Analysis of Pediatric Post-Vaccination Symptom Reports: An Unsupervised Learning Approach
Final Progress Report

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ABSTRACT

This capstone report presents the results of a comprehensive analysis of pediatric adverse events following immunization (AEFI) using data from the Vaccine Adverse Event Reporting System (VAERS) years 2017 to 2023. Investigation of pediatric symptom reports for children aged from birth to 21 years using market basket analysis revealed several noteworthy associations differentiated by pediatric age group and vaccine type. Local site reaction symptom associations proved to be common and frequent among all age groups and vaccine types. Symptom association results were analogous with Brighton Collaboration case definitions for AEFI conditions. Neonatal and infant AEFI symptom reports after receiving Hepatitis B vaccination corresponded to the clinical manifestations for Hypotonic-hyporesponsive episodes (HHE). COVID-19 and booster association findings correspond to known signs and symptoms of COVID-19 infection. Found AEFI symptom associations in children narrate possible adverse event progression and offer valuable information to educate clinical decision-making and public health vaccine safety surveillance.

INTRODUCTION

In an effort to reduce the lethality of a global pandemic through herd immunity, United States (US) citizens were encouraged by healthcare authorities to receive the novel mRNA-based COVID-19 vaccine (BNT162b2 from Pfizer- BioNTech or mRNA-1273 from Moderna) as 2 dose series after the U.S. Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) in December of 2020. The Centers for Disease Control and Prevention (CDC) and the FDA conduct post-licensure vaccine safety monitoring using the Vaccine Adverse Event Reporting System (VAERS), a spontaneous (or passive) reporting system. The significance of collecting spontaneous reports of post-vaccination symptoms, patient age, adverse outcomes (e.g., hospitalization, death, etc.) to monitor product safety after distribution, offers a unique opportunity to understand vaccine-vaccine symptom associations and assess population specific outcomes and experiences for both modern and routine immunizations (CDC, 2023).

With the rapid approval and distribution of the novel COVID-19 vaccine, now being integrated into standard practice and the US pediatric immunization schedule as of June 2022, it is important to explore the most recent symptom relationships of adverse events following childhood immunizations (AEFIs) to maintain pediatric pharmacovigilance for vaccination reactivity and continual safety maintenance. Current research utilizing VAERS data has focused on safety signal detection regarding AEFIs for individual vaccines and the adult population, however, there is a lack of evidence specifically analyzing symptom association trends within the pediatric population. Furthermore, methods for analyzing VAERS reports have not utilized machine learning and artificial intelligence association rule mining or market basket analysis

(MBA) to better understand relationships between AEFI symptoms; detecting hidden patterns in AEFI symptom reports (CDC, 2023).

This project aims at leveraging unsupervised machine learning to analyze VAERS data and learn possible associations between pediatric post-immunization symptoms reported as a result of an adverse event. Knowledge gained from any data-driven results may be useful in providing a clear view of clinical presentation of symptoms for adverse event cases.

The pediatric population in the US is defined as any child under the age of 21 years old (CDC, 2023). The Advisory Committee on Immunization Practices (ACIP) US recommended immunization schedule protects children by providing immunologic defense early in life, before a child comes into contact with any life-threatening disease. Children receive vaccinations early to mitigate high-risk to developing disease at a young age. Given pre- and post-COVID-19 pandemic VAERS data from 2017 to current (2023), pediatric adverse event reports will be utilized to describe and cluster pediatric post-vaccination symptom relationships. Understanding the learned associations between all pediatric reported symptoms, may aid clinician-patient communication by providing more accurate information for patient education allowing physicians to manage expectations regarding post-vaccination symptoms and clearly define adverse and emergent cases (CDC, 2023).

According to Seattle Children's Hospital, expected signs and symptoms post-immunization include signs of pain (fussiness or grimace in nonverbal children), swelling and redness at site of injection, and low grade fever (less than 104 degrees Fahrenheit). However, exacerbation of these symptoms more than 24 hours and adverse events such as anaphylaxis, non-stop crying, fever greater than 104 degrees Fahrenheit or any fever in immunocompromised children, vomiting, and persistent rash post-vaccination warrant immediate medical care (Seattle Children's Hospital, and Schmitt Pediatric Guidelines, 2023). An adverse event following immunization is defined as any untoward medical event that follows immunization and that does not necessarily have a causal relationship with the usage of the vaccine. The adverse event may be any unfavorable or unintended sign, abnormal laboratory finding, symptom, or disease. An event that results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect is considered to be a serious adverse event (serious AEFI). Any medical event that requires intervention to prevent one of the outcomes above may also be considered as serious. Analyzing patterns in reported symptoms using unsupervised machine learning may streamline prompt identification for adverse reactions in children at all development stages and distinguish between expected, nonurgent and unexpected, emergent symptom development. Learned symptom associations of VAERS pediatric patient experiences may validate current clinical guidance or offer opportunity for reevaluation of pediatric immunization practices

acknowledging the confidence and support of frequently reported symptoms following immunization (Pan American Health Organization, and World Health Organization, 2021).

Collaborators

This project is facilitated in accordance with Georgetown University's Health Informatics and Data Science Program, MedStar Health Data Human Factors in Healthcare Team, and the CDC and FDA-managed public Vaccine Adverse Event Reporting System database. All agencies have the overarching mission of making a positive impact in the advancement of healthcare while prioritizing innovation and stakeholder needs. Georgetown University, and specifically, the Innovation Center for Biomedical Informatics (ICBI) prides itself on building an academic community dedicated to creating and communicating knowledge where students and faculty are encouraged to be life-long learners - accepting responsibility of becoming active participants in civic life and living generously in service to others. Concerned with being a trusted leader in caring for people and advancing healthcare, MedStar Health carries a similar mission to serve all stakeholders in the community by integrating a patient-first mindset, valuing integral systems and staff, and embracing positive change and innovation through the collaboration of diverse perspectives. Affiliated with Georgetown University School of Medicine and operating more than 120 entities, including ten hospitals in the Baltimore–Washington metropolitan area of the United States, MedStar Health's active University partnership and large health organization role exhibits a shared vision for preserving and advancing the health of the surrounding community.

In the context of this project, the FDA and CDC's commitment to maintaining the VAERS dataset meets the mission and vision of their own organization as well as Georgetown University and MedStar Health. The FDA and CDC both value the advancement of healthcare by facilitating the regulation of medical innovations that make products more effective, safe, and affordable while also aiding the public to obtain accurate, science-based information they need to consciously use medical products and foods to maintain and improve their health. Designed to detect unusual or unexpected patterns of adverse events that may indicate a possible safety problem with a vaccine, VAERS data is aligned with the CDC and FDA's mission by providing valuable information necessary to further assess possible safety concerns.

Understanding the vaccine symptom associations using machine learning methods are aligned with all agency missions and visions. New insights of hidden patterns and associations between vaccine profiles and reported symptoms positively contributes to the advancement of pediatric medicine through information gain which can lead to actionable intervention and inform clinical decision making to protect public health interests.

Pediatric Immunization Schedule and AEFI Case Definitions

As of September 2021, a child should receive up to 28 vaccinations including series and booster doses as recommended by the CDC as well as annual influenza vaccination and now COVID-19 mRNA vaccine with routine booster doses. A child may receive additional booster doses of a certain vaccination as determined by their primary care provider (PCP) based on risk and titer evaluation. Children may receive up to 24 immunizations by the age of 2 years old and up to 5 injections in a single visit. In recent years, the count of vaccines has risen significantly to safeguard against a broader range of diseases. However, due to remarkable technological advancements, children now receive fewer antigens - key components in vaccines responsible for triggering an immune system response. These advancements have allowed for the development of vaccines that provide protection against multiple diseases while minimizing the overall antigen exposure and ensuring a safer and more efficient immunization process (National Center for Immunization and Respiratory Diseases, and CDC, 2022).

Vaccines - like all drugs or medical interventions - are neither 100 percent risk-free nor 100 percent effective. In 2005, the Brighton Collaboration developed standardized definitions (Brighton Collaboration case definitions or BCCDs) for AEFIs including six finalized AEFI definitions: fever, persistent crying, intussusception, nodule at injection site, and generalized convulsive seizure. In 2020, the Pan American Health Organization and World Health Organization (WHO) released revised definitions in congruence with Brighton Collaboration definition recommendations to comprise a comprehensive list of defined AEFIs including but not limited to anaphylaxis, guillain-barre syndrome (GBS), thrombosis and thrombocytopenia, syncope, joint pain or arthralgia, hypotonic-hyporesponsive episode (HHE), local reactions (redness, swelling, pain at injection site), and febrile seizures (Pan American Health Organization, and World Health Organization, 2021). These case definitions guide data collection, analysis, and presentation of immunization safety. As defined by the Brighton Collaboration, AEFIs can be categorized and arranged according to severity and life-threatening or altering impact on a scale of 1 (mild impact) to 3 (serious, life threatening) where local reactions may be categorized as Level 1, vomiting is considered intermediate/moderate impact at Level 2, and a patient experiencing an HHE may be classified as Level 3 (Kohl, Katrin S., et al., 2008). The retrospective application of BCCDs and WHO case definitions for VAERS data was found reliable for providing a standardized interpretation of reported information and subsequent classification of AEFIs (Kohl, Katrin S., et al., 2008). Therefore, BCCDs and WHO case definitions will be referenced to evaluate and interpret data-driven symptom association results for the purpose of this project.

METHODS

Data Pre-Processing

The VAERS datasets from 2017 to the present year (2023) were concatenated and consolidated, focusing on patients aged from birth to 21 years. Data pre-processing involved several steps to ensure data quality and consistency. The first focus was imputing and/or removing missing values. Patients without a reported age were excluded from the analysis. Binary columns with missing values were filled with "No" and then imputed as 1 and 0 to indicate "Yes" and "No," respectively. Next, extraneous values were addressed. The allergies column was standardized by categorizing specific food, drug, and environmental allergies into single-word or phrase descriptors based on user inputs. Frequent values were addressed first to streamline imputation. Generic medication names were restored to their original names for consistency. Any missing, inappropriate, or uncertain values were imputed as "No Known Drug Allergies" (NKDA). Following the pre-processing of patient reported allergies, vaccination names and types were reduced to include only the routine pediatric immunizations recommended by the United States pediatric general practice guidelines. Vaccines with similar codes were grouped together, and overarching terms were used to reduce naming variability. For example, DTAP was imputed for all DTAP-VAERS-grouped naming codes according to the VAERS guidebook.

The process of identifying a disease, condition, or injury and formulating a clinical diagnosis relies on patient reported and observed signs and symptoms. Distinguishing between a clinical diagnosis term and symptoms is significant to maintain accurate and clear association results. VAERS collects any and all symptoms reported by patients and/or guardians. Columns SYMPTOM1 through SYMPTOM5 represent the first 5 symptoms reported. If a patient experiences more than 5 symptoms, a new row is created with the same VAERS patient ID to account for additional symptoms. If a patient records less than 5 symptoms, the next symptom column is left empty or ‘No adverse event’ is recorded. Upon examination, the symptom columns also included medical diagnoses. The US SNOMED standard medical diagnostic codes were employed to differentiate between clinical diagnosis terms and symptoms accurately. This step aimed to filter out misreported diagnoses that were erroneously labeled as symptoms. By doing so, the analysis focused on relevant symptom data. Two separate CSV files were created to capture filtered and unfiltered symptoms data, one containing SNOMED-filtered data and another with all reported symptoms (even if defined as diagnosis).

Exploratory Data Analysis

The initial concatenated data frame consisted of 231,618 patients and 37 features. After data pre-processing, the final data frame included 220,204 observations with 23 features. The observations were arranged into age subsets - neonates (216), infants (36,630), toddlers (40,471), children (44,647), and adolescents (98,240). For market basket analysis, only symptom columns

corresponding to each age subset were considered. However, retaining other features allowed for a comprehensive understanding of the data and context of relevant findings.

Based on the US recommended pediatric immunization schedule, the retained vaccination types included COVID19 (including booster vaccination), Hepatitis B (HepB), DTaP (Diphtheria, tetanus, and whooping cough), Diphtheria, tetanus (DT), Hib (Haemophilus influenzae type b), IPV (Polio), PCV (Pneumococcal), RV (Rotavirus), Flu (Influenza), Varicella (Chickenpox), MMR (Measles, mumps, and rubella), HepA (Hepatitis A), Meningococcal conjugate vaccine, HPV vaccine, and Tdap/Td (tetanus, diphtheria, and pertussis). Among these, COVID19, DTAP, FLU (H1N1), MMR, and HPV had the highest number of observations in the VAERS dataset. Each age subset was evaluated to understand the distribution of vaccine types and corresponding adverse event reports. The figures below correspond to adverse event symptom reports and vaccines administered in neonates, infants, toddlers, children, adolescents (See Figures 1-5).

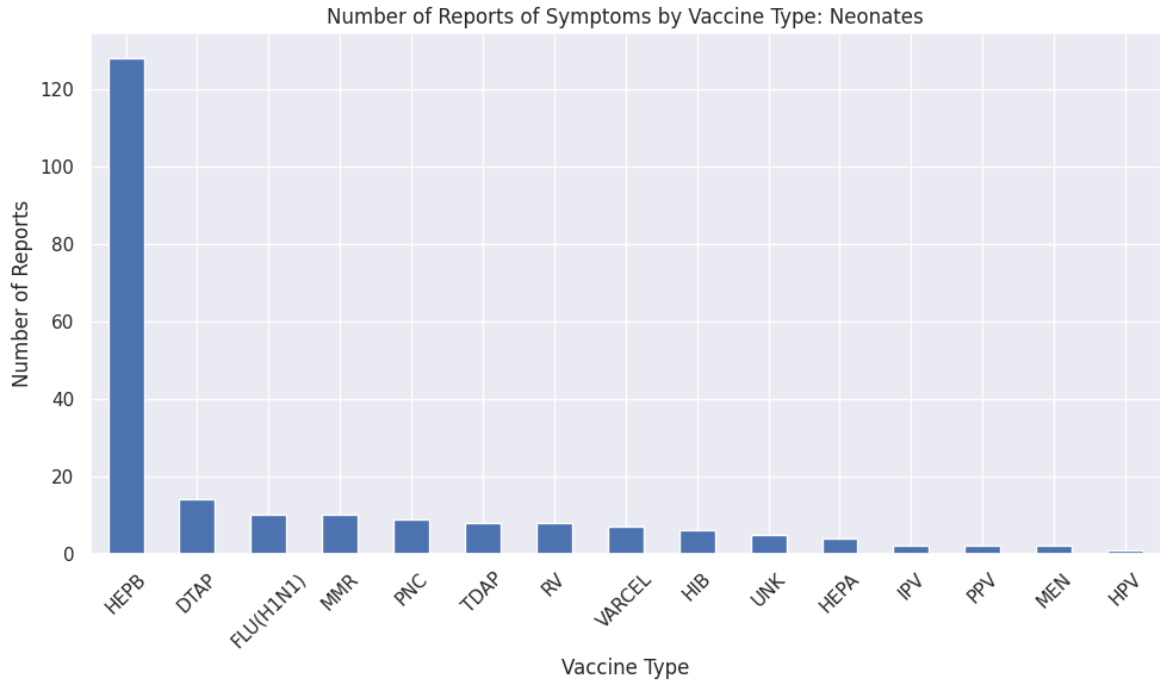

Figure 1: Number of VAERS reports of post-vaccination symptoms by vaccine type in neonates.

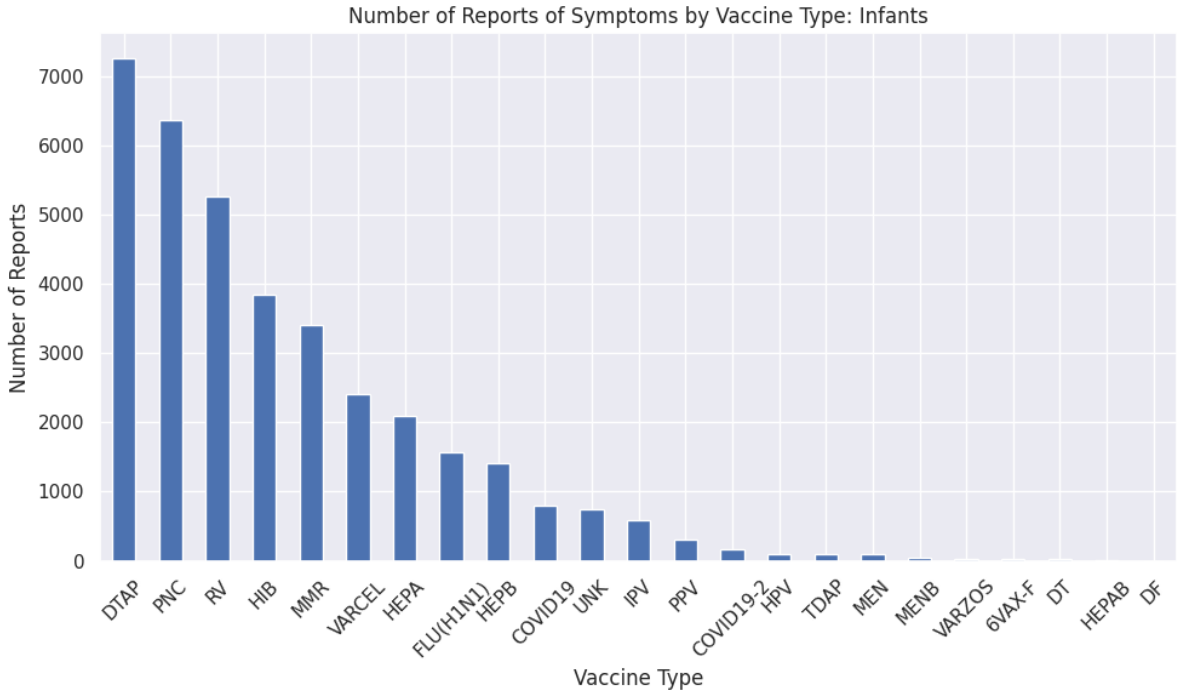

Figure 2: Number of VAERS reports of post-vaccination symptoms by vaccine type in infants.

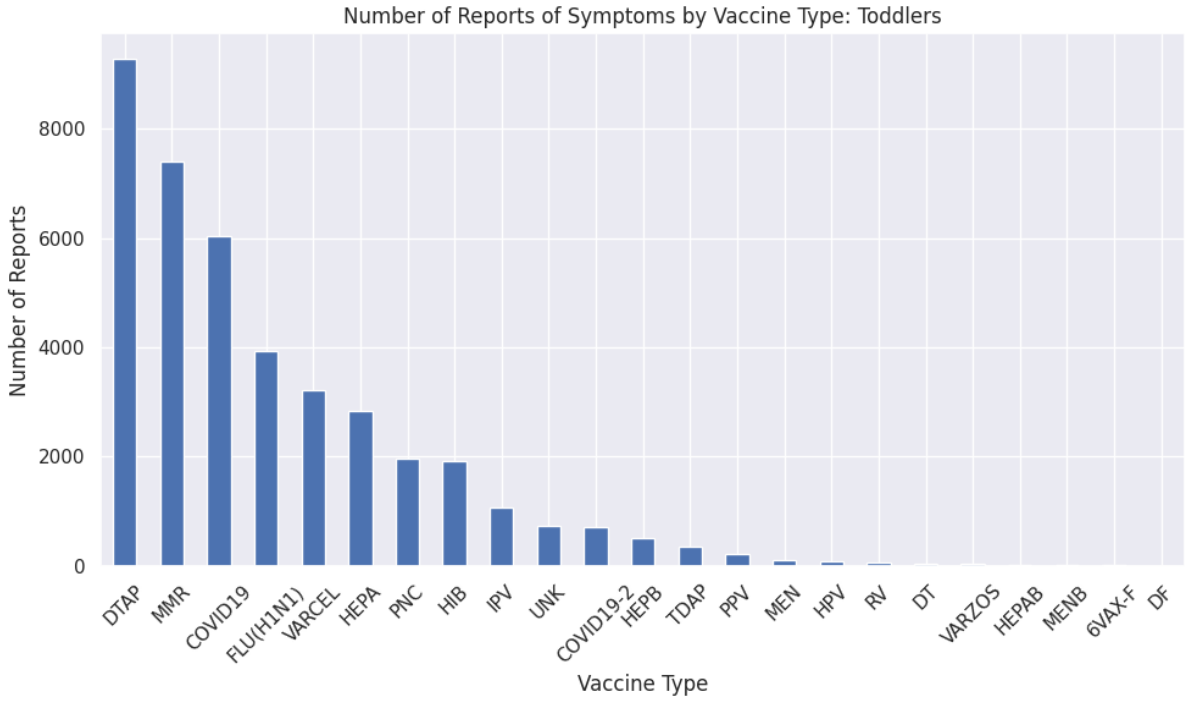

Figure 3: Number of VAERS reports of post-vaccination symptoms by vaccine type in toddlers.

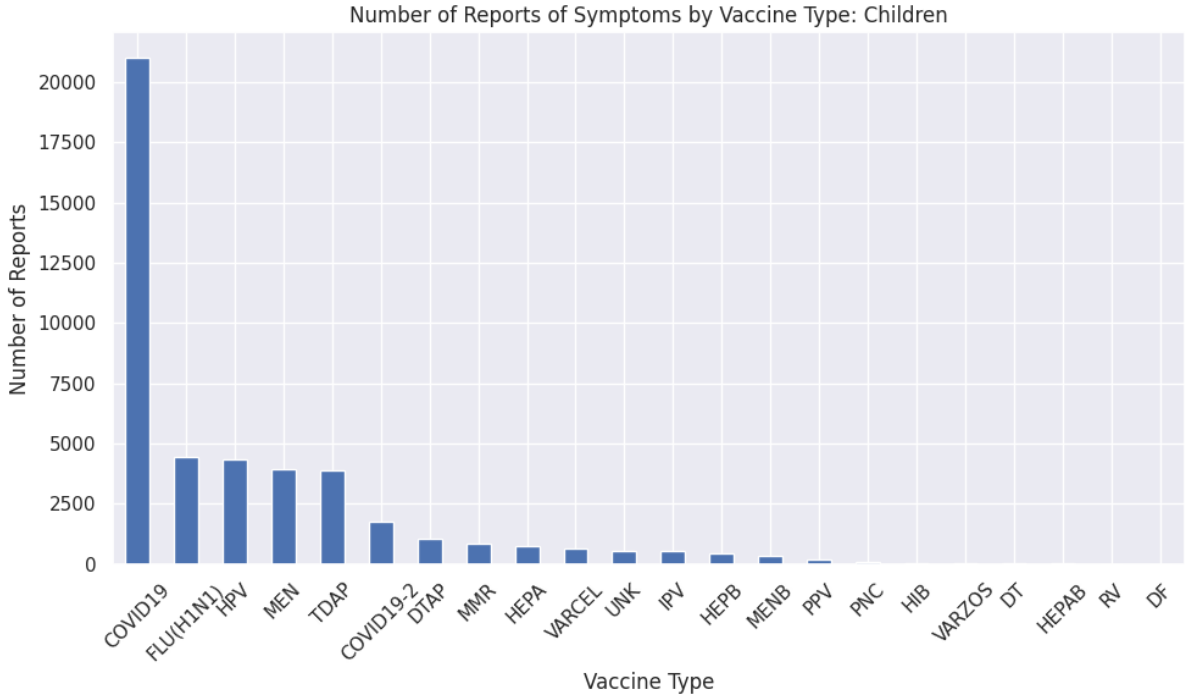

Figure 4: Number of VAERS reports of post-vaccination symptoms by vaccine type in children.

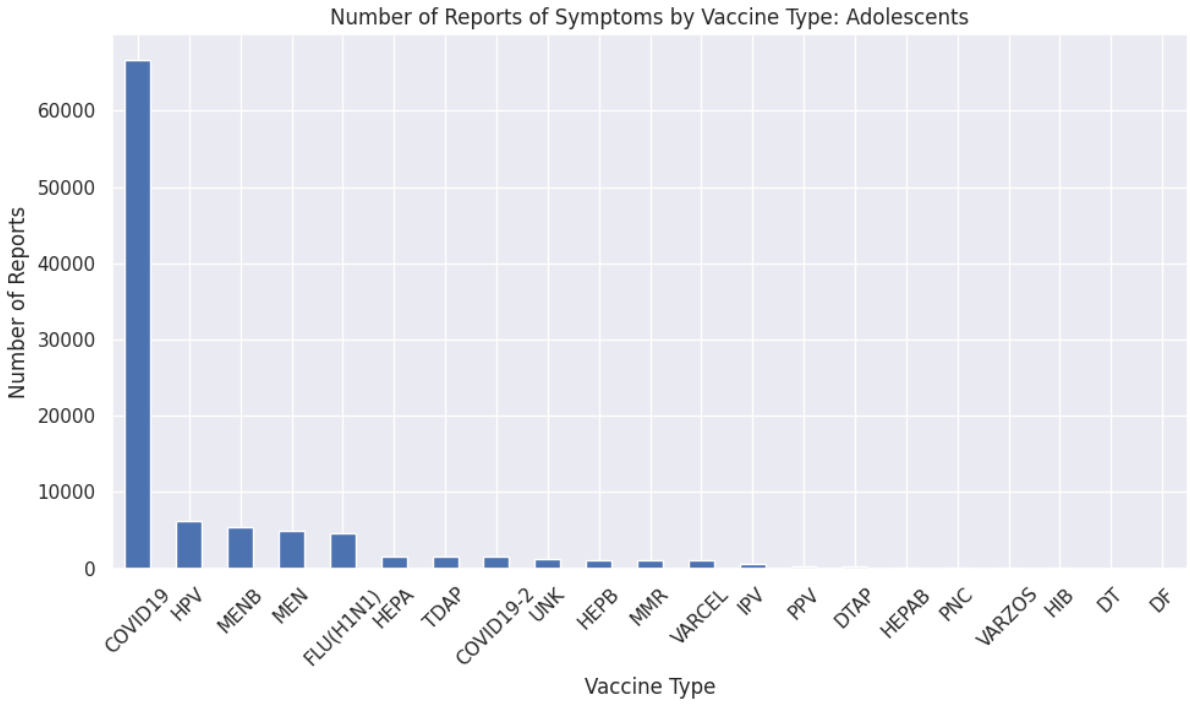

Figure 5: Number of VAERS reports of post-vaccination symptoms by vaccine type in adolescents.

Notably, while filtering symptoms based on SNOMED codes, it was observed that relevant symptoms, such as "fever," were inadvertently removed from the data. Consequently, the original symptom matrix of reported data was retained for analysis, under the assumption that associations will be assessed for clinical relevance following market basket analysis. If diagnoses are identified within the unsupervised learning results, their significance will be interpreted by clinical professionals. Word clouds were generated for each age subset to understand the frequency of reported symptom terms (see below). The subsequent sections of this report will delve into the results of the market basket analysis, discuss the identified associations between pediatric vaccines and reported symptoms, and provide insights for clinical practice and public health initiatives.

Unsupervised Machine Learning Method: Market Basket Analysis

Market basket analysis (MBA) is a data mining technique that identifies associations between items frequently purchased or observed together. In the context of this study, market basket analysis will be utilized to uncover associations between pediatric vaccines and reported symptoms in the VAERS dataset. In this analysis, each vaccination will be considered as an “item”, and the reported symptoms will be treated as the "baskets" or sets of items. The

parameters used in market basket analysis include support, confidence, and lift. Support refers to the proportion of cases where a particular vaccine and symptom combination occurs, while confidence measures the likelihood of observing a symptom given the administration of a specific vaccine. Lift indicates the strength of the association between a vaccine and a symptom, with values greater than 1 indicating a positive association. By applying market basket analysis to the VAERS data, the aim is to uncover meaningful associations between pediatric immunizations and reported symptoms, providing valuable insights into potential post-vaccination symptom associations. These findings will help guide clinical decision-making, improve patient communication, and inform public health strategies to address vaccine safety concerns.

To conduct the market basket analysis, the Apriori algorithm, available through the Apriori package in Python, will be employed. The Apriori algorithm efficiently generates frequent itemsets and association rules from transactional datasets. In this study, the VAERS dataset will be transformed into a transactional format, where each patient's vaccination and reported symptoms will be treated as a separate transaction. Prior to running the Apriori algorithm, all empty strings, NA values, and instances where the reported adverse event is labeled as "no adverse event" will be filtered out. These filtering steps are essential to ensure the quality and relevance of the data used in the market basket analysis. By applying the Apriori algorithm to the preprocessed dataset, we can uncover significant associations between pediatric vaccines and reported symptoms, facilitating a deeper understanding of post-vaccination symptom profiles and aiding in clinical decision-making and public health interventions.

RESULTS

Neonate Patient Group

The vaccine recommended by the Advisory Committee on Immunization Practices (ACIP) and approved by the Centers for Disease Control and Prevention (CDC) and American Academy of Pediatrics (AAP) for children ages 0 days (birth) to 28 days old is the Hepatitis B (HepB) vaccination. Of 216 neonatal VAERS reports, 128 (59.3%) records were associated with Hepatitis B type immunization. Neonates administered any other type of vaccination (88 (40.7%) patient records) were considered to have the wrong product administered or vaccine product administered outside of the recommended window for immunization. Of the 128 Hepatitis B neonatal VAERS reports, 65 (50.8%) were female and 63 (49.2%) were male (See Table 1).

MBA unsupervised machine learning was performed for all 216 neonatal records to derive symptom associations. With a minimum support of 0.01, minimum confidence of 0.8, lift of 1, and length set at 2, a total of 93 association rules were derived from neonatal adverse event post-vaccination symptom reports. Most notably, upper abdominal pain is associated with

dyspnea and projectile vomiting (confidence: 1, lift: 1.13) and decreased urinary output is associated with crying and decreased appetite (confidence: 1, lift: 1.13).

Filtered by vaccine, MBA performed on a filtered subset of Hepatitis B type neonatal reports. Using a minimum support interval set at 0.01, minimum confidence of 0.5, minimum lift set at 1, and length of 2, AEFI symptom association rules were derived for the neonatal subgroup. Hypotonia is associated with cyanosis (confidence: 1, lift: 18.28) as well as lethargy (confidence: 0.5, lift: 10.66). Insomnia is associated with the report of malaise (confidence: 0.66, lift: 42.66). Muscle twitching is associated with poor feeding (confidence: 1, lift: 25.6). Finally, unresponsive to stimuli is associated with reports of vomiting (confidence: 0.5, lift: 10.66) (See Table 2).

Infant Patient Group

ACIP vaccination recommendations for children aged 1 month to 1 year old include 2nd and 3rd doses of HepB, Rotavirus (RV), Diphtheria, tetanus, and acellular pertussis (DTaP), Haemophilus influenzae type b (Hib), Pneumococcal conjugate (PVC), Inactivated poliovirus (IPV), COVID-19, annual Influenza (Flu), the 1st dose of the Measles, mumps, rubella (MMR) series, Varicella (VAR), and Hepatitis A (HepA). There are a total of 13,133 unique infant VAERS reports with 12,627 (96.1%) records in relation with the ACIP recommended vaccination types for infant aged children while 3.85% of patients received the wrong product or an immunization at an inappropriate age. Of the 12,627 observations, females comprised 51.2% (6463 reports) of the data while males made up 48.8% (6164 reports) of reported adverse events for infants (See Table 1).

Initial MBA was performed for infant aged children with a minimum support value set at 0.001, minimum confidence of 0.5, lift of 1, and length 2. A total of 53 symptom association rules were produced. Crying, injection site swelling, and injection site erythema were noted associations (confidence: 0.60, lift: 10.5) likely reported together. Lethargy, decreased appetite, and pyrexia were also likely to be reported in association (confidence: 0.59, lift: 3.96). Injection site mass, induration, and erythema were also noted associations (confidence: 0.58, lift: 13.4).

Infant adverse event reports were grouped and separated by vaccine type to understand post-vaccination symptom associations unique to each product type dose given to children between 1 month and 1 year of age. MBA symptom association rules were extracted for all ACIP recommended infant immunizations utilizing the same MBA metric parameters as described above. Associations were ignored if clinically ambiguous or irrelevant such as a condition or administration note (i.e. “wrong product administered”). AEFI symptom association rules for vaccinations administered to VAERS infants had confidence ranging from 0.50 to 1 and life

values ranging from 2.16 to 525 respectively. The most associations were extracted from Hepb, DTaP, and influenza vaccines, however, all ACIP recommended immunizations produced relevant symptom association results as seen in Table 2. Similar to HepB AEFI symptom associations in neonates, hypotonia reported with cyanosis was also extracted for the infant population (confidence: 0.50, lift: 7.5). Additionally, DTaP AEFI symptom associations showed high confidence and lift. A decrease in infant appetite, diarrhea, and insomnia were associated with each other (confidence: 0.62, lift: 14.8), while an increase in appetite was likely reported with symptoms of crying and cough (confidence: 0.5, lift: 45.6). A decrease in infantile blood pressure with chills, diarrhea, and decrease in body temperature were observed to have a high likelihood of being reported together when support was lowered from 0.01 to 0.001 (confidence: 1, lift: 93). With this same support metric, an increased white blood cell count - indicative of a possible infection - with skin edema and a vesicular rash had high association (confidence: 1, lift: 93). Vaccination against chickenpox (Varicella) (confidence: 0.55, lift: 57.4) as well as the influenza (confidence: 0.5, lift: 3.6) vaccination saw seizure associated with pyrexia (See Table 2).

Toddler Patient Group

Children ages 1 year to 5 years of age receive final series doses of neonatal and infant immunizations. Per ACIP guidelines, toddlers receive their final round of HepB, Rotavirus (RV), Diphtheria, tetanus, and acellular pertussis (DTaP), Diphtheria and tetanus (DT), Haemophilus influenzae type b (Hib), Pneumococcal conjugate (PVC), Inactivated poliovirus (IPV), COVID-19, and annual Influenza (Flu). Toddlers may also receive the 1st dose of the Measles, mumps, rubella (MMR) series, Varicella (VAR), and Hepatitis A (HepA) series if not given at 12 month visit. Additionally, toddlers will receive their 2nd dose of MMR and HepA nearing the end of the toddler stage at age 4 to 6 years. 21,800 unique toddler adverse event reports were recorded in the VAERS dataset. 21,153 (97.0%) are in relation with the ACIP recommended vaccination types for toddler aged children. Of 40,471 VAERS toddler AEFI observations, 11,032 (52.2%) are female and 10,121 (47.8%) are male (See Table 1).

MBA run for all toddler observations resulted in 27 symptom association rules. MBA metric parameters were set at minimum support of 0.001, confidence at 0.8, lift of 1, and length 2. Results from this analysis included a high volume of local site reactions associated highly with other local site reactions such as injection site swelling associated with injection site erythema, edema, warmth, pain, and induration. Knowing these results, MBA was performed for each individual vaccination type. For most toddler vaccinations, similar results were obtained. Pain, swelling, warmth, injection site mass, and erythema were likely to be reported and associated with each other. However, toddlers receiving DT immunization displayed AEFI symptom associations for abnormal physical weakness (asthenia), headache, disorientation, crying, and

hypotension (confidence: 0.50, lift: 20.5). Additionally, abdominal pain, hypotonia, and erythema were most likely to be reported together in toddlers post-DT vaccination (confidence: 1, lift: 41) (See Table 2).

Child Patient Group

Children ages 5 years to 12 years old receive their last dose of the DTaP series, final dose of the IPV series, COVID19 booster shots (if needed), annual influenza vaccination, 2nd dose of MMR and Varicella series if not given during toddler stage, first dose of Tetanus, diphtheria, & acellular pertussis (Tdap), and possibly first dose of Human papillomavirus (HPV) series. There are 30,816 unique VAERS observations for children where 29,116 (94.5%) are ACIP recommended vaccine related reports. Of 29,116 VAERS observations, 14,414 (49.5%) are female and 14,702 (50.5%) are male AEFI reports (See Table 1).

Table 1. Cohort Characteristics.

Age Group	Age Range	Number of Reports	Average Age (years)	Standard Deviation of Age	Hospitalization (%)
Neonates	0-28 days	216	0.0 years`	0.00	25.0%
Infants	1-12 months	13,133	0.5 years	0.34	16.57%
Toddlers	1-5 years	21,800	3.0 years	1.43	6.28%
Children	5-12 years	30,816	10.0 years	1.96	6.15%
Adolescents	12-21 years	68,202	17.1 years	2.37	9.80%

Preliminary MBA performed for all pediatric reports aged 5 to 12 years old produced 56 AEFI symptom association rules. Similar to toddler results, symptom associations for children mostly comprised local site reactions such as injection site erythema associated with injection site swelling, warmth, rash, induration, and pain. The minimum support metric was lowered to 0.001 from 0.01 and minimum confidence was set at 0.5 to analyze for any further variability in symptom associations, however, results contained association rules analogous to results of the original support and confidence parameters.

Segmented into separate ACIP recommended vaccine type groups, MBA was performed on subsets of child AEFI reports. Association rules produced for each vaccine type were analogous with the results of the preliminary MBA child AEFI symptom associations including all local site reactions. However, COVID-19 immunizations in children produced AEFI symptom

association rules for chills associated with nausea and headache (confidence: 0.50, lift: 11.5). Furthermore, COVID-19 booster vaccinations in children extracted association rules for seizure likely to be reported with pallor and syncope (confidence: 1, lift: 54) as well as flushing reported with dizziness and hyperhidrosis (excessive sweating) (confidence: 0.60, lift: 208.8). For children who received Diphtheria and tetanus (DT) vaccination near 11 to 12 years of age, gastrointestinal symptoms and/or abdominal pain were noted as strong and frequent association rules including upper abdominal pain associated with decreased activity, dizziness, disturbance in attention, and arthralgia or joint pain (confidence: 1 lift: 18). Abdominal pain was also associated with pyrexia or fever, vomiting, and diarrhea (confidence: 1, lift: 18). Children who received the first part of the HPV series during childhood, local site reactions such as erythema associated with injection site swelling and pain (confidence: 0.63, lift: 11.1) were likely to be reported together (See Table 2).

Adolescent Patient Group

Pediatric patients aged 12 to 21 years of age are advised to receive the 1st and 2nd dose of meningococcal vaccine (Men), meningococcal B (MenB), HPV series, Tetanus, diphtheria, & acellular pertussis (Tdap) at 12 years old if not received during childhood period, COVID-19 and COVID-19 booster vaccinations, and the annual influenza vaccine. There are 68,202 unique reports for adolescent AEFIs, however, only 28,587 (41.9%) reports are according to ACIP recommendation. Of 28,587 unique patient reports, 14,080 (49.3%) are female and 14,507 (50.7%) are male (See Table 1).

Initial MBA performed on all adolescent AEFI reports 56 symptom association rules were produced. Metric parameters for MBA were set to minimum support 0.001, minimum confidence 0.5, lift as 1, and length of 2. Resulting association rules included local site reactions such as injection site erythema, pain, swelling, warmth, induration, and pruritus. Local site reaction associations were observed to be highest in confidence and lift amongst all results. All other association rules produced were irrelevant and not defined symptoms.

MBA was performed for vaccine types received by adolescents with a higher support threshold of 0.01 and the same confidence and lift metric parameters. MBA for adolescents receiving the meningococcal vaccination extracted AEFI symptom association rules where decreased appetite, fatigue, and headache were likely to be reported together (confidence: 0.5, lift: 6.45) as well as erythema, nausea, and patient feeling hot (possibly fever) (confidence: 1, lift: 812.33). The latter symptom association rule for nausea, erythema, and patient feeling hot was also derived for the meningococcal B vaccination in addition to nausea, hypotension, pallor appearance (confidence: 0.54, lift: 13.4) and abdominal pain, nausea, and headache (confidence: 0.5, lift: 3.6). Local site reaction associations were seen with the annual influenza vaccination

and HPV series. Tdap vaccination MBA results for adolescents produced several association rules. Decreased appetite, cough, fatigue, dizziness, and physical weakness were likely to be reported together (confidence: 0.66, lift: 81.4). Additionally, loss of consciousness (LOC), hypotonia, and pallor appearance were noted associations (confidence: 0.75, lift: 9.76). Upper abdominal pain and nausea were also associated with a pallor appearance (confidence: 1, lift: 13). In congruence with current findings of COVID-19 infection signs and symptoms, adolescent AEFI symptom association rules included loss of sense of taste associated with loss of sense of smell (confidence: 0.74, lift: 322.7) as well as fatigue, chills, nausea, and headache (confidence: 0.52, lift: 6.69) likely to be reported together post-COVID-19 vaccination. However, the COVID-19 boost vaccination MBA results included more specific and sensitive symptom associations such as fatigue likely to be reported with hypotension and lethargy (confidence: 0.66, lift: 87.2) as well as patient reports of feeling cold with an increase in heart rate (confidence: 0.66, lift: 116.3). For adolescents who are classified as at-risk and recommended by the ACIP to receive the Dengue fever (DF) vaccination symptom associations included an increase in blood pressure likely to be reported with vomiting, dizziness, palpitations, and nausea (See Table 2).

DISCUSSION

` Unsupervised learning methods of association rule mining using MBA extracted distinct AEFI symptom patterns analogous to current AEFI case definitions or BCCDs. It is important to note disturbance to regular childhood activity (i.e. dietary intake and/or excretion, sleep, activity level, etc) may be cause for concern as children are inherently a healthy population (Seattle Children's Hospital, and Schmitt Pediatric Guidelines, 2023). Local site reaction associations were seen with all age groups and vaccination types. As previously discussed, exacerbation of these symptoms overtime may warrant more urgent medical care as infection or anaphylaxis progresses (Seattle Children's Hospital, and Schmitt Pediatric Guidelines, 2023).

Neonatal administration of ACIP recommended HepB vaccination revealed symptom associations corresponding to signs and symptoms for the clinical triad of HHE disease progression (sudden onset of hypotonia, hyporesponsiveness, and pallor or cyanotic appearance occurring within 48 hours after childhood immunizations) (Vigo, Alessandro et al., 2017). The same hypotonia symptom associations and HHE symptom triad were also extracted for infant-aged children receiving the HepB vaccination. Because HepB immunization is a multi-dose series, clinicians may refer to previous neonatal experience or post-vaccination symptom history to understand an infant’s risk of HHE development and what to anticipate for patient care. Additionally, symptom associations for abdominal/gastrointestinal disturbances correlate with Brighton Collaboration case definitions for intussusception - a life-threatening illness that occurs when a portion of the intestine folds - indicated by sudden, loud persistent

crying, vomiting, stool mixed with blood and/or mucus, and abdominal pain (Kohl, Katrin S., et al., 2008). Furthermore, specific symptom associations related to COVID-19 and COVID-19 booster vaccinations in children and adolescents were identified, such as chills with nausea and headache, fatigue with hypotension and lethargy, and loss of sense of taste with loss of sense of smell. These findings are in line with known symptoms of COVID-19 infection, demonstrating the sensitivity of the analysis in capturing relevant associations (CDC, 2023).

The separation of age groups and distinction between vaccine-specific symptom association rules resulted in a view of possible age-specific immunization experiences for pediatric patients. As a vulnerable population with significantly less health data to determine possible risk for AEFI simply due to age and finite medical history, pediatric AEFI symptom association rules offer a clinical guide for likelihood of symptom presentations and disease progression. Results from this analysis highlight the likelihood of symptoms being reported with one another. Clinical interpretation of symptom severity - understanding the possible cascade of symptoms such as neonatal cyanosis reported with hypotonia - may aid medical intervention as previously unforeseeable progression of AEFIs are better anticipated.

Limitations and Future Research

There are several caveats to passive spontaneous reporting and the VAERS data set. Data is limited to safety signal detecting and cannot be used to prove direct vaccine-AEFI or serious AEIF causation. Because of passive surveillance, hypotheses should be cautioned to acknowledge the subjective nature of voluntary adverse event reporting. VAERS reports vary in quality and completeness and can be completed by anyone (patients, physicians, family members, etc.). Although data preprocessing was thorough, VAERS reports often lack details and are prone to containing errors. For example, age calculations may be inaccurate and thus disturb the validity of results.

The use of unsupervised learning methods, particularly MBA, in analyzing the VAERS dataset has proven to be a powerful tool in uncovering associations between pediatric vaccines and reported AEFI symptoms. These findings provide valuable insights for clinical decision-making, improving patient education and experience expectations, and informing public health strategies to address vaccine safety concerns. By identifying specific AEFI symptom associations, healthcare professionals can better understand the likelihood of potential adverse event and disease progressions following vaccination. However, it is essential to interpret the severity and clinical relevance of found associations, considering the complexities of individual patient conditions and medical history. Future studies and collaboration with clinical professionals and relevant organizations such as the Brighton Collaboration, FDA, and ACIP, can

further validate and refine the identified associations, contributing to continuous improvement of vaccine safety surveillance and patient care.

Table 2. Market-Basket Analysis (MBA) of Pediatric Vaccination Symptom Associations.

	Neonate 0 to 28 days of age Support: 0.01 Confidence: 0.5 Lift: 1 Length: 2	Infant 1 to 12 months of age Support: 0.01 Confidence: 0.5 Lift: 1 Length: 2	Toddler 1 to 5 years of age Support: 0.01 Confidence: 0.5 Lift: 1 Length: 2	Child 5 to 12 years of age Support: 0.01 Confidence: 0.5 Lift: 1 Length: 2	Adolescent 12 to 21 years of age (US pediatric definition) Support: 0.01 Confidence: 0.5 Lift: 1 Length: 2
HepB (subunit)	Hypotonia, cyanosis C: 1 L:18.28 Hypotonia, lethargy C: 0.5 L:10.66 Insomnia , Malaise C: 0.66 L:42.66 Muscle twitching, poor feeding C: 1 L: 25.6 Unresponsive to stimuli, vomiting C: 0.5 L: 10.66	Injection site swelling, erythema C: 0.527 L: 16.22 Hypophagia, vomiting, diarrhea C: 0.5 L: 17.8 Min support: 0.001 Hypotonia, cyanosis, crying C: 0.5 L: 7.5 Min support: 0.001 Crying, discomfort, decreased appetite C: 0.66 L: 34.9 Min Support: 0.001	NA (Wrong product administered)*	NA (Wrong product administered)*	NA (Wrong product administered)*

DTaP (subunit)	NA (Wrong product administered)*	Injection site swelling, erythema C: 0.62 L: 14.8 Decreased appetite, diarrhea, insomnia C: 1 L: 93 Min Support: 0.001 Cough, crying, increased appetite C: 0.5 L: 45.6 Min support: 0.001 Blood pressure decreased, chills, diarrhea, body temperature decreased C: 1 L: 93 Min support: 0.001 WBC increased, skin edema, vesicular rash C: 1 L: 93 Min support: 0.001	Injection site swelling, erythema, induration, warmth C: 0.5 L: 3.8	Injection site erythema, warmth, swelling C: 0.58 L: 10.6	NA (Wrong product administered)*
PNC (subunit)	NA (Wrong product administered)*	Decreased appetite, rash, pyrexia C: 0.66 L: 3.8	Injection site swelling, induration, erythema C: 0.81 L: 6.39	NA (Wrong product administered)*	NA (Wrong product administered)*

		Injection site swelling, erythema, bradycardia, apnea C: 0.58 L: 84.3 Min support: 0.001			
Hib (subunit)	NA (Wrong product administered)*	Injection site warmth, erythema, injection site mass C: 1 L: 20.26 Pyrexia, platelet count increased, rash C: 0.83 L: 12.8 Decreased appetite, pyrexia, lethargy, vomiting C: 0.72 L: 4 Min support: 0.001	Injection site erythema, warmth, swelling C: 0.58 L: 7.48 Irritability, pyrexia C: 0.52 L: 2.98	NA (Wrong product administered)*	NA (Wrong product administered)*
MEN (subunit)	NA (Wrong product administered)*	NA (Wrong product administered)*	NA (Wrong product administered)*	Injection site pain, pruritus, erythema C: 0.93 L: 6.98	Decreased appetite, fatigue, headache C: 0.5 L: 6.45 Erythema, feeling hot, nausea C: 1 L: 812.33
MENB (subunit)	NA (Wrong product administered)*	NA (Wrong product administered)*	NA (Wrong product administered)*	NA (Wrong product administered)*	Nausea, hypotension, pallor C: 0.54 L: 13.4

					Erythema, feeling hot, nausea C: 1 L: 909 Abdominal pain, nausea, headache C: 0.5 L: 3.6
Flu (inactivated)	NA (Wrong product administered)*	Seizure, vomiting, pyrexia C: 0.5 L: 3.6 Nausea, pallor, vomiting C: 0.66 L: 525 Cough, nasal congestion, pyrexia C: 1 L: 6.7 Febrile convulsion, skim warm, irritability C: 1 L: 18.3 Decreased appetite, rash, pyrexia C: 1 L: 6.7	Warmth, erythema, swelling C: 0.5 L: 5.7	Warmth, erythema, swelling, pain C: 0.57 L: 8.58	Pain, pruritus, swelling, erythema C: 0.55 L: 86.4 Vomiting, chills, pyrexia C: 0.83 L: 16.2
HepA (inactivated)	NA (Wrong product administered)*	Body temperature increased, decreased appetite, irritability C: 0.6 L: 9.9	NA (Wrong product administered)*	Swelling, erythema C: 0.72 L: 14	NA (Wrong product administered)*

		Decreased appetite, rash, irritability CI: 0.5 L: 8.2			
IPV (inactivated)	NA (Wrong product administered)*	Lethargy, pyrexia C: 0.52 L: 3.09	Pain, warmth, swelling, erythema C: 0.68 L: 7.8	Pruritus, swelling C: 0.66 L: 16.4 Swelling, erythema, warmth C: 0.6 L: 55.4	NA (Wrong product administered)*
MMR (live)	NA (Wrong product administered)*	Injection site swelling, warmth, mass, erythema C: 0.66 L: 59.7 Decreased appetite, rash, irritability, pyrexia C: 0.5 L: 2.16 Petechiae, contusion, platelet count decreased C: 0.66 L: 70.9	Warmth, erythema, swelling C: 0.8 L: 4.4	Warmth, erythema, swelling C: 0.57 L: 15.7	NA (Wrong product administered)*
RV (live)	NA (Wrong product administered)*	Decreased appetite, lethargy, pyrexia C: 0.5 L: 4.2 Rash, pyrexia, peripheral swelling C: 1 L: 7.7 Injection site pain, swelling, erythema	NA (Wrong product administered)*	NA (Wrong product administered)*	NA (Wrong product administered)*

		C: 7.77 L: 25.7			
VARCEL (live)	NA (Wrong product administered)*	Injection site induration, warmth, erythema, mass C: 1 L: 10.72 Injection site cellulitis, warmth, induration C: 0.75 L: 34.7 Decreased appetite, erythematous rash, pyrexia C: 0.6 L: 8.8 Seizure, pyrexia C: 0.55 L: 57.4	Swelling, erythema, warmth C: 0.5 L: 7.39	Warmth, erythema, pruritus C: 0.63 L: 13.49	NA (Wrong product administered)*
TDaP (toxoid)	NA (Wrong product administered)*	NA (Wrong product administered)*	NA (Wrong product administered)*	NA (Wrong product administered)*	Decreased appetite, cough, fatigue, dizziness, asthenia C: 0.66 L: 81.4 Eyelid rash, feeling hot, pyrexia C: 0.66 L: 353.1 Upper abdominal pain, pallor, nausea C: 1 L: 13 Cyanosis, anxiety

					C: 1 L: 88.27 LOC, hypotonia, pallor C: 0.75 L: 9.76
DT (toxoid)	NA (Wrong product administered)*	NA (Wrong product administered)*	Asthenia, headache, disorientation, crying, hypotension C: 0.5 L: 20.5 Injection site induration, warmth, erythema, mass C: 1 L: 41 Abdominal pain, hypotonia, erythema C: 1 L: 41	Upper abdominal pain, decreased activity, dizziness, disturbance in attention, arthralgia C: 1 L: 18 Abdominal pain, nausea, vomiting, diarrhea, pyrexia C: 1 L: 18 Decreased appetite, fatigue, pyrexia, pain in extremity C: 1 L: 18 Injection site induration, warmth, erythema, mass C: 1 L: 18	NA (Wrong product administered)*
COVID19 (mRNA)	NA (Wrong product administered)*	Headache, chills, malagiya C: 0.53 L: 13.6	No Instances**	Chills, nausea, headache C: 0.5 L: 11.5	Fatigue, chills, nausea, headache C: 0.52 L: 6.69 Swelling, pruritus, erythema C: 0.5 L: 80.9

					Ageusia, anosmia C: 0.74 L: 322.7
COVID19-2 (mRNA)	NA (Wrong product administered)*	Pyrexia, cough C: 1 L: 40.25	No Instances**	Seizure, pallor, syncope C: 1 L: 54 Flushing, dizziness, hyperhidrosis C: 0.6 L: 208.8	Unresponsive to stimuli, syncope, vomiting, nausea C: 1 L: 157.1 Erythema, fatigue, headache, swelling C: 1 L: 130.9 Feeling cold, heart rate increased C: 0.66 L: 116.3 Fatigue, hypotension, lethargy C: 0.66 L: 87.2
HPV (subunit)	NA (Wrong product administered)*	NA (Wrong product administered)*	NA (Wrong product administered)*	Erythema, swelling, pain C: 0.63 L: 11.1	Pain, erythema, swelling, warmth C: 0.52 L: 38.9 Dysmenorrhea, dizziness C: 0.55 L: 4.8
DF (live attenuated)**	NA (Wrong product administered)*	NA (Wrong product administered)*	NA (Wrong product administered)*	NA (Wrong product administered)*	Blood pressure increased, vomiting, dizziness, palpitations, nausea C: 1 L: 10

*NA (Wrong product administered): Vaccine out of age window for recommended administration per US pediatric immunization guidelines.
**No Instances: Symptom associations for vaccination were not found for age group.
***Dengue Fever (DF): Only applicable for patients at-risk for infection and recommended to receive DF immunization.
C: MBA confidence metric or the likelihood of observing symptom ‘A’ given the administration of a specific vaccine.
L: MBA lift metric or the strength of the association between a vaccine and symptom(s), values >1 indicate positive association.

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