



## LJMU Research Online

Flora, J, Khan, W, Jin, J, Jin, D, Hussain, A, Dajani, K and Khan, B

**Usefulness of Vaccine Adverse Event Reporting System for Machine-Learning Based Vaccine Research: A Case Study for COVID-19 Vaccines**

<https://researchonline.ljmu.ac.uk/id/eprint/17401/>

### Article

**Citation** (please note it is advisable to refer to the publisher's version if you intend to cite from this work)

**Flora, J, Khan, W ORCID logoORCID: <https://orcid.org/0000-0002-7511-3873>, Jin, J, Jin, D, Hussain, A ORCID logoORCID: <https://orcid.org/0000-0001-8413-0045>, Dajani, K and Khan, B ORCID logoORCID: <https://orcid.org/0000-0001-8549-2099> (2022) Usefulness of Vaccine Adverse Event Reporting**

LJMU has developed [LJMU Research Online](#) for users to access the research output of the University more effectively. Copyright © and Moral Rights for the papers on this site are retained by the individual authors and/or other copyright owners. Users may download and/or print one copy of any article(s) in LJMU Research Online to facilitate their private study or for non-commercial research. You may not engage in further distribution of the material or use it for any profit-making activities or any commercial gain.

The version presented here may differ from the published version or from the version of the record. Please see the repository URL above for details on accessing the published version and note that access may require a subscription.

For more information please contact [researchonline@ljmu.ac.uk](mailto:researchonline@ljmu.ac.uk)

<http://researchonline.ljmu.ac.uk/>



Article

# Usefulness of Vaccine Adverse Event Reporting System for Machine-Learning Based Vaccine Research: A Case Study for COVID-19 Vaccines

James Flora <sup>1</sup>, Wasiiq Khan <sup>2</sup> , Jennifer Jin <sup>1</sup>, Daniel Jin <sup>3</sup>, Abir Hussain <sup>4</sup> , Khalil Dajani <sup>1</sup> and Bilal Khan <sup>1,5,\*</sup>

<sup>1</sup> Department of Computer Science and Engineering, California State University San Bernardino, 5500 University Parkway, San Bernardino, CA 92407, USA; 006981423@coyote.csusb.edu (J.F.); jennifer.jin@csusb.edu (J.J.); khalil.dajani@csusb.edu (K.D.)

<sup>2</sup> School of Computer Science and Mathematics, Liverpool John Moores University, Liverpool L3 3AF, UK; w.khan@ljmu.ac.uk

<sup>3</sup> Division of Vascular & Interventional Radiology, Department of Radiology, Loma Linda University Medical Center, Loma Linda, CA 92354, USA; djin@llu.edu

<sup>4</sup> Department of Electrical Engineering, University of Sharjah, Sharjah P.O. Box 27272, United Arab Emirates; abir.hussain@sharjah.ac.ae

<sup>5</sup> Institute of the Environment and Sustainability, University of California Los Angeles, Los Angeles, CA 90095, USA

\* Correspondence: bilal.khan@csusb.edu; Tel.: +1-(909)-537-5428

**Abstract:** Usefulness of Vaccine-Adverse Event-Reporting System (VAERS) data and protocols required for statistical analyses were pinpointed with a set of recommendations for the application of machine learning modeling or exploratory analyses on VAERS data with a case study of COVID-19 vaccines (Pfizer-BioNTech, Moderna, Janssen). A total of 262,454 duplicate reports (29%) from 905,976 reports were identified, which were merged into a total of 643,522 distinct reports. A customized online survey was also conducted providing 211 reports. A total of 20 highest reported adverse events were first identified. Differences in results after applying various machine learning algorithms (association rule mining, self-organizing maps, hierarchical clustering, bipartite graphs) on VAERS data were noticed. Moderna reports showed *injection-site-related* AEs of higher frequencies by 15.2%, consistent with the online survey (12% higher reporting rate for *pain in the muscle* for Moderna compared to Pfizer-BioNTech). AEs {*headache, pyrexia, fatigue, chills, pain, dizziness*} constituted >50% of the total reports. *Chest pain* in male children reports was 295% higher than in female children reports. *Penicillin* and *sulfa* were of the highest frequencies (22%, and 19%, respectively). Analysis of uncleaned VAERS data demonstrated major differences from the above (7% variations). Spelling/grammatical mistakes in allergies were discovered (e.g., ~14% reports with incorrect spellings for *penicillin*).

**Keywords:** COVID-19; VAERS; adverse events; vaccine development; association rule mining; self-organizing maps; hierarchical clustering; bipartite graphs; vaccine analysis workflow



**Citation:** Flora, J.; Khan, W.; Jin, J.; Jin, D.; Hussain, A.; Dajani, K.; Khan, B. Usefulness of Vaccine Adverse Event Reporting System for Machine-Learning Based Vaccine Research: A Case Study for COVID-19 Vaccines. *Int. J. Mol. Sci.* **2022**, *23*, 8235. <https://doi.org/10.3390/ijms23158235>

Academic Editor: Nima Aghaeepour

Received: 14 June 2022

Accepted: 21 July 2022

Published: 26 July 2022

**Publisher's Note:** MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.



**Copyright:** © 2022 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

## 1. Introduction

VAERS, an online passive reporting system, co-sponsored by the US Center for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA), and the agencies of US Health and Health Services (HHS) are specifically geared towards assessing the safety of newly developed vaccines along with other priorities that include: (i) the detection of new, unusual, or rare vaccine adverse events, (ii) the monitoring of the increase in known events, (iii) the identification of potential risk factors for particular types of adverse events (AEs), (iv) the determination of possible reporting clusters, (v) the recognition of persistent safe-use problems, and (vi) the provision of national safety monitoring to public health emergencies, such as a large-scale pandemic influenza vaccination program [1–3]. Due to its spontaneous reporting nature, VAERS data is not recommended for discerning

the cause of AEs from the vaccine after an AE is reported. Although the availability and utilization of high-quality vaccine data for decision support and vaccine safety is critical, public reports prior to a vaccine authorization by VAERS can be useful in determining AEs and in providing valuable insights for a streamlined vaccine manufacturing and policy development.

VAERS datasets have been used in various studies for recommendations and proactive strategies for regulatory bodies (CDC and FDA) [4–21]. To date, only limited studies have comprehensively focused on the protocols to be followed when VAERS datasets are used for statistical analyses (Supplementary Materials—Section S1). For example, a study compiled VAERS reports on Guillain-Barre Syndrome (GBS) in regard to influenza vaccines and identified correlations between the AE and the syndrome, including the attributes age and gender [14]. Two distinct datasets were utilized (i.e., 80,059 US (VAERS FLU3, 1990–2017) reports and 13,550 European reports (all FLU vaccination, 2003–2016)) to develop a logistic regression model for predicting 83 different AEs with prediction accuracies of 77.5% and 75.5% (area under the curve (AUC) measures) for VAERS and European FLU vaccine datasets, respectively. Patient age (as quantized into the ranges of {0.5–17, 18–49, 50–64, and 65+} years) and gender were considered as model attributes. Syndrome to AE correlation was carried using Chi-squared test which demonstrated nine AEs (*pyrexia, chills, nausea, pruritus, rash, urticaria, injection site pain, injection site swelling, and injection site erythema*) to be negatively associated with GBS while 13 other AEs (*muscle spasms, hypertension, dysphagia, hyperglycemia, diabetes mellitus, dysuria, depression, apnea, fecal incontinence, constipation, urinary incontinence, dysuria, urinary tract infection, and urinary retention*) were positively associated with GBS but with low prevalence (<1%). The study acknowledged that VAERS data are screened by the CDC for the removal of duplicates.

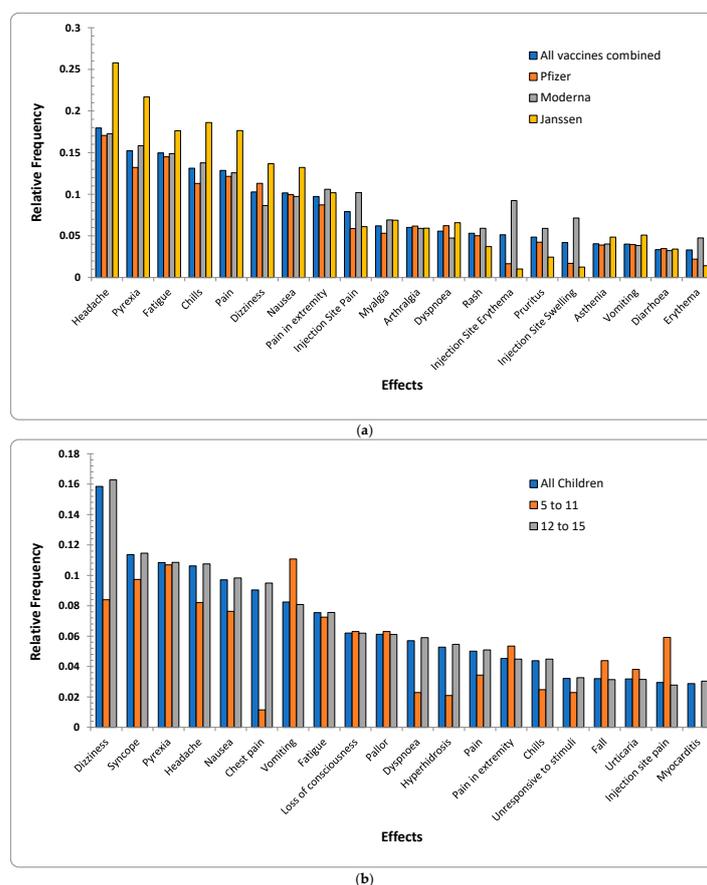
A study emphasized that the identification of duplicate pairs in VAERS for the application of data-mining algorithms on VAERS data that, without robustly handling duplicate cases, can have deleterious effects on quantitative analyses leading to spurious conclusions on vaccine safety [22]. A probabilistic approach was developed to link duplicate pairs allowing a systematic approach of deduplicating the VAERS database using the structured field data as well as non-structured textual data of AEs via event-based text-mining approach. Another useful analysis of the validity of VAERS reports via expert judgement was carried out that demonstrated the lower likeliness of an AE being associated with a vaccine [19]. A total of 100 VAERS reports of the AE following immunization (AEFI) were analyzed where 83% achieved majority agreement over the results of the causality assessment, while 17% of the reports were considered for further discussion by the expert panel. From the 100 reports, 3%, 20%, and 20% of the AEFI were identified as being definitely, probably, and possibly related to the vaccine, respectively, while 53% of the AEFIs were classified as unlikely or unrelated to the vaccine.

Data provenance methods and preprocessing techniques based on only a passive reporting system require careful attention when carrying out data-driven exploratory analysis and applying statistical approaches on VAERS data in order to avoid misleading/incorrect conclusions. The factors contributing to the robust and accurate analyses of such data include the handling of: (i) duplicate records, (ii) missing values (submitting incomplete VAERS forms), (iii) limited-form fields (up to 5 symptoms in one report) leading to duplicates, (iv) spelling/grammatical mistakes via robust and appropriate text mining approaches, (v) outliers and data standardization/normalization, (vi) data heterogeneity, and (vi) the binning of continuous variables (such as age) into groups to avoid bias when applying probabilistic/frequentist approaches. Accordingly, the present study proposes the aforementioned data provenance and preprocessing techniques for robust statistical analyses with the help of a case study for COVID-19 vaccine data collected from VAERS. Dynamic trends in unstructured temporal COVID-19 vaccine data from VAERS were analyzed via self-organizing maps (SOMs), association rule mining (ARM), and hierarchical clustering (HC) techniques in order to provide a detailed data-driven evaluation of multi-AE associations and complex patterns. Reports from VAERS and a qualitative online survey

were incorporated to: (i) identify the frequently reported AEs after COVID-19 vaccines, (ii) assess their correlations with respect to various demographics (age groups, gender, and allergies), and (iii) provide a baseline decision support for predictive capability when de-identified data become available from regulatory agencies as well as the vaccine producers. Such analysis can be useful for determining the proportion of reports involving specific AEs and a vaccine can be compared to the proportion of reports involving the same AEs and other vaccines [2].

## 2. Results

Figure 1a,b shows the relative frequencies of the 20 most-reported AEs for all age groups per three vaccine manufacturers and children of ages up to (and inclusive of) 15 years old, respectively. AEs for each vaccine manufacturer were significantly consistent. There were 13 AEs {*arthralgia, asthenia, chills, dizziness, dyspnoea, fatigue, headache, injection site pain, myalgia, nausea, pain, pain in extremity, pyrexia*} that were common for all three vaccine manufacturers. Survey data also reported {*headache, aches, chills, pain in muscle, dizziness, nausea, vomiting, and rash*} to be the most commonly reported AEs (Table 1). *Rash* was replaced by *injection site pain* for children's data (Figure 1b) when duplicates and spelling mistakes were corrected in the VAERS reports.



**Figure 1.** (a) Relative frequencies of the top 20 AEs appeared in VAERS reports for all age groups per the three vaccine producers (Pfizer-BioNTech, Moderna, and Janssen). (b) Relative frequencies of the top 20 AEs appeared in VAERS reports for children (discretized age groups of 5–11 years). The subset {*chest pain, Dyspnoea, hyperhidrosis, and myocarditis*} was among the lowest-reported AEs for age group (5–11 years) in comparison to the AEs reported for the group 12–15 and other 16 most commonly reported AEs.

**Table 1.** Summary of the 20 most commonly reported AEs in VAERS reports and online survey data per three vaccine producers.

Effects		Vaccine Manufacturer				
VAERS	Survey Data	Pfizer-BioNTech	Pfizer-BioNTech Survey Data Points	Moderna	Moderna Survey Data Points	Janssen
Headache	Headache	48,253 (17.05%)	44 (35.77%)	51,816 (17.27%)	31 (46.97%)	15,234 (25.78%)
Pyrexia	Aches	37,418 (13.22%)	53 (43.09%)	47,476 (15.82%)	44 (66.67%)	12,811 (21.68%)
Fatigue	Tired	41,022 (14.49%)	78 (63.41%)	44,642 (14.88%)	48 (72.73%)	10,409 (17.62%)
Chills	Chills	31,965 (11.29%)	54 (43.90%)	41,313 (13.77%)	44 (66.67%)	11,001 (18.62%)
Pain	Pain in muscle	34,395 (12.15%)	49 (39.84%)	37,716 (12.57%)	34 (51.52%)	10,424 (17.64%)
Dizziness	Dizziness	32,001 (11.31%)	2 (1.63%)	25,924 (8.64%)	13 (19.70%)	8075 (13.67%)
Nausea	Nausea	28,179 (9.96%)	13 (10.57%)	29,220 (9.74%)	11 (16.67%)	7815 (13.23%)
Pain in Extremity	NA	24,708 (8.73%)	NA	31,813 (10.60%)	NA	6019 (6.11%)
Myalgia	NA	15,027 (5.31%)	NA	20,728 (6.91%)	NA	4059 (6.87%)
Arthralgia	NA	17,469 (6.17%)	NA	17,713 (5.90%)	NA	3504 (5.93%)
Injection site pain	NA	16,621 (5.87%)	NA	30,632 (10.21%)	NA	3610 (6.11%)
Dyspnoea	NA	17,612 (6.22)	NA	14,207 (4.74%)	NA	3895 (6.59%)
Rash	Itchy Skin/Rash	14,178 (5.01%)	1 (0.81%)	17,739 (5.91%)	2 (3.03%)	2194 (3.71%)
Pruritus	NA	12,013 (4.24%)	NA	17,697 (5.90%)	NA	1451 (2.46%)
Injection site erythema	NA	4685 (1.66%)	NA	27,730 (9.24%)	NA	600 (1.02%)
Asthenia	Strange Feeling	11,067 (3.91%)	10 (8.13%)	12,092 (4.03%)	15 (22.73%)	2869 (4.86%)
Vomiting	Vomiting	11,205 (3.96%)	NA	11,523 (3.84%)	2 (3.03%)	3009 (5.09%)
Injection-site swelling	Enlarged lymph nodes	4815 (1.70%)	NA	21,406 (7.14%)	1 (1.52%)	740 (1.25%)
Diarrhoea	NA	9819 (3.47%)	NA	9682 (3.23%)	NA	2018 (3.42%)
Erythema	NA	6242 (2.21%)	NA	14,227 (4.74%)	NA	838 (1.42%)

**Note:** Numbers in the table indicate the number of VAERS samples that reported corresponding AE and the percentage shows the percent of all patients in VAERS reports that were vaccinated by the given vaccine manufacturer. Survey data for Janssen were not available.

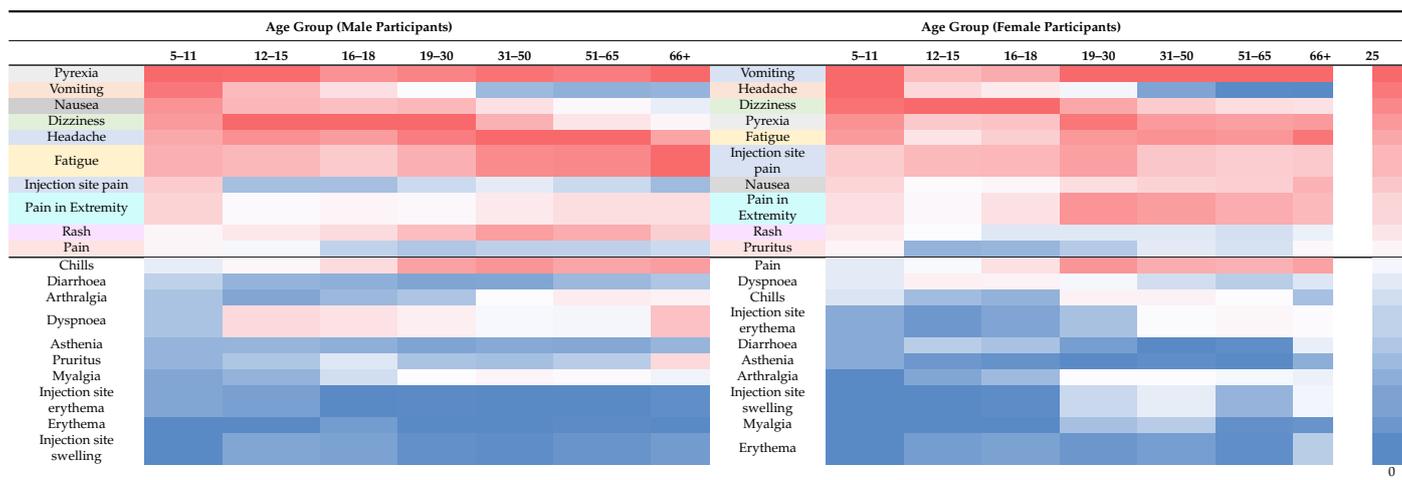
Interestingly, four *injection-site-related* AEs (*injection site—(erythema, pruritus, swelling, warmth)*) were among the top 20 AEs for Moderna ( $p$ -value  $< 2.2 \times 10^{-16}$  for Moderna vs. {Pfizer-BioNTech, Janssen} with respect to the top 20 AEs including *injection-site-related* AEs). Survey data also showed 51% of the samples for Moderna with *pain in muscle* as opposed to only 39% samples for Pfizer-BioNTech reporting *pain in muscle* (Table 1). This may be due to the fact that Moderna uses a 100-microgram dose as opposed to the 30-microgram used by Pfizer-BioNTech, causing increased reactogenicity [23]. Additionally, although the etiology of delayed large local reactions due to Moderna is unclear, a delayed-type hypersensitivity reaction to the excipient polyethylene glycol can be a potential etiology [24]. The above visual exploration without duplicate-row removal (Supplementary Materials—Figures S1 and S2) showed relative frequencies of the above 20 AEs to be lower by up to 7% (Supplementary Materials—Figure S1) than the frequencies observed in the cleaned data (Figure 1a). Similarly, the AEs for children showed differences of up to 4% (Figure 1b and Figure S2 (Supplementary Materials)).

The subset (*dizziness, pyrexia, headache, nausea, vomiting, fatigue, dyspnoea, pain, pain in extremity, chills, rash*) was common among adults (including children (Figure 1a)) and children (Figure 1b). None of the *injection-site-related* AEs (*injection site—(pain, erythema, swelling, warmth)*) were among highly reported AEs in children's reports. Additionally, (*arthralgia, asthenia, myalgia, pruritus, erythema*) only appeared in the 20 most reported AEs for adults where (*chest pain, syncope, loss of consciousness, pallor, hyperhidrosis, urticaria, fall, unresponsive to stimuli, myocarditis*) were reported only among children. The above differ-

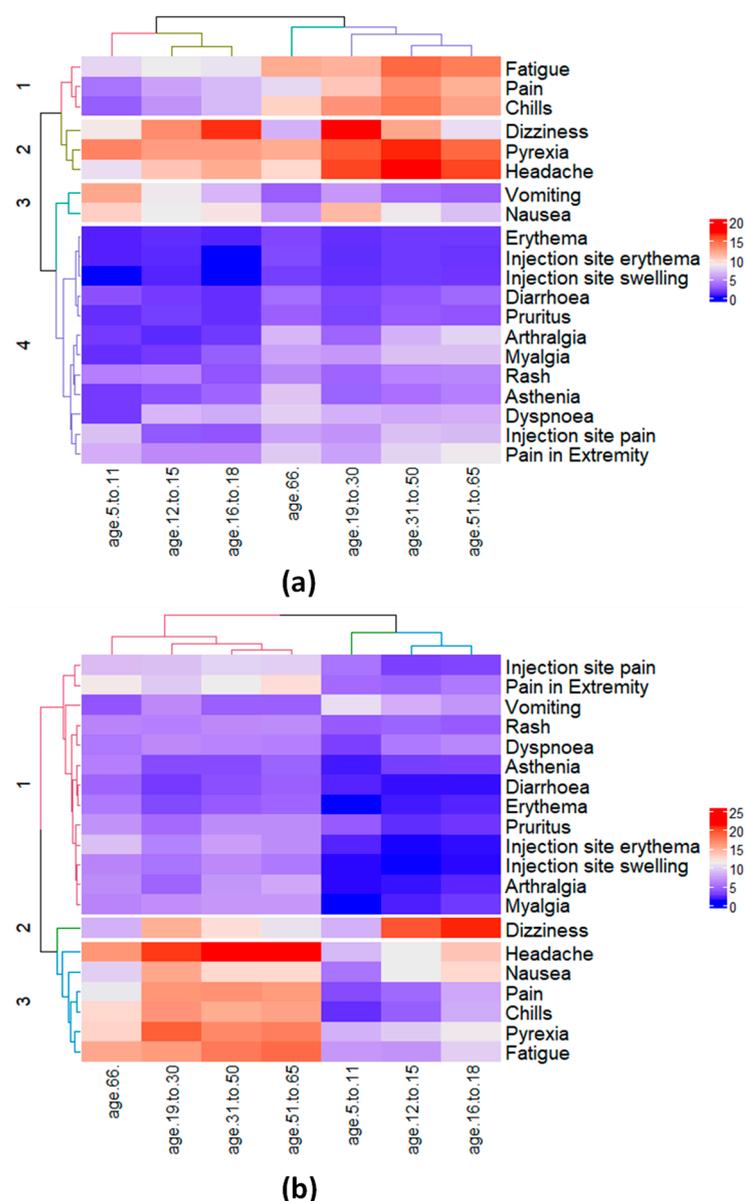
ences may arise due to the Pfizer-BioNTech dose for children being only 10 micrograms compared to 30 micrograms for adults.

As given in the heatmap in Table 2, although in a different order based on their percentage, all 20 highest-reported AEs for both children’s genders were the same. An important pattern in children’s VAERS reports was found to have *chest pain* reported to be 3 times higher in male reports than in female reports (chi-squared test  $p$ -value:  $5.74 \times 10^{-62}$ ). Based on the number of occurrences, *vomiting* was ranked as the top effect for female as opposed to the 2nd for male children ( $p$ -value: 0.56 indicating no significant correlation of vomiting with gender). It is noted, however, that for the VAERS dataset with duplicates, *headache* appeared as the top-ranked effect for female (Table S3) as opposed to 5th-ranked for male children ( $p$ -value: 0.61). Additionally, *injection site pain* ranked a level higher for female (6th) compared to male children (7th), with  $p$ -value: 0.59 (i.e., no significant correlation of *injection site pain* with gender). Other correlation tests with  $p$ -values are {*Dizziness*:  $3.8 \times 10^{-14}$ , *Pyrexia*:  $8.21 \times 10^{-6}$ , *Fatigue*:  $4 \times 10^{-3}$ , *Nausea*:  $4 \times 10^{-4}$ , *Pain in Extremity*: 0.77, *Rash*: 0.88, *Pain*: 0.075, *Chest Pain*:  $5.74 \times 10^{-62}$ }. It is also noted that the ratio of female VAERS COVID-19 reports is higher than male reports, which is consistent with other VAERS vaccine ratios (e.g., flu vaccine for 2021 had the number of reports as female: 5222, and male: 2375).

**Table 2.** The 20 most commonly reported AEs ranked with respect to the age groups and gender based on the percentage of VAERS samples reporting the corresponding AE (minimum 0% to maximum 25%). Heatmap cells are colored according to the percentage of reported samples, and the AEs are sorted according to the percentage of reported VAERS samples for age group 5–11.

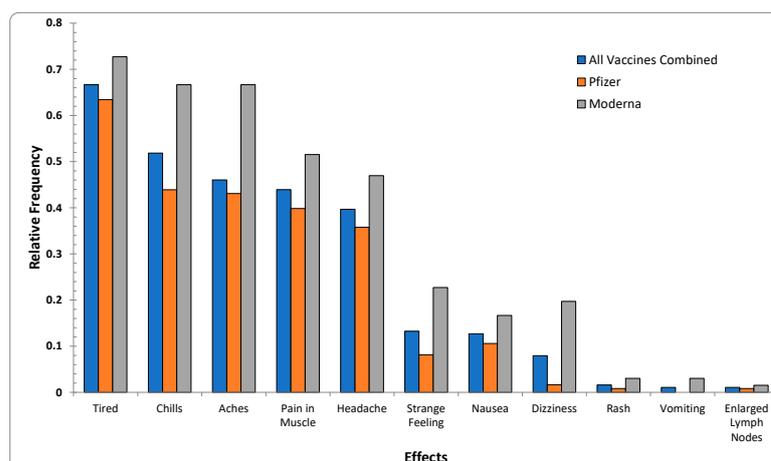


When grouped into clusters via an unsupervised HC approach, male children and young adults (i.e., age groups of 18 inclusive and under) were clustered in one group (i.e., Cluster III with blue dendrogram), as shown in Figure 2. For male children, {*dizziness, headache, pyrexia*} were grouped in the same cluster (Cluster II) with {*nausea, vomiting*} to be in the adjacent cluster (Cluster III), consistent with the grouping provided in Table 2. Furthermore, {*fatigue, chills, pain*} for male children were clustered in Cluster I. Interestingly, the HC approach demonstrated tolerance in grouping datasets with and without duplicates, as no difference in Figures 2 and S3 was observed. Overall, VAERS reports for male participants in Clusters I and II (*fatigue, chills, pain, dizziness, headache, pyrexia*) were to be of the highest percentage, as confirmed in Table 2. Consequently, due to {*dizziness, headache, nausea, pyrexia*} being reported more commonly between the age groups of 12–15 and 16–18 for female, they were grouped in the same cluster as shown in Figure 2, while 5–11 grouped in adjacent cluster. Consistent with Table 2, *injection-site-related* AEs in female and male children were grouped in clusters I and IV with lower-reporting percentages in Figures 2 and S3, respectively.



**Figure 2.** Hierarchical clustering of the 20 most commonly reported effects and 7 age groups for (a) male and (b) female participants. For male participants (a) the effects {*pyrexia*, *vomiting*, and *nausea*} and {*dizziness*, *pyrexia*} were reported to be the most commonly reported effects for the two children age groups 5–11 and 12–15, respectively. For female participants (b), the effects {*headache*, *pyrexia*, *nausea*, *vomiting*, and *dizziness*} were reported to be the most commonly reported effects for children age group 5–11 and 12–15, respectively, with the addition of *nausea* among the 3rd most-reported effect for age group 12–15.

It is noted that, despite comprehensive data preprocessing steps, reports submitted through VAERS have not undergone data-quality assurance/control strategies, thus posing challenges for the verification of the analysis. To overcome the challenge of the uncertainty and reliability of the VAERS reports and confirm the AE similarities, an exploration of the online survey data was also conducted (Figure 3). As illustrated in Table 1 and Figure 3, from a set of 11 AEs compiled from 211 participants, {*headache*, *chills*, *dizziness*, *nausea*, *itchy skin/rash*, *vomiting*} also appeared in the 20 most reported AEs in the VAERS reports.



**Figure 3.** Relative frequencies of the 11 AEs appearing in survey data reports for all age groups per the two vaccine producers (Pfizer-BioNTech, Moderna). The subset {headache, chills, dizziness, nausea, itchy skin/rash, vomiting} was the same as 6 of the 20 most-reported effects in VAERS reports.

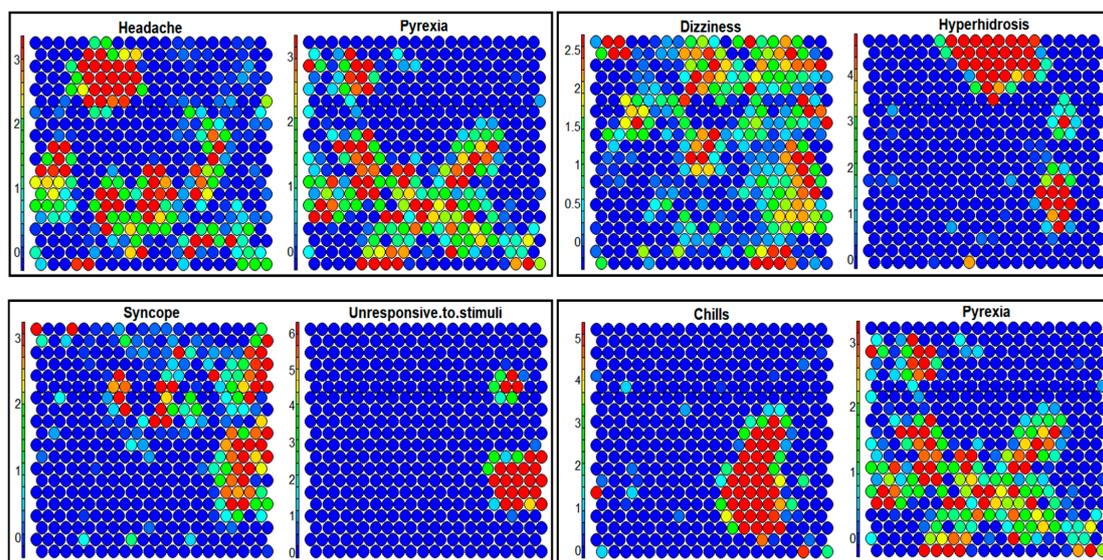
2.1. Associations of the Most Commonly Reported AEs via ARM and SOM

The interrelationships of AEs from VAERS reports were analyzed via ARM and SOM with respect to two major age groups [ $<16, \geq 16$ ]. Assessment of the interrelationships of AEs for children revealed 16 non-redundant association rules (ARs) (Table 3). From a subset of one-to-one rules, the existence of *Hyperhidrosis* or *flushing* was shown to imply the existence of *dizziness* with lift-over 3 ( $R_{2,10}$ ). *Chest pain* was found to be prominent with dependency over the subset {*Electrocardiogram ST segment elevation, Chest X-ray normal, Echocardiogram normal, Myocarditis, Electrocardiogram normal, C-reactive protein increased, Troponin increased*} with a lift value of  $>8$  ( $R_{3,5,7-9,11,13}$ ). Additionally, it was also noticed that *hyperhidrosis* was associated with *flushing* with a high lift value of 18.8 ( $R_9$ ). Although fatigue appeared among the top 6 AEs for children based on its individual frequency, its correlation with any other AE could not qualify it for the top 14 ARs (Table 3 and Figure 1).

**Table 3.** Non-redundant association rules for post-COVID-19 vaccine AEs reported in VAERS reports for children based on cleaned with duplicate rows merged. Rule 14 was the only non-redundant many-to-one rule identified for children. The highlighted regions in gray represent a subset of rules with relatively high counts in the dataset ( $>200$ ) and include {*dizziness, hyperhidrosis, syncope, unresponsive to stimuli, pyrexia, chills, myocarditis*}, which were also among the 20 most commonly reported AEs in children when explored based on their individual frequencies.

Rule	Antecedent	Consequent	Support	Confidence	Lift	Count
R-1	Flushing	Hyperhidrosis	0.016	0.80	15.18	149
R-2	Flushing	Dizziness	0.013	0.69	4.34	128
R-3	Electrocardiogram ST segment elevation	Chest pain	0.012	0.92	10.18	114
R-4	Unresponsive to stimuli	Syncope	0.023	0.72	6.35	223
R-5	Chest X-ray normal	Chest pain	0.011	0.79	8.70	103
R-6	Echocardiogram normal	Troponin increased	0.011	0.55	16.59	108
R-7	Echocardiogram normal	Chest pain	0.018	0.87	9.62	172
R-8	Myocarditis	Chest pain	0.021	0.74	8.22	205
R-9	Electrocardiogram normal	Chest pain	0.017	0.68	7.52	163
R-10	Hyperhidrosis	Dizziness	0.028	0.52	3.31	266
R-11	C-reactive protein increased	Chest pain	0.012	0.67	7.46	118
R-12	Chills	Pyrexia	0.027	0.62	5.76	263
R-13	Troponin increased	Chest pain	0.028	0.85	9.46	270
R-14	Headache, Pain	Pyrexia	0.011	0.54	4.98	101

The ARM employs a frequentist approach to calculate the *Support*, *Confidence*, and *Lift* (Supplementary Materials—Section S2.2.1), for which duplicate reports can pose a significant challenge. Therefore, a new report or reports with spelling/grammar mistakes can impact the generality and specificity of the ARs, impacting such analysis with duplicates present in the VAERS data. As illustrated in Tables S4–S7 (Supplementary Materials), the ARs for children and each vaccine producer indicated significant differences from those identified when duplicates were removed (Tables 3 and 4). For example,  $R_6$  (*Echocardiogram normal* → *Troponin increased*) for the non-redundant ARs for children (Table 3) demonstrated that the highest *lift* value of 16.6 was initially not identified as a non-redundant AR in Table S4 (Supplementary Materials). Additionally, seven rules ( $R_{3,5,7-9,11,13}$ ) reported *chest pain* in the consequent cleaned VAERS data for children (Table 3) whereas none of the ARs in Table S4 (Supplementary Materials) reported *chest pain* in the consequent VAERS data with duplicates. ARs ( $R_{4,10,12,14}$ ) when verified via SOM in Figure 4 demonstrate the relationships of  $\{\{Unresponsive\ to\ stimuli\} \rightarrow Syncope\}, \{Hyperhidrosis\} \rightarrow Dizziness\}, \{Chills\} \rightarrow Pyrexia\}, \{Headache, pain\} \rightarrow Pyrexia\}$ . However, SOM may also suffer from misleading correlations from uncleaned VAERS data due to the iterative nature of 2D-map refinement (Table S4 (Supplementary Materials) and Figure 4).



**Figure 4.** SOM analysis of the top 20 most reported AEs from the reports filtered for children (age 15 (inclusive) and under) for all vaccines. Association of AEs  $\{chills, dizziness, headache, hyperhidrosis, pyrexia, syncope\}$  in the form of 2D cluster similarities is demonstrated as shown in the rules  $R_{4,10,12,14}$  in Table 3.

Analysis of the ARs for the AEs of all age groups was also conducted for the three vaccine types (Table 4). In the set of ARs for Pfizer-BioNTech, *headache* appeared in the consequent of 10 ARs, with  $\{chills, myalgia, pyrexia, pain, fatigue, nausea\}$  in antecedents with count values  $> 3000$  ( $R_{5,6,8,10-16}$ ). Although the above distributions appeared to be dispersed without demonstrating a discernible pattern (Figure 4), the overall distributions showed similarities in the SOM component planes. However, with duplicates present, only two ARs ( $R_{19,20}$ ) had *headache* in the consequent (Supplementary Materials, Table S5), due to the fact that the entries for *headache* were distributed with duplicates, increasing the frequency with which *headache* appeared. Another observation (Table 4) showed 7 out of 25 ARs for Moderna listed *injection-site-related* effects (e.g., *injection site*  $\{pruritus, pain, induration, warmth, swelling, erythema\}$ ) in either the antecedent or the consequent with *Injection site swelling* → *injection site erythema* ( $R_5$ ) having the second highest count of 13,561. Additionally, the distributions for  $\{injection\ site\ (erythema, pain, swelling), pain\ in\ extremity\}$  were also interrogated via SOM (Supplementary Materials—Figure S6) to validate

the existence of correlations among these AEs as indicated by the rules ( $R_{1,2,4,5,7,8,15,16}$ ) in Table 4. The similarity between AEs as represented by the 2D SOM is indicative of the coexistence of their correlations (i.e., the existence of a base AE implies the existence of another AE as given by the distributions on a 2D map).

**Table 4.** Non-redundant association rules for AEs reported in VAERS reports for the three vaccines.

Non-redundant association rules for post-COVID-19 vaccine AEs reported in VAERS reports for Pfizer-BioNTech vaccine. Rules 4–16 were non-redundant many-to-one rules identified for Pfizer-BioNTech. The highlighted regions in gray represent the subset of rules with relatively high counts in the dataset (>6000). The rules below include {*pyrexia, fatigue, headache, nausea, vomiting, chills, pain, myalgia*}, which were also among the 20 most commonly reported AEs for VAERS reports for Pfizer-BioNTech when explored based on their individual frequencies.

Rule	Antecedent	Consequent	Support	Confidence	Lift	Count
R-1	Body temperature	Pyrexia	0.016	0.86	6.53	4572
R-2	Vomiting	Nausea	0.022	0.54	5.46	6095
R-3	Chills	Pyrexia	0.063	0.56	4.24	17,925
R-4	Chills, Myalgia	Fatigue	0.011	0.53	3.65	3085
R-5	Chills, Myalgia	Headache	0.013	0.62	3.61	3588
R-6	Myalgia, Pyrexia	Headache	0.013	0.58	3.40	3589
R-7	Nausea, Pain	Chills	0.012	0.50	4.46	3352
R-8	Chills, Nausea	Headache	0.018	0.60	3.52	5110
R-9	Nausea, Pain	Pyrexia	0.012	0.51	3.83	3371
R-10	Nausea, Pain	Headache	0.014	0.60	3.49	3967
R-11	Nausea, Pyrexia	Headache	0.017	0.59	3.45	4838
R-12	Fatigue, Nausea	Headache	0.019	0.57	3.36	5334
R-13	Chills, Pain	Headache	0.024	0.54	3.17	6879
R-14	Chills, Fatigue	Headache	0.025	0.56	3.26	7058
R-15	Fatigue, Pain	Headache	0.022	0.52	3.05	6130
R-16	Fatigue, Pyrexia	Headache	0.025	0.52	3.05	7008

Non-redundant association rules for post-COVID-19 vaccine AEs for Moderna vaccine. Rules 7–25 were many-to-one rules. The highlighted regions represent rules with relatively high count (>10,000). The rules below include {*pyrexia, headache, nausea, vomiting, fatigue, chills, pain, injection site pain/swelling/warmth/pruritus/erythema, myalgia*}, which were also among the 20 most commonly reported AEs for VAERS reports for Moderna when explored based on their individual frequencies.

R-1	Injection site induration	Injection site erythema	0.01	0.66	7.19	3716
R-2	Injection site warmth	Injection site erythema	0.03	0.70	7.55	10,203
R-3	Vomiting	Nausea	0.02	0.56	5.72	6423
R-4	Injection site pruritus	Injection site erythema	0.04	0.67	7.25	13,393
R-5	Injection site swelling	Injection site erythema	0.05	0.63	6.87	13,591
R-6	Chills	Pyrexia	0.08	0.57	3.63	23,724
R-7	Injection site pruritus, Injection site warmth	Injection site swelling	0.01	0.51	7.09	3430
R-8	Injection site pain, Injection site pruritus	Injection site swelling	0.01	0.52	7.24	3177
R-9	Arthralgia, Chills	Headache	0.01	0.60	3.45	3215
R-10	Arthralgia, Fatigue	Headache	0.01	0.55	3.21	3372
R-11	Arthralgia, Pyrexia	Headache	0.01	0.57	3.27	3262
R-12	Chills, Myalgia	Headache	0.02	0.57	3.28	4685
R-13	Fatigue, Myalgia	Headache	0.02	0.55	3.20	4555
R-14	Myalgia, Pyrexia	Headache	0.02	0.53	3.07	4696
R-15	Chills, Injection site pain	Headache	0.01	0.54	3.14	3263
R-16	Chills, Pain in extremity	Headache	0.01	0.51	2.96	3515
R-17	Nausea, Pain	Chills	0.01	0.55	3.99	4193

Table 4. Cont.

R-18	Nausea, Pain	Pyrexia	0.01	0.55	3.47	4187
R-19	Nausea, Pain	Headache	0.02	0.60	3.50	4606
R-20	Chills, Nausea	Headache	0.02	0.60	3.48	6599
R-21	Fatigue, Nausea	Headache	0.02	0.58	3.38	6077
R-22	Nausea, Pyrexia	Headache	0.02	0.58	3.36	6198
R-23	Fatigue, Pain	Headache	0.02	0.52	3.04	6744
R-24	Chills, Fatigue	Headache	0.03	0.55	3.17	8765
R-25	Fatigue, Pyrexia	Headache	0.03	0.51	2.95	8442

Non-redundant association rules for post-COVID-19 vaccine AEs for Janssen vaccine. Rules 11–14 were many-to-one rules. The highlighted regions represent rules with relatively high count (>4000). The rules below include {*pyrexia, fatigue, headache, pain, nausea, chills, vomiting, myalgia*}, which were also among the 20 most commonly reported AEs for VAERS reports for Janssen when explored based on their individual frequencies.

R-1	Body temperature	Pyrexia	0.02	0.85	3.94	1223
R-2	Decreased appetite	Fatigue	0.01	0.53	2.99	609
R-3	Vomiting	Nausea	0.03	0.54	4.12	1638
R-4	Myalgia	Headache	0.04	0.56	2.17	2268
R-5	Nausea	Headache	0.07	0.52	2.01	4051
R-6	Pain	Pyrexia	0.09	0.50	2.32	5237
R-7	Pain	Headache	0.09	0.50	1.96	5261
R-8	Chills	Headache	0.10	0.55	2.14	6058
R-9	Fatigue	Headache	0.09	0.51	1.97	5275
R-10	Pyrexia	Headache	0.11	0.51	1.99	6574
R-11	Myalgia, Nausea	Pyrexia	0.01	0.57	2.64	614
R-12	Fatigue, Myalgia	Pyrexia	0.02	0.52	2.42	942
R-13	Nausea, Pain	Chills	0.02	0.55	2.98	1318
R-14	Fatigue, Pain	Chills	0.03	0.52	2.77	1869

ARs for Janssen (Table 4) showed that 6 of 14 ARs reported *headache* in the consequent, with {*fatigue, pain, pyrexia, chills, myalgia, nausea*} appearing in the antecedent (Supplementary Materials—Figure S7). This is in contrast with Pfizer-BioNTech and Moderna, where the AR with highest count was *chills* → *pyrexia*, *pyrexia* → *headache* had the highest count of 6574 ( $R_{10}$ ). An interesting AR  $R_2$  indicated a noteworthy observation {*decreased appetite* → *fatigue*}, with a 609 count value for Janssen. The AR  $R_{10}$  was also demonstrated with the help of SOM (Supplementary Materials—Figure S7) showing similarity for *pyrexia* and *headache*, despite the lack of indication of definitive clusters in the SOM.

## 2.2. Interrelations of Vaccine AEs via Bipartite Graphs

The interrelationships between the 20 most commonly reported AEs and the three vaccines were also interrogated via bipartite graphs [25–27] (Figures 5, S8 and S9). As shown in Figure 5, *headache* was most often reported for all 3 vaccines with a relative existence of 11%. The *injection-site-related* AEs {*injection site (erythema, pain, swelling)*} are of a higher relative percentage for Moderna (5%, 6%, and 4%) compared to those for Pfizer-BioNTech (1%, 4%, and 1%) and Janssen (1%, 3%, and 1%). The relationships of allergies with the 20 most-reported AEs in Figure 5e showed *penicillin* and *sulfa* to have the highest occurrences with 22% and 19% frequency, respectively. In the same figure, *penicillin* and *sulfa* appear to be uniformly distributed among all 20 AEs with *headache*, *fatigue*, and *pyrexia* having the highest percentages. Additionally, *gluten* from 3% of VAERS reports demonstrated a correlation with *fatigue* in 11% of data after cleaning and data

pre-processing steps. Such a percentage suggests that the AR of *gluten* with *fatigue* may be supported with a higher level of confidence than the AR of *sulfa* with *fatigue*. Studies have reported that a significant percentage (31%) of patients with a self-reported *gluten* sensitivity had a lack of energy (third-highest symptom). Reports with non-coeliac *gluten* sensitivity also appear to correlate with {*depression, anxiety, headache, fatigues, reflux, and irritable bowel syndrome*} [25]. One study found that 82% of those newly diagnosed with coeliac disease complained of *fatigue*. Limited literature also indicates that *fatigue* can potentially be caused by *malnutrition*, induced by *intestinal damage* causing *malabsorption* of nutrients [26]. *Fatigue* can also be caused by *anemia*, which frequently appears in patients with coeliac disease [27].

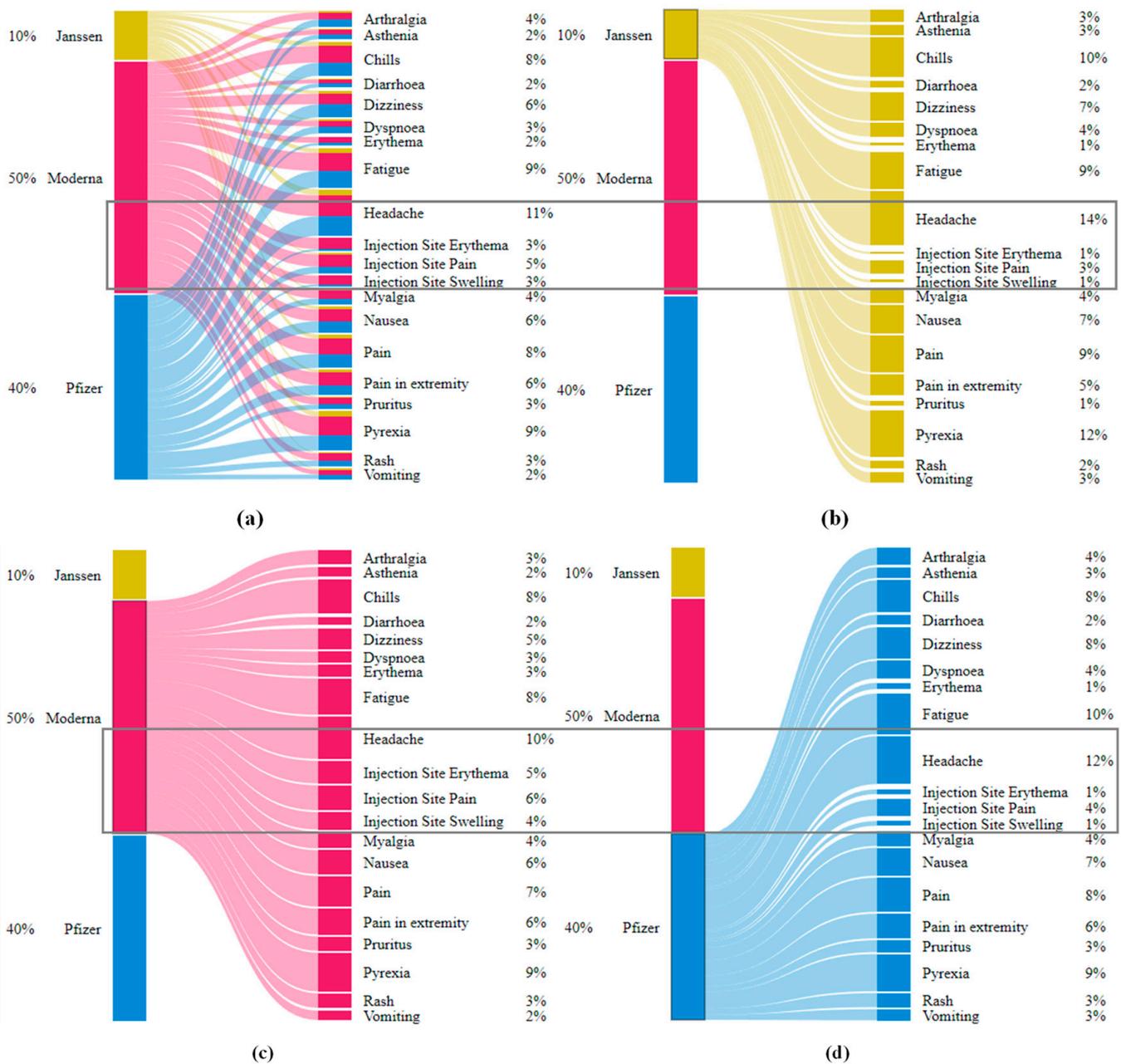
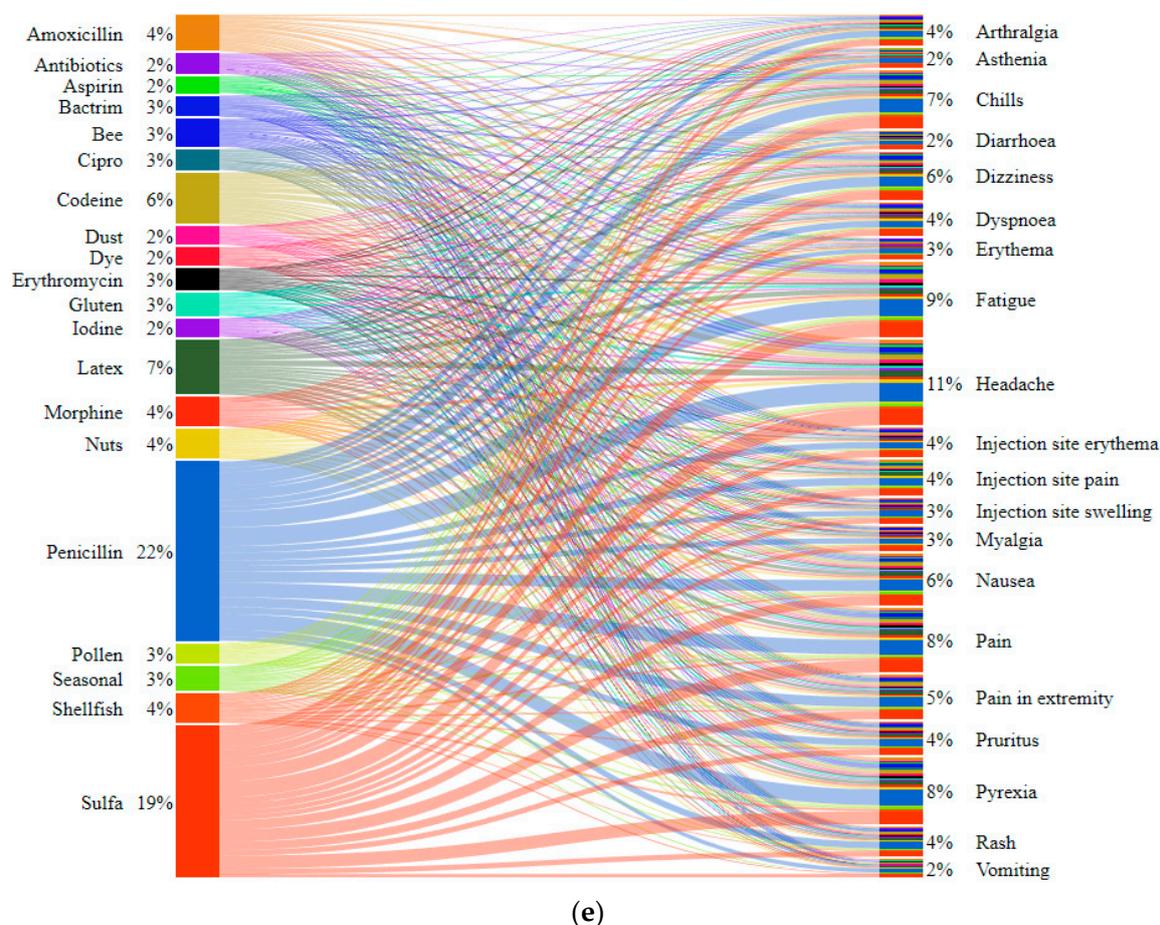


Figure 5. Cont.



**Figure 5.** Bipartite graphs for the correlations of 20 most commonly reported AEs with the 3 vaccine producers (Pfizer-BioNTech, Moderna, and Janssen). (a) Shows the distribution of the entire VAERS dataset with respect to all the vaccine producers, and (b–d) show the distributions of the effects with respect to each vaccine. (e) Shows the correlations of 20 most commonly reported AEs with reported allergies in VAERS data. The allergies *penicillin* and *sulfa* collectively appear to be in 41% of the 643,522 VAERS reports.

It is noted that the VAERS data that included 5 distinct symptoms reported as 5 attributes in free-form text were of significant percentage with spelling mistakes. For example, *penicillin* was reported with various spelling variations such as {*penecellin*, *penecillin*, *penecilin*}, and sulfates was reported as {*sulfa*, *sulpha*, *sulfides*, *sulfite*, *sulfate*}. Another notable spelling mistake in the present analysis was the use of words “*vaccination site*” and “*injection site*” interchangeably such as *vaccination site* {*pain*, *mass*, *induration*, *swelling*, *warmth*, *inflammation*} and *injection site* {*pain*, *mass*, *induration*, *swelling*, *warmth*, *inflammation*}. The words “*vaccination site*” were replaced with “*injection site*” for consistency.

### 3. Discussion

The usefulness of the VAERS data for the statistical analysis of vaccines was illustrated with the help of a case study for COVID-19 vaccine data. It was emphasized that, due to the specific reporting format by VAERS online submission portal, its passive nature and access to the public can have an impact on any machine-learning (ML)/data-mining approach when careful data preprocessing approaches are omitted (i.e., removing/merging duplicates in VAERS, discretizing numeric attributes, handling missing values, and fixing spelling/grammar errors). With the help of these data provenance and preprocessing techniques, it is hoped that vaccine research and development can utilize and streamline the protocols when ML techniques are applied to VAERS data. The present study proposes

a set of recommendations supported by the application of various ML algorithms that are critical to applying modeling approaches to or exploratory analyses of VAERS data. An online survey was also conducted, providing 211 distinct reports of the COVID-19 post-vaccination effects from participants in the US. Various useful data preprocessing/cleaning techniques were pinpointed, which should be considered to be part of VAERS.

It is noted that, although models of various types have been developed for different vaccine reports based on exploratory data analyses and the application of ML techniques on VAERS data [4,6,7,9–13,15,16,20,28], the model development for evolving VAERS data can be exposed to unseen situations that would neither be available for model training nor for validation. Despite the anticipated outcome from the ML perspective, the monitoring and testing strategies should be carefully implemented. Studies utilizing VAERS data for vaccine safety based on ML techniques require the following best practices.

### 3.1. Flexibility of Model Features

Data and model-feature provenance strategies should be documented, including feature definitions, data ranges, meta-level requirements, and privacy controls. Structure of the developed ML model should be made flexible for new feature addition and updates to existing features.

### 3.2. Robust Model-Development Pipelines

Model development for vaccine AE identification and predictive capability should be reviewed, tested, and updated for the continuous refinement of existing workflows. Modularity in terms of model applicability on all or selected slices of data should be accomplished through a robust development pipeline, and model parameters should be tuned upon the availability of new data.

### 3.3. ML Model Verification

In order to enhance model applicability and reproducibility, validation (via unit, system, and integration testing) should be ensured before deployment into the production environment, or any policy or recommendation is proposed. Appropriate model maintenance and documentation strategies should be implemented, and transparency in terms of step-by-step debugging (on single data instances) should be demonstrated.

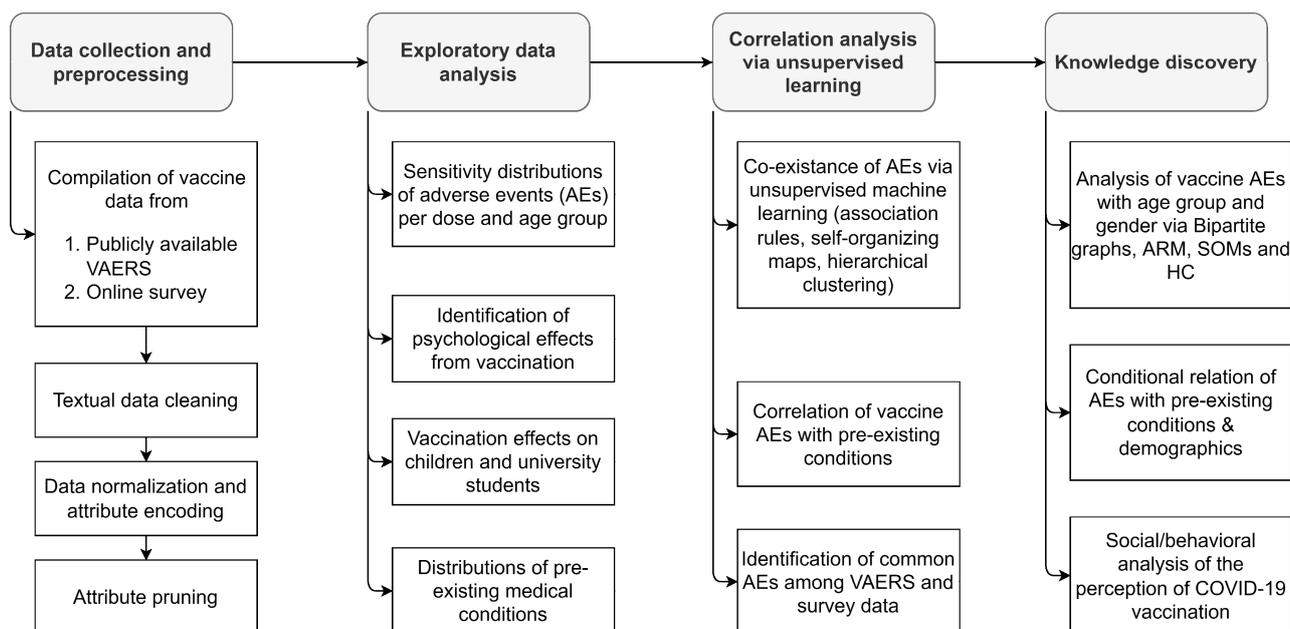
### 3.4. Model Stability and Efficiency

Model efficiency should be carefully evaluated via robust tests to ensure the reasonable use of computational resources in order to provide accurate predictions. Such tests can be based on model-training speed, use of RAM, and throughput in a real-time learning environment. Additionally, automation test cases can be developed to verify model prediction accuracy and stability (in terms of predictive accuracy) over time, as well as latency issues.

## 4. Materials and Methods

Analysis of the psychological and physical effects of COVID-19 vaccines along with the discovery of correlations among the most commonly reported AEs was conducted as per the workflow described in Figure 6. Vaccine data for Pfizer-BioNTech, Moderna, and Janssen were obtained via VAERS, which was accompanied by a primary dataset collected from an online survey comprising information on post-vaccine AEs and public perception of the COVID-19 vaccine. Online survey data were designed to fill data gaps in the absence of other closely monitored data repositories such as v-safe [29], whose data have not yet been made available for public and research communities. The overarching goal of the present study of VAERS and the online survey data was to pinpoint critical data provenance and management protocols for robust statistical analysis and predictive modeling of vaccines with a case study of COVID-19 vaccines. Particular steps to assess the efficacy of data-driven techniques applied on VAERS data were based on: (i) the exploration of the post-vaccination effects of COVID-19 vaccines on various age groups (particularly

children under the age of 16), (ii) the determination of the frequencies of reported AEs after each dose of COVID-19 vaccines, (iii) the evaluation of the co-existence of common post-vaccine AEs via unsupervised ML approaches, and (iv) the assessment of potential relationships of pre-existing conditions (e.g., allergies) with the AEs. Active reporting via an online survey was also aimed for to further assess the impact of COVID-19 vaccination via the reported AEs, evaluate psychological perception of COVID-19 vaccination, and compare the VAERS reports with an active and systematically controlled system that incorporates quality data into COVID-19 vaccine domain knowledge.



**Figure 6.** Workflow for the analysis of psychological and physical effects of COVID-19 vaccines on populations based on various demographics.

#### 4.1. Compilation, Preprocessing, and Exploration of VAERS Data

Two distinct datasets were compiled with 905,976 and 211 data samples from VAERS (filtered to prune rows for the three COVID-19 vaccines) and an online survey, respectively. The VAERS reports consisted of vaccine- and patient-related attributes that included vaccine identification (VAX type, VAX manufacturer, VAX lot, VAX dose series, VAX route, VAX site, VAX name), free-form textual attributes {US state, gender, allergies, hospital, disability, current illness}, binary attributes {birth defects, prior visit, ER visit}, age (numeric), and vaccination date (date). VAERS reports that did not list any AEs were removed, reducing the dataset size to 892,213 reports. Data cleaning was then performed to merge duplicate reports and fix spelling/grammar mistakes, resulting in a total of 643,522 reports. The age attribute was discretized into 7 groups (5–11, 12–15, 16–18, 19–30, 31–50, 51–65, and 66+) for the purpose of identifying the age-to-AE correlation via bipartite plots (Section 3.3). Data statistics per manufacturer for each of the above age groups and genders are given in Tables 5 and S1, along with the numbers of categories for each attribute in both datasets from VAERS (original without removing duplicates (Table S1) and after data preprocessing (Table 5)) and the online survey. A summary of the content of the datasets (without the removal of duplicate records) is also provided in Table S2, which lists the number of data samples for each of the 20 most commonly reported AEs along with their percentage per manufacturer.

**Table 5.** Number of VAERS reports categorized with respect to the age group and gender along with their percentage per the three vaccine producers. For robust statistical analysis of vaccine data, duplicate reports were merged into distinct rows resulting into 643,522 rows compared to the total 905,976 reports with duplicates.

Age Group (Years)	Vaccine					
	Pfizer-BioNTech		Moderna		Janssen	
	Male	Female	Male	Female	Male	Female
5–11	233 (0.30%)	251 (0.14%)	13 (0.02%)	13 (0.01%)	3 (0.02%)	3 (0.01%)
12–15	4133 (5.36%)	4525 (2.55%)	96 (0.13%)	106 (0.05%)	43 (0.23%)	38 (0.13%)
16–18	3498 (4.54%)	4396 (2.48%)	2645 (3.59%)	3587 (1.83%)	761 (4.13%)	753 (2.52%)
19–30	10,556 (13.69%)	24,146 (13.62%)	8533 (11.58%)	21,883 (11.19%)	4054 (22.00%)	5087 (17.03%)
31–50	22,658 (29.39%)	66,760 (37.65%)	19,198 (25.06%)	64,711 (33.08%)	6561 (35.61%)	11,901 (39.83%)
51–65	18,109 (23.49%)	45,575 (25.71%)	18,917 (25.68%)	52,060 (26.62%)	4960 (26.92%)	8754 (29.30%)
66+	17,898 (23.22%)	31,645 (17.85%)	24,260 (32.93%)	53,212 (27.21%)	2045 (11.10%)	3342 (11.19%)
Total	77,085	177,298	73,662	195,572	18,427	29,878

**Note:** The number of samples per vaccine manufacturer and their percentages were calculated using clean data by removing those samples where any of the four attributes (age, gender, vaccine manufacturer, and symptom) were listed as “unknown.” There were 63,189 reports with missing age values, which were also removed from the above analysis, followed by the merger of duplicate rows in the dataset.

VAERS reports for children of age under 16, with a total of 12,489 VAERS samples, were also collected and analyzed separately in order to explore the commonality between the AEs with respect to different age groups. The goal of this analysis was to discover meaningful patterns (i.e., AEs) that appear collectively in children when compared to adults or differences as the age group progresses to an older population. Data from children’s reports were also cleaned where rows that reported any attribute (column) from {age group, gender, symptom, and vaccine manufacturer} as “unknown” were removed. Additionally, reports indicating “product administered to patient of inappropriate age” while reporting no AEs were also removed. Cleaned data after the removal of reports with “product administered to patient of inappropriate age” comprised of 9457 reports with distributions of 9142, 228, and 87 for Pfizer-BioNTech, Moderna, and Janssen, respectively (Table 5). The AEs submitted in children’s VAERS reports were also separated in the form of heatmaps (Table 2) with respect to the gender in order to identify gender similarities/dissimilarities with the help of cell colors based on the percentage of the corresponding AEs. The AEs for all genders in Table 2 were sorted based on the age group (Sections 2 and 2.1) of 5–11 years old. A non-cleaned version of the VAERS reports (i.e., the reports with duplicates) is provided in Table S1.

#### 4.2. Exploratory Data Analysis of the COVID-19 Vaccines’ Effects

The initial exploratory analysis for VAERS data was conducted to determine the frequencies of AEs to support advanced analysis. The 20 most commonly reported AEs were first used to assess their associations, as shown in Table 1. Similar to Tables 5 and S1, statistics based on non-cleaned data are reported in Table S2, demonstrating significant differences from Table 1, which could have a significant impact on the performance and robustness if a statistical approach is applied.

#### 4.3. Correlation Analysis of AEs Based on Age Groups and Allergies

Unsupervised ML approaches utilizing ARM and SOMs (Supplementary Materials—Section S2.2.1) were applied on VAERS and survey data, where the endpoints were analyzed to explore the relationships among AEs and reported allergies. Unsupervised learning is useful for visual data exploration to find hidden data groups in order to better understand the correlation of the AEs with existing medical conditions without any predictions or testing the underlying hypotheses. ML approaches are also helpful for applying statistical

approaches to cluster/group similar biological effects to enhance the applicability domain of the vaccines as well as recommend proactive strategies for vaccine safety. Furthermore, as new data become available, analyzing the relationships among post-COVID-19 vaccine AEs and other reported demographical characteristics via ML approaches can be helpful in designing improved versions of vaccines (e.g., COVID-19 pills) for COVID-19 vaccine safety. Mapping the relationships (i.e., associations) among the reported post-COVID-19 vaccine AEs via unsupervised ML techniques is particularly helpful in revealing useful patterns, streamlining COVID-19 vaccine safety standards and the development of robust models for proactive strategies and recommendations. Through these relationships, one can assess the co-occurrence of certain AEs and infer the reasons that the emergence of one or more AE may lead to other AE(s) that are correlated due to biological or other relevant reasons. The ARM of AEs was also accompanied by confirmatory cluster analysis approaches based on hierarchical clustering.

ARM has been applied in various disciplines [28,30–37]. Irrespective of the domain of interest, triggering of one or more AE can imply the triggering of other AEs, consistent with the crosstalk between various physical AEs and perceptual indicators. The ARM of the AEs after each vaccine dose can be used to identify many-to-many relationships and propose a data-driven hypothesis-generation technique. A detailed description of ARM can be found in the Supplementary Materials (Section S2.2.1). ARs in the present study were also validated with the help of the SOM analysis, demonstrating the VAERS data distribution on 2D maps. Cluster analysis via SOMs has been demonstrated to be useful for discovering relationships in complex multidimensional datasets in cross-disciplinary areas of research and development [38–41]. SOM clustering applies competitive learning, preserves topological structure of the input space, and transforms the output to a lower dimension (i.e., 2-D map of cells within SOM clusters). Further discussion on SOM can be found in the Supplementary Materials (Section S2.2.1). The utility of SOMs for data visualization and feature selection has also been demonstrated for exploratory data analyses [34,38,39,41–47]. For the analysis via ARM and SOM, open-source libraries were utilized, which are freely available online (R Studio arules—version 1.7-3 [48] (for ARM), kohonen version 3.0.11 [49] (for SOM analysis), hclust version 3.6.2 [50] (for HC), and Python stats.chisquare [51] (for statistical significance test)).

The interrelationships of the AEs with allergies and other personalized factors (age group and gender) were identified via bipartite graphs (Section 2.2 and Section S2.2.2). Bipartite graphs established in the present study are useful for the exploratory analysis of potential allergies, age groups and genders that may be indicative of the occurrence of one or more common AEs. Moreover, bipartite graphs allow for the bidirectional exploration of COVID-19 vaccine data for detailed information about specific AEs and their causal (i.e., {allergy, age group, gender} → AE) or a diagnostic reasoning (i.e., AE → {allergy, age group, gender}). Graphical displays of correlations between reported AEs and allergies can help explore the frequencies of certain AEs, interrogate comparisons between them and their occurrences given certain pre-existing conditions, identify similarity/distribution among reports that demonstrated similar AEs, and assess potential causes of AEs given certain pre-existing conditions [47]. For example, it can be seen in Figure 5 that *Age group of 31–50 years old* has been reported to have the highest percentage (36%) among all of the 20 commonly reported AEs. Each bar in the bipartite graph is further split into sub-bars representing its distribution in terms of the available categories for each of the three variables {age group, gender, and allergies} across 20 AEs. The bars on the left side of the bipartite graphs list the 20 most commonly reported AEs. The bipartite graphs in the present study were created using the open-source JavaScript library from d3.js [52].

**Supplementary Materials:** The following supporting information [53–56] can be downloaded at: <https://www.mdpi.com/article/10.3390/ijms23158235/s1>.

**Author Contributions:** J.F.: Data analysis, model development, writing—draft preparation, W.K.: Preparation and approval of online survey for data collection on vaccine perception, workflow devel-

opment and review, writing—draft preparation. J.J.: Distribution and collection of COVID-19 vaccine data from online survey, workflow development, writing—draft preparation. D.J.: literature review of vaccine effects, writing—draft preparation. A.H.: Preparation and approval of online survey for data collection on vaccine perception, workflow development, writing—draft preparation. K.D.: Study review and approval, project supervision, writing—draft review. B.K.: Study conceptualization, project supervision, data analysis, workflow development and model review, writing—draft preparation and review. All authors have read and agreed to the published version of the manuscript.

**Funding:** This research received no external funding.

**Institutional Review Board Statement:** Not applicable.

**Informed Consent Statement:** Not applicable.

**Data Availability Statement:** Vaccine data from both datasets (VAERS—905,976 VAERS reports, and 211 data samples from online survey) in Excel file format are available in the submitted Supplementary Materials. Online survey used to collect user data in PDF format is available in the submitted Supplementary Materials (Psychological impacts and perception of vaccination and pandemic across the globe.pdf).

**Acknowledgments:** The independent study (CSE Course Number: 5953) was supported by the Department of Computer Science and Engineering, California State University San Bernardino (CSUSB).

**Conflicts of Interest:** The authors declare no conflict of interest.

## References

1. U.S. Department of Health and Human Services (HHS). About VAERS-Background and Public Health Importance 2022. Available online: <https://vaers.hhs.gov/about.html> (accessed on 23 May 2022).
2. Shimabukuro, T.T.; Nguyen, M.; Martin, D.; DeStefano, F. Safety monitoring in the Vaccine Adverse Event Reporting System (VAERS). *Vaccine* **2015**, *33*, 4398–4405. [[CrossRef](#)] [[PubMed](#)]
3. Ball, R.; Braun, M.M.; Chen, R.T.; Ellenberg, S.S.; English-Bullard, R.; Haber, P.; Zhou, W. Surveillance for safety after immunization: Vaccine Adverse Event Reporting System (VAERS)—United States, 1991–2001. In *MWWR. Surveillance Summaries: Morbidity and Mortality Weekly Report. Surveillance Summaries*; CDC: Atlanta, GA, USA, 2003.
4. Su, J.R. Myopericarditis Following COVID-19 Vaccination: Updates from the Vaccine Adverse Event Reporting System (VAERS) [Internet]. Team. CDCC-19 VTFVS, Editor. Atlanta, GA; (ACIP Meeting COVID-19 Vaccines; Volume 202113). Available online: <https://stacks.cdc.gov/view/cdc/110920> (accessed on 23 May 2022).
5. Myers, T.R.; McNeil, M.M.; Ng, C.S.; Li, R.; Marquez, P.L.; Moro, P.L.; Cano, M.V. Adverse events following quadrivalent meningococcal diphtheria toxoid conjugate vaccine (Menactra®) reported to the Vaccine Adverse Event Reporting System (VAERS), 2005–2016. *Vaccine* **2020**, *38*, 6291–6298. [[CrossRef](#)] [[PubMed](#)]
6. VAERS. VAERS Data 2021. Available online: <https://vaers.hhs.gov/data/datasets.html?> (accessed on 23 May 2022).
7. Miller, E.R.; McNeil, M.M.; Moro, P.L.; Duffy, J.; Su, J.R. The reporting sensitivity of the Vaccine Adverse Event Reporting System (VAERS) for anaphylaxis and for Guillain-Barré syndrome. *Vaccine* **2020**, *38*, 7458–7463. [[CrossRef](#)] [[PubMed](#)]
8. Botsis, T.; Nguyen, M.D.; Woo, E.J.; Markatou, M.; Ball, R. Text mining for the Vaccine Adverse Event Reporting System: Medical text classification using informative feature selection. *J. Am. Med. Inform. Assoc.* **2011**, *18*, 631–638. [[CrossRef](#)] [[PubMed](#)]
9. Du, J.; Xiang, Y.; Sankaranarayananpillai, M.; Zhang, M.; Wang, J.; Si, Y.; Tao, C. Extracting postmarketing adverse events from safety reports in the vaccine adverse event reporting system (VAERS) using deep learning. *J. Am. Med. Inform. Assoc.* **2021**, *28*, 1393–1400. [[CrossRef](#)]
10. Lian, A.T.; Du, J.; Tang, L. Using a Machine Learning Approach to Monitor COVID-19 Vaccine Adverse Events (VAE) from Twitter Data. *Vaccines* **2022**, *10*, 103. [[CrossRef](#)]
11. Sujatha, R.; Venkata Siva Krishna, B.; Chatterjee, J.M.; Naidu, P.R.; Jhanjhi, N.Z.; Charita, C.; Baz, M. Prediction of Suitable Candidates for COVID-19 Vaccination. *Intell. Autom. Soft Comput.* **2022**, *32*, 525–541. [[CrossRef](#)]
12. Xie, J.; Zhao, L.; Zhou, S.; He, Y. Statistical and Ontological Analysis of Adverse Events Associated with Monovalent and Combination Vaccines against Hepatitis A and B Diseases. *Sci. Rep.* **2016**, *6*, 34318. [[CrossRef](#)]
13. Miller, E.R.; Lewis, P.; Shimabukuro, T.T.; Su, J.; Moro, P.; Woo, E.J.; Cano, M. Post-licensure safety surveillance of zoster vaccine live (Zostavax®) in the United States, Vaccine Adverse Event Reporting System (VAERS), 2006–2015. *Hum. Vaccin Immunother.* **2018**, *14*, 1963–1969. [[CrossRef](#)]
14. Luo, C.; Jiang, Y.; Du, J.; Tong, J.; Huang, J.; Lo Re, V., III; Chen, Y. Prediction of post-vaccination Guillain-Barré syndrome using data from a passive surveillance system. *Pharm. Drug Saf.* **2021**, *30*, 602–609. [[CrossRef](#)]
15. Miller, N.Z. Vaccines and sudden infant death: An analysis of the VAERS database 1990–2019 and review of the medical literature. *Toxicol. Rep.* **2021**, *8*, 1324–1335. [[CrossRef](#)] [[PubMed](#)]

16. Baker, M.A.; Kaelber, D.C.; Bar-Shain, D.S.; Moro, P.L.; Zambarano, B.; Mazza, M.; Klompas, M. Advanced Clinical Decision Support for Vaccine Adverse Event Detection and Reporting. *Clin. Infect. Dis.* **2015**, *61*, 864–870. [[CrossRef](#)] [[PubMed](#)]
17. Sukumaran, L.; McNeil, M.M.; Moro, P.L.; Lewis, P.W.; Winiiecki, S.K.; Shimabukuro, T.T. Adverse events following measles, mumps, and rubella vaccine in adults reported to the vaccine adverse event reporting system (VAERS), 2003–2013. *Clin. Infect. Dis.* **2015**, *60*, e58–e65. [[CrossRef](#)]
18. Moro, P.L.; Woo, E.J.; Paul, W.; Lewis, P.; Petersen, B.W.; Cano, M. Post-Marketing Surveillance of Human Rabies Diploid Cell Vaccine (Imovax) in the Vaccine Adverse Event Reporting System (VAERS) in the United States, 1990–2015. *PLoS Negl. Trop. Dis.* **2016**, *10*, e0004846. [[CrossRef](#)] [[PubMed](#)]
19. Loughlin, A.M.; Marchant, C.D.; Adams, W.; Barnett, E.; Baxter, R.; Black, S.; Jakob, K. Causality assessment of adverse events reported to the Vaccine Adverse Event Reporting System (VAERS). *Vaccine* **2012**, *30*, 7253–7259. [[CrossRef](#)] [[PubMed](#)]
20. Myers, T.R.; McNeil, M.M.; Ng, C.S.; Li, R.; Lewis, P.W.; Cano, M.V. Adverse events following quadrivalent meningococcal CRM-conjugate vaccine (Menveo<sup>®</sup>) reported to the Vaccine Adverse Event Reporting system (VAERS), 2010–2015. *Vaccine* **2017**, *35*, 1758–1763. [[CrossRef](#)]
21. Gatti, M.; Raschi, E.; Moretti, U.; Ardizzoni, A.; Poluzzi, E.; Diemberger, I. Influenza vaccination and myo-pericarditis in patients receiving immune checkpoint inhibitors: Investigating the likelihood of interaction through the vaccine adverse event reporting system and vigibase. *Vaccines* **2021**, *9*, 19. [[CrossRef](#)]
22. Kreimeyer, K.; Menschik, D.; Winiiecki, S.; Paul, W.; Barash, F.; Woo, E.J.; Botsis, T. Using Probabilistic Record Linkage of Structured and Unstructured Data to Identify Duplicate Cases in Spontaneous Adverse Event Reporting Systems. *Drug Saf.* **2017**, *40*, 571–582. [[CrossRef](#)]
23. Hervé, C.; Laupèze, B.; Del Giudice, G.; Didierlaurent, A.M.; Tavares Da Silva, F. The how's and what's of vaccine reactogenicity. *npj Vaccines* **2019**, *4*, 39. [[CrossRef](#)]
24. Banerji, A.; Wickner, P.G.; Saff, R.; Stone Jr, C.A.; Robinson, L.B.; Long, A.A.; Blumenthal, K.G. mRNA Vaccines to Prevent COVID-19 Disease and Reported Allergic Reactions: Current Evidence and Suggested Approach. *J. Allergy Clin. Immunol. Pract.* **2021**, *9*, 1423–1437. Available online: <https://pubmed.ncbi.nlm.nih.gov/33388478> (accessed on 18 November 2021). [[CrossRef](#)]
25. Croall, I.D.; Trott, N.; Rej, A.; Aziz, I.; O'Brien, D.J.; George, H.A.; Sanders, D.S. A Population Survey of Dietary Attitudes towards Gluten. *Nutrients* **2019**, *11*, 1276. Available online: <http://europepmc.org/abstract/MED/31195638> (accessed on 18 November 2021). [[CrossRef](#)] [[PubMed](#)]
26. Jordá, F.C.; Vivancos, J.L. Fatigue as a Determinant of Health in Patients With Celiac Disease. *J. Clin. Gastroenterol.* **2010**, *44*, 423–427. Available online: [https://journals.lww.com/jcge/Fulltext/2010/07000/Fatigue\\_as\\_a\\_Determinant\\_of\\_Health\\_in\\_Patients.13.aspx](https://journals.lww.com/jcge/Fulltext/2010/07000/Fatigue_as_a_Determinant_of_Health_in_Patients.13.aspx) (accessed on 12 April 2022). [[CrossRef](#)] [[PubMed](#)]
27. Freeman, H.J. Iron deficiency anemia in celiac disease. *World J. Gastroenterol.* **2015**, *21*, 9233–9238. [[CrossRef](#)]
28. Guzzi, P.H.; Milano, M.; Cannataro, M. Mining Association Rules from Gene Ontology and Protein Networks: Promises and Challenges. *Procedia Comput. Sci.* **2014**, *29*, 1970–1980. Available online: <http://www.sciencedirect.com/science/article/pii/S1877050914003585> (accessed on 23 May 2022). [[CrossRef](#)]
29. Schuchat, A.; Anderson, L.J.; Rodewald, L.E.; Cox, N.J.; Hajjeh, R.; Pallansch, M.A.; Wharton, M.; National Center for Immunization and Respiratory Diseases (NCIRD), Division of Viral Diseases. V-Safe After Health Checker. 2022; Volume 24, p. 1178. Available online: <https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/vsafe.html> (accessed on 23 May 2022).
30. Oellrich, A.; Jacobsen, J.; Papatheodorou, I.; Smedley, D. Using association rule mining to determine promising secondary phenotyping hypotheses. *Bioinformatics* **2014**, *30*, 52–59. [[CrossRef](#)] [[PubMed](#)]
31. Naulaerts, S.; Meysman, P.; Bittremieux, W.; Vu, T.N.; Vanden Berghe, W.; Goethals, B.; Laukens, K. A primer to frequent itemset mining for bioinformatics. *Brief. Bioinform.* **2015**, *16*, 216–231. Available online: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4364064/> (accessed on 11 March 2022). [[CrossRef](#)] [[PubMed](#)]
32. Park, S.H.; Reyes, J.A.; Gilbert, D.R.; Kim, J.W.; Kim, S. Prediction of protein-protein interaction types using association rule based classification. *BMC Bioinform.* **2009**, *10*, 36. [[CrossRef](#)]
33. Nafar, Z.; Golshani, A. Data Mining Methods for Protein-Protein Interactions. In Proceedings of the 2006 Canadian Conference on Electrical and Computer Engineering, Ottawa, ON, Canada, 7–10 May 2006; pp. 991–994.
34. Liu, R.; France, B.; George, S.; Rallo, R.; Zhang, H.; Xia, T.; Cohen, Y. Association rule mining of cellular responses induced by metal and metal oxide nanoparticles. *Analytical* **2014**, *139*, 943–953. [[CrossRef](#)]
35. Mallik, S.; Mukhopadhyay, A.; Maulik, U.; Bandyopadhyay, S. Integrated analysis of gene expression and genome-wide DNA methylation for tumor prediction: An association rule mining-based approach. In Proceedings of the 2013 IEEE Symposium on Computational Intelligence in Bioinformatics and Computational Biology (CIBCB), Singapore, 16–19 April 2013; pp. 120–127.
36. Martinez, R.; Pasquier, N.; Pasquier, C. GenMiner: Mining non-redundant association rules from integrated gene expression data and annotations. *Bioinformatics* **2008**, *24*, 2643–2644. [[CrossRef](#)]
37. Alves, R.; Rodriguez-Baena, D.S.; Aguilar-Ruiz, J.S. Gene association analysis: A survey of frequent pattern mining from gene expression data. *Brief. Bioinform.* **2010**, *1*, 210–224. [[CrossRef](#)]
38. Chon, T.S. Self-Organizing Maps applied to ecological sciences. *Ecol. Inform.* **2011**, *6*, 50–61. [[CrossRef](#)]
39. Tamayo, P.; Slonim, D.; Mesirov, J.; Zhu, Q.; Kitareewan, S.; Dmitrovsky, E.; Golub, T.R. Interpreting patterns of gene expression with self-organizing maps: Methods and application to hematopoietic differentiation. *Proc. Natl. Acad. Sci. USA.* **1999**, *96*, 2907–2912. [[CrossRef](#)] [[PubMed](#)]

40. Törönen, P.; Kolehmainen, M.; Wong, G.; Castrén, E. Analysis of gene expression data using self-organizing maps. *FEBS Lett.* **1999**, *451*, 142–146. Available online: <http://www.ncbi.nlm.nih.gov/pubmed/18003033> (accessed on 23 May 2022). [[CrossRef](#)]
41. Bullinaria, J.A. *Self Organizing Maps: Fundamentals* 2004. Available online: <http://www.cs.bham.ac.uk/~jxb/NN/I16.pdf> (accessed on 3 June 2017).
42. Dettmer, J.; Benavente, R.; Cummins, P.R.; Sambridge, M. Trans-dimensional finite-fault inversion. *Geophys. J. Int.* **2014**, *199*, 735–751. [[CrossRef](#)]
43. Giralt, F.; Espinosa, G.; Arenas, A.; Ferre-Gine, J.; Amat, L.; Girones, X.; Cohen, Y. Estimation of infinite dilution activity coefficients of organic compounds in water with neural classifiers. *AIChE J.* **2004**, *50*, 1315–1343. [[CrossRef](#)]
44. Liu, R.; Lin, S.; Rallo, R.; Zhao, Y.; Damoiseaux, R.; Xia, T.; Cohen, Y. Automated Phenotype Recognition for Zebrafish Embryo Based In Vivo High Throughput Toxicity Screening of Engineered Nanomaterials. *PLoS ONE* **2012**, *7*, e35014. [[CrossRef](#)]
45. Rallo, R.; France, B.; Liu, R.; Nair, S.; George, S.; Damoiseaux, R.; Cohen, Y. Self-Organizing Map Analysis of Toxicity-Related Cell Signaling Pathways for Metal and Metal Oxide Nanoparticles. *Environ. Sci. Technol.* **2011**, *45*, 1695–1702. Available online: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4418424/> (accessed on 23 May 2022). [[CrossRef](#)]
46. Rhodes, B.C.; Mahaffey, J.A.; Cannady, J.D. Multiple self-organizing maps for intrusion detection. In Proceedings of the 23rd National Information Systems Security Conference, Baltimore, MD, USA, 16–19 October 2000.
47. Greenacre, M.; Primicerio, R. *Multivariate Analysis of Ecological Data*; Fundación BBVA: Bilbao, Spain, 2013.
48. Hahsler, M.; Grün, B.; Hornik, K. Arules—A Computational Environment for Mining Association Rules and Frequent Item Sets. *J. Stat. Softw.* **2005**, *14*, 1–25. [[CrossRef](#)]
49. Wehrens, R.; Kruisselbrink, J. Flexible Self-Organizing Maps in kohonen 3.0. *J. Stat. Softw.* **2018**, *87*, 1–18. [[CrossRef](#)]
50. Kokoska, S.; Zwillinger, D. *CRC Standard Probability and Statistics Tables and Formulae*, 1st ed.; CRC Press: Boca Raton, FL, USA, 2000.
51. Murtagh, F.; Legendre, P. Ward’s Hierarchical Agglomerative Clustering Method: Which Algorithms Implement Ward’s Criterion? *J. Classif.* **2014**, *31*, 274–295. [[CrossRef](#)]
52. Pasha. biPartite Graphs—bl.ocks.org. 2022. Available online: <http://bl.ocks.org/NPashaP/3ba0031d3d555afca4713e5264455025> (accessed on 23 May 2022).
53. Dormann, C.F.; Strauss, R. A method for detecting modules in quantitative bipartite networks. *Methods Ecol. Evol.* **2014**, *5*, 90–98. [[CrossRef](#)]
54. Dormann, C.F.; Fründ, J.; Blüthgen, N.; Gruber, B. Indices, Graphs and Null Models: Analyzing Bipartite Ecological Networks. *Open Ecol. J.* **2009**, *2*, 7–24. [[CrossRef](#)]
55. Dormann, C.F.; Gruber, B.; Fründ, J. Introducing the bipartite package: Analysing ecological networks. *Interaction* **2008**, *1*, 2413793.
56. Zhang, C.; Zhang, S. *Association Rule Mining: Models and Algorithms*; Springer: Berlin/Heidelberg, Germany, 2002.