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-tetanus-acellular pertussis (DTaP) vaccines in the United States by using data from the Vaccine Adverse Event Reporting System (VAERS), a spontaneous reporting surveillance system.

METHODS: We searched VAERS for US reports of DTaP vaccinations occurring from 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 nondeath 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 5627 (11.2%) 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 (9913; 19.8%), injection site swelling (7542; 15.0%), erythema (5599; 11.2%), and injection site warmth (4793; 9.6%). For 3 of the DTaP vaccines, we identified elevated values for vaccination errors using Empirical Bayesian data mining.

CONCLUSIONS: No new or unexpected adverse events were detected. The observed disproportionate reporting for some nonserious vaccination errors calls for better education of vaccine providers on the specific indications for each of the DTaP vaccines.

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WHAT'S KNOWN ON THIS SUBJECT: Prelicensure studies revealed that the most common adverse reactions to 6 US licensed diphtheria-tetanus-acellular pertussis vaccines (Infanrix, Daptacel, Pediarix, Pentacel, Kinrix, and Quadracel) were injection site and systemic reactions.

WHAT THIS STUDY ADDS: Postlicensure surveillance of adverse events after the 5 licensed diphtheria-tetanus-acellular pertussis vaccines over a 19-year-period did not find any new or unexpected safety concerns in the Vaccine Adverse Event Reporting System.

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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% to 90% effective in preventing serious pertussis disease.[1] Concerns about safety (particularly severe local reactions, febrile seizures, and reports of acute encephalopathy after vaccination) led to the development and licensure of diphtheria-tetanus-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 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 recommended DTaP for all 5 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 with DTwP.[4] DTwP is no longer licensed nor is it available for use in the United States.[4]

Currently, there are 2 DTaP vaccines licensed in the United States for the entire 5-dose series: Infanrix (GlaxoSmithKline Biologicals, Rixensart, Belgium) and Daptacel (Sanofi Pasteur, Ltd, Swiftwater, PA), which were approved in 1997 and 2002, respectively.[5,6] In addition, the following 4 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 influenzae* type b (Hib) 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 fifth dose in the 5-dose series. Prelicensure studies of these vaccines revealed that the most common AEs after vaccination were injection site and systemic reactions.[5–10]

Postmarketing observational studies have shown that the DTaP-containing vaccines have a good safety record.[11–22] In 2 studies of DTwP and DTaP vaccines conducted in the Vaccine Adverse Event Reporting System (VAERS) in the early 1990s, 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 United States; 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 United States.

METHODS

VAERS

VAERS is a US national vaccine safety surveillance system created in 1990 and coadministered by the Centers for Disease Control and Prevention (CDC) and the FDA. It receives spontaneous reports of AEs after vaccination. Vaccination errors not describing an AE may also be reported.[25] With VAERS, whether an AE is causally associated with vaccination generally cannot be assessed, but it may be useful for detecting potential vaccine safety signals.[25] VAERS accepts reports from vaccine manufacturers, health care 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 by using the Medical Dictionary for Regulatory Activities (MedDRA), a clinically validated, internationally standardized terminology.[26] A VAERS report may be assigned 1 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 is the highest level of the MedDRA hierarchy that provides the broadest classification for AEs (eg, nervous system disorders).[27] Reports are classified as serious or nonserious. A report is considered serious on the basis of the Code of Federal Regulations (21) definition if 1 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 nonserious DTaP vaccine reports. Quadracel was not included

in our search because 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 nondeath serious reports after DTaP vaccines. The primary diagnostic category was assigned into a System Organ Class.[27] We also searched for all reports of anaphylaxis after DTaP vaccines by using the following specific MedDRA PTs: anaphylactic reaction, anaphylactic shock, anaphylactoid reaction, and anaphylactoid shock. Reports of anaphylaxis were classified by using the Brighton Collaboration case definition or physician's diagnosis.[29]

Data Mining

We used Empirical Bayesian 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 7 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 nonserious US reports as of December 31, 2016. We conducted the analyses using the Multi-Item γ Poisson Shrinker algorithm[30,31] in Oracle's Empirica Signal System. The main statistical scores computed are the Empirical Bayes Geometric Mean, EB05, and EB95, the latter of which represent the 90% confidence interval. We used EB05 ≥2.0 as a cutoff (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 a causal relationship between a vaccine and an AE; vaccine-event combinations identified as potential signals by data mining methods may be useful to generate a hypothesis that can be tested with controlled studies.[31,32]

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 (P.L.M. and M.C.), represented potential confounders or were noninformative or unspecific. Unspecific conditions are those referring to symptoms, signs, or laboratory tests and/or results that may not be assignable to a particular cause, condition, or category. Unspecific events may have myriad causes and are often noninformative 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 United States from January 1, 1991, through December 31, 2016 (Table 1). DTaP vaccines were reported as administered concurrently with 1 or more other vaccines in 43 984 (87.7%) reports. Among all DTaP vaccine reports, 5627 (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 (9913; 19.8%), injection site swelling (7542; 15.0%), erythema (5599; 11.2%), and injection site warmth (4793; 9.6%) (not shown in tables). Table 2 shows the 10 most common PTs reported for serious and nonserious reports.

Death Reports

In total, 844 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 male infants; the predominant age group was infants <6 months of age (318 of 350; 90.9%).

Nondeath Reports

Characteristics of a random sample of 240 nondeath serious reports (5% of the total 4783 nondeath serious reports) occurring after the 5 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 nondeath serious reports were

TABLE 1 Characteristics of All Reports After Currently Licensed DTaP Vaccines in VAERS Among Persons Vaccinated From January 1, 1991, Through December 31, 2016 (Receipt March 17, 2017)

Characteristics	No. (%)
Total reports	50 157[a]
Serious	5627 (11.2)
Median age (interquartile range), mo	19 (35)
Age <6 y	46 836 (93.4)
Male sex	25 781 (51.4)
Median onset interval (range), d	1 (0–5115)
DTaP vaccines (n = 50 282)[a]	
DTaP (Infanrix)	17 484 (34.8)
DTaP (Daptacel)	13 153 (26.2)
DTaP-HepB-IPV (Pediarix)	8906 (17.7)
DTaP-IPV-Hib (Pentacel)	5464 (10.9)
DTaP-IPV (Kinrix)	5275 (10.4)
DTaP vaccines given in combination with other vaccines	43 984 (87.7)
Most common vaccine combinations given concomitantly[b]	
MMR II	15 021 (34.6)
Polio	14 229 (32.4)
Pneumococcal vaccine (Prevnar7)[c]	11 794 (26.8)
Varicella (Varivax)	8772 (19.9)
Rotavirus vaccine	8266 (16.4)
Hib (ActHib)	7530 (17.1)
Type of reporter (n = 49 272)[d]	
Vaccine provider	31 478 (62.8)
Other[e]	11 842 (23.6)
Manufacturer	3359 (6.7)
Parent	2593 (5.2)
Subject recovered by the time VAERS form was submitted	31 677 (63.2)

HepB, hepatitis B; MMR II, measles, mumps, and rubella II.
[a] Some individuals received >1 DTaP vaccine.
[b] Concomitant vaccines are not mutually exclusive.
[c] Prevnar 13 given with DTaP in 6427 (14.6%) reports not shown.
[d] Eight hundred and eighty-five reports with missing reporter information.
[e] Secretary or office assistant.

neurologic conditions (60; 25.0%), followed by gastrointestinal conditions (56; 23.3%), and general disorders and vaccine administration site conditions (47; 19.6%). Seizure was the most common diagnosis among neurologic 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 coadministered with DTaP vaccine in all except 2 reports of intussusception.

Anaphylaxis Reports

The automated search of anaphylaxis reports after DTaP vaccines resulted in 182 reports with 1 or more of the specific MedDRA PTs. Clinical review revealed 12 reports of allergic nonanaphylactic reactions, 7 with other nonhypersensitivity 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 postvaccination. Most of the DTaP vaccines administered (94.4%) were given concomitantly with other routinely recommended vaccines.[33] Among the 163 reports of anaphylaxis or possible anaphylaxis, 62 reports met Brighton Level (BL) category 1, 33 met BL category 2, and 1 met BL category 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, 5467 included any DTaP vaccine temporarily associated with the reported events. The analysis revealed an elevated EB05 (≥2.0) for 9 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 nonserious 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 3 types of vaccination errors disproportionally reported: incorrect product formulation (n = 26; no AEs reported), product quality issue (n = 23), and drug administered at inappropriate site (n = 19). Most AEs reported (53%; 36 of 68) after these vaccination errors included mild injection site reactions. Most (74%; 17 of 23) reports of incorrect product formulation administered involved inadvertent administration of only 1 of the components of the vaccine (ie, 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.

TABLE 2 Serious and Nonserious AEs ($N = 50\,157$) in DTaP Recipients Reported to VAERS, 1991–2016

MedDRA Code, Severity[a]	*N* (%)
Serious	5476 (100)
Pyrexia	1959 (34.8)
Vomiting	1565 (27.8)
Irritability	1238 (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 (10.0)
Nonserious	44 530 (100)
Injection site erythema	12 444 (27.9)
Pyrexia	7954 (17.9)
Injection site swelling	7349 (16.5)
Erythema	5345 (12.0)
Injection site warmth	4670 (10.5)
Injection site edema	3186 (7.2)
Injection site pain	3124 (7.0)
Injection site induration	3084 (6.9)
Rash	2932 (6.6)
Urticaria	2800 (6.3)

[a] The MedDRA codes reflect the 10 most frequent codes appearing in serious and nonserious 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 PT.

TABLE 3 Confirmed Cause of Death Among Death Reports After the Administration of DTaP Vaccines in VAERS

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

[a] Confirmed by review of death certificate, autopsy report, or medical record.

[b] Other causes include the following: 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); and neoplasms (2).

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 prelicensure trials and postlicensure studies for these vaccines.[5–10]

The most common PTs observed among nonserious and serious reports were injection site reactions (eg, injection site erythema) and certain systemic reactions (eg, fever, vomiting), findings consistent with those from prelicensure clinical trials.[5–10] Several postmarketing 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 revealed that for children aged 12 to 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% to 4% of individuals.[34] Febrile seizures may be related to febrile infections and have also been associated with DTwP, pneumococcal 13-valent conjugate, and trivalent inactivated influenza vaccines.[34] Seizures had been observed sporadically during prelicensure clinical trials for Pentacel, Daptacel, Pediarix, and Infanrix.[5–8] The authors of 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 revealed a small increased risk for febrile seizures during the 24 hours after a child receives the inactivated influenza vaccine at the same time as the pneumococcal 13-valent conjugate 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 United States among infants.[35] Similarly, SIDS was the second leading cause of death

TABLE 4 Diagnostic Categories for the Random Sample of 240 Reports of AEs After DTaP Vaccines in VAERS Among Persons Vaccinated January 1, 1991, Through December 31, 2016 (Receipt March 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 AEs in this group.
[d] One report met BL criteria 1, 1 met BL 2, 1 met BL 3, and 1 was not verified as a Guillain-Barré syndrome case.
[e] Other includes 1 report each of cardiac disorder, endocrine disorder, eye disorder, and metabolism and nutrition disorder.

among children aged 0 to 18 months in the VSD.[36] The authors of a recent study in Taiwan assessed the risk of sudden unexplained infant death after DTaP vaccine administration, which was introduced in that country in 2010,[37] and found DTaP vaccine administration did not increase the risk of sudden unexplained infant death. SIDS in the United States 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.[38–40] There is a large body of evidence in which it is shown that vaccination is not causally associated with SIDS,[41–44] including an Institute of Medicine review in 2003 that rejected a causal association between the DTwP vaccine (which is no longer in use in the United States) and SIDS, as well as between exposure to multiple simultaneous vaccines and SIDS.[40] It would not be uncommon to observe a coincidental close temporal relationship between vaccination and SIDS because this condition peaks at a time when children receive a relatively large number of recommended vaccinations.[43] Other common causes of death observed (eg, asphyxia or suffocation, pneumonia, or sepsis or septicemia) are consistent with the top 10 leading causes of death in the vaccinated age groups.[35]

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.[45,46] We also found higher disproportional reporting mainly for other labeled events, "intussusception," "hematochezia," 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.[46–49] 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 coadministered 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 (eg, seizures, high fever, or apneic events) reported as ALTE by the attending physician. ALTE has been replaced by the term "brief resolved unexplained event."[50]

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 Advisory Committee on Immunization Practices recommendations and package insert indications may help alleviate and prevent these errors.

Although our study cannot be compared with controlled, denominator-based studies, the authors of 2 observational studies in the VSD assessed the safety of DTaP-IPV-Hib (Pentacel) and DTaP-IPV (Kinrix).[17,18] The authors of the first study compared children aged 6 weeks to 2 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, and myelitis; or nonanaphylactic allergic reaction. The second study of Kinrix in children aged 4 to 6 years did not find a statistically significant increased risk of meningitis and/or 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 data sets by using controlled epidemiologic methodologies. As a passive surveillance system, VAERS has several inherent limitations that call for careful interpretation of its findings. Some of these limitations include over- or underreporting, 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 vaccines; therefore, it does not provide denominator data to calculate incidence rates of AEs.

Our review did not include the recently licensed Quadracel vaccine because few reports for this vaccine had been received in VAERS at the time of data extraction.[10] The safety of this vaccine will be assessed once a larger number of reports has been received.

CONCLUSIONS

In this assessment of the safety of DTaP vaccines (Infanrix, Daptacel, Kinrix, Pediarix, and Pentacel), we did not identify any new or unexpected safety issues. However, the presence of vaccination errors calls for measures to prevent their occurrence. CDC and FDA will continue to monitor AEs after DTaP vaccination in VAERS.

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ABBREVIATIONS

AE: adverse event
ALTE: apparent life-threatening event
BL: Brighton Level
CDC: Centers for Disease Control and Prevention
DTaP: diphtheria-tetanus-acellular pertussis
DTwP: whole cell pertussis–containing
EB05: fifth percentile of the confidence interval for the Empirical Bayes geometric mean
FDA: Food and Drug Administration
Hib: *Haemophilus influenzae* type b
IPV: inactivated polio vaccine
MedDRA: Medical Dictionary for Regulatory Activities
PT: preferred term
SIDS: sudden infant death syndrome
VAERS: Vaccine Adverse Event Reporting System
VSD: Vaccine Safety Datalink

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