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

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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®, GlaxoSmithKline Biologicals, Rixensart, Belgium] for use in adolescents aged 10–18 years on May 3, 2005, and a second Tdap [ADACEL®, 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

☆ *Disclaimer*: The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention and Food and Drug Administration.

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

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

[a] 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.
[b] Fatal.
[c] Bronchitis, Staphylococcal sepsis, and varicella zoster virus like rash.
[d] 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 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[a] $N = 2090$
Demographic:			
Age, median (range)	13y (10–18 y)	42y (19–64 y)	22y (2 m–87 y)
Gender, male (%)	440 (48)	180 (18)	666 (32)
Clinical:			
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.
[a] Including reports with missing age and age outside of Tdap vaccine indication.