Clinical Drug Investigation (2025) 45:665–675
https://doi.org/10.1007/s40261-025-01466-3

ORIGINAL RESEARCH ARTICLE

# Spontaneous Reports of Adverse Reactions with Fatal Outcomes After COVID-19 Vaccination During the National Vaccination Campaign in Sweden

**Marja-Leena Nurminen[1] · Per Lindemo[1] · Anders Sundström[2,3] · Björn Zethelius[1,4] · Maria Larsson[1] · Sofia Attelind[1,5] · Nicklas Pihlström[1] · Rickard Ljung[1,6] · Veronica Arthurson[1]**

Accepted: 22 July 2025 / Published online: 12 August 2025


## Abstract

**Background and Objectives** Reports of suspected adverse drug reactions are of a great importance for the safety monitoring of new vaccines to identify potential safety risks promptly and to ensure necessary measures for risk mitigation. We reviewed the reports of fatal adverse drug reactions after coronavirus disease 2019 (COVID-19) vaccination with Comirnaty®, Spikevax®, and Vaxzevria® during the national vaccination campaign in Sweden.

**Methods** Swedish reports of suspected adverse drug reactions with fatal outcomes after COVID-19 vaccines were retrieved from the EudraVigilance database. Vaccination data were obtained from the National vaccination register. Reporting rates were calculated by dividing the number of adverse drug reaction reports with fatal outcomes by the number of people exposed to at least one dose of the COVID-19 vaccines or by the number of vaccine doses given. A causality assessment of adverse drug reaction reports was performed by clinically qualified reviewers.

**Results** More than 26 million doses of COVID-19 vaccines were administered and 456 reports of suspected adverse drug reactions with fatal outcomes were reported during 27 December, 2020–31 May, 2023. The reporting rate was 5.7 fatal outcomes per 100,000 persons vaccinated with at least one dose of any COVID-19 vaccine or 1.7 per 100,000 vaccine doses given. Most of the fatalities were related to patients' pre-existing conditions, predominantly among people aged 70 years or older. Only ten of the reported fatalities (0.1 per 100,000 persons vaccinated) were assessed as consistent with a causal association to COVID-19 vaccination.

**Conclusions** Adverse drug reactions with fatal outcomes after COVID-19 vaccines in Sweden were very rare. No new safety concerns were observed in this study.

**Key Points**

Lethal side effects after a coronavirus 2019 vaccination were infrequent.

Most of the fatal cases were reported in persons aged 70 years and older with multiple pre-existing chronic diseases.

No new potential risks with the vaccines were found.

## 1 Introduction

The coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 was first detected in China in December 2019. At the end of January 2020, the World Health Organization declared the outbreak of COVID-19 as a public health emergency of international concern and shortly afterwards in March 2020 the spread of the disease as a global pandemic [1]. During the first year of the COVID-19 pandemic without vaccines, over 462,600 persons were tested positive for severe acute respiratory syndrome coronavirus 2 in Sweden. Of these persons, almost 42,500 were hospitalized and nearly 9500 died (mean age 83.5 years) because of severe COVID-19 [2–4].

In December 2020, the European Commission approved the first COVID-19 vaccine, messenger ribonucleic acid (mRNA) vaccine with the brand name Comirnaty®

Extended author information available on the last page of the article

(BNT162b2), developed by BioNTech and Pfizer [5]. Shortly afterwards, another mRNA-based vaccine, Spikevax® (mRNA-1273) by Moderna, and a recombinant adenovirus vector-based vaccine, Vaxzevria® (ChAdOx1 nCoV-19) by AstraZeneca, were approved [6, 7]. Nuvaxovid® (NVX-CoV2373), a severe acute respiratory syndrome coronavirus 2 recombinant spike protein vaccine by Novavax, was authorized at the end of 2021 [8]. These four vaccines have been used in Sweden for protection against severe and life-threatening COVID-19 during the national vaccination campaign. The primary vaccination series consisted of two vaccine doses followed by additional booster doses to maintain the protection against severe COVID-19. Vaccination against COVID-19 was voluntary and free of charge.

The COVID-19 vaccination campaign started in Sweden on 27 December, 2020. Since the risk for severe disease and death due to COVID-19 has been particularly high among older people living in nursing homes or receiving home help services [9, 10], this vulnerable population was prioritized to receive their vaccination first [11]. The prioritization also included the nursing home staff and other personnel involved in the care of these risk groups, and persons with diseases or conditions identified as risk factors for severe COVID-19 [11].

Although clinical trials with tens of thousands of participants were carried out before the authorization of the various COVID-19 vaccines with acceptable safety profiles, some rare or very rare adverse drug reactions (ADRs) may only become evident after massive vaccination programs when a larger amount of people are vaccinated. For example, the 1975–76 swine influenza vaccination campaign in the USA was associated with a slightly increased risk of Guillain–Barré syndrome [12]. A more recent example is narcolepsy in children and adolescents following Pandemrix® during the 2009 influenza pandemic in Sweden and several other European countries [13]. Clinical trials are usually conducted on a selected population, which may differ from the population receiving the vaccine. Additional data are required on the safety of COVID-19 vaccines in specific groups, such as older frail people or persons with medical risk conditions or comorbidities. Spontaneous ADR reporting is an essential part of the post-authorization safety surveillance, which may allow the detection of possible new risks.

The World Health Organization declared in May 2023 that COVID-19 was no longer a global health emergency [1]. Here, we describe the suspected ADRs with fatal outcomes that were spontaneously reported after COVID-19 vaccination during the national immunization campaign in Sweden from 27 December, 2020 up to the end of May 2023.

## 2 Methods

### 2.1 Data Sources

The Swedish Medical Products Agency (MPA) encouraged healthcare professionals (HCPs; physicians, nurses or pharmacists) and patients/consumers (non-HCPs) to report all suspected ADRs related to COVID-19 vaccines even if there was no certainty that the reaction was caused by the vaccine. In addition, reporting is obligatory for the healthcare sector in Sweden [14]. Healthcare managers are formally responsible for ensuring ADR reporting compliance. The safety surveillance for COVID-19 vaccines at the Swedish MPA has been described previously [15, 16].

Adverse drug reaction reports submitted to the Swedish MPA from HCPs and patients/consumers were registered in the Swedish ADR database. Adverse drug reactions were coded using the *Medical Dictionary for Regulatory Activities* terminology (versions 24.0-26.0) [17]. One report can include more than one suspected ADR as well as more than one vaccine dose or more than one suspected vaccine or other medical products [18]. The reports were then further submitted electronically to EudraVigilance, the European ADR database maintained by the European Medicines Agency (EMA). In addition, the marketing authorization holders (MAHs) of the COVID-19 vaccines submitted to EudraVigilance all suspected ADRs that had been brought to their attention [18]. The ADR report information in the EudraVigilance is accessible by the stakeholders (Swedish MPA, EMA, and MAHs) in accordance with the EudraVigilance access policy and the European Union data protection legislation [19].

All spontaneous reports originated from Sweden and containing ADRs with fatal outcomes, in which COVID-19 vaccines were suspected, were retrieved from EudraVigilance with a data lock point on 31 May, 2023. Identified duplicate reports submitted by both the Swedish MPA and MAHs were announced to the EMA, who combined the information from the duplicates into a single report [20]. Exposure to COVID-19 vaccines up to the end of May 2023 was obtained from the national vaccination register kept by the Public Health Agency of Sweden. Reporting rates were calculated by dividing the number of ADR reports with fatal outcomes by the number of persons vaccinated with at least one dose of a COVID-19 vaccine. Reporting rates were also calculated by dividing the number of ADR reports with fatal outcomes by the number of vaccine doses administered.

### 2.2 Causality Assessment

A thorough case-by-case analysis of all ADR reports with fatal outcomes was independently performed by two clinically qualified internal reviewers followed by a validation review by a third clinically qualified internal reviewer. A discussion was performed in the case of uncertainty on how to interpret the clinical information or how to classify a case, to reach a consensus among the three. Only three out of the 456 cases had to be discussed among all reviewers to reach a consensus. Blinding to vaccination status was deemed unfeasible, as all the relevant details, such as vaccine product, earlier vaccination status, and plausible time window, are important to address a possible causal association of the reaction and vaccine. The ADR reports were assessed using the World Health Organization's classification for adverse events for immunization [21]. The causality assessment classification for vaccine pharmacovigilance is provided in the Electronic Supplementary Material.

## 3 Results

Since COVID-19 vaccines became available in Sweden at the end of December 2020, almost 8 million individuals have received at least one vaccine dose (Comirnaty®, Spikevax®, Vaxzevria®, or Nuvaxovid®) following delivery of over 26.3 million doses up to 31 May, 2023 (national vaccination register) [Table 1]. During this period, over 113,800 spontaneous reports of suspected ADRs after administration of COVID-19 vaccines in Sweden have been submitted to

**Table 1** Characteristics of spontaneous reports with fatal outcomes received after COVID-19 vaccination during COVID-19 vaccination campaign in Sweden

| | Comirnaty® | Spikevax® | Vaxzevria® | Total |
|---|---|---|---|---|
| Number of individuals vaccinated | 7,384,218 | 2,835,322 | 741,296 | 7,942,271[a] |
| Number of vaccine doses given | 20,451,389 | 4,514,295 | 1,340,706 | 26,306,390 |
| | *n* (%) | *n* (%) | *n* (%) | Total *n* (%) |
| Number of reports from HCPs (%) | 266 (76%) | 40 (75%) | 33 (60%) | 337 (74%)[b] |
| Number of reports from non-HCPs (%) | 85 (24%) | 13 (25%) | 22 (40%) | 119 (26%)[b] |
| Sex | | | | |
| Female | 192 (55%) | 23 (43%) | 23 (42%) | 235 (52%)[b] |
| Male | 158 (45%) | 30 (57%) | 32 (58%) | 220 (48%) |
| Unknown | 1 | 0 | 0 | 1 |
| Age group (years) | *N* | *n* | *n* | *n* (%) |
| 10–19 | 2 | 1 | 0 | 3 (0.7%) |
| 20–29 | 2 | 0 | 0 | 2 (0.4%) |
| 30–39 | 5 | 3 | 0 | 8 (1.8%) |
| 40–49 | 7 | 2 | 0 | 9 (2.0%) |
| 50–59 | 16 | 4 | 1 | 21 (4.6%) |
| 60–69 | 40 | 8 | 13 | 60 (13.1%)[b] |
| 70–79 | 75 | 20 | 29 | 124 (27.2%) |
| 80–89 | 131 | 8 | 7 | 145 (31.8%)[b] |
| 90+ | 69 | 7 | 1 | 76 (16.7%)[b] |
| Unknown | 4 | 0 | 4 | 8 (1.8%) |
| Total number of reports (%) | 351 (77%) | 53 (11.6%) | 55 (12.1%) | 456[b] |
| Reporting rate per 100,000 persons vaccinated | 4.8 | 1.9 | 7.4 | 5.7[a] |
| Reporting rate per 100,000 vaccine doses administered | 1.7 | 1.2 | 4.1 | 1.7 |

*COVID-19* coronavirus disease 2019, *HCP* healthcare professional (physician, nurse, or pharmacist)

Spontaneous reports received between 27 December, 27, 2020 and 31 May, 2023

[a]Total number of individuals vaccinated refers to persons received at least one dose of Comirnaty®, Spikevax®, or Vaxzevria®

[b]Total number of fatal case reports was 456; in three of the reports (all about female individuals, two HCP reports and one non-HCP report), two different COVID-19 vaccines were suspected (Comirnaty® and Spikevax® in one report within the age group 90 + years and in one report within the age group 60–69 years, and Vaxzevria® and Comirnaty® in one report within the age group 80–89 years)

EudraVigilance by the Swedish MPA or the MAHs. Of the total amount of the reports in EudraVigilance, 87% concerned non-serious ADRs, most of which (e.g., pyrexia, headache, fatigue, chills, vaccination-site reactions) are already labeled in the product information of the vaccines [5–8].

### 3.1 Reporting Rate of Fatal ADRs

A fatal outcome after COVID-19 vaccination was described in 456 spontaneous reports (Table 1), corresponding to 0.4% of the total amount of the ADR reports of COVID-19 vaccines in Sweden. A crude estimate of the reporting rate of fatal ADRs was 5.7 per 100,000 persons vaccinated with at least one dose of COVID-19 vaccine and 1.7 per 100,000 vaccine doses administered (Table 1). No fatal cases related to Nuvaxovid® were reported. However, this vaccine was used to a limited extent, i.e., to fewer than 12,000 persons up to the end of May 2023. Comirnaty® was the dominant COVID-19 vaccine used during the national vaccination campaign (Table 1).

### 3.2 Sources of ADR Reports

Healthcare professionals submitted most of the spontaneous reports (74%) with fatal outcomes after COVID-19 vaccination (Table 1). The proportion of reports of fatal ADRs by patients or consumers was much lower than the proportion of all ADR reports related to COVID-19 vaccines (26% vs 82%, respectively). The amount of ADR reports with fatal outcomes was at the highest within the older age groups and 76% of the reports concerned individuals aged 70 years or more (Table 1).

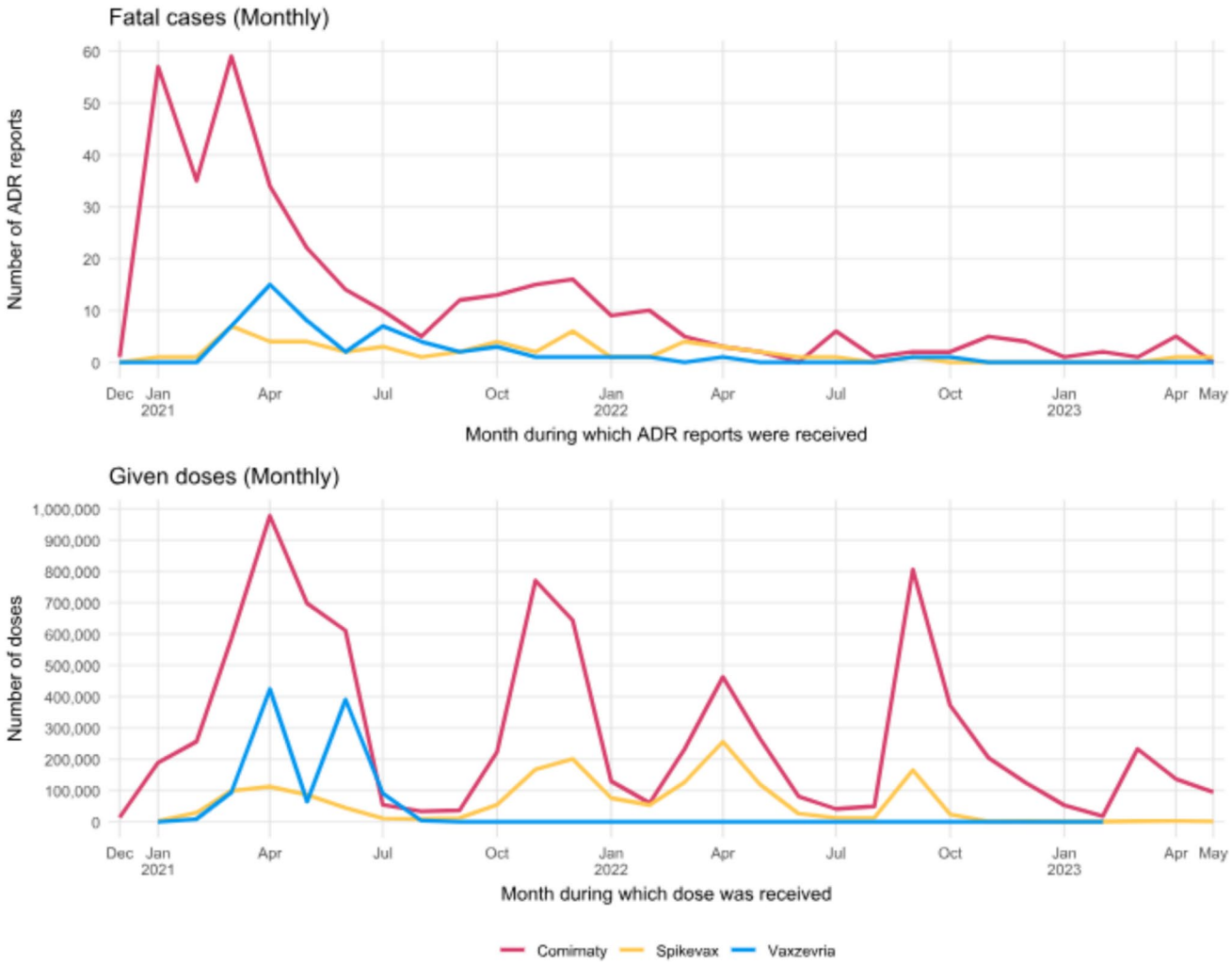


**Fig. 1** Number of spontaneous adverse drug reaction (ADR) reports with fatal outcomes after vaccination with coronavirus disease 2019 vaccines Comirnaty®, Spikevax®, and Vaxzevria® and numbers of doses given of the vaccines during the period from 27 December, 2020 up to 31 May, 2023 in Sweden

**Table 2** Number of spontaneous adverse drug reaction reports with fatal outcomes in Sweden per dose of COVID-19 vaccines

| | Comirnaty® | Spikevax® | Vaxzevria® | Total |
|---|---|---|---|---|
| Dose 1 | 139 (39.6%) | 12 (22.6%) | 32 (58.2%) | 183 (40.1%) |
| Dose 2 | 118 (33.6%) | 18 (34.0%) | 17 (30.9%) | 153 (33.6%) |
| Dose 3 | 52 (14.8%) | 14 (26.4%) | - | 66 (14.5%) |
| Dose 4 | 10 (2.8%) | 4 (7.5%) | - | 14 (3.1%) |
| Dose 5 | 5 (1.4%) | 1 (1.9%) | - | 6 (1.3%) |
| Dose unknown | 25 (7.1%) | 4 (7.5%) | 5 (9.1%) | 34 (7.5%) |
| Total | 351 | 53 | 55 | 456[a] |

*COVID-19* coronavirus disease 2019

[a]Total number of case reports was 456. In three of the reports, two different COVID-19 vaccines were suspected. In this table, only the last dose of vaccine is presented (Spikevax® dose 3 in two of the reports and Comirnaty® dose 3 in one report)

Most of the spontaneous reports with fatal outcomes (54%) were reported between the beginning of January 2021 and the end of April 2021, when older frail people with assisted living in their homes or in nursing homes received their two-dose primary vaccination series (Fig. 1, Table 2). In 19% of the reports, fatal ADRs were reported after the booster doses (dose 3, 4, or 5) of Comirnaty® or Spikevax®. Of these reports, only eight concerned bivalent COVID-19 mRNA booster vaccines (Comirnaty® original plus omicron BA.1 or BA.4-5 subvariants). The dose number or the date of the vaccination was not specified in 7% and 5% of the reports, respectively.

**Table 3** Medical history and the most common comorbidities of the vaccinees with suspected adverse drug reactions with fatal outcomes after COVID-19 vaccinations

| Medical history/comorbidities | Comirnaty® | Spikevax® | Vaxzevria® | Total (%) |
|---|---|---|---|---|
| Hypertension | 124 | 16 | 21 | 161 (35%) |
| Ischemic heart disease | 76[a] | 11[a] | 14 | 100[a] (22%) |
| Dementia or cognitive disorder | 83[a] | 5[a] | 4 | 91[a] (20%) |
| Lung disorder | 65 | 10 | 7 | 82 (18%) |
| Cardiac failure | 64 | 7 | 5 | 76 (17%) |
| Diabetes mellitus | 62 | 7 | 6 | 75 (16%) |
| Neoplasm malignant | 57[a] | 10[a] | 9[a] | 73[a] (16%) |
| Cerebrovascular disorder | 54 | 8 | 4 | 66 (14%) |
| Atrial fibrillation | 46 | 4 | 4 | 54 (12%) |
| Renal disorder | 34 | 9 | 3 | 46 (10%) |
| Palliative care | 24 | 2 | 0 | 26 (6%) |
| Thyroid disorder | 23 | 2 | 4 | 29 (6%) |
| COVID-19 | 17 | 4 | 2 | 23 (5%) |
| Valvular heart disease | 19 | 2 | 1 | 22 (5%) |
| Hyperlipidemia | 11 | 3 | 7 | 21 (5%) |
| Depression | 17 | 4 | 0 | 21 (5%) |
| Obesity/overweight | 17 | 2 | 2 | 21 (5%) |
| Cardiac pacemaker user | 14 | 2 | 3 | 19 (4%) |
| Liver disorder | 14 | 1 | 2 | 17 (4%) |
| Anxiety | 11 | 1 | 0 | 12 (3%) |
| Pulmonary embolism | 9 | 1 | 2 | 12 (3%) |
| Parkinson's disease | 10 | 0 | 1 | 11 (2%) |
| Epilepsy | 7 | 2 | 1 | 10 (2%) |
| Home care | 25 | 4 | 3 | 32 (7%) |
| Nursing home resident | 93[a] | 6[a] | 2 | 99[a] (22%) |
| Multimorbidity (≥3 medical conditions) | 190[a] | 29[a] | 22 | 239[a] (52%) |
| Concomitant drugs not reported | 170[a] | 34[a] | 29 | 232[a] (51%) |
| Medical history not reported | 33 | 5 | 10 | 48 (11%) |

*COVID-19* coronavirus disease 2019

[a]Total number of fatal case reports was 456. Two different vaccines were suspected in three of the reports (Comirnaty® and Spikevax® in two reports, and Comirnaty® and Vaxzevria® in one report each). One report can include one or more diseases in the medical history

### 3.3 Comorbidities

More than half of the fatal cases had multiple comorbidities, of which hypertension, ischemic heart disease, lung disorders, cardiac failure, diabetes mellitus, and various cancers were the most common underlying diseases (Table 3). Nearly 30% of fatal cases received home care or resided in nursing homes. Dementia or cognitive disorder was reported in 19% of the fatal cases. Palliative care had already been initiated before the vaccination in some of the fatal cases. Medical history was not described in 11% of the reports, and the information on concomitant medications was lacking in over half of the reports (Table 3). An autopsy report was provided with 97 (21%) of the spontaneous reports with fatal outcomes. An autopsy was performed additionally in 40 (9%) of the fatal cases, but the autopsy report was not provided for evaluation. No autopsy was carried out in 101 (22%) of the cases, and it was not notified if an autopsy was performed in almost half of the reports ($n = 218$, 48%).

### 3.4 Most Reported Suspected ADRs

The most reported suspected ADRs with fatal outcomes were cardiac arrest followed by pulmonary embolism, myocardial infarction, and hemorrhagic or ischemic stroke (Table 4). Most of the fatal cases had underlying cardiovascular disease or other conditions or risk factors predisposing to these reactions. In 17% of the fatal cases, it was indicated in the medical records, autopsy reports, or by the reporter that the death was not suspected to be causally related to vaccination.

### 3.5 Causality Assessment

COVID-19 was reported as an ADR in 17 of the fatal falls. Of these reports, five were assessed as vaccination failures, i.e., suspected lack of efficacy, as COVID-19 was diagnosed with a positive test result after the timepoint where protection with the two-dose primary vaccination series should have been obtained in line with the recommendations given in the product information of the vaccines [5–7]. These five reports of vaccination failures were assessed as consistent with a causal association to COVID-19 vaccines. In 11 (65%) of the 17 reports with fatal COVID-19, the time after the vaccination was too short to obtain the anticipated protection against the infection, and in one case, the death occurred 7 months after the vaccination.

Among the fatal reactions that were assessed as consistent with a causal association to COVID-19 vaccines were three reports concerning thrombocytopenia with thrombosis and/or bleeding with platelet-activating antibodies against platelet factor 4 after vaccination with adenovirus vector vaccine Vaxzevria®. In addition, there were 12 fatal cases reported as myocarditis in persons aged 13−82 years after mRNA vaccines Comirnaty® and Spikevax® (Table 4). However, in over half of these cases, other conditions than myocarditis were defined as the causes of death in the autopsy, such as pneumonia, ruptured aortic dissection, acute myocardial infarction, cardiac sarcoidosis, and vasculitis with bleeding

**Table 4** Most common ADRs with a fatal outcome reported after COVID-19 vaccinations in Sweden

| Reported reaction | Comirnaty® | | | Spikevax® | | | Vaxzevria® | | | Total |
|---|---|---|---|---|---|---|---|---|---|---|
| | Male | Female | Total | Male | Female | Total | Male | Female | Total | |
| Cardiac arrest | 25 | 21[a] | 46[a] | 6 | 3[a] | 9[a] | 8 | 5 | 13 | 68[a] |
| Pulmonary embolism | 17 | 15[a] | 32[a] | 5 | 3[a] | 8[a] | 4 | 7 | 11 | 50[a] |
| Myocardial infarction | 20 | 16 | 36 | 3 | 1 | 4 | 7 | 3 | 10 | 50 |
| Cerebral hemorrhage | 12 | 16[a] | 28[a] | 0 | 1 | 1 | 2 | 4[a] | 6[a] | 34[a] |
| Cardiac failure | 9 | 15 | 24 | 4 | 2 | 6 | 1 | 0 | 1 | 31 |
| Pneumonia | 12 | 11[a] | 23[a] | 2 | 1 | 3 | 3 | 1[a] | 4[a] | 29[a] |
| Ischemic stroke | 4 | 10 | 14 | 2 | 3 | 5 | 0 | 4 | 4 | 23 |
| Respiratory failure | 9 | 7 | 16 | 2 | 0 | 2 | 1 | 1 | 2 | 20 |
| COVID-19 | 5 | 8 | 13 | 1 | 1 | 2 | 1 | 1 | 2 | 17 |
| Sepsis | 6 | 6 | 12 | 3 | 1 | 4 | 1 | 0 | 1 | 17 |
| Pulmonary edema | 6 | 7 | 13 | 0 | 0 | 0 | 1 | 1 | 2 | 15 |
| Renal failure | 7 | 5 | 12 | 1 | 0 | 1 | 0 | 0 | 0 | 13 |
| Myocarditis | 6 | 1[a] | 7[a] | 4 | 0 | 4 | 1 | 1[a] | 2 | 12[a] |

*ADR* adverse drug reaction, *COVID-19* coronavirus disease 2019

Spontaneous ADR reports received between 27 December, 2020 and 31 May, 2023. One report can include one or more ADRs

[a]In three of the reports, two different COVID-19 vaccines were suspected (Comirnaty® and Spikevax® in two reports, and Comirnaty® and Vaxzevria® in one report each)

and pneumonia in a patient with spread abdominal cancer. In one person with congenital heart disease and an earlier heart valve operation, the cause of death was *Staphylococcus aureus* sepsis with endocarditis. Two fatal cases of myocarditis after Comirnaty® were assessed as consistent with a causal association to the vaccine.

In summary, ten fatal cases (0.1 per 100,000 persons vaccinated) were assessed as consistent with a causal association to vaccination: five fatal cases with vaccination failure, three with thrombosis with thrombocytopenia syndrome (TTS) after Vaxzevria®, and two with myocarditis after Comirnaty®.

## 4 Discussion

We have reviewed all COVID-19 vaccine-related ADR reports with fatal outcomes during the vaccination campaign in Sweden. The reporting rates in our study (5.7 per 100,000 persons vaccinated with at least one dose of COVID-19 vaccines and 1.7 per 100,000 vaccine doses administered) were similar in order of magnitude to those observed for fatal reports following COVID-19 vaccinations in the USA in the Vaccine Adverse Event Reporting System (VAERS) [43.6 per million vaccinated persons] [22] and in Victoria, Australia in the Surveillance of Adverse Events Following Vaccination in the Community (SAFEVIC) [3.98 per 100,000 vaccine doses in the first 3 months and 0.71 per 100,000 vaccine doses in the following 21 months] [23].

Of the reported 456 fatal cases, only ten were assessed as consistent with a causal association to vaccination. Half of the reports concerned myocarditis and TTS, which are now known as very rare adverse reactions of some COVID-19 vaccines. Special warnings and precautions for use have already been included in the product information of the relevant COVID-19 vaccines because of myocarditis [5, 6, 8] or TTS [7], and these ADR reports raise no new safety concerns. Vaccination failure, i.e., a lack of protection against vaccine-preventable disease in appropriately and fully vaccinated persons [24], was assessed as consistent with a causal association to vaccination in five reports regarding persons with verified COVID-19 after the two-dose primary series of COVID-19 vaccines.

The ADR reporting was at the highest within the older age groups, most of the reports concerned individuals aged 70 years and above. The reported fatalities occurred frequently in patients with multiple pre-existing chronic conditions, such as cardiovascular diseases, diabetes, dementia, lung, renal, or liver disorders, or various cancers, which are the known leading causes of death in Sweden and in other high-income countries [25, 26]. In many of the reports, the underlying medical condition was deemed to be a more plausible explanation for the death than COVID-19 vaccination. In some individuals, palliative care had already been initiated before the vaccination. Many of the reported deaths occurred in nursing home residents or in persons receiving home care, which were two groups that had a high mortality also during the first year of the pandemic before the vaccines were available [9, 10]. Vaccines are currently the best method to prevent severe or fatal COVID-19 infections in this vulnerable population [27].

Pulmonary embolism was one of the most reported ADRs with fatal outcomes after COVID-19 vaccines. However, most of the individuals had underlying health conditions known to be strong or moderate predisposing risk factors for pulmonary embolism, such as earlier thromboembolism, recent myocardial infarction, active cancer, heart failure, or respiratory failure [28]. During a massive vaccination campaign, some cases of pulmonary embolism are to be expected because the annual incidence rates range from 39 to 115 per 100,000 persons with the highest incidence in older individuals [28]. No apparent associations were observed between COVID-19 vaccinations and pulmonary embolism in a recent nationwide cohort study in Sweden [29]. Similarly, no increased risk for pulmonary embolism has been found in other large safety studies with COVID-19 mRNA vaccines, conducted in different settings [30, 31]. In some studies, adenovirus vector vaccine Vaxzevria was associated with an excess risk for venous thromboembolism [30, 33], which may present with a manifestation of TTS related to this vaccine [34]. COVID-19 infection by itself has also been identified as a risk factor for venous thromboembolism and pulmonary embolism [31, 35, 36]. The excess risk for pulmonary embolism may remain elevated after 6 months in patients with severe COVID-19 [36].

Myocardial infarction and ischemic or hemorrhagic stroke were also among the most reported fatal reactions after COVID-19 vaccinations. Nevertheless, most of the affected individuals had multiple pre-existing cardiovascular risk factors for these conditions, such as hypertension, diabetes, hyperlipidemia, and obesity. No increased risk for myocardial infarction or stroke after COVID-19 vaccines has been observed in large safety studies [30, 32, 37], whereas COVID-19 infection is associated with an increased risk for myocardial infarction [30, 38] and ischemic or hemorrhagic stroke [31, 37, 38].

The primary purpose of spontaneous reporting is to detect new safety concerns. Analysis of post-marketing safety data has identified some serious but very rare ADRs associated with COVID-19 vaccines. Such a reaction was TTS with the adenovirus vector vaccine Vaxzevria®, which may have contributed to three reports with fatal outcomes in Sweden, of which the first was received in early March 2021. Soon after, that EMA's Pharmacovigilance Risk Assessment Committee started a review of this safety signal and concluded that TTS should be a listed ADR in

the product information of Vaxzevria® [34]. Thrombosis with thrombocytopenia syndrome is characterized by the occurrence of thrombosis at unusual sites, such as cerebral venous sinus and splanchnic veins, accompanied by thrombocytopenia, bleeding, and the production of platelet-activating antibodies against platelet factor 4 [39, 40]. This very rare type of thrombosis has been estimated to occur in about 1 in 100,000 vaccinated persons [41]. Thrombosis with thrombocytopenia syndrome cases have also occurred after another adenovirus vector vaccine Jcovden® (Ad26.COV2-S [recombinant]) [39], but this COVID-19 vaccine was never used in the vaccination program in Sweden. As TTS occurred more frequently in relatively young individuals, the usage of Vaxzevria® was restricted by the Public Health Agency of Sweden only to persons aged over 65 years as a precautionary measure [42]. At the end of March 2024, Vaxzevria® was withdrawn in the European Union at the request of the MAH because of commercial reasons [7]. There is no solid evidence that TTS is associated with COVID-19 mRNA vaccines, and the very low reporting rate suggests that cases represent a background rate [43].

Another serious but very rare ADR associated with COVID-19 vaccines is myocarditis. A consistent causal association between myocarditis and mRNA vaccines has also been considered in some of the Swedish ADR reports with fatal outcomes. An analysis from a Nordic cohort study pointed to an association with mRNA COVID-19 vaccines, especially with Spikevax® [44]. After the authorization, myocarditis has been identified as a very rare adverse reaction occurring in less than 1 in 10,000 people vaccinated with mRNA vaccines. Myocarditis risk was primarily seen within the first 2 weeks after the second vaccine dose and mainly affected younger male individuals. In October 2021, the Public Health Agency of Sweden suspended the use of Spikevax® in persons aged 30 years or younger, advising that they should be given Comirnaty® instead [42]. Vaccination with Nuvaxovid® has also been associated with an increased risk for myocarditis and is not recommended in Sweden to persons aged 30 years or younger [42].

Because of several limitations, spontaneous reports alone are often insufficient for determining a causal association between a reported reaction and vaccination. A typical limitation is the amount and quality of information provided. Because of the lack of information on the vaccination date and/or onset of the suspected ADRs, details of the medical history, comorbidities or concomitant medications, or autopsy results in many of the reports, the evaluation did not find sufficient evidence to suggest a reasonable possibility of a causal association between the reported ADR and the COVID-19 vaccine. Autopsy reports are of great value when evaluating spontaneous reports with fatal outcomes. They contribute by defining the cause of death and confirm or rule out the reported diagnoses and a causal association between vaccination and death.

Another challenge in assessing fatal ADRs is the difficulties of disentangling the role of underlying comorbid conditions leading to death from a suspected ADR. In a patient with a severe disease, the vaccine could be a trigger leading to an aggravated condition. Hence, the connection to vaccination may be underestimated in some cases.

Underreporting is also a general limitation when drawing conclusions from spontaneous ADR reporting. However, vaccine adverse effects bring media attention and heightened public awareness, which has been shown to stimulate reporting [45, 46]. Information on spontaneous reports of the COVID-19 vaccines was frequently published on the Swedish MPA's website. The ten-fold increase in ADRs reported during the pandemic compared with previous years might indicate that HCPs and consumers have been more prone to report suspected ADRs for the COVID-19 vaccines than they would be for other drugs and vaccines.

## 5 Conclusions

A review of all reports of fatal ADRs during the national COVID-19 vaccination campaign in Sweden raises no new safety concerns. The few cases that were assessed as consistent with a causal association to vaccination concerned myocarditis, TTS, and vaccine failure, which are already known as very rare adverse reactions. Most of the fatal cases that were not consistent with a causal association considered persons with high age, living in nursing homes or receiving home care services, and with multiple pre-existing health problems. Many of the deaths attributed to COVID-19 vaccinations in Sweden would probably have occurred regardless of vaccination because of patients' pre-existing severe health problems. Most of the reported ADRs did not provide evidence of a causal link with vaccine exposure but can rather be regarded as serious medical events only temporally related to vaccination.

**Supplementary Information** The online version contains supplementary material available at https://doi.org/10.1007/s40261-025-01466-3.

## Declarations

**Funding** Open access funding provided by Medical Products Agency. The study was conducted as a pharmacovigilance activity by the Swedish MPA, which is a Swedish Government agency. The study has received no external funding.

**Conflicts of interest/competing interests** Marja-Leena Nurminen, Per Lindemo, Anders Sundström, Björn Zethelius, Maria Larsson, Sofia Attelind, Nicklas Pihlström, Rickard Ljung, and Veronica Arthurson

have no conflicts of interest that are directly relevant to the content of this article.

**Ethics approval** This study was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the Swedish Ethical Review Authority (2020-06859, 2021-02186).

**Consent to participate** Not applicable.

**Consent for publication** Not applicable.

**Availability of data and material** The data of this article are not publicly available because of the EMA's policy of access to EudraVigilance data for medical products for human use in accordance with Regulation (EU) 2016/679, the General Data Protection Regulation and Regulation (EU) 2018/1725, and the European Union data protection legislation. For more information, see: https://www.ema.europa.eu/en/documents/other/european-medicines-agency-policy-access-eudravigilance-data-medicinal-products-human-use_en.pdf.

**Code availability** Not applicable.

**Authors' contributions** MLN drafted the manuscript and constructed the tables. NP constructed the graphs. MLN, PL, ML, and SA provided the ADR data. AS and NP accomplished the statistics on mortality and hospitalizations due to COVID-19, positive COVID-19 tests, and exposure to COVID-19 vaccines from nationwide healthcare register data. BZ administered the submission. RL and VA supervised the project. All authors reviewed, edited, and approved the final version of the manuscript.



## References

1. World Health Organization. Coronavirus disease (COVID-19) pandemic. who.int. https://www.who.int/europe/emergencies/situations/covid-19. Accessed 11 June 2025.
2. The Public Health Agency of Sweden. Public health data [in Swedish]. https://fohm-app.folkhalsomyndigheten.se/Folkhalsodata/pxweb/sv/A_Folkhalsodata/. Accessed 11 June 2025.
3. The National Board of Health and Welfare. The state of healthcare: Covid-19 [in Swedish]. https://www.socialstyrelsen.se/statistik-och-data/statistik/alla-statistikamnen/lagesbild-covid-19-influensa-och-rs-statistik/. Accessed 11 June 2025.
4. The National Board of Health and Welfare. Statistical database for causes of death [in Swedish]. https://sdb.socialstyrelsen.se/if_dor/val.aspx. Accessed 11 June 2025.
5. European Medicines Agency (EMA). Comirnaty. https://www.ema.europa.eu/en/medicines/human/EPAR/comirnaty.. Accessed 11 June 2025.
6. European Medicines Agency (EMA). Spikevax (previously COVID-19 vaccine Moderna). https://www.ema.europa.eu/en/medicines/human/EPAR/spikevax. Accessed 11 June 2025.
7. European Medicines Agency (EMA). Vaxzevria (previously COVID-19 Vaccine AstraZeneca). https://www.ema.europa.eu/en/medicines/human/EPAR/vaxzevria. Accessed 11 June 2025.
8. European Medicines Agency (EMA). Nuvaxovid. https://www.ema.europa.eu/en/medicines/human/EPAR/nuvaxovid. Accessed 11 June 2025.
9. Ballin M, Bergman J, Kivipelto M, Nordström A, Nordström P. Excess mortality after COVID-19 in Swedish long-term care facilities. J Am Med Dir Assoc. 2021;22(8):1574–80.
10. Rosengren A, Lundberg CE, Söderberg M, Santosa A, Edqvist J, Lindgren M, et al. Severe COVID-19 in people 55 and older during the first year of the pandemic in Sweden. J Intern Med. 2022;292(4):641–53. https://doi.org/10.1111/joim.13522.
11. EDCD. Overview of the implementation of COVID-19 vaccination strategies and deployment plans in the EU/EEA. https://www.edcd.europa.eu/sites/default/files/documents/Overview-of-the-implementation-of-COVID-19-vaccination-strategies-anddeploymentplans-14-June-2021.pdf. Accessed 11 June 2025.
12. Schonberger LB, Bregman DJ, Sullivan-Bolyai JZ, Keenlyside RA, Ziegler DW, Retailliau HF, et al. Guillain–Barre syndrome following vaccination in the national influenza program, United States, 1976–1977. Am J Epidemiol. 1979;110(2):105–23. https://doi.org/10.1093/oxfordjournals.aje.a112795.
13. Granath F, Gedeborg R, Smedje H, Felthelius N. Change in risk for narcolepsy over time and impact of definition of onset date following vaccination with AS03 adjuvanted pandemic A/H1N1 influenza vaccine (Pandemrix) during the 2009 H1N1 influenza pandemic. Pharmacoepidemiol Drug Saf. 2019;28(8):1045–53.
14. Swedish Medical Products Agency's regulation (LVFS 2012:14) on pharmacovigilance of medicinal products for human use, 19§. [in Swedish]. lvfs-2012-14-konsoliderad.pdf. Accessed 11 June 2025. https://www.lakemedelsverket.se/globalassets/dokument/lagar-och-regler/hslf-fs/lvfs-2012-14-konsoliderad.pdf
15. Kälkner KM, Sundström A, Nurminen M-L, Larsson M, Ljung R, Arthurson V. Optimizing safety surveillance for COVID-19 vaccines at the Swedish Medical Products Agency. Drug Saf. 2023;46(3):319–21. https://doi.org/10.1007/s40264-023-01275-7.
16. Ljung R, Sundström A, Grünewald M, Backman C, Feltelius N, Gedeborg R, et al. The profile of the COvid-19 VACcination register SAFEty study in Sweden (CoVacSafe-SE). Upsala J Med Sci. 2021. https://doi.org/10.48101/ujms.v126.8136.
17. Medical Dictionary for Regulatory Activities (MedDRA). https://www.meddra.org. Accessed 11 June 2025.
18. European Medicines Agency (EMA). Guideline on good pharmacovigilance practices (GVP). Module VI: collection, management and submission of reports of suspected adverse reactions to medical products (Rev 2). https://www.ema.europa.eu/en/documents/other/european-medicines-agency-policy-access-eudravigilance-data-medicinalproducts-human-use_en.pdf.
19. European Medicines Agency (EMA). European Medicines Agency policy on access to EudraVigilance data for medicinal products for human use. EV access policy_document_2024 revision 5. https://www.ema.europa.eu/en/human-regulatory-overview/post-authorisation/pharmacovigilance-post-authorisation/goodpharmacovigilance-practices-gvp. Accessed 18 June 2025.
20. European Medicines Agency (EMA). Guideline on good pharmacovigilance practices (GVP). Module VI Addendum I: duplicate management of suspected adverse reaction reports. Accessed 4

Feb 2025. https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-good-pharmacovigilance-practices-gvpmodule-vi-addendum-i-duplicate-management-suspected-adverse-reaction-reports_en.pdf
21. World Health Organization (WHO). Causality assessment of an adverse event following immunization (AEFI): user manual for the revised WHO classification, 2nd ed., 2019 update. who.int. https://www.ema.europa.eu/en/human-regulatory-overview/post-authorisation/pharmacovigilance-post-authorisation/goodpharmacovigilance-practices-gvp. Accessed 11 June 2025.
22. Day B, Menschik D, Thompson D, Jankosky C, Su J, Moro P, et al. Reporting rates for VAERS death reports following COVID-19 vaccination, December 14, 2020–November 17, 2021. Pharmacoepidemiol Drug Saf. 2023;32(7):763–72. https://doi.org/10.1002/pds.5605.
23. Laemmle-Ruff I, Fryk JJ, Shenton P, Clothier HJ, Parsons S, Iles L, et al. Detailed review of mortality reported following COVID-19 vaccination in Victoria, Australia: 2021–2023. Vaccine. 2024;42(26): 126368. https://doi.org/10.1016/j.vaccine.2024.126368.
24. Heininger U, Bachtiar NS, Bahri P, Dana A, Dodoo A, Gidudu J, et al. The concept of vaccination failure. Vaccine. 2012;30:1265–8. https://doi.org/10.1016/j.vaccine.2011.12048.
25. Brooke HL, Talbäck M, Hörnblad J, Johansson LA, Ludvigsson JF, Druid H, et al. The Swedish cause of death register. Eur J Epidemiol. 2017;32:765–73. https://doi.org/10.1007/s10654-017-0316-1.
26. Warraich HJ, Marston HD, Califf RM. Addressing the challenge of common chronic diseases: a view from the FDA. N Engl J Med. 2024;390(6):490–2. https://doi.org/10.1056/NEJMp2313217.
27. Nilsson L, Andersson C, Kastbom L, Sjödahl R. Association between vaccination and preventive routines on COVID-19-related mortality in nursing home facilities: a population-based systematic retrospective chart review. Prim Health Care Res Dev. 2022;23(e75):1–7. https://doi.org/10.1017/S1463423622000640.
28. Konstantinides SV, Meyer G, Becattini C, Bueno H, Geersing G-J, Harjola V-P, et al. 2019 ESC guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). Eur Heart J. 2020;41(4):543–603. https://doi.org/10.1093/eurheartj/ehz405.
29. Zethelius B, Attelind S, Westman G, Ljung R, Sundström A. Pulmonary embolism after SARS-CoV-2 vaccination. Vaccine X. 2024;21: 100571. https://doi.org/10.1016/j.jvacX.2024.100571.
30. Botton J, Jabagi MJ, Bertrand M, Baricault B, Drouin J, Le Vu S, et al. Risk for myocardial infarction, stroke, and pulmonary embolism following COVID-19 vaccines in adults younger than 75 years in France. Ann Intern Med. 2022;175(9):1250–7. https://doi.org/10.7326/M22-0988.
31. Barda N, Dagan N, Ben-Shlomo Y, Kepten E, Waxman J, Ohana R, et al. Safety of the BNT162b2 mRNA Covid-19 vaccine in a nationwide setting. N Engl J Med. 2021;385(12):1078–90. https://doi.org/10.1056/NEJMoa2110475.
32. Jabagi MJ, Botton J, Bertrand M, Weill A, Farrington P, Zureik M, et al. Myocardial infarction, stroke, and pulmonary embolism after BNT162b2 mRNA COVID-19 vaccine in people aged 75 years or older. JAMA. 2022;327(1):80–2. https://doi.org/10.1001/jama.2021.21699.
33. Hviid A, Hansen JV, Thiesson EM, Wohlfahrt J. Association of AZD1222 and BNT162b2 COVID-19 vaccination with thromboembolic and thrombocytopenic events in frontline personnel: a retrospective cohort study. Ann Intern Med. 2022;175(4):541–6. https://doi.org/10.7326/M21-2452.
34. European Medicines Agency (EMA). AstraZeneca's COVID-19 vaccine: EMA finds possible link to very rare cases of unusual blood clots with low blood platelets. https://www.ema.europa.eu/en/news/astrazenecas-covid-19-vaccine-ema-finds-possible-link-very-rare-cases-unusual-blood-clots-low-blood. Accessed 11 June 2025.
35. Katsoularis I, Fonseca-Rodriguez O, Farrington P, Jerndal H, Häggström Lundevaller E, Sund M, et al. Risks of deep vein thrombosis, pulmonary embolism, and bleeding after covid-19: nationwide self-controlled cases series and matched cohort study. BMJ. 2022;376: e069590. https://doi.org/10.1136/bmj-2021-069590.
36. Sjöland H, Lindgren M, Toska T, Hansson P-O, Glise Sandblad K, Alex C, et al. Pulmonary embolism and deep venous thrombosis after COVID-19: long-term risk in a population-based cohort study. Res Pract Thromb Haemost. 2023;7(5): e100284. https://doi.org/10.1016/j.rpth.2023.100284.
37. Stefanou M-I, Palaiodimou L, de Aguiar de Sousa D, Theodorou A, Bakola E, Katsaros DE, et al. Acute arterial ischemic stroke following COVID-vaccination: a systematic review and meta-analysis. Neurology. 2022;99:e1465–74. https://doi.org/10.1212/WNL.0000000000200996.
38. Katsoularis I, Fonseca-Rodriguez O, Farrington P, Fors Conolly A-M. Risk of acute myocardial infarction and ischaemic stroke following COVID-19 in Sweden: a self-controlled case series and matched cohort study. Lancet. 2021;398(10300):599–607. https://doi.org/10.1016/S0140-6736(21)00896-5.
39. Greinacher A, Thiele T, Warkentin TE, Weisser K, Kyrie PA, Eichinger S, et al. Thrombotic thrombocytopenia after ChAdOx1 nCov-19 vaccination. N Engl J Med. 2021;384(22):2092–101. https://doi.org/10.1056/NEJMoa2104840.
40. Schultz NH, Sørvoll IH, Michelsen AE, Munthe LA, Lund-Johansen F, Ahlen MT, et al. Thrombosis and thrombocytopenia after ChAdOx1 nCoV-19 vaccination. N Engl J Med. 2021;384(22):2124–30. https://doi.org/10.1056/NEJMoa2104882.
41. Dabbiru VAS, Müller L, Schönborn L, Greinacher A. Vaccine-induced immune thrombocytopenia and thrombosis (VITT): insights from clinical cases, in vitro studies and murine models. J Clin Med. 2023;12(19):6126. https://doi.org/10.3390/jcm12196126.
42. Public Health Agency of Sweden. What happened and when during pandemic? [in Swedish]. https://www.folkhalsomyndigheten.se/smittskydd-beredskap/utbrott/utbrottsarkiv/covid-19-pandemin-2019-2023/nar-handevad-under-pandemin/. Accessed 11 June 2025.
43. See I, Lale A, Marquez P, Streiff MB, Wheeler AP, Tepper NK, et al. Case series of thrombosis with thrombocytopenia syndrome after COVID-19 vaccination: United States, December 2020 to August 2021. Ann Intern Med. 2022;175(4):513–22. https://doi.org/10.7326/M21-4502.
44. Karlstad Ø, Hovi P, Husby A, Härkänen T, Selmer RM, Pihlström N, et al. SARS-CoV-2 vaccination and myocarditis in a nordic cohort study. JAMA Cardiol. 2022;7(6):600–12. https://doi.org/10.1001/jamacardio.2022.0583.
45. Ferner RE, Stevens RJ, Anton C, Aronson JK. Spontaneous reporting to regulatory authorities of suspected adverse reactions to COVID-19 vaccines over time: the effect of publicity. Drug Saf. 2022;45(2):137–44. https://doi.org/10.1007/s40264-021-01138-z.
46. Oosterhuis I, Scholl J, van Puijenbroek E, Kant A, van Hunsel F. Optimizing safety surveillance for COVID-19 vaccines at the national pharmacovigilance centre Lareb: one year of COVID-19 vaccine experience. Drug Saf. 2023;46(1):65–75. https://doi.org/10.1007/s40264-022-01253-5.

## Authors and Affiliations

**Marja-Leena Nurminen[1] · Per Lindemo[1] · Anders Sundström[2,3] · Björn Zethelius[1,4] · Maria Larsson[1] · Sofia Attelind[1,5] · Nicklas Pihlström[1] · Rickard Ljung[1,6] · Veronica Arthurson[1]**

✉ Björn Zethelius
bjorn.zethelius@lakemedelsverket.se

Marja-Leena Nurminen
marja-leena.nurminen@lakemedelsverket.se

Per Lindemo
per.lindemo@lakemedelsverket.se

Anders Sundström
p.anders.sundstrom@uu.se

Maria Larsson
maria.larsson@lakemedelsverket.se

Sofia Attelind
sofia.attelind@lakemedelsverket.se

Nicklas Pihlström
niklas.pihlstrom@lakemedelsverket.se

Rickard Ljung
rickard.ljung@ki.se

Veronica Arthurson
veronica.arthurson@lakemedelsverket.se

1 Use and Information Division, Swedish Medical Products Agency, PO Box 26, 751 03 Uppsala, Sweden

2 Uppsala Monitoring Centre, Uppsala, Sweden

3 Department of Pharmacy, Uppsala University, Uppsala, Sweden

4 Department of Public Health, Clinical Geriatrics, Uppsala University, Uppsala, Sweden

5 Department of Medical Sciences, Clinical Pharmacogenomics, Uppsala University, Uppsala, Sweden

6 Institute of Environmental Medicine, Karolinska Institute, Stockholm, Sweden