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Randomized study of immune responses to two Tdap vaccines among adolescents primed with DTaP and comparison with results among adolescents primed with DTwP

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ABSTRACT

Background: It has been reported that persons primed with acellular (DTaP) pertussis vaccines have reduced duration of pertussis protection compared with those primed with whole-cell (DTwP) vaccines. However, due to the rapid transition to acellular vaccines, studies attempting directly to compare protection among DTaP-primed vs DTwP-primed individuals are subject to confounding by age and other limitations of ecological studies. Using validated assay results and stored sera from multiple Tdap studies, we evaluated two licensed Tdap vaccines among DTaP-primed adolescents to allow comparison with results obtained in the same laboratory from earlier studies involving DTwP-primed adolescents.

Methods: Participants 11–12 years of age who had received exactly 5 doses of DTaP vaccine prior to 7 years of age were randomly assigned in 2012 to receive one of two licensed Tdap vaccines. Serum specimens obtained pre- and post-vaccination were assayed for responses to the vaccines. Current results were then compared to results obtained in the same laboratory from prior randomized Tdap studies conducted among adolescents primed with DTwP or DTaP.

Results: Both Tdap vaccines produced strong antibody responses to diphtheria and tetanus; responses to contained pertussis antigens were consistent with the differing levels of those antigens in each Tdap vaccine. However, postvaccination pertussis antibody responses were as much as 71% lower in these DTaP-primed adolescents compared with responses among DTwP-primed adolescents in a prior study of the same two Tdap vaccines. In contrast, results from the present study were similar to those seen in another study of Tdap among DTaP-primed adolescents.

Discussion: Taken together, these results from randomized clinical trials provide direct evidence of reduced antibody responses to both licensed Tdap vaccines among adolescents primed with DTaP vaccine, compared with adolescents primed with DTwP vaccine.

Clinical trial registry number: ClinicalTrials.gov, NCT01629589.

1. Introduction

The epidemiology of pertussis in the US has changed in recent years, with reports of increasing attack rates among children aged 7–10 years, reduced duration of protection following receipt of tetanus, reduced diphtheria, and acellular pertussis vaccine (Tdap) at early adolescence, and an apparent cohort effect consistent with the hypothesis that infants who initially received diphtheria, tetanus, and whole-cell pertussis vaccine (DTwP) have better duration of protection following childhood and adolescent pertussis vaccination than do those who received diphtheria, tetanus, and acellular pertussis vaccine (DTaP), with the strength of this effect related to the number of DTwP doses received prior to receipt of DTaP or Tdap vaccine [1–3]. Data from studies in mice and baboons appear to provide a possible immunological explanation for these observations [4,5]. However, there are DTwP-using countries that have also noted increases in pertussis attack rates and apparent cohort effects, and there are aP-using countries that have not observed these findings [6–8]. In jurisdictions that replace wP with aP vaccines, the transition typically is rapid and complete, making it

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difficult to exclude the possibility that these observations represent confounding, eg by age, or to conduct an experimental clinical trial directly comparing pertussis responses following Tdap among an otherwise homogenous population in which some were primed with DTaP, others with DTwP.

In order to extend the lower age indication for Adacel® vaccine (Tdap5, Sanofi Pasteur, Swiftwater, PA) from 11 to 10 years, we conducted a randomized prospective clinical trial (Marshall et al. [9], study Td519; see Table 1) that compared immune responses among persons aged 10 years vs 11 years. As expected, results in the 10-year-olds were similar to those in the 11-year-olds; but unexpectedly, pertussis antibody results in both groups were markedly lower than results from the pivotal Tdap5 US licensure study (Pichichero et al., study Td506 [10]) performed a decade earlier. We considered a number of possible explanations, including laboratory error; changes in the assay over time; changes in the manufacture or characteristics of the vaccine over time; a problem (eg, cold chain or manufacturing error) with the specific lot of vaccine used in study Td519; and changes in the study populations over time (including the fact that the licensure study population was DTwP-primed, whereas the Td519 population was entirely DTaP-primed). A thorough investigation failed to develop any evidence to support change or error in the assay or in the manufacturing of the vaccine as the cause of this change in antibody responses (see Table 2).

To further investigate these findings and to understand whether these observations were specific to Tdap5 vaccine or were similar for both Tdap vaccines licensed in the US, we took advantage of the fact that we had conducted a randomized study (Englund et al., study Td516 [11,12]) comparing Tdap5 with Boostrix® vaccine (Tdap3, GlaxoSmithKline, Research Triangle Park, NC) some years earlier, in which all participants had been primed with DTwP. The present study (study Td551) essentially repeats that prior study, but now among subjects primed with DTaP.

Table 1
Studies referenced in this report.

Study code PI and reference	Immunogenicity sample	Ages enrolled	Vaccination history[a]
Td506[b] Pichichero [10]	527 given Tdap5 516 given Td	11–17 y, enrolled Aug 2001 to Mar 2002	Only DTwP vaccine was available for the primary series; most would also have received DTwP for doses 4–5, but some may have received DTaP for those doses.
Td516 Englund [11,12]	305 given Tdap5 304 given Tdap3	11–18 y, enrolled May to Sep 2006	A few may have received DTaP during the primary series, but most would have received DTwP. Most would have been boosted with DTaP at doses 4–5.
Td519 Marshall [9]	613 age 10 y, 608 age 11 y All given Tdap5	10–11 y, enrolled Mar to Jun 2011	Receipt of DTwP unlikely; by 1999, 96% of US doses were DTaP [16].
Td551 Present study	196 given Tdap5 194 given Tdap3	11–12 y, enrolled Jun to Sep 2012	Receipt of DTwP unlikely; by 1999, 96% of US doses were DTaP [16].

DTaP = diphtheria-tetanus-acellular pertussis vaccine; DTwP = diphtheria-tetanus-whole-cell pertussis vaccine.
Note: all studies were conducted by Sanofi Pasteur and all sera were assayed (or, in the case of study Td506, re-assayed) by the Sanofi Pasteur Global Clinical Immunology laboratory.
[a] In the US, DTaP vaccine was first approved for the 4th and 5th doses in the vaccination series on December 17, 1991 and was first approved for the primary series on July 31, 1996.
[b] Showing only the adolescent subgroup for Td506.

Table 2
Td551 antibody responses, per-protocol analysis set.

	Tdap5 (N = 196)	Tdap3 (N = 194)
	Geometric mean concentrations of antibodies (95% CI)	
Anti-PT		
Pre-dose	5.6 (4.7, 6.7)	5.7 (4.7, 6.9)
Post-dose	31.0 (27.0, 35.7)	44.1 (39.0, 49.9)
Anti-FHA		
Pre-dose	22.7 (19.0, 27.2)	22.7 (19.4, 26.6)
Post-dose	255 (228, 286)	318 (292, 347)
Anti-PRN		
Pre-dose	12.3 (10.5, 14.4)	10.3 (9.0, 11.9)
Post-dose	263 (223, 310)	252 (214, 295)
Anti-FIM		
Pre-dose	6.0 (4.9, 7.2)	6.6 (5.3, 8.0)
Post-dose	346 (269, 446)	11.1 (8.8, 14.0)

	Seroprotection: Number and (%) seroprotected			
	Tetanus	Diphtheria	Tetanus	Diphtheria
Pre-dose				
≥0.1 IU/mL	172 (87.8)	135 (68.9)	177 (91.2)	139 (71.7)
≥1.0 IU/mL	33 (16.8)	28 (14.3)	48 (24.7)	26 (13.4)
Post-dose				
≥0.1 IU/mL	196 (1 0 0)	196 (1 0 0)	194 (1 0 0)	194 (1 0 0)
≥1.0 IU/mL	195 (99.5)	183 (93.4)	194 (1 0 0)	186 (95.9)
Booster response	194 (99.9)	189 (96.4)	191 (98.5)	188 (96.9)

PT, pertussis toxoid; FHA, filamentous hemagglutinin; PRN, pertactin; FIM, fimbriae types 2 and 3.

2. Methods

2.1. Study design

This phase IV, open-label, randomized, multicenter study was conducted in the US in accordance with the Declaration of Helsinki and Good Clinical Practice, as defined by the International Conference on Harmonization. The study protocol was approved by the institutional review boards at all study sites. Parents or legal representatives provided written informed consent prior to initiation of any study-related procedures. This study was registered under identifier NCT01629589 at ClinicalTrials.gov.

Participants were enrolled at 8 participating pediatric practices located across the US during June to September 2012 and were randomly assigned in a 1:1 ratio to receive either Tdap5 vaccine or Tdap3. Vaccine was administered intramuscularly into the deltoid at visit 1. Participants provided blood samples for immunogenicity assessments pre-vaccination at visit 1 and at visit 2 (26–35 days post-vaccination).

2.2. Participants

Eligible participants were 11 to <13 years of age at the time of vaccination and had received exactly 5 doses of pertussis-containing vaccine at <7 years of age. Adolescents were excluded from participating in the study if they had: immunodeficiency; receipt of immunosuppressive therapy or radiation therapy within the preceding 6 months; long-term systemic corticosteroid therapy for >2 consecutive weeks within the previous 3 months; prior receipt of any whole-cell pertussis-containing vaccine; confirmed pertussis disease within the past 2 years; previous severe reaction to pertussis, diphtheria, or tetanus vaccine; receipt of immune globulins, blood, or blood-derived products in the past 3 months; hypersensitivity to any vaccine components; receipt of any vaccine within 30 days before receiving study vaccine (except that influenza vaccine was allowed between 30 and 15 days before receiving study vaccine) or planned to receive another vaccine before visit 2; seropositivity for human immunodeficiency virus, hepatitis B virus, or hepatitis C virus; thrombocytopenia, bleeding disorders, or receipt of anticoagulants within 3 weeks prior to vaccination; history of Guillain-Barré syndrome; or history of chronic illness that could interfere with trial conduct or completion. In the event of acute febrile illness or moderate or severe acute illness or infection at the intended time of vaccination, investigators could postpone vaccination until illness had resolved.

2.3. Vaccines

Each 0.5-mL dose of Tdap5 vaccine (Lot C4169AA) contained tetanus toxoid (5 Lf), diphtheria toxoid (2 Lf), pertussis toxoid (PT; 2.5 μg), filamentous hemagglutinin (FHA; 5 μg), pertactin (PRN; 3 μg), fimbriae types 2 and 3 (FIM; 5 μg), aluminum phosphate adjuvant (1.5 mg), and 2-phenoxyethanol (0.6%) formulated in sodium phosphate-buffered isotonic sodium chloride solution. Each 0.5-mL dose of Tdap3 vaccine (Lot AC52B080AA) contained tetanus toxoid (5 Lf), diphtheria toxoid (2.5 Lf), PT (8 μg), FHA (8 μg), PRN (2.5 μg), aluminum hydroxide adjuvant (≤0.39 mg), residual formaldehyde (≤100 μg), polysorbate 80 (≤100 μg), and sodium chloride (4.5 mg). Vaccines were injected in the deltoid muscle using 1″ needles.

2.4. Serology

Serum specimens were collected immediately prevaccination and 26–35 days post-vaccination. All serological testing was conducted by Global Clinical Immunology laboratory (GCI; Sanofi Pasteur, Swiftwater, PA) using methods as previously described [9]. Laboratory personnel were blinded to vaccine allocation.

In brief, antibodies to diphtheria toxoid were measured by the ability of test sera to protect Vero cells from diphtheria toxin challenge (seroneutralization assay); antibodies to tetanus toxoid, PT, FHA, PRN, and FIM were measured by enzyme-linked immunosorbent assay (ELISA).

2.5. Reactogenicity and safety

Participants were monitored for 15 min after vaccination for immediate reactions. From visit 1 through visit 2, participants' parents or legal representatives recorded the onset and grade of unsolicited adverse events (AEs), serious AEs (SAEs), and unsolicited adverse reactions (ARs). AEs were classified as grade 1 (no interference with activity), grade 2 (some interference with activity), or grade 3 (prevented normal daily activity). AEs were described using the Medical Dictionary for Regulatory Activities (MedDRA) version 14.0.

2.6. Statistical considerations

A sample size of 400 participants (200 per group) was planned for this descriptive study in order to provide at least 90% power to test the equality of mean postvaccination pertussis antibody levels versus prior studies Td516 and Td519. To allow 5% loss, targeted enrollment was 210 per group. Randomization used scratch-off randomization lists prepared by Sanofi Pasteur Biostatistics, which were generated using a block permutation method designed to ensure approximately equal numbers of subjects in each vaccine group overall and per site. In addition, the randomization and stratification ensured that no more than 2/3 of study subjects were male or female overall and per site. Statistical analyses (including comparisons to results of prior studies) were performed using SAS® software version 9.1 (SAS Institute, Cary, NC, USA). No formal hypothesis testing was performed.

The safety analysis set included all participants who received vaccination and safety was analyzed according to the vaccine actually received. The full analysis set included all participants who had a valid post-vaccination serology result. The per-protocol analysis set included all participants who met protocol-specified criteria, were vaccinated, and had valid pre- and post-vaccination serology results. The immunogenicity analyses were performed on the per-protocol analysis set and were confirmed on the full analysis set.

Tetanus and diphtheria immunogenicities were evaluated using frequencies and proportions of pre- and post-vaccination antibody concentrations ≥0.1 IU/mL and ≥1.0 IU/mL; pre- and post-vaccination geometric mean concentrations (GMCs) of antibodies; and booster response rates for each vaccine group. For Tdap5 recipients, booster response was defined as a 4-fold increase in pre- to post-vaccination antibody concentrations for participants with a pre-vaccination concentration ≤2.56 IU/mL for diphtheria and ≤2.7 IU/mL for tetanus, and defined as a 2-fold increase for participants with a pre-vaccination concentration >2.56 IU/mL for diphtheria and >2.7 IU/mL for tetanus. For Tdap3 recipients, booster response was defined as a post-vaccination concentration >4 times the lower limit of quantitation (LLOQ) for participants with a pre-vaccination concentration <LLOQ, a post-vaccination concentration >4 times the pre-vaccination concentration for participants with a pre-vaccination concentration between LLOQ and 4 times the LLOQ, or a post-vaccination concentration at least twice the pre-vaccination concentration for participants with a pre-vaccination concentration >4 times the LLOQ. Booster response rate definitions were based on those used in prior studies of each vaccine, as reported in the respective Prescribing Information.

Immunogenicity of pertussis was assessed using pre- and post-vaccination GMCs of antibodies to PT, FHA, PRN, and FIM among participants in each vaccine group.

3. Results

3.1. Participants

Of 423 adolescents enrolled in the study (Fig. 1), 212 were assigned to the Tdap5 arm (one of whom erroneously received Tdap3 vaccine and was included in that group in the safety analysis set) and 211 to the Tdap3 arm (one of whom did not receive vaccine). Demographic characteristics were similar between the Tdap5 and Tdap3 groups: 50.1% of the participants were male, mean age was 11.6 (standard deviation [SD], 0.5) years, and 81.2% were white (Supplementary Table 1). Of the 422 participants who received a vaccination, all were included in the safety analysis set, 421 (99.5%) were included in the full analysis set, and 390 (92.2%) were included in the per-protocol analysis set (196 in the Tdap5 group and 194 in the Tdap3 group). Fourteen participants discontinued the study: 5 withdrew (none due to adverse events), 3 were lost to follow-up, and 6 had protocol violations (Fig. 1).

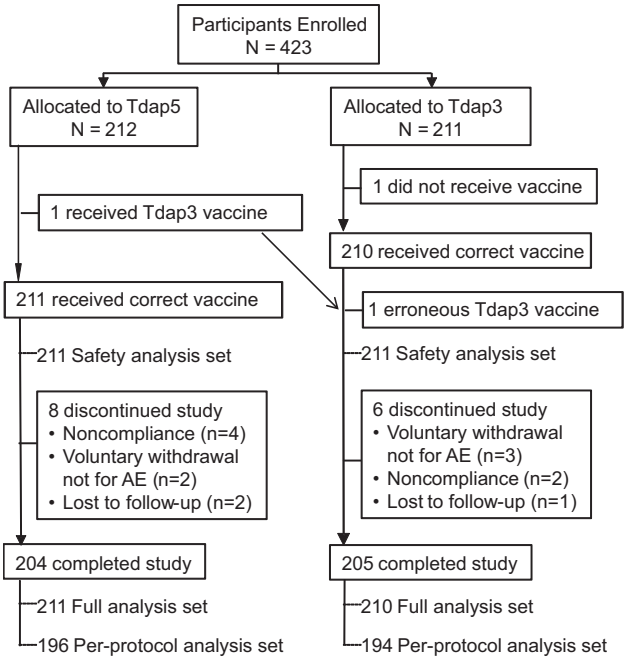

Fig. 1. Participant disposition.

3.2. Reactogenicity and safety

Two participants in the Tdap5 arm experienced an immediate reaction: 1 participant with nausea and 1 participant with headache. Overall, 209 participants (99 Tdap5 and 110 Tdap3) reported unsolicited AEs and 107 participants (49 Tdap5 and 58 Tdap3) reported an AR during the study (Supplementary Table 2). No SAEs were reported. The most commonly reported unsolicited AEs were headache (10.0% of Tdap5 recipients; 14.7% of Tdap3 recipients) and oropharyngeal pain (5.2% Tdap5; 1.9% Tdap3). The most commonly reported unsolicited AR was injection site pain (16.1% Tdap5; 20.4% Tdap3). Most AEs and ARs occurred within the first 3 days after vaccination and were grade 1 or grade 2 in intensity.

3.3. Immunogenicity

Pre-vaccination antibody measures were similar between the two groups (Table 3). The proportions of participants with tetanus and diphtheria post-vaccination antibody levels $\geq$0.1 IU/mL and $\geq$1.0 IU/mL were nearly 100% in both study groups. Tetanus and diphtheria booster response rates ranged from 96.4% to 99.9%.

Responses to contained pertussis antigens were consistent with the differing levels of those antigens in each Tdap vaccine. Post-vaccination GMCs for PT and FHA were higher in the Tdap3 arm; post-vaccination GMCs for PRN were similar in the two arms; and postvaccination GMCs for FIM were higher in the Tdap5 arm.

4. Discussion

The study found that the rates and severities of adverse events following vaccination were similar for Tdap5 and Tdap3 and were consistent with prior studies. Immune responses to the two vaccines differed as expected based on their differing formulations. However, comparison of the present pertussis antibody responses with those obtained in prior studies revealed important similarities and differences.

Direct comparisons of more recent Tdap vaccine clinical trial results with those obtained when the study populations were DTwP-primed are not necessarily reliable, as changes over time in vaccine manufacturing, laboratory assays, population characteristics, or pertussis transmission rates cannot be excluded. However, characteristics of the studies listed in Table 1 may mitigate these concerns: all were randomized experimental studies conducted by Sanofi Pasteur using similar procedures (including time of sera collection), and sera from all were assayed by a single laboratory (GCI) employing consistent, FDA-accepted assays. Moreover, when it was noted that study Td519 produced results materially lower than those seen in the earlier studies Td506 and

Table 3
Post-vaccination geometric mean concentrations (EU/mL) of antibodies for pertussis antigens present in both Tdap5 and Tdap3 for the indicated studies (per-protocol analysis sets). See Table 1 for overview of the studies.

Antibody (EU/mL)	Tdap5 (95% CI)					Tdap3 (95% CI)		
	Td506 N = 527[a]	Td516 N = 301-305[b]	Td519 N = 1221	Td551 N = 196	Td551/ Td516 Ratio	Td516 N = 304	Td551 N = 194	Td551/ Td516 Ratio
Priming vaccine	DTwP	DTwP	DTaP	DTaP		DTwP	DTaP	
Anti-PT	135[c] (125–146)	86.7 (78.8, 95.4)	31.0 (29.4, 32.8)	31.0 (27.0, 35.7)	0.35 (0.30, 0.40)	136 (123, 150)	44.1 (39.0, 49.9)	0.32 (0.28, 0.38)
Anti-FHA	215 (200–230)	241 (218, 266)	228 (218, 239)	255 (228, 286)	1.06 (0.91, 1.24)	403 (366, 444)	318 (292, 347)	0.79 (0.69, 0.91)
Anti-PRN	345 (313–379)	323 (280, 372)	454 (428, 482)	263 (223, 310)	0.80 (0.64, 1.00)	463 (395, 543)	252 (214, 295)	0.55 (0.43, 0.69)

PT, pertussis toxoid; FHA, filamentous hemagglutinin; PRN, pertactin.
[a] Showing only the adolescent Tdap5 group from study Td506, which also included adults 18–64 years.
[b] Varies by antigen. Based on re-analysis of Td516 conducted in 2016.
[c] Anti-PT results shown are from a reassay of 482 original specimens with sufficient remaining sera, conducted in 2007 following introduction of a more purified PT coating antigen. All subsequent studies (including Td516, Td519, and Td551) were assayed using the new coating antigen.

Td516, sera from all 3 studies were reassayed in parallel (data not shown). Results were consistent with prior results for each study and confirmed that the assays were stable over time. In addition, a manufacturing investigation conducted at that time failed to identify any evidence of variation in process, materials, control and release test data, or stability data that might explain the lower results in study Td519 compared with studies Td506 or Td516. Accordingly, Study Td551 was conducted to evaluate whether the difference in priming vaccine (DTwP vs DTaP) might explain the substantial difference in antibody responses in study Td519 versus the earlier studies.

Table 3 shows post-vaccination antibody concentrations from the present study versus prior studies (see Table 1 for descriptions of prior studies). The first comparison is to study Td516 (Englund et al. [11,12]), which was conducted 6 years earlier and also compared Tdap5 and Tdap3. For both Tdap vaccines, the anti-PT GMTs were only one third as high in the present study (whose subjects were DTaP-primed) compared with the earlier study (whose subjects were primed with DTwP): 35% as high (95% CI, 30%–40%) for Tdap5 recipients and 32% as high (95% CI, 28%–38%) for Tdap3 recipients. Anti-PRN responses were also reduced, although not so markedly, among the present study cohorts as compared with the DTwP-primed cohorts from the earlier study: 80% as high (95% CI, 64%–100%) for Tdap5 recipients and 55% as high (95% CI, 43%–69%) for Tdap3 recipients. In contrast, the anti-FHA results were not markedly different in the two studies (6% higher for Tdap5 recipients and 21% lower for Tdap3 recipients).

We can also compare the results for the present Tdap5 group with those from study Td519 (Marshall et al. [9]), conducted a year earlier in the same age cohort to support a Tdap5 license extension application. As shown in Table 3, results for anti-PT and anti-FHA are similar in these two recent studies, in which all subjects were primed with DTaP.

Of particular interest is the fact that the ratios of antibodies in the DTaP-primed (present study) to DTwP-primed (study Td516) cohorts showed generally similar patterns for the two vaccines (Tdap5 and Tdap3), suggesting strongly that the effect of priming vaccine (DTwP vs DTaP) on response to subsequent Tdap is not specific to a single Tdap, but rather a class effect, likely related to the known differences in cellular immune responses to acellular vs whole-cell pertussis vaccines [13]. Priming with whole-cell pertussis vaccine produces a largely Th1/Th17 response, whereas priming with acellular pertussis vaccine results in a Th2-dominant response [13,14]. Van der Lee et al. compared humoral and cellular immune responses to Tdap among pre-adolescents primed with DTaP or DTwP and found lower vaccine antigen-specific humoral, B-cell, and Th1 cell responses in aP-primed compared with wP-primed children [14]. Their wP-primed study participants were born during the period 1997–2003, prior to the Dutch switch from DTwP to DTaP in 2005, whereas their aP-primed participants were born in 2007 or later [15]. Their participants all received a single brand of wP or aP vaccine during infancy and then vaccines from that same aP manufacturer for their school-entry and adolescent aP boosters; none of these vaccines were available in the US. In contrast, our study participants received a variety of US-licensed wP or aP vaccines during childhood and were randomized to receive one of the two licensed Tdap vaccines. Our findings thus reinforce and extend those of van der Lee et al. by evaluating the effects of both licensed Tdap vaccines among persons who received a variety of aP and wP vaccines, all of which were different from those received by their study participants.

A limitation of our study was that it did not measure cellular immune responses; such measurements also were not available for any of the other studies in Table 1. Although it is clear that cellular immune responses are important in determining protection from pertussis, particularly over the long term, they are not used by any regulatory agency for licensure of pertussis vaccines, probably because no correlate of protection has been defined. It is often said that there is no pertussis antibody correlate of protection, but that concept is widely misunderstood. In fact, all regulatory agencies base licensure of follow-on pertussis vaccines (eg, Tdap or multicomponent combination vaccines) on demonstration of non-inferiority of antibody compared with results obtained in an effectiveness trial, and it has been shown that for a specific pertussis vaccine formulation, antibody levels do predict protection [16,17]. However, it is true that knowledge of protective antibody levels for one pertussis vaccine does not allow prediction of protection for an unrelated pertussis vaccine.

Precision of our estimates of mean pertussis antibody levels was limited by the sample sizes of each study, but we believe it to be adequate for the purposes. Potential confounders for the comparisons across studies might include the differing age ranges enrolled to each study (but this should not affect the comparison across vaccines), potential differences in community exposures to *Bordetella pertussis* across the studies, and variability over time in assays or products (but, as described, these were searched for and not found). In addition, the standardized interval between vaccination and measurement of post-immunization antibody levels (26–35 days in every study) does not permit evaluation of the possibility of differential waning of antibody levels over time.

In conclusion, we believe that the present study, taken together with the results from prior randomized clinical trials conducted by the same sponsor and assayed in the same laboratory using consistent and validated assays, provides direct evidence of reduced antibody responses to the two licensed Tdap vaccines among persons primed with DTaP vaccine, compared with persons primed with DTwP vaccine.

Declaration of Competing Interest

All authors were employees of Sanofi Pasteur at the time of the study; Dr. Decker has since retired. All authors participated in the conception, design, oversight, analysis, and reporting of the study; wrote or revised the manuscript; approve of the final manuscript; and attest they meet the ICMJE criteria for authorship.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2019.07.015.

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