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Serious adverse drug reactions associated with anti-SARS-CoV-2 vaccines and their reporting trends in the EudraVigilance database

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A serious adverse reaction (SADR) may follow a vaccination against SARS-CoV-2 infection. We aimed to explore symptoms and reporting trends of SADRs to anti-SARS-CoV-2 vaccines based on the EudraVigilance database. This retrospective observational study analysed 250,966 suspected SADRs (with 62.8% reported in females), following the administration of 733,837,251 vaccine doses against SARS-CoV-2. Pfizer BioNTech (Comirnaty-Tozinameran), Moderna (Spikevax-Elastomeran), Janssen (Jcovden) and AstraZeneca (Vaxzevria) vaccines were analysed. The assessment included 897 types of SADRs across 12 categories. The most common clinical manifestations of SADRs to anti-SARS-CoV-2 vaccines vaccines encompassed neuropsychiatric (n = 121,877), cardiovascular (n = 78,167), as well as musculoskeletal and connective tissue disorders (n = 63,994). After summarising all SADRs, vaccination with Comirnaty was associated with the lowest risk of experiencing SADRs (754/million administered doses), followed by Spikevax (785/million doses), Jcovden (1,248/million doses) and Vaxzevria (2,301/million doses; p < 0.001). Regarding the vaccine administration timelines, the reporting of SADRs tends to be delayed and occurs over a longer time (p < 0.001). SADRs associated with anti-SARS-CoV-2 vaccines seem to be relatively rare. Compared to adenovirus-based vector vaccines (Jcovden, Vaxzevria), mRNA vaccines appear to offer improved safety profiles (Comirnaty, Spikevax). The risk of SADR to any SARS-CoV-2 vaccine seems to be outweighed by the benefits of active immunization against the virus.

Keywords SARS-CoV-2 infection, COVID-19, Pharmacovigilance, Vaccination, Serious adverse drug reaction

Protection against SARS-CoV-2 infections in vaccinated populations is highly efficacious and has resulted in a reduction in the number of reported highly symptomatic SARS-CoV-2 infections as well as hospitalisations, intensive care unit admissions and deaths[1–4]. Moreover, clinical studies have proved that the vaccines also have a very favourable safety profile[1–5]. European Medicines Agency (EMA) states that the benefits in terms of protection against severe disease caused by a SARS-CoV-2 infection outweigh the risk of potential side effects[6,7].

Nevertheless, in certain patients, there is a possibility of experiencing adverse drug reactions (ADRs) following vaccination due to injected substances[1,3,5–8]. According to the definition of EMA, an ADR is a noxious and unintended response to a vaccine[9]. ADRs may be classified as mild, moderate or serious. A serious adverse drug reaction (SADR) is described as "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[9–11]. Even though such events are more rarely observed than the mild or moderate ADRs, given the substantial number of

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administered vaccines as well as the vaccination intensity against SARS-CoV-2, the potentially SADRs can also, result in a heavy burden on the healthcare system, especially on the emergency departments.

To date, a variety of suspected SADRs to the anti-SARS-CoV-2 vaccines have been described[3,7,12]. For vaccines authorised in the European Economic Area (EEA), data on such events are spontaneously reported in the EudraVigilance database that is led by EMA[10,11]. To date, there have been studies that aimed to analyse records on anti-SARS-CoV-2 vaccine safety from this database[13–19]. Most of them usually focus on a selected human body system or a single clinical presentation like anaphylaxis or thrombosis[13–19]. Thus, there is a need for large-scale studies that would provide a head-to-head comparison of the most commonly observed potential SADRs to various anti-SARS-CoV-2 vaccines and that would describe multiple postvaccination SADRs from many human body systems. To address this knowledge gap, we analyzed the most frequent clinical manifestations of suspected SADRs to vaccines against SARS-CoV-2, which will aid in faster and more accurate diagnosis, treatment and monitoring of the SADRs after anti-SARS-CoV-2 vaccine administration. This may prevent possible life-threatening complications, which is of great clinical value. Additionally, as the potential SADRs are documented on a spontaneous basis, it is necessary to evaluate the trends in gathering clinical data with the help of a spontaneous reporting system, based on the example of SADRs to anti-SARS-CoV-2 vaccines.

Therefore, we aimed to explore symptoms and reporting trends of suspected adverse drug reactions associated with anti-SARS-CoV-2 vaccines.

Results

In total, 250,966 suspected SADRs linked to four anti-SARS-CoV-2 vaccines were analyzed (Fig. 1). The assessment encompassed 897 types of suspected SADRs grouped into 12 clinical categories. After summarising all adverse drug reactions, vaccination with Comirnaty was associated with the lowest risk of experiencing SADRs (754/million administered doses), followed by Spikevax (785/million doses), Jcovden (1,248/million doses) and Vaxzevria (2,301/million doses; $p < 0.001$, Fig. 2). The data regarding all analysed SADRs (n = 897) and their categories (n = 12) can be accessed in Supplementary Material 2 or via an online web application that can be downloaded as Supplementary Material 3.

General characteristics

About 60% of all documented potential SADRs after administering an anti-SARS-CoV-2 vaccine were submitted by non-healthcare professionals (Supplementary Material 4). Over 70% of all SADRs were reported for patients aged 18–65 years old. SADRs documented for children were rare. The frequencies were equal to 3.3% for Comirnaty, 1.1% for Spikevax, 0.3% for Jcovden and 0.1% for Vaxzevria ($p < 0.001$). For Comirnaty, Spikevax and Vaxzevria, females constituted over 60% of the cohort ($p < 0.001$). For Vaxzevria and Jcovden, most of the suspected SADRs seem to occur within the first year of the vaccine administration (74.1% and 59.5%, respectively). This was different for Comirnaty and Spikevax (47.7% and 37.6%, respectively; $p < 0.001$).

Clinical manifestations of suspected SADRs associated with anti-SARS-CoV-2 vaccines

The most common clinical manifestations of potential SADRs associated with vaccinations against SARS-CoV-2 encompassed neuropsychiatric (n = 121,877), cardiovascular (n = 78,167) as well as musculoskeletal and connective tissue disorders (n = 63,994; Tables 1, 2). The most rarely observed clinical categories of suspected SADRs linked to any analysed vaccine included endocrine (n = 1,949), renal and urinary (n = 4,495), as well as immune system disorders (n = 7,582).

Comirnaty and Spikevax seems to have a very similar safety profile, as the SADRs from the corresponding clinical categories occurred with similar frequencies. In the "obstetrical and gynaecological disorders" category, administration of Comirnaty or Spikevax was potentially associated with the highest likelihood of experiencing an SADR (22.3 per million doses [PMD] and 22.2 PMD, respectively). In all other categories, a vaccination with Vaxzevria was linked to the greatest risk of an SADR.

The most prevalent suspected SADRs associated with anti-SARS-CoV-2 vaccination were headache (n = 45,505), myalgia (n = 27,110), nausea (n = 21,253), dyspnoea (n = 21,168), dizziness (n = 20,702), arthralgia (n = 19,710), pain in extremities (n = 14,014), paraesthesia (n = 13,420), arrhythmia (n = 9,719), pulmonary embolism (n = 9,541), vomiting (n = 9,288), tachycardia (n = 9,170), syncope (n = 8,666), palpitations (n = 8,239) and hypoaesthesia (n = 7,780).

Overall, there were statistically significant differences between the vaccines in terms of the frequencies of the majority of the specific SADRs (Tables 1, 2, Supplementary Materials 2 and 3). The frequencies of the clinical categories of SADRs were also significantly different among the studied vaccines.

Myocarditis, pericarditis, anaphylaxis, Guillain-Barré syndrome and thrombosis with thrombocytopenia syndrome—SADRs of special interest

Myocarditis, pericarditis, anaphylaxis, Guillain-Barré syndrome and thrombosis with thrombocytopenia syndrome (TTS) are reported by EMA to be the SADRs of "special interest"[20,21].

According to the data collected in our study, there were 6,380, 4,804 and 1,702 cases of myocarditis, pericarditis and myopericarditis, which are ranked as the 19th, 24th and 76th most common potential SADRs (Table 3). The total frequency of all three potentially associated with anti-SARS-CoV-2 vaccination pathologies seems to be the highest for Spikevax (20.8 PMD), followed by Comirnaty (16.7 PMD), Jcovden (10.5 PMD) and Vaxzevria (8.2 PMD; $p < 0.001$). Further on, the total number of anaphylactic reaction/anaphylactic shock cases linked to vaccination against SARS-CoV-2 was 2,923 and was most often noted for Jcovden (total frequency of 7.0 PMD), followed by Vaxzevria (6.5 PMD), Comirnaty (3.7 PMD) and Spikevax (2.5 PMD; $p < 0.001$). The Guillain-Barré syndrome was reported for 1,727 patients, and was most commonly linked to vaccination with Jcovden (10.8 PMD), next Vaxzevria (9.1 PMD), Comirnaty (1.5 PMD) and Spikevax (1.4 PMD). The TTS

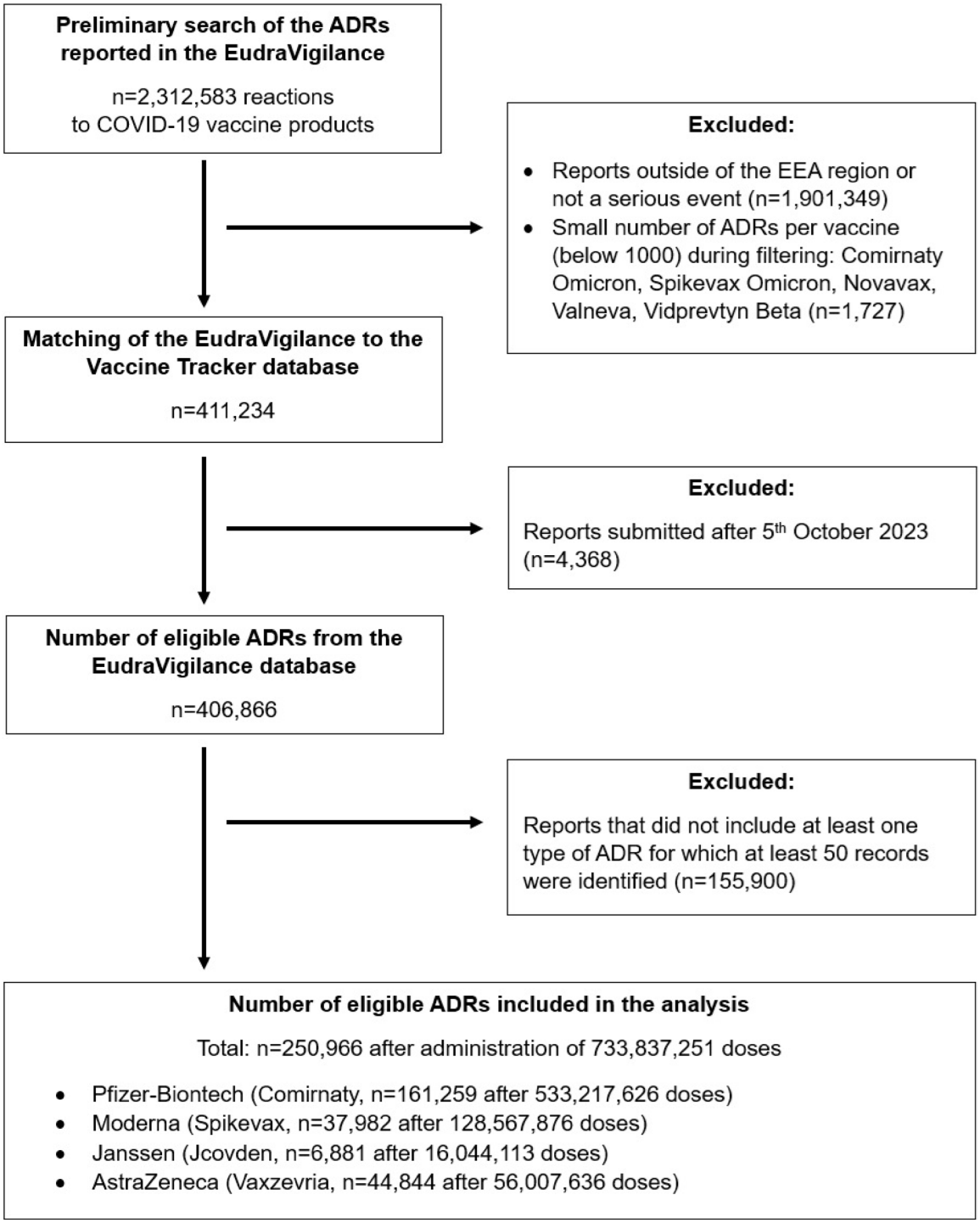

Fig. 1. Study design.

was documented in 198 cases, and was most frequently associated with the immunisation using Vaxzevria (2.8 PMD) and Jcovden (1.5 PMD), as well as being very low for Comirnaty (< 0.1 PMD) and Spikevax (< 0.1 PMD; $p < 0.001$). However, when all thrombosis-related events are taken into consideration (n = 22,507 in total), then the overall rates are the highest for Vaxzevria (128.6 PMD), then Jcovden (49.3 PMD), Comirnaty (21.1 PMD) and Spikevax (19.1 PMD; $p < 0.001$).

Exploration of longitudinal changes

Considering all suspected SADRs documented for Comirnaty, the time series curve representing the relative intensity of the SADRs reporting was shifted to the right, to the curve depicting the administration of vaccine doses ($p < 0.001$; main data: Fig. 3a-d, all data: Supplementary Material 5). The same trend was observed for

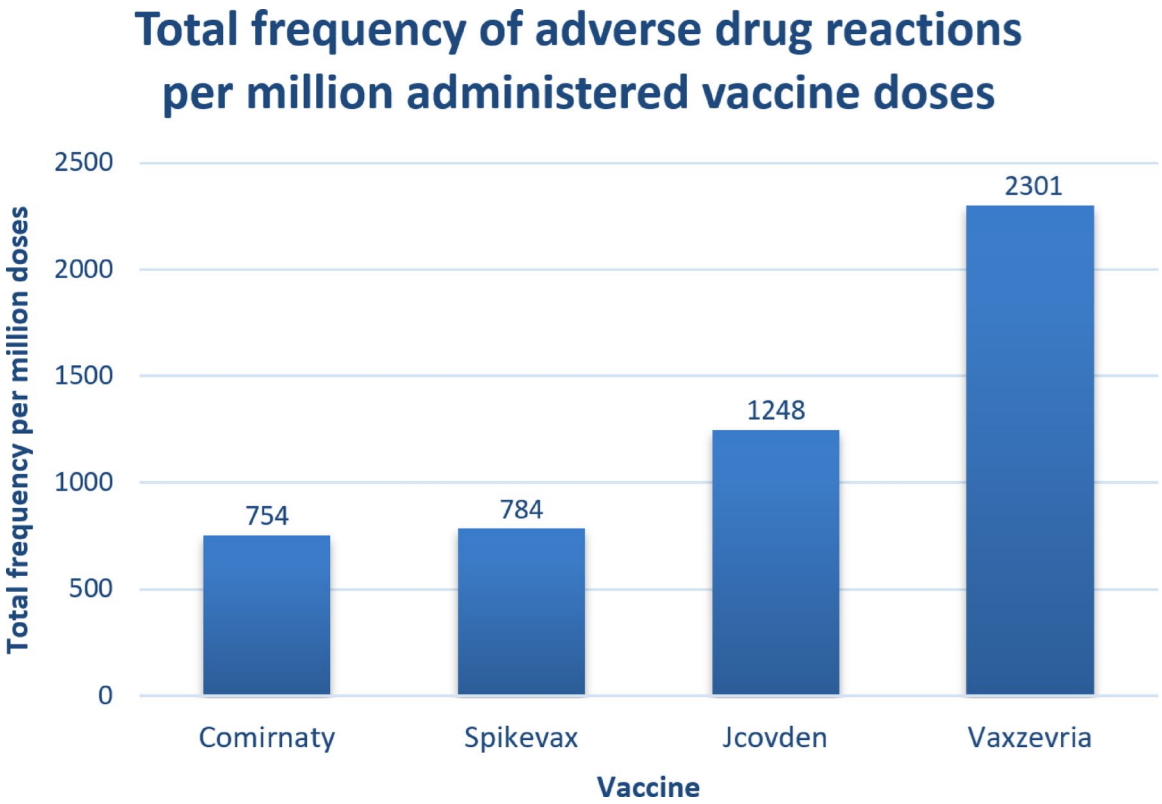

Fig. 2. Total frequency of adverse drug reactions per million administered vaccine doses.

Spikevax and Jcovden ($p < 0.001$). For Vaxzevria, the intensity of SADR reporting and vaccine dose administration was high at the beginning of the pandemic. The administration of the vaccine doses tends to decrease steeply after the summer of 2021 and was followed by a less steep decline in the reporting of the potential SADRs ($p < 0.001$). For all analysed vaccines, the timelines representing the intensity in SADR reporting showed a much smoother pattern over time compared to the curves depicting vaccine administration. Additionally, there appeared to be no clear overlap between the SADR reporting curves and the vaccine administration curves, suggesting a possible disconnect or temporal separation between the two trends.

Hierarchical clustering

In hierarchical clustering, four large clusters of time series showing the weekly fluctuations in the number of the reported suspected SADRs were revealed: (1) orange cluster, mostly represented by SADRs to Vaxzevria; (2) green cluster, formed by SADRs linked to vaccination with Comirnaty; (3) red cluster, depicting potential SADRs to Spikevax; (4) purple cluster, showing SADRs that were principally reported after Jcovden administration (Fig. 4). Further on, when the smallest clusters that aggregate just two adjacent time series curves were analysed, it appeared that the vaccine, rather than the clinical category of the reported SADRs, could have been a clustering factor. Therefore, the type of vaccine administered, rather than the clinical category of the potential SADRs, tends to be the primary variable influencing the time series pattern of suspected SADR categories, observed across both the largest and smallest clusters.

Discussion

In this retrospective, observational study, 250,966 records of suspected SADRs following the administration of 733,837,251 vaccine doses against SARS-CoV-2 were explored. The main findings of our study are: (1) SADRs potentially associated with anti-SARS-CoV-2 vaccines seems to be rare and tend to manifest most commonly as neuropsychiatric, cardiovascular as well as musculoskeletal and connective tissue disorders; (2) regarding the administration of vaccine doses, the reporting of suspected SADRs following vaccination appears to be delayed and occurs over a longer time; (3) a monitoring platform based on a spontaneous ADR reporting system is an essential and effective data collection tool for long-term vaccine safety surveillance.

EMA recommends grouping the reported ADR frequency as follows: ≥ 1/10 administered doses as very common, ≥ 1/100 to < 1/10 as common, ≥ 1/1,000 to < 1/100 as uncommon, ≥ 1/10,000 to < 1/1,000 (≥ 100/1,000,000 to < 1000/1,000,000) as rare, and < 1/10,000 (< 100/1,000,000) as very rare. According to the results of our analysis, the summarized frequency of all SADRs potentially linked to anti-SARS-CoV-2 vaccination appears to be the lowest for Comirnaty (754 PMD) and Spikevax (785 PMD), followed by Jcovden (1,248 PMD) and Vaxzevria (2,301 PMD; $p < 0.001$; Fig. 2). Therefore, according to EMA's classification, the frequency of suspected SADRs for Vaxzevria and Jcovden vaccines tends to be uncommon as well as rare for Comirnaty and

Adverse drug reaction	Sum	Comirnaty	Spikevax	Jcovden	Vaxzevria	p-value
Headache	45,505	41.6	51.6	102.6	239.8	< 0.001
Myalgia	27,110	24.9	34.9	60.8	132.1	< 0.001
Nausea	21,253	19.5	27.4	44.0	104.6	< 0.001
Dyspnoea	21,168	24.9	25.1	36.4	55.7	< 0.001
Dizziness	20,702	22.5	24.2	44.3	72.1	< 0.001
Arthralgia	19,710	19.6	24.5	36.4	85.4	< 0.001
Pain in extremity	14,014	14.4	16.4	26.2	58.1	< 0.001
Paraesthesia	13,420	16.0	13.6	28.0	37.3	< 0.001
Arrhythmia	9719	12.2	12.9	15.0	15.2	< 0.001
Pulmonary embolism	9541	10.2	9.9	16.1	39.4	< 0.001
Vomiting	9288	8.9	11.3	17.0	43.9	< 0.001
Tachycardia	9170	10.9	11.2	14.4	22.4	< 0.001
Syncope	8666	8.6	12.6	34.3	27.6	< 0.001
Palpitations	8239	9.8	10.8	11.0	19.3	< 0.001
Hypoaesthesia	7780	9.2	7.8	16.9	22.7	< 0.001
Lymphadenopathy	7607	9.4	10.8	7.8	12.4	< 0.001
Rash	7495	8.5	9.6	12.8	21.7	< 0.001
Diarrhoea	6873	7.5	6.9	11.8	27.1	< 0.001
Myocarditis	6380	8.3	10.4	5.6	3.3	< 0.001
Hypertension	6377	7.8	5.9	9.2	17.8	< 0.001
Abdominal pain	6321	6.6	7.1	11.0	26.3	< 0.001
Deep vein thrombosis	5778	5.8	5.5	10.0	28.8	< 0.001
Tinnitus	5030	5.9	6.1	11.5	12.5	< 0.001
Pericarditis	4804	6.3	7.2	3.4	4.2	< 0.001
Loss of consciousness	4784	4.9	6.2	15.9	16.3	< 0.001
Cough	4733	5.7	4.7	9.3	12.6	< 0.001
Vertigo	4509	5.0	5.1	6.7	15.5	< 0.001
Pruritus	4237	4.8	5.8	4.3	11.7	< 0.001
Hyperhidrosis	4233	3.9	4.8	15.6	20.0	< 0.001
Limb discomfort	4230	4.2	5.6	10.3	17.1	< 0.001

Table 1. The rate of the thirty most frequently reported suspected ADRs per million vaccine doses administered. The data regarding all analysed ADRs (n = 897) and their categories (n = 12) can be accessed in the Supplementary Material 2 or via an online web application that can be downloaded as Supplementary Material 3.

Category of adverse drug reactions	Sum	Comirnaty	Spikevax	Jcovden	Vaxzevria	p-value
Neuropsychiatric disorders	121,877	130.6	135.7	260.5	457.0	< 0.001
Cardiovascular disorders	78,167	91.6	91.9	122.3	215.4	< 0.001
Musculoskeletal and connective tissue disorders	63,994	65.4	76.3	127.4	262.6	< 0.001
Gastroenterological disorders	48,076	49.6	55.9	87.4	198.3	< 0.001
Respiratory, thoracic and mediastinal disorders	43,047	49.7	46.6	71.4	133.9	< 0.001
Skin and subcutaneous tissue disorders	29,109	31.6	36.9	54.2	96.3	< 0.001
Ear and eye disorders	26,656	29.8	29.8	47.3	89.5	< 0.001
Obstetrical and gynecological disorders	17,094	22.3	22.2	18.8	21.4	0.016
Hematooncological disorders	15,476	17.3	17.5	24.5	52.2	< 0.001
Immune system disorders	7582	9.4	7.8	12.8	17.8	< 0.001
Renal and urinary disorders	4495	5.1	5.6	9.2	12.9	< 0.001
Endocrine disorders	1949	2.5	2.4	2.3	3.3	0.001

Table 2. The rate of the most frequently reported categories of suspected ADRs per million vaccine doses administered. The data regarding all analysed ADRs (n = 897) and their categories (n = 12) can be accessed in the Supplementary Material 2 or via an online web application that can be downloaded as Supplementary Material 3.

Adverse drug reaction	Sum	Comirnaty	Spikevax	Jcovden	Vaxzevria	p-value
Myocarditis	6380	8.3	10.4	5.6	3.3	< 0.001
Pericarditis	4804	6.3	7.2	3.4	4.2	< 0.001
Myopericarditis	1702	2.1	3.2	1.4	0.8	< 0.001
Total for myo/pericarditis	***12,886***	***16.7***	***20.8***	***10.5***	***8.2***	***< 0.001***
Anaphylactic reaction	2086	2.7	1.8	3.9	4.7	< 0.001
Anaphylactic shock	837	1.0	0.7	3.1	1.8	< 0.001
Total for anaphylaxis	***2923***	***3.7***	***2.5***	***7.0***	***6.5***	***< 0.001***
Guillain–Barre syndrome	***1727***	***1.5***	***1.4***	***10.8***	***9.1***	***< 0.001***
Deep vein thrombosis	5778	5.8	5.5	10.0	28.8	< 0.001
Thrombosis	3945	3.8	3.6	10.5	20.5	< 0.001
Thrombocytopenia	2572	1.9	1.7	7.7	20.5	< 0.001
Venous thrombosis	1673	1.7	1.5	2.7	7.9	< 0.001
Venous thrombosis limb	997	1.1	0.9	1.3	4.4	< 0.001
Immune thrombocytopenia	994	0.9	0.8	3.1	5.9	< 0.001
Superficial vein thrombosis	974	0.9	0.7	1.0	6.0	< 0.001
Thrombophlebitis	895	0.9	0.7	1.2	4.8	< 0.001
Cerebral venous sinus thrombosis	866	0.7	0.6	2.7	6.0	< 0.001
Cerebral venous thrombosis	383	0.4	0.3	1.1	2.3	< 0.001
Cerebral thrombosis	343	0.3	0.2	0.5	1.9	< 0.001
Portal vein thrombosis	320	0.2	0.2	0.9	2.4	< 0.001
Ophthalmic vein thrombosis	278	0.3	0.3	0.1	1.2	< 0.001
Retinal vein thrombosis	220	0.2	0.2	0.1	1.3	< 0.001
Peripheral artery thrombosis	219	0.2	0.1	0.4	1.3	< 0.001
Thrombosis with thrombocytopenia syndrome	198	< 0.1	< 0.1	1.5	2.8	< 0.001
Mesenteric vein thrombosis	191	0.2	0.2	0.2	1.3	< 0.001
Pulmonary thrombosis	161	0.2	0.2	0.2	0.9	< 0.001
Pelvic venous thrombosis	153	0.2	0.1	0.3	0.7	< 0.001
Jugular vein thrombosis	136	0.1	0.1	0.2	0.8	< 0.001
Retinal vascular thrombosis	118	0.1	0.1	0.2	0.5	< 0.001
Subclavian vein thrombosis	116	0.1	0.1	0.1	0.4	< 0.001
Haemorrhoids thrombosed	110	0.1	0.1	0.2	0.6	< 0.001
Coronary artery thrombosis	108	0.1	0.1	0.6	0.5	< 0.001
Arterial thrombosis	102	0.1	0.1	0.4	0.7	< 0.001
Thrombotic thrombocytopenic purpura	92	0.1	0.1	0.2	0.3	< 0.001
Thrombocytosis	91	0.1	0.1	0.1	0.4	< 0.001
Cerebral artery thrombosis	80	0.1	0.1	0.2	0.6	< 0.001
Aortic thrombosis	78	0.1	0.1	0.2	0.6	< 0.001
Carotid artery thrombosis	70	0.1	0.1	0.2	0.5	< 0.001
Transverse sinus thrombosis	67	0.1	0.0	0.2	0.5	< 0.001
Superior sagittal sinus thrombosis	64	0.0	0.1	0.3	0.6	< 0.001
Vena cava thrombosis	62	0.0	0.1	0.3	0.4	< 0.001
Thrombocytopenic purpura	53	0.1	0.1	0.2	0.2	< 0.001
Total for thrombosis	***22,507***	***21.1***	***19.1***	***49.3***	***128.6***	***< 0.001***

Table 3. Rates of the suspected adverse reactions of "special interest" per million vaccine doses administered. The data regarding all analysed SADRs (n = 897) and their categories (n = 12) can be accessed in the Supplementary Material 2 or via an online web application that can be downloaded as Supplementary Material 3. Bold italics indicate the total numbers of serious adverse drug reactions (SADRs) of special interest: (1) myocarditisand pericarditis, (2) anaphylaxis, (3) Guillain-Barré syndrome, and (4) thrombosis.

Spievax. This data suggests a potentially superior safety profile of modern mRNA vaccines against SARS-CoV-2 (Comirnaty and Spikevax) in comparison to the vector vaccines (Jcovden and Vaxzevria). Moreover, the efficacy reported for adenovirus-vectored vaccines is about 65%[22,23]. For mRNA vaccines, the claimed efficiency is over 90%[2,3,22,24]. Thus, in addition to indicating a good safety profile that was also documented in other studies, mRNA vaccines appear to offer better protection against SARS-CoV-2 infections[2,3,22,24]. Both Comirnaty and Spikevax seem to have very similar efficacy and safety profiles and there is no definitive "number one" vaccine[2,3,24].

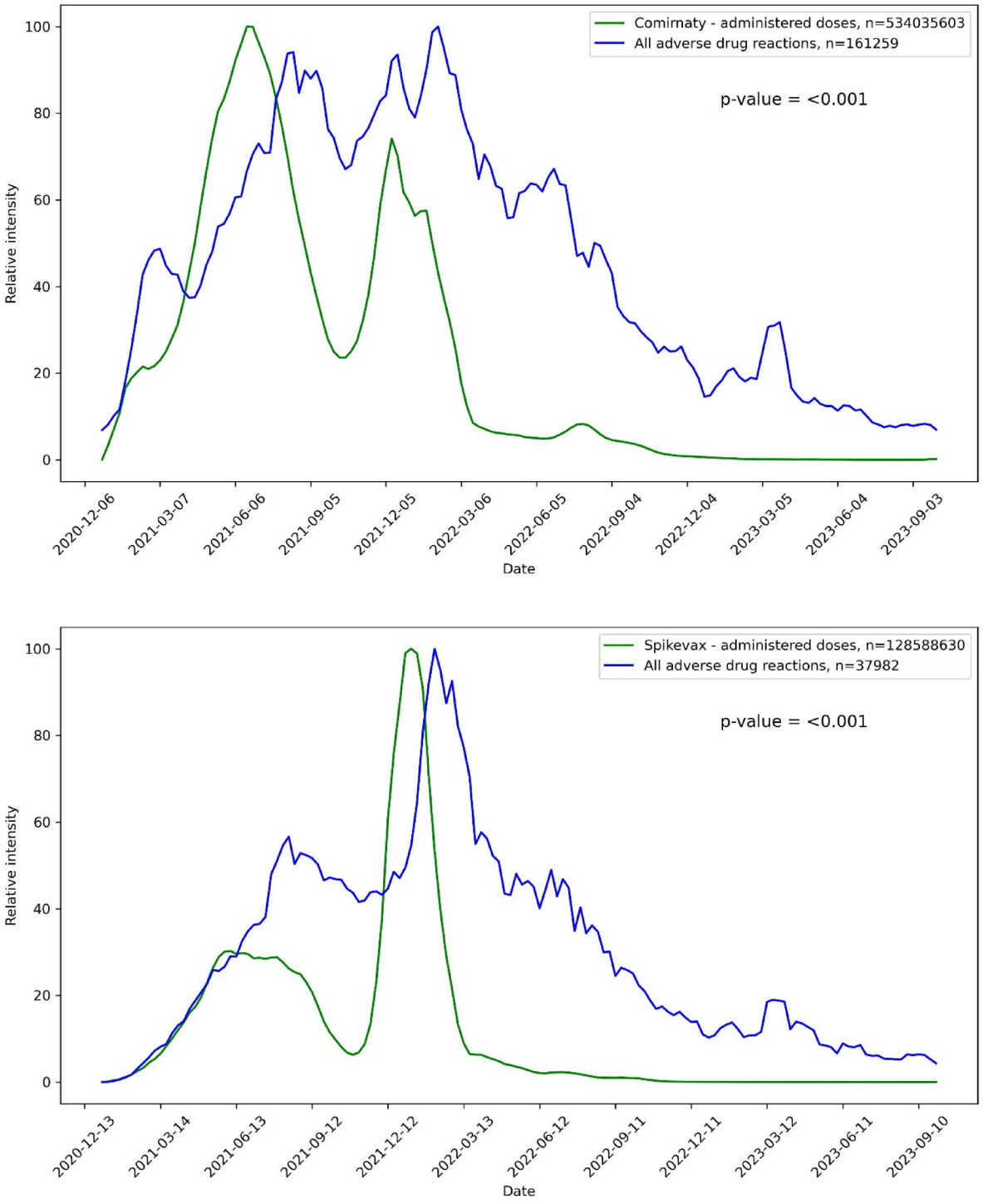

Fig. 3. (**a**) Time series representing the number of administered vaccine doses and the number of reported suspected adverse drug reactions – Comirnaty. (**b**) Time series representing the number of administered vaccine doses and the number of reported suspected adverse drug reactions – Spikevax. (**c**) Time series representing the number of administered vaccine doses and the number of reported suspected adverse drug reactions – Jcovden. (**d**) Time series representing the number of administered vaccine doses and the number of reported suspected adverse drug reactions – Vaxzevria.

Further on, based on our calculations, the most observed clinical manifestations of suspected SADRs linked to anti-SARS-CoV-2 vaccines encompassed neuropsychiatric, cardiovascular as well as musculoskeletal and connective tissue disorders (Tables 1, 2, Supplementary Materials 2 and 3). The 15 most frequently documented potential SADRs included headache, myalgia, nausea, dyspnoea, dizziness, arthralgia, pain in extremities, paraesthesia, arrhythmia, pulmonary embolism, vomiting, tachycardia, syncope, palpitations and hypoaesthesia.

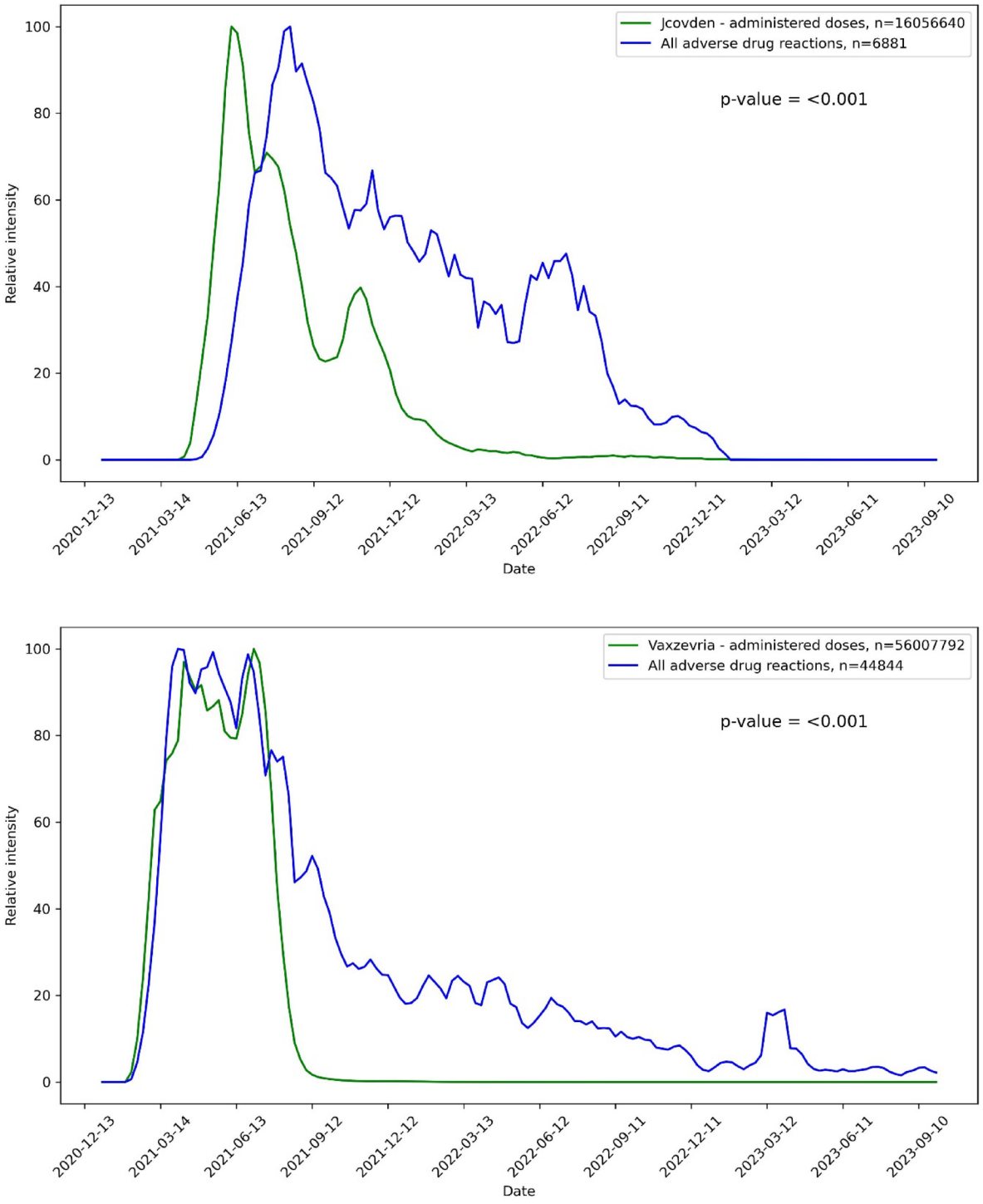

Fig. 3. (continued)

The majority of these SADRs are unspecific symptoms that can be reported by the patients themselves or can be diagnosed during a routine clinical examination. An exception to this are cases of arrhythmia and pulmonary embolism, which are more specific and usually require additional diagnostic modalities as the gold standard (electrocardiogram and computed tomography pulmonary angiogram, respectively)[25,26]. Moreover, the occurrence of all described potential SADRs may be a pathophysiological molecular reaction to a postvaccination stimulation of the immune system[27]. Following our data, except for rare headaches after Jcovden administration as well as headaches, myalgia and nausea after vaccination with Vaxzevria, all other associated SADRs can likely be classified with the use of EMA guidelines as "very rare" (< 100/1,000,000 doses), which can be considered a promising result.

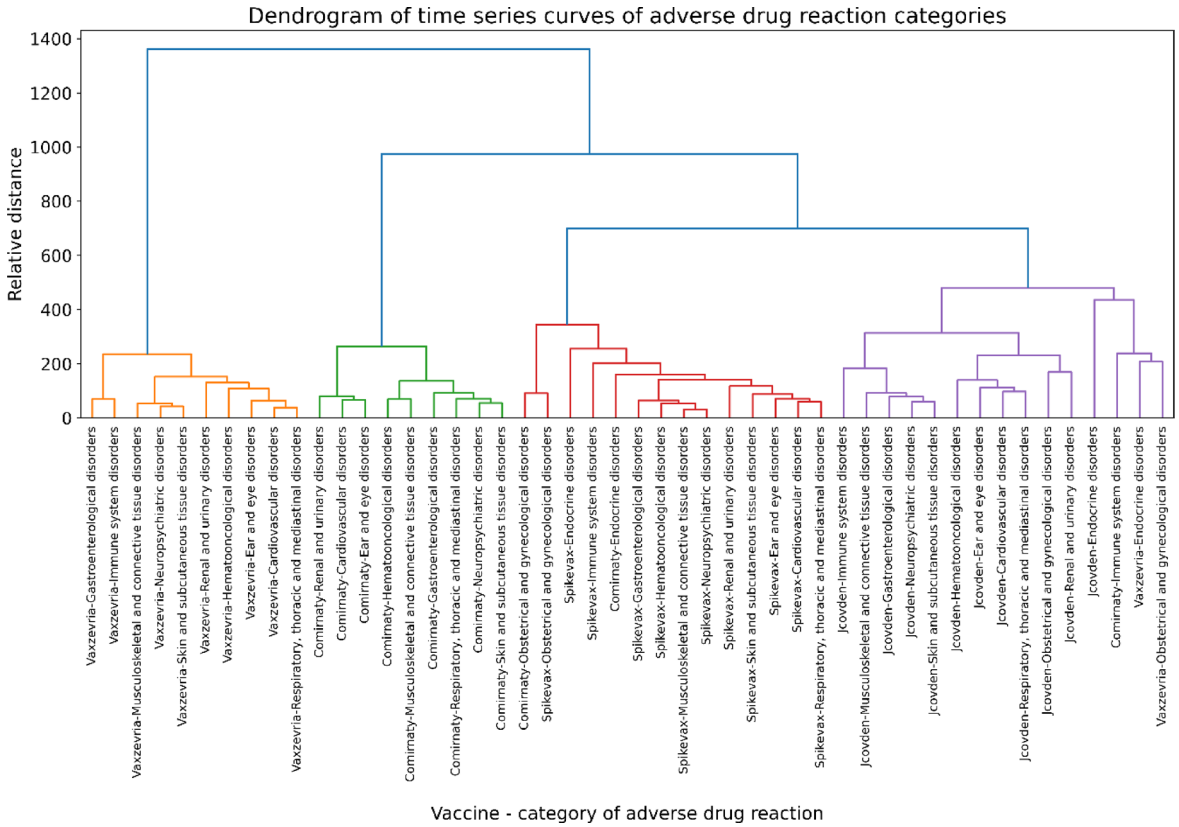

Fig. 4. Dendrogram representing the similarity between the time series curves of adverse drug reaction categories.

Moreover, the EMA anti-SARS-CoV-2 vaccine product characteristics are documents that describe the use of medicine and provide the estimated frequency of the ADRs[28–32]. They summarize all available data, incorporating the results of randomized controlled trials and phase III registration trials, considered a gold standard in evidence-based medicine and are the basis of information for healthcare professionals[28–33]. According to these sources, the most common suspected SADRs associated with SARS-CoV-2 vaccination in our analysis are in-line with the EMA[28–32]. Thus, our data align with the official product characteristics of the SARS-CoV-2 vaccines, suggesting the reliability and accuracy of our study.

However, EMA reports just the expected frequency of the ADRs, whereas the seriousness of the ADRs is not reported. Therefore, our study provides a more precise insight into the frequency of suspected SADRs linked to anti-SARS-CoV-2 vaccines and cannot be directly compared to the EMA's product characteristics. In the future, the reporting of both the frequency and severity of the potential ADRs by EMA could provide a more detailed summary to clinicians as well as contain fine-grained research data on the expected complications of vaccinations.

Patients recruited to randomised controlled trials on anti-SARS-CoV-2 vaccine safety reported most commonly general pain, headaches, fatigue, injection-site pain, injection-site erythema, myalgia, arthralgia, nausea, vomiting and chills[2,3,23,24]. Further on, the frequency of serious postvaccination ADRs was rare[2,3,23,24]. It occurred in less than 1% of the vaccinated cohort[2,3,23,24]. These prospective data are comparable to the insights from our retrospective study. Thus, the risk of SADR to the studied vaccine appears to be outweighed by the benefit of active immunisation against the SARS-CoV-2 infection and its complications like hospitalization, intensive care unit admission, severe long-term disability or death[2,3,23,24].

Myocarditis, pericarditis, anaphylaxis, Guillain-Barré syndrome and thrombosis with thrombocytopenia syndrome are reported by EMA to be the SADRs of "special interest"[5,8,20,21,34]. According to the data collected in our study, myocarditis (n = 6,380), pericarditis (n = 4,804) and myopericarditis (n = 1,702) were ranked as the 19th, 24th and 76th (Table 3). Thus, they were relatively frequently reported when compared with all studied cases of SADRs. Moreover, the total frequency of myo/pericarditis seems to be higher for mRNA vaccines (Comirnaty and Spikevax) when compared with adenovirus-based vaccines (Jcovden and Vaxzevria; $p < 0.001$).

Following the global study based on the World Health Organisation (WHO) pharmacovigilance database, the reported odds ratio (ROR, interpreted as "the higher, the stronger the association") were also significantly higher for mRNA vaccines (ROR 37.77; 95% CI 37.00–38.56) compared to Ad5-vectored vaccines (ROR 1.40; 95% CI 1.34–1.46) and inactivated whole-virus anti-SARS-CoV-2 vaccines (ROR 0.22; 95% CI 0.17–0.29)[35]. Gao et al. noted that the associated relative risk (RR) between anti-SARS-CoV-2 vaccination and the risk of myo/pericarditis was larger for mRNA vaccines: RR 4.15 (95% CI 1.87–9.22) for Spikevax and RR 2.19 (95% CI

1.46–3.29) for Comirnaty when compared with viral vector-based products (RR 1.11; 95% CI 0.81–1.53)[36]. This data is in line with other published studies[5,35,37]. Thus, there might be an association pointing to an increased risk of postvaccination inflammation of the heart tissue.

Further on, the total number of anaphylactic reaction/anaphylactic shock cases linked to vaccination against SARS-CoV-2 was 2,923 and was most often noted for Jcovden (total frequency of 7.0 PMD), followed by Vaxzevria (6.5 PMD), Comirnaty (3.7 PMD) and Spikevax (2.5 PMD; $p < 0.001$). According to the study by Boufidou et al., extremely rare fatalities—occurring at rates of 0.04 (95% CI: 0.03–0.06) per million doses for anaphylactic reactions and 0.02 (95% CI: 0.01–0.03) per million doses for anaphylactic shock—were more commonly linked to vector-based vaccines than to mRNA-based ones, both in the US and Europe[38]. Conversely, other studies suggest that this association remains inconclusive[39–41]. Nonetheless, healthcare professionals should remain vigilant, as anaphylaxis may occur following any vaccination, including those against SARS-CoV-2[39].

The Guillain-Barré syndrome was noted for 1,727 patients, and was most commonly linked to vaccination with Jcovden (10.8 PMD), next Vaxzevria (9.1 PMD), Comirnaty (1.5 PMD) and Spikevax (1.4 PMD; $p < 0.001$). This is consistent with other reports indicating a stronger association between post-vaccination Guillain-Barré syndrome and vector-based vaccines compared to mRNA-based vaccines[20,42,43].

In our analysis, TTS was identified in 198 cases and was most frequently associated with immunisation using Vaxzevria (2.8 PMD) and Jcovden (1.5 PMD), while rates for Comirnaty and Spikevax were markedly lower (< 0.1 PMD each; $p < 0.001$). However, a rare condition may sometimes go undiagnosed due to its low prevalence, making it essential to consider other related diseases within the same clinical group to ensure a more accurate and comprehensive diagnostic approach. Therefore, when considering all thrombosis-related events collectively ($n = 22,507$), the overall reporting rates were highest for Vaxzevria (128.6 PMD), followed by Jcovden (49.3 PMD), Comirnaty (21.1 PMD), and Spikevax (19.1 PMD; $p < 0.001$). These findings, indicating a higher likelihood of very rare thrombosis with thrombocytopenia syndrome following adenoviral vector-based vaccine administration compared to mRNA-based vaccines, are consistent with data reported by the EMA as well as with results from other large-scale studies conducted across diverse populations and geographic regions[44–47].

The timelines representing the weekly relative intensity of suspected SADRs reporting tends to be delayed compared to the curve representing the administration of vaccine doses. Moreover, the intensity of potential SADR reporting was more distributed in time and did not overlap with the administration of vaccine doses ($p < 0.001$; Fig. 3a–d and Supplementary Material 5). Nevertheless, the SADR reporting curves were visually similar to the vaccine administration timelines. Further on, the lag in SADR reporting and the smoother distribution in time were also observed for most clinical categories of the suspected SADRs. These trends were noted across all investigated vaccines, though further confirmation of these findings is required in prospective studies.

Based on the prospective studies, the greatest part of the SADRs tends to occur within a week after the vaccine injection[2,3,23,24]. According to the EMA's "Clinical Safety Data Management: Definitions and Standards for Expedited Reporting", all serious and unexpected events should be reported no later than 15 calendar days after first knowledge, whereas a life-threatening or fatal ADR must be reported promptly and within 7 calendar days of initial awareness[48]. Thus, the maximal delay from the SADR onset to its reporting should be maximally equal to three or four weeks. When the peak intensities of vaccine administration and SADR reporting are considered, our data show that this requirement was met for Vaxzevria and Spikevax. The most notable delays appeared to be associated with Comirnaty, suggesting a possible trend in this regard. However, for all vaccines, the SADR reporting tends to be more distributed in time than vaccine administration ($p < 0.001$). Therefore, the time from the event onset to spontaneous reporting should be shorter to meet the EMA's guidelines[48]. Moreover, this trend also underscores the importance of free-of-charge long-term spontaneous reporting systems used for global post-approval vaccine safety monitoring. Without the introduction of the EudraVigilance database, it would not be possible to investigate numerous potential postvaccination SADRs that were reported over an extended period. We endorse the maintenance of an open-source European pharmacovigilance database for future voluntary and spontaneous reporting of potential ADRs to authorized medicines. In addition to that, to improve adherence to the EMA's ADR reporting guidelines, an educational intervention could be introduced in healthcare facilities that are responsible for vaccinations. Studies have proven that it can increase the reporting rate of the ADRs and pharmacovigilance knowledge. Workshops rather than telephone-based interventions are reported to be the most effective in improving spontaneous ADR reporting[49,50].

Hierarchical clustering is an unsupervised machine learning algorithm that groups data based on their relative similarity. The clustering was based on the timelines showing the weekly fluctuations in the reporting of the SADR clinical categories. We found four possible large clusters, each one potentially corresponding to one analysed vaccine (Fig. 4). Moreover, also for the smallest clusters the type of vaccine administered, not the clinical category of the reported SADRs, is likely to have been the primary clustering factor. The shapes of timelines depicting the changes in the intensity of clinical categories reporting were similar to each other within one administered vaccine type, which is also noticeable in the visual comparison of the Figures.

In June 2021, EMA officially raised awareness of "clinical care recommendations to manage TTS that might be potentially associated with vaccination with Vaxzevria or Jcovden"[21]. This warning rapidly spread out on social media platforms and in the news[51,52]. Such events might have potentially shifted the focus of the medical professionals to one clinical category of suspected SADRs, in this case, cardiovascular disorders.

However, our hierarchical clustering suggests that across both large and small clusters the administered vaccine was the primary grouping variable. Therefore, the spontaneous reporting of the SADRs to anti-SARS-CoV-2 vaccines seemed to be independent of other possible shaping factors like ongoing discussions in the media. Based on the example of the EudraVigilance database, it also appears to provide confirmation of the robustness of a voluntary and spontaneous reporting system of potential ADRs for vaccine safety monitoring.

One of the limitations of this study is the difficulty in establishing a direct cause-effect relationship between the vaccination event and a suspected adverse drug reaction[53]. Some of the most commonly reported SADRs,

for example, "pain in extremities", "arrhythmia" or "pulmonary embolism" might be ageing-related conditions and might have been reported due to the high populational risk of such diseases[25]. Moreover, our study is a retrospective, observational study, which due to its study design cannot be used to confirm causal inference[54]. To address these limitations, the causative relationship should be investigated in prospective studies[54]. However, such studies are relatively rare due to their expensiveness and complexity. Moreover, the retrospective design of our study allowed us to comprehensively examine a very large sample of over 250,000 records of 897 types of SADRs, which is highly unlikely to be collected in any prospective study. Further on, the results of our study are consistent with the data gathered by the EMA. Thus, our research can be considered a cornerstone for future prospective research on SADRs to anti-SARS-CoV-2 vaccines.

The study is based on data from European databases, which may not fully capture the ethnic diversity present in global populations. As a result, the findings may not be generalizable to non-European or more heterogeneous populations. This limitation highlights the need for further research in more diverse cohorts to validate the study's conclusions.

Due to the absence of randomization, unmeasured variables could serve as confounding factors, presenting a methodological limitation in our retrospective study. Additionally, the analyses are vulnerable to recall bias, as participants may have had to recall the potential link between the vaccination and the SADRs. Moreover, with limited clinical characteristics recorded for each entry in the EV database, it was not possible to provide a detailed clinical phenotype of patients who might be at the highest risk of experiencing SADRs.

The EudraVigilance database is based on a spontaneous reporting system. Such monitoring systems might be subject to under-reporting of the ADRs[55,56]. It is estimated that on average, about 95% of all ADRs are under-reported. To reduce this bias, we decided to focus on SADRs only, which have a lower under-reporting rate of approximately 80%[55,56]. Moreover, serious events tend to be more consistently reported because of their higher clinical significance[55].

In our study, we used the EudraVigilance-based system organ class (clinical category). However, some symptoms and diseases could be grouped into more than one clinical category. For example, "syncope" can be a manifestation of severe dehydration, a vasovagal reflex or arrhythmia[57]. "Pulmonary embolism" can be considered a pulmonary or cardiovascular complication. Therefore, for future assessment of suspected ADRs, it would be beneficial to group symptoms and diseases into more than one organ class.

Conclusions

To conclude, the EudraVigilance monitoring platform based on a spontaneous ADR reporting system seems to be an essential, effective and reliable data collection tool for long-term vaccine safety surveillance. SADRs potentially linked to anti-SARS-CoV-2 vaccination appear to be rare, and the risk of SADR to any studied vaccine seems to be outweighed by the benefit of active immunisation against the SARS-CoV-2 infection. The SADRs most often associated with anti-SARS-CoV-2 vaccines are neuropsychiatric, cardiovascular as well as musculoskeletal and connective tissue disorders. Compared to adenovirus-based vector vaccines, mRNA vaccines appear to offer better protection against SARS-CoV-2 infections and improved safety. Regarding the vaccine administration timelines, the reporting of SADRs tends to be delayed and occurs over a longer time.

Methods

This retrospective, observational study was performed following the Strengthening the Reporting of Observational Studies in Epidemiology Statement: Guidelines for Reporting Observational Studies (STROBE)[58].

Data extraction

On 8th April 2024, a search of the EudraVigilance database was conducted to identify any spontaneously reported suspected ADRs linked to anti-SARS-CoV-2 vaccines[10,11]. No filters were applied. The first search yielded a combined count of 2,312,583 anonymised records of ADRs related to fourteen different vaccines against SARS-CoV-2 (Fig. 1).

Further on, to collect data on the number of vaccine doses administered in the EEA region, the ECDC Vaccine Tracker database was searched for eligible records[59]. The data were available on a weekly basis, from 7th December 2020 to 5th October 2023. According to this data, for all approved vaccines in the EU/EEA, in total over 980 million doses were administered.

Data filtering

To adjust the region in the EudraVigilance database to the ECDC database, any records reported not within the EEA region were excluded. Moreover, to consider ADRs of major clinical significance, ADRs whose severity grade was identified as "serious" (SADRs) were analysed, and non-serious events were excluded (in total n = 1,901,349; Fig. 1). Further on, for the Comirnaty Omicron, Novavax, Spikevax Omicron, Valneva, and Vidprevtyn Beta products the number of reported SADRs per vaccine was very low (below 1000) and these records were also excluded from the investigation (n = 1,727 records for 10 vaccine products). In addition to that, any reports added to the EudraVigilance database after the 5th of October 2023 were removed (n = 4,368). Thus, the EudraVigilance database matched the time (from 07/12/2020 to 05/10/2023) and region (EEA) of the ECDC database.

In total, 406,866 suspected SADRs associated with the four most reported vaccines: Pfizer BioNTech Comirnaty (Tozinameran, n = 268,102), Moderna Spikevax (Elastomeran, n = 48,275), Janssen Jcovden (n = 17,875) and AstraZeneca Vaxzevria (n = 72,614) were included in the analysis. The total number of administered vaccine doses for the four investigated vaccines (Comirnaty, Vaxzevria, Spikevax and Jcovden) was equal to 733,837,251 doses.

Next, data on all available types of SADRs as well as the clinical category (system organ class), to which the given type of SADR belongs, were collected from the EudraVigilance database (n = 13,056 types of SADRs in 27 clinical categories—Supplementary Material 1). As we wanted to focus on clinical manifestations of suspected SADRs, types of SADRs that belonged to clinical categories described as "disorders" related to various human body systems (for example "cardiac disorders" or "psychiatric disorders") were included in the further investigation. In contrast, groups of SADRs that (1) were very general; (2) were highly unlikely to be a complication of anti-SARS-CoV-2 vaccination (a causative relationship was improbable); (3) encompassed SADRs that were not directly related to clinical symptoms following a vaccination against SARS-CoV-2 were excluded from the analysis: "general disorders and administration site conditions", "infections and infestations", "investigations", "injury, poisoning and procedural complications", "product issues", "social circumstances" and "surgical and medical procedures". The number of excluded types of SADRs accounted for n = 7,731.

The remaining 20 categories were organized into 12 broader groups (Supplementary Material 1). Further on, types of SADRs for which at least 50 records were identified were considered in the evaluation (n = 897).

Records of suspected SADRs that reported at least one of the 897 types of SADRs were included in the final evaluation (n = 250,966—Fig. 1).

Cross-sectional analysis

Demographic characteristics of the investigated cohort were computed. The SADR records were grouped by the administered vaccine. Moreover, the frequency of potential SADRs per one million administered vaccine doses was calculated, by dividing the number of suspected SADRs from EudraVigilance by the total number of doses administered for each investigated vaccine, as recorded in the ECDC database.

Exploration of longitudinal changes

For each "vaccine – group of potential SADRs" pair, a time series data reflecting weekly fluctuations in the number of suspected SADRs was computed. Further on, a corresponding time series representing weekly changes in the number of administered vaccine doses over time was also calculated. A rolling average with a window of 4 (equivalent to one month) was used to smooth the time series.

Next, the relative frequencies were calculated for each analyzed time series by comparing the weekly frequency to the highest observed frequency within that specific time series. The peak frequency was standardized to 100, and all other frequencies were scaled proportionally between 0 and 100 based on this peak value.

Hierarchical clustering

To perform exploratory analyses of previously computed time series curves an unsupervised machine learning technique, hierarchical clustering, was implemented[60]. This algorithm was chosen as it shows the natural grouping of the data (time series curves), without specifying the number of groups (clusters) as an input hyperparameter[60]. The time series were grouped based on the similarity index – the more similar the curves of time series data are to each other, the shorter the mathematical distance between them. The similarity index was calculated between each pair of time series curves. Next, the resulting arrangement of clusters was visually represented as a dendrogram.

The length of each branch in a dendrogram corresponds to the distance (dissimilarity) between clusters. When branches merge at a lower height, it suggests that the time series curves being combined are more similar to each other.

Statistical analysis

Categorical data were summarised using counts, frequencies and proportions. Statistical significance was assessed by grouping the data into contingency tables and using the Chi-square test with Yates' correction.

Python 3.10 with Pandas 2.1.3 and Scikit-learn 1.2.1 libraries was used to perform all analyses. The threshold of two-sided statistical significance was set at $p < 0.05$ (5%).

Data availability

The data supporting this article can be found within the article itself, its online supplementary materials, and the EudraVigilance (1) and ECDC "Vaccine Tracker" (2) databases. (1) https://www.adrreports.eu/en/search.html. (2) https://vaccinetracker.ecdc.europa.eu/public/extensions/COVID-19/vaccine-tracker.html.

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Conceptualisation: W.N., L.D.S.; methodology: W.N., J.R., L.D.S., R.B.D.; investigation: W.N., G.N.; statistical analysis: W.N.; writing—original draft preparation: W.N., G.N.; writing—review and editing: J.R., M.N., L.D.S., R.B.D.; supervision: M.N., L.D.S., R.B.D. All authors have read and agreed to the published version of the manuscript.

Declarations

Competing interests

The authors declare no competing interests.

Ethics approval and consent to participate

This study is a retrospective analysis of a fully anonymized open-access database. Therefore, for this study, the need for ethical approval 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

The need for 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.

Additional information

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