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The safety of immunizing with tetanus–diphtheria–acellular pertussis vaccine (Tdap) less than 2 years following previous tetanus vaccination: Experience during a mass vaccination campaign of healthcare personnel during a respiratory illness outbreak☆

Elizabeth A. Talbot[a,b,*], Kristin H. Brown[c], Kathryn B. Kirkland[a], Andrew L. Baughman[c], Scott A. Halperin[d], Karen R. Broder[c]

[a] Dartmouth Medical School, Hanover, NH, USA
[b] NH DHHS, Concord, NH, USA
[c] CDC, Atlanta, GA, USA
[d] Dalhousie University, Halifax, Nova Scotia, Canada

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ABSTRACT

Background: Tdap is recommended for health care personnel (HCP) aged <65 years who received tetanus diphtheria or tetanus toxoid immunization (Td/TT) ≥2 years earlier. During a medical center Tdap vaccination campaign, we assessed the safety of use of a Td/TT to Tdap interval <2 years in HCP. We also describe reactogenicity in HCP who were aged ≥65 years or pregnant.
Methods: HCP vaccinated with Tdap were surveyed to assess time since last Td/TT (≥2 years vs. <2 years), age, pregnancy status, and injection site adverse events (AEs) during the 2 weeks after Tdap. AE rates were calculated and compared by non-inferiority analysis using a predetermined margin of 10%. We searched clinic logbooks to assess for clinically important adverse events during the 2 months after Tdap.
Results: Of the 4524 vaccinated HCP, 2221 (49.1%) completed a safety survey which met criteria for analysis. Non-inferiority analysis found that rates of moderate and/or severe injection site AEs were not significantly greater in those vaccinated <2 years than in those vaccinated ≥2 years after previous Td/TT. Three serious adverse events were reported during the 2 months after vaccination, none in persons who were ≥65 years, pregnant or received Td/TT <2 years before.
Conclusions: Our findings add to the body of evidence that a short interval between Td/TT and a single dose of Tdap is safe.

1. Introduction

Pertussis is an infectious respiratory disease that causes significant morbidity and occasionally mortality [1,2]. In 2005, two tetanus and diphtheria toxoids and acellular pertussis vaccine with reduced antigen content (Tdap) vaccines were licensed for use in adolescents and one was licensed for use in adults, offering a new opportunity to reduce the burden of pertussis [3,4]. In addition to routine adolescent and adult immunization, the Advisory Committee on Immunization Practices (ACIP) has recommended Tdap use for health care personnel (HCP) aged <65 years who received tetanus diphtheria or tetanus toxoid immunization (Td/TT) ≥2 years earlier [1]. Before Tdap availability, an interval of at least 5 years was recommended between booster doses of tetanus and diphtheria toxoid vaccines (Td/TT) because of concern about increased local reactogenicity in individuals who received Td/TT at a short interval [3]). In initial clinical trials, Tdap was administered to persons who received their last Td/TT vaccine ≥5 years earlier [5]; however, a Canadian post-licensure safety study of adolescents suggested that intervals as short as 2 years are safe [6]. There is limited information on safety at shorter intervals. Tdap is not licensed or recommended for use in persons ≥65 years of age and it is not routinely recommended for pregnant women [7].

To evaluate the safety of shorter intervals, we conducted an observational postlicensure safety study among HCP who were vaccinated during a suspected pertussis outbreak at a New England medical center [8]. Our primary objectives were to assess the safety of administering Tdap to HCP at an interval shorter than 2 years

☆ The findings and conclusions in this report are those of the author(s) and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

* Corresponding author at: Infectious Diseases and International Health, 1 Medical Center Drive, Lebanon, NH 03756, USA. Tel.: +1 603 650 8840; fax: +1 603 650 6199.
E-mail address: elizabeth.talbot@dartmouth.edu (E.A. Talbot).

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Table 1
Characterization of injection site reactions in this study compared to previous safety studies.

Reaction	Severity[a]	This study	Previous studies	
			Trial[5]	Halperin[6]
Pain	Mild	Noticeable, but did not interfere with usual activities	Noticeable but did not interfere with activities	Aware of symptom but did not interfere with usual activity
	Moderate	Interfered with usual activities, but did not require medical attention and/or missing work	Interfered with activities but did not require medical attention/absenteeism	Caused interference with usual activities
	Severe	Unable to do usual activities and/or go to work and/or required medical attention	Incapacitating, unable to perform usual activities, may have or did necessitate medical care or absenteeism	Unable to go to school or do usual activities
Redness	Mild[b]	<24.26 mm (1 in.)	<10 mm	<10 mm
	Moderate	≥24.26 mm–<48.52 mm (2 in.)	10 mm–<35 mm	10 mm–<50 mm
	Severe	≥48.52 mm	≥35 mm ≥ 50.8 mm[c]	≥50 mm
Swelling	Mild[b]	<24.26 mm	<10 mm	<10 mm
	Moderate	≥24.26 mm–<48.52 mm	10 mm–<35 mm	10 mm–<50 mm
	Severe	≥48.52 mm	≥35 mm ≥ 50.8 mm[c]	≥50 mm

[a] Any = Mild + Moderate + Severe.
[b] Symptom is present (does not include symptom not experienced).
[c] Two different severe end points assessed.

since previous Td/TT and to assess the risk for clinically important adverse events after Tdap in the HCP population. A secondary objective was to describe reactogenicity of Tdap among a small group of pregnant women and persons aged 65 years and older.

2. Methods

2.1. Study setting and definitions

From April 1 through May 31, 2006, Tdap (ADACEL® [sanofi pasteur, Swiftwater, PA] vaccine was offered to all HCP at least 18 years of age during a suspected outbreak of pertussis at a tertiary care medical center in New England. Tdap was offered free of charge to HCP recommended to receive the vaccine under the (then provisional) ACIP guidelines [9] (routine group) and also to HCP not routinely recommended for Tdap, including those who reported receiving their previous tetanus containing vaccine (Td/TT) <2 years earlier, those ≥65 years of age, and those who were pregnant (non-routine groups). Those seeking vaccination signed a consent form and received a Vaccine Information Statement [10].

HCP were defined according to the Healthcare Infection Control Practices Advisory Committee (HICPAC) and ACIP definition [11], and included all persons working or volunteering at the medical center. The protocol was approved by the Dartmouth College Committee for the Protection of Human Subjects; it was also submitted to the CDC Institutional Review Board which exempted it from review. Participation was voluntary and did not influence eligibility to receive Tdap, and participants received no compensation.

2.2. Survey and data collection

A web-based survey was developed to capture adverse events (AEs) among HCP who received Tdap during the campaign, and promoted through signs and emails; paper copies were also distributed. HCP received reminders through update emails, and 50 HCP were surveyed over the phone in order to increase response from non-routine Tdap vaccine recipients. Day zero was vaccination day. The survey was originally designed to be answered on days 1, 3, 7 and 14 after vaccination (referred to as the "daily survey"), but many respondents did not comply with the suggested frequency and timing of responses, so the survey was revised to retrospectively capture the adverse event experience during the 2 weeks after vaccination (referred to as the "2-week survey"). Respondents were asked to provide demographic information and whether they had been vaccinated with Td/TT < 2 or ≥2 years ago. Survey responses were excluded from analysis if they were missing necessary identifiers, included no responses to the AE questions, or responded to the survey outside the pre-defined window (3–7 days after vaccination for the daily survey, and 14–30 days for the 2-week survey). Data were collected using SurveyMonkey® electronic survey software, and SAS version 9.1 was used for data cleaning and analysis.

2.3. Adverse events assessed through the surveys

Respondents were asked whether they experienced any AE within 30 min of vaccination; the question included specific prompts for wheezing, rash, dizziness, and fainting. The survey also solicited AEs with onset more than 30 min after vaccination: fever and three injection-site reactions (pain, redness, and swelling). Subjects were asked to estimate the size of redness and swelling with reference to a U.S. quarter (diameter 24.26 mm, or 1 in., since this would facilitate a standard measure in the likelihood that all subjects would not have a ruler available for measure. Fever was defined as "feeling feverish" and/or a temperature measured to be >100.4 F (38 °C). Solicited injection site AEs were classified as mild, moderate or severe using definitions comparable to those used in US prelicensure trials and in the Canadian interval study [5,6], as shown in Table 1. Respondents were asked "did you see a healthcare provider because of symptoms you experienced after vaccination?"; if yes, the respondent was considered to have a post-vaccination medical visit. Respondents also had opportunities to report other (unsolicited) AEs in several open-ended questions. The survey also advised those who had questions about their symptoms to report to the medical center's Occupational Medicine Clinic, where a log of all encounters was kept and reviewed by investigators.

2.4. Serious adverse events

Consistent with international standards and the U.S. Code of Federal Regulations [12], serious adverse events (SAEs) were defined as any adverse experience anytime after vaccination that resulted in any of the following outcomes: death, a life-threatening adverse experience, inpatient hospitalization or prolongation of existing hospitalization or a persistent or significant disability/incapacity, a congenital anomaly, or an important medical event that, based upon medical judgment, may have required medical or

surgical intervention to prevent one of those outcomes. Designation of a medical event as an SAE does not imply causal association with vaccination.

To identify clinically important adverse events, including SAEs, we reviewed the survey responses, the Occupational Medicine Clinic log and reports from clinicians who treated vaccinated persons. Vaccine recipients with potentially serious symptoms were contacted. To identify SAEs in the form of congenital malformations among infants born to pregnant women who were vaccinated, we contacted every woman who reported pregnancy or possible pregnancy in the survey or on the vaccine consent forms, and asked them to confirm pregnancy, stage, and outcome.

2.5. Statistical analysis

Rates of injection site AEs were assessed for each survey population. For respondents who completed a daily survey on multiple days (e.g., on days 3 and 7), the most severe outcome recorded for each solicited AE was used for all analyses. For groups of special interest, rates were calculated for any, moderate, severe, and combined moderate and severe AEs.

2.6. Noninferiority analyses

A non-inferiority analysis was performed to measure the effect of Td/TT to Tdap vaccine interval on rates of injection site reactions, subjective fever, and healthcare visits using both the 2-week and daily survey analysis populations [13]. The analysis was modeled on pre-licensure trial analyses comparing rates of AEs after Tdap and Td [5]. For each outcome, the rate in the non-routine group was considered statistically higher than the rate in the routine group if the upper limit of the 95% two-sided confidence interval for the rate difference [14] was greater than the pre-determined margin of 10% (consistent with pre-licensure trials and the Canadian interval study [5,6]). The non-inferiority analysis was restricted to non-pregnant respondents aged 18–64 years old.

2.7. Adverse events in those ≥65 years of age or pregnant

Frequencies of solicited AEs were evaluated in those ≥65 years of age and pregnant women who had received their last Td/TT ≥2 years prior to the survey. Statistical analysis was not performed because of small sample sizes.

3. Results

From April 1 to May 31, 2006, 4524 (71.9%) of the medical center's 6289 HCP were vaccinated with Tdap. Among vaccinated HCP, 2676 (59.1%) completed a survey: 1375 completed 2-week surveys, 1551 completed daily surveys, and 250 completed both (Fig. 1). After excluding those with incomplete data, 971 2-week survey and 1250 daily survey respondents were included in the analysis.

The entire medical center employee population, the vaccinated employee population, and the 2-week and daily survey analysis populations were all similar with regard to sex and age (Table 2). Both analysis populations (2-week and daily survey respondents) included fewer employees with a clinical job type than the overall medical center employee population (48.0% vs. 60.1%, $p < .01$, and 40.0% vs. 60.1%, $p < .01$). Reported Td/TT vaccination status was similar between the 2-week and daily survey populations, among whom 11.1% and 12.2%, respectively, had, by report, received Td/TT <2 years before Tdap vaccination. For the web respondents, the average time between vaccination and response was 15 days (range 13–30); for the phone interviews, the average time was 16 days (range 13–25).

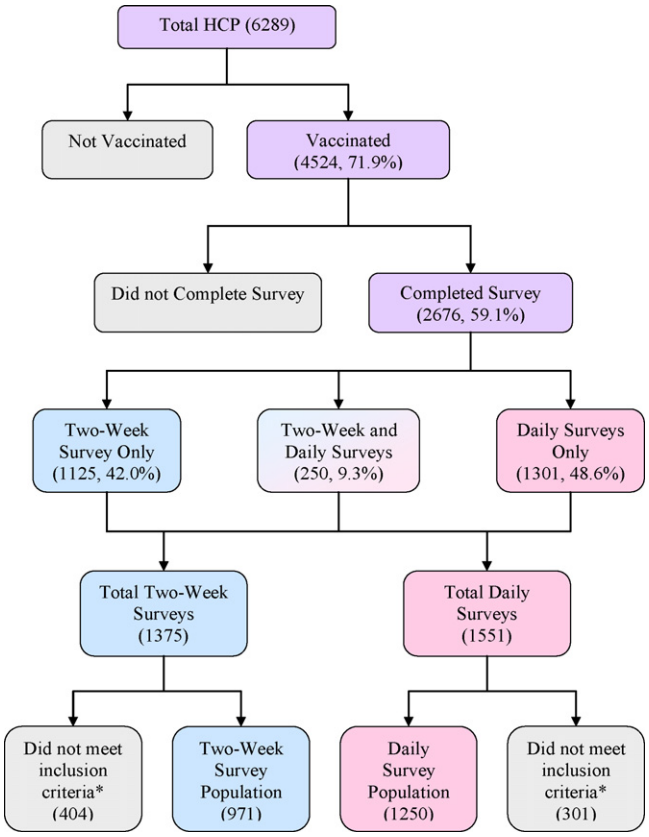

Fig. 1. Flow from total HCP population to analytic population.

3.1. Injection site AEs among the 2-week and daily survey populations

Among the 971 respondents to the 2-week survey, 70.3% reported experiencing any injection site reaction: 69.6% reported pain, 19.8% reported redness, and 25.5% reported swelling. Among the 1250 respondents to the daily survey, 83.2% reported experiencing any injection site reaction: 80.6% reported pain, 26.1% reported redness, and 35.0% reported swelling.

3.2. Non-inferiority analysis of AEs in those 18–64 years old and not pregnant

In the non-inferiority analysis of 2-week survey responses, rates of moderate or severe injection site reactions were not significantly greater in those vaccinated <2 years than in those vaccinated ≥2 years after previous Td/TT (Table 3). Compared with the routine group, rates of any redness were higher among those who reported having received Td/TT <2 years before (23.5% vs. 19.6%, delta = 3.8, 95% C.I. [−6.0 to 13.7], Table 3). Similar to the 2-week survey results, the non-inferiority analysis of daily survey responses found rates of moderate or severe reactions were not significantly higher in those vaccinated <2 years than in those vaccinated ≥2 years after previous Td/TT. Compared with those vaccinated ≥2 years after previous Td/TT, rates of any swelling were higher among those who reported having received Td/TT <2 years before (37.8% vs. 33.4%, delta = 4.4, 95% C.I. [−4.4 to 13.2]). Rates of subjective fever were higher in the <2 year than ≥2 year interval groups (15.2% vs. 11.4%, delta = 3.8, 95% C.I. [−2.6 to 10.2]); 95% of these subjects did not report a documented fever of >100.4 F (38 °C).

Table 2
Demographic characteristics of the medical center employees, employees vaccinated during the campaign, and the 2-week survey and daily survey analysis populations.

	Medical center employees		Analysis populations	
	All employees $n = 5319$[a]	Vaccinated HCP $n = 3279$[a]	2-Week survey $n = 971$	Daily survey $n = 1250$
Sex				
Female	3875 (72.9%)	2436 (74.3%)	679 (76.9%)	999 (79.9%)
Age				
Median (range)	45 (17–78)	NA	46 (18–76)	45 (19–74)
Job type				
Clinical[b]	3198 (60.1%)	1949 (59.4%)	422 (48.0%)[##]	494 (40.0%)[##]
Non-clinical[c]	2121	1330	457	742
Td/TT history				
Never	NA	NA	37	16
≥2 years			640	915
<2 years			114 (11.1%)	153 (12.2%)
Unknown			180	166
Age ≥ 65	123 (2.3%)	62 (1.9%)	26 (2.7%)[d]	24 (1.9%)[e]
Pregnant	NA	16	16	15

NA: not available. HCP: healthcare personnel.
[a] Demographic information was available for 5319 of 6289 medical center employees and 3279 of 4524 vaccinated HCP. These populations may not completely overlap (e.g., volunteers and medical students are represented in the HCP population but not in the employee population).
[b] Clinical: doctors, nurses, medical students, other staff who provide medical care.
[c] Non-clinical: financial, administrative, and laboratory staff who do not provide direct medical care.
[d] Of 914 with known age.
[e] Of 1235 with known age.
[##] Significantly different from all employees, $p < .01$.

3.3. Descriptive analysis of AEs in those ≥65 years of age or pregnant

Based on self-reports, 26 2-week survey and 24 daily survey respondents were ≥65 years of age, and 16 2-week survey and 15 daily survey respondents were pregnant at the time of vaccination. Rates of solicited AEs are shown in Tables 4 and 5. Of the 20 pregnant women, 1 reported severe swelling at the injection site and 2 reported feeling feverish (without documented fever) in the 2 weeks after Tdap; they recovered without treatment. Although statistical analysis was not performed on the ≥65 years of age and pregnant respondent groups because of their small sample sizes, inclusion of these groups in the non-inferiority analysis of those 18–64 years old and not pregnant did not change the results

3.4. Immediate and unsolicited adverse events

Two of 1286 survey respondents with data available about the prompted symptom of breathing difficulties reported wheezing immediately after vaccination. The first patient had a history of

Table 3
Non-inferiority comparison of rates of injection site reactions, subjective fever, and medical visits after Tdap vaccination among 18–64 year olds who reported being vaccinated <2 years after previous Td/TT vaccination and ≥2 years after Td/TT vaccination.

Solicited AE	2-Week surveys					Daily (days 3–7) surveys				
	Tdap < 2 years after Td $N = 97$		Tdap ≥ 2 years after Td $N = 578$		Δ(95% C.I.)	Tdap < 2 years after Td $N = 145$		Tdap ≥ 2 years after Td $N = 880$		Δ(95% C.I.)
	N_1[a]	%	N_2[a]	%		N_1[a]	%	N_2[a]	%	
Pain										
Any	84	67.9	520	73.5	−5.6 (−16.3–5.1)	143	82.5	852	80.2	2.4 (−4.4–9.1)
Moderate	84	10.7	520	15.8	−5.1 (−12.4–2.3)	143	14.0	852	17.8	−3.9 (−10.1–2.4)
Severe	84	0.0	520	0.8	−0.8 (−1.5–0.0)	143	2.8	852	0.8	2.0 (−0.8–4.8)
Moderate/severe[d]	84	10.7	520	16.5	−5.8 (−13.2–1.5)	143	16.8	852	18.7	−1.9 (−8.5–4.8)
Redness										
Any	81	23.5	504	19.6	**3.8 (−6.0–13.7)**[b]	135	25.2	797	25.1	0.1 (−7.8–8.0)
Moderate	81	2.5	504	2.4	0.9 (−3.5–3.7)	135	5.2	797	4.4	0.8 (−3.2–4.8)
Severe	81	3.7	504	4.6	0.9 (−5.4–3.6)	135	3.0	797	3.5	−0.6 (−3.7–2.6)
Moderate/severe	81	6.2	504	6.9	−0.8 (−6.5–4.9)	135	8.2	797	7.9	0.2 (−4.7–5.2)
Swelling										
Any	81	24.7	507	26.0	−1.3 (−11.5–8.8)	135	37.8	805	33.4	**4.4 (−4.4–13.2)**[b]
Moderate	81	6.2	507	4.5	1.6 (−3.9–7.2)	135	5.9	805	7.8	−1.9 (−6.3–2.5)
Severe	81	2.5	507	3.9	−1.5 (−5.3–2.3)	135	6.7	805	4.2	2.4 (−2.0–6.9)
Moderate/severe	81	8.6	507	8.5	0.2 (−6.4–6.7)	135	12.6	805	11.9	0.7 (−5.4–6.7)
Subjective fever[c]	83	9.6	499	10.0	−0.4 (−7.3–6.5)	138	15.2	823	11.4	**3.8 (−2.6–10.2)**[b]
Medical visit	89	3.4	528	2.5	0.9 (−3.1–4.9)	145	0.7	880	1.3	−0.0 (−5.0–1.5)

Refer to methods for definitions.
[a] Number with response data.
[b] Did not meet non-inferiority criteria.
[c] Of those reporting fever, 9 reported a measured temperature >100.4 F (38 °C) and 164 reported subjective fever ("feeling feverish").
[d] Moderate and severe were combined because these AEs may represent all clinically significant events.

Table 4
Rates of injection site reactions, subjective fever, and medical visits reported after Tdap vaccination among 20[a] pregnant respondents who reported being vaccinated ≥2 years after previous Td/TT vaccination.

Solicited AE	2-Week surveys $N=10$		Daily (days 3–7) surveys $N=14$	
	N_1[b]	%	N_1[b]	%
Pain				
Any	10	80.0	14	78.6
Moderate	10	10.0	14	7.1
Severe	10	0	14	0
Redness				
Any	10	30.0	13	30.8
Moderate	10	0	13	0
Severe	10	0	13	0
Swelling				
Any	10	10.0	13	30.8
Moderate	10	0	13	0
Severe	10	0	13	7.7
Subjective fever[c]	10	20.0	14	7.1
Medical visit	10	0	14	42.9

[a] Includes 4 people who responded to both surveys.
[b] Number with response data.
[c] All reported subjective fever.

reactive airways disease which by the patient's report was active at the time of vaccination. The day after vaccination, the patient saw a physician, was provided fexofenadine HCl, and recovered without sequelae. This patient had received previous Td/TT ≥2 years prior to current Tdap vaccination. The second respondent with breathing difficulties is described in the SAE section below.

One survey respondent who also reported receiving previous Td/TT ≥2 years prior reported the onset of angioedema 6 days after vaccination. This respondent reported having a history of anaphylaxis and allergic symptoms to multiple antigen triggers. The reported angioedema resolved without medication or medical attention.

Four of the 1278 with response to the specific survey prompt about skin events reported hives or rash. One of the four was prescribed an oral corticosteroid treatment and another was advised to take diphenhydramine. Two of these 4 survey respondents reporting hives or rash had received Td/TT ≥2 years prior to current Tdap vaccination; all four were <65 years old and not pregnant.

Table 5
Rates of injection site reactions, subjective fever, and medical visits reported after Tdap vaccination among 32[a] respondents ≥65 years of age who reported being vaccinated ≥2 years after previous Td/TT vaccination.

Solicited AE	2-Week surveys $N=22$		Daily (days 3–7) surveys $N=17$	
	N_1[b]	%	N_1[b]	%
Pain				
Any	20	35.0	16	56.3
Moderate	20	0	16	0
Severe	20	5.0	16	0
Redness				
Any	19	5.3	15	13.3
Moderate	19	5.3	15	0
Severe	19	0	15	13.3
Swelling				
Any	19	15.8	14	28.6
Moderate	19	0	14	0
Severe	19	0	14	0
Subjective fever[c]	21	0	16	6.3
Medical visit	22	0	17	29.4

[a] Includes 7 people who responded to both surveys.
[b] Number with response data.
[c] All reported subjective fever.

One of the 1272 respondents with available data about the survey prompt for "fainting" reported fainting that the patient attributed to Tdap, although it occurred several days after vaccination. The patient went to the emergency department, provided a history consistent with syncope after other vaccinations, was found to have a normal physical exam, and recovered with no specific treatment. Review of survey free text and the Occupational Medicine Clinic's log identified two medically attended unsolicited AEs. One vaccine recipient developed erythema around the vaccine site 2–3 days after vaccination (without fever or swelling) that was diagnosed as cellulitis, and was treated for seven days with cephalexin with resolution of the erythema. Another vaccine recipient experienced diffuse myalgias 1 day after vaccination, followed by headache that was consistent with previous migraine headaches, diarrhea and fatigue. She recovered with nonsteroidal anti-inflammatory treatment. Other reports which appeared mild or unrelated to vaccination included presumed viral infection with symptoms including sore throat, rhinorrhea, and/or fever (13), myalgias/arthralgias (4), headache (4), fatigue (4), and urinary tract infection (2).

3.5. Serious adverse events

Three SAEs were identified among HCP, all of whom reported Td/TT ≥2 years prior to current Tdap vaccination; none were pregnant or aged ≥65 years. One case of eosinophilic nephritis was confirmed in a 39-year-old patient who had a cadaveric renal transplant 7 years before vaccination. The patient was noted to have peripheral eosinophilia during a routine evaluation 2 days after vaccination. The patient experienced compromised renal function which was diagnosed as eosinophilic nephritis by kidney biopsy 4 weeks after vaccination. The patient recovered after a course of corticosteroids. One case of Guillain-Barré syndrome (GBS) was identified. This 37-year-old patient with no previous history of adverse events following vaccination noted bilateral symmetric ascending weakness 10 days after vaccination. Absent deep tendon reflexes were documented; the patient had electrophysiologic studies that were consistent with demyelination, and a diagnosis of GBS was made by a neurologist. By 6 weeks after onset, the patient had completely recovered.

The third patient with an SAE had wheezing immediately following vaccination; the patient was given one dose of epinephrine at the vaccination clinic and transported to the emergency department. She recovered without further treatment or sequelae.Table 6 summarizes these immediate, unsolicited and serious adverse events.

3.6. Pregnancy outcomes

Interviews with all vaccine recipients who reported possible or confirmed pregnancy confirmed 16 women were pregnant at the time of vaccination. Four, 8, and 4 women were in first, second and third trimesters, respectively. All 16 reported giving birth to full-term infants who had normal newborn evaluations

4. Discussion

In our Tdap safety assessment in adults, although rates of any injection-site redness (in the 2 week cohort) and any swelling (in the daily cohort) were higher after intervals of <2 years vs. ≥2 years, rates of moderate and/or severe injection site reactions were not higher in the <2 year vs. the ≥2 years group, among non-pregnant persons aged <65 years. Moreover, rates of moderate and/or severe injection site reactions were relatively low (<20%) in all groups and similar to results from pre-and post-licensure trials [5,6,15]. Our data suggest shorter intervals are generally safe.

Table 6
Immediate, unsolicited and severe adverse events and characteristics among those vaccinated with Tdap.

Event type	Description	Details	Interval from previous Td/TT	Outcome
Immediate	Wheezing	History of RAD[a], noted active wheezing at time of current Tdap vaccination	≥2 years before current Tdap	Treated with fexofenadine and recovered without sequelae
	Angioedema	Began 6 days after Tdap vaccination; history of anaphylaxis and allergies to multiple antigen triggers	≥2 years before current Tdap	No treatment; recovered without sequelae
	Syncope	Occurred several days after Tdap vaccination; history of syncope after other vaccinations	Unknown	Reported to ED[b]; recovered without specific treatment or sequelae
Unsolicited	Rash/hives	4 Persons reported	2 of these persons reported ≥2 years before current Tdap	One received corticosteroid and one received diphenhydramine
	Possible cellulitis	Developed erythema at vaccine site 2-3 days after vaccination; no fever or swelling	Unknown	Treated for 7 days with cephalexin and recovered without sequelae
	Myalgias, headache	Had onset of myalgias one day after Tdap vaccination, then headache (reported as consistent with previous migraines), diarrhea, and fatigue	Unknown	Took nonsteroidal anti-inflammatory agent and recovered without sequelae
Serious adverse	Wheezing	Immediate onset of wheezing after vaccination	≥2 years before current Tdap	Given epinephrine at vaccination clinic; transported to ED[b] where no additional treatment was given; recovered without sequelae
	Eosinophilic nephritis	History of cadaveric renal transplant 7 years prior to current Tdap. Asymptomatic peripheral eosinophilia noted 2 days after vaccination, and biopsy confirmed diagnosis 4 weeks after vaccination	≥2 years before current Tdap	Treated with corticosteroids and recovered without sequelae
	GBS[c]	Bilateral symmetric ascending weakness 10 days after Tdap vaccination; EPS[d] and neurologist confirm diagnosis	≥2 years before current Tdap	Hospitalization not requiring mechanical ventilation; complete recovery by 6 weeks

[a] RAD reactive airway disease.
[b] ED: emergency department.
[c] GBS. Guillain-Barré syndrome.
[d] EPS: electrophysiology study.

SAEs and immediate AEs after Tdap were rare in our study. One SAE was a case of GBS. Causal attribution of GBS to vaccination in this individual was not possible. GBS may be causally related to receipt of tetanus toxoid-containing vaccine [16]; however, a recent post-licensure analysis powered to detect a relative risk between 4 and 5 did not find an increased risk for GBS after Tdap [17].

Halperin et al. evaluated the safety of Tdap (ADACEL®) administered to 7001 preadolescents and adolescents at various intervals at least 2 years after previous Td/TT [6]. Eight cohorts were vaccinated at intervals ranging from 2 to 9 years since their last Td/TT, and each of these cohorts was compared with a control cohort of participants vaccinated 10 or more years after their last Td/TT. In non-inferiority analyses, AE rates in the cohort vaccinated with Tdap 2 years after their previous Td/TT were not greater than in the control cohort [6]. Our work in an adult population extends the findings of this study because we show that Tdap can be safety used at an interval <2 years after Td/TT.

Results of a recent randomized trial also suggest shorter intervals are safe in adults [18]. Beytout et al assessed the safety of a combination Tdap-inactivated poliovirus vaccine (IPV), administered 1 month after Td-IPV. The safety profiles were similar between 249 subjects receiving Tdap-IPV and 251 subjects receiving placebo injection [18]. In another recent study in the Vaccine Safety Datalink, the risk of medically attended local reactions in adolescents and young adults with varying patterns of receipt of diphtheria toxoid containing vaccines was low and did not differ with concomitant or sequential administration of diphtheria toxoid containing vaccines [19].

Tdap is not licensed or recommended for use in persons ≥65 years of age and it is not routinely recommended for pregnant women. Although the sample size was small, we found no unsolicited events and no SAEs in these groups. Compared to persons <65 years of age, we observed lower rates of most solicited injection-site AEs in the older adults. While this finding is generally consistent with the ADACEL® prelicensure trial [5], larger numbers of older persons would be needed to draw conclusions regarding Tdap reactogenicity in older persons. Among daily (but not 2-week) survey respondents, rates of reporting a medical visit after Tdap appeared to be higher for older persons (29.4%) and pregnant women (42.9%) than routine groups. It is not clear if the increased healthcare utilization reflects a reporting bias among those completing daily surveys, a higher baseline rate of medical visits among these groups, or if a true increase occurred.

This study is subject to several limitations. The study may have overestimated rates of AEs because HCP who experienced more severe reactions may have been more likely to respond to the survey. This study also relied on self-reported Td/TT vaccine history, taken as long as a week after vaccination for the daily survey, and a month for the 2-week survey. To demonstrate that these self-reports were accurate, in a subset of these survey respondents, we compared self-reports of whether previous Td/TT was < or ≥2 years ago against the medical record and found 93% of reports were accurate [20]. In addition, results may not be applicable to populations other than adult HCP, particularly to adolescents who have higher rates of reactogenicity than adults after Tdap vaccine [5]. In our descriptive assessment of Tdap reactogenicity in persons HCP ≥65 years no serious safety issues were identified.

In summary, we found that injection site AE rates in HCP vaccinated with Tdap who received Td/TT ≥2 years and <2 years earlier were similar and consistent with pre-licensure results. Our study findings add to the body of evidence [6,18] that a short interval between Td/TT and a single dose of Tdap in adults is safe. Ongoing monitoring for Tdap safety remains important, but these data

support the existing ACIP recommendation that HCP may safely receive Tdap at an interval shorter than 2 years from the last dose of Td/TT [1], which may be useful in outbreak settings.

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