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ORIGINAL RESEARCH ARTICLE

Comparison of Adverse Events in Pregnant Persons Receiving COVID-19 and Influenza Vaccines: A Disproportionality Analysis Using Combined Data from US VAERS and EudraVigilance Spontaneous Report Databases

Leonardo Roque-Pereira[1] · Malede Mequanent Sisay[1] · Comfort K. Ogar[2] · Carlos E. Durán[1] · Eugene van Puijenbroek[3,5] · Daniel Weibel[1] · Katia Verhamme[4] · Miriam Sturkenboom[1]

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Abstract

Background Although multiple post-licensure studies demonstrated that coronavirus disease-2019 (COVID-19) vaccines are safe for use during pregnancy, none of them have identified a signal of disproportionate reporting.

Aim To assess the disproportionality in reported adverse events among pregnant persons receiving COVID-19 vaccination compared with influenza vaccines in spontaneous reporting databases.

Methods Individual case safety reports (ICSRs) with COVID-19 vaccines (Pfizer, AstraZeneca, Moderna and Johnson & Johnson) and influenza vaccines were retrieved from spontaneous reporting databases in the Vaccine Adverse Event Report System (VAERS) and the EudraVigilance (EV) system between 1 December 2020 and 31 October 2023. Both datasets were combined through a common data model. Pregnancy-associated ICSRs were identified using adaptations to the European Medicines Agency (EMA) algorithm based on age groups and key medical conditions. We compared the disproportionate reporting of High-Level Terms (HLT) after COVID-19 vaccines of interest (e.g. mRNA vaccine) with another COVID-19 viral vector-based/protein subunit and influenza vaccines during pregnancy. The proportional reporting ratio (PRR) with 95% confidence intervals (CIs) was calculated using a combined dataset. PRR met the predefined criteria (PRR $\geq$ 2, lower 95% CI $\geq$ 2 and $N \geq 3$), confirming a potential signal of disproportionate reporting (SDR).

Results A total of 22,383 pregnancy-related ICSRs were included. Five associations met the PRR threshold: inborn errors of steroid synthesis 35.1 (95% CI 7.8–158.3); non-site-specific embolism and thrombosis 15.9 (95% CI 3.1–82.2); general signs and symptoms not elsewhere classified (NEC) 11.17 (95% CI 3.3–38.1); peripheral nervous system disorders congenital NEC 4.2 (95% CI 2.3–7.7); and vascular anomalies congenital NEC 3.7 (95% CI 2.4–5.6), all associated with viral vector-based/protein subunit.

Conclusions Despite this analysis, several statistical disproportionalities were identified during pregnancy; the case-by-case analysis shows that embolism and thrombosis require prioritized investigation through proper causal inference studies.

1 Introduction

Pregnant women are considered more prone to severe viral respiratory infections due to physiological and anatomical changes during pregnancy [2]. As the coronavirus disease-2019 (COVID-19) pandemic caused by the severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) became the major health emergency of this century, severe COVID-19 during pregnancy was linked to increased maternal morbidity and mortality [3–5]. Consequently, the World Health Organization (WHO), along with national and regional health authorities, recommended vaccinating high-risk groups such as the pregnant population to reduce the risk of severe COVID-19 [6, 7].

Several COVID-19 vaccines have been granted marketing authorization. Four of these vaccines (i.e. Pfizer/BioNTech, Moderna, AstraZeneca, and Janssen) have been used in the USA and European countries. While multiple clinical trials have been conducted around the world to study the new COVID-19 vaccines, the pregnant population was not typically recruited for these trials. For instance, only 1.7% of the clinical trials included in the WHO registry

Extended author information available on the last page of the article

Key Summary Points

Although there are post-authorization safety studies using disproportionality analysis, essential to assess COVID-19 vaccine safety in pregnancy, none of them have identified signals of disproportionality.

This study combined data from Eudravigilance and VAERS using a Common Data Model.

Individual case safety reports associated with pregnancy were found in VAERS and EV using an adapted algorithm.

Despite of several elevated disproportionalities were identified, embolism and thrombosis in pregnancy should be investigated with proper causal inference methods.

were pregnancy-specific [8]. Therefore, post-authorization observational safety studies during the pregnancy period are essential to assess the safety profile of COVID-19 vaccines in this population. One approach to identify potential safety concerns with COVID-19 vaccines is to evaluate Individual Case Safety Reports (ICSRs) in large spontaneous reporting databases such as the American Vaccine Adverse Event Reporting Systems (VAERS) database and European EudraVigilance (EV) database [9, 10]. The ICSRs analysis can result in a safety signal, defined as information suggesting a new potential association or new aspects of a known association between vaccines and adverse events, warranting further investigation [11]. Disproportionality analysis is the most commonly used method to detect signals of disproportionate reporting (SDR) of drug/vaccine-event combinations in spontaneous reporting databases [11–13]. Several post-licensure vaccine safety studies using disproportionality analysis either in VAERS or in EV databases have not identified a SDR of prespecified conditions/adverse events following COVID-19 vaccines in pregnant women [14–16]. While these vaccine safety studies did not detect any adverse event in pregnant women for hypothesis generation, these findings should be interpreted with caution owing to the relatively small sample sizes. Therefore, integrating large databases, such as VAERS and EV, accounts for differences in COVID-19 vaccine uptake rates across the USA, Europe and the rest of the world, enhancing statistical power and probably improving the ability to identify rare but clinically important safety signals.

The objective of this study was to identify potential safety signals associated with COVID-19 vaccines as compared with influenza vaccines in pregnant population using VAERS and EV databases combined, with the aim of increasing the sample size. In addition, we aimed to generate reporting rates of pregnancy associated adverse events (AEs) with COVID-19 and influenza vaccines.

2 Methods

2.1 Study Design and Data Sources

This study used two population-based spontaneous reporting databases: (i) the VAERS database from the US Centers for Disease Control and Prevention (CDC) and US Food and Drug Administration (FDA) and (ii) the EV database under the European Union Medicines Regulatory Framework, operated by the European Medicines Agency (EMA). We analysed spontaneous reports received from 1 December 2020 to 31 October 2023.

The datasets were downloaded from the VAERS website on 20 January 2024 for COVID-19 vaccines and influenza vaccines using their respective vaccine codes: 'COVID19' and 'FLU'. The first author (L.R.P.) requested all EV data from EMA for the four COVID-19 vaccines centrally authorized by EMA until 27 March 2024 [17] (Pfizer, Moderna, AstraZeneca and Johnson & Johnson (J&J)) and any influenza vaccines authorized in the European Economic Area (EEA) which are not contraindicated in pregnancy. EV datasets were obtained from the EMA in three batches between 22 February 2024 and 25 April 2024.

The vaccines of interest were further classified into the following vaccine platforms: COVID-19 mRNA vaccines (Pfizer and Moderna vaccines), COVID-19 viral vector-based/protein subunit vaccines (AstraZeneca and J&J vaccines), and influenza vaccines. Influenza vaccines were not subcategorized by vaccine platforms since they were used as a comparator. The results of this study were evaluated at the vaccine platform level rather than at the vaccine manufacturer level.

2.2 Selection of ICSRs Related to Pregnant Population

The adverse events in the ICSRs were mapped to the Medical Dictionary for Regulatory Activities (MedDRA) Preferred Term (PT) and High-Level Term (HLT). To identify pregnancy-related ICSR, we adapted a novel algorithm developed by EMA [18] based on age groups and key medical conditions. First, we excluded case reports from patients younger than 12 years and older than 50 years of age. Next, we included all ICSRs whose PT was mapped to the MedDRA Standard Medical Queries (SMQ) level 2 (which applied a narrower set of specific medical terms than SMQ level 1 if they met any of the following key medical conditions: (i) pregnancy, labour and delivery complications

and risk factors (excluding abortions and stillbirth), (ii) termination of pregnancy and risk of abortion, (iii) neonatal disorders and (iv) familial and genetic disorders. The other medical conditions proposed in the novel algorithm [18] such as gestation period and intra-amniotic transplacental use as a route of administration were omitted from the inclusion criteria of this study because they are not included in VAERS. These steps were applied separately in the EV and VAERS databases.

2.3 Merging Datasets Using a Common Data Model (CDM) and Deduplication

For ICSRs with multiple updates (i.e. the same case report is reported at a later time, with additional or update information), we minimized the number of duplicate reports as follows: we first deduplicated each database (EV and VAERS) by applying an algorithm to identify ICSRs that exactly matched (including missing values) on all the following variables: ID report/unique case identification number, country/state, sex, age, vaccine manufacture/name, PT, recovered outcome and onset date. When duplicates were detected, the record with the lower proportion of missing data was retained. Second, we removed ICSRs with missing PT and/or missing ID report.

The data elements from pregnancy-associated ICSRs in EV and VAERS were mapped using a CDM proposed by Dodd C. et al.[19] (Online Resource 1). A second deduplication process was carried out across EV and VAERS to detect ICSR that appeared in both databases and potentially referred to the same ICSR. This was performed by using a combination of country/state, vaccine manufacture, PT, vaccine date, age, sex and onset date for an exact matching (including missing values) from VAERS and EV. When duplicates were detected, the record with the lower proportion of missing data was retained [19].

In a sensitivity analysis, the effect of deduplication was assessed by performing the disproportional reporting of HLT 'spontaneous abortion' in VAERS and EV separately and comparing the results with and without deduplication. HLT 'spontaneous abortion' was chosen because this HLT is commonly reported in the spontaneous reporting databases. Therefore, the PRR for this common HLT was calculated to determine whether our methodological choices had an effect on the performance of PRR before and after deduplication.

2.4 Disproportionality Analysis

The MedDRA HLT hierarchy level was chosen for disproportionality analysis because it allowed a broader aggregation (avoiding excessive granularity from PTs) and offered a more practical approach for efficient and less complex analysis compared with the PT level and SMQs. The vaccine-HLT combinations were evaluated by comparing the observed counts of each combination to their expected values in the database. This analysis employed statistical algorithms on the basis of 2×2 contingency tables, incorporating the reporting of HLTs in the mRNA COVID-19 vaccine of interest and compared with the reporting of HLTs in other COVID-19 vaccines (e.g. viral vector-based/protein subunit) and influenza vaccines. The proportional reporting ratio (PRR), chosen for its simplicity and interpretability, was applied to identify signal alerts. If the PRR met the predefined criteria, a potential signal of disproportionate reporting (SDR) was declared for the specific vaccine-HLT combination (Table 1).

A case-by-case analysis was conducted for SDRs identified in this research to review the key variables, if available, to prioritize further investigation. These variables included country, qualification of the reporter, age, vaccine date, time to onset, seriousness, outcome/fatal, PTs, concomitant or prior medications/vaccines, current conditions, medical history, and allergies for causality association assessment based on Bradford Hill criteria [20, 21].

2.5 Data Management and Quality Control

Adverse events were mapped to the hierarchy of the MedDRA dictionary version 27.0. All data processing and statistical analysis were performed using R version 4.3.1, with the package 'PhViD' and OpenEBGM [1]. The datasets were securely kept in the Digital Research Environment (DRE), a secure web-based environment [22]. The READUS-PV checklist was completed to increase transparency, completeness and accuracy in the reporting of disproportionality analyses conducted using ICSR databases (Online Resource 2) [20].

3 Results

A total of 3,841,892 ICSRs for COVID-19 vaccines and influenza vaccines in the general population were obtained from VAERS. We identified a total of 7663 pregnancy ICSRs after applying the adapted algorithm and the first deduplication. In EV, 8,440,522 ICSRs were found in the general population. We selected a total of 14,792 pregnancy ICSRs after applying the adapted algorithm and the first deduplication. The integration of these ICSRs from both EV and VAERS by CDM resulted in 22,383 eligible pregnancy ICSRs, as depicted in Fig. 1.

The characteristics of the 22,383 pregnancy-associated ICSRs are presented in Table 2. Most mRNA COVID-19 cases (8238 ICSRs) originated from the USA (43.6%), while 1599 ICSRs associated with COVID-19 viral vector-based/protein subunit came from European countries (52.6%;

Table 1 Common measure of association for 2 × 2 table in spontaneous reporting system (SRS) analyses

Vaccines	Adverse events of interest	All other adverse events
COVID-19 vaccine of interest	a	b
Other COVID-19/influenza vaccines	c	d
Signal metrics	Calculations	Criteria of SDR
PRR	$\frac{a/(a+b)}{c/(c+d)}$	PRR ≥ 2, lower limit of 95% CI ≥ 2 and $N \geq 3$ [47, 48]

Signal of disproportionate reporting (SDR) is declared when the thresholds for proportional reporting ratio (PRR) are met
Vaccines of interest: COVID-19 mRNA vaccines OR COVID-19 viral vector-based/protein subunit vaccines
· Comparison groups: influenza vaccine and one of COVID-19 vaccine type
· 'a' is the number of an adverse event (AE) of interest (e.g. High-Level Term (HLT)) notified with the selected COVID-19 vaccine(s) of interest
· 'c' the number of an AE of interest notified with the comparators (other COVID-19/influenza vaccines)
· 'b' the number of all other AE notified with the selected COVID-19 vaccine(s) of interest
· 'd' the number of all other AEs notified with comparators (other COVID-19/influenza vaccines)

Online Resource 3). Among the eligible pregnancy-associated ICSRs, 13,187 reports (58.9%) were coded as serious, with a higher percentage of serious cases linked to COVID-19 viral vector-based/protein subunit vaccines compared with mRNA COVID-19 vaccines (75.9% versus 56.7%). Serious reports due to 'other medically important condition' accounted for 7512 ICSRs (33.6%) of all pregnancy-associated ICSRs, while 408 ICSRs (1.8%) were reported as fatal. Although the median maternal age was broadly the same across groups of vaccine types, the percentage of patients 35 years or older was higher among those receiving COVID-19 vaccines (viral vector-based/protein subunit and mRNA vaccines) compared with influenza vaccines. The median time to onset of AE was longer for mRNA vaccines (9 days) compared with viral vector-based/protein subunit vaccines (4 days) and influenza vaccine (0 days). Most of the AEs' outcomes were either unknown or resolved across the vaccine platforms (Table 2).

The most frequent maternal outcome/HLTs (along with two most reported PTs) following COVID-19 or influenza vaccine administration were: 657 labour onset and length abnormalities (premature labour and premature delivery), 475 maternal complications of pregnancy NEC (ectopic pregnancy and morning sickness), 360 haemorrhagic complications of pregnancy (haemorrhage in pregnancy and premature separation of placenta), and 312 ICSRs obstetric therapeutic procedure (caesarean section and labour induction). This analysis excluded the 'exposure during pregnancy/foetal exposure' HLT as described in Table 3 for most reported PTs (Online Resource 4 – complete list of PTs of most reported HLT).

For neonatal/foetal outcomes, the most frequently reported HLTs (along with most reported PTs) following COVID-19 or influenza vaccine administration were: 4186 ICSRs of spontaneous abortions (spontaneous abortions and threatened abortion), 533 ICSRs of stillbirth and foetal death (foetal death and stillbirth), and 221 ICSRs of gestational age and weight conditions (premature baby and low-birth-weight baby) as described in Table 4 for most reported PTs (Online Resource 4 – complete list of PTs of most reported HLT).

3.1 Disproportionality Analysis

Figure 2 shows the list of HLTs with PRR ≥ 2 and $N \geq 3$: the three highest PRRs for HLT associated with mRNA vaccines were: 'genetic mitochondrial abnormalities NEC' with a PRR of 4.61 (95% confidence interval (CI) 0.6–34.0), 'normal pregnancy, pregnancy, delivery' with 3.5 (95% CI 1.7–7.0) and 'food Malabsorption & intolerance' with 3.0 (95% CI 0.7–12.7). However, the lower limits of the 95% CI for these HLTs were also below 2 (refer to Table 1 for SDR criteria). The five highest PRRs for HLT associated with viral vector-based/protein subunit vaccines were: 'Inborn errors of steroid synthesis' 35.1 (95% CI 7.8–158.3); 'non-site specific embolism and thrombosis' 15.9 (95% CI 3.1–82.2); 'General signs and symptoms NEC' 11.17 (95% CI 3.3–38.1); 'Peripheral nervous system disorders congenital NEC' 4.2 (95% CI 2.3–7.7); and 'Vascular anomalies congenital NEC' 3.7 (95% CI 2.4–5.6), as shown in Fig. 2.

The HLTs 'Inborn errors of steroid synthesis', 'Coagulopathies', 'non-site specific embolism and thrombosis' and 'Vascular anomalies congenital NEC' associated with viral vector-based/protein subunit met the SDR criteria proposed in this study (Fig. 2).

3.2 Sensitivity Analyses and a Case-by-Case Analysis of SDRs

The PRRs results of HLT 'spontaneous abortion', evaluated as part of the sensitivity analysis in VAERS and EV

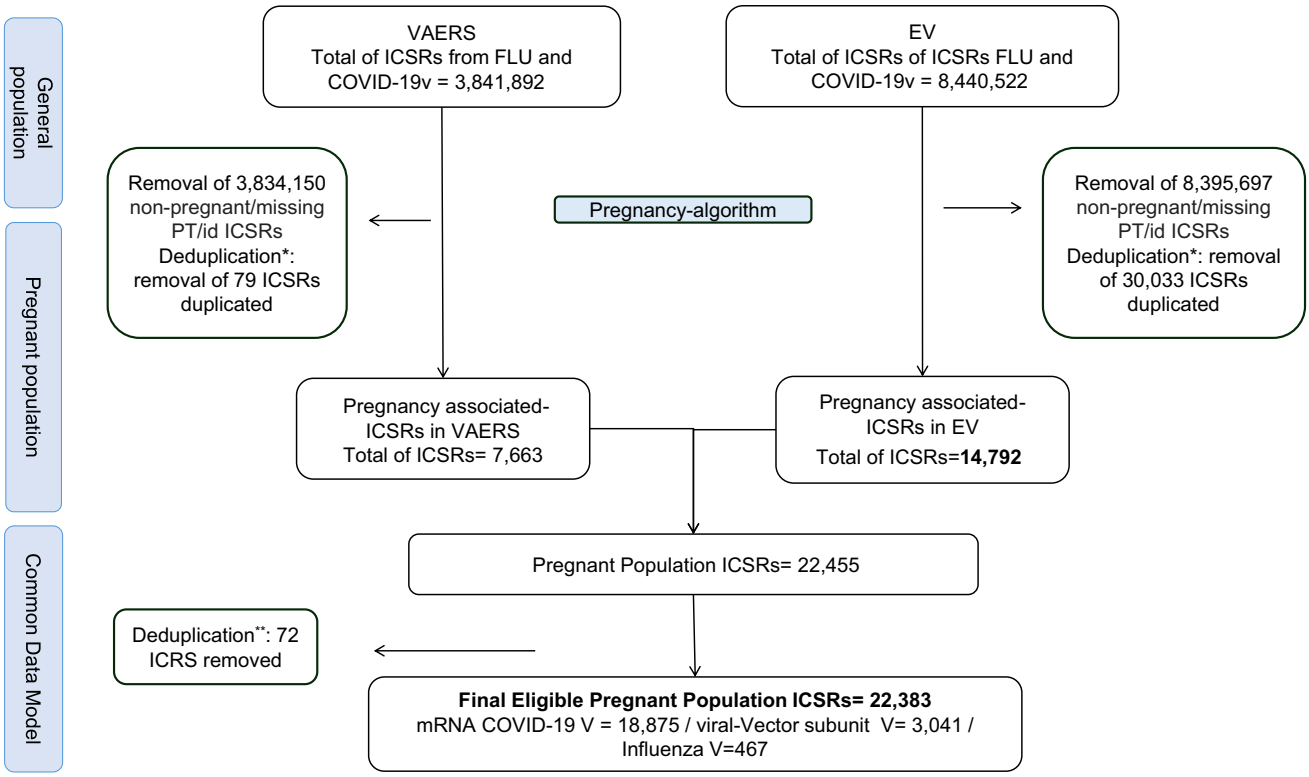

Fig. 1 Flowchart of the eligibility of pregnancy-related ICSRs from VAERS and EV databases combined using CDM. *The first deduplication in each dataset is described in the section Merging Datasets Using a Common Data Model (CDM) and De-duplication. In the Vaccine Adverse Event Reporting System (VAERS) dataset, only the first report of a case is included in the public dataset. Multiple entries occur when reports list more than five symptoms, causing the same VAERS ID to appear in separate rows [49]. So, we transformed the data into unique rows per symptom (Preferred Term (PT)) and vaccine within each individual case safety report (ICSR). During process from wide to long format, rows with missing symptoms or multiple vaccine antigens were removed, ensuring each row contained a single product-event pair before the first deduplication. In contrast, EudraVigilance's long data are already structured by product-event pair (one product name per row, with each row representing a single ID and PT), requiring no preprocessing prior to deduplication. This structural transformation may explain the variation in the proportion of deduplicated cases between VAERS and EudraVigilance (EV). **The second deduplication in each dataset is described in the section Merging Datasets Using a CDM and De-duplication

individually – both with and without deduplication – were consistent (Online Resource 5).

Key variables following SDRs associated with viral vector-based/protein subunit COVID-19 vaccines are presented in Online Resource 6. The case-by-case assessment and the associated causality analysis are detailed in Table 5; of the 11 cases of inborn errors of steroid synthesis (HLT), 10 originated from Brazil. All five cases of 'Non-site specific embolism and thrombosis' HLT involved postpartum thrombosis, with three classified as serious. One case was confirmed via medical imaging. For congenital vascular anomalies (HLT), arteriovenous and vascular malformations were most frequently reported, with onset times from 3 to 50 days. Seven ICSRs of 'General signs and symptoms' HLT and 17 of 'Peripheral nervous system disorders' HLT from the UK and Ireland were linked to 'High-pitched crying' and 'Paroxysmal extreme pain disorder', respectively.

4 Discussion

This study presents the potential safety signal of disproportionate reporting associated with COVID-19 vaccines in pregnant women compared with reports of AEs in pregnant women exposed to influenza vaccines using a combination of two large spontaneous reporting datasets: the US VAERS and the European EV. We chose influenza vaccines as the comparator because it is considered a 'safe' vaccine during pregnancy in line with other studies [23–27].

Our main finding of 'non-site specific embolism and thrombosis' SDR associated with viral vector-based/protein subunit COVID-19 vaccines administered to pregnant persons is not consistent with other post-licensure vaccine safety studies based on disproportionality analysis that have not found SDR during pregnancy [14, 15, 28]. It is postulated that the design of our study which combined two large spontaneous reporting databases and the data comparison of COVID-19 vaccines versus influenza vaccines may have

Table 2 The characteristics of pregnancy-related individual case safety reports (ICSRs) following COVID-19 and influenza vaccines

Characteristics	Characteristics/subgroups	COVID-19 mRNA vaccines $N = 18,875$	COVID-19 viral vector-based/protein subunit vaccines $N = 3041$	Influenza vaccines $N = 467$
Country or region	Europe (*N* %)	6789 (35.97)	1599 (52.58)	110 (23.55)
	USA (*N* %)	8238 (43.65)	608 (19.99)	171 (36.62)
	Other countries[a] (*N* %)	1681 (8.91)	580 (19.07)	50 (10.71)
	Unknown[b] (N %)	2167 (11.48)	254 (8.35)	136 (29.12)
Maternal age	Maternal age in years, median (Q1–Q3)	33 (30 - 36)	33 (29–37)	32 (29–35)
	Reports with maternal age ≥ 35 years (N %)	5678 (30.08)	946 (31.11)	101 (21.63)
Seriousness criteria	Serious[c] (*N* %)	10697 (56.67)	2309 (75.93)	181 (38.76)
	Serious sub-category: other medically important condition[c] (*N* %)	6030 (31.95)	1350 (44.39)	132 (28.27)
	Non-serious (*N* %)	5903 (31.27)	531 (17.46)	175 (37.47)
Outcome of adverse events	Fatal (*N* %)	339 (1.80)	63 (2.07)	6 (1.28)
	Not resolved (*N* %)	3431 (18.18)	506 (16.64)	53 (11.35)
	Resolved with sequelae	562 (2.98)	58 (1.91)	4 (0.86)
	Resolving (*N* %)	942 (4.99)	195 (6.41)	12 (2.57)
	Resolved	6626 (35.1)	777 (25.55)	100 (21.41)
	Unknown (*N* %)	6975 (36.95)	1442 (47.42)	292 (62.53)
Time to onset in days	Median time to onset (Q1–Q3[d])	4 (0.81–28)	9 (1–37)	0 (0–2)

[a]ICSRs reported outside Europe and USA such as Argentina, Australia, Bahrain, Brazil, Brunei Darussalam, Canada, Chile, China, Colombia, Costa Rica, Egypt, French Polynesia, Guatemala, Hong Kong, Indonesia, Iraq, Israel, Japan, Jordan, Kazakhstan, Kenya, Korea (Republic of), Lebanon, Malaysia, Maldives, Mexico, Palestine (State of), Peru, Philippines, Puerto Rico, Qatar, Singapore, South Africa, Taiwan (Province of China), Thailand, Tunisia, Turkey, Vietnam

[b]ICSRs for which country was not reported/unknown/'Unknown'

[c]Serious includes reports with AEs which met one of the seriousness criteria provided by the reporter: resulted in death, life-threating, AE which required inpatient hospitalization or prolongation of existing hospitalization, resulted in a disability or incapacity, or resulted in congenital anomaly and other medically important condition

[d]Q1–Q3: Quartile 1 to Quartile 3. Gestational age at the time of vaccination is unknown since it is not captured as standard data element in EudraVigilance (EV) and Vaccine Adverse Event Reporting System (VAERS) datasets

Table 3 Most reported maternal outcome High-Level Terms and Preferred Terms for COVID-19 vaccines and influenza vaccines in pregnant population

High-Level Term (HLT)	Preferred Term (PT)	COVID-19 mRNA vaccine	Viral vector-based/protein subunit	Influenza	Total
Total pregnancy ICSRs		$N = 18,875$	$N = 3041$	$N = 467$	$N = 22,383$
Labour onset and length abnormalities	Premature labour	185 (1.0)	17 (0.6)	4 (0.9)	206 (0.9)
	Premature delivery	155 (0.8)	24(0.8)	6 (1.3)	185 (0.8)
	Premature rupture of membranes	92 (0.5)	13 (0.4)	2 (0.4)	107 (0.5)
Obstetric therapeutic procedures	Caesarean section	203 (1.1)	25 (0.8)	5 (1.1)	233 (1.0)
	Labour induction	40 (0.2)	3 (0.1)	1 (0.2)	44 (0.2)
Haemorrhagic complications of pregnancy	Haemorrhage in pregnancy	164 (0.9)	11 (0.4)	4 (0.9)	179 (0.8)
	Premature separation of placenta	83 (0.4)	18 (0.6)	1 (0.2)	102 (0.5)
	Subchorionic haemorrhage	24 (0.1)	5 (0.2)	0	29 (0.1)

The 'exposure during pregnancy/foetal' HLT was omitted from this most reported maternal outcome table despite being reported in the eligible pregnancy ICSRs of this study. Online Resource 4 contains the comprehensive list of PTs of most reported HLT

Table 4 Most reported neonatal/foetal outcome High-Level Terms and Preferred Terms for COVID-19 vaccines and influenza vaccines in pregnant persons population

High-Level Term (HLT)	Preferred Term (PT)	COVID-19 mRNA vaccine	Viral vector-based/ protein subunit	Influenza	Total
Total pregnancy ICSRs		*N* = 18,875	*N* =3041	*N* = 467	*N* = 22,383
Abortions spontaneous	Abortion spontaneous	3547 (18.8)	537 (17.7)	38 (8.1)	4122 (18.4)
	Abortion threatened	23 (0.1)	6 (0.2)	1 (0.2)	30 (0.1)
	Abortion spontaneous complete	12 (0.1)	3 (0.1)	1 (0.2)	16 (0.1)
Stillbirth and foetal death	Foetal death	330 (1.7)	30 (1.0)	5 (1.1)	365 (1.6)
	Stillbirth	148 (0.8)	16 (0.5)	3 (0.6)	167 (0.7)
Gestational age and weight conditions	Premature baby	168 (0.9)	11 (0.4)	5 (1.1)	184 (0.8)
	Low-birth-weight baby	15 (0.1)	2 (0.1)	2 (0.4)	19 (0.1)

The 'exposure during pregnancy/foetal' HLT was omitted from this most reported maternal outcome table despite being reported in the eligible pregnancy ICSRs of this study. Online Resource 4 contains the comprehensive list of PTs of most reported HLT

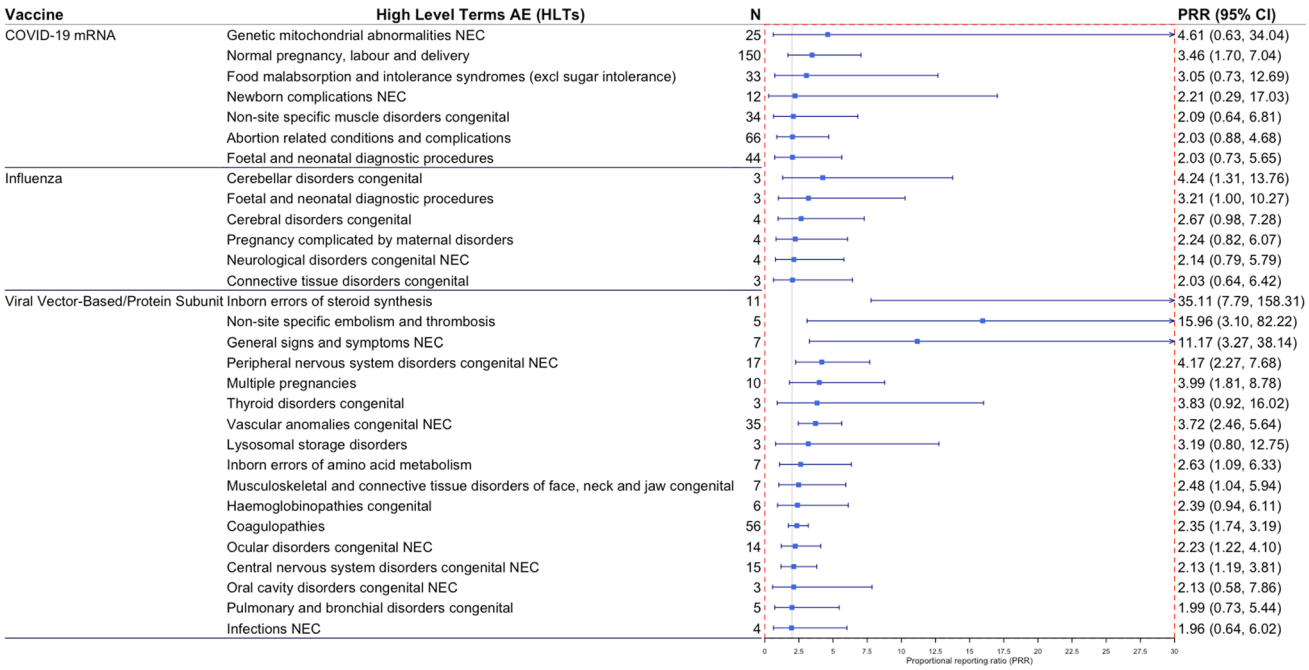

Fig. 2 PRR forest plot of vaccine-HLT combination (PRR ≥ 2). The disproportionate reporting of HLTs in COVID-19 vaccines of interest (e.g. mRNA vaccine) was estimated on the basis of the overall reporting of HLTs in other COVID-19 vaccines (e.g. viral vector/subunit protein) and influenza vaccines. The threshold of proportional reporting ratio (PRR) = 2 is represented by the vertical grey line

led to the identification of new and rare SDRs associated to the first (COVID-19 viral vector-based/protein subunit vaccines). However, the most frequent ICSR was 'spontaneous abortion' (*N* = 4122 ICSRs) followed by stillbirth/foetal death (*N* = 532). The PRR of 1.2 (95% CI 1.1–1.3) for 'spontaneous abortion' associated with COVID-19 mRNA vaccines aligns with results from other safety studies using disproportionality analysis (DA) [14, 15]. Our key findings should also be interpreted with caution as they represent potential associations with a COVID-19 vaccine rather than definitive evidence of a causal association.

We found a larger number of ICSRs (22,383) received between 1 December 2020 and 31 October 2023, compared with other safety studies using disproportionality analysis [14, 15, 28]. The majority of the eligible ICSRs in this study came from the USA (40%), followed by Europe (38%), reflecting the fact that VAERS only includes ICSRs from the USA, whereas EV mainly includes reports from Europe but also from other countries, which may reflect the reporting requirements of European regulations that vaccine manufacturers must comply with [29, 30]. Among the eligible ICSRs in each vaccine platform, the percentage of

Table 5 Key features of case-by-case analysis associated with viral vector-based/protein subunit COVID-19 vaccines

High-Level Terms (HLTs) which met SDR criteria	Preferred Terms (PTs) trends	Other key variables trends
Inborn errors of steroid synthesis	7 of 11 cases of inborn errors of steroid synthesis HLT	Ten of eleven individual case safety reports (ICSRs) were from Brazil. There is not a specific trend of time to onset from COVID-19 vaccine and onset date of PT (range: 2–11 days). Most of the outcomes were either resolved or resolving. These are rare congenital enzyme deficiencies caused by inherited mutations. Other variables such as current and prior conditions, laboratory results and concomitant medications are not reported.
Non-site-specific embolism and thrombosis	5 cases reported 'Postpartum thrombosis' as PT	Five cases reported 'Postpartum thrombosis' as PT. Three of five cases were classified as serious. Patient's age ranged from 24 to 37 years old, and the time of onset for one case was around 60 days after COVID-19 vaccines, and in the other case, the AE occurred on the same day as COVID-19 vaccination. In one case, the ultrasound confirmed deep vein thrombosis (DVT) in the distal to proximal left peroneal veins, and in another case, thrombosis was diagnosed on computed tomography angiography (CTA) of the brain and magnetic resonance imaging (MRI) of the brain in a patient with a medical history of herpes simplex vulvovaginitis. In the other four cases, variables such as current and prior conditions, allergies and concomitant medications were not reported.
Vascular anomalies congenital not elsewhere classified (NEC)	Out of 35 PTs, the most common PTs reported were arteriovenous malformation (9 ICSRs) followed by vascular malformation (7 ICSRs)	The onset time varied from 3 to 50 days. In total, 31 ICSRs were serious (one fatal outcome), and 1 ICSR was not serious. The patient age when reported ranged from 22 to 49 years. When reporter qualification was provided: 7 ICSRs were physician/heathcare professional (HCP), while 5 cases came from consumer. The details of other variables such as current and prior conditions, laboratory results, and concomitant medications were not reported in all cases expect for one patient who had a family history of blood clotting disorders.
General signs and symptoms NEC	All 7 ICSRs refer to PT 'High-pitched crying'	Seven ICSRs were reported in the UK and Ireland in 2021. These were assessed as serious with no specific trend in terms of outcome. Other variables such as time to onset, concomitant or prior medications/vaccines, current conditions, medical history, qualification of reporter and allergies are unknown.
Peripheral nervous system disorders congenital NEC	All 17 ICSRs refer to 'Paroxysmal extreme pain disorder' PT	Seventeen ICSRs were reported in the UK and Ireland in 2021. There is not a specific trend of time to onset from COVID-19 vaccine and onset date of PT (range: 1–89 days). There was very limited or no information for other key variables. Other variables such as time to onset, concomitant or prior medications/vaccines, current conditions, medical history, qualification of reporter and allergies were unknown.

patients who are 35 years of age or older is marginally higher for ICSRs with viral vector-based/protein subunit vaccines compared with mRNA vaccine vaccines, which may also have contributed to the higher number of serious AEs. We found that 39% of ICSRs reported with influenza were classified as serious which is lower compared with COVID-19 vaccines. More than half of the serious ICSRs for all vaccines of interest in this study were classified according to the seriousness criterion 'other medically important condition'. This high proportion of serious ICSRs due to 'other medically important condition' is in line with a previous study [15]. In this situation, it is expected that the reporter used their own scientific judgement to choose this option, as the AE did not result in death, hospitalization, congenital anomaly or permanent disability but is still of significant concern [31].The higher rates of serious cases associated with COVID-19 vaccines compared with influenza vaccine might be due to the potentially high number of case reports with COVID-19 vaccines in pregnancy owing to the recommendations from WHO for large-scale passive surveillance systems of COVID-19 vaccines in pregnant women [32], fear of the unknown side effects of the vaccine in pregnant women, together with social media disinformation and medical mistrust [33, 34]. The rates of fatal outcomes of AEs in the pregnant population were similar between the two COVID-19 vaccine platforms. The rate of 1.8% (402/21,916 ICSRs) refers to cases reported as fatal outcome in relation to all ICSRs reported following COVID-19 vaccines, which is slightly lower than the rates of fatal ICSRs previously reported with another observational study which applied DA (2.07%) [15]. The lower rate of fatal case reports in our finding may be explained by differences in study period, the use of EV and VAERS datasets, and how pregnancy-associated ICSRs were retrieved. The analysis of serious and fatal ICSRs identified in this study should be treated with caution. These cases represent adverse events reported in EV and VAERS for COVID-19 vaccines and influenza vaccines and are not conclusive evidence of vaccine harm during pregnancy.

The reporting rates of pregnancy-associated HLTs with COVID-19 and influenza vaccines were generally low in relation to the total number of ICSRs found in this research. The rate of HLT 'spontaneous abortion' is the most frequently reported event among COVID-19 vaccine platforms, with a higher reporting rate compared with influenza vaccine-ICSRs (17–18% versus 8%). Despite this apparent increase in reporting rates for spontaneous abortion following COVID-19 vaccination, there is no evidence of casual association linking COVID-19 vaccination to an increased risk of spontaneous abortion [35]. These low reporting rates of pregnancy-associated AEs other than 'spontaneous abortion/stillbirth' were also consistent with studies using disproportionality analysis [14, 15].

An SDR for HLT associated with mRNA vaccines was not identified, as it did not meet SDR criteria (PRR ≥ 2, 95% CI ≥ 2 and $N \geq 3$). We reviewed the five SDRs through case-by-case analysis to identify key variables for causal association between viral vector-based/protein subunit COVID-19 vaccines and SDRs when information was reported. Eleven ICSRs with inborn errors of steroid synthesis refer to congenital enzyme deficiencies primarily reported in Brazil, which are more likely the result of inherited mutations among Brazilian patients [36, 37] rather than being caused by COVID-19 vaccines. In addition, the 95% CI for inborn errors of steroid synthesis is wide owing to the small numbers, which indicates a limited readability of PRR estimate. The seven cases classified under 'General signs and symptoms NEC' ('High-pitched crying') and 17 under 'Peripheral nervous system disorders congenital' ('Paroxysmal extreme pain disorder') were reported in a specific country or region. However, no consistent pattern of key variables was observed to support causality association. The 35 congenital vascular anomalies included various vascular malformations which poses a limitation to the study's scope since they were diagnosed in adults rather than neonates. These diagnoses may also be linked to information recorded in the parent child report [38], despite the exclusion of ICSRs under 12 years of age.

Although non-site-specific embolism and thrombosis are considered an SDR in a limited number of cases (all PT postpartum thrombosis), two in five of the ICSRs were supported by ultrasound and magnetic resonance imaging (MRI). During pregnancy, the risk of venous cerebral thrombosis, deep vein thrombosis (DVT) and pulmonary embolism is higher than in the postpartum period compared with the non-pregnant population [39]. Vaccine-induced immune thrombotic thrombocytopenia (VITT) has been more commonly associated with viral vector DNA vaccines such as AstraZeneca (Vaxzevria) [40, 41] and Johnson & Johnson (Ad26.COV2.S) [42], typically occurring within 5–30 days of vaccination [43]. A comprehensive systematic review showed that the majority of the patients with cerebral venous sinus thrombosis (CVST) and VITT following these COVID-19 vaccines were women whose symptoms occurred within 1 week of the first dose of vaccine (range 4–19 days) [44]. Although pregnant women have an increased risk of thromboembolism due to risk factors related to the pathophysiology of pregnancy [39], the systematic review by Pischel et al. found no causal association of adenovirus-based vaccine and thrombosis with thrombocytopenia syndrome (TTS) in clinical trials with pregnant women [45]. Raffetti et al. reported a contrasting finding, observing a higher

incidence rate ratio of maternal venous thromboembolism in pregnant women who received the COVID-19 viral vector vaccine, but not the COVID-19 mRNA vaccine, compared with unvaccinated women. The adjusted hazard ratios were 1.54 (95% CI 1.10–2.16) for the viral-vector vaccine and 1.02 (95% CI 0.70–1.50) for the mRNA vaccines [46]. This aligns with our finding of the SDR 'non-site specific embolism and thrombosis' HLT associated with viral vector-based/protein subunit COVID-19 vaccines. Thus, our findings enhance a better understanding of current and limited knowledge of embolism and thrombosis associated with COVID-19 vaccines in pregnant women.

By utilizing a novel method that integrated large spontaneous reporting datasets from the VAERS and EV, we analysed the most frequently reported AEs classified in MedDRA PT and HLT for both COVID-19 and influenza vaccines through an adapted algorithm to identify pregnancy-associated ICSRs. Our findings suggest that although rare, embolism and thrombosis events may be safety signals associated with COVID-19 viral vector-based/protein subunit vaccination in pregnant women. Therefore, this safety signal of disproportionate reporting warrants further assessment in vaccine safety studies to assess the risk of thromboembolic events in pregnant and/or postpartum women who received COVID-19 vaccines.

It is important to acknowledge the limitations of this study. The pregnancy algorithm used to [18] identify pregnancy-related ICSRs in VAERS and EV inadvertently selected some ICSRs related to congenital vascular anomalies. These cases were subsequently deemed to fall outside the scope of the study's objective, potentially reflecting the limitation of the adapted algorithm, which does not achieve 100% precision of the algorithm. This limitation stems from the fact that the original algorithm, from which it was adapted, also has a positive predictive value of 90% [18]. As the numbers of ICSRs of some HLTs are relatively low in the pregnancy ICSRs of this study, PRR values may be highly variable. Therefore, HLTs with less than three ICSRs were not assessed in this study due to the limitations of the PRR method. Although the analysis included a relatively large number of concurrent vaccine-HLT combinations, we did not perform multiplicity correction. There is also a potential risk of reporting bias owing to lawsuit action; the direct verification of a cluster of eligible ICSRs with lawyer involvement was not feasible owing to the limitations in the reporting source of VAERS and EV forms. The Weber and notoriety effect might have impacted the reporting rates of ICSRs associated with COVID-19 vaccines. The limitations in key variables of the case-by-case analysis may have affected the causality assessment of this research.

5 Conclusions

We identified a signal of disproportionate reporting (non-site-specific embolism and thrombosis) associated with viral vector-based/protein subunit COVID-19 vaccines through disproportionality analysis, despite limitations such as the precision of pregnancy-related ICSRs and the high proportion of COVID-19 mRNA vaccines. It is imperative to reinforce that this represents a hypothesis-generating signal rather than definite evidence of causal association between COVID-19 vaccine and this AE. Therefore, we recommend conducting a safety study to compare the risk of embolism, thromboembolism and haemorrhage/coagulation disorders during pregnancy and after giving birth. This study aims to assess whether a specific COVID-19 vaccine type and/or pregnancy trimester vaccination increases the risk of these events.

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Declarations

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Conflicts of interest Leonardo Roque-Pereira is an employee of Roche/Genentech. Nonetheless, this paper only reflects the personal views of the stated authors. Eugene Van Puijenbroek is an Editorial Board Member of the journal *Drug Safety*. Eugene Van Puijenbroek was not involved in the selection of peer reviewers for the manuscript nor any of the subsequent editorial decisions. The other authors have no conflicts of interest to declare.

Ethical Approval No ethics approval was required for this study as it includes essentially only public data transformation. It should be noted that the original data are either publicly available, or data are anonymized and cannot be linked to a patient. An independent quality check has been carried out by Utrecht Medical Centre University to ensure compliance with legislation and regulations (regarding informed consent procedure, data management, privacy aspects and legal aspects). This study does not fall under the scope of the Dutch Medical Research Involving Human Subjects Act (WMO) and therefore does not require approval from an accredited MREC in the Netherlands.

Consent to Participate This study includes only anonymized and publicly available patient-related data.

Consent for Publication Not applicable.

Availability of Data and Materials The raw dataset from VAERS is available in the public domain. The raw data from EudraVigilance were provided by the European Medicines Agency (EMA) after a formal request. Therefore, the authors made some data available in the supplementary materials, omitting the report ID. The Electronic

Supplementary Materials/Online Resources can be accessed in the following data repository: Roque-Pereira, L. (2025). Online Resources/Supplementary Materials for the article: Comparison of adverse events in pregnant persons receiving COVID-19 and influenza vaccines: a disproportionality analysis using combined data from US VAERS and EudraVigilance spontaneous report databases. Zenodo. https://doi.org/https://doi.org/10.5281/zenodo.1497683.

Code Availability MedDRA Dictionary version 27.0 was used for the classification of Preferred Terms into the High-Level Group Terms. All data processing and statistical analysis were performed using R version 4.3.1, with the package 'PhViD' and OpenEBGM [1]. A virtual folder titled Digital Research Environment (DRE) was created on 30 January 2024.

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Authors and Affiliations

Leonardo Roque-Pereira[1] · Malede Mequanent Sisay[1] · Comfort K. Ogar[2] · Carlos E. Durán[1] · Eugene van Puijenbroek[3,5] · Daniel Weibel[1] · Katia Verhamme[4] · Miriam Sturkenboom[1]

✉ Leonardo Roque-Pereira
L.RoquePereira@umcutrecht.nl

Malede Mequanent Sisay
m.m.sisay@umcutrecht.nl

Comfort K. Ogar
c.k.ogar@uu.nl

Carlos E. Durán
C.E.DuranSalinas@umcutrecht.nl

Eugene van Puijenbroek
e.vanpuijenbroek@lareb.nl

Daniel Weibel
D.M.Weibel@umcutrecht.nl

Katia Verhamme
k.verhamme@erasmusmc.nl

Miriam Sturkenboom
M.C.J.Sturkenboom@umcutrecht.nl

[1] Department of Data Science and Biostatistics, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, the Netherlands

[2] Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, the Netherlands

[3] PharmacoTherapy, Epidemiology, Economics, University of Groningen, Groningen Research Institute of Pharmacy, Groningen, the Netherlands

[4] Department of Medical Informatics, Erasmus University Medical Center, Rotterdam, the Netherlands

[5] Pharmacovigilance Centre Lareb, 's-Hertogenbosch, the Netherlands