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Safety Surveillance of Diphtheria and Tetanus Toxoids and Acellular Pertussis (DTaP) Vaccines

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Abstract

Objective: To assess the safety of currently licensed diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccines in the US using data from the Vaccine Adverse Event Reporting System (VAERS), a spontaneous reporting surveillance system.

Methods: We searched VAERS for US reports for DTaP vaccinations occurring during January 1, 1991, through December 31, 2016, and received by March 17, 2017. We reviewed available medical records for all death reports and a random sample of reports classified as non-death serious. We used empirical Bayesian data mining to identify adverse events that were disproportionally reported after DTaP vaccination.

Results: VAERS received 50,157 reports after DTaP vaccination; 43,984 (87.7%) of them reported concomitant administration of other vaccines, and 5,627 (11%) were serious. Median age at vaccination was 19 months (interquartile range 35 months). The most frequently reported events were injection site erythema (12,695; 25.3%), pyrexia (9,913; 19.8%), injection site swelling (7,542; 15.0%), erythema (5,594; 11.2%), and injection site warmth (4,793; 9.6%). For three of

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Contributors' Statement

Pedro L. Moro: Dr. Moro conceptualized and designed the study, reviewed medical records and reports, conducted part of the analysis, drafted the initial manuscript, and approved the final manuscript as submitted.

Silvia Perez-Vilar, Marthe Bryant-Genevier: Drs. Perez-Vilar, Bryant-Genevier conducted the data mining analyses, reviewed and revised the manuscript, and approved the final manuscript as submitted.

Hajime Kamiya, Maria Cano: Drs. Kamiya, and Cano reviewed medical records and reports, reviewed and revised the manuscript, and approved the final manuscript as submitted.

Paige Lewis: Ms. Lewis conducted the analysis, reviewed and revised the manuscript, and approved the final manuscript as submitted.

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the DTaP vaccines, empirical Bayesian data mining identified elevated values for vaccination errors.

Conclusion: No new or unexpected AEs were detected. The observed disproportionate reporting for some non-serious vaccination errors calls for better education of vaccine providers on the specific indications for each of the DTaP vaccines.

Introduction

Whole cell pertussis-containing (DTwP) vaccine was developed in the 1930s and used widely in clinical practice by the mid-1940s [1]. DTwP vaccine was 70%–90% effective in preventing serious pertussis disease [1]. Concerns about safety, particularly severe local reactions, febrile seizures and reports of acute encephalopathy following vaccination, led to the development and licensure of diphtheria, tetanus, and acellular pertussis (DTaP) vaccines [2–4]. The first DTaP vaccine was approved by the Food and Drug Administration (FDA) for use in the United States (US) in 1991, and recommended in place of DTwP for the fourth and fifth doses of the recommended series among children ≥15 months of age [4]. In 1997, the Advisory Committee on Immunization Practices (ACIP) recommended DTaP for all five doses in the childhood vaccination schedule. DTaP is reported to have mild local and systemic adverse reactions and less frequent serious adverse events (AEs) compared to DTwP [4]. DTwP is no longer licensed nor is it available for use in the US [4].

Currently, there are two DTaP vaccines licensed in the US for the entire 5 dose series: Infanrix® (GlaxoSmithKline) and Daptacel® (Sanofi Pasteur), approved in 1997 and 2002, respectively [5,6]. In addition, four combination DTaP-containing vaccines have been licensed: 1) Pediarix® (GlaxoSmithKline Biologicals) a combination of DTaP, hepatitis B vaccine, and inactivated polio vaccine (IPV) approved in December 2002 [7] and approved for use as a 3 dose series; 2) Pentacel® (Sanofi Pasteur, Ltd) a combination of a DTaP-IPV component and Haemophilus *influenza* type b conjugate vaccine) licensed in June 2008 [8] as a 4 dose series; 3) Kinrix® (GlaxoSmithKline Biologicals); and 4) Quadracel® (Sanofi Pasteur, Ltd), each a combination of DTaP and IPV, licensed in June 2008 [9] and in March 2015 [10], respectively, as a 5^{th} dose in the 5 dose series. Pre-licensure studies of these vaccines showed that the most common AEs following vaccination were injection site and systemic reactions [5–10].

Post-marketing observational studies have shown that the DTaP-containing vaccines have a good safety record [11–22]. In two studies of DTwP and DTaP vaccines conducted in the Vaccine Adverse Event Reporting System (VAERS) in the early 1990's, no major safety concerns were identified. AEs and hospitalizations were less common with DTaP than with DTwP [23,24]. However, these initial VAERS studies covered short periods of time and did not include the DTaP vaccines currently available in the US; therefore, the safety information provided in these analyses are limited [23,24]. In the current study, we used VAERS to assess the safety of currently available DTaP vaccines in the U.S.

Material and Methods

VAERS

VAERS is a U.S. national vaccine safety surveillance system, created in 1990 and co-administered by the Centers for Disease Control and Prevention (CDC) and the FDA. It receives spontaneous reports of AEs following vaccination. Vaccination errors not describing an AE may also be reported [25]. VAERS generally cannot assess whether an AE is causally associated with vaccination, but it may be useful for detecting potential vaccine safety signals [25]. VAERS accepts reports from vaccine manufacturers, healthcare providers, vaccine recipients and others. The VAERS report form collects information on age, sex, vaccines administered, dose and lot number, the AE experienced, and health history. Signs and symptoms of AEs are coded by trained personnel using the Medical Dictionary for Regulatory Activities (MedDRA), a clinically validated, internationally standardized terminology [26]. A VAERS report may be assigned one or more MedDRA preferred terms (PTs). A PT is a distinct descriptor for a symptom, sign, disease, diagnosis, therapeutic indication, investigation, surgical, or medical procedure, or medical, social, or family history characteristic [26], but PTs are not necessarily medically confirmed diagnoses. System Organ Class (SOC) is the highest level of the MedDRA hierarchy that provides the broadest classification for AEs (e.g. nervous system disorders) [27]. Reports are classified as serious or non-serious. A report is considered serious based on the Code of Federal Regulations (21-CFR) definition if one or more of the following are reported: death, life-threatening illness, hospitalization or prolongation of existing hospitalization, or permanent disability [28]. For serious reports, medical records are routinely requested and made available to VAERS personnel.

We searched the VAERS database for reports after DTaP vaccination received by March 17, 2017 for persons given any of the currently licensed DTaP vaccines from January 1, 1991 through December 31, 2016. Non-US reports and duplicate reports were excluded. We summarized the most common MedDRA terms for serious and non-serious DTaP vaccine reports. Quadracel® was not included in our search as very few reports had been received by VAERS at the time of data extraction.

Clinical review of serious reports—All death reports after DTaP vaccines were manually reviewed by a physician. The cause of death was obtained from the autopsy report, death certificate, or medical records. In this review, we made no attempt to assess causality of the reported AEs. We conducted a clinical review of a simple random sample of 5% of non-fatal serious reports after DTaP vaccines. The primary diagnostic category was assigned into a SOC [27]. We also searched for all reports of anaphylaxis after DTaP vaccines using the following specific MedDRA PTs: anaphylactic reaction, anaphylactic shock, anaphylactoid reaction, and anaphylactoid shock. Reports of anaphylaxis were classified using the Brighton Collaboration case definition or physician's diagnosis [29].

Data mining—We used Empirical Bayesian (EB) data mining adjusted for sex and year of receipt of the report [30] to identify DTaP vaccine-event combinations reported more frequently than expected among children up to seven years of age. In the first analysis, we

restricted the analysis to serious US reports entered in VAERS as of December 31, 2016. In the second analysis, we included all serious and non-serious US reports as of December 31, 2016. We conducted the analyses using the Multi-Item Gamma Poisson Shrinker (MGPS) algorithm [30,31] in Oracle's Empirica™ Signal System. The main statistical scores computed are EBGM, EB05, EB95, representing the Empirical Bayes Geometric Mean and the 90% confidence interval. We used EB05≥2.0 as cut-off (the pair is being reported at least twice as often as expected) to define vaccine-event pairs requiring further evaluation [31]. Elevated data mining statistics should not be interpreted as evidence of causal relationship between a vaccine and an AE; vaccine-event combinations identified as potential signals by data mining methods may be useful to generate hypothesis that can be tested with controlled studies [32,33].

We clinically reviewed the DTaP vaccine reports with PTs that exceeded the data mining threshold. We excluded reports of AEs described in the vaccine package insert and those that, in the judgment of the clinicians (PM, MC), represented potential confounders or were non-informative or unspecific. Unspecific conditions are those referring to symptoms, signs or laboratory tests/results that may not be assignable to a particular cause, condition or category. Unspecific events may have myriad causes and are often non-informative on their own. For the remaining reports, we reviewed all reports for vaccine-events pairs with disproportionate reporting if the total number of reports was ≤50. For vaccine-event pairs containing >50 reports, we reviewed a simple random sample of 20% of the total.

Because VAERS is a routine surveillance program designed to improve an immunization program, it does not meet the definition of research; therefore, this work was not subject to Institutional Review Board evaluation and informed consent requirements.

Results

VAERS received 50,157 reports involving receipt of DTaP vaccines (Infanrix®, Daptacel®, Pediarix®, Kinrix®, Pentacel®) in the US from January 1, 1991 through December 31, 2016 (Table 1). DTaP vaccines were reported as administered concurrently with one or more other vaccines in 43,984 (87.7%) reports. Among all DTaP vaccine reports, 5,627 (11.2%) were coded as serious, including 844 (1.7%) death reports. The most frequently reported PTs for all reports were injection site erythema (12,695; 25.3%), pyrexia (9,913;19.8%), injection site swelling (7,542; 15.0%), erythema (5,599; 11.2%), and injection site warmth (4,793; 9.6%) (not shown in tables). Table 2 shows the 10 most common PTs reported for serious and non-serious reports.

Clinical review of serious reports

Death reports—Eight hundred forty-four deaths were reported to VAERS after receipt of DTaP vaccines. Death certificates, autopsy reports or medical records were obtained for 725 (85.9%) reports (Table 3). Among these 725 reports, the most frequent cause of death (350 of 725; 48.3%) was sudden infant death syndrome (SIDS). Most SIDS cases (217 of 350; 62.0%) occurred among males; the predominant age group was infants <6 months of age (318 of 350; 90.9%).

Non-death reports—Characteristics of a random sample of 240 non-death serious reports (5% of the total 4,783 non-death serious reports) occurring after the five currently licensed DTaP vaccines included in our analyses are shown in Table 4. They were similar when single DTaP and combination DTaP-containing vaccines were assessed separately (data not shown). The most common diagnostic categories among non-death serious reports were neurological conditions (60; 25.0%), followed by gastrointestinal (56; 23.3%), and general disorders and vaccine administration site conditions (47; 19.6%). Seizure was the most common diagnosis among neurological conditions (48 of 60; 80%); 13 were reported as febrile seizures. The most common gastrointestinal diagnosis was intussusception (44 of 56; 78.6%); rotavirus vaccine was reported as co-administered with DTaP vaccine in all except two reports of intussusception.

Anaphylaxis reports—The automated search of anaphylaxis reports after DTaP vaccines resulted in 182 reports with one or more of the specific MedDRA PTs. Clinical review revealed 12 reports of allergic non-anaphylactic reactions, 7 with other non-hypersensitivity conditions, and 163 reports of anaphylaxis or possible anaphylaxis. Among the 163 reports of anaphylaxis, the median age was 4 years (range 0–14 years). Among 103 reports for which the symptom onset time could be determined, 75 (73%) occurred within 30 minutes post vaccination. Most of the DTaP vaccines administered (94.4%) were given concomitantly with other routinely recommended vaccines [35]. Among the 163 reports of anaphylaxis or possible anaphylaxis, 62 reports met Brighton Level (BL) category 1, 33 BL 2, and one BL 3. Thirty-seven did not meet BL criteria, but were considered as anaphylaxis by the attending physician. Thirty reports did not contain sufficient information for evaluation of BL.

Data mining—The first disproportionality analysis included a total of 18,240 serious US reports. Of them, 5,467 included any DTaP vaccine temporarily associated with the reported events. The analysis revealed an elevated EB05 (≥2.0) for nine vaccine-event pairs, all of them related to injection site reactions, urticaria, and anaphylaxis.

The second analysis included a total of 159,818 serious and non-serious US reports; 46,798 corresponded to DTaP vaccines.. The data mining analyses revealed an elevated EB05 for 55 vaccine-event pairs for DTaP vaccines that fulfilled criteria to be reviewed. . No new or unexpected AEs were detected but we identified three types of vaccination errors disproportionally reported: incorrect product formulation (n=26; no adverse events reported), product quality issue (n=23), and drug administered at inappropriate site (n=19). Most AEs reported (53%; 36/68) after these vaccination errors included mild injection site reactions. Most (74%; 17/23) reports of incorrect product formulation administered involved inadvertent administration of only one of the components of the vaccine (i.e., vaccine administrator neglected to combine all the components per the manufacturer's package insert).

Discussion

We performed a review of AE reports received over the course of 19 years after administration of currently licensed DTaP vaccines in VAERS. This included automated

analysis of all reports, clinical review of death reports and a sample of serious reports, and data mining analyses to assess disproportionate reporting. Our findings were consistent with those from pre-licensure trials and post-licensure studies for these vaccines [5–10].

The most common PTs observed among non-serious and serious reports were injection site reactions (e.g., injection site erythema) and certain systemic reactions (e.g., fever, vomiting), findings consistent with those from pre-licensure clinical trials [5–10]. Several post-marketing studies also noted the occurrence of these AEs [11–22]. A retrospective cohort study in the Vaccine Safety Datalink (VSD) found that the rate of local reactions after DTaP vaccines was higher than for inactivated influenza or hepatitis A vaccines. The study also found that for children aged 12–35 months, vaccination in the arm was associated with a significantly greater risk of local reactions compared with vaccination in the thigh [14].

Seizures or convulsions ranked as the fourth most common PT among serious reports. Febrile convulsions are a type of seizures relatively common in childhood, occurring in 2–4% of individuals [33]. Febrile seizures may be related to febrile infections and have also been associated with DTwP, 13-valent pneumococcal conjugate, and trivalent inactivated influenza (TIV) vaccines [34]. Seizures had been observed sporadically during pre-licensure clinical trials for Pentacel®, Daptacel®, Pediarix®, and Infanrix® [5–8]. A retrospective observational study in the VSD did not find an increased risk of seizures among children aged 6 weeks to 23 months who received DTaP [12]. A recent safety study on simultaneous administration of DTaP with other vaccines showed a small increased risk for febrile seizures during the 24 hours after a child receives the inactivated influenza vaccine (IIV) at the same time as the pneumococcal 13-valent conjugate (PCV13) vaccine or DTaP [20].

Among death reports for which sufficient records were available for review, SIDS was the leading cause of death (48%), which is consistent with infant mortality data that places SIDS as the fourth leading cause of death in the US among infants [36]. Similarly, SIDS was the second leading cause of death among children aged 0–18 months in the VSD [37]. A recent study in Taiwan assessed the risk of sudden unexplained infant death (SUID) following DTaP which was introduced in that country in 2010 [38] and found DTaP did not increase the risk of SUID. SIDS deaths in the US have been declining since the early 1990s for a variety of factors that include recommended changes in sleeping position and environment, clarification of the case definition, and diagnostic coding shifts [39–41]. There is a large body of evidence showing that vaccination is not causally associated with SIDS [42–44], including an Institute of Medicine (IOM) review in 2003 that rejected a causal association between the whole cell pertussis–containing vaccine (which is no longer in use in the United States) and SIDS, and between exposure to multiple simultaneous vaccines and SIDS [41]. It would not be uncommon to observe a coincidental close temporal relationship between vaccination and SIDS as this condition peaks at a time when children receive a relatively large number of recommended vaccinations [44]. Other common causes of death observed (e.g. asphyxia or suffocation, pneumonia, sepsis or septicemia) are consistent with the top ten leading causes of death in the vaccinated age groups [36].

Through data mining, we found disproportional reporting for injection site reactions. Increased local reactogenicity after a booster of DTaP-containing vaccines has been well

documented, and it has been potentially attributed to cellular and humoral immune responses to the vaccine [46,47]. We also found higher disproportional reporting mainly for other labeled events, ‘intussusception,’ ‘haematochezia’ and other related gastrointestinal conditions that may have been related to the concomitant administration of rotavirus vaccines, for which the associations with intussusception and/or hematochezia have been well documented [47–50]. Through our clinical review of a sample of serious DTaP reports, we also noted that intussusception was the most common diagnosis among gastrointestinal events, and in all these selected reports, rotavirus vaccines were co-administered with a DTaP vaccine. Data mining findings involving the PT ‘apparent life threatening event (ALTE)’ did not report a specific condition, but rather a variety of serious conditions (e.g., seizures, high fever, apneic events) reported as ALTE by the attending physician. ALTE has been replaced by the term BRUE which stands for “brief resolved unexplained event” [51].

A number of vaccination errors were disproportionally reported for DTaP vaccines. Some of these errors involved the administration of the incorrect vaccine or vaccine formulation or administration of vaccine at the wrong site. Education and training of providers on ACIP recommendations and package insert indications may help alleviate and prevent these errors.

Although our study cannot be compared with controlled, denominator-based studies, two observational studies in the VSD assessed the safety of DTaP-IPV-Hib (Pentacel®) and DTaP-IPV (Kinrix®) [17,18]. The first study compared children aged six weeks to two years who received DTaP-IPV-Hib (Pentacel®) with children who received other DTaP-containing vaccines. Children who received DTaP-IPV-Hib vaccine had a statistically significant higher risk of fever, but no increased risk was observed for seizure, meningitis/encephalitis/myelitis, or non-anaphylactic allergic reaction. The second study of Kinrix® in children aged 4 to 6 years did not find a statistically significant increased risk of meningitis/encephalitis, seizures, stroke, Guillain-Barré Syndrome, Steven-Johnson syndrome, anaphylaxis, serious allergic reactions other than anaphylaxis, and serious local reactions.

Strengths of VAERS include its broad national scope and timeliness [25]. VAERS may be particularly useful for detecting potential safety signals which can be further evaluated in larger datasets using controlled epidemiological methodologies. As a passive surveillance system, VAERS has several inherent limitations which call for careful interpretation of its findings. Some of these limitations include over- or under-reporting, biased reporting, and inconsistency in quality and completeness of reports [25]. VAERS generally cannot assess if a vaccine caused an AE. VAERS does not collect data on number of vaccinees, therefore, it does not provide denominator data to calculate incidence rates of AEs.

Our review did not include the recently licensed Quadracel® vaccine since few reports for this vaccine has been received in VAERS at the time of data extraction [52]. The safety of this vaccine will be assessed once a larger number of reports is received.

Conclusion

This assessment of the safety of DTaP vaccines (Infanrix®, Daptacel®, Kinrix®, Pediarix®, and Pentacel®) did not identify any new or unexpected safety issue. However, the presence

of vaccination errors calls for measures to prevent their occurrence. CDC and FDA will continue to monitor AEs following DTaP vaccination in VAERS.

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What's known on this subject:

Pre-licensure studies showed that the most common adverse reactions to five US licensed DTaP vaccines (Infanrix, Daptacel, Pediarix, Pentacel, Kinrix, and Quadracel) were injection site and systemic reactions.

What this study adds:

Post-licensure surveillance of adverse events after the five licensed DTaP vaccines over a 19 year-period did not find any new or unexpected safety concerns in the Vaccine Adverse Event Reporting System.

Table 1.

Characteristics of all reports after currently licensed Diphtheria and tetanus toxoids and acellular pertussis vaccine adsorbed (DTaP) Vaccines in VAERS vaccinated from January 1, 1991 through December 31, 2016 (receipt March 17, 2017)

Characteristics	No. (%)
Total reports	50,157[a]
Serious	5,627 (11.2)
Median age (interquartile range) months	19 (35)
Age less than 6 years	46,836 (93.4)
Male	25,781 (51.4)
Median onset interval (range) days	1 (0 – 5,115)
DTaP vaccines (n=50,282)[a]	
DTaP (Infanrix®)	17,484 (34.8)
DTaP (Daptacel®)	13,153 (26.2)
DTaP-HepB-IPV (Pediarix®)	8,906 (17.7)
DTaP-IPV-Hib (Pentacel®)	5,464 (10.9)
DTaP-IPV (Kinrix®)	5,275 (10.4)
DTaP vaccines given in combination with other vaccines	43,984 (87.7)
Most common vaccine combinations given concomitantly *	
MMRII	15,021 (34.6)
Polio	14,229 (32.4)
Pneumococcal vaccine (Prevnar7®)[b]	11,794 (26.8)
Varicella (Varivax®)	8,772 (19.9)
Rotavirus vaccine	8,266 (16.4)
Haemophilus influenza Type B (ActHib®)	7,530 (17.1)
Type of reporter (n= 47,968)[c]	
Vaccine provider	31,478 (62.8)
Other[d]	11,842 (23.6)
Manufacturer	3,359 (6.7)
Parent	2,594 (5.2)
Subject recovered by the time the VAERS form was submitted	31,677 (63.2)

[a]Some individuals received more than one DTaP vaccine

[b]Prevnar 13 given with DTaP in 6,427 (14.6%) reports not shown

[c]885 reports with missing reporter information

[d]Secretary, office assistant

*Concomitant vaccines are not mutually exclusive

Abbreviations: DTaP (Diphtheria Toxoid-Tetanus Toxoid-Acellular Pertussis Vaccine)

Table 2.

Serious and Non-serious Adverse Events (N=50,157) in DTaP recipients Reported to the Vaccine Adverse Event Reporting System, 1991–2016

MedDRA Code, Severity[a]	N (%)
Serious	5,476 (100)
Pyrexia	1,959 (34.8)
Vomiting	1,565 (27.8)
Irritability	1,238 (22.0)
Convulsion	939 (16.7)
Intussusception	817 (14.5)
Crying	761 (13.5)
Diarrhea	747 (13.3)
Lethargy	648 (11.5)
Hypotonia	567 (10.1)
Cough	560 (110.0)
Non-serious	44,530 (100)
Injection site erythema	12,444 (27.9)
Pyrexia	7,954 (17.9)
Injection site swelling	7,349 (16.5)
Erythema	5,345 (12.0)
Injection site warmth	4,670 (10.5)
Injection site edema	3,186 (7.2)
Injection site pain	3,124 (7.0)
Injection site induration	3,084 (6.9)
Rash	2,932 (6.6)
Urticaria	2800 (6.3)

[a]The MedDRA codes reflect the 10 most frequent codes appearing in serious and non-serious reports made after receipt of DTaP vaccines. Reports for all licensed DTaP products included in this study have been combined and other vaccines may have been administered concomitantly with the DTaP vaccine. A report may contain ≥1 Preferred Term.

Table 3.

Confirmed cause of death among death reports after the administration of DTaP vaccines in VAERS

Cause of death*		No. (%)
Total		725
Sudden Infant Death Syndrome		350 (48.3)
Undetermined		98 (13.5)
Injury, poisoning and certain other consequences of external causes **Asphyxia or suffocation**	**49 (6.8)**	70 (9.7)
Diseases of the respiratory system **Pneumonia**	**24 (3.3)**	49 (6.8)
Diseases of the circulatory system		28 (3.9)
Certain infections and parasitic diseases **Sepsis or septicemia**	**20 (2.8)**	29 (4.0)
Congenital malformations, deformations and chromosomal abnormalities		26 (3.6)
Diseases of the Nervous system		26 (3.6)
Diseases of the digestive system **Intussusception**	**6 (0.8)**	18 (2.5)
External causes of morbidity		10 (1.4)
Other†		21 (2.9)

*Confirmed by review of death certificate, autopsy report, or medical record.

†Other causes include: Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified (8), complications of prematurity (5), certain conditions originating in the perinatal period (3), Endocrine, nutritional and metabolic diseases (3), neoplasms (2)

Table 4.

Diagnostic categories for the random sample of 240 reports of adverse events after Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine (DTaP) Vaccines in VAERS among persons vaccinated January 1, 1991 through December 31, 2016 (receipt 03/17/2017)

Diagnostic category	N (%)
Nervous system disorders	60 (25.0)
Seizures[a]	48
Gastrointestinal disorders	56 (23.3)
Intussusception[b]	44
General disorders and administration site conditions	47 (19.6)
Local reactions[c]	20
Immune system disorders	23 (9.6)
Anaphylaxis[d]	11
Infections and Infestations	19 (7.9)
Respiratory, thoracic and mediastinal disorders	16 (6.7)
Blood and lymphatic system disorders	6 (2.5)
Psychiatric disorders	5 (2.1)
Musculoskeletal and connective tissue disorders	3 (1.3)
Other[e]	4 (1.7)

[a] Febrile seizures comprised 13 reports

[b] Rotavirus vaccine given concurrently in 42 reports

[c] Local reactions comprised 45.2% of adverse events in this group

[d] One report met Brighton criteria level (BL) 1, one BL 2, one BL 3, and one was not verified as a GBS case

[e] Other includes one report each of cardiac disorder, endocrine disorder, eye disorder, and metabolism and nutrition disorder