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Adverse events after Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis (Tdap) Vaccine administered to adults 65 years of age and older reported to the Vaccine Adverse Event Reporting System (VAERS), 2005–2010☆,☆☆

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ABSTRACT

Background: Tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccine was not licensed for use in adults aged ≥65 years due to lack of sufficient efficacy and safety data.
Objective: To characterize reports to the Vaccine Adverse Event Reporting System (VAERS) among adults aged ≥65 years who received Tdap vaccine 'off-label' to assess for potential vaccine safety concerns.
Methods: We searched VAERS for US reports of adverse events (AEs) in subjects aged ≥65 years who received Tdap vaccine from 9/1/2005 to 9/08/2010. Medical records were requested for all reports coded as serious (death, hospitalization, prolonged hospitalization, permanent disability, life-threatening-illness). Proportional reporting ratio (PRR) was used to assess for higher proportionate reporting for AEs after Tdap compared with Td reports in subjects aged ≥65 years.
Results: VAERS received 243 reports following Tdap administered to persons aged ≥65 years. Eleven (4.5%) reports were serious, including two deaths. Most common AEs were local reactions in 100 (41.2%) reports. Seventy-eight (32.1%) reports contained coding terms that denoted inappropriate administration of vaccine. 'Cough' was the only term associated with disproportionately higher reporting after Tdap compared with Td. Six of seven Tdap reports containing the term 'Cough' were non-serious. Clinical review of serious reports identified no unusual patterns of AEs.
Conclusion: Our VAERS review of the 'off-label' use of Tdap vaccine in adults ≥65 years did not find any safety concerns that warrant further study. These data will provide useful baseline information to assist CDC and FDA with monitoring efforts as permissive recommendations for Tdap in older persons are adopted.

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1. Introduction

The Advisory Committee on Immunization Practices (ACIP) has recommended a single dose of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine (Tdap) for adolescents and adults aged 11–64 years since 2006 to prevent tetanus, diphtheria and pertussis [1,2]. These recommendations were consistent with licensed indications for the two Tdap products licensed in the United States [3,4]. Neither Tdap vaccine product is licensed for use in adults aged ≥65 years due to lack of sufficient efficacy and safety data. Decennial tetanus and diphtheria toxoids (Td) boosters have been recommended for adults aged ≥65 years to protect against tetanus and diphtheria [2]. However, Td does not protect against pertussis, which older persons may acquire and transmit to their close contacts [5–9]. Use of Tdap has been recommended for adults in the licensed age group as a "cocooning" strategy to protect infants aged <12 months, who are at risk for severe pertussis, from becoming infected [2,10].

During 2010 California experienced a historic rise in the number of pertussis cases: as of November, 2010, 6631 cases of pertussis (confirmed, probable or suspect) were reported to the CA Department of Public Health including 10 deaths (all infants) [11]. This

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☆☆ *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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outbreak led public health authorities in CA to broaden Tdap vaccine recommendations in July 2010 to include children 7–9-year-old and adults' aged ≥65 years [12]. Concurrently, the ACIP Pertussis Working group identified lack of licensure of Tdap for persons aged ≥65 years as a programmatic gap for optimal coverage. On October 28, 2010, the ACIP voted to recommend that adults aged ≥65 years who have or who anticipate having close contact with an infant less than age 12 months receive a single dose of Tdap vaccine to protect against pertussis and reduce the likelihood of transmission of pertussis to infants less than 12 months of age [13].

To provide information about the safety profile of Tdap to California health officials and inform ACIP deliberations (prior to the vote to recommend vaccination to this age group) we conducted a review of reports to the Vaccine Adverse Event Reporting System (VAERS), a national vaccine safety monitoring system, in adults aged ≥65 years following 'off-label' Tdap vaccination during 2005–2010.

2. Methods

2.1. Vaccine adverse events reporting system

VAERS is a national vaccine safety surveillance system created in 1990 and co-administered by the Food and Drug Administration (FDA) and the Centers for Disease Control and Prevention (CDC) which receives voluntary reports of adverse events (AEs) following immunization [14]. VAERS accepts reports from vaccine manufacturers, healthcare providers, vaccine recipients and others. The VAERS report form collects information on age, gender, vaccine information, the adverse event experience and health history. Signs and symptoms of adverse events are coded by trained personnel and entered into a database using the Medical Dictionary for Regulatory Activities (MedDRA) a clinically validated, internationally standardized terminology [15]. A VAERS report may be assigned one or more MedDRA preferred terms (PTs). Reports are classified as serious or non-serious. A report is considered serious based on the Code of Federal Regulations if one of the following is reported: death, life-threatening illness, hospitalization or prolongation of hospitalization or permanent disability [16]. For serious reports, medical records are requested and made available to VAERS personnel as part of routine surveillance activities regardless of the vaccine(s) involved.

We analyzed VAERS reports received by September 8, 2010 for adults aged ≥65 years vaccinated with Tdap and Td during September 1, 2005 through August 27, 2010. Non-US reports and duplicate reports were excluded.

2.2. Disproportionate reporting analysis

Frequencies of MedDRA coding terms were calculated. Among the VAERS reports in adults aged ≥65 years, we assessed for disproportionately higher reporting of adverse events after Tdap compared with Td. For each MedDRA PT, we compared the proportion of Tdap reports with the PT with the proportion of Td reports with the PT using the proportional reporting ratio (PRR) and its 95% confidence interval (CI). We identified MedDRA PTs with significant disproportionality by applying Evans' criteria (PRR ≥2.0, Chi-square ≥4.0, and number of reports ≥3 in the Tdap group) [17,18]. Calculations were performed using SAS version 9.2 (SAS Institute, Cary, NC).

2.3. Clinical review of reports

One medical officer (PM) conducted an independent clinical review of all VAERS reports and associated medical records for serious reports when available. A primary diagnostic category was assigned to each report, using a system previously described [19]. We used the Brighton collaboration definition for Guillain-Barré Syndrome (GBS) to verify cases of reported GBS [20].

Because VAERS is a routine surveillance program that does not meet the definition of research, it is not subject to Institutional Review Board review and informed consent requirements.

Table 1
Characteristics of VAERS reports after tetanus-toxoid, reduced diphtheria-toxoid, and acellular pertussis (Tdap) and tetanus and diphtheria toxoids (Td) vaccines in adults ≥65 years, September 1, 2005–September 8, 2010.

Characteristic	Tdap	Td
	N (%)	
No of reports	243	404
No of reports with ≥1 adverse event	164 (67.5)	401 (99.3)
Serious	11 (4.5)	28 (6.9)
Deaths	2	3
Female gender[a]	180 (74.1)	315 (78.0)
Median age, (range) years	70.0 (65 – 101)	70.0 (65 – 92)
Age groups (years)		
65–69	121 (49.8)	186 (46.0)
70–74	71 (29.2)	107 (26.5)
75–79	36 (14.8)	69 (17.1)
80–84	11 (4.5)	30 (7.4)
85–89	1 (0.4)	9 (2.2)
≥90	3 (1.2)	3 (0.7)
Type of reporter		
Vaccine provider[b]	131 (53.9)	208 (51.5)
Other	84 (34.6)	148 (36.6)
Manufacturer	14 (5.8)	25 (6.2)
Patient	14 (5.8)	23 (5.7)
Tdap[c] or Td[d] given alone	158 (65.0)	204 (50.5)
Recovered at time of report[e]	131 (53.9)	208 (51.5)

[a] One report with unknown gender.
[b] Includes vaccine administrators and healthcare providers.
[c] Most common vaccines given simultaneously were Pneumococcal polysaccharide vaccine (PPV23) and trivalent inactivated influenza vaccine (TIV) in 17.3% and 2.9% reports, respectively.
[d] Most common vaccines given simultaneously were PPV23 and Zoster vaccine in 21.8% and 5.0% reports, respectively.
[e] Condition same as prior to vaccination.

3. Results

From September 1, 2005 through September 8, 2010, VAERS received 11,022 total Tdap reports among all age groups. Of these, 243 reports (2.2%) were among adults aged ≥65 years (Table 1). Eleven of the 243 reports (4.5%) after Tdap were coded as serious, including two deaths. One hundred eighty (74.1%) reports occurred in females and the median age was 70.0 years (range 65–101). About half (53.9%) of the reports came from a vaccine provider. In 158 reports (65%), Tdap was administered alone. During the same time period, VAERS received 404 Td-related reports in adults aged ≥65 years, which were similar in all respects to reports following Tdap (Table 1). During 2005–2010, the largest number of AEs reported following Tdap among those aged ≥65 years occurred in 2008 ($n = 63$).

3.1. Coding terms and proportional reporting ratios

The 243 reports to VAERS after Tdap resulted in a total of 388 MedDRA PTs. The five most frequent MedDRA PTs were injection site erythema (61/243;25.1%), inappropriate schedule of drug administration (45/243;18.5%), injection site pain (38/243;15.6%), wrong drug administered (34/243;14%), and injection site swelling (33/243;13.6%). Seventy-eight (32.1%) reports were coded with

one or more of the following MedDRA PTs indicating administration of a vaccine to an individual for whom the vaccine was not indicated: inappropriate schedule of drug administration, wrong drug administered, or medication error. Of these 78 reports indicating administration error, 10 described one or more AE, and 68 did not describe an AE. Eight reports described neither an AE nor an administration error and were coded with the PT "unevaluable event". In contrast, only 2 of 404 Td reports in subjects aged ≥65 years had any of the PT codes indicating administration error.

Among all reports for adults aged ≥65 years, we found disproportionately higher reporting of the PT "cough" in reports after Tdap vs after Td (PRR = 5.8, 95% CI = 1.2–27.8, Chi Square ≥4.0). When we restricted the analysis to reports that described at least one AE, we continued to find disproportionality for the PT "cough" (7 reports among 164 Tdap reports vs 2 reports among 401 Td reports, PRR = 8.6, 95% CI = 1.8–40.8, Chi Square ≥4.0). Of the 7 Tdap reports, five were female vaccinees and the median age was 71 (range 65–79). Six were non-serious reports and one was serious. Among the non-serious reports, diagnoses included: 2 with influenza like-illness, 2 with asthma exacerbation or dyspnea/wheezing, 2 with injection site reactions with headache and dizziness or chills and headache. Among the 6 non-serious reports, three patients required emergency room visits; two recovered by the time the VAERS form was submitted, one had not recovered, and recovery information was unknown for the other 3. The one serious report was a 77-year-old female who was diagnosed with generalized weakness and cough. The patient was not hospitalized but the report indicated she had not recovered and the reporter considered the event life threatening resulting in permanent disability.

4. Clinical review

Among 164 reports where at least one AE was reported, we had sufficient information to classify 153 non-serious and 11 serious reports into a primary diagnostic category. The most frequent diagnostic category overall was local injection site reactions, which accounted for 100 (41.2%) reports (Table 2). Other non-infectious events, comprised mainly of constitutional signs and symptoms, accounted for 14 (5.8%) reports, including the serious report with a MedDRA PT of cough described above. The neurological and respiratory categories each had fewer than 5 reports.

The 11 serious reports included two deaths in persons with several underlying conditions. One of the deaths occurred in a 77-year-old male who received Tdap and yellow fever vaccine on the same date and 2 days later presented with fever, nausea and generalized weakness. The patient was hospitalized 1 week after vaccination and died 19 days after vaccination from multiorgan failure due to septic shock. The second death occurred in a 66-year-old female who received only Tdap and who, 2 days after vaccination, presented with shortness of breath, which worsened in the following 6 weeks. The patient died 2 months after vaccination; the cause of death was indicated to be pulmonary hypertension due to acute interstitial lung disease. Of the 9 non-fatal serious reports, diagnostic categories were other non-infectious ($n = 3$), neurological ($n = 3$), infectious ($n = 2$), and injection site pain ($n = 1$). In 4 of these reports Tdap was the only vaccine administered, in 5 Tdap was administered with pneumococcal polysaccharide vaccine, and in 2 with Yellow Fever vaccine. The 3 serious neurologic cases included one report of GBS confirmed using Brighton criteria in a 71-year-old male who had onset of symptoms 34 days after administration of Tdap and pneumococcal polysaccharide vaccine, one case of Bells Palsy in a 67-year-old woman and one case of encephalitis in a 70-year-old female.

Table 2
Diagnostic categories and main diagnosis for reports of adverse events after Tetanus-toxoid, reduced diphtheria-toxoid, and acellular pertussis (Tdap) vaccine, in subjects ≥65 years in the Vaccine Adverse Event Reporting System (VAERS), September 1, 2005–September 8, 2010 ($n = 243$).

Diagnostic category[a]	All *N* (%)	Serious
Local reactions[b]	100 (41.2)	1
Other non-infectious	22 (9.1)	
Constitutional reactions (e.g. fever, headache)	14	
Local reaction (at pneumococcal vaccine injection site)		
Dizziness	3	
Fever of unknown origin	1	1
Generalized weakness	1	1
Musculoskeletal	14 (5.8)	
Arm pain	8	
Arthralgia	4	
Myalgia	2	
Allergy (non-anaphylaxis allergic reactions)	10 (4.1)	
Neurological	5 (2.1)	
Brachial neuritis	2	
Guillain-Barré syndrome	1	1
Encephalitis	1	1
Bell's palsy	1	1
Respiratory	5 (2.1)	
Influenza-like illness	2	
Dyspnea	1	
Fever, cough	1	
Asthma exacerbation	1	
Other Infectious	3 (1.2)	
Viral meningitis	1	1
Herpes Zoster	1	
Septic joint	1	1
Deaths	2 (0.8)	
Acute interstitial lung disease	1	1
Septic shock	1	1
No adverse events reported	79 (32.5)	
Total	243	11

[a] Non-fatal reports classified based on body system categories.
[b] Two reports described a cluster of 4 subjects each who experienced local reactions.

5. Comments

In our 5 year-review of Tdap reports in adults aged ≥65 years in VAERS, we did not find any unusual or unexpected cluster of adverse events. We found higher proportional reporting for the term 'cough' after Tdap compared with Td, but clinical review revealed that a majority of these were non-serious reports with mild conditions and no common clinical pattern. The most common reported AEs after Tdap were local injection reactions (i.e. injection site erythema, swelling, or pain), which occurred in almost half of all reports. Constitutional reactions (e.g., fever, chills and malaise) were reported less frequently. The pattern of reports that described local or constitutional reactions were consistent with similar reactions described in clinical prelicensure trials [4]. Two of the serious reports were cases of severe pain at the injection site. Similar reactions were observed in 1.1% of participants of the prelicensure clinical trials [4].

Guillain-Barré Syndrome is an acute, immune mediated paralytic disorder of the peripheral nervous system [21]. The background incidence of GBS among males aged ≥65 years in the United Kingdom and the US is approximately 4.6 cases per million inhabitants [22]. We found one case of GBS following Tdap and Pneumococcal vaccination in whom the interval between vaccination and symptom onset (34 days) was within the window of biologic plausibility if a causal association were suspected [23]; however, we cannot determine if the receipt of either vaccine contributed to the GBS. Despite its rarity, concerns about the risk of developing GBS following administration of vaccines have been present since an association was first noticed after administration of the 1976–1977 A/New Jersey ("swine influenza") vaccine

and with a rabies vaccine that is no longer licensed for use in the United States [24,25]. In 1994, a review by the Institute of Medicine (IOM) found that the evidence favored acceptance of a causal relation between diphtheria and tetanus toxoids and GBS [26] based on a single report of re-challenge in which an individual experienced GBS after two different tetanus toxoid vaccinations. A study in the Vaccine Safety Datalink (VSD) [27] assessed the risk for GBS after 2 million doses of Tdap in subjects aged 10–64 years during the period 2005–2009 over the course of 42 days. This study found no evidence of an association between Tdap and an increased risk for GBS. An earlier study of the association between GBS and Td vaccine in two active surveillance systems found that the number of cases of GBS observed after Td was less than the number expected by chance alone [28].

Encephalitis is a rare neurological outcome that has been inconsistently associated with pertussis vaccines in some studies [29]. In 1991, the IOM vaccine safety committee concluded that the evidence (all in children) was consistent with a causal relation between diphtheria and tetanus toxoids and whole cell pertussis vaccine (DTwP) and acute encephalopathy [2,30]. Encephalitis or encephalopathy with onset within 72 h of vaccination in infants and children is recognized by the National Vaccine Injury Compensation Program (NVICP) as a possible effect of pertussis antigen-containing vaccines, and can be compensable as an injury [31]. A case-control study of more than 2 million children did not find an association with encephalopathy among DTwP recipients [32]. A study by the VSD did not identify an association between Tdap and encephalopathy–encephalitis–meningitis in persons aged 10–64 years [33]. The one report in our review which described a mild case of encephalitis occurred within 24 h of Tdap vaccination and was considered by the attending physician to be a case of post-vaccine encephalitis; however, we did not attempt to assess causality since it is difficult with the data available to VAERS and beyond the scope of this report.

As a national surveillance system VAERS has the advantage that it may be used to detect signals of potential vaccine safety concerns, which can be further explored in carefully designed epidemiological studies. However, any finding in VAERS needs to be interpreted with caution given the inherent limitations of passive surveillance systems, such as over- or under-reporting, biased reporting, and inconsistency in quality and completeness of reports. The reporting efficiency of AEs in older persons may be lower than it is in younger persons due to lack of awareness of VAERS among healthcare providers of older persons who administer fewer vaccines than pediatricians. It is also important to realize that VAERS generally cannot assess causality between an adverse event and administration of a vaccine.

We reviewed VAERS reports after Tdap vaccination among adults aged ≥65 years during a time when Tdap was not nationally recommended for this age group. We did not find any safety concerns that would warrant further study. The majority of the AEs reported to VAERS in our review were described as mild and comprised injection site reactions, consistent with the safety profile of Tdap in adults <65 years in pre-licensure clinical trials [4] and in post-marketing surveillance in the Vaccine Safety Datalink project [27,32]. Our review of VAERS data suggest that the safety profile of Tdap vaccine in adults aged ≥65 years was similar to that of adults ≥65 years who received Td vaccine, which has a good track record for safety [34]. However, it is important to realize that the AEs reported to VAERS following administration of Tdap vaccine in adults aged ≥65 years reflect the 'off-label' use of a vaccine that was not licensed in this age group during the period of this review; one-third of reports did not report an AE but reported only the incorrect use of the vaccine in this age group. In January, 2011 ACIP recommendations for permissive Tdap use in persons aged ≥65 years were published [13]. Although we anticipate Tdap will continue to have a good safety profile, as persons aged ≥65 years are increasingly vaccinated it will be important to continue safety monitoring. Rare events may appear as larger numbers of people are vaccinated in this age group or if individuals with more co-morbidities receive Tdap that might not have been previously receiving the vaccine. CDC and FDA will continue monitoring AEs in VAERS after receipt of Tdap in adults aged ≥65 years.

6. Conclusion

In this review we described AE reports in adults aged ≥65 years who received Tdap 'off-label' prior to the approval of a permissive recommendation for Tdap use in this age group. We identified 243 reports; most (232;95.5%) were non-serious and one-third did not describe an adverse event. Although our review was subject to limitations of a spontaneous reporting system and assessed a population for whom Tdap was not recommended, we identified no safety concerns. Our findings suggest that the safety profile of Tdap is similar to that of Td in older persons. These data will provide useful baseline information to assist with monitoring efforts as the new ACIP recommendation for permissive use of Tdap in persons aged ≥65 years is adopted.

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