Drugs - Real World Outcomes (2023) 10:263–270
https://doi.org/10.1007/s40801-023-00355-5

ORIGINAL RESEARCH ARTICLE

Myopericarditis Associated with the Novavax COVID-19 Vaccine (NVX-CoV2373): A Retrospective Analysis of Individual Case Safety Reports from VigiBase

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Accepted: 30 January 2023 / Published online: 14 February 2023

Abstract

Background Myocarditis and pericarditis have been associated most notably with mRNA vaccines, but the association with a recently authorized adjuvated vaccine (NVX-CoV2373) is controversial.

Objective The aim was to analyze the cases of myocarditis and pericarditis in association with NVX-CoV2373 reported to the World Health Organization (WHO) global database of individual case safety reports (ICSRs) for drug monitoring (VigiBase), applying disproportionality analyses.

Patients and methods The main characteristics of the ICSRs reporting myopericarditis with NVX-CoV2373 have been summarized. Reporting odds ratios (RORs) as a measure of disproportionality for reported myopericarditis (November 1967–August 2022) have been calculated for NVX-CoV2373; mRNA and adenoviral vector-based vaccines were also included as a reference.

Results In total, 61 ICSRs included NVX-CoV2373. Most of the reports originated in Australia (50; 82.0%); 24 (39.3%) were considered serious. None of them were fatal. The median age of individuals was 35.5 years old, and most were males (38; 62.3%). Chest pain was the most common co-reported event 43 (70.5%). The median induction period was 3 days after immunization. Increased disproportionality for myopericarditis was found for NVX-CoV2373 (ROR 14.47, 95% confidence interval [CI] 11.22–18.67) and mRNA vaccines: BNT162b2 (ROR 17.15, 95% CI 16.88–17.42) and mRNA-1273 (ROR 6.92, 95% CI 6.77–7.08). Higher values were found in males. The adenoviral vector-based vaccine Ad26.COV2.S showed slightly increased disproportionality (ROR 1.83, 95% CI 1.70–1.98), whereas no increased disproportionality was found for ChAdOx1.

Conclusions NVX-CoV2373 vaccine showed a similar increased disproportionality as mRNA vaccines. More evidence from controlled studies is necessary; however, a precautionary approach is warranted. Healthcare professionals should be aware of the potential occurrence of myopericarditis with this new vaccine.

Key Points

Data from the World Health Organization (WHO) Program for International Drug Monitoring database (VigiBase) were examined to calculate reporting odds ratios (RORs) for reporting of myopericarditis with NVX-CoV2373 vaccine, relative to other vaccines and drugs.

NVX-CoV2373 and mRNA vaccines were associated with significantly elevated RORs for myopericarditis and higher values for males.

Healthcare professionals should be aware of the potential occurrence of myopericarditis associated with this vaccine.

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1 Introduction

The NVX-CoV2373 coronavirus disease 2019 (COVID-19) vaccine (Novavax) is a new adjuvated protein-based vaccine combining the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike protein with Matrix-M adjuvant, recently authorized for emergency use by the Food and Drug Administration (FDA), to prevent COVID-19 in individuals 12 years of age and older [1]. The vaccine was previously authorized in Australia, Canada, UK and the European Union [2].

Due to clinical trial evidence, the FDA issued a warning for increased risks of myocarditis and pericarditis, which was included in the Fact Sheet for Healthcare Providers [3]. Conversely, no warning nor any mention of the risk of myocarditis or pericarditis is available in the Summary of Product Characteristics (SmPC) issued by the European Medicines Agency (EMA) [4]. Myocarditis and pericarditis were early signals associated with mRNA vaccines that emerged in Israel on 2021 [5, 6]. Since then, the causality evidence has accumulated, and both mRNA vaccines, BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna), have listed these events in their product label.

Misalignment of regulatory decisions between regulatory agencies may suggest the presence of conflicting evidence. The aim of the present study was to describe and analyze the cases of myocarditis and pericarditis with COVID-19 vaccines reported to the World Health Organization (WHO) global database of individual case safety reports (ICSRs) applying disproportionality analysis.

2 Methods

We searched in the WHO global database of ICSRs (VigiBase) for ICSRs from inception on November 14, 1967, to August 23, 2022. VigiBase is maintained and developed on behalf of the WHO by the Uppsala Monitoring Centre (UMC), situated in Uppsala, Sweden (https://www.who-umc.org/). We utilized a de-duplicated dataset version of VigiBase including 31,703,998 ICSRs (database version 28/8/2022). The ICSRs were accessed using the VigiLyze tool.

The following COVID-19 vaccines of interest were considered in the searches: NVX-CoV2373 (COVID-19 vaccine prot. subunit [NVX CoV 2373]), Pfizer-BioNTech (Tozinameran; active ingredient variant), Moderna (COVID-19 vaccine mRNA; mRNA 1273), Ad26.COV2.S (COVID-19 vaccine NRVV Ad26 [JNJ 78436735]) and AstraZeneca (COVID-19 vaccine NRVV Ad [ChAdOx1 nCoV-19]). The main adverse reaction of interest was myopericarditis and included the following preferred terms of the Medical Dictionary for Regulatory Activities (MedDRA) Terminology (version 25.0; http://www.meddra.org/): "myocarditis" and/or "pericarditis" and/or "myopericarditis." Myopericarditis or the combined outcome "myocarditis or pericarditis" have been used in previous studies [7] and in reports by regulatory agencies and health authorities [8, 9]. Secondarily, we also explore disproportionality for the preferred terms "myocarditis" and "pericarditis" separately.

ICSRs were described in terms of source of report, patient age, gender, seriousness according to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Harmonized Tripartite Guideline on clinical safety regarding definitions and standards for expedited reporting (E2A) [10], and outcome (recovery, fatality). The induction period was calculated (when available) as the time between the start of the drug treatment and the clinical diagnosis of pericarditis and myocarditis in the ICSRs. Co-reported drugs and vaccines were described.

Disproportionality analysis was performed using a case–non-case approach through the calculation of the reporting odds ratio (ROR) and the 95% confidence interval (CI) using Woolf's method [11]. ROR values > 1.0 indicate a higher than expected reporting rate, but do not necessarily mean differences in the risk probability for the adverse reaction [12, 13].

mRNA vaccines served as a positive control for the increased disproportionality of the event since they have been described as causal regarding myopericarditis risk, whereas adenoviral vector-based vaccines ChAdOx1 and Ad26.COV2.S were also included as a reference since they have been also associated with myopericarditis reports, but a definite association has not been established at the moment [14].

To test the consistency of the disproportionality, we performed sensitivity analysis according to the origin of the reports (country/region), according to the period from first to last report received of myopericarditis with NVX-CoV2373, considering ICSRs reported with vaccines only (Anatomical Therapeutic Chemical [ATC] classification group: J07) and according to the dataset type (de-duplicated dataset and non–de-duplicated dataset). All analyses were conducted using Stata version 17.0 MP (Stata- Corp LP, College Station, Texas, USA).

3 Results

Following our search, 61,812 ICSRs of myopericarditis were found. From these, 61 ICSRs included the NVX-CoV2373 vaccine; 45 (73.8%) reported pericarditis, 11 (18.0%) myocarditis, four (6.6%) myopericarditis and one

(1.6%) both terms (myocarditis and pericarditis) (Table 1). For nine ICSRs (14.8%), there was more than one suspected COVID-19 vaccine (i.e., heterologous vaccination regimens including NVX-CoV2373 and other suspected COVID-19 vaccines): five (55.6%) indicated mRNA-1273 vaccine (Moderna) and four (44.4%) BNT162b2 vaccine (Pfizer-BioNTech). In four cases, NVX-CoV2373 was utilized as a booster: two were administered after mRNA-1273 and two after BNT162b2. Only three ICSRs (4.9%) mentioned concomitant medication (other than vaccines): tranexamic acid, cannabidiol and flecainide. Twenty-four reports (39.3%) were considered serious: 19 caused/prolonged hospitalization, three were life-threatening, one was disabling/incapacitating and 11 were considered to pose other medically important conditions (note that the same report can be reported with more than one seriousness criterion). None of them were fatal. Of the 32 ICSRs with available information on outcome, at the time of the study, 20 persons had failed to recover from the adverse reaction, eight were recovering and only four had recovered (one of them with sequelae). The median induction period for myopericarditis from vaccination (after the most recent immunization) estimated from 40 ICSRs was 3 days (interquartile range [IQR] 1–11). Most of the reports originated in Australia (50; 82.0%), followed by European countries: Germany (6; 9.8%), France (2; 3.3%) and Italy (1; 1.6%). Two ICSRs originated in the United States (US) (2; 3.3%) (Table 1).

The median age of the patients was 35.5 years old (IQR 28–47). Most of the reports involved males (38; 62.3%). The ICSRs included a median of five adverse reactions (IQR 2–9); ten ICSRs reported exclusively myopericarditis. "Chest pain" and "chest discomfort" were common co-reported adverse events (43 [70.5%] and nine [14.8%], respectively), followed by heart rate and rhythm anomalies (palpitations [14; 23.0%] and tachycardia [7; 11.5%]), dyspnea (15; 24.6%), arthralgia (11; 18.0%), dizziness (10; 16.4%) and lethargy (10; 16.4%). A complete list of co-reported events is available in the "Supplementary Appendix" (see the electronic supplementary material).

Overall, an increased disproportionality for myopericarditis was found for the NVX-CoV2373 vaccine (ROR 14.47, 95% CI 11.22–18.67) and the mRNA vaccines: BNT162b2 (ROR 17.15, 95% CI 16.88–17.42) and mRNA-1273 (ROR 6.92, 95% CI 6.77–7.08). No increased disproportionality was found for the adenoviral vector-based vaccine ChAdOx1 (ROR 0.80, 95% CI 0.76–0.85) (Table 2). Ad26.COV2.S registered increased disproportionality with a lesser magnitude than mRNA vaccines and NVX-CoV2373. Consistent results were found in males and females, with the highest disproportionality values for Pfizer-BioNTech and NVX-CoV2373 vaccines (Table 3). Disproportionality for the NVX-CoV2373 vaccine was found in the age groups 18–44 and 45–65 in both sexes, but with higher values in males (Table 4). Disproportionality was found also for the preferred terms "myocarditis" and "pericarditis" considered individually (Table 1). Similar results were found in sensitivity analysis when restricting the database to vaccine-only reports, restricting the study period to the reporting period of myopericarditis with NVX-CoV2373 vaccine, or when excluding data from Australia (the country that provided more reports of interest), USA or European countries. However, when restricting the analyses to ICSRs reporting vaccines only, the NVX-CoV2373 and mRNA vaccines

Table 1 Characteristics of the ICSRs of associated myopericarditis and NVX-CoV2373 vaccine collected from VigiBase (through August 23, 2022)

	Number	%
Reporting Country		
Australia	50	82.0
Germany	6	9.8
France	2	3.3
United States of America	2	3.3
Italy	1	1.6
Reporters		
Physician	13	21.3
Pharmacist	2	3.3
Other health professional	1	1.6
Consumer/non-health professional	22	36.1
Unknown	23	37.7
Reporting month		
Mar 2022	22	36.1
April 2022	17	27.9
May 2022	4	6.6
Jun 2022	6	9.8
Jul 2022	8	13.1
Aug 2022	4	6.6
Sex		
Male	38	62.3
Female	23	37.7
Age at onset, years		
18–44	29	63.9
45–64	17	27.9
65–74	2	3.3
Unknown	3	4.9
Adverse reaction		
Myocarditis	11	18.0
Pericarditis	45	73.8
Myopericarditis	4	6.6
Myocarditis and pericarditis	1	1.6
Seriousness		
Non-serious	37	60.7
Serious	24	39.3

ICSR individual case safety report

Table 2 Reporting odds ratio (ROR) values for myocarditis, pericarditis myopericarditis and COVID-19 vaccines (overall)

	Overall (both sexes)		ROR (95% CI)
	Cases/non-cases		
	Exposed	Non-exposed	
Myocarditis			
NVX-CoV2373	12/2150	33,897/31,668,039	5.21 (2.96–9.20)
mRNA vaccines			
BNT162b2	18,922/2,208,001	14,987/29,462,188	16.85 (16.49–17.21)
mRNA-1273	5683/820,020	28,226/30,850,169	7.57 (7.36–7.79)
Adenoviral vector-based			
Ad26.COV2.S	374/187,301	33,535/31,482,888	1.87 (1.69–2.08)
ChAdOx1	515/832,776	33,394/30,837,413	0.57 (0.52–0.62)
Pericarditis			
NVX-CoV2373	46/2116	27,825/31,674,111	24.75 (18.47–33.15)
mRNA vaccines			
BNT162b2	16,207/2,210,716	11,664/29,465,511	18.52 (18.08–18.97)
mRNA-1273	3575/822,128	24,296/30,854,099	5.52 (5.33–5.72)
Adenoviral vector-based			
Ad26.COV2.S	285/187,390	27,586/31,488,837	1.74 (1.54–1.95)
ChAdOx1	733/832,558	27,138/30,843,669	1.00 (0.93–1.08)
Myopericarditis			
NVX-CoV2373	61/2101	61,751/31,640,085	14.47 (11.22–18.67)
mRNA vaccines			
BNT162b2	34,660/2,192,263	27,152/29,449,923	17.15 (16.88–17.42)
mRNA-1273	9574/816,129	52,238/30,826,057	6.92 (6.77–7.08)
Adenoviral vector-based			
Ad26.COV2.S	667/187,008	61,145/31,455,278	1.83 (1.70–1.98)
ChAdOx1	1309/831,982	60,503/30,810,204	0.80 (0.76–0.85)

CI confidence interval, *COVID-19* coronavirus disease 2019

remained with a statistically significant increased disproportionality (Supplementary Appendix).

4 Discussion

In this global database of ICSRs including more than 33 million reports, an increased disproportionality signal was found for NVX-CoV2373 vaccine in line with the mRNA vaccines, and the Pfizer-BioNTech vaccine in particular. The signal was consistent when taking into account sex and age. The increased disproportionality remained statistically significant in the sensitivity analysis after excluding Australian data, which made up most of the reports. The disproportionality was slightly more elevated in males and consistent across different analyses.

Myocarditis after immunization has been described with live vaccinia virus vaccines [15] and more recently also with the COVID-19 vaccines [16, 17]. Among COVID-19 vaccinations, the highest incidence of myopericarditis has been observed with mRNA vaccines [7]. Evidence of risk from controlled studies for non–mRNA vaccines is scarce, although a self-controlled case series found excess risk of myopericarditis (and not pericarditis) after the first dose of ChAdOx1 vaccine [18, 19]. However, major evidence of a risk association comes predominantly from studies with mRNA vaccines. In a hospital-based case–control study performed in France, an increased risk of myocarditis associated with BNT162b2 and mRNA-1273 vaccines was identified in the week after immunization (first or second dose); moreover, an increased risk of pericarditis was identified in the week after the second dose [20]. Another large cohort study, including 23 million participants from four Nordic countries, found a higher risk of myopericarditis associated with BNT162b2 and mRNA-1273 vaccines, showing an incident risk ratio (IRR) of 6.57 and 1.75, respectively [21]. Recently, a retrospective cohort study using claims databases in the US found an increased risk of myopericarditis after COVID-19 mRNA vaccination, with IRRs of 1.71 and 2.17 after the second dose for BNT162b2 and mRNA-1273, respectively. No statistically significant risk differences regarding myopericarditis among the two mRNA vaccines were found [22].

Table 3 Reporting odds ratio (ROR) values for myocarditis, pericarditis myopericarditis and COVID-19 vaccines by sex

	Males		ROR (95% CI)	Females		ROR (95% CI)
	Cases/non-cases			Cases/non-cases		
	Exposed	Non-exposed		Exposed	Non-exposed	
Myocarditis						
NVX-CoV2373	7/643	22,569/11,636,777	5.61 (2.66–11.82)	5/1482	10,732/18,160,248	5.71 (2.37–13.74)
mRNA vaccines						
BNT162b2	12,557/687,699	10,019/10,949,721	19.96 (19.44–20.49)	6253/1,491,365	4484/16,670,365	15.59 (15.00–16.20)
mRNA-1273	4167/258,868	18,409/11,378,552	9.95 (9.62–10.29)	1479/554,733	9258/17,606,997	5.07 (4.80–5.36)
Adenoviral vector-based						
Ad26.COV2.S	274/85,998	22,302/11,551,422	1.65 (1.46–1.86)	96/98,776	10641/18,062,954	1.65 (1.35–2.02)
ChAdOx1	280/252,088	22,296/11,385,332	0.57 (0.50–0.64)	224/558,417	10,513/17,603,313	0.67 (0.59–0.77)
Pericarditis						
NVX-CoV2373	29/621	14,689/11,644,657	37.02 (25.50–53.74)	17/1470	12,668/18,158,312	16.58 (10.27–26.75)
mRNA vaccines						
BNT162b2	8537/691,719	6181/10,953,559	21.87 (21.16–22.60)	7601/1,490,017	5084/16,669,765	16.73 (16.14–17.33)
mRNA-1273	2018/261,017	12,700/11,384,261	6.93 (6.61–7.26)	1547/554,665	11,138/17,605,117	4.41 (4.18–4.65)
Adenoviral vector-based						
Ad26.COV2.S	198/86,074	14,520/11,559,204	1.83 (1.59–2.11)	86/98,786	12,599/18060,996	1.25 (1.01–1.54)
ChAdOx1	370/251,998	14,348/11,393,280	1.17 (1.05–1.29)	350/558,291	12,335/17,600,791	0.89 (0.80–0.99)
Myopericarditis						
NVX-CoV2373	38/612	37,552/11,621,794	19.22 (13.85–26.67)	23/1464	23,130/18,147,850	12.33 (8.16–18.61)
mRNA vaccines						
BNT162b2	20,980/679,276	16,610/10,943,130	20.35 (19.94–20.77)	13,500/1,484,118	9653/16,665,196	15.70 (15.30–16.12)
mRNA-1273	6458/256,577	31,132/11,365,829	9.19 (8.94–9.44)	3061/553,151	20,092/17,596,163	4.85 (4.67–5.03)
Adenoviral vector-based						
Ad26.COV2.S	480/85,792	37,110/11,536,614	1.73 (1.58–1.89)	182/98,690	22,971/18,050,624	1.45 (1.25–1.68)
ChAdOx1	686/251,682	36,904/11,370,724	0.84 (0.78–0.91)	600/558,041	22,553/17,591,273	0.84 (0.77–0.91)

CI confidence interval, *COVID-19* coronavirus disease 2019

Table 4 Reporting odds ratio (ROR) values of myopericarditis with NVX-CoV2373 by sex and age group

	Males		ROR (95% CI)	Females		ROR (95% CI)
	Cases/non-cases			Cases/non-cases		
	Exposed	Non-exposed		Exposed	Non-exposed	
Age						
< 18	0/9	3245/1,129,162	–	0/5	905/1,083,197	-
18–44	29/292	16,516/2,174,668	13.08 (8.93–19.16)	10/701	7991/4,451,985	7.95 (4.26–14.84)
45–65	7/224	5434/2,958,098	17.02 (8.02–36.13)	9/566	5423/4,732,946	13.88 (7.18–26.82)
> 65	0/43	2485/2,712,906	–	2/156	2261/3,640,180	20.64 (5.11–83.32)[a]

CI confidence interval

[a]Caution should be taken with the interpretation of this ROR value since the number of reports with myopericarditis is less than < 3

Consistent with the previous studies, we found both mRNA vaccines associated with a high disproportionality for myopericarditis. On the other hand, the induction period after immunization with NVX-CoV2373 was 3 days, similar to the mRNA-induced myocarditis, which occurred in the first days after the most recent immunization [23].

The pivotal randomized clinicals trials with the NVX-CoV2373 vaccine included North American and British populations [24, 25]. Two cases of myocarditis were identified in 30,058 vaccinated individuals and one case among 19,982 who received placebo [26], which would account for a non-statistically significant increase of myocarditis risk (relative risk 1.33, 95% CI 0.12–14.66). Moreover, during the extensions of the clinical trials, three additional cases of myocarditis were identified in immunized patients. This evidence was differently interpreted. The FDA considered a precautionary approach and assumed the risk to be certain since no cases of myocarditis were detected in any of the mRNA vaccine trials [27]. On the other hand, the EMA did not consider myocarditis as an "identified risk" since the incidence of myocarditis of three cases per 14,513 person-years would not be higher than the baseline risk of myocarditis in the general population (background rate) estimated at 1.6-4.6 per 14,513 person-years from European data (EU-Access study) [26]. However, caution should be taken when using background rates from different populations to rule out vaccine risks since there is considerable heterogeneity between geographies and databases that can lead to unreliable inferences [28].

The mechanism of action for vaccine-induced myopericarditis remains to be elucidated. It has been observed that vaccines triggering an intense immune response such as mRNA vaccines could be associated with a higher risk of myocarditis [21]. Several mechanisms affected by the immune–genetic background, age and sex have been hypothesized to explain the risk of myocarditis with mRNA vaccines. First, it could be due to mRNA immune reactivity; second, the Spike protein antigen could induce a cross-reaction of SARS-CoV-2 spike glycoproteins with myocardial contractile proteins; and, lastly, hyperimmunity could burst due to hormone-related factors contributing to the sex-specific differences observed in both COVID-19 mRNA vaccines (more risk in young males) [29, 30]. The mRNA vaccines use a lipid nanoparticle component that encapsulates the mRNA strand encoding the S-protein sequence and which may confer immune reactivity. Interestingly, the NVX-CoV2373 also uses a nanoparticle delivery vehicle to assemble in S-proteins. On the contrary, no nanoparticles are used in the adenoviral vector-based vaccines ChAdOx1 and Ad26.COV2.S [31]. More research would be needed to understand the role of nanoparticles in the potential risk of vaccine-induced myocarditis. The highest disproportionality values were observed in males. The reason for the male predominance in myopericarditis is unknown. Testosterone is thought to play a role, via a combined mechanism of inhibition of anti-inflammatory cells and enhancement of a T helper type 1 (Th1) immune response, whereas estrogen has inhibitory effects on proinflammatory T cells, with a decrease in cell-mediated immune responses [32]. A higher disproportionality was found in older women; in this regard, it has been described that postmenopausal women show a higher incidence of pericarditis [33]. No evidence towards an increased disproportionality trend was found for younger ages with NVX-CoV2373. Caution should be taken with this observation since the lack of reports in non-adults made impossible a complete analysis on younger ages.

Although an important proportion of the cases were life-threatening, none of them were fatal. Other reported cases for mRNA vaccines have shown a low fatality rate [14]. It is worth to note that at least one-third of the cases were reversible and that a greater risk of hospitalization and death has been observed in association with COVID-19 infection than with COVID-19 vaccination [18, 19].

4.1 Limitations

Our study also has several limitations. The data source for this study is a spontaneous report database from which no definitive causation associations can be drawn. There are other inherent limitations of the passive pharmacovigilance systems, such as a lack of denominators and underreporting, which have been described elsewhere [34]. On the other hand, the capacity to identify potential disproportionality signals is also increased in a global pharmacovigilance database over smaller national databases [35]. Moreover, the possibility of duplicate reporting cannot be ruled out; nevertheless, we used a de-duplicated dataset version to minimize this potential bias. Some patients did not recover from the adverse reaction, and at the moment of the study realization, we did not have latter updates regarding follow-up of outcomes, and this might have led to outcomes not being identified (i.e., recoveries and fatalities). Although common symptoms of myopericarditis such as chest pain were often co-reported, other relevant information such as viral testing for myocarditis was lacking from the reports. On the other hand, myocarditis events may have been missed because of inaccuracies in the coding of the events or diagnostic misclassification. In addition, potential bias can also occur, such as notoriety bias due to the media attention that myocarditis has attained. However, the consistency of the disproportionality was evaluated through different sensitivity analyses.

5 Conclusions

In conclusion, myopericarditis associated with COVID-19 vaccines seem to be an adverse reaction of a different frequency according to the type of vaccine. The new NVX-CoV2373 vaccine shows an increased disproportionality for myopericarditis similar to mRNA vaccines. More evidence

from controlled studies is necessary; however, a precautionary approach is warranted. Healthcare professionals should be aware of the potential occurrence of myopericarditis with this new vaccine.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40801-023-00355-5.

Acknowledgements We thank the Uppsala Monitoring Centre (UMC; Uppsala, Sweden) and the Pan American Network of Pharmacovigilance for their valuable support. We also thank Dr. Salvador Alvarado from the UMC for the helpful suggestions and comments on sensitivity analysis.

Declarations

Funding CIBERSAM, Valencia, Spain provided the necessary funds for the publication of this research.

Conflict of interest The authors declare that they have no conflict of interest. The opinions expressed in this article are those of the authors and do not necessarily reflect the views of the Pan American Health Organization (PAHO), its Board of Directors or the countries they represent.

Ethics approval Information on all cases gathered from the VigiBase database of individual case safety reports is deidentified, and ethical approval is not needed.

Consent to participate Not applicable.

Consent for publication Not applicable.

Availability of data and materials The dataset used in this study is publicly available at the following URL: https://osf.io/g958w/?view_only=1994d666ab7c4a09a0d413dbdfd18cc0**.**

Code availability Not applicable.

Author contributions DMS and JLC conceived and designed the study. DMS and JFM investigated and analyzed the data. DMS and MTI drafted the manuscript. RT and JFM reviewed the manuscript and supervised the work. All authors read and approved the final manuscript.

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