BMC Infectious Diseases

RESEARCH

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Long-term trends in reporting of cardiac adverse drug reactions to COVID-19 vaccines - an exploratory analysis of the EudraVigilance database

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Abstract

Background Vaccination against COVID-19 could be followed by a serious cardiac adverse drug reaction (SCADR), which is a noxious, unintended response to the administered vaccine and is life-threatening, usually requires hospitalisation and may result in death. We aimed to explore long-term trends in reporting of SCADRs to COVID-19 vaccines.

Methods In this retrospective, longitudinal, observational study, suspected (potentially linked to vaccination) SCADRs to Comirnaty (Pfizer BioNTech), Spikevax (Moderna), Vaxzevria (AstraZeneca) and Jcovden (Janssen) vaccines were extracted from the EudraVigilance database ($n = 87{,}000$). This data was coupled with the corresponding weekly number of administered vaccine doses from the Vaccine Tracker database ($n = 733{,}837{,}251$).

Results The most frequently documented categories of SCADRs included arrhythmia ($n = 29{,}936$), thrombosis ($n = 21{,}381$), inflammation (myocarditis and pericarditis, $n = 13{,}421$), blood pressure abnormalities ($n = 10{,}535$) and syncopes ($n = 10{,}363$), both during the first year and for the whole vaccination period. During the first year of vaccine distribution, the total number of SCADRs per million administered vaccine doses was 77.3 (Comirnaty), 76.4 (Spikevax), 115.3 (Jcovden) and 230.3 (Vaxzevria). These values changed significantly when the whole period of vaccinations was considered (145.6, 146.3, 203.5, 320.5, respectively; $p < 0.001$). Concerning vaccine administration timelines, the reporting of suspected adverse drug reactions appears to be more widely distributed over time ($p < 0.05$).

Conclusions The frequency of reporting suspected SCADRs after COVID-19 vaccinations appears to change dynamically over time. Concerning the administration of vaccine doses, the reporting of potential post-vaccination ADRs seems to be more distributed in time. These observations suggest that post-approval long-term monitoring of suspected ADRs may be valuable for improving data capture and supporting vaccine safety assessment. This underlines the potential importance of comprehensive surveillance in the context of infectious diseases and vaccine development programs.

Keywords Adverse drug reactions, COVID-19, Comirnaty, EudraVigilance, Pharmacovigilance, Vaccine safety

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Introduction

Vaccines against Coronavirus disease 2019 (COVID-19) are confirmed to be highly effective in preventing COVID-19 infections [1–4]. Vaccinating reduces the risk of symptomatic infection, hospitalisations, including in intensive care units, and death [1–5]. The European Medicines Agency (EMA) clearly states that the benefit of active immunization and protection against COVID-19 outweighs the risk of potential side effects [6].

However, in some patients, potential postvaccination adverse drug reactions (ADRs) may occur [4, 7–9]. EMA defines an ADR as a noxious and unintended response to a medicine [10]. All ADRs can be classified as mild, moderate or serious (severe) [6]. According to EMA, a serious ADR is "a reaction that corresponds to any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect" [10–12]. Serious ADRs to COVID-19 vaccines could be connected with different organ damage [4, 6, 13, 14]. The most commonly described serious cardiac adverse drug reactions (SCADRs) that are potential complications of COVID-19 vaccinations include myocarditis, thrombosis and pulmonary embolism [7–9, 15–18].

Data on suspected ADRs to COVID-19 vaccines authorised by EMA are collected in the EudraVigilance database [11, 12]. In this monitoring system, everyone can voluntarily submit a potential postvaccination ADR report on a "spontaneous" basis [11, 12]. 'Spontaneous reports' are referred to as such because they occur during a clinician's evaluation of a patient, where the clinician suspects that a drug could be linked to the clinical event [19]. According to data from registration trials, randomised controlled trials and cohort studies, as well as officially published EMA product characteristics, the frequency of observed cardiac ADRs is rare (≥ 1/10,000 to < 1/1,000) or very rare (< 1/10,000) [4, 6, 14]. Nevertheless, even though SCADRs are relatively rare, given the massive number of administered COVID-19 vaccine doses, postvaccination ADRs may also contribute to a substantial number of hospital admissions and deaths [6, 20, 21]. Therefore, the regular evaluation of spontaneous reporting and monitoring systems of suspected ADRs is crucial for ensuring the safety of COVID-19 vaccines. This most commonly focuses on estimating the frequency (incidence) of the potential ADRs [4, 6, 9, 13, 21]. However, to date, there have been no large-scale studies that would comprehensively explore long-term trends in spontaneous reporting of suspected SCADRs to COVID-19 vaccines. Finally, there is a knowledge gap regarding the relationships between the number of spontaneously reported suspected cardiac ADRs and the actual number of administered COVID-19 vaccine doses. Overall, insights gained from such a study could provide a cornerstone for future public health policies regarding spontaneous ADR reporting and, based upon it, vaccine safety monitoring.

Aim

To explore long-term trends in spontaneous reporting of suspected SCADRs to COVID-19 vaccines.

Methods and materials

This longitudinal, observational study was performed according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: Guidelines for Reporting Observational Studies [22].

Database search

The EudraVigilance database was searched to find any suspected adverse drug reactions (ADRs) to vaccination against COVID-19. The last search was conducted on 10th March 2024. No filters were used. The initial search returned a total of 2,302,495 ADRs to fourteen COVID-19 vaccine products (Fig. 1) [23].

In addition to that, the European Centre for Disease Prevention and Control (ECDC) Vaccine Tracker database was searched to gather data regarding the total number of vaccine doses administered in the European Economic Area (EEA). The data were available for every week, from 7th December 2020 to 5th October 2023. In total, over 1.4 billion doses were distributed, and over 980 million doses were administered for all vaccines approved in the EU/EEA [20].

Data filtering

To analyse corresponding data from the EudraVigilance database to the Vaccine Tracker database, any records from the EudraVigilance database that were reported from outside of the EEA region were excluded. Moreover, ADRs whose severity was marked as non-serious were also excluded (in total $n = 1{,}889{,}534$, Fig. 1). Moreover, fewer than 1,000 ADRs were reported for Comirnaty Omicron, Spikevax Omicron, Novavax, Valneva, and Vidprevtyn Beta products ($n = 1{,}727$). Thus, 10 vaccine products were excluded from further analysis (Table 1). In total, 411,234 suspected ADRs for the four most commonly administered vaccines: Moderna Spikevax (Elastomeran, $n = 48{,}275$), Pfizer BioNTech Comirnaty (Tozinameran, $n = 268{,}102$), AstraZeneca Vaxzevria ($n = 72{,}614$) and Janssen Jcovden ($n = 17{,}875$) were available.

Next, to match the time from the Vaccine Tracker database, any reports of suspected ADRs added to the EudraVigilance database after the 5th of October 2023 were removed ($n = 4{,}368$).

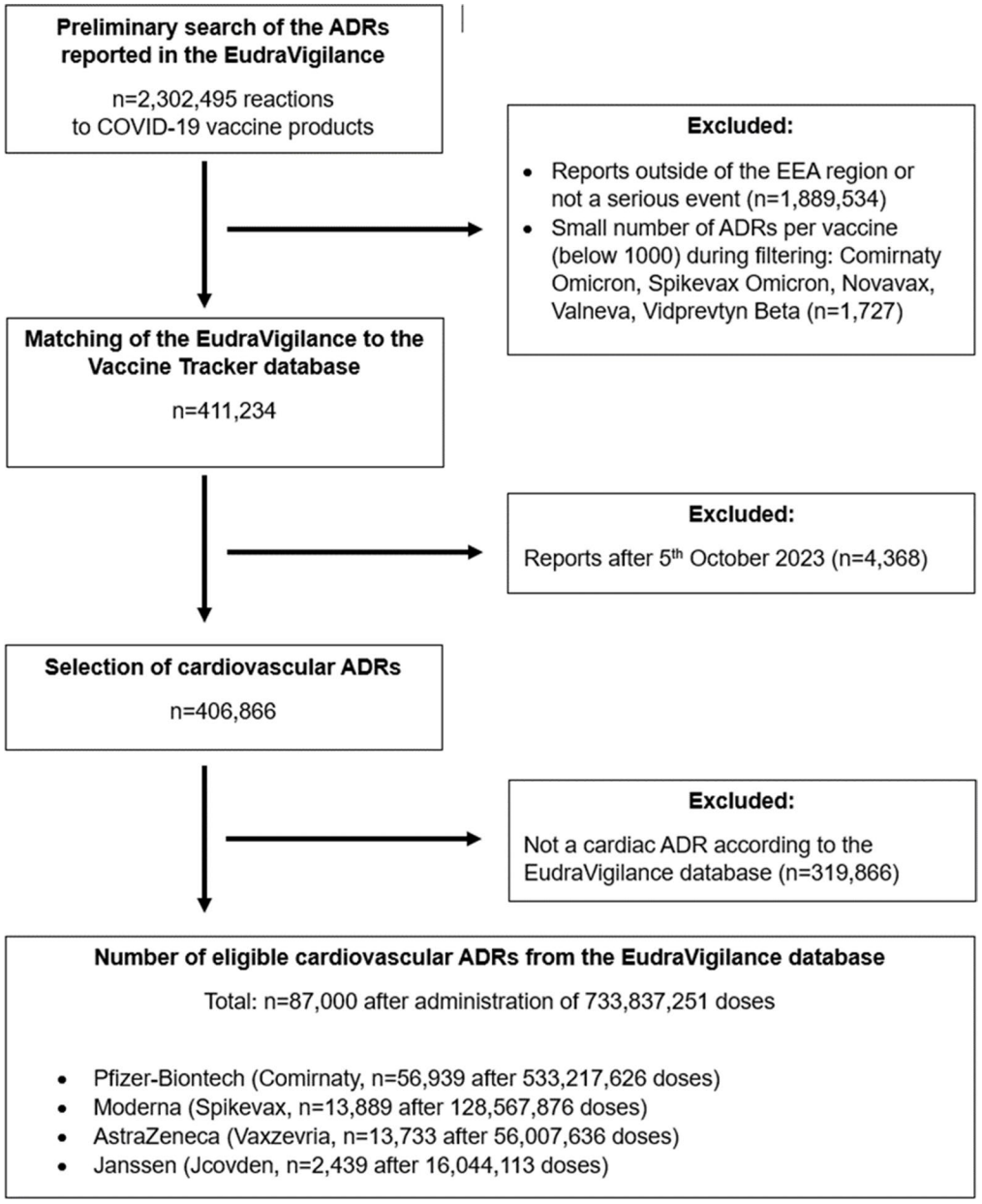

Fig. 1 Study design

Table 1 General characteristics of vaccines included in the study

Product name in the EudraVigilance database	Number of cases in the EudraVigilance database	Number of cases from the European Economic Area	Number of instances after filtering - all adverse drug reactions	Number of cases after filtering - cardiovascular adverse drug reactions	Number of total vaccine doses administered
COVID-19 MRNA VACCINE MODERNA (ELASOMERAN)	385,780	292,535	48,275	13,889	128,567,876
COVID-19 MRNA VACCINE PFIZER-BIONTECH (TOZINAMERAN)	1,257,508	1,036,994	268,102	56,939	533,217,626
COVID-19 VACCINE ASTRAZENECA (CHADOX1 NCOV-19)	552,233	180,535	72,614	13,733	56,007,636
COVID-19 VACCINE JANSSEN (AD26.COV2.S)	71,840	59,640	17,875	2439	16,044,113

Further on, for each of the analysed vaccines, the number of vaccine doses administered in the EEA countries per week was collected (Table 1, Supplementary Material S1) [20]. Overall, between 7 December 2020 and 5 October 2023, a total of 733,837,251 doses of the four eligible COVID-19 vaccines were administered.

Identification of cardiac adverse drug reactions

To find adverse drug reactions linked to the heart and cardiac system only, a catalogue of conditions categorised as "cardiac disorders" and "vascular disorders" as well as "syncope" and "pulmonary embolism" was extracted from the EudraVigilance database. In total, there were 527 entries (Supplementary Material S2). Among these, for 59 pathologies, no records were found. Furthermore, 227 adverse drug reactions were excluded from subsequent analysis because of a very low number of reports (fewer than 10 cases per ADR).

Afterwards, an expert in the field of cardiology (LDS) examined the remaining ADR pathologies. ADR pathologies were excluded from further analysis if they fell into one of the following categories: (1) labelled as valvular heart disease with an unlikely "post-vaccination" cause; (2) whose descriptions were too general and did not point to a more specific pathology, for example, "cardiac disorder"; (3) were categorized as "other reactions" not directly linked to heart disease or chronic conditions with an improbable "post-vaccination" cause. This elimination process accounted for 90 pathologies. Subsequently, the specific names of eligible serious cardiac ADRs (151 in total) were grouped into 10 broad, clinically-driven categories such as arrhythmia, blood pressure abnormality (mainly hypo/hypertension and blood pressure fluctuations), cardiomyopathy, conduction disorder, heart failure, inflammation (mainly myocarditis and pericarditis), ischemia, life-threatening event, syncope and thrombosis (see Supplementary Material S2).

Further on, records from the EudraVigilance database that were not classified as one of the 151 SCADRs were excluded ($n = 319{,}866$, Fig. 1). In total, 87,000 records were classified as suspected SCADRs for four vaccines: Spikevax ($n = 13{,}889$ after 128,567,876 doses), Comirnaty ($n = 56{,}939$ after 533,217,626 doses), Vaxzevria ($n = 13{,}733$ after 56,007,636 doses) and Jcovden ($n = 2{,}439$ after 16,044,113 doses).

Data analysis

To calculate general population characteristics, suspected SCADRs were grouped as observed during the first year after the introduction of each of the COVID-19 vaccines or during the whole period of vaccine administration (Table 2).

To determine the frequency of potential SCADRs per one million administered vaccine doses, the information from the EudraVigilance database regarding potential SCADRs was combined with the total number of doses administered for each vaccine as documented in the ECDC database. Importantly, the reporting rates were calculated as the number of reports per million vaccine doses administered. These represent the frequency of submitted reports in the passive surveillance system (EudraVigilance database) and should not be interpreted as true incidence or risk estimates, as spontaneous reporting is subject to under- or over-reporting, stimulated reporting, and a lack of systematic case verification [24–26].

Exploration of changes in time

To illustrate temporal patterns in reporting, we generated time series curves for each vaccine and category of

Table 2 Demographic data regarding suspected serious cardiac adverse drug reactions to COVID-19 vaccines

Characteristics	ADRs reported up to one year after the administration of the first dose of the vaccine.	ADRs reported one year after the administration of the first dose of the vaccine.	*p*-value
Count (n)	44,945 (51.7)	42,055 (48.3)	-
Primary Source Qualification: Healthcare Professional - count (%)	14942.0 (33.2)	22271.0 (53.0)	< 0.001
Primary Source Qualification: Non-Healthcare Professional - count (%)	30003.0 (66.8)	19784.0 (47.0)	
Patient Age Group: child - count (%)	3171.0 (7.1)	2552.0 (6.1)	< 0.001
Patient Age Group: 18–64 Years - count (%)	32992.0 (73.4)	27133.0 (64.5)	
Patient Age Group: More than 85 Years - count (%)	958.0 (2.1)	2110.0 (5.0)	
Patient Age Group: 65–85 Years - count (%)	7824.0 (17.4)	10260.0 (24.4)	
Patient Sex: Male - count (%)	18925.0 (42.1)	17722.0 (42.1)	< 0.001
Patient Sex: Female - count (%)	24946.0 (55.5)	23923.0 (56.9)	
Patient Sex: Not Specified - count (%)	1074.0 (2.4)	410.0 (1.0)	
vaccine: Spikevax - count (%)	9042.0 (20.1)	4847.0 (11.5)	< 0.001
vaccine: Comirnaty - count (%)	31260.0 (69.6)	25679.0 (61.1)	
vaccine: Vaxzevria - count (%)	3572.0 (7.9)	10161.0 (24.2)	
vaccine: Jcovden - count (%)	1071.0 (2.4)	1368.0 (3.3)	

suspected SCADRs, showing weekly changes in the number of reports (main charts: Figs. 3a, 3b, 3c, and 3d; all charts: Supplementary Material S5). In parallel, weekly vaccination uptake for each vaccine was plotted to provide context for reporting trends. To reduce short-term fluctuations and highlight broader trends, all curves were smoothed using a 4-week rolling average, corresponding approximately to one month. This approach allows direct visual comparison between vaccination rates and the dynamics of reported SCADRs over time. Next, relative frequency, defined as the weekly frequency relative to the peak observed frequency for a given characteristic, was computed for all analysed time series. The peak frequency was set at 100, and all other values were scaled accordingly (from 0 to 100).

Hierarchical clustering

To classify previously calculated time series curves representing weekly changes in the number of reported SCADRs by similarity index, hierarchical clustering was used [27, 28]. Hierarchical clustering, which is an unsupervised learning algorithm, organises data into a tree-like structure called a dendrogram, where similar curves are grouped based on the relative distance (similarity) between them [27, 28].

First, for each vaccine and category of suspected SCADRs, we quantified the similarity between weekly time series curves representing relative changes in reported events. Using these similarity distances, a hierarchical clustering algorithm was applied to group SCADR categories based on temporal reporting patterns. The resulting clusters are visualised as a dendrogram (Fig. 4), where the height of each branch reflects the distance between clusters. Branches that merge at lower heights indicate categories with more similar reporting dynamics, allowing identification of SCADRs that exhibit comparable temporal patterns across vaccines.

Statistical analysis

Categorical data was summarised with the use of frequencies and proportions. The Chi-square test with Yates' correction was used to check for statistical significance.

All analyses were performed using Python 3.10 as well as Pandas 2.1.3 and Scikit-learn 1.2.1 libraries. The threshold of two-sided statistical significance was set at $p < 0.05$ (5%).

Results

In total, 87,000 records were classified as suspected cardiac ADRs to COVID-19 vaccines and were reported after administration of 733,837,251 doses (Fig. 1; Table 2, Supplementary Material S2). Most of the ADRs were documented for Comirnaty ($n = 56{,}939$), followed by Spikevax ($n = 13{,}889$), Vaxzevria ($n = 13{,}733$) and Jcovden ($n = 2{,}439$, $p < 0.001$). The majority of potential ADRs were submitted for patients aged 18–64 years old (about 70%) and patients aged 65–85 years old (about 20%). About 56% of all ADRs reported occurred in female patients.

Changes in the frequency of reporting of SCADRs

The total frequencies of specific SCADRs were lower during the first year of vaccinations compared to the whole available period. The lowest frequencies were noticed for Comirnaty (77.3 and 145.6 PMD) and Spikevax (76.4 and 146.3 PMD), followed by Jcovden (115.3 and 203.5 PMD) and Vaxzevria, for which the highest values were observed (230.3 and 320.5 PMD; $p < 0.05$, Fig. 2).

For Comirnaty, the most commonly reported SCADRs during the first year were arrhythmias (17.2 PMD), thrombosis (16.0 PMD), and blood pressure

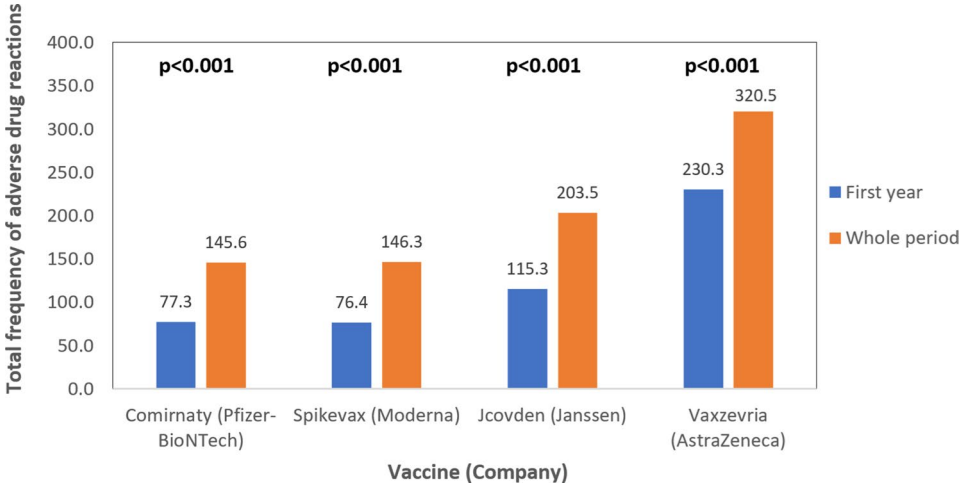

Fig. 2 Total number of adverse drug reactions per million administered vaccine doses during the studied vaccination periods

abnormalities (9.5 PMD), with arrhythmias (38.3 PMD), thrombosis (23.4 PMD) and inflammation (18.6 PMD) remaining most frequent over the full vaccination period.

For Spikevax, arrhythmias (17.3 PMD), thrombosis (13.6 PMD), and inflammation (12.1 PMD) were most frequent during the first year, increasing to arrhythmias (38.5 PMD), inflammation (22.0 PMD), and thrombosis (20.7 PMD) for the entire period.

For Jcovden, thrombosis (26.7 PMD), syncope (26.5 PMD), and arrhythmias (17.2 PMD) predominated in the first year, with arrhythmias (42.3 PMD), syncope (38.8 PMD), and thrombosis (37.3 PMD) most frequent across the full period.

For Vaxzevria, the leading SCADRs in the first year were thrombosis (79.8 PMD), arrhythmias (47.3 PMD), and blood pressure abnormalities (22.6 PMD), rising to thrombosis (101.1 PMD), arrhythmias (69.3 PMD), and syncope (31.6 PMD) for the entire time frame, representing the highest reporting rates among all vaccines studied.

For each analysed vaccine, the frequencies of reported SCADR categories differed significantly between the first year and the entire vaccination period ($p < 0.05$). Likewise, most specific SCADRs also showed significant differences in reporting frequencies across these periods for every vaccine (Supplementary Material S4).

Events of special interest – thrombosis and myo/pericarditis

Myo/pericarditis, included within the broader "inflammation" category, ranked 5th in frequency after the first year ($n = 5{,}062$) but increased to the 3rd most reported category over the full study period ($n = 13{,}421$; Tables 3 and 4). Notably, the reporting rates of myo/pericarditis were higher for mRNA vaccines, with Spikevax and Comirnaty showing 22.0 and 18.6 PMD, respectively, compared with adenovirus-based vaccines, which had 11.2 PMD for Jcovden and 9.2 PMD for Vaxzevria across the entire analysed period.

Thrombosis was the most frequently reported category of adverse drug reactions (ADRs) during the first year of COVID-19 vaccinations ($n = 12{,}755$) and remained the second most frequently reported category when considering the entire observation period ($n = 21{,}381$; Table 4). In contrast to myo/pericarditis, reporting rates were higher for adenovirus-based vaccines, with Vaxzevria and Jcovden showing 101.1 and 37.3 reports per million doses (PMD), respectively, compared with mRNA vaccines, which exhibited 23.4 PMD for Comirnaty and 20.7 PMD for Spikevax for the full vaccination period.

Time series curves

For Vaxzevria, one peak in the relative number of administered vaccine doses and a corresponding steep peak in the relative number of reported SCADRs were observed (Fig. 3d). For Comirnaty, Spikevax and Jconvden, two-peak vaccine administration curves were revealed (Figs. 3a, 3b, and 3c). Compared to Vaxzevria, they were followed by smoother peaks in the relative number of reported SCADRs. Of note, for all analysed vaccines, the curves depicting the reporting of SCADRs tended to be much smoother (more distributed in time) than the vaccine administration curves. For Comirnaty and Jcovden, the peak numbers of suspected SCADRs appeared to be shifted to the right in comparison with the curves representing vaccine dose administration. This suggests that for these vaccines, the peak reporting of potential post-vaccination ADRs may be delayed. Moreover, the curves of administered doses and suspected SCADRs did not fully overlap ($p < 0.05$ for all vaccines).

Detailed time series curves for each category of suspected SCADRs and every vaccine are presented in Supplementary Material S5.

Time series curves – thrombosis and myo/pericarditis

For Vaxzevria, the time series curves of vaccine administration and thrombosis-related event reporting were relatively aligned ($p = 0.065$), with the reporting peak appearing to coincide with the main peak of vaccine administration (Supplementary Material S5). In contrast, for the other vaccines analysed, the reporting curves were generally shifted to the right, indicating a temporal delay relative to vaccination ($p < 0.05$). Regarding inflammation-related events, all reporting curves appeared delayed compared with vaccination curves ($p < 0.001$). Notably, the reporting curve for Jcovden exhibited a pattern that did not clearly correspond to the vaccination curve, whereas for the remaining vaccines, the shapes of the reporting and vaccination curves were more closely aligned.

Hierarchical clustering

Hierarchical clustering analysis revealed four distinct clusters of time series data representing weekly fluctuations in reported SCADRs incidence associated with various vaccine formulations. Cluster 1 exhibited predominantly SCADRs related to Comirnaty, while Cluster 2 primarily comprised SCADRs observed following administration of Spikevax. Cluster 3 was characterised by a preponderance of SCADRs linked to Vaxzevria, whereas Cluster 4 was predominantly composed of SCADRs reported for Jcovden.

Notably, smaller clusters (formed by combining two or three vaccine categories) tended to aggregate around the specific vaccine administered, rather than the category of SCADRs itself. This observation suggests that the administered vaccine plays a more significant role in shaping

Table 3 Frequency of adverse drug reactions per million administered doses during the first year of vaccinations. The table presents the 30 most common SCADRs. All SCADRs are available in the supplementary material S4

Adverse drug reaction	*n*	Comirnaty	Jcovden	Spikevax	Vaxzevria	*p*-value
Pulmonary embolism	5694	7.6	12.7	6.5	31.2	< 0.001
Syncope	4252	5.2	22.7	8.3	18.1	< 0.001
Tachycardia	3918	5.8	5.6	5.5	16.6	< 0.001
Deep vein thrombosis	3668	4.5	7.3	4.1	23.7	< 0.001
Hypertension	3573	5.7	5.5	3.6	13.7	< 0.001
Palpitations	2950	4.3	4.6	4.6	11.9	< 0.001
Arrhythmia	2360	3.6	3.2	3.5	8.6	< 0.001
Pericarditis	2076	3.6	1.8	4.5	2.7	< 0.001
Myocarditis	2072	3.6	1.6	5.5	1.3	< 0.001
Thrombosis	1905	2.1	6.0	1.9	13.4	< 0.001
Atrial fibrillation	1448	2.3	1.3	2.0	5.4	< 0.001
Heart rate increased	1446	1.9	3.3	2.2	7.1	< 0.001
Hypotension	1434	2.2	4.8	2.0	5.1	< 0.001
Presyncope	1110	1.7	4.1	1.7	3.3	< 0.001
Myocardial infarction	1056	1.5	2.6	1.1	5.1	< 0.001
Venous thrombosis	965	1.2	1.7	0.9	6.2	< 0.001
Cardiac failure	885	1.5	1.2	1.1	2.3	< 0.001
Angina pectoris	806	1.3	1.9	1.2	2.2	< 0.001
Hypertensive crisis	720	1.2	1.0	0.9	2.3	< 0.001
Superficial vein thrombosis	707	0.8	0.9	0.7	5.3	< 0.001
Circulatory collapse	694	0.9	3.0	0.9	3.3	< 0.001
Acute myocardial infarction	687	1.0	1.6	0.7	3.2	< 0.001
Myopericarditis	684	1.1	0.7	2.2	0.4	< 0.001
Cardiac arrest	599	1.0	1.4	0.7	1.9	< 0.001
Venous thrombosis limb	571	0.8	0.7	0.6	3.5	< 0.001
Categories of adverse drug reactions						
Thrombosis-category	12,755	16.0	26.7	13.6	79.8	< 0.001
Arrhythmia-category	11,625	17.2	17.2	17.3	47.3	< 0.001
Blood pressure abnormality-category	6037	9.5	11.6	6.9	22.6	< 0.001
Syncope-category	5288	6.8	26.5	9.9	21.1	< 0.001
Inflammation-category	5062	8.7	4.4	12.2	5.4	< 0.001
Ischemia-category	3234	4.8	8.0	4.0	13.5	< 0.001
Life threatening-category	2028	3.0	6.4	2.6	8.0	< 0.001
Heart failure-category	1096	1.8	1.6	1.4	3.1	< 0.001
Conduction disorder-category	707	1.1	1.3	0.9	2.4	< 0.001
Cardiomyopathy-category	228	0.4	0.5	0.3	0.8	< 0.001

the temporal dynamics of ADR incidence, regardless of cluster size.

Discussion

In this observational study, we analyse 87,000 suspected SCADRs after administration of 733,837,251 COVID-19 vaccine doses. We observed that (1) the frequency of reporting of suspected SCADRs appears to change dynamically over time; (2) concerning the administration of vaccine doses, the reporting of potential post-vaccination SCADRs seems to be more distributed in time; (3) therefore, post-approval long-term monitoring of suspected SCADRs may be important for improving data capture and supporting vaccine safety assessment.

The majority of SCADRs were documented for the most widely administered vaccine (Comirnaty - Pfizer BioNTech) as well as for the most frequently represented age group in the European population (18–85 years old; Fig. 1; Table 2) [29]. This pattern was observed both during the first year following the introduction of each COVID-19 vaccine and throughout the entire period of vaccine administration. For the entire vaccination period, frequencies of different ADR categories were in line with EMA's data (Table 4 and Supplementary Material S4) [4, 6, 14]. However, when expressed as the number of reports per million doses, the frequencies of SCADR categories were significantly higher across the entire study period than in the initial year of vaccinations (Tables 3 and 4, $p < 0.05$). A similar pattern was observed for the total

Table 4 Frequency of SCADRs per million administered doses during the whole vaccination period. The table presents the 30 most common SCADRs. All SCADRs are available in the supplementary material S4

Adverse drug reaction	*n*	Comirnaty	Jcovden	Spikevax	Vaxzevria	*p*-value
Arrhythmia	9719	13.0	15.0	13.3	15.2	< 0.001
Pulmonary embolism	9541	10.8	16.1	10.2	39.4	< 0.001
Tachycardia	9170	11.6	14.4	11.6	22.4	< 0.001
Syncope	8666	9.2	34.3	13.1	27.6	< 0.001
Palpitations	8239	10.4	11.0	11.2	19.3	< 0.001
Myocarditis	6380	8.9	5.6	10.7	3.3	< 0.001
Hypertension	6377	8.3	9.2	6.1	17.8	< 0.001
Deep vein thrombosis	5778	6.1	10.0	5.7	28.8	< 0.001
Pericarditis	4804	6.7	3.4	7.4	4.2	< 0.001
Thrombosis	3945	4.0	10.5	3.7	20.5	< 0.001
Angina pectoris	3342	4.4	6.2	4.8	4.6	0.008
Heart rate increased	3282	3.9	5.3	4.0	10.6	< 0.001
Atrial fibrillation	2952	3.8	2.7	3.5	7.4	< 0.001
Hypotension	2155	2.6	6.9	2.2	6.5	< 0.001
Myocardial infarction	2040	2.5	4.2	2.2	6.5	< 0.001
Cardiac failure	1930	2.7	2.1	2.1	3.5	< 0.001
Presyncope	1854	2.4	4.7	2.1	4.6	< 0.001
Myopericarditis	1702	2.3	1.4	3.3	0.8	< 0.001
Venous thrombosis	1673	1.9	2.7	1.5	7.9	< 0.001
Circulatory collapse	1429	1.7	4.4	1.8	3.9	< 0.001
Acute myocardial infarction	1350	1.6	2.7	1.6	4.3	< 0.001
Pericardial effusion	1289	1.8	0.8	1.6	1.7	0.004
Hypertensive crisis	1196	1.6	1.3	1.3	2.9	< 0.001
Cardiac arrest	1026	1.3	2.1	1.1	2.5	< 0.001
Venous thrombosis limb	997	1.1	1.3	0.9	4.4	< 0.001
Categories of adverse drug reactions						
Arrhythmia-category	29,936	38.3	42.3	38.5	69.3	< 0.001
Thrombosis-category	21,381	23.4	37.3	20.7	101.1	< 0.001
Inflammation-category	13,421	18.6	11.2	22.0	9.2	< 0.001
Blood pressure abnormality-category	10,535	13.6	18.2	10.5	29.4	< 0.001
Syncope-category	10,363	11.3	38.8	15.0	31.6	< 0.001
Ischemia-category	8670	11.0	16.9	11.2	19.8	< 0.001
Life threatening-category	3932	4.9	9.0	4.8	10.2	< 0.001
Heart failure-category	2432	3.3	2.9	2.6	4.8	< 0.001
Conduction disorder-category	1509	2.0	2.5	1.7	3.6	< 0.001
Cardiomyopathy-category	644	0.8	1.3	0.8	1.2	0.012

frequencies of specific SCADRs (Fig. 2, $p < 0.05$). These findings underscore the importance of long-term vaccine safety monitoring, as analyses conducted shortly after the initial peak of vaccine administration may have underestimated the true frequency of suspected SCADRs.

The most frequently reported categories of suspected SCADRs were arrhythmia, thrombosis, inflammation (myocarditis and pericarditis), blood pressure abnormalities, and syncope, both during the first year and across the entire vaccination period (Tables 3 and 4). These findings seem to be consistent with previous studies, which have identified thrombosis, pulmonary embolism, myocarditis, pericarditis, and arrhythmias as the most commonly reported cardiac adverse events following vaccination [17, 30–33]. Further on, based on the literature data, the onset of the SCADRs was up to 7 days [17, 30–33]. Following the EMA's "Clinical Safety Data Management: Definitions and Standards for Expedited Reporting" statement, life-threatening or fatal ADRs should be reported as soon as possible and no later than 7 calendar days after first knowledge, whereas all other serious, unexpected ADRs should be documented no later than 15 calendar days after first knowledge [34]. Therefore, in the case of COVID-19 vaccines, the distribution curve of reported suspected ADRs should have a delay (shift to the right on the figure) of about 3–4 weeks. Our data suggest that, in relation to the timing of vaccine administration, the reporting of potential postvaccination ADRs appears somewhat delayed for Comirnaty and Jcovden, while for Spikevax and Vaxzevria the delay

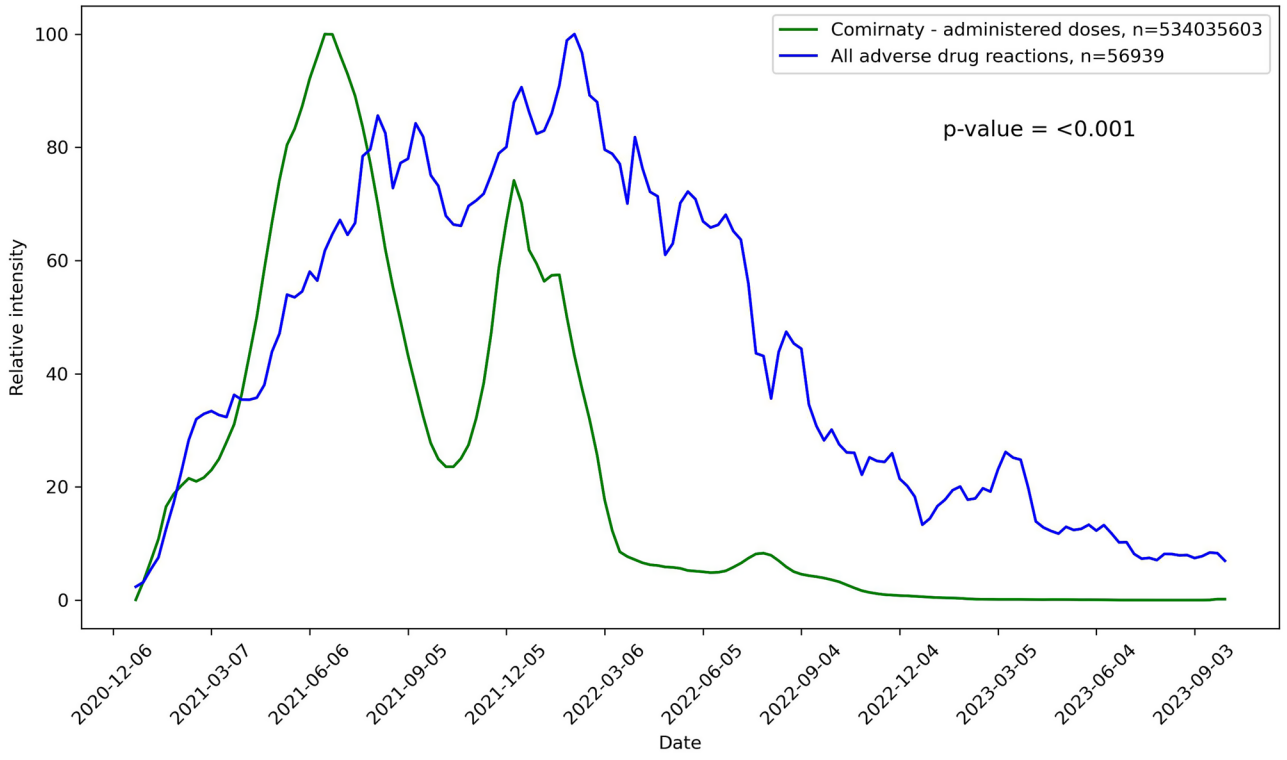

Fig. 3a Timelines representing the number of administered vaccine doses and reported suspected adverse drug reactions – Comirnaty

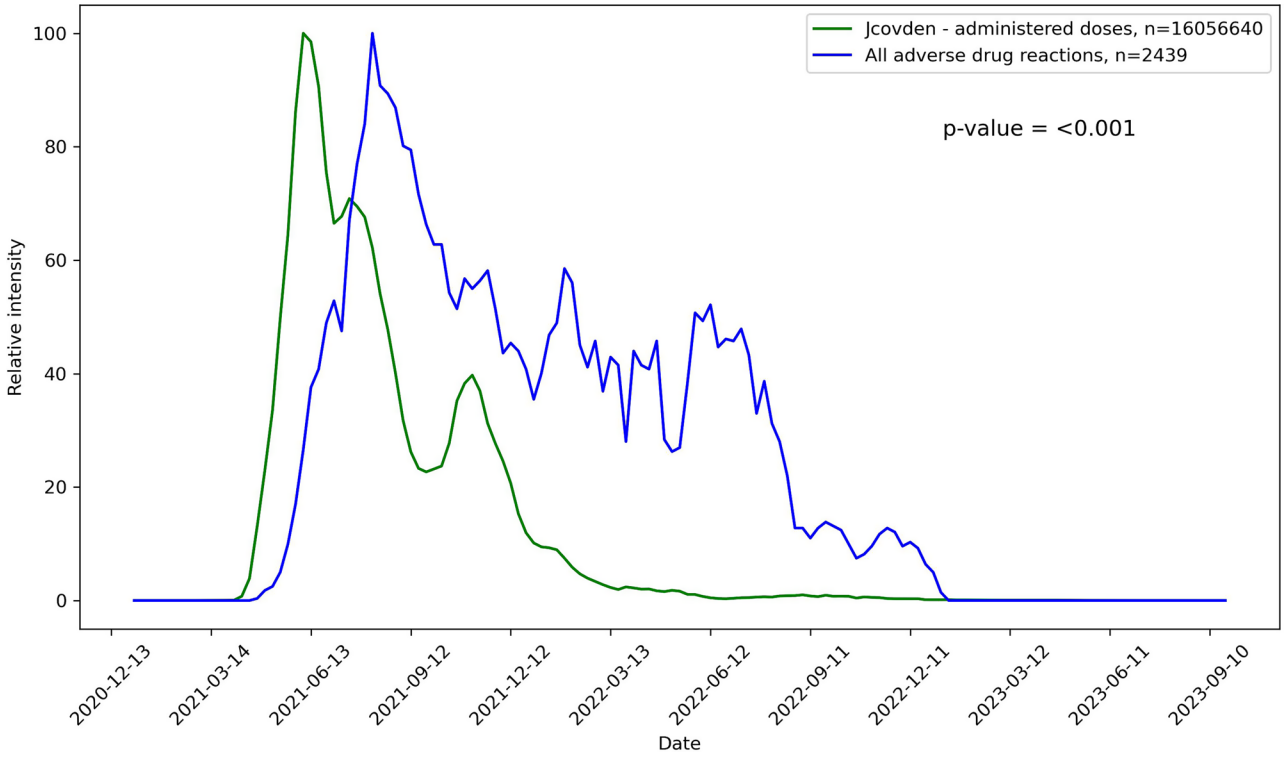

Fig. 3b Timelines representing the number of administered vaccine doses and reported suspected adverse drug reactions – Jcovden

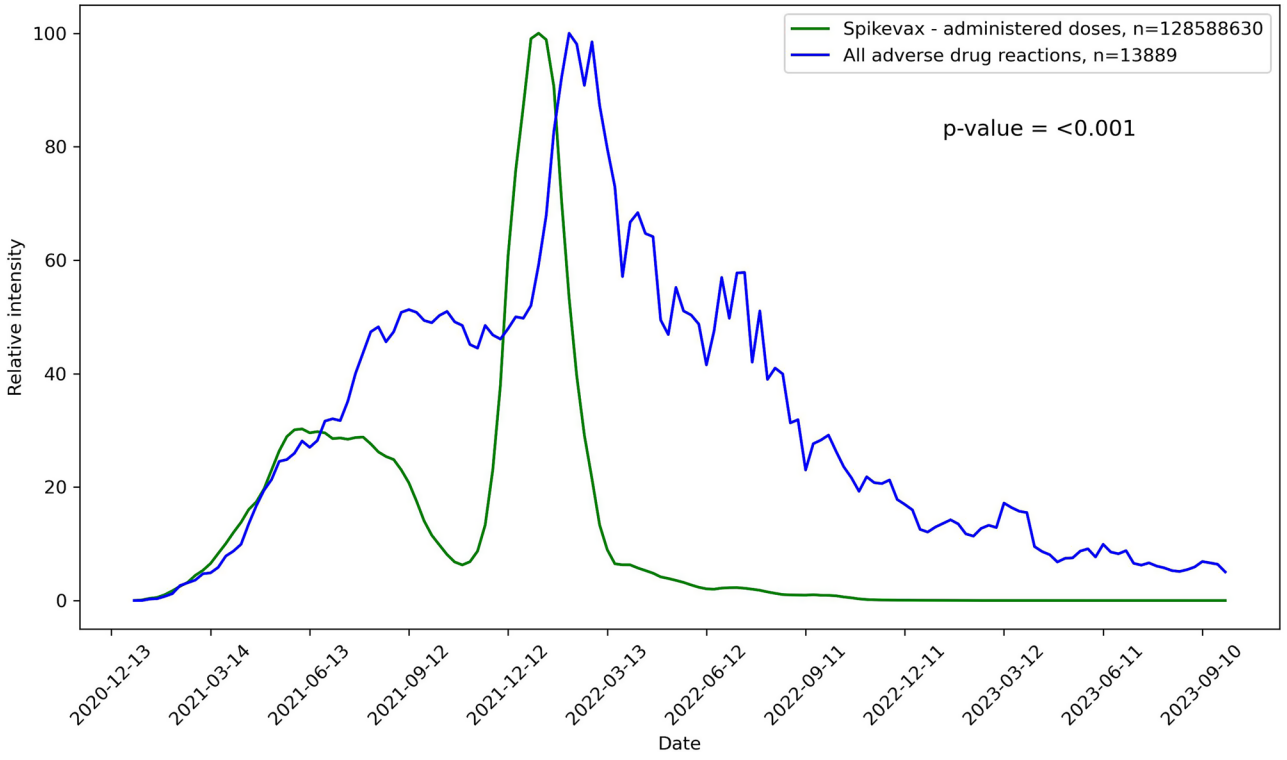

Fig. 3c Timelines representing the number of administered vaccine doses and reported suspected adverse drug reactions – Spikevax

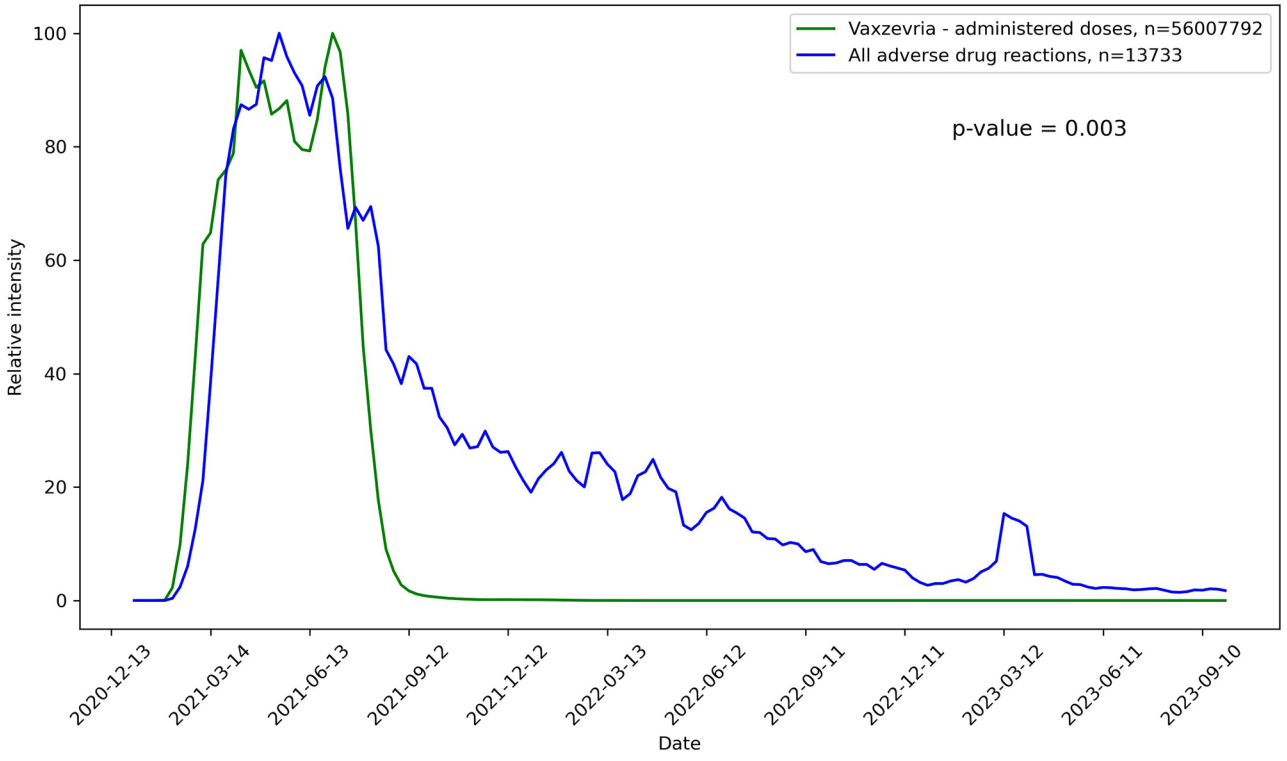

Fig. 3d Timelines representing the number of administered vaccine doses and reported suspected adverse drug reactions – Vaxzevria

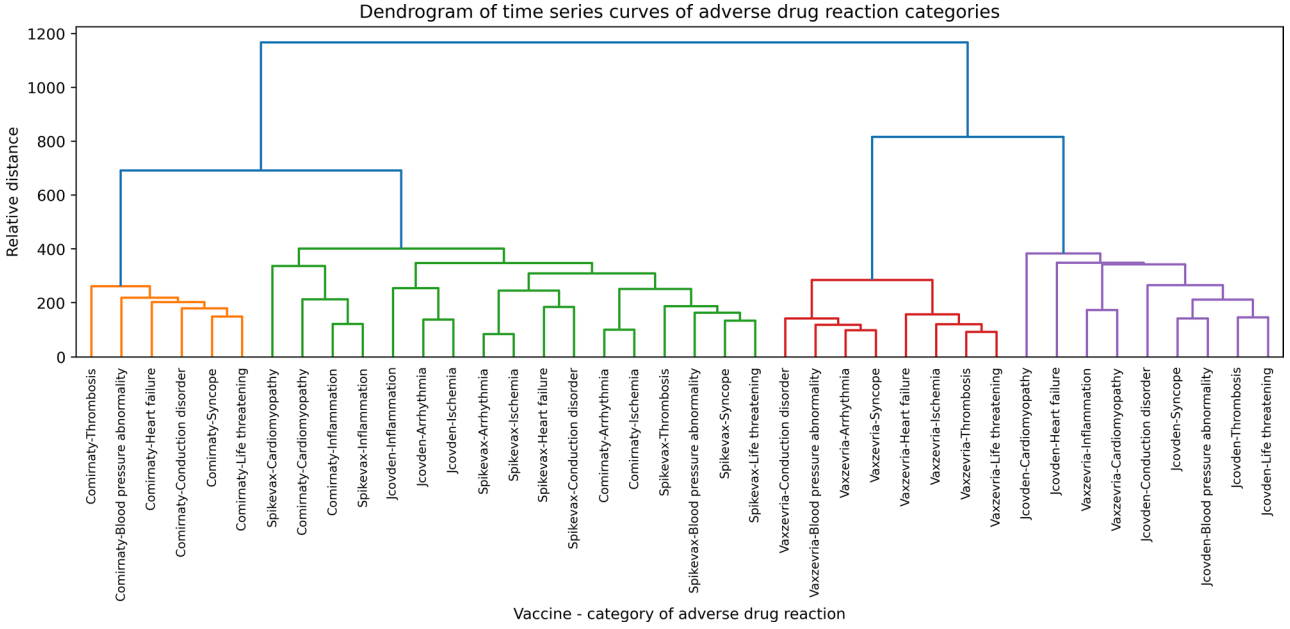

Fig. 4 Dendrogram representing hierarchical clustering of time series curves

seems less pronounced. Additionally, for all vaccines studied, the reporting of SCADRs is more dispersed over time compared with the vaccine administration curves ($p < 0.05$, Figs. 3a, 3b, 3c, and 3d). Thus, in future vaccine safety monitoring programs, the SCADRs should be reported with a shorter delay after the occurrence of the medical event to meet the EMA guidelines' criteria [34]. Conversely, the EudraVigilance database provides valuable information from spontaneously reported ADRs collected during post-approval vaccine monitoring [11, 12]. Our study illustrates that many potential postvaccination ADRs would remain unnoticed without such data, underscoring the importance of open-access pharmacovigilance resources.

The observed nonoverlapping of the curves depicting the administration of the COVID-19 vaccine and the corresponding reporting of suspected ADRs may also result from the under-reporting of the ADRs [24, 35]. According to literature data, over 90% of all ADRs and about 80% of serious ADRs remain under-reported [24, 35]. Studies have shown that an educational intervention, both passive and active, increases the ADR reporting rate and sometimes improves pharmacovigilance knowledge. Moreover, it may also result in a more positive attitude towards ADR reporting [36, 37]. Given the fact that the COVID-19 vaccination program was Europe's largest vaccination program, as well as the high value of post-approval vaccine monitoring, such projects are recommended and should be routinely introduced in every healthcare facility [6, 36, 37].

Additionally, the relatively higher number of reports of suspected severe cardiac adverse events observed later in the COVID-19 pandemic may reflect multiple, yet uninvestigated factors. For instance, the characteristics of the vaccinated population changed over time, as different target groups became eligible for vaccination [38, 39]. These shifts could have influenced both the actual occurrence of adverse events and the likelihood of reporting, potentially contributing to the temporal patterns observed in the data.

Behers et al. outline that even though the median time to symptoms presentation after vaccine administration was usually about 3 days, the ADR could also occur up to 90 days after vaccination [33]. Thus, the potentially observed delay in SCADR reporting in our study could also be attributed to the occurrence of a postvaccination complication with a prolonged latency period. However, Behers et al. observed such a prolonged onset of symptoms in single cases [10].

Further on, the frequency and latency of the reporting might have been potentially biased by the ongoing topics discussed in the media news and on social media platforms. For example, on 7th June 2021, EMA officially raised awareness of "clinical care recommendations to manage thrombosis with thrombocytopenia syndrome that might be potentially associated with vaccination with Vaxzevria or Jcovden" [40]. This was followed by a rise in the quantity of news and the dissemination of this information on X (formerly known as Twitter) and in the news [41, 42]. To address this issue, we performed hierarchical clustering and created a dendrogram that grouped the ADR category time series based on their relative distance, i.e. similarity (Fig. 4). Our analysis indicates that, across both major and minor clusters, the administered

vaccine appears to be the primary factor influencing the grouping of time series curves for suspected cardiac ADR categories, rather than the specific ADR category itself. In most cases, the temporal patterns of ADR reporting differed between vaccines, while curves for individual ADR categories were relatively consistent within each vaccine. This observation suggests that spontaneous reporting may have been influenced more by the type of vaccine administered than by ongoing media discussions about specific COVID-19 vaccine side effects. However, this interpretation should be considered with caution, as the observational nature of the data does not allow definitive conclusions regarding the impact of external factors, nor does it support causal inference as would be possible in a randomised controlled trial. Thus, spontaneous reporting of suspected cardiac ADRs to COVID-19 vaccines may provide useful signals, although their reliability could be influenced by multiple factors.

In summary, the exact reasons underlying the observed reporting patterns are difficult to determine. The shapes of the reporting curves and potential underreporting or latency cannot be precisely quantified. However, several factors may contribute, including: (1) reporting delays and deviations from the deadlines outlined in EMA guidelines, (2) changes in media coverage of adverse drug reactions, (3) underreporting, (4) vaccination of different target groups as the pandemic progressed and (5) the prolonged or late-onset occurrence of certain drug reactions.

Events of special interest – thrombosis and myo/pericarditis

The EMA classifies myocarditis/pericarditis and thrombotic events as "events of special interest" in the context of potential complications following COVID-19 vaccination [40, 43]. According to data published by the Heart Failure Association of the European Society of Cardiology, the incidence of post-COVID-19 infection myocarditis is estimated at approximately 400–1400 cases PMD, whereas after vaccination, the reported rates are nearly ten-fold lower, ranging between 20 and 150 PMD [44]. In our analysis, the observed reporting rates were substantially lower, from 4.4 to 12.2 reports per million doses, which suggests that some events may have been underreported [24].

Regarding thrombotic events, the literature indicates that they occur very rarely after COVID-19 vaccination, with the highest risk associated with the Vaxzevria vaccine [45, 46]. This pattern is consistent with the reporting rates observed in our study (from 20.7 PMD to 101.1 PMD).

Further on, the temporal distribution (i.e., right-shifted delay) and the overall shape of the reporting curves for these events of special interest closely resembled those of the general reporting curves encompassing all adverse drug reactions assessed (Figs. 3a, 3b, 3c, and 3d; Supplementary Material S5). Exceptions were observed for Vaxzevria and Jcovden. For Vaxzevria, thrombosis-related reporting closely followed vaccine administration ($p = 0.065$), whereas for Jcovden, the reporting pattern did not correspond to the vaccine administration curve.

Limitations

Our study is based on the merging of data from two large sources: EudraVigilance and ECDC Vaccine Tracker. To overcome this bias, we adjusted the data from EudraVigilance, where the suspected ADRs were reported, to match the time (up to 4th October 2023), region (EEA) and frequency (weekly changes) for which the numbers of administered vaccines in the Vaccine Tracker database were documented. Moreover, due to the structure of the EudraVigilance database, the study could not differentiate between adverse events following first, second, or booster doses of the vaccine, which may limit the ability to assess dose-specific reporting rates.

It is important to note that EudraVigilance does not provide detailed patient-level information such as exact age, comorbidities, or concurrent medications, which limits the granularity of our analysis and the ability to adjust for potential confounders. In addition to that, the EudraVigilance database does not provide open-source access to the "time to SCADR symptoms presentation after vaccine administration". Such information could deepen our understanding of the discussed delays in SCADR reporting and provide additional metrics for further evaluation of compliance with the EMA's guidelines on timely SCADR reporting [34].

Additionally, while media coverage may influence the reporting of adverse events, the impact of such external factors cannot be directly assessed and quantified within our study. Although we discuss the potential role of media attention as a confounding variable, our longitudinal observational design does not allow for causal inference in the same way a randomised controlled trial would, and therefore any observed associations between reporting patterns and external influences should be interpreted cautiously [24–26].

Further on, over 90% of all ADRs and 80% of serious ADRs remain under-reported [24, 35]. To ensure high data quality, we decided to analyse serious cardiac ADRs only, because they are more consistently reported. Moreover, severe ADRs are connected with a higher risk of hospitalisation, persistent disability and death and are therefore of higher clinical significance [6, 11, 12].

Moreover, an important limitation of this analysis is that the reporting rates presented here do not reflect incidence [12, 23]. Passive surveillance systems are designed for signal detection rather than for estimating risk, and

the data are influenced by factors such as underreporting, heightened awareness, and reporting biases [24–26]. Therefore, the reported data should be interpreted as crude reporting frequencies rather than true measures of risk.

Conclusions

The frequency of reporting suspected SCADRs after COVID-19 vaccinations appears to change dynamically over time. Concerning the administration of vaccine doses, the reporting of potential post-vaccination ADRs seems to be more widely distributed in time. These observations suggest that post-approval long-term monitoring of suspected ADRs may be valuable for improving data capture and supporting vaccine safety assessment. This underlines the potential importance of comprehensive surveillance in the context of infectious diseases and vaccine development programs.

Abbreviations

ADR	Adverse drug reaction
COVID-19	Coronavirus disease 2019
ECDC	European Centre for Disease Prevention and Control
EEA	European Economic Area
EMA	European Medicines Agency
SCADR	Serious cardiac adverse drug reaction
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology Statement

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12879-025-12023-w.

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

Supplementary Material 5

Acknowledgements

Not applicable.

Author contributions

The conceptualisation was done by WN. The methodology was contributed by WN, JR, and LDS. WN conducted the investigation and performed the statistical analysis. WN and GN wrote the original draft. WN prepared the tables. GN prepared the figures. JR, MN, and LDS participated in reviewing and editing the manuscript. MN and LDS provided supervision. All authors have read and agreed to the published version of the manuscript.

Funding

This research received no external funding.

Data availability

The datasets supporting the conclusions of this article are included within the article, in its online supplementary material, as well as in the EudraVigilance and ECDC Vaccine Tracker databases.

Declarations

Ethics approval and consent to participate

This study is a retrospective analysis of a fully anonymised open-access database. Therefore, for this study, the need for ethical approval and informed consent to participate from the participant was waived according to the regulations of the Bioethical Committee of the Medical University of Gdańsk and the guidelines of the Ministry of Health of Poland. This study was carried out according to the Declaration of Helsinki.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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Received: 25 July 2024 / Accepted: 23 October 2025
Published online: 14 November 2025

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