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No disproportionate reporting of inflammatory arthritis following COVID-19 vaccination: a pharmacovigilance study using VAERS data

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ABSTRACT

Objectives: To assess whether inflammatory arthritis was disproportionately reported as an adverse event following COVID-19 vaccination compared to other vaccines, using data from the Vaccine Adverse Event Reporting System (VAERS).

Methods: We performed a retrospective analysis of VAERS data from December 2020 to December 2024, focusing on inflammatory arthritis as adverse event following administration of the BNT162b2, mRNA-1273, and Ad26.COV2.S vaccines. Data on vaccine dose, demographic characteristics, and symptom onset were collected. A structured query based on MedDRA terms was used to identify the reports of inflammatory arthritis. Crude reporting rate of arthritis was calculated. Disproportionality analysis was conducted using the proportional reporting ratio (PRR), reporting odds ratio (ROR), and Bayesian information component (IC), initially comparing COVID-19 vaccines to all other vaccines in VAERS, and then with stratification by age, sex, and comparator vaccine (influenza and herpes zoster).

Results: Among 651,850 valid reports, 5580 events of inflammatory arthritis were identified, yielding a CRR of 13.8 cases per million doses administered. Most reports involved females (72 %) and occurred within a median of 2 days post-vaccination. In the overall population, inflammatory arthritis was not disproportionately reported after COVID-19 vaccination (PRR: 0.999, 95 % CI: 0.883 to 1.130; ROR: 0.878, 95 % CI: 0.777 to 0.994; IC: –0.008, 95 % CrI: –0.046 to 0.030). Disproportionality analysis in subgroups confirmed the absence of signal across age and sex strata.

Conclusion: Our findings demonstrate that there is no disproportionate reporting of inflammatory arthritis following COVID-19 vaccination compared to other vaccines, supporting the overall safety of COVID-19 vaccines.

Introduction

Rheumatoid arthritis, psoriatic arthritis, and axial spondyloarthritis represent the most common forms of inflammatory arthritis [1–3]. These conditions typically present with inflammation of synovial, tenosynovial, or entheseal tissues [4]. In the United States, 1 % to 2 % of people suffer from inflammatory arthritis, which results from intricate relationships between environmental risk factors and genetic predisposition [3,5,6]. Apart from these primary forms, individuals may also acquire other types, like reactive arthritis, which is caused by an infection usually of the gastrointestinal or genitourinary tract [7,8]. Additionally, there have been cases of inflammatory arthritis occurring post-immunization, predominantly following influenza vaccination, albeit not exclusively restricted to it [9,10]. An analysis of the Vaccine Adverse Event Reporting System (VAERS) found that individuals who received the herpes zoster vaccine had 2.2 times the odds of developing

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arthritis compared to those who were unexposed [11]. Moreover, a different VAERS-based investigation found a link between adult hepatitis B or rubella vaccinations and persistent arthritis that lasted longer than a year [12].

The VAERS database was established in 1990 by the Centers for Disease Control and Prevention (CDC) to facilitate passive surveillance of vaccines approved by the Food and Drug Administration (FDA) [13]. Records of possible side effects after immunizations, including musculoskeletal symptoms like inflammatory arthritis, are gathered in this database. According to the World Health Organization (WHO) definition, an adverse event following immunization (AEFI), is defined as "*any untoward medical occurrence which follows immunization, and which does not necessarily have a causal relationship with the usage of the vaccine. The adverse event may be any unfavourable or unintended sign, abnormal laboratory finding, symptom or disease*" [14]. This concept emphasizes how crucial it is to differentiate vaccine-related adverse effects from coincidental health problems, especially in extensive immunization programs.

Vaccination has been recognized as one of the most important public health interventions, significantly reducing the global burden of infectious diseases [15]. Many life-threatening illnesses, especially those that caused significant childhood mortality, have essentially been eradicated thanks to vaccines since the 1960s, when national immunization programs were widely established and coordinated [16]. The rapid spread of COVID-19, caused by severe acute respiratory syndrome coronavirus (SARS-CoV-2), prompted unprecedented research efforts to develop a global immunization program [17]. The FDA authorized the emergency use of three vaccinations within months of the pandemic outbreak [18]. These included the BNT162b2 (Pfizer Inc/BioNTech SE), the Ad26.Cov2.S (Janssen Pharmaceuticals/Johnson & Johnson), and mRNA-1273 (Moderna Inc) [18].

By lowering mortality and decreasing hospitalizations and admissions to intensive care units, these vaccinations have been crucial in containing the COVID-19 pandemic [19,20]. Since its inception in December 2020, the VAERS database has been gathering reports of AEFIs, including autoimmune and inflammatory disorders [21,22]. With the rapid increase in COVID-19 vaccine administration, particularly in 2021, cases of post-vaccination arthritis have been documented in case reports and surveillance data [23–27]. According to a review of published case reports, 45 patients experienced either a flare in their pre-existing arthritis or a new-onset of arthritis, with most of these cases occurring in the first week following COVID-19 vaccination [24]. Although COVID-19 vaccines have been associated with potentially autoimmune phenomena, the biological mechanisms underlying this immune response remain unclear and manifestations of inflammatory arthritis have received limited attention, with no large-scale analyses conducted to date [28–34].

Using VAERS data, we aimed to examine inflammatory arthritis as an AEFI related to COVID-19 vaccination, by analysing its reporting patterns and conducting disproportionality analyses in comparison with other vaccines. We opted to focus specifically on inflammatory arthritis for multiple reasons. Arthritis represents a clinically significant and reasonably common category of immune-mediated events that can be accurately identified using standardized terminology in pharmacovigilance databases, therefore minimizing heterogeneity and misclassification. Secondly, preliminary pharmacovigilance signals and case reports have repeatedly identified inflammatory arthritis as a post-vaccination occurrence, particularly in relation to COVID-19 immunization [23,24]. Third, arthritis-related adverse events can profoundly affect daily functioning and quality of life, even if temporary, therefore necessitating examination [35]. Ultimately, we sought to deliver a focused analysis that enhances extensive safety investigations by presenting more detailed insights into arthritis-specific reporting trends within the framework of COVID-19 vaccine safety surveillance.

Materials and methods

Data source

VAERS is a publicly available database that allows for the submission of reports by healthcare providers, vaccine recipients, parents or guardians of minor patients, vaccine manufacturers, and regulatory agencies [36]. The reports include de-identified and anonymized information, such as demographics (age, sex, state of residence), medical history, current medications, comorbidities, administered vaccines with dose and lot number, the onset date of adverse events, and a comprehensive clinical description. The information is structured into three distinct datasets: VAERSDATA, VAERSSYMPTOMS, and VAERSVAX. Each report in the VAERS database is assigned a unique identification code, known as the VAERS ID, which allows for the linkage of information across different datasets related to the same adverse event report.

Upon submission, reports undergo a thorough review by trained professionals who utilize the Medical Dictionary for Regulatory Activities (MedDRA) to assign medical terminology. This system is recognized internationally and is clinically validated for classification purposes [37]. Submitting a false VAERS report is a serious offense under federal law, potentially leading to fines and imprisonment [38].

One of the key advantages of VAERS is its ability to detect unexpected patterns or rare adverse events, which may be difficult to identify during vaccines development due to the limited number of trial participants [39–41]. Furthermore, it aids in recognizing possible risk factors associated with these occurrences. The database is completely open for access, and there are no specific permissions needed to analyse its data or disseminate results [31].

Data extraction

The data from VAERS were sourced from the publicly accessible database of the CDC and downloaded in their raw format as CSV files [42]. Data from December 2020 to September 2021 were included in the analysis, as this period corresponds to the administration of the two-dose primary vaccination cycle before the widespread introduction of booster doses. Indeed, COVID-19 vaccinations commenced in December 2020, with the CDC's Advisory Committee on Immunization Practices (ACIP) advising the introduction of a booster dose in the latter part of September 2021 [43–45]. Considering the possibility of survivorship bias, we opted to focus this study on the primary vaccination cycle, since individuals who encountered adverse events during the initial two doses may have been less inclined to receive booster doses [46,47]. However, to ensure a thorough evaluation of inflammatory arthritis as an AEFI related to COVID-19 vaccine, including late events, we incorporated all reports accessible up to December 2024. The VAERSDATA, VAERSSYMPTOMS, and VAERSVAX datasets from 2020 and 2021 were combined using the identification code variable as the connecting element. Records lacking details regarding age, sex, vaccine administration date, or symptom onset date were omitted from the analysis. A systematic search query was subsequently implemented on the dataset to identify reports of inflammatory arthritis. Considering the diverse descriptions of inflammatory arthritis, a thorough compilation of MedDRA Preferred Terms was incorporated into the search. The terms included were: "Inflammatory arthritis", "Arthritis", "Rheumatoid arthritis", "Polyarthritis", "Autoimmune arthritis", "Seronegative arthritis", "Joint swelling", "Joint effusion" and "Synovitis". The selection of MedDRA terms was conducted by three rheumatologists, based on an initial exploratory analysis of the data, expert consensus, and clinical relevance, to guarantee that all pertinent AEFIs of inflammatory arthritis related to COVID-19 vaccination were included. The investigation of reports including at least one of the selected terms was conducted considering all symptoms in the VAERSSYMPTOM dataset.

Handling of duplicate records

Duplicate and multi-entry reports in VAERS were meticulously handled to ensure the precision of the data. Since VAERS permits the documentation of a maximum of five MedDRA-coded symptoms per entry, instances where a patient reported more than five symptoms led to multiple rows associated with the same identification code [48]. These were merged into a single entry in order to consolidate all reported symptoms. Conversely, instances where the same identification code was recorded multiple times with matching patient demographics, vaccination date, symptom onset date, and vaccine dose were identified as genuine duplicate records and subsequently eliminated. Nonetheless, if the same identification code was recorded at different times, the entries were kept distinct, as each report might relate to an adverse event following a different dose [49].

Statistical analysis

In descriptive analysis we considered each single report as a statistical unit. Demographic and vaccination data were reported using mean and standard deviation (SD) or median and interquartile range (IQR) for non-normal data, and absolute and relative frequency. To calculate the crude reporting rate (CRR) of arthritis per million doses, we used official data on the total number of COVID-19 vaccine doses administered in the United States through the end of September 2021, aggregated from CDC sources and covering the three authorized SARS-CoV-2 vaccines [50]. Disproportionality analysis was conducted to evaluate the frequency of inflammatory arthritis reports following COVID-19 vaccination in comparison to other vaccines within the VAERS database. Three measures were employed: the proportional reporting ratio (PRR), the reporting odds ratio (ROR), and the information component (IC) [51–53].

The PRR was determined by comparing the proportion of inflammatory arthritis reports in individuals who received immunization with COVID-19 vaccines to the proportion of inflammatory arthritis in those who received all other vaccines, along with their 95 % confidence intervals (CIs). A signal was deemed statistically significant if the PRR was over 2 and the lower bound of its 95 % CI was above 1. The ROR was calculated by comparing the odds of inflammatory arthritis being reported after COVID-19 vaccination to the odds after all other vaccines. A statistically significant signal was defined as an ROR whose lower bound of the 95 % confidence interval exceeded 1.

Alongside these conventional frequentist approaches, we also implemented the IC, a Bayesian measure that calculates the observed to expected reporting ratio. Unlike methods such as the PRR and the ROR, which rely on CIs derived from repeated sampling, the IC is based on the full probability distribution and uses credible intervals (CrIs) typical of Bayesian models [54]. This allows to account for variability in reporting frequencies, making it particularly effective in detecting rare adverse events. A signal of disproportionate reporting is considered present when the lower bound of the 95 % Crl (IC025) exceeds zero [53].

Initially, disproportionality analyses were performed by comparing reports of inflammatory arthritis after COVID-19 vaccination with those related to all other vaccines in the VAERS database. Subsequently, to control for potential discrepancies in reporting patterns, the disproportionality analyses were stratified by sex and age establishing three age groups: $\leq$40 years, 41–59 years, and $\geq$60 years. Moreover, to evaluate the robustness of our findings we calculated disproportionality comparing COVID-19 vaccines with the herpes zoster and influenza vaccines. Both herpes zoster and influenza vaccines ranked among the most administered vaccines in the general population in VAERS dataset. This comparison was performed specifically in individuals aged $\geq$60 years because this age group represents the primary target population for both vaccines [55,56].

All statistical analyses and graphical visualizations were performed using R Studio (R Foundation for Statistical Computing, Vienna, Austria). Disproportionality analyses were conducted with the "pvda" package, while data visualization was realized using "ggplot2" and "fmsb".

Ethical considerations

Given that VAERS operates as a standard surveillance program aimed at improving immunization initiatives and this study employed de-identified data that are publicly accessible in accordance with CDC regulations, it did not require evaluation by an Institutional Review Board or informed consent [57].

Results

Demographic description

During the study period, a total of 403.2 million doses of COVID-19 vaccines were administered in the United States and 976,752 adverse event reports related to these vaccines were reported in VAERS [50]. After removing duplicate reports, a total of 651,850 reports remained, accounting for 0.002 % of all administered doses. Among these, a total of 5580 reports (47 % BNT162b2; 45 % mRNA-1273; 8 % Ad26.Cov2.S) documented inflammatory arthritis as an AEFI related to COVID-19 vaccination, generating a CRR of 13.8 cases per million administered doses.

Most reports of inflammatory arthritis were relative to females (n = 4029), representing 72 % of the cases. The median age of individuals reporting an AEFI of inflammatory arthritis was 58 years, with an IQR of 46 to 68 years. Data concerning the administered vaccine dose was accessible for 4999 reports. Among these, inflammatory arthritis was observed more frequently following the initial dose, accounting for 56 % of cases. The median duration from the administration of the vaccine to the appearance of inflammatory arthritis was 2 days (IQR 0–15). Stratification by sex revealed a shorter onset interval in females, with a median delay of 2 days (IQR 0–14), compared to 3 days in males (IQR 1–21). The demographic description is shown in Table 1.

The median onset interval exhibited slight variations when the data were stratified according to vaccine type. Reports after the BNT162b2 (Pfizer Inc/BioNTech SE) vaccine had a median onset of 2 days (IQR 0–12), whereas reports following the mRNA-1273 (Moderna Inc) vaccine had a median onset of 3 days (IQR 1–21). Reports related to the Ad26.Cov2.S (Janssen Pharmaceuticals/Johnson & Johnson) vaccine showed a median onset of 2 days (IQR 1–14). Analysing the temporal trends of COVID-19 vaccine doses administered (based on official data aggregated from CDC sources), the total reports of adverse events following COVID-19 vaccination, and the reports of inflammatory arthritis from December 2020 to September 2021, we observed a similar pattern across the three variables (Fig. 1) [50]. The peaks in inflammatory arthritis reports corresponded with periods of higher vaccine administration and overall reporting of AEFIs, indicating a consistent temporal relationship among these measures. Regarding the recovery

Table 1
Demographic description of inflammatory arthritis as an AEFI related to COVID-19 vaccine from December 2020 to September 2021.

Variable	
Reports of adverse events, n	651,850
Reports of inflammatory arthritis, n	5580
Females, n (%)	4029 (72)
Age (years), median (IQR)	58 (46-68)
First dose, n (%)	2816 (56) *
Time from vaccination to onset of inflammatory arthritis (days), median (IQR)	2 (0–15)
Individuals with inflammatory arthritis in their medical history, n (%)	693 (12)

Table 1 legend. IQR: interquartile range; * information available in 4999 cases.

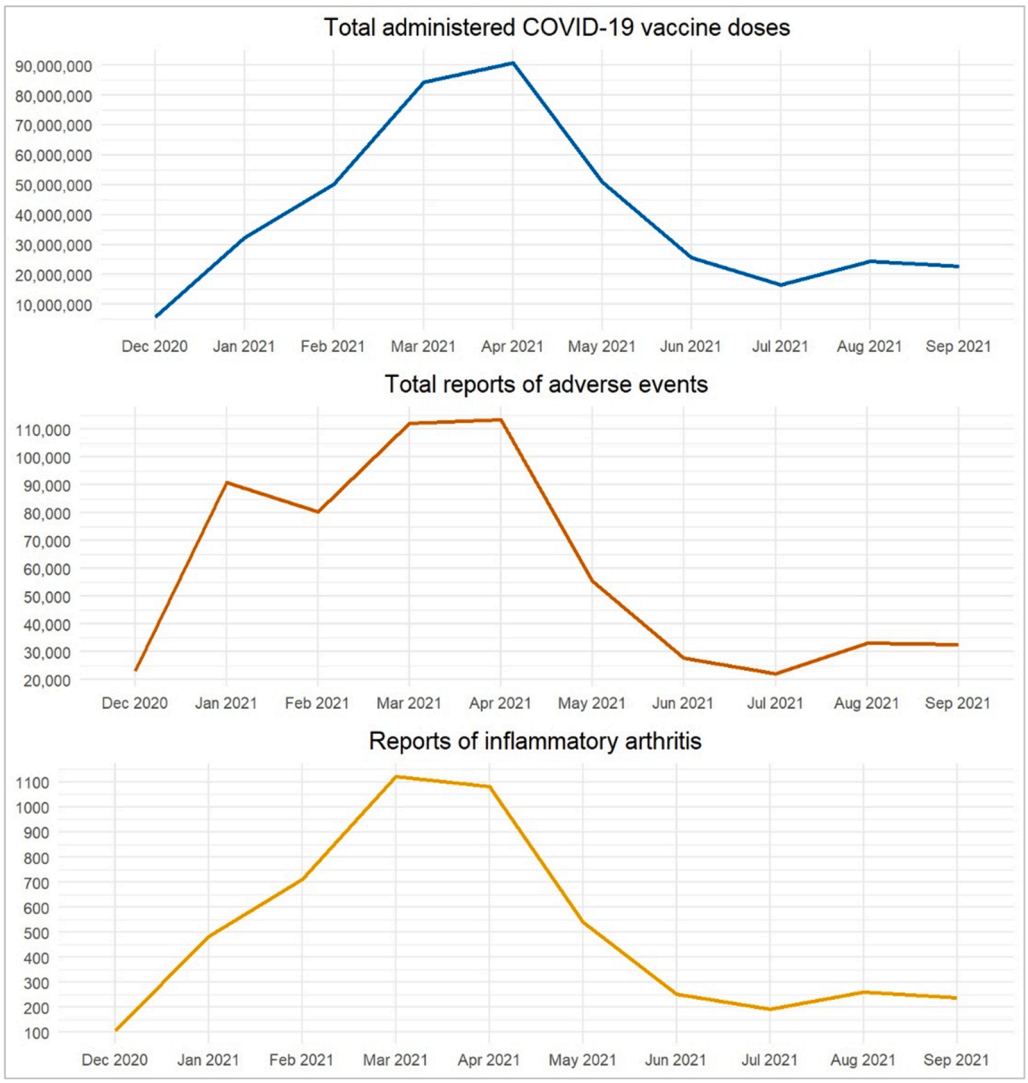

Fig. 1. Temporal trends of doses of COVID-19 vaccine administered, total reports of adverse events following COVID-19 vaccination, and reports of inflammatory arthritis.

status of affected individuals, 79 % of patients did not recover by the time of reporting.

An examination of the medical history data showed that in 693 cases (12 %), the individual had a potentially pre-existing form of inflammatory arthritis, inferred from the presence of the same MedDRA preferred terms used to identify inflammatory arthritis as an adverse event. This indicates that some of these reports could reflect exacerbations of pre-existing arthritis instead of new-onset cases. Comparing individuals with pre-existing arthritis and those without any MedDRA term related to inflammatory arthritis in their medical history, there was no significant difference in the median delay from vaccination to the onset of inflammatory arthritis between the two groups.

Geographic distribution analysis showed that most reports of inflammatory arthritis originated from California ($n = 586$), Florida ($n = 366$), Texas ($n = 299$), New York ($n = 279$), and Michigan ($n = 220$) (Fig. 2). These states consistently reported higher volumes of AEFIs, likely reflecting population size and vaccination coverage. Additionally, we examined the most common MedDRA terms co-reported with arthritis. Most of these terms were related to musculoskeletal pain, including "arthralgia" "peripheral swelling" "pain in extremity", "pain", "fatigue", "myalgia", "gait disturbance," and "mobility decreased" (Fig. 3).

Disproportionality analysis

COVID-19 vaccines vs. all other vaccines

In the overall population, reports of inflammatory arthritis after COVID-19 vaccination were not significantly elevated when compared to reports following all other vaccines. The PRR was 0.999 (95 % CI: 0.883 to 1.130), the ROR was 0.878 (95 % CI: 0.777 to 0.994), and the IC was –0.008 (95 % CrI: –0.046 to 0.030), all of which are below the threshold that indicates a disproportionality signal.

Sex-stratified analyses revealed similar findings. Among males, the PRR was 0.983 (95 % CI: 0.786 to 1.230), the ROR was 0.983 (95 % CI: 0.784 to 1.232), and the IC was –0.001 (95 % CrI: –0.074 to 0.070) showing no significant disproportionality. Among females, lower PRR (0.823, 95 % CI: 0.711 to 0.951) and ROR (0.821, 95 % CI: 0.709 to 0.951) values were observed, indicating that arthritis was reported less frequently following COVID–19 vaccination compared to other vaccines in this group, while the IC was –0.011 (95 % CrI: –0.056 to 0.033). The results of all disproportionality analyses are shown in Table 2.

Age-stratified disproportionality analysis

The analysis of age groups showed no disproportionality in the reporting of arthritis. Among individuals aged 40 years or younger, the PRR was 0.982 (95 % CI: 0.746 to 1.292), the ROR was 0.982 (95 % CI:

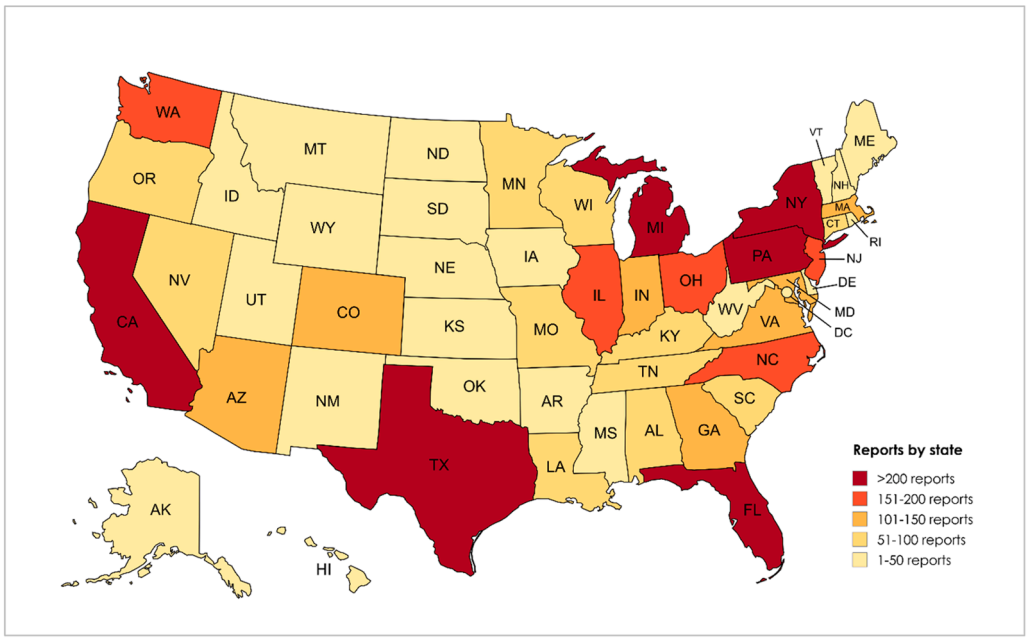

Fig. 2. Distribution of VAERS reports of inflammatory arthritis as an AEFI related to COVID-19 vaccines by state, from December 2020 to September 2021.

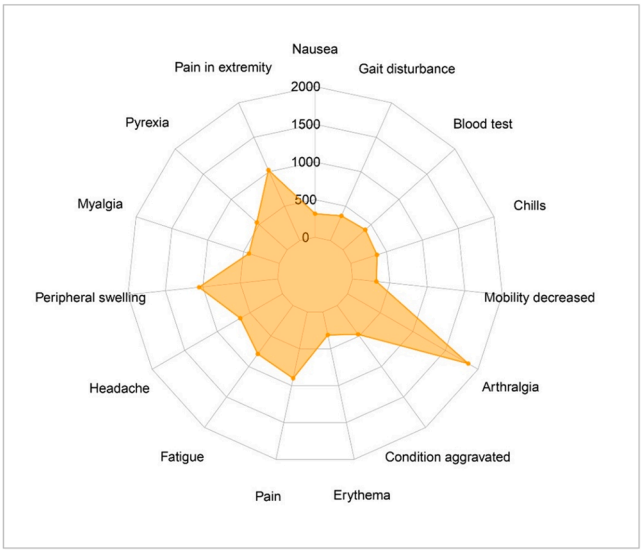

Fig. 3. Frequencies of other adverse events associated with arthritis reports.

0.746 to 1.293), and the IC was –0.002 (95 % CrI: –0.099 to 0.093), indicating no significant association. In this age group, males showed a PRR of 0.663 (95 % CI: 0.451 to 0.976), a ROR of 0.662 (95 % CI: 0.449 to 0.976), and an IC of –0.058 (95 % CrI: –0.257 to 0.127). In contrast, females exhibited a slightly elevated PRR of 1.273 (95 % CI: 0.855 to 1.897), a ROR of 1.274 (95 % CI: 0.854 to 1.901), and an IC of 0.014 (95 % CrI: –0.098 to 0.123). While the point estimates for females were higher than for males, the CIs encompassed the null value, suggesting a lack of statistically significant disproportionality.

In the age group of 41–59 years, there was a lower incidence of arthritis reported after COVID-19 vaccination in comparison to other vaccines. The overall PRR was 0.669 (95 % CI: 0.545 to 0.822), the ROR was 0.666 (95 % CI: 0.541 to 0.820), and the IC was –0.020 (95 % CrI: –0.081 to 0.040). Among males, the PRR was 1.007 (95 % CI: 0.614 to 1.651), the ROR was 1.007 (95 % CI: 0.614 to 1.659) and the IC was 0.000 (95 % CrI: –0.125 to 0.120), indicating no significant signal. Females in this age group exhibited a PRR of 0.599 (95 % CI: 0.478 to 0.750), a ROR of 0.595 (95 % CI: 0.473 to 0.748) and an IC of –0.027 (95 % CrI: –0.098 to 0.043), confirming a lower reporting frequency in this subgroup.

Among individuals aged 60 years or older, the overall PRR was calculated to be 0.783 (95 % CI: 0.653 to 0.939), with the ROR at 0.781 (95 % CI: 0.459 to 0.939) and the IC measured at –0.014 (95 % CrI: –0.071 to 0.041). Males demonstrated a PRR of 0.796 (95 % CI: 0.568 to 1.114), a ROR of 0.794 (95 % CI: 0.565 to 1.116), and an IC of –0.012 (95 % CrI: –0.114 to 0.086). In contrast, females showed a PRR of 0.782 (95 % CI: 0.630 to 0.970), a ROR of 0.779 (95 % CI: 0.626 to 0.970), and an IC of –0.015 (95 % CrI: –0.083 to 0.052).

COVID-19 vaccines vs. influenza and herpes zoster vaccines (≥60 years)

No significant disproportionality was observed when comparing COVID-19 vaccines with influenza vaccines in individuals aged 60 years or older. The overall PRR was 1.207 (95 % CI: 0.650 to 2.239), the ROR was 1.209 (95 % CI: 0.648 to 2.256), and the IC was 0.001 (95 % CI: –0.055 to 0.057). In the male cohort, the PRR was calculated at 1.216 (95 % CI: 0.393 to 3.762), the ROR stood at 1.218 (95 % CI: 0.390 to 3.803), and the IC was determined to be 0.001 (95 % CrI: –0.101 to 0.099). Females exhibited a PRR of 1.206 (95 % CI: 0.576 to 2.525), a ROR of 1.209 (95 % CI: 0.573 to 2.594), and an IC of 0.001 (95 % CI: –0.067 to 0.068).

In the analysis of COVID-19 vaccines versus herpes zoster vaccines in individuals aged 60 and above, the overall PRR was 1.662 (95 % CI: 1.083 to 2.549), the ROR was 1.669 (95 % CI: 1.085 to 2.568), and the IC was 0.008 (95 % CrI: –0.049 to 0.063). In the male population, the PRR was calculated to be 1.493 (95 % CI: 0.711 to 3.135), the ROR was found to be 1.498 (95 % CI: 0.710 to 2.987), and the IC was determined to be 0.006 (95 % CrI: –0.049 to 0.104). Females exhibited the highest point estimates, with a PRR of 1.753 (95 % CI: 1.038 to 2.961), a ROR of 1.762 (95 % CI: 1.039 to 3.161), and an IC of 0.009 (95 % CI: –0.060 to 0.075).

Discussion

Vaccination is a highly effective public health strategy, significantly decreasing global illness and death rates linked to infectious diseases [58]. Since the initiation of national immunization programs in the 1960s, numerous diseases that once contributed substantially to childhood mortality have been almost eliminated [15]. According to

Table 2
Disproportionality analysis.

Group	COVID-19 vaccine Reports of inflammatory arthritis / Total reports	Comparator Reports of inflammatory arthritis / Total reports	PRR	PRR 95 % CI	ROR	ROR 95 % CI	IC	IC 95 % CrI
COVID vaccine vs all other vaccines								
Overall	5580 / 652,047	268 / 27,539	0.999	0.883 to 1.130	0.878	0.777 to 0.994	–0.008	–0.046 to 0.030
Males	1551 / 203,881	80 / 10,337	0.983	0.786 to 1.230	0.983	0.784 to 1.232	–0.001	–0.074 to 0.070
Females	4029 / 448,166	188 / 17,202	0.823	0.711 to 0.951	0.821	0.709 to 0.951	–0.011	–0.056 to 0.033
≤40 years	869 / 212,546	54 / 12,917	0.982	0.746 to 1.292	0.982	0.746 to 1.293	–0.002	–0.099 to 0.093
≤40 years males	217 / 65,164	29 / 5776	0.663	0.451 to 0.976	0.662	0.449 to 0.976	–0.058	–0.257 to 0.127
≤40 years females	652 / 147,382	25 / 7195	1.273	0.855 to 1.897	1.274	0.854 to 1.901	0.014	–0.098 to 0.123
41 to 59 years	2163 / 210,368	94 / 6119	0.669	0.545 to 0.822	0.666	0.541 to 0.820	–0.020	–0.081 to 0.040
41 to 59 years males	534 / 57,594	16 / 1737	1.007	0.614 to 1.651	1.007	0.611 to 1.659	0.000	–0.125 to 0.120
41 to 59 years females	1629 / 152,774	78 / 4382	0.599	0.478 to 0.750	0.595	0.473 to 0.748	–0.027	–0.098 to 0.043
≥60 years	2548 / 229,133	120 / 8449	0.738	0.653 to 0.939	0.781	0.459 to 0.939	–0.014	–0.071 to 0.041
≥60 years males	800 / 81,123	35 / 2824	0.796	0.568 to 1.114	0.794	0.565 to 1.116	–0.012	–0.114 to 0.086
≥60 years females	1748 / 148,010	85 / 5625	0.782	0.630 to 0.970	0.779	0.626 to 0.970	–0.015	–0.083 to 0.052
COVID vaccine vs Influenza vaccine in individuals ≥60 years								
Overall	2548 / 229,133	10 / 1085	1.207	0.650 to 2.239	1.209	0.648 to 2.256	0.001	–0.055 to 0.057
Males	800 / 81,123	3 / 370	1.216	0.390 to 3.803	1.218	0.390 to 3.803	0.001	–0.101 to 0.099
Females	1748 / 148,010	7 / 715	1.206	0.576 to 2.525	1.209	0.573 to 2.549	0.001	–0.067 to 0.068
COVID vaccine vs Herpes Zoster vaccine in individuals ≥60 years								
Overall	2548 / 229,133	21 / 3138	1.662	1.083 to 2.549	1.669	1.085 to 2.568	0.008	–0.049 to 0.063
Males	800 / 81,123	7 / 1060	1.493	0.711 to 3.135	1.498	0.710 to 2.987	0.006	–0.096 to 0.104
Females	1748 / 148,010	14 / 2078	1.753	1.038 to 2.961	1.762	1.039 to 3.161	0.009	–0.060 to 0.075

Table 2 legend: CI: confidence interval; CrI: credible interval; IC: information component; PRR: proportional reporting ratio; ROR: reporting odds ratio.

estimates from the World Health Organization, immunization is responsible for saving 2–3 million lives each year [16]. The COVID-19 pandemic prompted an accelerated advancement in vaccine development, significantly contributing to the decrease in severe illness and mortality [19,20]. However, as with any medical intervention or vaccine, rare adverse events may occur, necessitating robust post-marketing surveillance [59].

The VAERS has facilitated real-world safety monitoring throughout the COVID-19 mass vaccination campaign, offering a unique chance to investigate the emergence of rare, potentially immune-mediated conditions [13]. Among these, inflammatory arthritis represents a concern for rheumatologists, as similar conditions have previously been described in case reports following other vaccinations, including influenza and hepatitis B [10,60–62]. The COVID-19 pandemic provided the unprecedented possibility to study these associations on a larger scale [63].

In our study, we analysed VAERS data to investigate inflammatory arthritis as an AEFI related to COVID-19 vaccination. We observed a CRR of 13.8 cases per million doses administered. While this rate is not negligible, it is within the range of other vaccine-associated adverse events. In addition to the most commonly reported adverse events described in the literature, such as itching and injection site pain, which are typically mild and self-limiting reactions, several rare but potentially immune-mediated conditions have been documented following COVID-19 vaccination [64,65]. For instance, myocarditis and pericarditis have been reported at estimated frequencies of approximately 73 per million doses for BNT162b2, 51 per million for mRNA-1273, and 5 per million for Ad26.COV2.S, particularly in younger male recipients [28]. Similarly, data from CDC surveillance indicate that Guillain-Barré Syndrome occurred at a rate of 7.8 cases per million doses after administration of the Janssen vaccine. Conversely, vaccine-associated uveitis has been documented at a lower rate, ranging from 0.35 to 0.57 cases per million doses across the three FDA-authorized vaccines [33]. The analysis suggests that although inflammatory arthritis is not among the most frequently documented AEFIs, it occurs more commonly than certain other infrequent events.

Our observations indicated a higher prevalence of reports from female recipients, aligning with the established epidemiological trends of inflammatory arthritis within the broader population. Data from epidemiological studies indicate that as many as 75 % of individuals with rheumatoid arthritis are female, and the lifetime risk of developing inflammatory arthritis is significantly elevated in women [66,67]. Consequently, the observed sex distribution is both biologically plausible and anticipated.

The findings from our disproportionality analysis revealed no significant increase in the reporting of inflammatory arthritis following COVID-19 vaccination when compared to other vaccines within the VAERS database. Both frequentist (PRR, ROR) and Bayesian (IC) methods consistently produced values that fell below the thresholds commonly employed for identifying pharmacovigilance signals. This finding was consistent throughout the entire population and in analyses stratified by sex and age, highlighting the strength of the results. Notably, in females, the PRR and ROR values were significantly under 1, indicating that inflammatory arthritis was documented even less often

after COVID-19 vaccination than with other vaccines. Although this finding does not imply a protective effect, it further supports the absence of a pro-inflammatory arthritis signal associated with COVID-19 vaccines. The analyses stratified by age also revealed no disproportionality.

A recent European study using the EudraVigilance database also investigated the incidence of autoimmune and rheumatic post-COVID-19 AEFIs, indicating a signal for inflammatory arthritis, especially linked to mRNA vaccines [68]. Although our findings may initially appear divergent, substantial differences in database structure, case origin, and analytical methodology are essential to contextualize the results [69]. EudraVigilance operates under a compulsory framework where adverse events are reported by national regulators and marketing authorization holders utilizing structured formats [70]. Conversely, VAERS is an open-access, spontaneous reporting system that encompasses cases filed directly by healthcare professionals, patients, and caregivers, hence improving early signal identification for symptom-driven illnesses such as arthritis [36]. Collectively, these studies offer complementary insights. EudraVigilance benefits from meticulous data curation and an extensive reporting framework inside the regulatory network, whereas our VAERS-based methodology capitalizes on early detection, detailed symptom-level data, and an accessible public dataset. These differences highlight the importance of interpreting pharmacovigilance signals according to the context and operational advantages of each system.

In our study, the comparison with other widely used vaccines provided further insights. In the evaluation of arthritis reporting among individuals aged 60 and older, we found no significant differences between the COVID-19 and influenza vaccines. Nonetheless, a weak disproportionality signal was observed when comparing COVID-19 vaccines to herpes zoster vaccines, particularly in older females, as the lower bound of the 95 % CI for the ROR exceeded 1, indicating statistical significance. However, this signal was not corroborated by the other disproportionality measures. The PRR remained below the commonly accepted threshold of 2, and the Bayesian IC was not significant, with the IC025, representing the lower bound of the 95 % CrI, remaining below zero.

This discrepancy highlights an important methodological consideration. In analyses characterized by relatively low event counts, frequentist measures like PRR and ROR can yield unstable estimates, thereby heightening the risk of false positives [71]. In contrast, the IC is less sensitive to statistical noise in smaller strata, owing to its Bayesian framework that integrates prior probability and accounts for variability in reporting patterns [72]. Consequently, the IC offers a more cautious and reliable estimate under conditions of limited data. In our view, greater weight should be given to the Bayesian results in this specific context.

This study has some limitations that should be acknowledged. First and foremost, VAERS is a passive surveillance system and is inherently subject to underreporting, stimulated reporting, and variable data completeness [73,74]. Reports may include imprecise or unverified clinical details, and duplicate entries cannot always be reliably removed. Although we excluded records with missing demographic or essential temporal information, residual issues in data quality are possible.

Another important limitation is the inability to infer causality. Methods like PRR, ROR, and IC reveal associations within the database; however, they fail to consider individual clinical trajectories or external confounders [75]. These methods focus on identifying signals rather than establishing a causal relationship. The observed signal between COVID-19 and herpes zoster vaccines, as analysed through PRR, which was not corroborated by ROR and IC, highlights the potential instability of frequentist methods in strata characterized by low event counts [53,76]. Moreover, even with stratification based on age and sex, the possibility of confounding by indication remains unaddressed. For instance, individuals with pre-existing autoimmune or rheumatic disorders might have experienced variations in vaccination rates or a higher likelihood of reporting symptoms. However, it is important to note that this study did not aim to establish a causal relationship between COVID-19 vaccination and inflammatory arthritis. The findings from VAERS may act as signals for generating hypotheses rather than providing conclusive evidence of an association [77,78]. Any potential signal identified through data mining techniques warrants further examination using controlled epidemiological approaches, while also considering confounding factors and biases.

Despite these limitations, the study has several strengths. The analysis incorporates data from a comprehensive national pharmacovigilance system, capturing more than 650.000 reports of adverse events following COVID-19 vaccination in the United States throughout the specified study period. By concentrating on the two-dose primary vaccination cycle, we mitigated the risk of survivorship bias associated with booster uptake and established a more consistent exposure population. The identification of inflammatory arthritis through the selection of MedDRA terms was conducted via expert consensus among rheumatologists, thereby improving clinical sensitivity and specificity. The study also utilized both frequentist and Bayesian disproportionality methods, included stratification based on age and sex, and conducted comparisons of findings across various vaccine types, particularly those aimed at similar demographic groups, such as influenza and herpes zoster vaccines in older adults. This comprehensive approach facilitated a more thorough and contextual understanding of the data.

Finally, it is important to consider our findings in the broader context of systemic autoimmune rheumatic diseases (such as connective tissue diseases, vasculitis, and idiopathic inflammatory myositis). Although some immunopathological mechanisms may overlap with inflammatory arthritis, these conditions may differ substantially in epidemiology, clinical spectrum, and pharmacovigilance reporting patterns. We therefore believe that they warrant a dedicated and methodologically distinct analysis, which we plan to address in a separate study.

In summary, we investigated the occurrence and reporting patterns of inflammatory arthritis as a potential AEFI after COVID-19 vaccination by utilizing VAERS data from the initial vaccination phase. We found a CRR of 13.8 cases of inflammatory arthritis per million administered doses, a figure that might gain relevance when considered alongside reporting rates of other potentially autoimmune AEFIs. Our disproportionality analysis did not reveal a consistent safety signal when comparing COVID-19 vaccines to other vaccines. Although inflammatory arthritis was reported following COVID-19 vaccination, the frequency of these events remained consistent with expected background levels, suggesting no increased risk relative to other vaccines. Nevertheless, ongoing pharmacovigilance and additional epidemiological studies are essential to elucidate the immunologic foundations and temporal relationships of post-vaccination arthritis. These initiatives are crucial for sustaining public trust in vaccination programs and for assisting clinicians in assessing post-vaccine rheumatologic symptoms.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Contributors

JC, GT, and AZ contributed to data analysis and interpretation of results. JC, PR, and FU were responsible for drafting the manuscript. GT and AZ were involved in sample and data collection. PR, FU, and AZ contributed to the study design. JC is the guarantor and accepts full responsibility for the integrity of the work and the accuracy of the data. All authors critically reviewed and revised the manuscript and approved the final version for submission.

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Competing interest

The authors declare no competing interests related to this study.

Data availability statement

All data analysed in this study are publicly available.

Ethics approval

Not required for analysis of publicly available VAERS data.

Patient consent for publication

Not applicable.

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