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ORIGINAL ARTICLE

Randomized Controlled Trial of the Safety and Immunogenicity of Revaccination With Tetanus-Diphtheria-Acellular Pertussis Vaccine (Tdap) in Adults 10 Years After a Previous Dose

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Background. Reduced-antigen-content tetanus, diphtheria, and acellular pertussis (Tdap) vaccine is recommended in many countries for boosting immunity in adolescents and adults. Although immunity to these antigens wanes with time, currently available Tdap products are not labeled for repeat administration in the United States.

Methods. We performed an observer-blinded, randomized controlled trial in 1330 adults aged 18 to <65 years who received either the Tdap (n = 1002) or tetanus-diphtheria (Td) (n = 328) vaccine 8 to 12 years after a dose of Tdap vaccine administered previously. Solicited adverse events following immunization were documented for 7 days after vaccination, and serious adverse events and adverse events of medical significance were documented for 6 months after vaccination. Levels of antibodies against component vaccine antigens were measured before and 1 month after vaccination.

Results. A solicited adverse event was reported by 87.7% of Tdap and 88.0% of Td vaccine recipients. We found no significant differences in the rates of injection-site reactions, systemic reactions, or serious adverse events between the vaccine groups. A robust antibody response to each pertussis antigen in the Tdap-vaccinated group was found; postvaccination-to-prevaccination geometric mean antibody concentration ratios were 8:1 (pertussis toxoid), 5.9 (filamentous hemagglutinin), 6.4 (pertactin), and 5.2 (fimbriae 2 and 3). Postvaccination geometric mean concentrations of tetanus antibody (4.20 and 4.74 IU/mL, respectively) and diphtheria antibody (10.1 and 12.6 IU/mL, respectively) were similar in the Tdap and Td groups, and the rates of seroprotection against tetanus and diphtheria were >99% in both groups.

Conclusions. A second dose of Tdap vaccine in adults approximately 10 years after a previous dose was well tolerated and immunogenic. These data might facilitate consideration of providing Tdap booster doses to adults.

Keywords. booster; diphtheria; pertussis; Tdap; tetanus; tetanus, diphtheria, and acellular pertussis vaccine.

Pertussis vaccine has been a cornerstone of pediatric vaccination schedules for nearly 8 decades [1]. The World Health Organization (WHO) recommends that all children receive a primary series of pertussis vaccine during infancy and booster doses depending on local epidemiology and resources [2]. Although various immunization schedules are used, in North America, children receive pertussis vaccine at 2, 4, 6, and 15 to 18 months of age and a preschool dose at 4 to 6 years of age [3, 4]. An adolescent booster dose with a reduced-antigen formulation of tetanus, diphtheria, and acellular pertussis (Tdap) is given routinely in a number of jurisdictions [5, 6]. In North America, adults who have never received a Tdap vaccine are recommended to receive a single dose in place of the decennial tetanus-diphtheria (Td) booster [6, 7].

On the basis of antibody-persistence data [8–12] and modeling studies [13], protection after the adolescent or adult dose of Tdap vaccine was predicted to persist for up to 10 years. However, results of studies of pertussis outbreaks among adolescents suggested that the effectiveness of Tdap vaccine may wane more rapidly [14]. Several studies reported the safety and immunogenicity of a repeat dose of Tdap vaccine given after an interval of 5 or 10 years [15–18], which led to regulatory approval in Canada for repeated Tdap dosing in adults [19]. We performed a large

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clinical trial to compare the tolerability and immunogenicity of a repeat dose of Tdap vaccine to that of Td vaccine in adults previously immunized with Tdap vaccine to support regulatory approval of a repeat dose of Tdap in the United States.

METHODS

Study Design

This study was an observer-blinded, phase IV, randomized controlled clinical trial performed at 27 sites in the United States and 2 sites in Canada. Study visits took place between November 30, 2011, and February 17, 2016. Each participant provided written informed consent before every study procedure. The study was approved by the research ethics board at each site (ClinicalTrials.gov identifier NCT01439165).

Study Population

Healthy adults aged 18 to <65 years who had previously received a dose of Tdap vaccine (Adacel, Sanofi Pasteur, Swiftwater, Pennsylvania) in a prelicensure clinical trial in the United States or as part of a routine adolescent immunization program in Canada approximately 10 years (range, 8–12 years) earlier were eligible to participate in the study. The first participants were enrolled in the United States, and enrollment was expanded to Canada after no further eligible participants from the previous study cohort were available. Exclusions to participation were anyone who had received any tetanus-, diphtheria-, or pertussis-containing vaccine since receipt of the qualifying dose of Tdap vaccine 8 to 12 years earlier; was pregnant; was breastfeeding; was a woman of childbearing potential but not using an effective form of birth control or abstinence for 4 weeks before and after vaccination; had a chronic illness or medical condition that might interfere with participation in the trial; had a known or suspected congenital or acquired immunodeficiency; had physician-diagnosed or laboratory-confirmed pertussis in the previous 10 years; had a suspected hypersensitivity or previous severe reaction to a pertussis-, tetanus-, or diphtheria-containing vaccine; had received blood or blood-derived products in the previous 3 months; had received any vaccine within 30 days before receiving study vaccine (except for influenza vaccine, which was allowed up to 15 days before the study vaccine) or had plans to receive another vaccine before the second study visit; had participated in another interventional clinical trial; had reported seropositivity to human immunodeficiency virus (HIV), hepatitis B virus, or hepatitis C virus; had thrombocytopenia or a bleeding disorder that would be a contraindication for an intramuscular injection; had a history of Guillain-Barré syndrome; and/or had moderate or severe illness at the time of vaccination.

Study Vaccines

Each 0.5-mL dose of Tdap vaccine (Adacel) contained 5 limit of flocculation units (Lf) of tetanus toxoid, 2 Lf diphtheria toxoid, 2.5 μg pertussis toxoid (PT), 5 μg filamentous hemagglutinin (FHA), 3 μg pertactin (PRN), 5 μg fimbriae 2 and 3 (FIM), 1.5 mg aluminum phosphate, and 0.6% (vol/vol) 2-phenoxyethanol. The control vaccine was tetanus and diphtheria toxoids, adsorbed (Td) (TENIVAC, Sanofi Pasteur), which contained 5 Lf tetanus toxoid, 2 Lf diphtheria toxoid, 1.5 mg aluminum phosphate, and 0.5% (vol/vol) 2-phenoxyethanol per 0.5-mL dose. Both vaccines were supplied in single-dose glass vials. Concomitant vaccines were not administered in this study.

Study Procedures

At the first visit, after written informed consent was given, a medical history was obtained, a history-directed physical examination was performed, blood was collected via venipuncture for baseline testing, and, for female participants, a urine or serum pregnancy test was performed. Participants were allocated randomly via a central computerized system in a 3:1 ratio to receive Tdap or Td vaccine as an intramuscular injection in the deltoid muscle of the nondominant arm. Participants were observed for 20 minutes for immediate adverse events (AEs) and were instructed on the use of an AE diary card. Participants were contacted on day 8 (range, 8–10 days) postimmunization to remind them to bring their completed diary card to the follow-up visit on day 28 postimmunization (range, 26–35 days). During that visit, the diary cards were collected and reviewed, blood was collected for serology, and a serious AE (SAE) memory aid was provided to participants to record any important medical events in the ensuing months. A final study contact occurred via telephone on day 180 postimmunization (range, 180–210) to review the 6-month memory aid for any medical events of significance.

AE Monitoring

Temperature and solicited AEs were recorded daily by each participant on a diary card for 1 week after immunization; unsolicited AEs were collected until the follow-up serology visit 1 month after immunization. Solicited injection-site events were erythema, swelling, and pain. Systemic solicited AEs were fever, headache, malaise, and myalgia. AE severity was described as grade 1 (erythema or swelling measuring ≥25 to ≤50 mm, temperature of ≥38.0 to ≤38.4°C, and, for all other AEs, no interference with activity), grade 2 (erythema or swelling measuring ≥51 to ≤100 mm, temperature of ≥38.5 to ≤38.9°C, and, for all other AEs, some interference with activity), or grade 3 (erythema or swelling measuring >100 mm, temperature of ≥39°C, and, for all other AEs, prevention of daily activity). Medically attended AEs and SAEs were collected until the end of participation in the study after the 6-month telephone contact.

Immunogenicity

Sera collected on days 0 and 28 were assayed for antibodies against diphtheria and tetanus toxins and *Bordetella pertussis* antigens (PT, FHA, PRN, and FIM); all assays were performed in the laboratories of Sanofi Pasteur in Swiftwater, Pennsylvania, by technicians who were unaware of vaccine allocation. Tetanus antibodies

were measured by enzyme-linked immunosorbent assay (ELISA) and expressed in international units per milliliter (IU/mL) using the WHO human reference standard TE3; the lower limit of quantification (LLOQ) of the assay was 0.01 IU/mL. Diphtheria antibodies were measured by toxin microneutralization on Vero cells and expressed in international units per milliliter using the WHO international standard; the LLOQ was 0.005 IU/mL. Pertussis antibodies against PT, FHA, PRN, and FIM were measured by ELISA and expressed as ELISA units per milliliter (EU/mL) using a company reference serum standard; the LLOQ was 4 EU/mL for PT, PRN, and FIM antibodies and 3 EU/mL for FHA antibodies.

Statistical Analysis

The safety analysis was performed on all vaccinated participants according to the vaccine they actually received. The primary immunogenicity analysis was performed on the per-protocol data set, defined as participants who met the inclusion criteria, did not meet the exclusion criteria, received study vaccine according to the randomization schedule, received vaccine and had blood collected in the specified time windows, did not receive any protocol-restricted vaccines or medications, and had a valid result on serological testing. The primary immunogenicity analysis was also conducted using the full analysis data set, which comprised all participants who received study or control vaccine and had at least 1 serology result available. For solicited AEs and for unsolicited AEs and SAEs grouped according to the Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term, point estimates and 95% confidence intervals (CIs) of the AE rates were calculated using the normal approximation for quantitative data and exact binomial distribution for proportions. For immunogenicity data, geometric mean concentrations (GMCs) and 95% CIs were calculated for each antibody measured before and after immunization. For diphtheria and tetanus antibodies, frequencies and proportions (with 95% CIs) of participants with an antibody concentration of ≥0.01, ≥0.1, or ≥1.0 IU/mL before and after immunization were calculated. Rates of booster response (and their 95% CI), defined as at least a 2-fold increase in antibody level after vaccination when the prevaccination concentration was higher than a predefined cutoff value or at least a 4-fold increase after vaccination when the prevaccination concentration was at or less than the cutoff value, were calculated. Cutoff values, based on normative data from previous studies, were 2.7 IU/mL for tetanus, 2.56 IU/mL for diphtheria, 93 EU/mL for PT, 170 EU/mL for FHA, 115 EU/mL for PRN, and 285 EU/mL for FIM.

The hypotheses for the primary end points were that the proportion of participants who achieved a postvaccination tetanus antibody concentration of ≥0.1 IU/mL and booster response would be noninferior in Tdap vaccine recipients compared to Td recipients; the anti-pertussis antibody GMCs induced by Tdap vaccine would be noninferior to those induced by 3 (for FHA, PRN, and FIM) or 4 (for PT) doses of diphtheria, tetanus, acellular pertussis (DTaP) vaccine given to infants and toddlers in prelicensure clinical trials [20, 21]; and pertussis booster responses induced by revaccination with Tdap vaccine would be noninferior to expected booster responses derived from the use of Tdap vaccine in people aged 21 to <65 years in a pivotal prelicensure clinical trial [22]. Noninferiority of GMCs was declared if the lower bound of the 2-sided 95% CI of the ratio Tdap vaccine to comparator was >0.66, and noninferiority of the booster responses was declared if the lower bound of the 95% CI of the difference in proportions was greater than −10%.

The total planned sample size was 1332 participants (999 participants randomly assigned to receive Tdap vaccine and 333 to receive Td vaccine). Assuming a 5% drop-out rate before the day 28 visit, the planned evaluable sample size allowed a

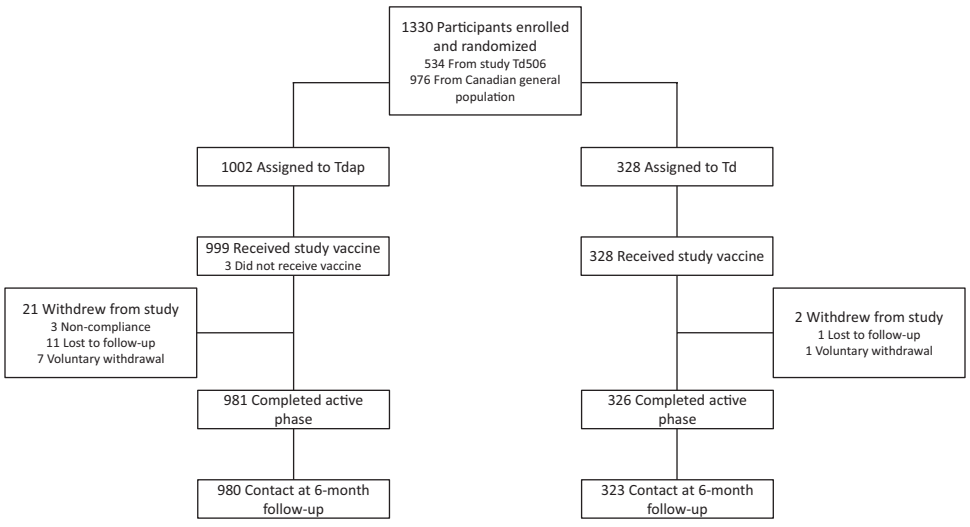

Figure 1. Flow of participants through the study. Abbreviations: Td, tetanus-diphtheria; Tdap, tetanus, diphtheria, and acellular pertussis.

Table 1. Summary of Participant Characteristics

Characteristic	Tdap (N = 1002)	Td (N = 328)
Sex (n [%])		
Male	356 (35.5)	116 (35.4)
Female	646 (64.5)	212 (64.6)
Age (mean [SD]) (y)	28.9 (10.0)	29.2 (10.6)
Age group (n [%])		
18 to <49 y	917 (91.5)	297 (90.5)
49 to <65 y	85 (8.5)	31 (9.5)
18 to <65 y	1002 (100.0)	328 (100.0)
Racial origin (n [%])		
Asian	6 (0.6)	3 (0.9)
Black or African American	23 (2.3)	8 (2.4)
White	956 (95.4)	310 (94.5)
American Indian or Alaska Native	1 (0.1)	2 (0.6)
Native Hawaiian or other Pacific Islander	1 (0.1)	0 (0.0)
Mixed origin	15 (1.5)	5 (1.5)
Ethnicity (n [%])		
Hispanic or Latino	10 (1.0)	3 (0.9)
Not Hispanic or Latino	992 (99.0)	325 (99.1)

Abbreviations: N, number of randomized participants; n, number of participants with the specified characteristic; SD, standard deviation; Td, tetanus-diphtheria; Tdap, tetanus, diphtheria, and acellular pertussis.

power of 90% to demonstrate the noninferiority for tetanus and diphtheria seroprotection (≥0.1 IU/mL) and booster response hypotheses and for the pertussis antibody GMC and booster response hypotheses.

RESULTS

Participant Flow

A total of 1330 participants were enrolled; 1002 were allocated randomly to receive Tdap vaccine and 328 to receive Td vaccine (Figure 1). A total of 999 (99.7%) of the Tdap group and 100% of the Td group were immunized. All but 21 (2.1%) of the Tdap group and 2 (0.6%) of the Td group completed the follow-up serology visit. Reasons for noncompletion included loss to follow-up (1.1% of the Tdap group and 0.3% of the Td group), noncompliance with the protocol (0.3% of the Tdap group), and voluntary withdrawal unrelated to an AE (0.7% of the Tdap group and 0.3% of the Td group) (Figure 1). A total of 980 (97.8%) participants in the Tdap group and 323 (98.5%) in the Td group completed the full 6-month follow-up. A total of 948 (94.6%) Tdap vaccine recipients and 317 (96.6%) Td vaccine

Table 2. Summary of Solicited Reactions Within 7 Days After Vaccination

	Tdap (N = 999)		Td (N = 328)	
Reaction	n/M	% (95% CI)	n/M	% (95% CI)
Solicited				
Any	912/982	92.9 (91.1–94.4)	302/325	92.9 (89.6–95.5)
Grade 3	87/982	8.9 (7.2–10.8)	29/325	8.9 (6.1–12.6)
Injection-site reaction				
Any	861/982	87.7 (85.5–89.7)	286/325	88.0 (84.0–91.3)
Grade 3	38/982	3.9 (2.8–5.3)	9/325	2.8 (1.3–5.2)
Pain				
Any	855/982	87.1 (84.8–89.1)	284/325	87.4 (83.3–90.8)
Grade 3	35/982	3.6 (2.5–4.9)	9/325	2.8 (1.3–5.2)
Erythema				
Any	63/982	6.4 (5.0–8.1)	18/325	5.5 (3.3–8.6)
Grade 3	2/982	0.2 (0.0–0.7)	0/325	0 (0.0–1.1)
Swelling				
Any	68/981	6.9 (5.4–8.7)	26/325	8.0 (5.3–11.5)
Grade 3	3/981	0.3 (0.1–0.9)	0/325	0 (0.0–1.1)
Systemic reaction				
Any	712/982	72.5 (69.6–75.3)	233/325	71.7 (66.5–76.5)
Grade 3	65/982	6.6 (5.1–8.4)	25/325	7.7 (5.0–11.1)
Fever				
Any	9/978	0.9 (0.4–1.7)	6/325	1.8 (0.7–4.0)
Grade 3	2/978	0.2 (0.0–0.7)	1/325	0.3 (0.0–1.7)
Headache				
Any	407/982	41.4 (38.3–44.6)	127/325	39.1 (33.7–44.6)
Grade 3	26/982	2.6 (1.7–3.9)	13/325	4.0 (2.1–6.7)
Malaise				
Any	327/982	33.3 (30.4–36.3)	100/325	30.8 (25.8–36.1)
Grade 3	29/982	3.0 (2.0–4.2)	12/325	3.7 (1.9–6.4)
Myalgia				
Any	571/982	58.1 (55.0–61.3)	189/325	58.2 (52.6–63.6)
Grade 3	29/982	3.0 (2.0–4.2)	10/325	3.1 (1.5–5.6)

Abbreviations: CI, confidence interval; N, number of participants analyzed according to the safety analysis set; M, number of participants with available data for the relevant end point; n, number of participants who experienced the end point; Td, tetanus-diphtheria; Tdap, tetanus, diphtheria, and acellular pertussis.

recipients were included in the per-protocol immunogenicity analysis; the most common reason for exclusion from the per-protocol analysis was not providing a postimmunization serology sample in the proper time window (24 [2.4%] Tdap vaccine recipients and 6 [1.8%] Td vaccine recipients).

Composition

The Tdap and Td groups were similar in their demographics (Table 1). Nearly two-thirds of the participants were women, and the mean participant ages were 28.9 years (Tdap group) and 29.2 years (Td group). More than 90% of both groups were between 18 and 49 years of age, and more than 94% of both groups were Caucasian.

Adverse Events

Rates of solicited AEs following immunization were similar in Tdap and Td vaccine recipients (Table 2). A total of 87.7% (95% CI, 85.5%–89.7%) of Tdap vaccine recipients and 88.0% (95% CI, 84.0%–91.3%) of Td vaccine recipients reported at least 1 injection-site reaction; a grade 3 reaction was reported by only 3.9% (95% CI, 2.8%–5.3%) of Tdap vaccine recipients and 2.8% (95% CI, 1.3%–5.2%) of Td vaccine recipients.

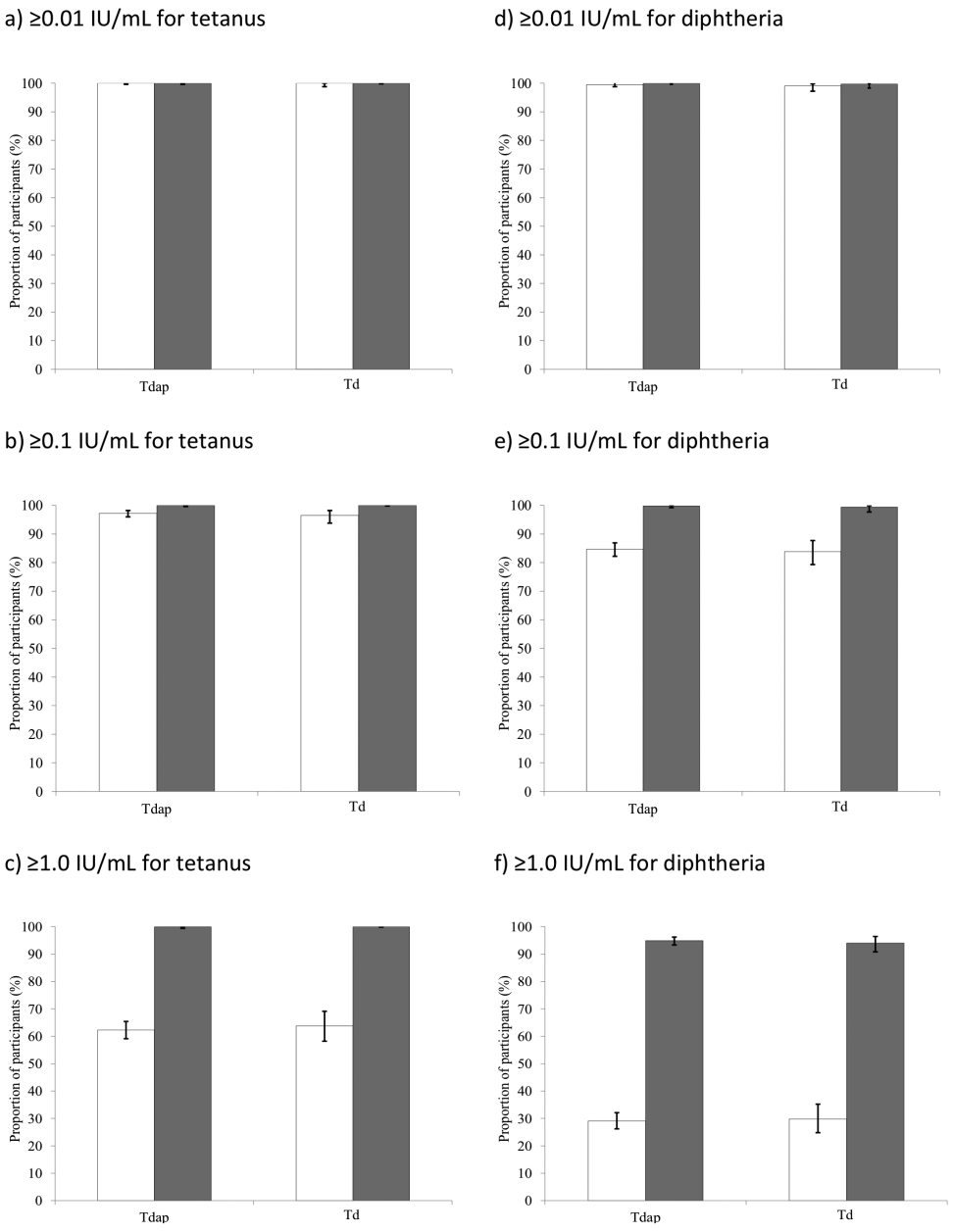

Figure 2. Proportion of participants who achieved an antibody concentration of ≥0.01 IU/mL (a), ≥0.1 IU/mL (b), or ≥1.0 IU/mL (c) for tetanus and ≥0.01 IU/mL (d), ≥0.1 IU/mL (e), or ≥1.0 IU/mL (f) for diphtheria. Error bars indicate 95% confidence intervals (per-protocol analysis set). White bars represent prevaccination data; gray bars represent postvaccination data. Abbreviations: Td, tetanus-diphtheria; Tdap, tetanus, diphtheria, and acellular pertussis.

Injection-site pain was the most common AE and was reported by 87.1% (95% CI, 84.8%–89.1%) of Tdap vaccine recipients and 87.4% (95% CI, 83.3%–90.8%) of Td vaccine recipients; only 3.6% (95% CI, 2.5%–4.9%) of Tdap vaccine recipients and 2.8% (95% CI, 1.3%–5.2%) of Td vaccine participants reported grade 3 injection-site pain. Systemic AEs were reported by 72.5% (95% CI, 69.6%–75.3%) of Tdap vaccine recipients and 71.7% (95% CI, 66.5%–76.5%) of Td vaccine recipients; grade 3 events were reported by 6.6% (95% CI, 5.1%–8.4%) and 7.7% (95% CI, 5.0%–11.1%), respectively. Myalgia was the most common systemic AE, reported by 58.1% (95% CI, 55.0%–61.3%) of Tdap vaccine recipients and 58.2% (95% CI, 52.6%–63.6%) of Td vaccine recipients. Fever was uncommon, reported by only 0.9% (95% CI, 0.4%–1.7%) of Tdap vaccine recipients and 1.8% (95% CI, 0.7%–4.0%) of Td vaccine recipients. Similar proportions of Tdap and Td vaccine recipients reported unsolicited AEs (26.2% and 25.9%, respectively); no apparent differences in the nature or frequency of any of the unsolicited AEs grouped according to the MedDRA system or preferred terms were found.

A total of 8 (0.8%) participants in the Tdap group and 1 (0.3%) participant in the Td group reported an SAE; none were considered vaccine related. A 23-year-old woman became pregnant approximately 12 days after her Tdap vaccination and experienced a spontaneous abortion 38 days after vaccination. The SAEs posttonsillectomy bleeding, mononucleosis and tonsillitis, breast neoplasm, abdominal pain, Crohn's disease, Pickwickian syndrome, and partial bowel obstruction (Tdap group) and a fractured arm (Td group) occurred 25 to 149 days after vaccination.

Immunogenicity

All participants achieved a protective level of tetanus antibody after vaccination (Figure 2b), and more than 99% of the participants in both groups achieved a protective level of diphtheria antibody (Figure 2e). Postvaccination GMCs in the Tdap vaccine recipients increased 5.2- to 8.1-fold over prevaccination GMCs and exceeded 100 EU/mL for each of the 4 pertussis antigens, whereas no increase from prevaccination levels in Td vaccine recipients occurred (Table 3). Anti-diphtheria GMCs were similar in the Td and Tdap groups; Td vaccine recipients achieved higher anti-tetanus GMCs than the Tdap vaccine recipients. Booster responses to the pertussis antigens in the Tdap group were 77.5% (95% CI, 74.6%–80.2%) for PT, 68.9% (95% CI, 65.8%–71.8%) for FHA, 65.3% (95% CI, 62.2%–68.3%) for PRN, and 56.8% (95% CI, 53.6%–60.0%) for FIM, and they were negligible in the Td group (Figure 3). Diphtheria antibody booster responses were similar in the Tdap group (83.2% [95% CI, 80.6–85.5%]) and Td group (84.1% [95% CI, 79.6%–88.0%]). Tetanus booster responses tended to be lower in the Tdap group (74.5% [95% CI, 71.6%–77.2%]) than in the Td group (81.6% [95% CI, 76.9–85.7%]).

Prespecified noninferiority was demonstrated for seroprotection levels against diphtheria and tetanus in recipients of Tdap vaccine compared to recipients of Td vaccine (Table 4). Noninferiority of booster response rates in the Tdap group

Table 3. Geometric Mean Concentrations

	Tdap (N = 948)		Td (N = 317)	
Vaccine and Time Point	M	GMC (95% CI)	M	GMC (95% CI)
Tetanus (IU/mL)				
Before vaccination	944	1.18 (1.10–1.27)	315	1.16 (1.02–1.31)
After vaccination	948	10.1 (9.59–10.6)	317	12.6 (11.5–13.7)
Diphtheria (IU/mL)				
Before vaccination	945	0.449 (0.411–0.491)	315	0.435 (0.371–0.511)
After vaccination	948	4.20 (3.93–4.48)	317	4.74 (4.18–5.38)
Pertussis toxin (EU/mL)				
Before vaccination	906	12.6 (11.6–13.6)	300	10.8 (9.36–12.4)
After vaccination	935	102 (94.9–110)	298	12.4 10.8–14.3)
Filamentous hemagglutinin (EU/mL)				
Before vaccination	945	35.4 (33.4–37.5)	315	34.1 (31.0–37.5)
After vaccination	948	209 (200–217)	317	35.1 (31.7–38.9)
Pertactin (EU/mL)				
Before vaccination	945	49.4 (45.5–53.8)	315	46.6 (40.3–53.9)
After vaccination	948	318 (302–334)	317	52.4 (45.3–60.8)
Fimbriae 2 and 3 (EU/mL)				
Before vaccination	945	143 (134–152)	315	136 (123–152)
After vaccination	948	745 (711–781)	317	154 (138–172)

Abbreviations: CI, confidence interval; EU, ELISA units; GMC, geometric mean concentration; N, number of participants analyzed according to the per-protocol analysis set; M, number of participants with available data for the end point; Td, tetanus-diphtheria; Tdap, tetanus, diphtheria, and acellular pertussis.

versus those in the Td group was demonstrated for diphtheria but not for tetanus. Noninferiority of pertussis GMCs in the Tdap group versus either 3 doses (for FHA, PRN, and FIM) or 4 doses (for PT) of DTaP vaccine in children was achieved for all 4 antigens. Noninferiority of pertussis antibody responses in Tdap vaccine recipients compared to those in a prespecified reference cohort from a prelicensure vaccine Tdap study was achieved for PT and FHA but not for PRN or FIM.

DISCUSSION

In this study, more than 1000 adults received a dose of Tdap vaccine approximately 10 years after their first dose. The second dose was well tolerated, and its safety profile was indistinguishable from that of control participants who were immunized with Td vaccine. High antibody responses to all vaccine component antigens were elicited. The results of this study are consistent with those of previous studies of this vaccine in which

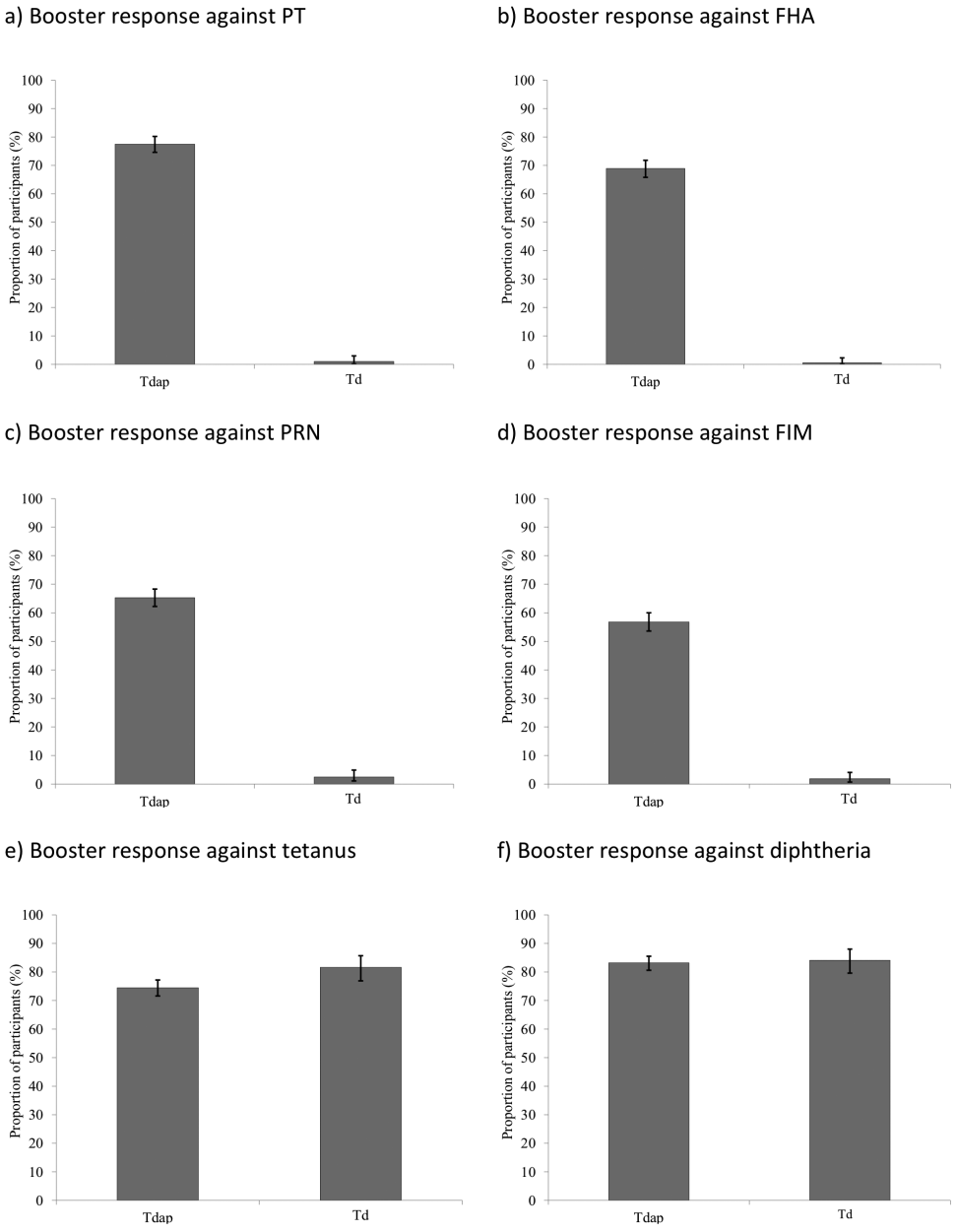

Figure 3. Proportion of participants who achieved a booster response against pertussis toxoid (PT) (a), filamentous hemagglutinin (FHA) (b), pertactin (PRN) (c), fimbriae 2 and 3 (FIM) (d), tetanus (e), and diphtheria (f). Error bars indicate 95% confidence intervals (per-protocol analysis set). Booster response was defined as at least a 2-fold increase after vaccination when the prevaccination concentration was higher than the cutoff value or at least a 4-fold increase after vaccination when the prevaccination concentration was at or less than the cutoff value. The cutoff values for the antigens and toxins were 93 EU/mL for PT, 170 EU/mL for FHA, 115 EU/mL for PRN, 285 EU/mL for FIM, 2.7 IU/mL for tetanus, and 2.56 IU/mL for diphtheria toxins. Abbreviations: Td, tetanus-diphtheria; Tdap, tetanus, diphtheria, and acellular pertussis.

second doses were given 5 years [16] and 10 years after the first dose [18]. In both of those studies, rates of headache, malaise (only collected in 1 study), myalgia, and injection-site pain were similar to those in our study; rates of injection-site erythema, swelling, and fever tended to be lower in our study. Antibody GMCs against the 4 pertussis antigens, diphtheria, and tetanus were remarkably similar in the 3 repeat-dosing studies.

Prespecified noninferiority thresholds for GMCs were met for all 4 pertussis antibodies, and prespecified seroprotection levels were met for diphtheria and tetanus antibodies. Noninferiority thresholds were met for booster responses to PT, FHA, and diphtheria but not PRN, FIM, or tetanus. Failure to meet the noninferiority criteria for booster responses might be attributable to decreased immunogenicity conferred by the vaccine antigens, high levels of preexisting antibody, and the predetermined antibody threshold criteria that were used; however, decreased immunogenicity is unlikely given the robust GMCs elicited against each of the antigens. Despite the noninferiority criterion for the booster response rate not being met, 100% of Tdap vaccine recipients achieved a seroprotective tetanus antibody concentration (≥0.1 IU/mL), and the Tdap vaccine induced a robust anti-tetanus GMC of 10.1 IU/mL, representing an 8.6-fold increase over the prevaccination GMC; therefore, the noninferiority comparison is unlikely to affect protection against tetanus. The prevaccination PRN and FIM antibody concentrations were higher in our study than those in the comparator study, but they were similar in the 2 studies for PT and FHA. The relatively high prevaccination antibody concentrations might have contributed to the participants' inability to mount a booster response to these antigens. The reasons for the higher prevaccination concentrations of antibodies to PRN and FIM are unknown but might be the result of natural boosting

Table 4. Summary of Noninferiority Comparisons for GMCs, Seroprotection, and Booster Response Rates for Pertussis Antigens and Tetanus and Diphtheria Toxins

	Comparison of GMCs for Pertussis Antigens: Tdap/Group 2[a]	
Antigen	GMC Ratio (95% CI)	Noninferiority Criteria Met[b]
PT (ELISA) (EU/mL)	1.04 (0.92 to 1.18)	Yes
FHA (ELISA) (EU/mL)	5.22 (4.51 to 6.05)	Yes
PRN (ELISA) (EU/mL)	2.94 (2.46 to 3.51)	Yes
FIM (ELISA) (EU/mL)	2.18 (1.84 to 2.60)	Yes
	Comparison of Booster Response Rates for Pertussis Antigens: Tdap Minus Expected Booster Response Rates Based on reference 22	
	Difference (% [95% CI])	Noninferiority Criteria Met[c]
PT (ELISA) (EU/mL)	16.12 (13.27 to 18.73)	Yes
FHA (ELISA) (EU/mL)	–4.21 (–7.23 to –1.34)	Yes
PRN (ELISA) (EU/mL)	–18.61 (–21.7 to –15.6)	No
FIM (ELISA) (EU/mL)	–19.07 (–22.3 to –16.0)	No
	Comparison of Seroprotection Rates for Tetanus and Diphtheria Toxins (% of Participants With an Antibody Concentration of ≥0.1 IU/mL): Tdap Minus Td	
	Difference (% [95% CI])	Noninferiority Criteria Met[d]
Tetanus toxin (ELISA) (IU/mL)	0.00 (–0.4 to 1.2)	Yes
Diphtheria toxin (TNA) (IU/mL)	0.42 (–0.3 to 2.1)	Yes
	Comparison of Booster Response Rates for Tetanus and Diphtheria Toxins: Tdap Minus Td	
Toxin	Difference (% [95% CI])	Noninferiority Criteria Met[d]
Tetanus toxin (ELISA) (IU/mL)	–7.12 (–12.0 to –1.7)	No
Diphtheria toxin (TNA) (IU/mL)	–0.95 (–5.4 to 4.0)	Yes

Abbreviations: CI, confidence interval; EU, ELISA units; FHA, filamentous hemagglutinin; FIM, fimbriae 2 and 3; GMC, geometric mean concentration; PRN, pertactin; PT, pertussis toxoid; Td, tetanus-diphtheria; Tdap, tetanus, diphtheria, and acellular pertussis; ELISA, enzyme-linked immunosorbent assay; TNA, toxin neutralization assay.

[a]Group 2: for PT GMCs, group 2 represents the group of participants in the M5A10 clinical trial who received 4 doses of DTaP [21]. For FHA, PRN, and FIM, group 2 represents the group of participants from the Sweden I clinical trial who received 3 doses of DTaP [20].

[b]Noninferiority was concluded if the lower limit of the 2-sided 95% CI of the ratio of GMCs between groups was >0.66 for each pertussis antigen.

[c]Noninferiority was concluded if the lower limit of the 2-sided 95% CI of the difference of booster response rates between participants receiving Tdap in the current study and expected booster response rates derived from participants aged 21 to <65 years in reference 22 was greater than –10% for each pertussis antigen.

[d]Noninferiority was concluded if the lower limit of the 2-sided 95% CI of the difference of seroprotection or booster response rates between groups was greater than –10% (or –5% if the booster response percentage of the Td group was >95%) for each tetanus or diphtheria toxin.

of these antibodies via exposure to pertussis or other species of *Bordetella* or other infectious agents such as *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* [23–25]. Although the booster response rates were lower than the prespecified thresholds derived from previous clinical trials with the same Tdap vaccine [22], the postvaccination GMCs met noninferiority testing and they were 2.9- and 2.2-fold higher, respectively, in the Tdap group than in prespecified historical DTaP controls [20, 21]. Also, in the current study, the Tdap vaccine induced 6.4- and 5.2-fold increases (postvaccination-to-prevaccination ratios) in PRN and FIM antibodies, respectively. On the basis of these results, it seems unlikely that the noninferiority comparison of booster response rates would affect clinical protection against pertussis.

Although this study is, to our knowledge, the largest clinical trial of revaccination with Tdap to date, it had several limitations. Participants recruited in the United States were those who had participated previously in a Tdap vaccine clinical trial and therefore might not be representative of the general population. This limitation was somewhat offset by our recruitment in Canada, where participants who had previously received the same brand of Tdap vaccine as part of the routine immunization schedule were recruited from the general population. Most important is that this study evaluated only repeat Tdap vaccination after an interval of approximately 10 years. At the time the study was designed and the interval selected, antibody persistence data and results of modeling studies had suggested that 10 years would be the optimal interval for Tdap boosters [8–13]. Studies of recent pertussis outbreaks among Tdap-vaccinated adolescents suggest more rapid waning of protection [14]. Although data exist to support the safety and tolerability of tetanus-, diphtheria-, and pertussis-containing vaccines administered at an interval as short as 1 month [26–29], data from direct evaluations of Tdap revaccination at intervals less than 4 to 5 years [16] are not yet available.

The results of this study provide additional data to support the use of booster doses of Tdap to maintain protection against pertussis in adults. Although the results provide reassurance about the safety and tolerability of and immunogenicity conferred by repeat Tdap booster doses, advisory committees still need to determine the optimal interval for booster doses by using data provided by routine pertussis surveillance and outbreak evaluations. Although the results of economic analyses have suggested that adult immunization with Tdap vaccine is cost-effective, those models have assumed an approximate duration of protection of 10 years [30, 31]. The cost-effectiveness of booster strategies with an interval of 3 to 4 years is not clear; more important is that the logistical ability to deliver such a program is questionable. In the United States, people who received their first Tdap vaccine dose as an adolescent are now approaching the age at which they are recommended to receive a decennial Td vaccine booster. Some providers might find it convenient or necessary (eg, because of the availability of vaccine or during an outbreak) to give such a booster as Tdap. Data from our trial would support this decision.

In summary, a booster dose of Tdap given approximately 10 years after a previous dose was well tolerated and immunogenic in and adults aged 18 to <65 years. These data provide additional support for the approval of a 10-year revaccination indication for Tdap vaccine if policy makers wish to introduce additional booster doses of Tdap vaccine for the control of pertussis among adults.

Notes

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