serious adverse events compared to mRNA and viral vector vaccines. The analysis showed that none of the vaccines had a higher incidence of serious adverse events than placebo groups, but it did rank inactivated vaccines as having the best safety profile. In addition, analysis of AEFI reports from the WHO Western Pacific Region between 2021 and 2022 revealed a higher incidence of AEFI associated with mRNA vaccines, followed by protein subunit vaccines, viral vector vaccines, and inactivated viral vaccines.[28–30] The differing findings between our study and those from systematic reviews may be attributed to several factors. First, variations in study design and population characteristics could influence the reported safety outcomes. In addition, differences in the monitoring period for adverse events can affect the detection of serious AEFIs; longer follow-up periods may reveal more instances of rare adverse events that short-term studies might miss. Lastly, variations in reporting practices and definitions of AEFI across studies can lead to inconsistencies in findings.

The cardiovascular system was the most involved organ system associated with the serious AEFI cases and the odds of the cardiovascular system causing death were higher compared to any other type of organ system included in our analysis. This finding was supported by a plethora of scientific articles that suggest an association between COVID-19 vaccination and cardiovascular system involvement. Most of the studies have reported a higher incidence of cardiovascular involvement with mRNA vaccines compared to any other type of vaccine, which was not present in our study; nevertheless, the tendency for cardiovascular system involvement after COVID-19 vaccination was evident in all these studies.[31–34]

Finally, the stark proportion of 30% of unclassifiable AEFI cases predicting higher odds of mortality is concerning. The presence of unclassifiable cases complicates the interpretation of vaccine safety data, as these cases may include individuals with preexisting conditions or comorbidities that could independently contribute to their adverse events. Furthermore, the significant number of unclassifiable cases underscores the need for ongoing surveillance and research into AEFIs; public health authorities must prioritize monitoring these events closely to identify emerging patterns, particularly as new variants and vaccines are introduced. Our findings also suggest potential gaps in reporting mechanisms or diagnostic criteria used during causality assessments. In addition, the substantial number of undetermined cases may lead to public concern regarding vaccine safety, potentially undermining vaccination efforts.

To address the challenges posed by unclassifiable AEFI cases, public health authorities should enhance surveillance systems by implementing active monitoring and standardized reporting protocols to ensure accurate data collection and causality assessments. Public education campaigns are essential to improve understanding of vaccine safety and the nature of AEFIs, helping to alleviate public concern. In addition, fostering collaboration among health authorities and investing in targeted research initiatives will provide deeper insights into unclassifiable cases and strengthen vaccine safety monitoring efforts.

Limitations

The data on only those serious AEFIs that were assessed for causality assessment by the National AEFI Committee were considered for current analysis which is an underestimate of the true burden of serious AEFI. Most healthcare professionals might not be ready to label the AEFI as serious because of a belief that these vaccines are safe. Even though our study had a fair sample

size, the number of AEFI cases reported from various parts of the county was highly variable, with some states reporting zero cases. Those states with high vaccination coverage reported higher number of serious AEFI cases as expected, which, in turn, reduces the ability to generalize the findings to the entire country. In addition, the real picture of AEFI-associated mortality may be different from the findings of our study as documented AEFI cases may be far fewer than actual due to unreported cases that might have been missed by the surveillance system. Data related to several other variables such as onset of AEFI symptoms, delay in getting resuscitation and appropriate care, number of doses after which AEFI was reported and socioeconomic variables were not available for analysis, which may or may not have an association with mortality. Furthermore, in around 30% of the reported serious AEFI cases, the causality assessment was not complete and was classified as undetermined and unclassified. Finally, a comparison group (those vaccinated and did not develop AEFI) was not present to truly elucidate the real effect of the vaccine on developing an AEFI.

Conclusion

This study investigated serious AEFI cases and their outcomes following COVID-19 vaccination, focusing on the role of demographic factors, vaccine type, and the affected organ systems. The majority of serious AEFIs were either coincidental or unclassifiable, with a higher proportion of reports associated with Covishield compared to Covaxin. While a significant portion of serious AEFIs resulted in death, many others involved hospitalization and recovery. The most common systems affected by AEFIs were cardiovascular, followed by respiratory and neuropsychiatric systems. Age and gender showed a significant association with the type of AEFI reported.

The analysis further revealed that certain factors, such as being female, being younger, having classified AEFIs, and experiencing AEFIs related to the gastrointestinal or neuropsychiatric systems, were associated with a lower risk of mortality. In addition, AEFIs reported from North and Western India, as well as those occurring during the winter season, were linked to a reduced likelihood of death.

In conclusion, this study underscores the complexity of serious AEFIs following COVID-19 vaccination and highlights the importance of demographic, geographic, and seasonal factors in influencing outcomes. Despite the study's limitations, including uneven reporting and incomplete causality assessments, these findings emphasize the need for vigilant monitoring and tailored care protocols, particularly for vulnerable populations, to mitigate risks associated with vaccination. Further research and global collaborations are essential to enhance understanding and management of AEFI outcomes across diverse contexts.

Declarations

Ethics approval and consent to participate

Since the study involved analysis of secondary data published and made publicly available by the Government of India, the ethical consideration has been waived off by the Institute Human Ethics Committee (IHEC), AIIMS, Gorakhpur. Consent to participate: Not applicable.

Consent for publication

Not applicable.

Author contributions

Abin Kulathunkal Rajan: Conceptualization, Data curation, Formal analysis, Methodology, Software, Visualization, Writing – original draft.

MD. Abu Bashar: Conceptualization, Data curation, Project administration, Resources, Supervision, Validation, Writing – review & editing.

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Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

The data that support the findings of this study are available from the corresponding author, Dr. MD. Abu Bashar upon reasonable request.

Writing assistance and third-party submissions

No writing assistance was received from any individual or organization other than the authors. No third party has been entrusted with the submission of the article.

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Supplemental material

Supplemental material for this article is available online.

References

1. Timeline of WHO's response to COVID-19, 2020, https://www.who.int/emergencies/diseases/novel-coronavirus-2019/interactive-timeline#! (accessed 1 March 2024).
2. COVID-19 cases | WHO COVID-19 dashboard, 2024, https://data.who.int/dashboards/covid19/cases?n=c (accessed 1 March 2024).
3. Voysey M, Clemens SAC, Madhi SA, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. *Lancet* 2021; 397(10269): 99–111.
4. Kulkarni PS, Padmapriyadarsini C, Vekemans J, et al. A phase 2/3, participant-blind, observer-blind, randomised, controlled study to assess the safety and immunogenicity of SII-ChAdOx1 nCoV-19 (COVID-19 vaccine) in adults in India. *EClinicalMedicine* 2021; 42: 101218.
5. Kamal D, Thakur V, Nath N, et al. Adverse events following ChAdOx1 nCoV-19 Vaccine (COVISHIELD) amongst health care workers: a prospective observational study. *Med J Armed Forces India* 2021; 77(Suppl 2): S283–S288.
6. Key real-world results for Sputnik V and Sputnik Light vaccines | Official website vaccine against COVID-19 Sputnik V, 2021, https://sputnikvaccine.com/about-vaccine/results/ (accessed 1 March 2024).
7. EMA. Guideline on good pharmacovigilance practices (GVP)-annex I-definitions (Rev 4), 2017, https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-annex-i-definitions-rev-4-superseded_en.pdf (accessed 2 March 2024).
8. Bellavite P. Causality assessment of adverse events following immunization: the problem of multifactorial pathology. *F1000Res* 2020; 9: 170.
9. Revised AEFI Guidelines: Executive Summary. 2015, https://mohfw.gov.in/sites/default/files/Revised%20AEFI%20Guidelines%20Execute%20Summary.pdf (accessed 2 March 2024).
10. Otero-Losada M, Petrovsky N, Alami A, et al. Disproportionality analysis of adverse neurological and psychiatric reactions with the ChAdOx1 (Oxford-AstraZeneca) and BNT162b2 (Pfizer-BioNTech) COVID-19 vaccines in the United Kingdom. *Expert Opin Drug Saf* 2023; 22(4): 343–349.
11. van Balveren L, van Puijenbroek EP, Davidson L, et al. A case series of Bacillus Calmette-Guérin scar reactivation after administration of both mRNA and viral vector COVID-19 vaccines. *Br J Clin Pharmacol* 2023; 89(7): 2113–2121.
12. Meher B. Vaccine pharmacovigilance in India: current context and future perspective. *Indian J Pharmacol* 2019; 51(4): 243.
13. Ha J, Song MC, Park S, et al. Deciphering deaths associated with severe serious adverse events following SARS-CoV-2 vaccination: a retrospective cohort study. *Vaccine X* 2024; 16: 100446.
14. Dul-Amnuay A. Case study of autopsy findings in a population of post-COVID-19 vaccination in Thailand. *Am J Forensic Med Pathol* 2024; 45(1): 45–50.
15. Suzuki H, Ro A, Takada A, et al. Autopsy findings of post-COVID-19 vaccination deaths in Tokyo Metropolis, Japan, 2021. *Leg Med (Tokyo)* 2022; 59: 102134.
16. Schneider J, Sottmann L, Greinacher A, et al. Postmortem investigation of fatalities following vaccination with COVID-19 vaccines. *Int J Legal Med* 2021; 135(6): 2335–2345.
17. Sessa F, Salerno M, Esposito M, et al. Autopsy findings and causality relationship between death and COVID-19 vaccination: a systematic review. *J Clin Med* 2021; 10(24): 5876.
18. Hulscher N, Hodkinson R, Makis W, et al. Autopsy findings in cases of fatal COVID-19

vaccine-induced myocarditis. *ESC Heart Fail* 2024; 11(4): 2476–2478.

19. AEFI Reports | Ministry of Health and Family Welfare | GOI. 2022, https://main.mohfw.gov.in/?q=Organisation/Departments-of-Health-and-Family-Welfare/immunization/aefi-reports (accessed 5 March 2024).

20. Budukh A, Bagal S, Thakur JS, et al. Pediatric cancer burden in different regions of India: analysis of published data from 33 population-based cancer registries. *Indian Pediatr* 2023; 60(7): 541–545.

21. Ministry of Earth Sciences (MoES) भारत मौसम ववज्ञान ववभाग India Meteorological Department Climate Research and Services (CRS) Statement on Climate of India during 2021 Temperatures. 2021, https://library.wmo.int/doc_num.php?explnum_id=10859 (accessed 2 March 2024)

22. Xu W, Wong G, Hwang YY, et al. The untwining of immunosenescence and aging. *Semin Immunopathol* 2020; 42(5): 559.

23. Day B, Menschik D, Thompson D, et al. Reporting rates for VAERS death reports following COVID-19 vaccination, December 14, 2020–November 17, 2021. *Pharmacoepidemiol Drug Saf* 2023; 32(7): 763–772.

24. Jeong HS and Chun BC. COVID-19 vaccine safety: background incidence rates of anaphylaxis, myocarditis, pericarditis, Guillain-Barré Syndrome, and mortality in South Korea using a nationwide population-based cohort study. *PLoS One* 2024; 19(2): e0297902.

25. Duijster JW, Lieber T, Pacelli S, et al. Sex-disaggregated outcomes of adverse events after COVID-19 vaccination: a Dutch cohort study and review of the literature. *Front Immunol* 2023; 14: 1078736.

26. Green MS, Peer V, Magid A, et al. Gender differences in adverse events following the Pfizer-BioNTech COVID-19 vaccine. *Vaccines (Basel)* 2022;10(2): 233.

27. Liu JY, Chen TJ and Hou MC. Does COVID-19 vaccination cause excess deaths? *J Chin Med Assoc* 2021; 84(9): 811–812.

28. Kouhpayeh H and Ansari H. Adverse events following COVID-19 vaccination: a systematic review and meta-analysis. *Int Immunopharmacol* 2022; 109: 108906.

29. Wu X, Xu K, Zhan P, et al. Comparative efficacy and safety of COVID-19 vaccines in phase III trials: a network meta-analysis. *BMC Infect Dis* 2024; 24(1): 234.

30. Chen M, Yuan Y, Zhou Y, et al. Safety of SARS-CoV-2 vaccines: a systematic review and meta-analysis of randomized controlled trials. *Infect Dis Poverty* 2021; 10(1): 94.

31. Faksova K, Walsh D, Jiang Y, et al. COVID-19 vaccines and adverse events of special interest: a multinational Global Vaccine Data Network (GVDN) cohort study of 99 million vaccinated individuals. *Vaccine* 2024; 42(9): 2200–2211.

32. Morales MJM, Maroo A, Kewan T, et al. Cardiovascular adverse events after COVID-19 vaccination. *Int J Anesth Crit Care* 2023; 2(1): 1–4.

33. Mahasing C, Doungngern P, Jaipong R, et al. Myocarditis and pericarditis following COVID-19 vaccination in Thailand. *Vaccines (Basel)* 2023; 11(4): 749.

34. Parmar K, Subramanyam S, Del Rio-Pertuz G, et al. Cardiac adverse events after vaccination—a systematic review. *Vaccines (Basel)* 2022; 10(5): 700.

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