



## U.S. Postlicensure safety surveillance for adolescent and adult tetanus, diphtheria and acellular pertussis vaccines: 2005–2007<sup>☆</sup>

Soju Chang<sup>a,\*</sup>, Patrick M. O'Connor<sup>b</sup>, Barbara A. Slade<sup>c</sup>, Emily Jane Woo<sup>a</sup>

<sup>a</sup> Office of Biostatistics and Epidemiology, Center for Biologics Evaluation and Research, U.S. Food and Drug Administration (FDA), Rockville, MD, United States

<sup>b</sup> Johns Hopkins Bloomberg School of Public Health, General Preventive Medicine Residency Program, Baltimore, MD, United States

<sup>c</sup> Immunization Safety Office, Division of Healthcare Quality Promotion, U.S. Centers for Disease Control and Prevention (CDC), Atlanta, GA, United States

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### ABSTRACT

**Background:** Pre-licensure clinical trials for two U.S. licensed tetanus toxoid, reduced diphtheria toxoid and acellular pertussis (Tdap) vaccines did not reveal any major safety concerns. However, routine use in large adolescent and adult populations could reveal rare and potentially serious adverse events (AEs). **Methods:** To characterize reported AEs following Tdap vaccination and identify potential safety concerns warranting further evaluation, we analyzed data from the Vaccine Adverse Event Reporting System (VAERS) and assessed the frequency and proportions of AEs and reporting rates (reports per 100,000 vaccine doses distributed).

**Results:** A total of 2090 reports (7% were serious; 55% listed Tdap alone) involving Tdap vaccines were submitted to VAERS May 2005–June 2007. The crude reporting rate was 10.2 per 100,000 vaccine doses distributed. The median age of vaccinees was 22 years, and the female to male ratio was about 2 to 1. The majority of reports described common local and systemic signs and symptoms, such as injection site reactions, fever, and headache. Rarely reported AEs included myopericarditis, demyelinating diseases of the central nervous system, Guillain–Barré Syndrome, syncope, encephalopathy/encephalitis, seizure, Bell's palsy, anaphylaxis, and thrombocytopenia.

**Conclusions:** Because adolescents and adults were not routinely vaccinated against pertussis in the past, this surveillance summary provides important – and reassuring – information about the use of Tdap in these age groups. Although subject to the limitations of passive surveillance, the findings of this VAERS review support the pre-licensure clinical trial data with regard to the safety of the U.S. licensed Tdap vaccines. Continued monitoring of clinically significant AEs that are temporally associated with Tdap vaccination and further assessment of such events using controlled observational studies may provide additional information about the safety of these vaccines.

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### 1. Introduction

Although the childhood diphtheria and tetanus toxoids and pertussis [whole cell/acellular pertussis] (DTwP/DTaP) vaccination series have been recommended to prevent tetanus, diphtheria, and pertussis cases and deaths, the number of reported pertussis cases has steadily increased since the 1980s, especially among adolescents and adults [1]. A total of 16,858 pertussis cases and 12 infant deaths were reported in 2009 [2]. Possible explanations

include a true increase in the burden of disease and an increase in the detection and reporting of pertussis cases. Immunity to pertussis wanes approximately 5–10 years after completion of childhood pertussis vaccination, leaving adolescents and adults susceptible to pertussis [1].

The United States Food and Drug Administration (FDA) licensed the first tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine (Tdap) [BOOSTRIX<sup>®</sup>, GlaxoSmithKline Biologicals, Rixensart, Belgium] for use in adolescents aged 10–18 years on May 3, 2005, and a second Tdap [ADACEL<sup>®</sup>, Sanofi Pasteur Limited, Toronto, Ontario, Canada] for use in adolescents and adults aged 11–64 years on June 10, 2005. Both Tdap vaccines are indicated for use as a single booster dose to prevent tetanus, diphtheria, and pertussis [3]. With limited sample sizes of pre-licensure clinical trials, rare adverse events (AEs) following immunization might not be detected until vaccines are introduced to the market for widespread use. Over 20 million doses of Tdap were distributed in the U.S. from May 2005 through June 2007 [Centers for Disease Control and

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\* Corresponding author at: Division of Epidemiology, Office of Biostatistics and Epidemiology, Center for Biologics Research and Evaluation, Food and Drug Administration, 1401 Rockville Pike, HFM-222, Rockville, MD 20852, United States. Tel.: +1 301 827 6088.

E-mail address: [soju.chang@nih.hhs.gov](mailto:soju.chang@nih.hhs.gov) (S. Chang).

Prevention (CDC)'s Biologics Surveillance System (BSS), 2008]. The objectives of this review were to describe the post-marketing safety profile of Tdap as reflected in reports to the Vaccine Adverse Event Reporting System (VAERS) and to identify potential safety concerns warranting further evaluation.

## 2. Materials and methods

VAERS, the U.S. national, passive surveillance system for vaccine AEs, was established in 1990 and is jointly managed by FDA and CDC [4]. Passive surveillance systems such as VAERS are subject to many limitations, including underreporting, incomplete information in many reports, inadequate data regarding the number of doses administered, and lack of unbiased comparison groups [4]. Causality between reported AEs and vaccines cannot usually be assessed from individual reports to VAERS.

We searched VAERS for AEs following Tdap, from May 3, 2005 through June 10, 2007. We focused on the first two years of licensure because we believe that clinically significant AEs – if any – are likely to be reported during the immediate period following vaccine licensure. We characterized demographics, such as age, gender, seriousness [5], onset interval (from vaccination date to onset of first sign/symptom after vaccination), vaccine product, and concomitant vaccination. We categorized serious events according to the principal clinical manifestations and also performed a stratified analysis by age group (adolescent: ages 10–18 years and adult: ages 19–64 years). Unless otherwise specified, we excluded missing data when calculating proportions. Analyses were performed using STATA 10.0 (Stata Corporation, College Station, TX, USA).

Although national vaccine distribution data are available, the numbers of doses administered by age and gender are not known. We calculated crude reporting rate (CRR) by dividing the number of Tdap VAERS reports by net Tdap doses distributed (CDC's BSS) for years 2005–2007 (annual doses distributed for 2005 and 2006 plus half of the annual doses distributed for 2007). The VAERS-based numerators may be affected by biases and underreporting.

Individual VAERS reports and medical records were reviewed (by the authors S.C. and P.M.O. and E.J.W.) for specific AEs of interest based on clinical severity, safety data from clinical trials, and potential association with the Tdap components. The case definitions of these AEs were adapted from The Brighton Collaboration [anaphylaxis, cellulitis at injection site, Guillain-Barré syndrome (GBS), seizure and thrombocytopenia] [6], medical literature [myopericarditis, syncope, Bell's palsy and encephalopathy/encephalitis] [7–10], and 1994 Institute of Medicine (IOM) report [diseases of the central nervous system (CNS)] [11].

## 3. Results

During the first two years after licensure, VAERS received 2090 reports following Tdap [ADACEL 80%, BOOSTRIX 19% and unknown 1%], out of a total of 43,977 VAERS reports in that time period.

**Table 1**  
Demographic and clinical characteristics of adverse events following Tdap immunization by age groups, VAERS, 2005–2007.

	Adolescents N = 915	Adults N = 1,029	All <sup>a</sup> N = 2090
<b>Demographic:</b>			
Age, median (range)	13y (10–18 y)	42y (19–64 y)	22y (2 m–87 y)
Gender, male (%)	440 (48)	180 (18)	666 (32)
<b>Clinical:</b>			
Serious (%)	66 (7)	63 (6)	138 (7)
Onset Interval, median (range)	1d (<24 h, 97 d)	1d (<24 h, 158 d)	1d (<24 h, 158 d)
Tdap vaccination alone (%)	357 (39)	734 (71)	1155 (55)

Note: y: year; m: month; d: day; h: hour.

<sup>a</sup> Including reports with missing age and age outside of Tdap vaccine indication.

**Table 2**  
Serious adverse events following Tdap immunization, VAERS, 2005–2007.

Serious adverse events <sup>a</sup>	138 (100%)
<b>Neurologic conditions</b>	
Guillain-Barré syndrome	41 (30%)
Bell's palsy	10
Seizure	7
Demyelinating diseases of CNS	4
Encephalopathy/Encephalitis	3
Other neurologic conditions	10
<b>General systemic symptoms</b>	
26 (19%)	
<b>Allergic reactions</b>	
12 (9%)	
Anaphylaxis	5
Other allergic reactions	7
<b>Infections</b>	
9 (6%)	
Viral meningitis	3
Pertussis	2
Influenza B <sup>b</sup>	1
Other infections <sup>c</sup>	3
<b>Injection site reactions/cellulitis</b>	
7 (5%)	
<b>Symptoms related to concomitant vaccines/drugs/food</b>	
7 (5%)	
<b>Cardiac conditions</b>	
6 (4%)	
Myopericarditis	3
Arrhythmia <sup>b</sup>	1
Myocardial infarction <sup>b</sup>	2
<b>Syncope</b>	
5 (4%)	
<b>Thrombocytopenia</b>	
4 (3%)	
<b>Exacerbation of pre-existing illnesses</b>	
4 (3%)	
<b>Other<sup>d</sup></b>	
17 (12%)	

<sup>a</sup> Serious reports are defined by the 21 Code of Federal regulations § 600.80 as any of the following outcomes: death, a life-threatening condition, hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Other medical important conditions (OMIC) may be considered serious adverse experiences when, based upon appropriate medical judgment, they may place the subject at risk for medical or surgical intervention to prevent one of the outcomes listed in this definition.

<sup>b</sup> Fatal.

<sup>c</sup> Bronchitis, Staphylococcal sepsis, and varicella zoster virus like rash.

<sup>d</sup> Type I diabetes mellitus, appendicitis, myositis, stomatitis, brain metastases in an adult with pre-existing breast cancer, conversion disorder, 2 medication errors (an episode of tachycardia and decreased oxygen saturation in a neonate admitted at an intensive care unit and allergy to pertussis vaccine during childhood), 2 seizure like events and 7 pregnancy-related conditions (3 spontaneous abortions, 1 term birth, 1 preterm birth, 1 stillbirth and 1 unknown fetal outcome).

Table 1 describes the demographics and clinical characteristics of Tdap reports. One hundred thirty-eight events (7%) were reported as serious, including 4 deaths (Table 2). The proportions of serious reports were approximately the same for the two products (6% and 8%) and did not vary substantially by age group (adolescent 7% and adult 6%), gender (male 8% and female 6%), or Tdap vaccination (alone 6% and concomitant 7%). Concomitant vaccines were listed in 935 (45%) Tdap reports, and 1155 (55%) identified Tdap alone.

**Table 3**  
Crude reporting rates and demographic and clinical characteristics of specific adverse events of interest following Tdap vaccination, VAERS, 2005–2007.

Specific AEs of interest <sup>a</sup>	Case n	Serious n (%)	Age (year) range (median)	Gender (female) n (%)	Tdap alone n (%)	Onset interval range (median) <sup>a</sup>	Crude reporting rate <sup>b</sup>
Injection site reactions							
Local reaction	750	2 (0.3)	2–81 (31)	541 (72)	477 (64)	<24 h–32 d (1 d) <sup>c</sup>	3.67
Cellulitis	45	5 (11)	4–87 (39)	30 (67)	34 (76)	<24 h–8 d (1 d)	0.22
Neurologic conditions							
Seizure	28	7 (25)	9–38 (15)	17 (61)	9 (32)	1 m–11 d (1 d)	0.14
Bell's palsy	13	7 (54)	11–67 (16)	7 (54)	6 (46)	4 h–43 d (6 d)	0.06
Guillain–Barré syndrome	10	10 (100)	11–61 (30)	4 (40)	4 (40)	1 d–56 d (25 d)	0.05
Demyelinating diseases of CNS <sup>a</sup>	4	4 (100)	11–16 (16)	3 (75)	1 (25)	15 d–59 d (24 d)	0.02
Encephalopathy/encephalitis	3	3 (100)	11–28 (12)	2 (67)	0 (0)	1 d–16 d (5 d)	0.01
Cardiac							
Myopericarditis	3	3 (100)	17–21 (17)	0 (0)	2 (67)	1 h–3 d (2 d)	0.01
Other medical conditions							
Syncope	27	5 (19)	11–30 (14)	15 (56)	6 (22)	1 m–15 m (1 m) <sup>d</sup>	0.13
Anaphylaxis	12	5 (42)	5–43 (13)	7 (58)	5 (42)	3 m–16 h (15 m)	0.06
Thrombocytopenia	5	4 (80)	11–55 (13)	2 (40)	2 (40)	13 d–30 d (19 d)	0.02
Fatal conditions							
Death	4	4 (100)	13–62 (34)	1 (25)	2 (50)	10 d–68 d (36 d)	0.02

<sup>a</sup> AEs: adverse events following immunization; d: day, h: hour, m: minute, CNS: central nervous system.

<sup>b</sup> Number of reports per 100,000 dose distributed.

<sup>c</sup> Onset interval from vaccination date to onset of first sign or symptom reported after vaccination, not necessarily interval after injection site reaction.

<sup>d</sup> Time interval was not reported for 12 cases.

The five most common concomitant vaccines were meningococcal conjugate quadrivalent (MCV4) [327/935 = 35%], hepatitis A (HAV) [23%], varicella (VAR) [19%], hepatitis B (HBV) [14%], and measles, mumps and rubella (MMR) [13%] vaccines. The onset of first symptom or and sign ranged from <1 day to 158 days (median 1 day; mean 2.5 days). Among non-serious reports, injection site reactions, fever, and headache were the most common events. The 10 most commonly reported AEs did not differ significantly for individuals receiving Tdap alone and those with concomitant vaccination (except for higher reporting of chills for Tdap alone and rash for concomitant vaccination) and for adults and adolescents, with the exception of a few AEs with higher reporting for adolescents (e.g., syncope, seizure, wheezing), and adults (e.g., influenza like illness, insomnia and sleep disorders). Specific AEs of interest based on the criteria stated in the methods are summarized in Table 3 and described below.

### 3.1. Deaths

There were 4 death cases. A 13-year-old boy died 14 days after Tdap. The autopsy report stated that the apparent cause of death was cardiac arrhythmia due to undetermined causes. A 53-year-old man with multiple cardiac and neurological conditions died of acute of acute myocardial infarction (AMI) 69 days after Tdap. A 62-year-old man with a history of hyperlipidemia died of AMI 10 days after Tdap, HAV, inactivated polio, typhoid Vi capsular polysaccharide inactivated, and yellow fever vaccines. A 15-year-old girl died of multi-organ failure, influenza B viral sepsis, and staphylococcal secondary infection 58 days after Tdap and human papillomavirus (HPV) vaccines.

### 3.2. Guillain–Barré syndrome (GBS)

The clinical presentation for 10 GBS cases included bilateral paresthesia, weakness, or reduced/absent deep tendon reflexes in the lower and/or upper extremities. The median onset interval was 25 days (range: 1 day–56 days). None required mechanical ventilation. Nerve conduction studies consistent with GBS and/or cytoalbuminologic dissociation [elevation of cerebrospinal fluid (CSF) protein above the laboratory normal, with total CSF white

cell count <50 cell/mm<sup>3</sup>] were reported for 5 vaccinees. Three vaccinees reported histories of upper respiratory infection or influenza like illness. All recovered or were recovering.

### 3.3. Bell's palsy

Of 13 Bell's palsy cases, the majority reported decreased movement of the corner of the mouth, decreased ability to close the eyes, or decreased movement of the forehead on the affected side. The median onset interval was 6 days (range: <1 day–43 days). All reported cases were unilateral, and most stated that the patient was recovering at the time of report.

### 3.4. Seizure

Of 28 seizure cases, 11 described generalized tonic–clonic motor manifestations and 2 were status epilepticus. The median age was 15 years (range: 9 years–38 years). Six cases were on or had history of anti-convulsive treatment or electroencephalogram abnormalities. Seven vaccinees reported a history of seizures, including 2 with a history of seizures following prior vaccination.

### 3.5. Demyelinating diseases of the central nervous system (CNS)

Demyelinating diseases of the CNS included optic neuritis (2 cases), transverse myelitis (1), and acute disseminated encephalomyelitis or ADEM (1). A 15 year old girl developed bilateral optic neuritis 18 days after Tdap and HAV. Funduscopy revealed bilateral disk edema with blurring of disk margins. A 16 year old girl developed left optic neuritis 59 days after Tdap and HPV. Magnetic resonance imaging (MRI) of the brain showed some slight enlargement of the left optic nerve. An 11 year old girl became paraplegic at the T10–T11 level 30 days after Tdap. During hospitalization she was diagnosed with idiopathic transverse myelitis. A 16 year old boy developed headache, photophobia, progressive weakness, decreased sensation, and urinary retention 15 days after Tdap and MCV4, followed by loss of consciousness and lethargy. Laboratory studies revealed CSF pleocytosis and an abnormal MRI of the brain identified diffuse parenchymal signal changes above

and below the tentorium, compatible with ADEM. His symptoms resolved approximately 7 weeks after vaccination.

### 3.6. Encephalopathy/encephalitis

There were 3 encephalopathy/encephalitis cases. An 11-year-old girl developed ataxia, dizziness, incoherent speech, lethargy, and altered mental status 2 days after Tdap and HBV. She was diagnosed with encephalopathy, which lasted 1 day. A 28-year-old woman developed nausea, vomiting, and headache 5 days after Tdap and 10 days after trivalent inactivated influenza vaccine (TIV). She was hospitalized with acute mental status changes, confusion, expressive aphasia, headache, neck pain and stiffness, and photophobia. Her serology was positive for cytomegalovirus IgG and IgM titers. She recovered and her discharge diagnosis was acute meningoencephalitis with encephalopathy. A 12-year-old boy developed severe headache, optic neuritis, Bell's palsy, and decreased vibratory sense in the left lower extremity 16 days after Tdap and MCV4. He was hospitalized twice with a primary diagnosis of encephalitis and secondary diagnoses of optic neuritis, encephalopathy, facial palsy, and *Mycoplasma* infection.

### 3.7. Anaphylaxis

There were 12 anaphylaxis cases (only 5 were reported as serious). Most presented with dermatological (e.g., urticaria) and respiratory (e.g., bronchospasm) or cardiovascular (e.g., hypotension) symptoms or signs within 1 hour of vaccination. All vaccinees recovered.

### 3.8. Other allergic reactions

There were 7 serious allergic reaction cases involving wheezing, pruritic rash and one physician diagnosed allergic reaction. The onset interval ranged from a few minutes to 4 days after Tdap. Three vaccinees reported a history of allergies.

### 3.9. Myopericarditis

Three vaccinees developed chest pain, with symptom onset ranging from less than 1 hour to 3 days after Tdap. All were found to have electrocardiogram (EKG) abnormalities (e.g., diffuse ST elevation), as well as elevated Troponin I and creatine kinase myocardial band cardiac enzymes. One had an MRI showing evidence of subepicardial enhancement, another had a cardiac catheterization demonstrating normal coronary arteries with left ventricular hypokinesis, and the third had an echocardiogram that revealed no pericardial effusions. One vaccinee fully recovered, and the recovery status of the other two was not reported.

### 3.10. Syncope

Of 27 syncope cases, 26 occurred in adolescents. One was reported as life-threatening, due to bradycardia, and one patient was hospitalized for a cardiac arrhythmia. The majority of cases occurred within 5 minutes of vaccination, lasted only few minutes, and was attributed to vasovagal reactions. Ten vaccinees fell, including one who developed a head contusion and one who incurred a laceration.

### 3.11. Thrombocytopenia

Five vaccinees developed petechiae, easy bruising, ecchymosis, or epistaxis, and 3 were diagnosed with idiopathic thrombocytopenic purpura. The median onset interval was 19 days (range:

13 days–30 days). All recovered except for 1 vaccinee with an unspecified outcome.

### 3.12. Reporting rates

Based on an estimated distribution of over 20 million doses in the U.S. during the first two years after licensure of Tdap, the CRR per 100,000 doses for all AEs and for serious events were 10.2 and 0.7, respectively. Table 3 describes the CRR for specific AEs of interest.

## 4. Discussion

The pre-licensure clinical trials demonstrated that the overall safety profile of Tdap was clinically comparable to that of U.S. licensed adult tetanus and diphtheria vaccines [3]. This review showed that the majority of reported AEs following Tdap described common local and systemic reactions listed in the Tdap package inserts. The proportion of serious reports after Tdap (7%) was lower than previously reported for other vaccines (14%) in VAERS. [12]

The overall CRR for Tdap was 10.2 per 100,000 net vaccine doses distributed. According to a VAERS surveillance summary, the reporting rate for the pediatric DTaP was 13 per 100,000 net vaccine doses distributed and the reporting rates for other vaccines ranged from 3 (TIV) to 156 (rotavirus vaccine) per 100,000 doses distributed [12]. The CRR for serious events after Tdap (0.7 per 100,000 net vaccine doses distributed) was lower compared to that reported for pediatric diphtheria, tetanus and pertussis-containing vaccines (2.9 per 100,000 net vaccine doses distributed) [12]. In a VAERS review of HPV reports, the overall and specific AEs (syncope, local reactions, GBS, anaphylaxis and death) reporting rates were, respectively, 53.9 (8.2, 7.5, 0.2, 0.1, and 0.1) per 100,000 doses distributed [13]. When interpreting such reporting rates, one should consider the differences in reporting bias, vaccine indication, case definition and ascertainment, timing of review, and concomitant vaccination.

The 4 reported deaths were very unlikely due to Tdap. Two adults with risk factors for coronary artery disease died of AMI. An autopsy attributed the death of an adolescent to a cardiac arrhythmia. Severe viral and bacterial infections led to multi-organ failure in the fourth death. Regarding the specific AEs of interest, in the 2012 IOM's report on evidence and causality of vaccine adverse effects, the review committee concluded that the evidence is inadequate to accept or reject a causal relationship between diphtheria toxoid-, tetanus toxoid-, or acellular pertussis-containing vaccines and myocarditis, ADEM, transverse myelitis, optic neuritis, Bell's palsy, GBS, encephalitis, encephalopathy, seizures, immune thrombocytopenic purpura, and anaphylaxis (except there was convincingly supports for tetanus toxoid) [14].

Myopericarditis has been reported after diphtheria, tetanus, and pertussis vaccine components in individuals aged 3 months to 31 years [15–19]. Of the 3 reports of myopericarditis after Tdap, none described possible etiologies (e.g., infectious agents, drugs, toxins, or autoimmune disorders) or permanent cardiac damage (e.g., chronic dilated cardiomyopathy). Beyond the temporal association, there was no evidence to support a causal link between Tdap and myopericarditis. The CRR for myopericarditis after Tdap is much lower than the background rate of 2.16 per 100,000 persons [7].

Few cases of demyelinating diseases of the CNS were reported in adolescents after Tdap. Although it is biologically plausible that vaccines might induce autoimmune reactions in susceptible individuals, limited information provided in the VAERS reports often does not allow causality assessment. It is possible that the severity of these neurological conditions observed soon after administration of newly licensed vaccines in a young population might have stimulated the reporting.

Ten GBS cases were identified in this review. Although the exact cause of GBS is still unknown, many cases are preceded by respiratory or gastrointestinal infections. An autoimmune response triggered by vaccine components might play a role in the development of GBS in susceptible individuals [11]. Two surveillance studies showed that the number of GBS cases observed after tetanus toxoid-containing vaccine was less than the number expected by chance alone [20].

Although the CRR for Bell's palsy after Tdap is higher than the overall dose-adjusted reporting rate of 0.02 per 100,000 doses distributed for the parenteral TIV during 1991–2001 [12], it did not exceed the expected background rate of 13 to 43 Bell's palsy cases per 100,000 person-years in the U.S. [21]. Because our review only involved the first 2 years after licensure of Tdap, it is important to continue monitoring the trend of Bell's palsy reported to VAERS overtime.

The 3 encephalopathy/encephalitis cases after Tdap may reflect only coincidental temporal association. The potential relationship of acellular pertussis-containing vaccines with encephalopathy/encephalitis needs to be systematically evaluated among adolescents and adults.

Most vaccinees with seizures reported after Tdap had no history of seizure disorders. Seizures have been reported in pediatric DTaP clinical trials, but not in Tdap trials. [3] Seizures, including febrile seizures, are relatively more common in younger children than adolescents.

Anaphylaxis is a serious but rare risk with vaccines. The rates of anaphylaxis observed after DTwP or DTaP ranged from 0 to 21.2 per million doses among children and adolescents in a study. [22] The CRR for anaphylaxis after Tdap is within these background rates. The lethal potential of anaphylaxis compels the utmost vigilance for signs and symptoms of anaphylaxis following vaccination.

The characteristics of syncope cases after Tdap were similar to those described in previous VAERS reviews [8,23]. Most of these cases occurred in adolescents and within 5 minutes of vaccination and mostly due to vasovagal reaction. As more vaccines are licensed for adolescent use, health providers need to take appropriate measures (e.g., 15 min observation after vaccination) to prevent injuries as recommended by the advisory groups [24].

Thrombocytopenia is a recognized risk of live MMR and VAR vaccines. For non-live virus vaccines thrombocytopenia might be elicited by an immunologic mechanism [25]. A VAERS review of thrombocytopenia showed that non-live virus vaccines accounted for 65% of those reports listing only one vaccine [26]. Large observational studies might clarify the potential risk of thrombocytopenia and non-live virus vaccines including Tdap.

Due to inherent limitations of passive surveillance systems, temporal associations between reported AEs and vaccines must be interpreted with caution. Clear causality usually cannot be inferred. However, use of standardized case definitions can improve the precision and comparability of VAERS-based data [27], and calculations of reporting rates can help to adjust for variations between product lot sizes or the extent of exposure to different manufacturers' products [12,28]. Ultimately, important hypothesized risks from VAERS can be studied using data from other sources (e.g., Vaccine Safety Datalink) [28]. Because of its national scope, VAERS can be valuable for hypothesis generation and detection of rare AEs [29].

Because adolescents and adults were not routinely vaccinated against pertussis in the past, this surveillance summary provides important – and reassuring – information about the use of Tdap in these age groups. The vast majority of AEs reported to VAERS in the first two years after Tdap licensure described non-serious events previously observed during clinical trials. Rare AEs of clinical importance were reported following Tdap and might warrant continued surveillance and consideration for further assessment in controlled observational studies.

## Contributors

Contributors to this work were full-time employees of the Food and Drug Administration (FDA) and Centers for Disease Control and Prevention (CDC) at the time the work was conducted. Support was derived entirely from the FDA and CDC. Dr. Patrick O'Connor was a resident of the Johns Hopkins Bloomberg School of Public Health, General Preventive Medicine Residency Program. Currently Dr. Soju Chang is a full-time employee of the National Institutes of Health, Dr. Patrick O'Connor is a full-time employee of CDC, and Dr. Barbara Slade is a retiree.

## References

- Broder KR, Cortese MM, Iskander JK, et al. Preventing tetanus, diphtheria, and pertussis among adolescents: use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccines recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 2006;55(March (RR-3)):1–34.
- Centers for Disease Control Prevention (CDC). Updated recommendations for use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis (Tdap) vaccine from the Advisory Committee on Immunization Practices, 2010. *MMWR Morb Mortal Wkly Rep* 2011;60(January (1)):13–5.
- Food and Drug Administration (FDA). Complete list of vaccines licensed for immunization and distribution in the US, Product information, <http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM093833>; 2012 [accessed 22.10.12].
- Chen RT, Rastogi SC, Mullen JR, et al. The Vaccine Adverse Event Reporting System (VAERS). *Vaccine* 1994;12(May (6)):542–50.
- Food and Drug Administration (FDA). Postmarketing safety reporting requirements for drug and biologic products, <http://www.fda.gov/Drugs/DrugSafety/ucm299833.htm>; 2012 [accessed 22.10.12].
- The Brighton Collaboration. Case definitions. <https://brightoncollaboration.org/public/what-we-do/standards/case-definitions.html>; 2012 [accessed 22.10.12].
- Arness MK, Eckart RE, Love SS, et al. Myopericarditis following smallpox vaccination. *Am J Epidemiol* 2004;160(October (7)):642–51.
- Braun MM, Patriarca PA, Ellenberg SS. Syncope after immunization. *Arch Pediatr Adolesc Med* 1997;151(March (3)):255–9.
- Zhou W, Pool V, DeStefano F, Iskander JK, Haber P, Chen RT. A potential signal of Bell's palsy after parenteral inactivated influenza vaccines: reports to the Vaccine Adverse Event Reporting System (VAERS) – United States, 1991–2001. *Pharmacoepidemiol Drug Saf* 2004;13(August (8)):505–10.
- Ray P, Hayward J, Michelson D, et al. Encephalopathy after whole-cell pertussis or measles vaccination: lack of evidence for a causal association in a retrospective case-control study. *Pediatr Infect Dis J* 2006;25(September (9)):768–73.
- Stratton KR, Howe CJ, Johnston Jr RB, editors. Institute of Medicine. Vaccine Safety Committee: adverse events associated with childhood vaccines: evidence bearing on causality. Washington, DC: National Academies Press; 1994.
- Zhou W, Pool V, Iskander JK, et al. Surveillance for safety after immunization: Vaccine Adverse Event Reporting System (VAERS) – United States, 1991–2001. *MMWR Surveill Summ* 2003;52(January (1)):1–24.
- Slade BA, Leidel L, Vellozzi C, et al. Postlicensure safety surveillance for quadrivalent human papillomavirus recombinant vaccine. *JAMA* 2009;302(August (7)):750–7.
- Stratton KR, Ford A, Rusch E, Clayton EW, editors. Institute of Medicine. Committee to review adverse effects of vaccines. Board on Population Health and Public Health Practice. Adverse effects of vaccines: evidence and causality. Washington, DC: The National Academies Press; 2012.
- Dilber E, Karagoz T, Aytemir K, et al. Acute myocarditis associated with tetanus vaccination. *Mayo Clin Proc* 2003;78(11):1431–3.
- Amsel SG, Hanukoglu A, Fried D, Wolyovovics M. Myocarditis after triple immunisation. *Arch Dis Child* 1986;61(April (4)):403–5.
- Boccaro F, Benhaïem-Sigaux N, Cohen A. Acute myopericarditis after diphtheria, tetanus, and polio vaccination. *Chest* 2001;120(August (2)):671–2.
- Helle EP, Koskenvuo K, Heikkilä J, Pikkarainen J, Weckstrom P. Myocardial complications of immunisations. *Ann Clin Res* 1978;10(October (5)):280–7.
- Wu SJ, Sun S, Li JY, Hu PY, Chien CY. Acute fulminant myocarditis after diphtheria, polio, and tetanus vaccination. *Asian Cardiovasc Thorac Ann* 2006;14(December (6)):e111–2.
- Tuttle J, Chen RT, Rantala H, Cherry JD, Rhodes PH, Hadler S. The risk of Guillain-Barré syndrome after tetanus-toxoid-containing vaccines in adults and children in the United States. *Am J Public Health* 1997;87(December (12)):2045–8.
- Mutsch M, Zhou W, Rhodes P, et al. Use of the inactivated intranasal influenza vaccine and the risk of Bell's palsy in Switzerland. *N Engl J Med* 2004;350(February (9)):896–903.
- Bohlke K, Davis RL, Marcy SM, et al. Risk of anaphylaxis after vaccination of children and adolescents. *Pediatrics* 2003;112(October (4)):815–20.

- [23] Centers for Disease Control Prevention (CDC). Syncope after vaccination – United States, January 2005–July 2007. *MMWR Morb Mortal Wkly Rep* 2008;57(May 17):457–60.
- [24] Centers for Disease Control Prevention (CDC). General recommendations on immunization – recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 2011;60(January (2)):1–64.
- [25] Cohen AD, Shoenfeld Y. Vaccine-induced autoimmunity. *J Autoimmun* 1996;9(December (6)):699–703.
- [26] Woo EJ, Wise RP, Menschik D, et al. Thrombocytopenia after vaccination: case reports to the US Vaccine Adverse Event Reporting System, 1990–2008. *Vaccine* 2011;29(February (6)):1319–23.
- [27] Kohl KS, Gidudu J, Bonhoeffer J, et al. The development of standardized case definitions and guidelines for adverse events following immunization. *Vaccine* 2007;25(August (31)):5671–4.
- [28] Food and Drug Administration (FDA). Guidance for industry: good pharmacovigilance practices and pharmacoepidemiologic assessment. <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126834.pdf>; 2012 [accessed 22.10.12].
- [29] Centers for Disease Control Prevention (CDC). Suspension of rotavirus vaccine after reports of intussusception – United States, 1999. *MMWR Morb Mortal Wkly Rep* 2004;53(September (34)):786–9.