COVID-19 Vaccine Adverse Events in the United States: A Temporal and Spatial Analysis

Yiming Li, Jianfu Li, Yifang Dang, Yong Chen, Cui Tao

Submitted to: JMIR Public Health and Surveillance
on: July 19, 2023

Table of Contents

COVID-19 Vaccine Adverse Events in the United States: A Temporal and Spatial Analysis

Yiming Li[1]; Jianfu Li[2]; Yifang Dang[1]; Yong Chen[3]; Cui Tao[2]

[1]McWilliams School of Biomedical Informatics The University of Texas Health Science Center at Houston Houston US
[2]Department of Artificial Intelligence and Informatics Mayo Clinic Jacksonville US
[3]Department of Biostatistics, Epidemiology, and Informatics Perelman School of Medicine University of Pennsylvania Philadelphia US

Corresponding Author:
Cui Tao
Department of Artificial Intelligence and Informatics
Mayo Clinic
Jacksonville
US

Abstract

Background: COVID-19, a highly contagious respiratory disease, has rapidly emerged as a global pandemic. By 3 March 2024, 103.4 million confirmed cases of COVID-19 had been reported in the United States. Vaccination against COVID-19 is currently considered one of the most effective strategies to control its spread. However, due to variations in populations and the ongoing development of vaccines, it is expected that a certain number of individuals may experience adverse events following immunization (AEFI) for COVID-19 vaccines.

Objective: In this study, we exclusively examined AEFI associated with COVID-19 vaccination reported by vaccine recipients. Our objective was to analyze the temporal and spatial characteristics of these reported AEFI to gain insights into their patterns and distribution.

Methods: We analyzed the administration data from the Centers for Disease Control and Prevention (CDC) (N = 663,822,575) and the reports from the surveillance system-Vaccine Adverse Event Reporting System (VAERS) (N = 900,522) between 2020 and 2022. To gain a broader understanding of reported post-vaccination AEFI, we categorized them into System Organ Classes (SOCs) according to the Medical Dictionary for Regulatory Activities (MedDRA). Additionally, temporal analysis was conducted to examine the trends of AEFI in all VAERS reports, those related to Pfizer and Moderna as well as the Top 10 AEFI trends in serious reports. We also compared the similarity of symptoms across various regions within the United States.

Results: Our findings revealed that the most frequently reported symptoms following COVID-19 vaccination were headache (N = 141,186), pyrexia (N = 122,120), and fatigue (N = 121,910). The most common symptom combination was chills and pyrexia (N = 56,954). Initially, General disorders and administration site conditions (SOC 22) were the most prevalent class reported. Moderna exhibited a higher reporting rate of AEFI compared to Pfizer. Over time, we observed a decreasing reporting rate for COVID-19-related AEFI. And the overall rates of AEFI between the Pfizer and Moderna vaccines were comparable. In terms of spatial analysis, the middle and north regions displayed a higher reporting rate of AEFI for COVID-19 vaccines, while the southeast and south central regions showed notable similarity in reported COVID-19 symptoms.

Conclusions: This study presents a potentially beneficial method for AEFI surveillance, especially for severe cases, which can intensify research efforts in areas where abnormal or severe presentations occur. The findings suggest that increasing vaccination coverage reduces the reported AEFI, thereby enhancing vaccine confidence. Our study highlights the importance of robust health policies for managing AEFI in future vaccination campaigns. Specifically, health authorities should consider implementing targeted monitoring programs to detect and manage AEFI early, especially for symptoms that were severe and frequently reported in our analysis. These programs can help improve public confidence in COVID-19 vaccines and effectively administering AEFI in future vaccination campaigns.

(JMIR Preprints 19/07/2023:51007)
DOI: https://doi.org/10.2196/preprints.51007

Preprint Settings

1) Would you like to publish your submitted manuscript as preprint?

✔ **Please make my preprint PDF available to anyone at any time (recommended).**
Please make my preprint PDF available only to logged-in users; I understand that my title and abstract will remain visible to all users.
Only make the preprint title and abstract visible.
No, I do not wish to publish my submitted manuscript as a preprint.

2) If accepted for publication in a JMIR journal, would you like the PDF to be visible to the public?

✔ **Yes, please make my accepted manuscript PDF available to anyone at any time (Recommended).**
Yes, but please make my accepted manuscript PDF available only to logged-in users; I understand that the title and abstract will remain v
Yes, but only make the title and abstract visible (see Important note, above). I understand that if I later pay to participate in <a href="http

Original Manuscript

COVID-19 Vaccine Adverse Events in the United States: A Temporal and Spatial Analysis

Yiming Li [1], Jianfu Li [2], Yifang Dang [1], Yong Chen [3], Cui Tao[2].

[1], McWilliams School of Biomedical Informatics, The University of Texas Health Science Center at Houston, Houston, TX 77030, USA

[2], Department of Artificial Intelligence and Informatics, Mayo Clinic, Jacksonville, FL 32224, USA

[3], Department of Biostatistics, Epidemiology, and Informatics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104, USA

Abstract

Background

The COVID-19 pandemic, caused by the SARS-CoV-2 virus, has had a profound global impact, leading to widespread morbidity and mortality. Vaccination against COVID-19 is a critical tool in controlling the spread of the virus and reducing the severity of the disease. However, the rapid development and deployment of COVID-19 vaccines have raised concerns about potential adverse events following immunization (AEFI). Understanding the temporal and spatial patterns of these AEFI is crucial for effective public health response and vaccine safety monitoring.

Objective

This study aims to analyze the temporal and spatial characteristics of the AEFI for COVID-19 vaccines in the United States reported to the Vaccine Adverse Event Reporting System (VAERS), thereby providing insights into the patterns and distributions of the AEFI, the safety profile of COVID-19 vaccines and identify potential risk factors associated with the AEFI.

Methods

We conducted a retrospective analysis of the administration data from the Centers for Disease Control and Prevention (CDC) (N = 663,822,575) and the reports from the surveillance system-VAERS (N = 900,522) between 2020 and 2022. To gain a broader understanding of reported post-vaccination AEFI, we categorized them into System Organ Classes (SOCs) according to the Medical Dictionary for Regulatory Activities (MedDRA). Additionally, temporal analysis was performed to examine the trends of AEFI in all VAERS reports, those related to Pfizer and Moderna as well as the Top 10 AEFI trends in serious reports. We also compared the similarity of symptoms across various regions within the United States.

Results

Our findings revealed that the most frequently reported symptoms following COVID-19 vaccination were headache (N = 141,186), pyrexia (N = 122,120), and fatigue (N = 121,910). The most common symptom combination was chills and pyrexia (N = 56,954). Initially, General disorders and administration site conditions (SOC 22) were the most prevalent class reported. Moderna exhibited a higher reporting rate of AEFI compared to Pfizer. Over time, we observed a decreasing reporting rate for COVID-19-related AEFI. And the overall rates of AEFI between the Pfizer and Moderna vaccines were comparable. In terms of spatial analysis, the middle and north regions displayed a higher reporting rate of AEFI for COVID-19 vaccines, while the southeast and south central regions showed notable similarity in reported COVID-19 symptoms.

Conclusion

This study provides valuable insights into the temporal and spatial patterns of the AEFI for COVID-19 vaccines in the United States. The findings underscore the critical need for increasing vaccination coverage, as well as ongoing surveillance and monitoring of AEFI. Implementing targeted monitoring programs can thereby facilitate the effective and efficient management of AEFI, enhancing public confidence in future COVID-19 vaccine campaigns.

Keywords

COVID-19, Vaccine, COVID-19 Vaccine, Adverse Drug Event, ADE, Vaccine Adverse Event Reporting System, VAERS, AEFI

Introduction

The COVID-19 pandemic, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), first identified in China in 2019 and quickly became an uncontrollable outbreak worldwide[1], [2], [3], [4]. As of March 2023, the World Health Organization (WHO) had reported 761,402,282 confirmed cases and 6,887,000 deaths from COVID-19 worldwide[5]. Covid-19 primarily spreads through respiratory droplets, and infection can bring about mild to severe symptoms, ranging from general fatigue, cough, fever, loss of taste and smell, diarrhea, severe pneumonia, to even death[3], [4], [6], [7]. Elderly individuals and those with underlying conditions like obesity, diabetes, and hypertension are at higher risk[8]. Long-term effects of COVID-19 include fatigue, muscle weakness, sleep difficulties, anxiety, and depression[9]. So far, vaccines are considered as the primary method to control the virus, with over 674,375,000 doses administered in the United States by April 2023[10], [11], [12], [13], [14]. Coccia demonstrated that nations enforcing stringent societal restrictions and obligations, achieved a high rate of full COVID-19 vaccination, reaching 77.17% (average stringency index of 62.97) by February 2022 [15]. Aldila et al. maintained that achieving higher levels of vaccination could lead to the eradication of COVID-19 in the population by approaching herd immunity, thereby protecting vulnerable individuals [16], [17]. Coccia revealed that administering an average of about 80 doses of vaccines per 100 inhabitants between countries can sustain a reduction in confirmed cases and deaths [18]. The growth of the pandemic wave in May 2021 increased the optimal level of vaccines to about 90 doses for reducing the numbers of COVID-19 related infections [18]. While a widespread vaccination campaign is essential to fight against infectious diseases, it alone is not sufficient as a public policy to mitigate the adverse effects of the COVID-19 pandemic crisis [13], [19]. Cases have shown that COVID-19 vaccines can trigger adverse events in multiple systems, including oral, digestive, hematological, immune, and nervous systems [20], [21], [22], [23], [24], [25], [26]. Common side effects include tenderness at the injection site, fever, fatigue, body aches, and headaches [27], [28], [29], [30]. To make matters worse, there have been reports of serious adverse events following immunization (AEFI), such as acute kidney injury, respiratory distress syndrome, coagulation disorders, and cardiac injuries associated with the COVID-19 vaccine[31]. Therefore, new vaccination strategies for nations must be highly responsive, flexible, resilient, scalable, and effective in reducing the negative impact of COVID-19 viruses [18], [32].

Temporal and spatial factors are critical in the spread of COVID-19, as evidenced by recent research. Coccia's systematic

review highlighted that high air and environmental pollution, as well as unsustainable environments, can facilitate the emergence and rapid spread of pandemics [33]. Coccia also emphasized the importance of an effective contact tracing system and timely isolation in reducing the transmission dynamics of infectious diseases within and between different outbreak areas, particularly for diseases with a latent pre-symptomatic phase [33]. Moreover, Coccia's analysis of seasonality in COVID-19 transmission revealed a correlation between lower temperatures and higher transmission rates, especially in colder regions [34]. Additionally, a spatial analysis demonstrated regional disparities in COVID-19 diffusion, with urban areas showing higher transmission rates than rural areas [35]. These findings underscore the significance of considering temporal and spatial factors in comprehending COVID-19 spread and suggest that AEFI related to COVID-19 vaccination may also demonstrate temporal and spatial trends, necessitating further exploration.

Temporal monitoring allows for the identification of trends, potential causal relationships, and patterns of AEFI over time [36]. Neglecting the heterogeneity or temporal trend of reporting rates across different years can result in missing significant signals, due to COVID-19 caused by prevailing strains of the SARS-CoV-2 virus, which has a substantial capacity to evolve [37], [38], [39]. Additionally, spatial analysis examines the similarity of AEFI across different regions, providing insights into spatial variations, vaccine brands, and populations [40]. The majority of AEFI are preventable [41]. Consequently, analyzing these reported AEFI enables public health researchers and officials to understand their spatial patterns, potential causal factors, and overall impact, supporting evidence-based decision-making and targeted interventions. VAERS (the Vaccine Adverse Event Reporting System), a comprehensive database that collects reports of AEFI across different states and time periods in the United States, proves instrumental in conducting temporal and spatial monitoring of COVID-19 vaccine reported AEFI [42].

Despite significant research on AEFI for COVID-19 vaccines using VAERS data, previous research has primarily focused on short-term data, neglecting comprehensive temporal and spatial analyses within the United States. Huang et al. developed a composite likelihood-based variance component model to analyze the temporal variation of AEFI reporting using VAERS data [43]. The method accounted for underreporting and zero-inflation in passive surveillance systems and identified 14 AEFI with significantly heterogeneous reporting rates over the years, including two events showing an increasing trend [43]. Cai et. al. proposed a random effects model to test the heterogeneity of reporting rates for vaccine-event combinations across multiple years in the VAERS database [37]. The method demonstrated high statistical power in detecting variations in reporting rates, highlighting potential safety issues associated with changes in influenza vaccines [37]. Askar and Züfle conducted a study on the similarity of adverse effects of COVID-19 vaccines across different states in the United States using data from the VAERS [40]. They applied a topic modeling approach to extract latent topics from the reported AEFI and identified spatial clusters of states exhibiting similar AEFI [40]. These findings underscore the variation in AEFI across states and emphasize the importance of further research to understand underlying causes, enhance comprehension of adverse effects, and address vaccine hesitancy [40]. However, the random effects model shows limitations in capturing the complex relationships among symptoms, whereas Latent Dirichlet allocation (LDA) may overlook semantic similarity between symptom compositions in different regions though it is innovative to identify spatial clusters of states with similar AEFI.

In this study, we aim to conduct a comprehensive temporal and spatial analysis of the AEFI for COVID-19 vaccination reported to VAERS. We utilized the Medical Dictionary for Regulatory Activities (MedDRA) as our medical terminology reference [23]. The rest of the paper is organized as follows. We begin with descriptive analyses of vaccine administration and VAERS data, examining factors such as gender, age, and manufacturer, with a specific focus on serious reports. Subsequently, we discuss how we investigate the temporal variation of AEFI and symptoms within different System Organ Classes (SOCs) throughout the study period, enabling a holistic analysis. By modeling weekly reported symptoms relative to administration, we accurately assess temporal variation, identifying associations between time periods and AEFI. In addition to the temporal analysis, we also conducted a spatial analysis using the BioWordVec_PubMed_MIMICIII embedding model. This approach allowed us to construct meaningful vectors that capture the nuances of symptom compositions, enabling us to examine the reporting rates of AEFI in different regions across the United States. Overall, our approach combines advanced embeddings, semantic similarity, and temporal modeling, providing comprehensive insights into AEFI reporting for COVID-19 vaccines.

Methods and Materials

Sample and data

We collected VAERS reports of AEFI for COVID-19 vaccines from 12/13/2020 to 12/28/2022. The reports consist of three Comma-Separated-Value (CSV) files - VAERSDATA.CSV, VAERSVAX.CSV, and VAERSSYMPTOMS.CSV - grouped by year. VAERSDATA contains demographic information, vaccination and adverse event timing, symptom descriptions, allergy history, and serious outcomes. VAERSVAX provides details on vaccine type and manufacturer for each adverse event, while VAERSSYMPTOMS lists the symptoms associated with each adverse event, as mapped from the Preferred Term (PT) in the MedDRA terminology. The three tables are linked by the primary key 'VAERS_ID'.

In addition, we curated COVID-19 vaccine administration data from the Centers for Disease Control and Prevention (CDC)'s COVID Data Tracker during the corresponding period. The COVID Data Tracker is a centralized database maintained by the CDC that provides up-to-date information on COVID-19 vaccine administration across the United States[11]. The COVID Data Tracker contains data on the number of vaccine doses distributed and administered, as well as breakdowns by state, demographic group, and vaccine type[11].

MedDRA is a standardized vocabulary for adverse event reporting, allowing for the consistent classification and analysis of adverse events across different pharmaceutical products and clinical studies[44]. The MedDRA Terminology comprises a structural hierarchy of five levels, including the SOC, the High Level Group Term (HLGT), the High Level Term (HLT), the PT, and the lowest Level Term (LLT). According to the MedDRA website, the current version of MedDRA (version 24.1 as of September 2021) contains over 84,000 PTs, which was used by VAERS code and classify adverse events reported to the system[45].

Measures of variables

We performed several key analyses to examine the characteristics of the AEFI following COVID-19 vaccination. AEFI is defined as any untoward occurrence following immunization [46]. In this study, we focused solely on AEFI reported to VAERS. We did not investigate whether these AEFI were caused by other factors occurring during the same study period (e.g., COVID-19 infection, symptoms arising from other diseases or interventions). CDC data on COVID-19 vaccine administration was used to determine the annual number of vaccinations. This information provides context and allows for comparison with the number of VAERS reports. We also summarized the number of VAERS reports and the symptoms reported, including unique symptoms. The number of COVID-19 vaccine administration and the reported AEFI were stratified by sex, age, and vaccine manufacturer. Additionally, we analyzed the occurrence of individual symptoms and the co-occurrence of symptom pairs.

We categorized the VAERS reports based on sex, age, and vaccine manufacturers in the following ways. Sex was classified into male, female, and unknown. The reports were divided into six age groups based on CDC-recommended cutoff thresholds (5, 12, 18, 65), and unknown was used for age data that was unavailable. The vaccine manufacturers covered the main COVID-19 vaccine manufacturers in the market, including Pfizer\BioNTech, Moderna, Janssen, Novavax, and unknown. We filtered out vaccinations that included a mixture of Pfizer and Moderna because it was not possible to determine from the reported data whether the AEFI resulted from Pfizer or Moderna. We also excluded three subjects who did not report any symptoms, resulting in a sample size of 5,493 subjects in total.

A report was classified as serious if it contains any of the following outcomes: death; life-threatening at the time of the event; inpatient hospitalization or prolongation of existing hospitalization; persistent or significant disability/incapacity; a congenital anomaly/birth defect; medically important event, based on medical judgment[31]. We designated cases as "serious reports" when the corresponding fields indicated any of the following conditions: "DIED", "L_THREAT" (life-threatening), "ER_VISIT" (emergency room visit), "X_STAY" (hospitalization or extended hospital stay), or "DISABLE" (persistent or significant disability/incapacity). To gain a deeper understanding of the AEFI associated with the COVID-19 vaccines in the serious reports, we conducted additional analyses of these reports, focusing on the composition of cases by sex, age group, and vaccine manufacturers.

Data analysis procedure

In order to categorize the reported symptoms, we mapped them to the SOC level, SOC is the top-level hierarchical structure used for broad categorization of medical concepts, based on etiology, manifestation site, or purpose[47]. In our

study, we suggested a straightforward approach for categorizing AEFI into SOCs. This method involves utilizing the internationally agreed order of the SOC (refer to Supplementary Table 1), which is determined by the relative importance of each SOC[48]. In VAERS, each reported symptom could be mapped to either one LLT or PT in MedDRA. Firstly, we matched the symptom to the corresponding LLT or PT, resulting in 66 symptoms matched to LLT and 12,050 symptoms matched to PT. For those symptoms matched to LLT, we further mapped them to the corresponding PT and identified the relevant SOC term. In cases where a report contains multiple symptoms that fall under a specific SOC, we record the occurrence of that SOC for each corresponding symptom in the analysis.

In our study, we conducted a thorough temporal analysis to monitor the reporting rate of AEFI (Equation (1)) for COVID-19 vaccines and individual SOCs on a weekly basis. This approach allowed us to closely track any temporal trends and evaluate the potential risks associated with COVID-19 vaccination, providing valuable insights for well-informed decisions in public health policy.

$$Reporting\,rate\,of\ AEFI = \frac{number\ of\ reported\ AEFI}{number\ of\ vaccinations\,administered} (1)$$

Furthermore, we ranked and analyzed the Top 10 symptoms reported in serious case reports over time. By examining the reporting rate of these symptoms, we gained a comprehensive understanding of their prevalence and impact. This analysis provides valuable insights into the severity and frequency of AEFI associated with COVID-19 vaccines.

Additionally, we conducted a separate temporal analysis specifically focusing on AEFI related to the Pfizer and Moderna vaccines. By analyzing these vaccines individually, we were able to gain a more in-depth understanding of the reported AEFI and identify any unique patterns or differences between vaccine manufacturers.

We conducted a spatial analysis of the case and serious case reporting rates for each state in the United States. To organize the states into standardized regions, we utilized the Standard Federal Regions as defined in the Circular A-105 released by the Office of Management and Budget in April 1974 (refer to Supplementary Table 2) [49].

Furthermore, we performed statistical analysis on the distribution of the AEFI within each region and generated vectors that take both AEFI and their frequencies into consideration. To assess the similarity of AEFI composition across different regions, we employed the BioWordVec_PubMed_MIMICIII embedding model. This model is based on the word2vec algorithm and specifically designed to enhance biomedical word embeddings. It leverages subword information and incorporates the vast PubMed and MIMIC-III datasets to create embeddings that capture the rich semantics of biomedical terms [50], [51]. By utilizing the BioWordVec_PubMed_MIMICIII embedding model, we can measure the semantic similarity between AEFI compositions in different regions. This analysis provides insights into the shared patterns and characteristics of AEFI across various geographic areas.

Results

Table 1 presents descriptive statistics for COVID-19 vaccination, with data divided into two sections: Administration data provided by CDC and reported AEFI in VAERS. Vaccination rates peaked in 2021 for both administration and VAERS data. Notably, VAERS reports for age groups 0-5 and 5-12 increased greatly in 2022 compared to the previous years. In terms of age, adults aged 18-65 were vaccinated the most and reported the highest number of AEFI, followed by elderly individuals aged 65+. Pfizer was the most commonly administered vaccine during the study period, but in 2021, there were more VAERS reports associated with Moderna.

Supplementary Figure 1 presents a comprehensive breakdown of the serious reports analyzed in this study. The total number of reports included was 900,522, with 42,366 classified as serious. Of these serious reports, 21,153 were reported by female patients and 20,275 by male patients. The highest proportion of serious VAERS reports was in the age group of 18-65 years, accounting for 48.82% of the total reports, followed by individuals aged 65 and older, who submitted 18,681 AEFI reports. Regarding vaccine manufacturers, Pfizer had the highest number of VAERS reports, with 20,623 cases, followed by Moderna with 16,936 cases. Serious reports of VAERS resulting from Janssen, Novavax, and unknown manufacturers constituted 11.34% of the total reports.

Of the serious reports, a total of 314,777 non-unique AEFI and 7,945 unique AEFI were identified. The most frequent AEFI reported were death (N=13,323), COVID-19 (N=6,431), dyspnea (N=6,199), SARS-CoV-2 test positive (N=5,036), and fatigue (N=3,610). The most frequent SOCs reported were investigations (N=93,716), general disorders and administration site conditions (N=48,164), nervous system disorders (N=31,689), respiratory, thoracic, and

mediastinal disorders (N=22,997), and surgical and medical procedures (N=14,982).

Table 1 Counts of COVID-19 vaccine administrations and Vaccine Adverse Event Reporting System reports following COVID-19 vaccination in the United States (2020-2022)

	2020	2021	2022
Administration Data			
Total	3,738,130	505,569,659[a]	154,514,786
Age			
[5,12)	-[b]	11,230,026	11,939,125
[12,18)	-[b]	30,175,230	9,754,269
[18-65)	-[b]	336,002,922	80,914,834
65+	-[b]	131,850,714	48,311,353
(0-5) (%) + Unknown	-[b]	-[b]	3,595,205
Manufacturer			
Pfizer\Biotech	2,630,115	294,240,716	98,581,346
Moderna	1,107,143	193,153,251	54,306,971
Janssen	0	17,640,334	1,312,374
Novavax	0	0	69,062
Unknown	872	535,358	245,033

Table 1 (Continued)

	2020	2021	2022
The Vaccine Adverse Event Reporting System Data			
Total	10,380	698,505	191,637
Sex			
Male (%)	1,942 (18.71%)	207,399 (29.69%)	70,916 (37.01%)

Female (%)	8,266 (79.63%)	465,475 (66.64%)	109,583 (57.18%)
Unknown (%)	172 (1.66%)	25,631 (3.67%)	11,138 (5.81%)
Age			
(0-5) (%)	5 (0.05%)	320 (0.05%)	2,676 (1.40%)
[5,12) (%)	0 (0%)	6,002 (0.86%)	9,245 (4.82%)
[12,18) (%)	25 (0.24%)	25,737 (3.68%)	8,117 (4.24%)
[18-65) (%)	9,383 (90.39%)	441,617 (63.22%)	93,105 (48.58%)
65+ (%)	514 (4.95%)	157,014 (22.48%)	54,846 (28.62%)
Unknown (%)	453 (4.36%)	67,815 (9.71%)	23,648 (12.34)
Manufacturer			
Pfizer\Biotech (%)	7,328 (70.6%)	308,256 (44.13%)	99,381 (51.86%)
Moderna (%)	3,029 (29.18%)	326,157 (46.69%)	82,727 (43.17%)
Janssen (%)	0 (0%)	62,570 (8.96%)	8,635 (4.51%)
Novavax (%)	0 (0%)	0 (0%)	199 (0.1%)
Unknown (%)	23 (0.22%)	1,522 (0.22%)	695 (0.36%)

[a] The data do not align with the total number of vaccinations administered by age group in 2021.

[b] The data are not available.

Next, we computed the number of occurrences of individual symptoms and symptom co-occurrences for all VAERS reports during the period of 2020-2022. The most frequently reported symptoms following COVID-19 vaccination was headache (N = 141,186), pyrexia (N = 122,120), and fatigue (N=121,910). The result is shown in Supplementary Figure 2 (detailed results are available in Supplementary Information: word_cloud.xlsx). The most frequent co-occurrence pair was chills + pyrexia (N=56,954).

In the Supplementary Information, you can find the file named 'Covid-19_vaccine_2020_2022.xlsx' which presents the Top 5 symptoms categorized by gender, vaccine manufacturer, and age group for the years 2020-2022. Furthermore, the Supplementary Information also provides the same information for each specific year (2020, 2021, and 2022). For the Janssen vaccine, the Top 5 symptoms reported are headache, pyrexia, chills, fatigue, and pain. The most common symptoms and AEFI for the Novavax vaccine are dizziness, followed by headache, fatigue, incorrect product formulation, and pain. Those receiving an unknown vaccine report COVID-19, headache, pyrexia, pain, and chills. For Moderna and Pfizer, the most common symptoms are headache, pyrexia, fatigue, pain, and chills. Adults aged 18-65 report these same symptoms, while the elderly also report SARS-CoV-2 test positivity. Teenagers report product errors, whereas infants and toddlers report fever and dosage issues. Children aged 5-12 report no adverse events and product errors.

Temporal analysis

Supplementary Figure 3 shows the serious case reporting rate associated with each COVID-19 vaccine manufacturer between 2020 and 2022. Among the vaccine manufacturers, Janssen had the highest reporting rate, followed by the unknown manufacturer, Novavax, Moderna, and Pfizer, in that order. Notably, in 2022, the reporting rate for Janssen (0.0009) was significantly higher compared to any other COVID-19 vaccine manufacturer from 2020 to 2022.

Supplementary Figure 4 provides insight into the reporting rate of serious cases associated with COVID-19 vaccine across different age groups between 2020 and 2022. It indicates that the reporting rate is higher in older age groups and increases with age. Additionally, the reporting rate for each age group peaked in 2021.

Figure 1 illustrates the trend in the proportion of reported SOCs and AEFI reported in VAERS associated with COVID-19 vaccines during the study period, using weekly reported data. The vertical red bars represent the proportion of VAERS reports among weekly administrations, while the lines represent the occurrences of AEFI in SOC out of the corresponding weekly administrations. Notably, the reporting symptoms of SOC 22 (General disorders and administration site conditions) are more prevalent compared to other symptoms. It is important to note that the figure may not reflect the actual rate of AEFI and corresponding SOCs due to reporting bias. However, it still provides valuable temporal insights into the development of AEFI related to COVID-19 vaccination. Interestingly, the local maxima observed in both bar graph and line graph align with the two peaks of the pandemic in the summer of 2021 and 2022. This suggests a potential correlation between the prevalence of AEFI and the intensity of the pandemic. Furthermore, the reporting rate of VAERS and SOC symptoms decreases over time, demonstrating that COVID-19-related AEFI are gradually being improved.

Figure 2 presents the trend in the serious case reporting rate proportion and the Top 10 reported AEFI related to serious reports in VAERS. The vertical red bars represent the proportion of serious VAERS reports among weekly administrations, while the lines represent the rate of the Top 10 AEFI in serious reports out of the corresponding weekly administrations. Our analysis indicates that the Top 10 reported AEFI in the serious cases include death, COVID-19, dyspnea, SARS-CoV-2 test positive, fatigue, pyrexia, pain, headache, blood test, and asthenia. Overall, a decreasing trend is observed, particularly after the initial period from December 2020 to April 2021. Notably, two points of local peak occur in October 2021 and August 2022. However, starting from December 2021, the reporting rate for the other AEFI decreases significantly over time, while the reports of death remain relatively consistent. Please note that the information provided is based on the analysis available up until December 2022, and subsequent updates to the data may reveal different trends or findings.

Figure 3 illustrates the trends in the case reporting rate and individual SOC reporting rate specifically for Pfizer. The vertical red bars represent the proportion of VAERS reports associated with Pfizer immunization among its weekly administrations, while the lines represent the occurrences of AEFI in SOC out of the corresponding weekly Pfizer administrations. In general, both the case reporting rate and the individual SOC reporting rate demonstrate a decreasing trend. However, there were instances in September 2021, March 2022, July 2022, and September 2022 when the case reporting rate and all SOC reporting rates reached a local maximum. Before June 2022, the reporting rate for SOC 22 (General disorders and administration site conditions) was the highest among all SOC reporting rates. However, it was later surpassed by SOC 24 (Injury, poisoning, and procedural complications).

Figure 4 displays the case reporting rate and individual SOC reporting rate specifically for Moderna. The vertical red bars represent the proportion of VAERS reports associated with Moderna immunization among its weekly administrations, while the lines represent the occurrences of AEFI in SOC out of the corresponding weekly Moderna administrations. Initially, both the case reporting rate and individual SOC reporting rate for Moderna were relatively high. Although there was a sharp decrease until June 2021, it experienced a rebound and reached a local peak in August 2021. Subsequently, there was a gradual decreasing trend observed. Prior to November 2021, the reporting rate for SOC 22 (General disorders and administration site conditions) far exceeded the other categories. However, from that point onwards, it became comparable to SOC 24 (Injury, poisoning, and procedural complications). In comparison to Figure 3, the peaks representing Moderna in SARS-CoV-2 Delta variant and SARS-CoV-2 Omicron variant periods are higher than those for Pfizer.

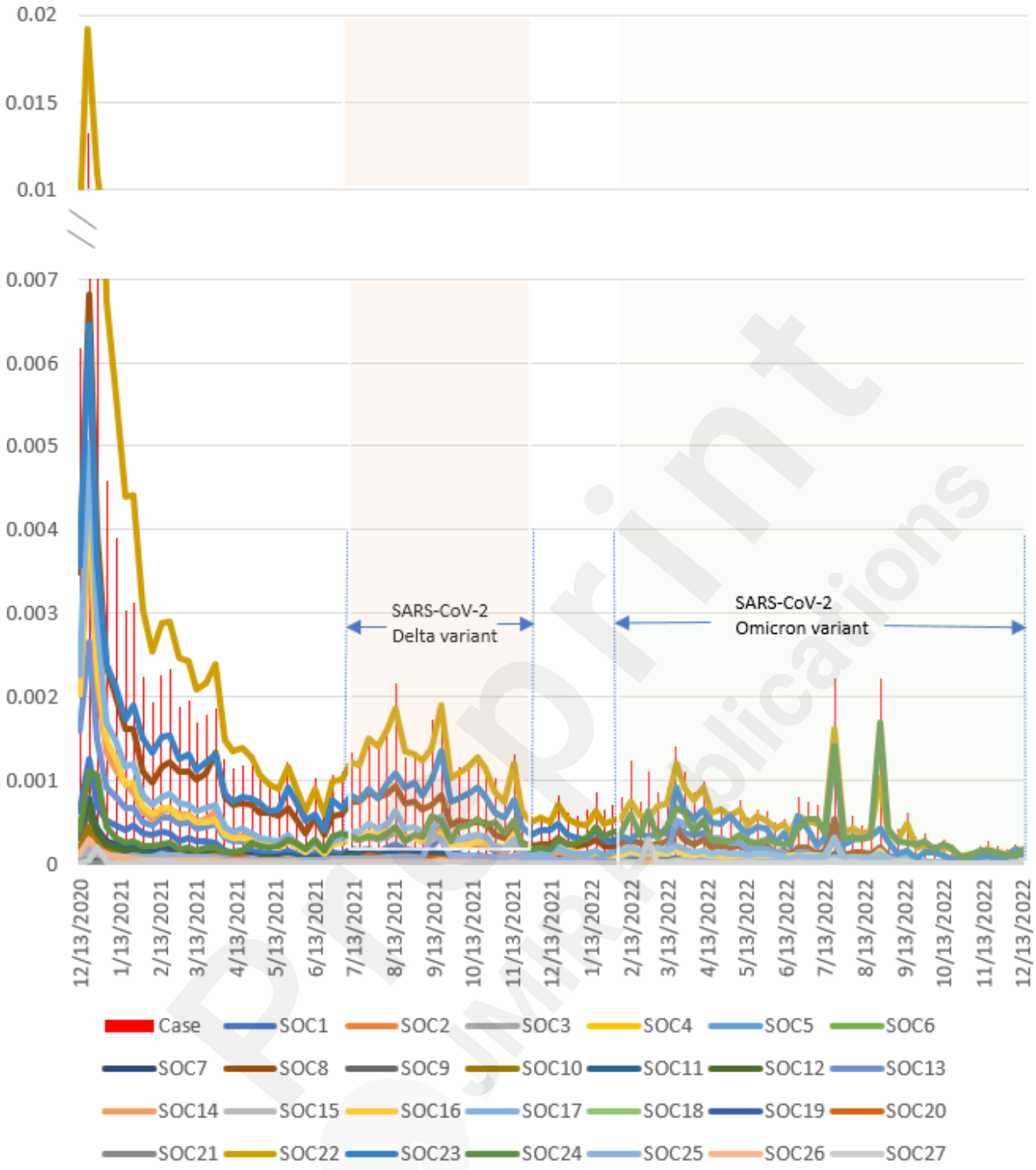


Figure 1 Case reporting rate and individual System Organ Class reporting rate associated with COVID-19 vaccines in the United States, 2020-2022

Note. SARS-CoV-2= severe acute respiratory syndrome coronavirus 2, SOC= System Organ Class

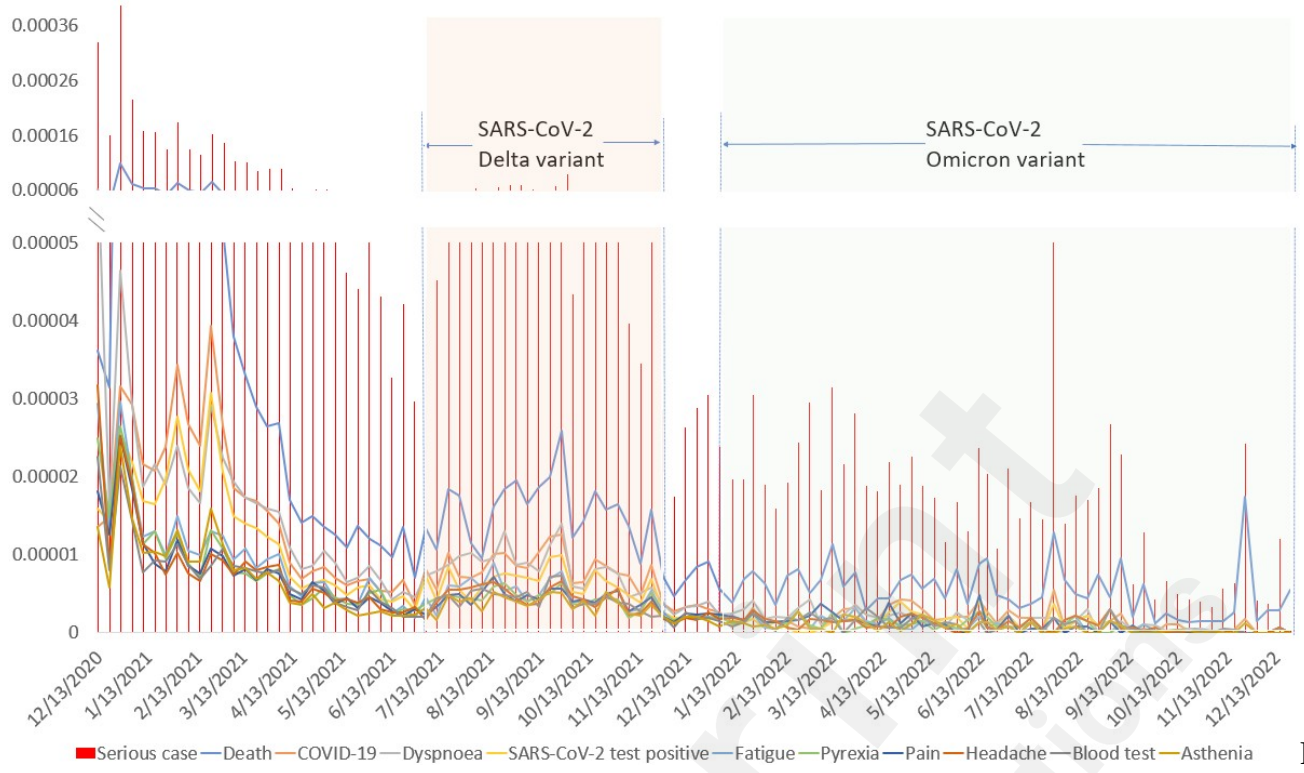


Figure 2 Serious case reporting rate and serious case Top 10 adverse event reporting rate for COVID-19 vaccines in the United States, 2020-2022

Note. SARS-CoV-2= severe acute respiratory syndrome coronavirus 2

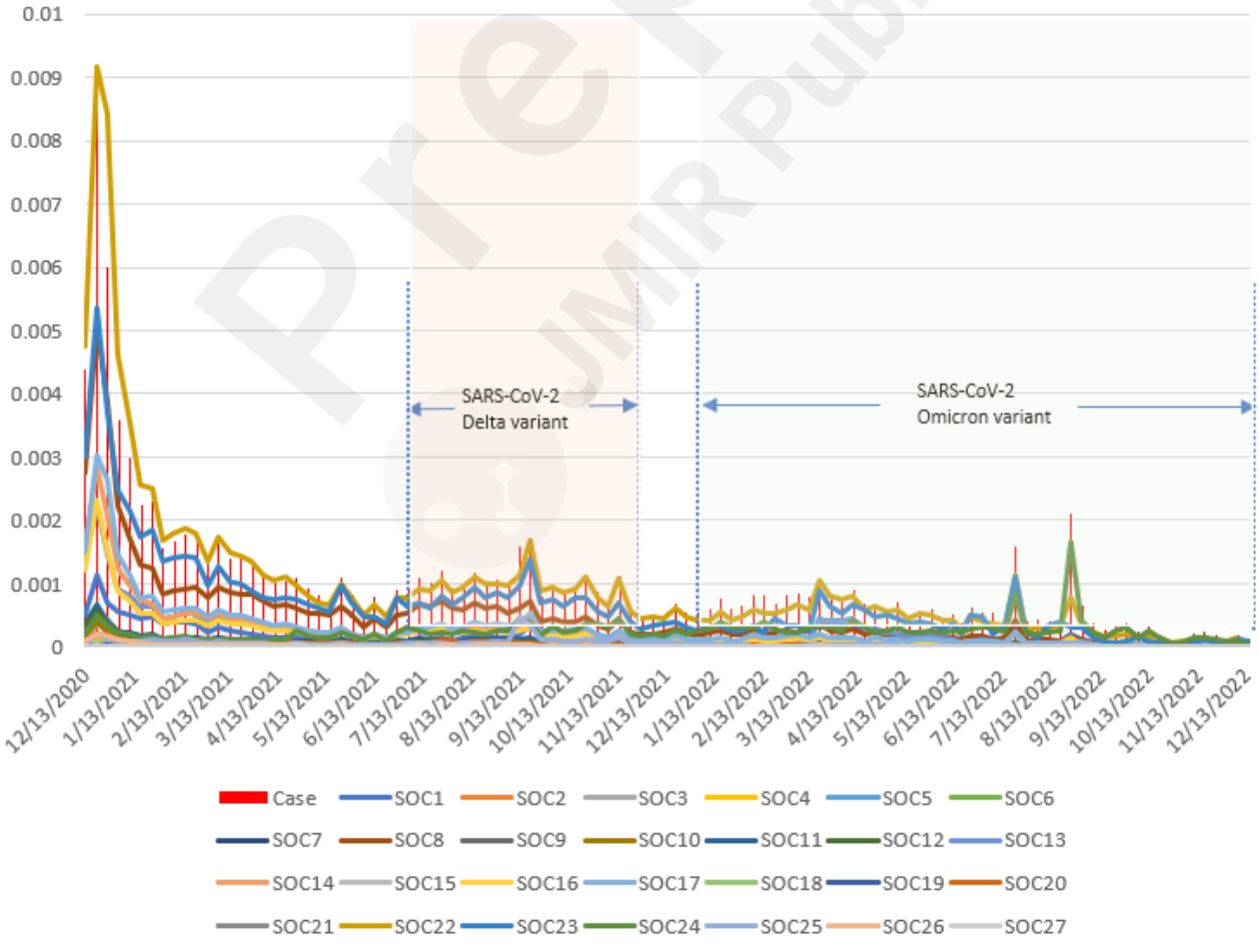


Figure 3 Case reporting rate and individual System Organ Class reporting rate for Pfizer vaccine in the United States, 2020-2022

Note. SARS-CoV-2= severe acute respiratory syndrome coronavirus 2, SOC= System Organ Class

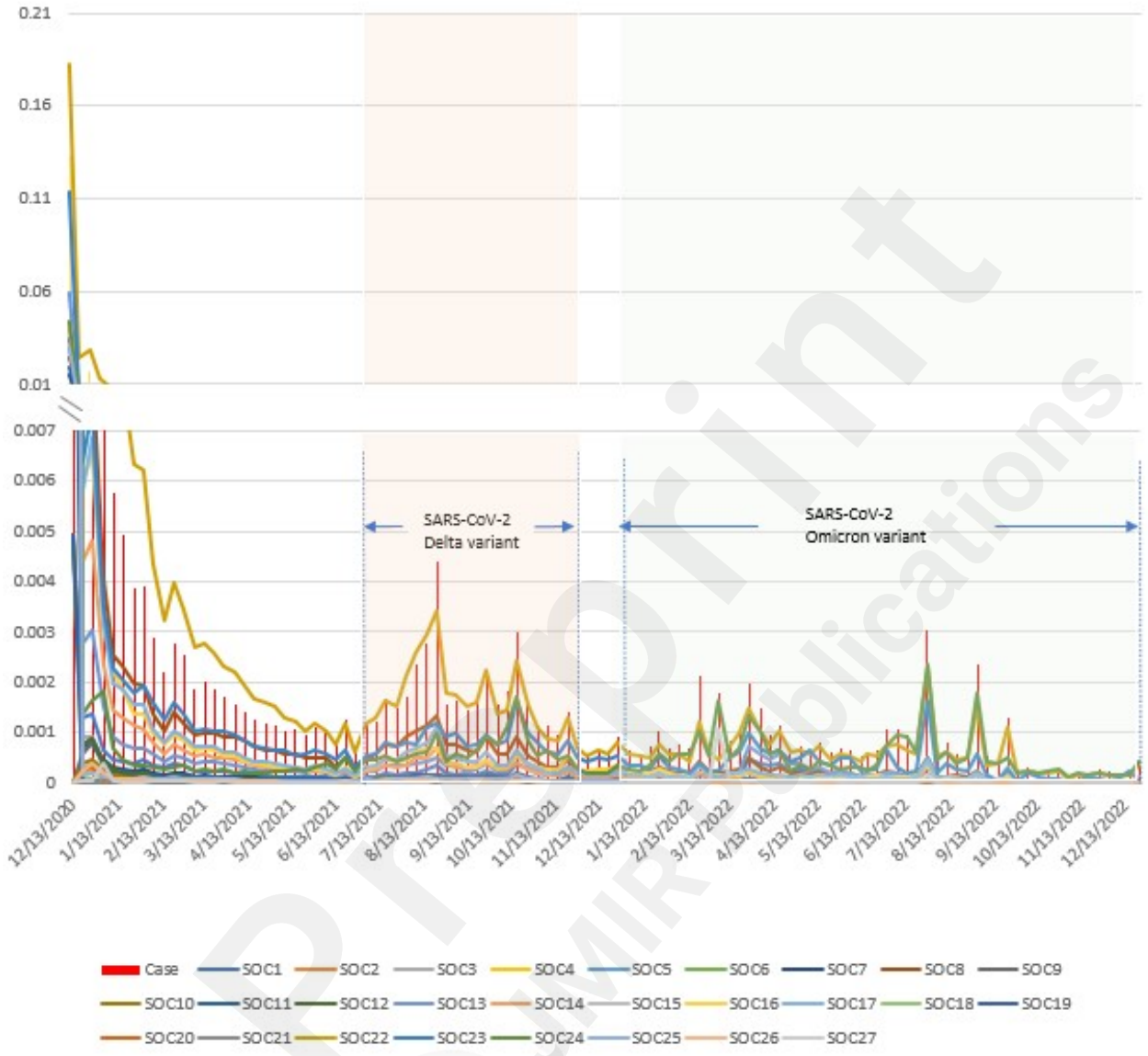


Figure 4 Case reporting rate and individual System Organ Class reporting rate for Moderna vaccine in the United States, 2020-2022

Note. SARS-CoV-2= severe acute respiratory syndrome coronavirus 2, SOC= System Organ Class

Spatial analysis

Figure 5 presents the VAERS reporting rate by state. It reveals that Montana (MT), Minnesota (MN), Michigan (MI), Colorado (CO), Indiana (IN), Alaska (AK) and Kentucky (KY) are the states with reporting rates exceeding 0.0015. Among these, IN recorded the highest reporting rate at 0.0025.

Figure 6 shows the VAERS serious case reporting rate. It turns out that MT, South Dakota (SD), KY, and Tennessee (TN) are the states with serious case reporting rates surpassing 100μ. Among them, SD has the highest reporting rate, reaching 205.26μ. In addition to the healthcare quality and higher confirmed cases relative to the population (especially for TN and KY), this can be partially attributed to their lower vaccination levels (see Supplementary Information: geography_seious_reporting_rate_by_state_vaccination.xlsx) compared to other states [52], [53]. Specifically, these three

states rank among the states with the least vaccination levels, with all three falling far below the average vaccination level nationwide. This lower vaccination rate may contribute to a higher proportion of AEFI being reported in these states, as individuals who choose to get vaccinated might be more likely to report any side effects they experience.

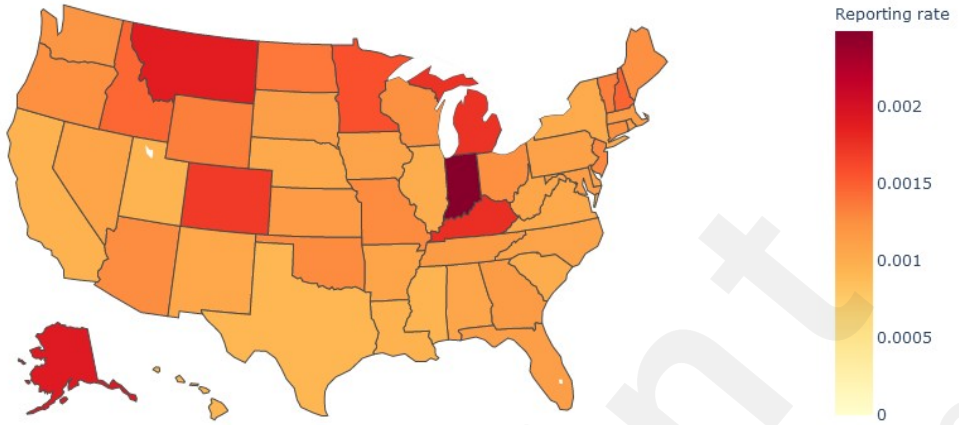


Figure 5 The reporting rate of COVID-19 vaccines in Vaccine Adverse Event Reporting System by state in the United States, 2020-2022

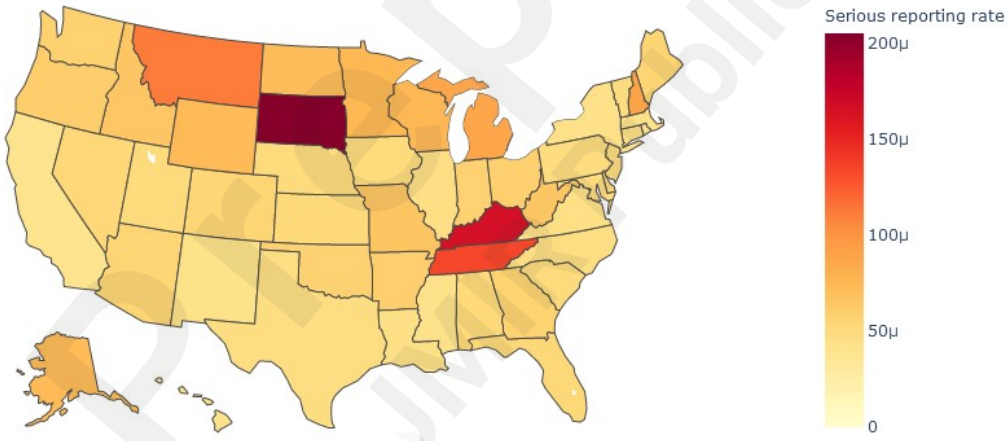
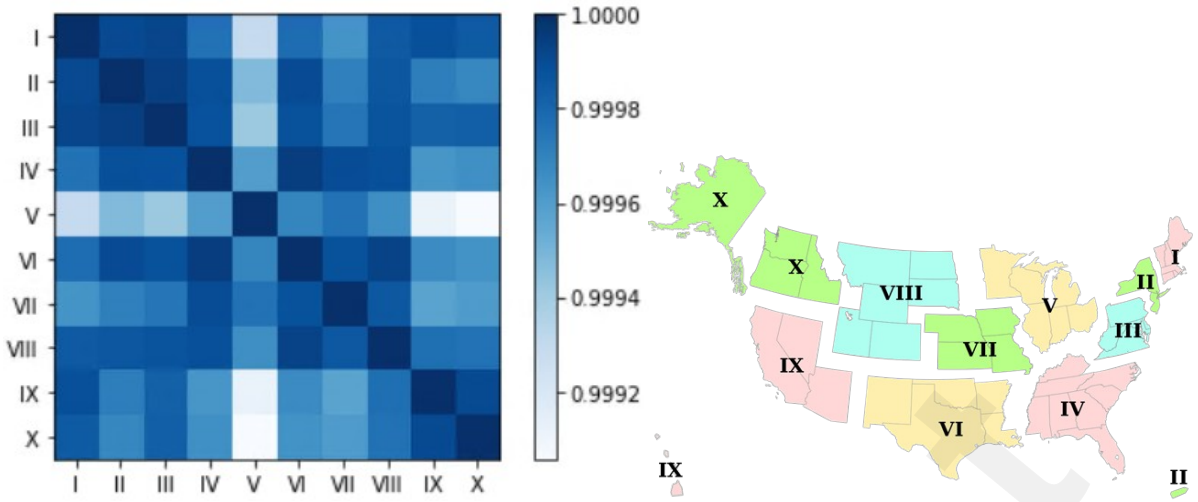


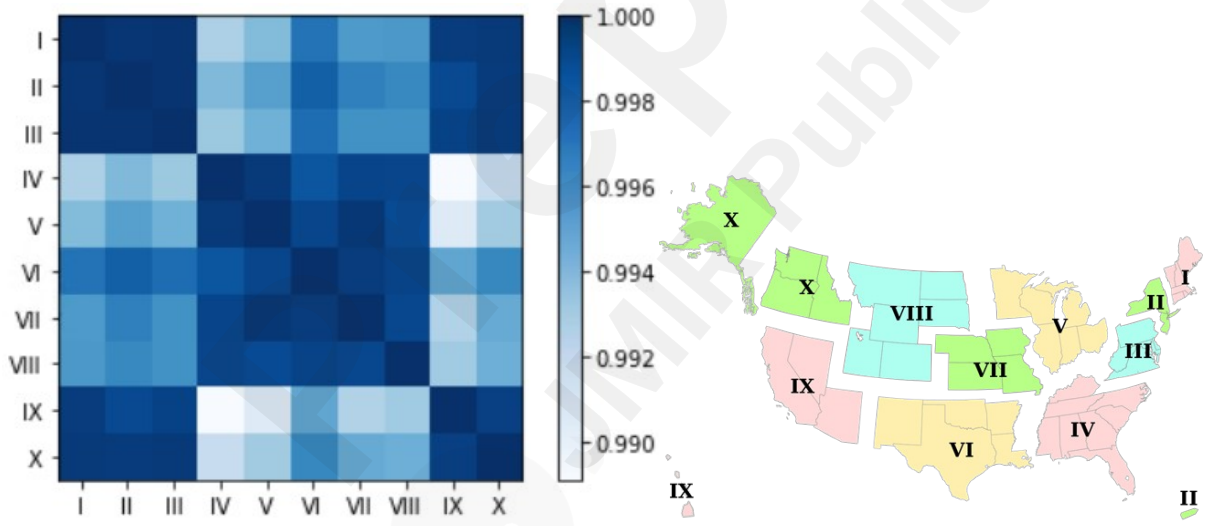
Figure 6 The serious case reporting rate of COVID-19 vaccines in Vaccine Adverse Event Reporting System by state in the United States, 2020-2022



(a) (b)

Figure 7 (a) The heatmap of the similarity of symptoms following COVID-19 vaccines between regions in the United States, 2020-2022 (b) Standard Federal Regions in the United States

Note. Figure 7(b) is adapted from Office of Management and Budget, “Circular A-105: Standard Federal Regions,” Apr. 1974 [49]



(a) (b)

Figure 8 (a) The heatmap of the similarity of symptoms for serious reports of COVID-19 vaccines between regions in the United States, 2020-2022 (b) Standard Federal Regions in the United States

Note. Figure 8(b) is adapted from Office of Management and Budget, “Circular A-105: Standard Federal Regions,” Apr. 1974 [49]

Figure 7 presents the heatmap showcasing the similarity of symptoms between regions within the United States. The similarity between all regions exceeds 0.99, indicating a high level of similarity in symptoms. Notably, Region IV and Region VI demonstrate the highest similarity, reaching an impressive value of 0.9999.

Figure 8 illustrates a heatmap for depicting the similarity of symptoms for serious reports among different regions within

the United States. The analysis reveals that the similarity between all regions exceeds 0.99, indicating a remarkable degree of similarity in reported symptoms. Notably, Region II and Region III demonstrate the highest level of similarity, with an exceptional value of 0.9998, suggesting a strong correlation in the symptoms reported between these regions. In a broader sense, based on the dark boxes shown in Figure 8, it appears that Region I, II, III, IX, and X cluster together with higher similarity within this group, whereas Region IV, V, VI, VII, and VIII indicates another clustering pattern.

Discussion

Our research has produced findings that underscore the clinical significance of our study (summarized in Table 2). Headache emerged as the predominant reported symptom associated with the vaccines made by Pfizer, Moderna, and Janssen. Notably, the top five reported symptoms for all three vaccines are headache, fatigue, pyrexia, pain, and chills, with only slight differences in order of rankings. The occurrence of headache can be attributed to the body's immune response to the vaccine, which triggers the generation of humoral and cellular immunity through a diverse range of mechanisms [54]. Some of these mechanisms may lead to inflammation and subsequent headaches [54].

Conversely, the most commonly reported symptom associated with the Novavax vaccine is dizziness. Research suggests that post-vaccination vertigo and dizziness are common in patients with Meniere Disease (MD) and vertebrobasilar artery insufficiency (VBI) [55]. MD is a disorder with immunological factors that exacerbate endolymphatic hydrops [55], [56]. Moreover, heightened osmolality levels in the inner ear can elevate pro-inflammatory cytokines and immune cell activation, which may lead to a possible systemic immune response and an increase in disease-specific IgG levels, thereby intensifying disease activity [55], [57], [58]. There have been instances where stable MD patients experienced vertigo following vaccination[55], [58]. VBI can induce vertigo through dysregulation of blood flow due to altered plasma viscosity, platelet aggregation, red blood cell deformability, and endothelial function [55]. In rare cases, vaccine-related immunization anxiety can trigger vertigo in patients with autoimmune encephalitis [55], [59], [60], [61], [62].

In addition to common AEFI, COVID-19 vaccinations have been associated with severe or rare AEFI, including autoimmune encephalitis (AIE), cerebral venous sinus thrombosis, Guillain-Barre syndrome (GBS), optic neuritis, and polymyositis. These complications, with reporting rates ranging from 1.89e-5 to 0.001, are often of autoimmune nature [23]. Many conditions observed in temporal association with vaccinations in this study were previously reported as potential autoimmune sequels of SARS-CoV-2 infection, sharing similar clinical and laboratory characteristics [63]. Vaccines containing SARS-CoV-2 antigens may enhance autoimmunity through mechanisms such as polyclonal or bystander activation, epitope spreading, or molecular mimicry [63], [64]. Alternatively, the inflammatory response induced by vaccination may enhance autoimmunity in predisposed patients, possibly by activating pre-existing autoimmune pathways similar to the pathogenesis of immune-related adverse events following administration of immune checkpoint inhibitors [63], [64], [65], [66]. Vaccination could also unmask previously asymptomatic autoimmunity in patients with new-onset autoimmune diseases [63]. Recent population-based studies have linked SARS-CoV-2 vaccinations to an increased incidence of GBS, especially following Ad26.COV2.S administration [63]. However, the possibility that new onset or flares of other neurological autoimmune conditions merely coincided with vaccinations against SARS-CoV-2 cannot be fully excluded [63]. Several pathogenic mechanisms have been proposed to explain how COVID-19 vaccines can lead to AIE, including molecular mimicry, neuro-inflammation, and the role of vaccine adjuvants, such as BNT162 adjuvant polyethylene glycol (PEG), which has been implicated in autoimmune syndrome induced by adjuvants (ASIA-syndrome) [23]. Moreover, vaccine-induced immune thrombotic thrombocytopenia (VITT) (reporting rate: 2.33e-5), though rare, is a consequential complication associated with vaccination [26]. In VITT, the ChAdOx1/PF4 complex may induce the production of anti-PF4 autoantibodies [26]. Trace amounts of ChAdOx1 may enter the bloodstream following intramuscular vaccine administration due to slight capillary damage, leading to the formation of a ChAdOx1/PF4 complex and triggering the production of autoantibodies [26], [67].

Our temporal analysis revealed a declining trend in symptoms across all SOCs, which may help alleviate vaccine hesitancy. The decrease in reported incidence of AEFI associated with COVID-19 vaccines can be attributed to various factors, including the rise in vaccination rates, the improvement of vaccine epidemiological surveillance, the growing experience and knowledge of healthcare providers and vaccine administrators, modifications implemented by vaccine manufacturers, and the decreasing number of COVID-19 cases due to public health measures and vaccination efforts [68], [69]. Interestingly, when comparing to Pfizer, Moderna has a relatively higher reporting rate of AEFI during the initial vaccination stage, SARS-CoV-2 Delta variant period, and SARS-CoV-2 Omicron variant period. This disparity in reported AEFI between Moderna and Pfizer, despite both vaccines utilizing the mRNA platform, can be attributed to multiple factors [70]. One possible reason is the higher dose of mRNA administered in each shot of the Moderna vaccine (100 micrograms) compared to the Pfizer vaccine (30 micrograms) [71]. The higher dose may trigger a stronger immune response in some individuals, increasing the likelihood of AEFI. Additionally, there is a difference in the dosing intervals

between the two vaccines. Pfizer doses are administered three weeks apart and Moderna doses administered one month apart [72]. The longer interval for Moderna could potentially allow for a more pronounced immune response, potentially contributing to a higher rate of reported AEFI. However, as more data was collected and larger populations were vaccinated, it became evident that the overall rates of AEFI between the two vaccines were comparable. This could be due to several factors such as increased familiarity and experience with the vaccines, improved reporting systems, and a better understanding of potential side effects.

Our spatial analysis revealed that the north and middle regions of the United States exhibit higher case and serious case reporting rates compared to the southeast and southwest regions. The elevated reporting rate of AEFI for COVID-19 vaccines in the middle and north regions could be attributed to several factors. One possible explanation is the disparity in vaccination coverage. The middle and north regions may have a lower proportion of vaccinated individuals, increasing the likelihood of AEFI being reported. Furthermore, variations in healthcare access across different regions can also contribute to differences in reporting rates.

The reported COVID-19 symptoms show a notable similarity between the southeast region (Region IV) and the south central region (Region VI). One possible explanation is the geographical proximity and shared demographics within these regions. When people live in close geographic proximity, they often share similar environmental exposures, lifestyles, and genetic backgrounds. These factors can contribute to a higher likelihood of experiencing similar symptoms when infected with COVID-19.

Interestingly, despite the geographical distance, the northwest (Region X) and northeast (Region I, II, and III) regions of the US also exhibit similarity in reported COVID-19 symptoms. The similarity is particularly pronounced for serious cases. This can be attributed to shared population characteristics, such as age distributions, cultural practices, or socioeconomic factors, which influence the prevalence and reporting of specific symptoms. Moreover, the presence of specific COVID-19 variants or strains within these regions could also contribute to the similarity in reported symptoms. Variants of the virus may exhibit unique characteristics, including symptom profiles, which can result in similarities in reported symptoms within specific regions.

Population migration and travel patterns can also play a role in the similarity of reported symptoms. Individuals residing in close proximity or frequently traveling between regions can contribute to the transmission and dissemination of specific COVID-19 strains, leading to similarities in symptom reporting. Additionally, similarities in healthcare infrastructure, medical practices, and access to testing facilities may contribute to the observed similarities in reported symptoms. Consistent testing protocols and diagnostic criteria across these regions can lead to a more uniform reporting of symptoms.

A comparative analysis with other countries can provide insights into the generalizability of our findings and the impact of different healthcare systems and vaccination strategies. For example, Abukhalil et al. conducted a questionnaire-based retrospective cross-sectional study to monitor AEFI for COVID-19 vaccines in Palestine[30]. They found that fever, chills, headache, fatigue, and pain were the most commonly reported AEFI [30]. Similarly, Bannister et al. analyzed questionnaires completed by participants from the Danish National Cohort Study of Effectiveness and Safety of SARS-CoV-2 Vaccines (ENFORCE) and revealed that fatigue, muscle pain, and headache were the most commonly reported AEFI[25]. Additionally, Nawaz et al. conducted a survey-based cross-sectional study in Pakistan and found that injection site pain, fatigue, and muscle ache were the most commonly reported AEFI for COVID-19 vaccines[22]. Through comparing data and trends across nations, we can identify similarities in AEFI reporting and population responses. Understanding these patterns can inform the development of more effective vaccination strategies to address AEFI for COVID-19 vaccines. Furthermore, comparing AEFI profiles across countries can contribute to the identification of rare or unusual patterns, prompting further investigation into potential vaccine-related risks or benefits.

Our analysis of AEFI for COVID-19 vaccines is comprehensive compared to existing research. Firstly, unlike previous studies, we utilized both vaccine administration data and the VAERS data. This approach allowed us to evaluate the reporting incidence of AEFI, rather than relying solely on absolute values. Utilizing both datasets has the advantage of providing a more accurate representation of AEFI associated with COVID-19 vaccines. Secondly, we analyzed three years of data to provide a more complete and convincing conclusion. Most studies have been conducted over a shorter period, which limits their scope and reliability. In contrast, our study analyzed AEFI for COVID-19 vaccines for a period of three years, which allowed us to assess the long-term AEFI of these vaccines. This approach also provides a more dynamic and objective understanding of the risks associated with COVID-19 vaccines. Our approach allowed us to identify the most common AEFI associated with COVID-19 vaccines and their underlying mechanisms. This information can help healthcare providers better manage and treat AEFI associated with COVID-19 vaccines. Last but not least, we harnessed the power of an embedding model to examine the similarity of symptoms across diverse regions. The model

can handle complex word structures and improve the representation of rare or unseen terms by considering subword units. This rationale enables us to extract more precise and meaningful insights from biomedical texts, and also facilitate various applications such as biomedical information retrieval, named entity recognition, and text classification. Overall, the embedding provides a valuable resource for advancing biomedical text analysis and accelerating biomedical research.

However, it is important to acknowledge that our study has several limitations. Firstly, the quality of the data is inadequate as we were unable to access certain administration data due to its unavailability in the CDC database, which could have added more depth to our analysis. Moreover, VAERS is a passive reporting system in which AEFI are not automatically collected, and anyone can submit VAERS reports, which sometimes lack details or contain errors [73]. As this study reports data collected by a surveillance system, it does not determine the safety of the vaccines but rather is prone to report the most frequently monitored and reported AEFI. Furthermore, it is crucial to note that VAERS does not validate the causation between the COVID-19 vaccine and the reported AEFI [73]. Secondly, we failed to include cases where patients had received a combination of Pfizer and Moderna vaccines, resulting in selection bias. Unfortunately, this also meant that we were unable to filter out such doses in the administration data. Nonetheless, it is important to note that the number of individuals who received mixed doses per week was minimal compared to the overall number of vaccinations, which mitigated the potential impact of this bias. Additionally, reporting bias cannot be entirely ruled out, as some individuals may choose not to report adverse events to VAERS due to various reasons, including reluctance, lack of awareness, or difficulties in accessing the reporting system. This could result in underreporting of certain AEFI and potentially affect the accuracy and completeness of our analysis. Lastly, there may be instances of history bias in our data, where the symptoms observed may not be attributed to the COVID-19 vaccine itself but rather to historical events or interventions that occurred during the same period. These external factors may confound the interpretation of the reported AEFI. Despite these limitations, we believe that our study provides a comprehensive analysis of AEFI for COVID-19 vaccines.

Table 2 Main results in this study and contributions compared to other studies

Aspect	Main Results	Contribution Compared to Other Studies
COVID-19 Administration Data	Vaccination rates peaked in 2021. Adults aged 18-65 were vaccinated the most. Pfizer was the most administered vaccine.	Provides insights into the timing of peak vaccination rates, aiding in understanding vaccination trends during the study period. Highlights the demographic group that received the highest vaccination coverage, aiding in targeting future vaccination campaigns.
VAERS Reports	VAERS reports indicated higher reporting rates among adults aged 18-65. Reporting rate for AEFI associated with COVID-19 vaccines higher in female and older age groups. Pfizer had the highest number of VAERS reports, followed by Moderna. Reporting rate for Janssen was significantly higher in 2022 compared to other vaccine manufacturers. Most frequently reported AEFI: headache, pyrexia, and fatigue. Most frequent co-occurrence pair: chills + pyrexia. Most frequent AEFI reported in serious reports [a]: death, COVID-19, dyspnea, SARS-CoV-2 test positive, and fatigue. Most frequent SOCs in serious reports [a]: investigations (SOC 23), general disorders and administration site conditions (SOC 22), nervous system disorders (SOC 8), respiratory, thoracic, and mediastinal disorders (SOC 13), and surgical and medical procedures (SOC 25).	Provides age and sex specific reporting rates, highlighting vulnerable populations and aiding in targeted interventions and vaccine recommendations Features differences in reporting rates among different age/sex groups and vaccine manufacturers, contributing to a better understanding of AEFI patterns. Identifies key symptoms and SOCs associated with COVID-19 vaccination, offering insights into common AEFI and areas of focus for vaccine epidemiological surveillance. Highlights common symptom patterns post-vaccination, aiding in the recognition of symptom clusters and potential treatment strategies.
Temporal Analysis	Trend in proportion of reported SOCs and AEFI showed a decrease over time. Reporting rate for Top 10 reported symptoms and AEFI related to serious reports showed an overall decreasing trend. AEFI reporting rate and individual SOC reporting rate for Pfizer and Moderna showed a decreasing trend over time. For Pfizer, SOC 22 (General disorders and administration site conditions) was the highest among all SOC reporting rates before being surpassed by SOC 24 (Injury, poisoning, and procedural complications) starting June 2022. For Moderna, the reporting rate for SOC 22 far exceeded the other categories initially, and it became comparable to SOC 24 from November 2021 onwards.	Indicates a potential decrease in AEFI over time, suggesting the effectiveness of monitoring and intervention strategies. Highlights manufacturer-specific trends in AEFI reporting, offering valuable insights for vaccine epidemiological surveillance.

Spatial Analysis	**• States with reporting rates exceeding 0.0015: Montana (MT), Minnesota (MN), Michigan (MI), Colorado (CO), Indiana (IN), Alaska (AK), and Kentucky (KY).** **• States with serious case reporting rates surpassing 100µ: Montana (MT), South Dakota (SD), Kentucky (KY), and Tennessee (TN).** **• Similarity between all regions exceeded 0.99, indicating a high level of similarity in symptoms between different regions in US.**	**• Identifies geographic variations in AEFI reporting rates, suggesting the need for targeted vaccine surveillance in high-reporting states.** **• Underscores the consistency of AEFI reporting patterns across different regions, supporting the generalizability of findings and the reliability of VAERS data.**

[a]A report was classified as serious if it contains any of the following outcomes: death; life-threatening at the time of the event; inpatient hospitalization or prolongation of existing hospitalization; persistent or significant disability/incapacity; a congenital anomaly/birth defect; medically important event, based on medical judgment[31]

Note. AEFI=adverse event following immunization, SARS-CoV-2= severe acute respiratory syndrome coronavirus 2, SOC= System Organ Class, VAERS= the Vaccine Adverse Event Reporting System, US= United States

Conclusion

The study introduces a potentially valuable approach to monitoring AEFI, particularly for serious cases, which could bolster research in regions experiencing unusual or severe adverse reactions. These findings imply that higher vaccination coverage may decrease reported AEFI, leading to increased confidence in vaccines. Our study highlights the importance of post-licensure monitoring in understanding AEFI associated with COVID-19 vaccines. While our analysis provides valuable insights into temporal and spatial patterns of reported symptoms, it is crucial to acknowledge the limitations in data quality, including reporting and selection biases. Moving forward, efforts should focus on improving surveillance methods to enhance the accuracy and representativeness of AEFI reporting. This study underscores the need for continuous monitoring, supporting the development of informed public health policies. Looking ahead, nations should prioritize implementing effective measures such as stringent lockdowns, widespread testing and contact tracing, robust healthcare infrastructure, and clear communication strategies. Additionally, ensuring equitable access to vaccines and promoting vaccine confidence are crucial for achieving optimal vaccination coverage. By implementing these strategies, nations can enhance their preparedness and response capabilities, reducing the impact of future pandemics.

Acknowledgement:

This article was partially supported by the National Institute of Allergy And Infectious Diseases of the National Institutes of Health under Award Numbers R01AI130460 and U24AI171008

Ethical considerations:

The original data collection was approved by an IRB. The present analysis did not receive approval/exemption from an IRB. The secondary analysis does not need a review from an IRB, as we used a publicly available data set from https://vaers.hhs.gov/data/datasets.html, and https://covid.cdc.gov/covid-data-tracker. The authors have permission to use the data.

Competing interests:

The authors declare that there are no competing interests.

Author contribution:

CT and YC were responsible for leading the experimental design, while YL contributed to the experimental design, conducted data analysis, and drafted the manuscript. CT provided support and manuscript editing. YL and JL performed data visualization, and YL and YD conducted data collection. All authors have reviewed and approved the final manuscript.

Data availability:

The data sets generated during and/or analyzed during this study are available in the CDC repository https://covid.cdc.gov/covid-data-tracker, and VAERS repository https://vaers.hhs.gov/data/datasets.html.

Abbreviations:

AEFI	adverse events following immunization
AIE	autoimmune encephalitis
AK	Alaska
ASIA-syndrome	autoimmune syndrome induced by adjuvants
CDC	Centers for Disease Control and Prevention
CO	Colorado
CSV	Comma-Separated-Value
GBS	Guillain-Barre syndrome
HLGT	High Level Group Term
HLT	High Level Term
IN	Indiana
KY	Kentucky
LDA	Latent Dirichlet allocation
LLT	lowest Level Term
MD	Meniere Disease
MedDRA	Medical Dictionary for Regulatory Activities
MI	Michigan
MN	Minnesota
MT	Montana
PEG	polyethylene glycol
PT	Preferred Term
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SD	South Dakota
SOC	System Organ Class
TN	Tennessee
VAERS	Vaccine Adverse Event Reporting System
VBI	vertebrobasilar artery insufficiency
VITT	vaccine-induced immune thrombotic thrombocytopenia
WHO	World Health Organization

References

[1] Q. Fernandes *et al.*, “Emerging COVID-19 variants and their impact on SARS-CoV-2 diagnosis, therapeutics and vaccines,” *Ann Med*, vol. 54, no. 1, pp. 524–540, doi: 10.1080/07853890.2022.2031274.

[2] C. Chaimayo *et al.*, “Rapid SARS-CoV-2 antigen detection assay in comparison with real-time RT-PCR assay for laboratory diagnosis of COVID-19 in Thailand,” *Virol J*, vol. 17, p. 177, Nov. 2020, doi: 10.1186/s12985-020-01452-5.

[3] S. Yamayoshi *et al.*, “Comparison of Rapid Antigen Tests for COVID-19,” *Viruses*, vol. 12, no. 12, p. 1420, Dec. 2020, doi: 10.3390/v12121420.

[4] S. H. Safiabadi Tali *et al.*, “Tools and Techniques for Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)/COVID-19 Detection,” *Clin Microbiol Rev*, vol. 34, no. 3, pp. e00228-20, May 2021, doi: 10.1128/CMR.00228-20.

[5] World Health Organization, “WHO Coronavirus (COVID-19) Dashboard.” [Online]. Available: https://covid19.who.int/

[6] P. Rai, B. K. Kumar, V. K. Deekshit, I. Karunasagar, and I. Karunasagar, “Detection technologies and recent developments in the diagnosis of COVID-19 infection,” *Appl Microbiol Biotechnol*, vol. 105, no. 2, pp. 441–455, Jan. 2021, doi: 10.1007/s00253-020-

11061-5.
[7] W.-J. Song *et al.*, “Confronting COVID-19-associated cough and the post-COVID syndrome: role of viral neurotropism, neuroinflammation, and neuroimmune responses,” *Lancet Respir Med*, vol. 9, no. 5, pp. 533–544, May 2021, doi: 10.1016/S2213-2600(21)00125-9.
[8] R. Silverio, D. C. Gonçalves, M. F. Andrade, and M. Seelaender, “Coronavirus Disease 2019 (COVID-19) and Nutritional Status: The Missing Link?,” *Adv Nutr*, vol. 12, no. 3, pp. 682–692, Jun. 2021, doi: 10.1093/advances/nmaa125.
[9] C. Huang *et al.*, “6-month consequences of COVID-19 in patients discharged from hospital: a cohort study,” *Lancet*, vol. 397, no. 10270, pp. 220–232, Jan. 2021, doi: 10.1016/S0140-6736(20)32656-8.
[10] S. U. Rehman, S. U. Rehman, and H. H. Yoo, “COVID-19 challenges and its therapeutics,” *Biomed Pharmacother*, vol. 142, p. 112015, Oct. 2021, doi: 10.1016/j.biopha.2021.112015.
[11] Centers for Disease Control and Prevention, “COVID Data Tracker,” US Department of Health and Human Services, CDC, Atlanta, GA, Apr. 2023. [Online]. Available: https://covid.cdc.gov/covid-data-tracker
[12] Y. Li *et al.*, “Unpacking adverse events and associations post COVID-19 vaccination: a deep dive into vaccine adverse event reporting system data,” *Expert Review of Vaccines*, vol. 23, no. 1, pp. 53–59, Dec. 2024, doi: 10.1080/14760584.2023.2292203.
[13] J. Li *et al.*, “Mapping Vaccine Names in Clinical Trials to Vaccine Ontology using Cascaded Fine-Tuned Domain-Specific Language Models,” *Res Sq*, p. rs.3.rs-3362256, Sep. 2023, doi: 10.21203/rs.3.rs-3362256/v1.
[14] Y. Li, J. Li, J. He, and C. Tao, “AE-GPT: Using Large Language Models to extract adverse events from surveillance reports-A use case with influenza vaccine adverse events,” *PLOS ONE*, vol. 19, no. 3, p. e0300919, Mar. 2024, doi: 10.1371/journal.pone.0300919.
[15] M. Coccia, “Improving preparedness for next pandemics: Max level of COVID-19 vaccinations without social impositions to design effective health policy and avoid flawed democracies,” *Environ Res*, vol. 213, p. 113566, Oct. 2022, doi: 10.1016/j.envres.2022.113566.
[16] C. Magazzino, M. Mele, and M. Coccia, “A machine learning algorithm to analyse the effects of vaccination on COVID-19 mortality,” *Epidemiol Infect*, vol. 150, p. e168, Sep. 2022, doi: 10.1017/S0950268822001418.
[17] D. Aldila, B. M. Samiadji, G. M. Simorangkir, S. H. A. Khosnaw, and M. Shahzad, “Impact of early detection and vaccination strategy in COVID-19 eradication program in Jakarta, Indonesia,” *BMC Research Notes*, vol. 14, no. 1, p. 132, Apr. 2021, doi: 10.1186/s13104-021-05540-9.
[18] M. Coccia, “Optimal levels of vaccination to reduce COVID-19 infected individuals and deaths: A global analysis,” *Environ Res*, vol. 204, no. Pt C, p. 112314, Mar. 2022, doi: 10.1016/j.envres.2021.112314.
[19] M. Coccia, “COVID-19 Vaccination is not a Sufficient Public Policy to face Crisis Management of next Pandemic Threats,” *Public Organization Review*, pp. 1–15, Oct. 2022, doi: 10.1007/s11115-022-00661-6.
[20] A. Riad, N. Schulz-Weidner, A. Dziedzic, H.-P. Howaldt, and S. Attia, “Oral side effects of COVID-19 vaccines in 32 European countries: Analysis of EudraVigilance reports,” *J Med Virol*, vol. 95, no. 5, p. e28771, May 2023, doi: 10.1002/jmv.28771.
[21] H. Miyazaki *et al.*, “Differences in Coronavirus disease - 19 vaccination related side effects

in patients with ulcerative colitis and Crohn's disease in Japan," *Indian J Gastroenterol*, vol. 42, no. 5, pp. 701–707, Oct. 2023, doi: 10.1007/s12664-023-01386-0.

[22] Z. Nawaz, M. Zahid, M. Sajjad, N. Azhar, N.-U.-E. Hasan, and A. S. Siddiqui, "Short Term Side Effects Of Inactivated COVID-19 Vaccines Among Pakistani Population: A Survey-Based Cross-Sectional Study," *J Pak Med Assoc*, vol. 73, no. 8, pp. 1592–1597, Aug. 2023, doi: 10.47391/JPMA.6885.

[23] K. Mansour *et al.*, "Seronegative acute encephalitis following COVID-19 vaccines: a case series of an overlooked diagnosis with literature review," *Eur J Clin Pharmacol*, vol. 79, no. 7, pp. 975–987, Jul. 2023, doi: 10.1007/s00228-023-03510-7.

[24] R. Naveen *et al.*, "Systemic sclerosis and COVID-19 vaccine safety: short-term insights from the global COVID-19 vaccination in autoimmune disease (COVAD) survey," *Rheumatol Int*, vol. 43, no. 7, pp. 1265–1275, Jul. 2023, doi: 10.1007/s00296-023-05310-9.

[25] W. P. Bannister *et al.*, "Association of Self-reported Systemic Reactions Following SARS-CoV-2 Vaccination With Immunological Response in the Danish National Cohort Study of Effectiveness and Safety of SARS-CoV-2 Vaccines (ENFORCE)," *Open Forum Infect Dis*, vol. 10, no. 6, p. ofad248, Jun. 2023, doi: 10.1093/ofid/ofad248.

[26] T.-C. Lin, P.-A. Fu, Y.-T. Hsu, and T.-Y. Chen, "Vaccine-Induced Immune Thrombotic Thrombocytopenia following BNT162b2 mRNA COVID-19 Booster: A Case Report," *Vaccines (Basel)*, vol. 11, no. 6, p. 1115, Jun. 2023, doi: 10.3390/vaccines11061115.

[27] M. T. Shakoor, M. P. Birkenbach, and M. Lynch, "ANCA-Associated Vasculitis Following Pfizer-BioNTech COVID-19 Vaccine," *Am J Kidney Dis*, vol. 78, no. 4, pp. 611–613, Oct. 2021, doi: 10.1053/j.ajkd.2021.06.016.

[28] L. R. Baden *et al.*, "Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine," *N Engl J Med*, vol. 384, no. 5, pp. 403–416, Feb. 2021, doi: 10.1056/NEJMoa2035389.

[29] R. Karaali *et al.*, "Homologous or heterologous COVID-19 vaccine schemes: comparison of immune responses and side effects," *Diagn Microbiol Infect Dis*, vol. 107, no. 2, p. 116017, Oct. 2023, doi: 10.1016/j.diagmicrobio.2023.116017.

[30] A. D. Abukhalil, S. S. Shatat, R. R. Abushehadeh, N. Al-Shami, H. A. Naseef, and A. Rabba, "Side effects of Pfizer/BioNTech (BNT162b2) COVID-19 vaccine reported by the Birzeit University community," *BMC Infect Dis*, vol. 23, no. 1, p. 5, Jan. 2023, doi: 10.1186/s12879-022-07974-3.

[31] J. Fraiman *et al.*, "Serious adverse events of special interest following mRNA COVID-19 vaccination in randomized trials in adults," *Vaccine*, vol. 40, no. 40, pp. 5798–5805, Sep. 2022, doi: 10.1016/j.vaccine.2022.08.036.

[32] M. Coccia, "Pandemic Prevention: Lessons from COVID-19," *Encyclopedia*, vol. 1, no. 2, Art. no. 2, Jun. 2021, doi: 10.3390/encyclopedia1020036.

[33] M. Coccia, "Sources, diffusion and prediction in COVID-19 pandemic: lessons learned to face next health emergency," *AIMS Public Health*, vol. 10, no. 1, pp. 145–168, Mar. 2023, doi: 10.3934/publichealth.2023012.

[34] M. Coccia, "Factors determining the diffusion of COVID-19 and suggested strategy to prevent future accelerated viral infectivity similar to COVID," *Sci Total Environ*, vol. 729, p. 138474, Aug. 2020, doi: 10.1016/j.scitotenv.2020.138474.

[35] M. Coccia, "COVID-19 pandemic over 2020 (withlockdowns) and 2021 (with vaccinations): similar effects for seasonality and environmental factors," *Environ Res*, vol. 208, p. 112711, May 2022, doi: 10.1016/j.envres.2022.112711.

[36] S. R. Ahmad, "Adverse Drug Event Monitoring at the Food and Drug Administration: Your

Report Can Make a Difference," *Journal of General Internal Medicine*, vol. 18, no. 1, p. 57, Jan. 2003, doi: 10.1046/j.1525-1497.2003.20130.x.
[37] Y. Cai *et al.*, "A signal detection method for temporal variation of adverse effect with vaccine adverse event reporting system data," *BMC Med Inform Decis Mak*, vol. 17, no. Suppl 2, p. 76, Jul. 2017, doi: 10.1186/s12911-017-0472-y.
[38] C. Stokel-Walker, "How are vaccines being adapted to meet the changing face of SARS-CoV-2?," *BMJ*, vol. 377, p. o1257, Jun. 2022, doi: 10.1136/bmj.o1257.
[39] C. A. Russell *et al.*, "Influenza vaccine strain selection and recent studies on the global migration of seasonal influenza viruses," *Vaccine*, vol. 26 Suppl 4, pp. D31-34, Sep. 2008, doi: 10.1016/j.vaccine.2008.07.078.
[40] A. Askar and A. Züfle, "Clustering Adverse Events of COVID-19 Vaccines Across the United States," in *Similarity Search and Applications*, N. Reyes, R. Connor, N. Kriege, D. Kazempour, I. Bartolini, E. Schubert, and J.-J. Chen, Eds., in Lecture Notes in Computer Science. Cham: Springer International Publishing, 2021, pp. 307–320. doi: 10.1007/978-3-030-89657-7_23.
[41] Y. Li *et al.*, "Artificial intelligence-powered pharmacovigilance: A review of machine and deep learning in clinical text-based adverse drug event detection for benchmark datasets," *Journal of Biomedical Informatics*, vol. 152, p. 104621, Apr. 2024, doi: 10.1016/j.jbi.2024.104621.
[42] R. T. Chen *et al.*, "The vaccine adverse event reporting system (VAERS)," *Vaccine*, vol. 12, no. 6, pp. 542–550, May 1994, doi: 10.1016/0264-410X(94)90315-8.
[43] J. Huang *et al.*, "Monitoring vaccine safety by studying temporal variation of adverse events using vaccine adverse event reporting system," *The Annals of Applied Statistics*, vol. 15, no. 1, pp. 252–269, Mar. 2021, doi: 10.1214/20-AOAS1393.
[44] E. G. Brown, L. Wood, and S. Wood, "The medical dictionary for regulatory activities (MedDRA)," *Drug Saf*, vol. 20, no. 2, pp. 109–117, Feb. 1999, doi: 10.2165/00002018-199920020-00002.
[45] International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), "MedDRA Version 24.1: What's New," 2021, [Online]. Available: https://admin.meddra.org/sites/default/files/guidance/file/000636_whatsnew_24_1.pdf
[46] M. A. Kim *et al.*, "COVID-19 Vaccine-associated Anaphylaxis and Allergic Reactions: Consensus Statements of the KAAACI Urticaria/Angioedema/Anaphylaxis Working Group," *Allergy Asthma Immunol Res*, vol. 13, no. 4, pp. 526–544, Jul. 2021, doi: 10.4168/aair.2021.13.4.526.
[47] MedDRA Maintenance and Support Services Organization (MSSO), "Introductory Guide MedDRA Version 25.1," Sep. 2022.
[48] J. Du, Y. Cai, Y. Chen, and C. Tao, "Trivalent influenza vaccine adverse symptoms analysis based on MedDRA terminology using VAERS data in 2011," *Journal of Biomedical Semantics*, vol. 7, no. 1, p. 13, May 2016, doi: 10.1186/s13326-016-0056-2.
[49] Office of Management and Budget, "Circular A-105: Standard Federal Regions," Apr. 1974.
[50] Y. Zhang, Q. Chen, Z. Yang, H. Lin, and Z. Lu, "BioWordVec, improving biomedical word embeddings with subword information and MeSH," *Scientific Data*, 2019.
[51] Q. Chen, Y. Peng, and Z. Lu, "BioSentVec: creating sentence embeddings for biomedical texts," in *The 7th IEEE International Conference on Healthcare Informatics*, 2019.
[52] "Rankings: Health Care Quality - Best States." Accessed: Mar. 23, 2024. [Online]. Available: https://www.usnews.com/news/best-states/rankings/health-care/healthcare-

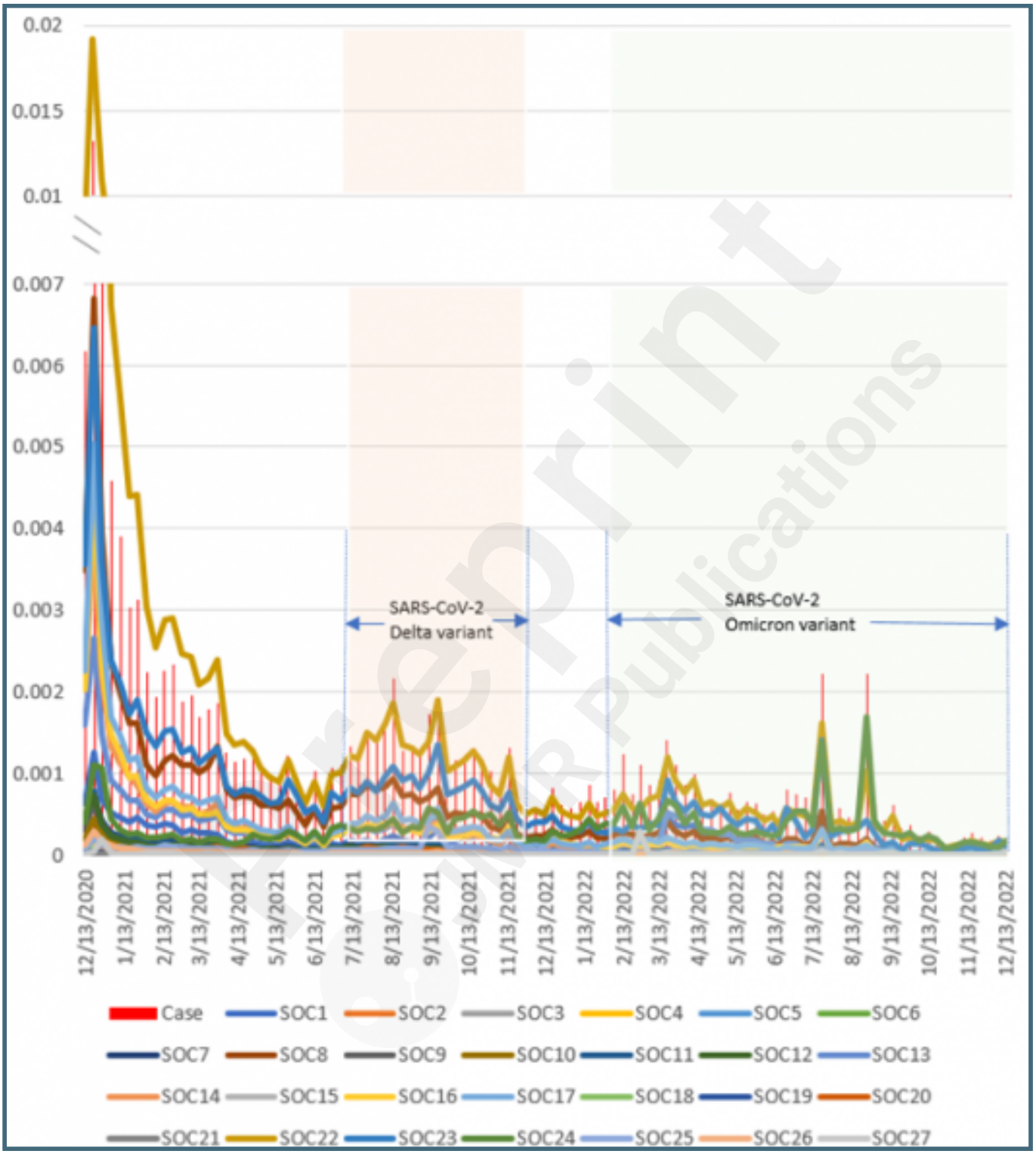
quality
[53] “United States COVID - Coronavirus Statistics - Worldometer.” Accessed: Mar. 23, 2024. [Online]. Available: https://www.worldometers.info/coronavirus/country/us/
[54] M. Castaldo *et al.*, “Headache onset after vaccination against SARS-CoV-2: a systematic literature review and meta-analysis,” *The Journal of Headache and Pain*, vol. 23, no. 1, p. 41, Mar. 2022, doi: 10.1186/s10194-022-01400-4.
[55] H.-Y. Yan and Y.-H. Young, “Vertigo/dizziness following COVID-19 vaccination,” *Am J Otolaryngol*, vol. 44, no. 2, p. 103723, 2023, doi: 10.1016/j.amjoto.2022.103723.
[56] L. Frejo *et al.*, “Extended phenotype and clinical subgroups in unilateral Meniere disease: A cross-sectional study with cluster analysis,” *Clin Otolaryngol*, vol. 42, no. 6, pp. 1172–1180, Dec. 2017, doi: 10.1111/coa.12844.
[57] M. Kleinewietfeld *et al.*, “Sodium chloride drives autoimmune disease by the induction of pathogenic TH17 cells,” *Nature*, vol. 496, no. 7446, pp. 518–522, Apr. 2013, doi: 10.1038/nature11868.
[58] H. Wichova, M. E. Miller, and M. J. Derebery, “Otologic Manifestations After COVID-19 Vaccination: The House Ear Clinic Experience,” *Otol Neurotol*, vol. 42, no. 9, pp. e1213–e1218, Oct. 2021, doi: 10.1097/MAO.0000000000003275.
[59] F. Zuhorn, T. Graf, R. Klingebiel, W.-R. Schäbitz, and A. Rogalewski, “Postvaccinal Encephalitis after ChAdOx1 nCov-19,” *Ann Neurol*, vol. 90, no. 3, pp. 506–511, Sep. 2021, doi: 10.1002/ana.26182.
[60] E. B. Marsh *et al.*, “COVID-19 and Vaccination in the Setting of Neurologic Disease,” *Neurology*, vol. 97, no. 15, pp. 720–728, Oct. 2021, doi: 10.1212/WNL.0000000000012578.
[61] F. Graus *et al.*, “A clinical approach to diagnosis of autoimmune encephalitis,” *Lancet Neurol*, vol. 15, no. 4, pp. 391–404, Apr. 2016, doi: 10.1016/S1474-4422(15)00401-9.
[62] R. W. Baloh and J. W. Spooner, “Downbeat nystagmus: a type of central vestibular nystagmus,” *Neurology*, vol. 31, no. 3, pp. 304–310, Mar. 1981, doi: 10.1212/wnl.31.3.304.
[63] L. D. Kaulen *et al.*, “Neurological autoimmune diseases following vaccinations against SARS-CoV-2: a case series,” *Eur J Neurol*, vol. 29, no. 2, pp. 555–563, Feb. 2022, doi: 10.1111/ene.15147.
[64] N. Agmon-Levin, Z. Paz, E. Israeli, and Y. Shoenfeld, “Vaccines and autoimmunity,” *Nat Rev Rheumatol*, vol. 5, no. 11, pp. 648–652, Nov. 2009, doi: 10.1038/nrrheum.2009.196.
[65] A. Marini *et al.*, “Neurologic Adverse Events of Immune Checkpoint Inhibitors: A Systematic Review,” *Neurology*, vol. 96, no. 16, pp. 754–766, Apr. 2021, doi: 10.1212/WNL.0000000000011795.
[66] T. J. Braaten *et al.*, “Immune checkpoint inhibitor-induced inflammatory arthritis persists after immunotherapy cessation,” *Ann Rheum Dis*, vol. 79, no. 3, pp. 332–338, Mar. 2020, doi: 10.1136/annrheumdis-2019-216109.
[67] P. Chen, I. Kovesdi, and J. T. Bruder, “Effective repeat administration with adenovirus vectors to the muscle,” *Gene Ther*, vol. 7, no. 7, pp. 587–595, Apr. 2000, doi: 10.1038/sj.gt.3301137.
[68] J. T. Granados-Riveron and G. Aquino-Jarquin, “Engineering of the current nucleoside-modified mRNA-LNP vaccines against SARS-CoV-2,” *Biomed Pharmacother*, vol. 142, p. 111953, Oct. 2021, doi: 10.1016/j.biopha.2021.111953.
[69] P. L. Stern, “Key steps in vaccine development,” *Ann Allergy Asthma Immunol*, vol. 125, no. 1, pp. 17–27, Jul. 2020, doi: 10.1016/j.anai.2020.01.025.

[70] A. Mandavilli, “Moderna vs. Pfizer: Both Knockouts, but One Seems to Have the Edge,” *The New York Times*, Sep. 22, 2021. Accessed: May 24, 2023. [Online]. Available: https://www.nytimes.com/2021/09/22/health/covid-moderna-pfizer-vaccines.html
[71] R. Gutman-Wei, “Is Moderna Really Better Than Pfizer—Or Is It Just a Higher Dose?,” The Atlantic. Accessed: May 24, 2023. [Online]. Available: https://www.theatlantic.com/health/archive/2021/10/pfizer-moderna-dose-which-vaccine-best/620501/
[72] “Pfizer COVID Vaccine vs. Moderna COVID Vaccine: Coronavirus Vaccination Differences and Side Effects,” RxList. Accessed: May 24, 2023. [Online]. Available: https://www.rxlist.com/pfizer_covid_vaccine_vs_moderna_covid_vaccine/drugs-condition.htm
[73] “VAERS | Vaccine Safety | CDC.” Accessed: Apr. 25, 2023. [Online]. Available: https://www.cdc.gov/vaccinesafety/ensuringsafety/monitoring/vaers/index.html

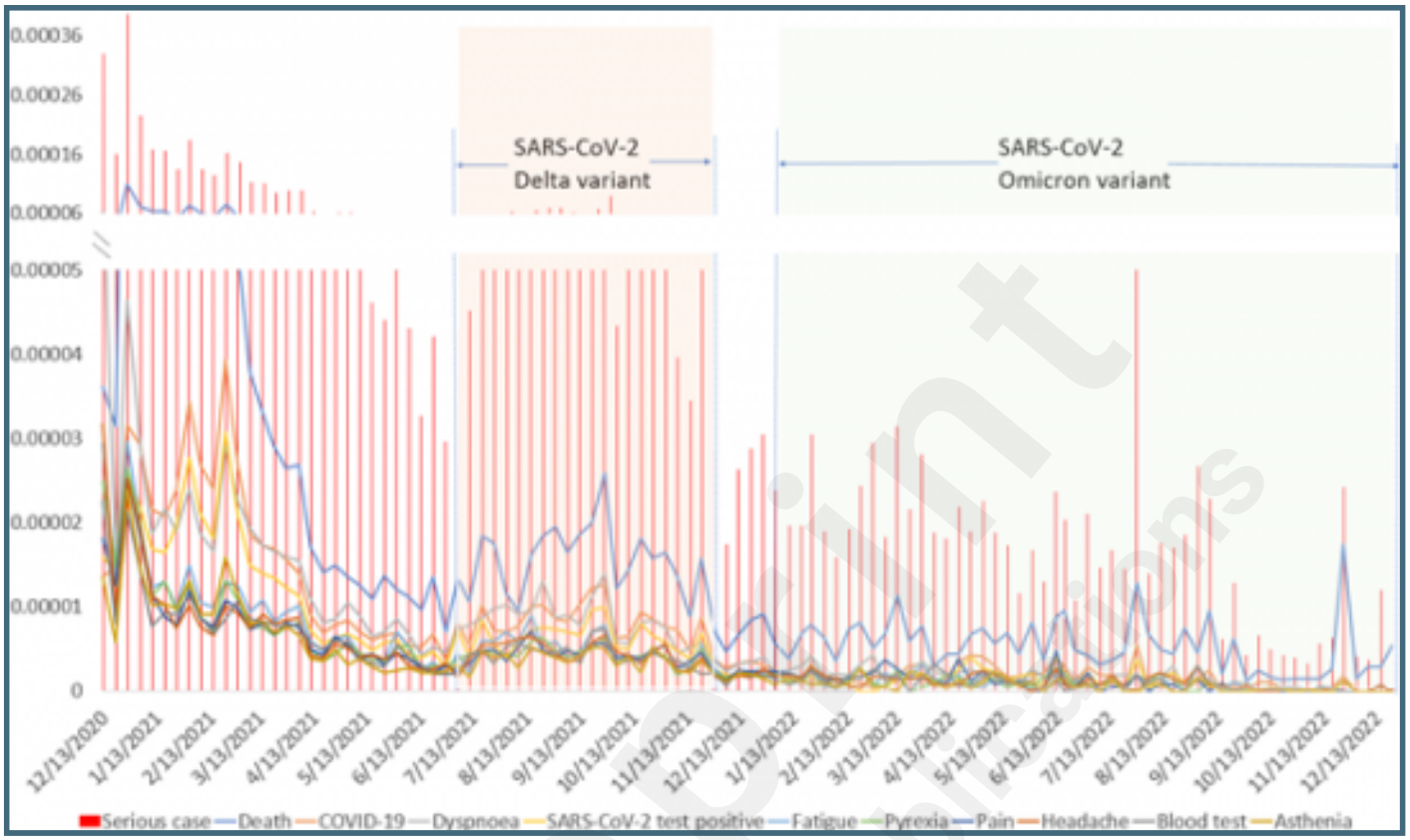
Supplementary Files

Figures

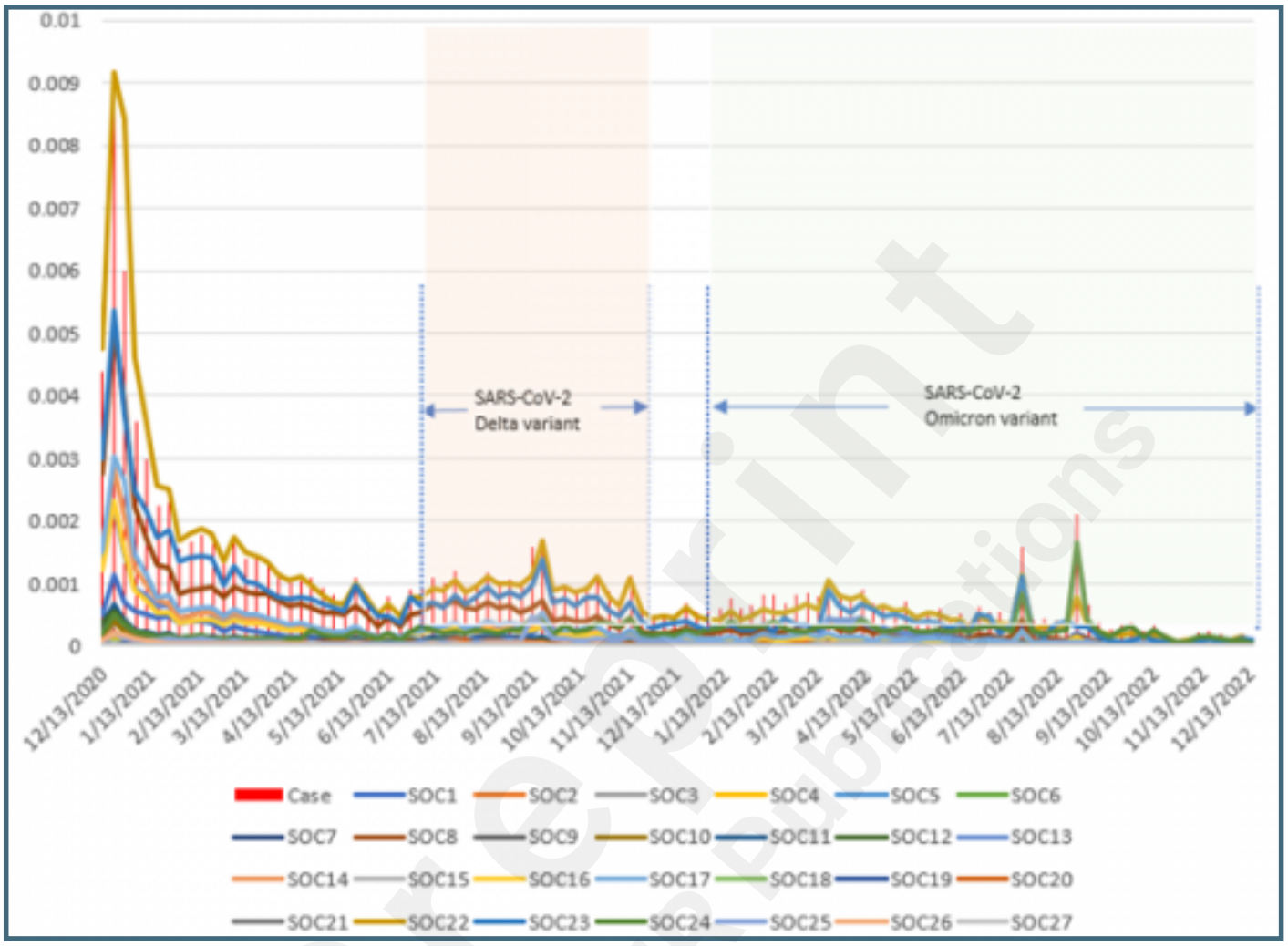
Case reporting rate and individual System Organ Class reporting rate associated with COVID-19 vaccines in the United States, 2020-2022 .



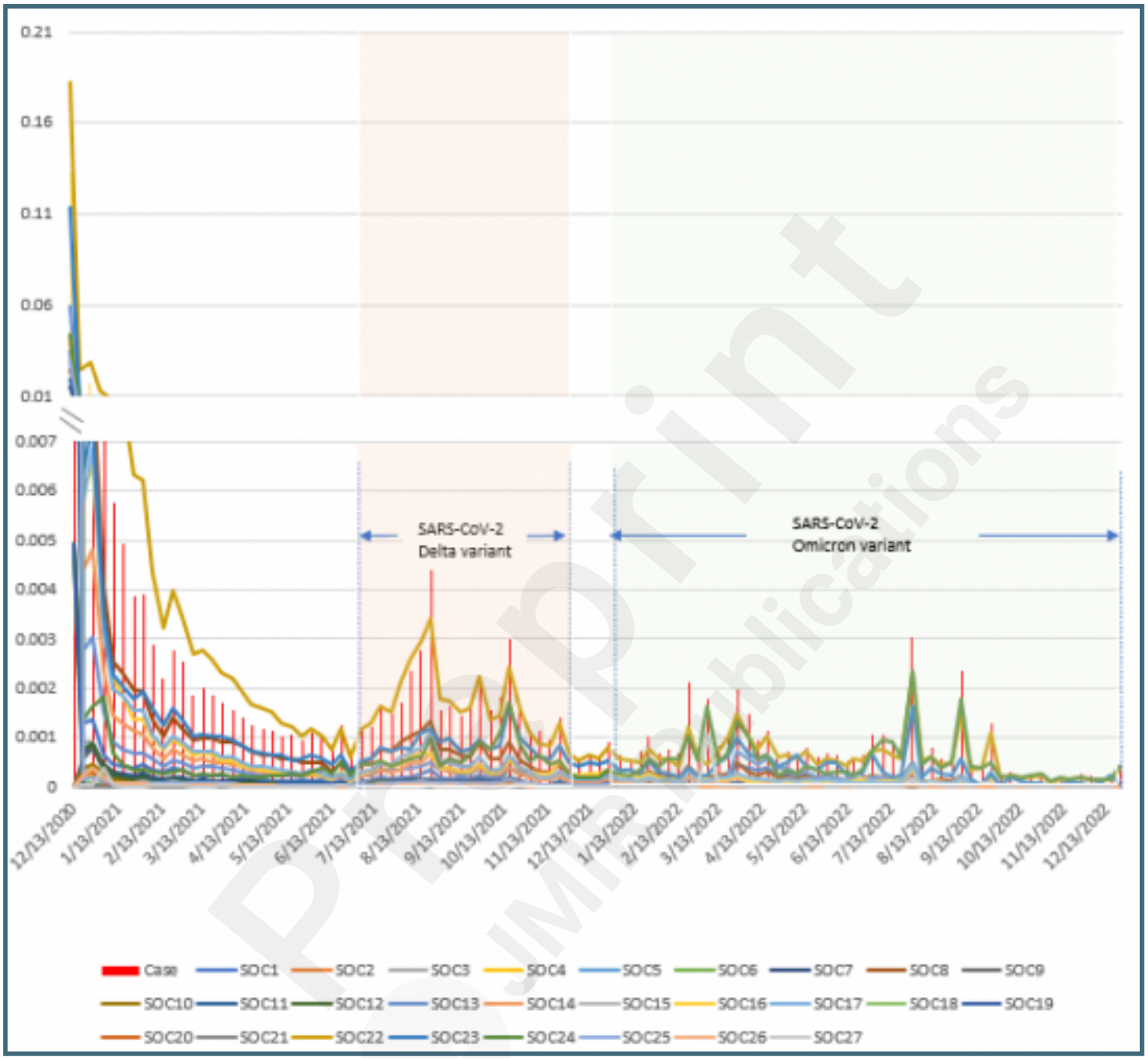
Serious case reporting rate and serious case Top 10 adverse event reporting rate for COVID-19 vaccines in the United States, 2020-2022.



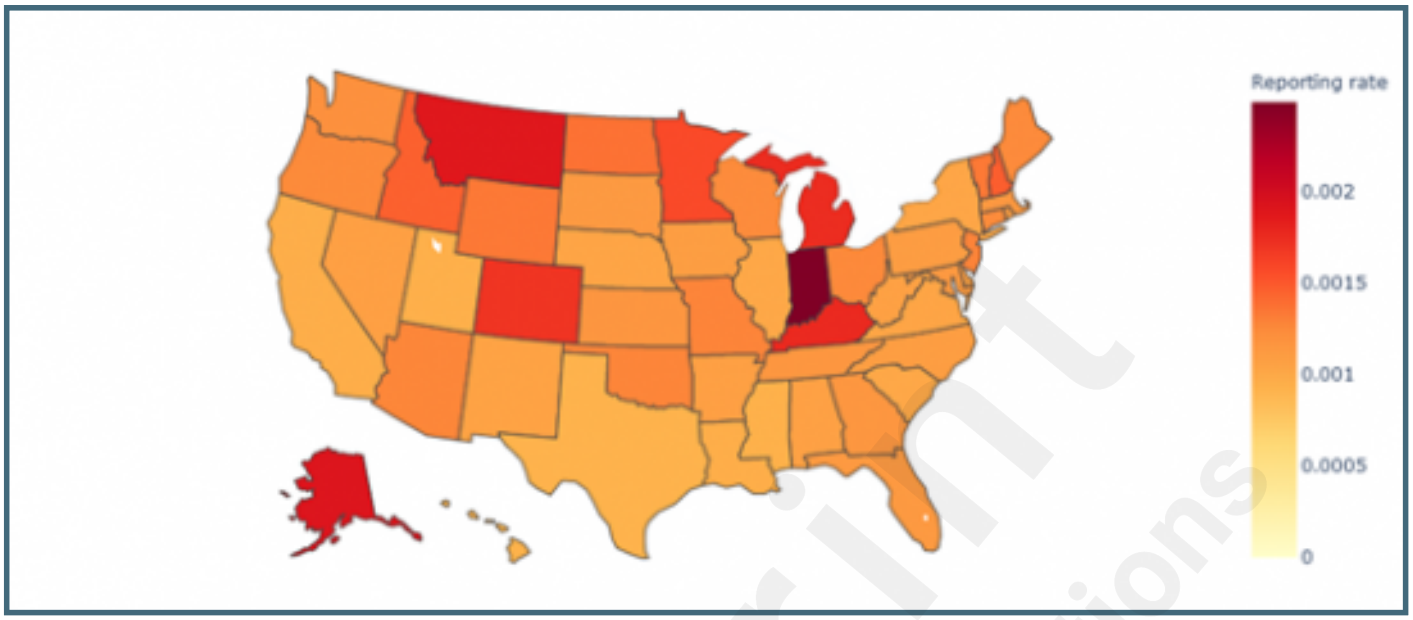
Case reporting rate and individual System Organ Class reporting rate for Pfizer vaccine in the United States, 2020-2022.



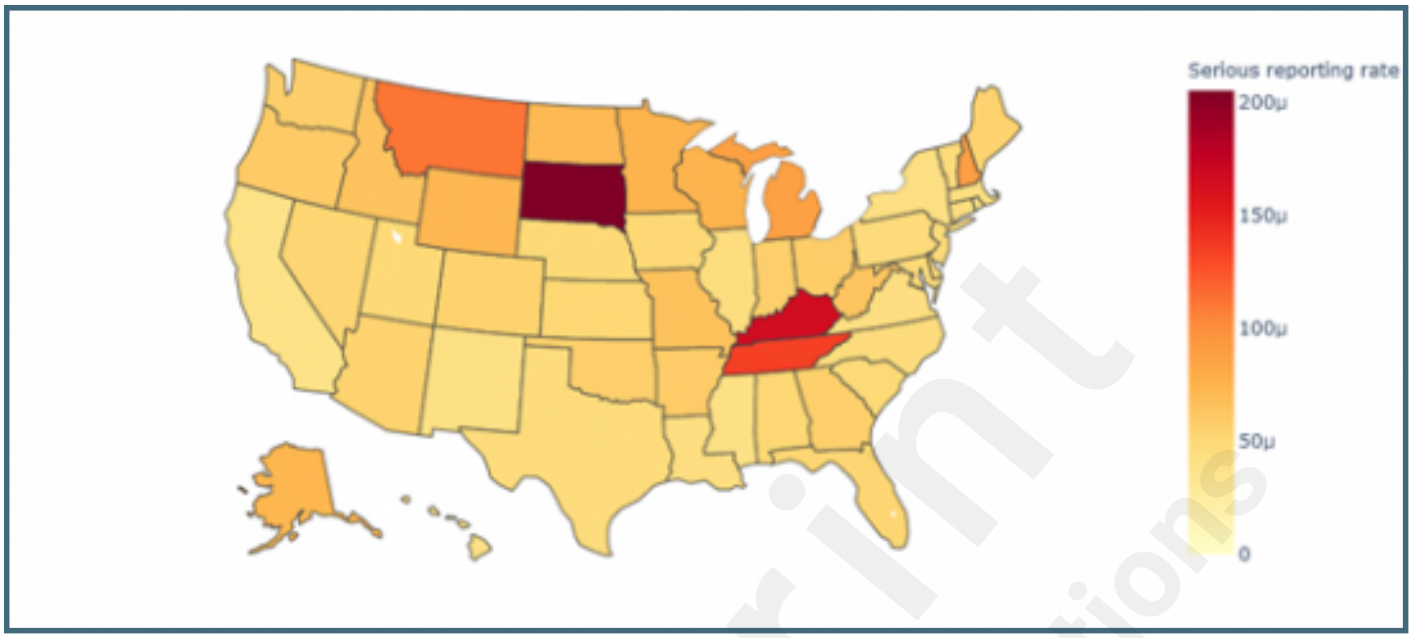
Case reporting rate and individual System Organ Class reporting rate for Moderna vaccine in the United States, 2020-2022.



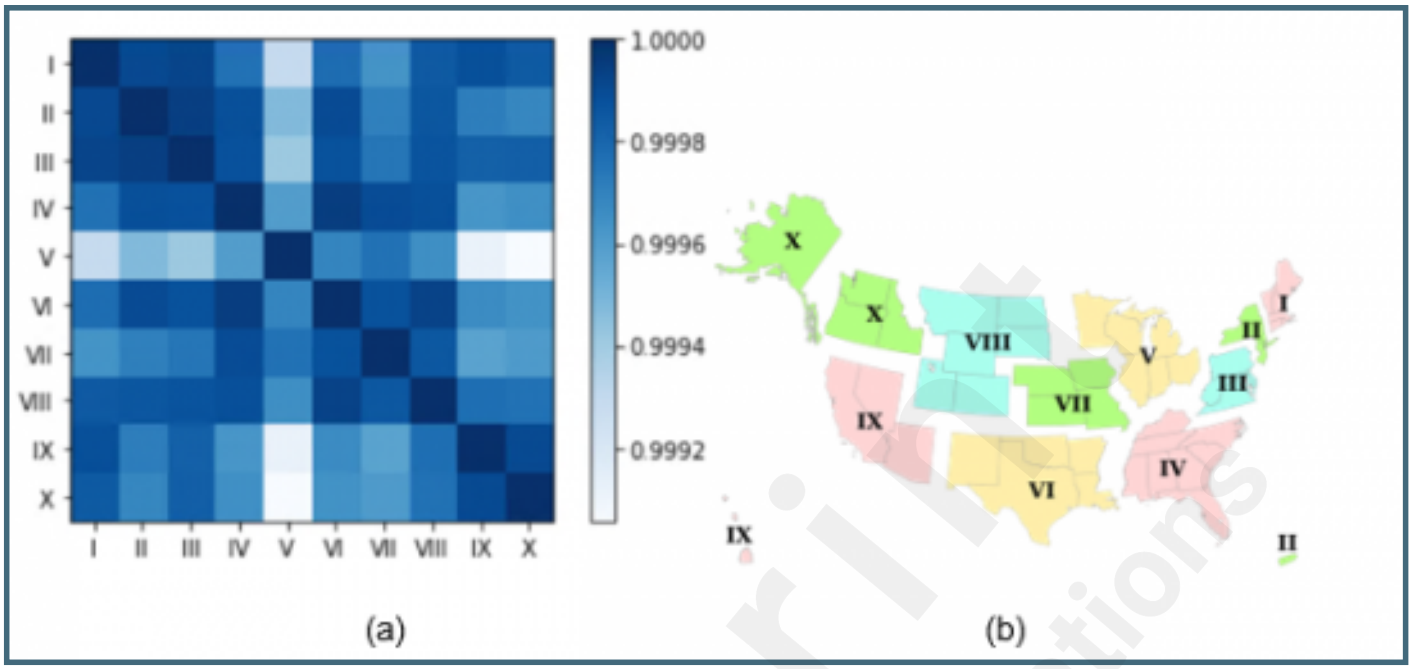
The reporting rate of COVID-19 vaccines in Vaccine Adverse Event Reporting System by state in the United States, 2020-2022.



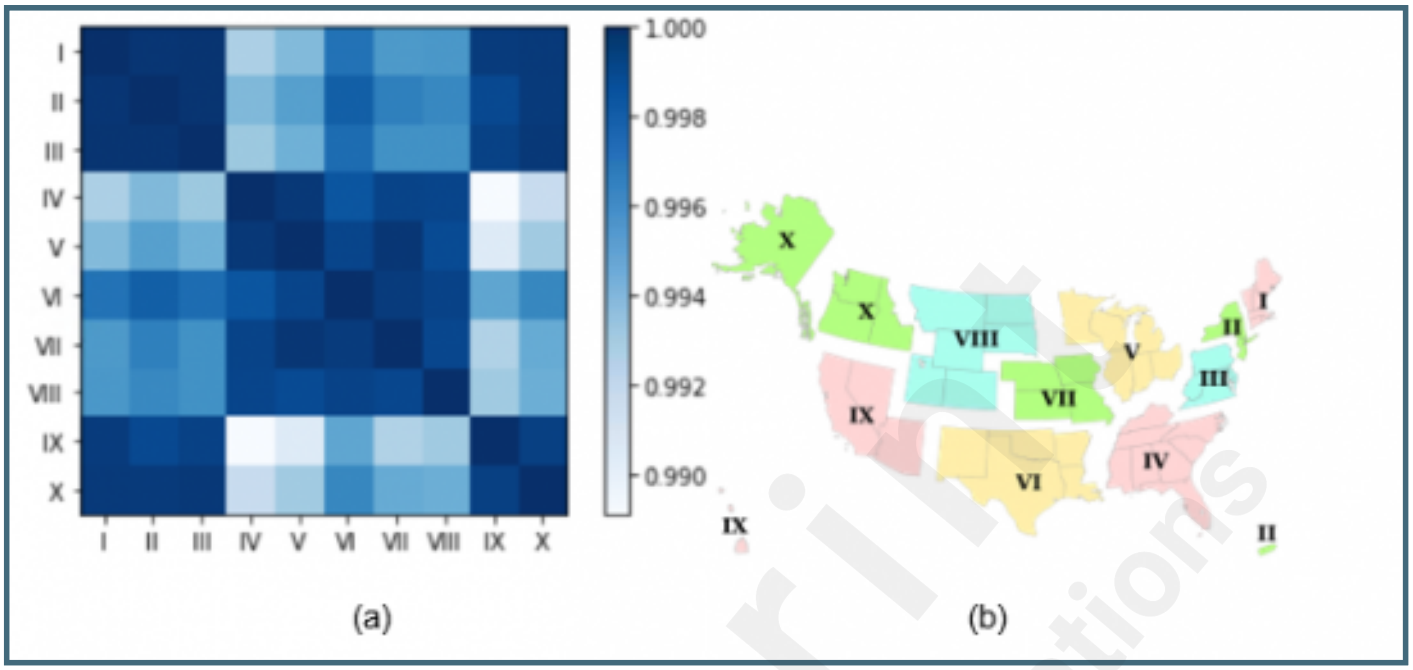
The serious case reporting rate of COVID-19 vaccines in Vaccine Adverse Event Reporting System by state in the United States, 2020-2022.



(a) The heatmap of the similarity of symptoms following COVID-19 vaccines between regions in the United States, 2020-2022
(b) Standard Federal Regions in the United States.



(a) The heatmap of the similarity of symptoms for serious reports of COVID-19 vaccines between regions in the United States, 2020-2022 (b) Standard Federal Regions in the United States.



Multimedia Appendixes

Untitled.
URL: http://asset.jmir.pub/assets/bfd010f446d11da0542acaf26d3cef89.zip