Safety and Immunogenicity of Tetanus-Diphtheria-Acellular Pertussis Vaccine Administered to Children 10 or 11 Years of Age

Gary S. Marshall,a Vitali Pool,b David P. Greenberg,b,c David R. Johnson,b Xiaohua Sheng,d Michael D. Deckerab

University of Louisville School of Medicine, Louisville, Kentucky, USAa; Medical Affairs, Sanofi Pasteur, Swiftwater, Pennsylvania, USA; Department of Pediatrics, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA; Clinical Department, Sanofi Pasteur, Swiftwater, Pennsylvania, USA; Department of Health Policy, Vanderbilt University School of Medicine, Nashville, Tennessee, USA

Boosting immunity to tetanus, diphtheria, and pertussis through the use of Tdap vaccines is routinely recommended at 11 to 12 years of age; some states, however, require Tdap for entry into middle school, which may begin at 10 years of age. This study was conducted to determine whether Tdap5 (Adacel), which is licensed for use in children beginning at 11 years of age, is as safe and immunogenic in 10-year-olds as it is in 11-year-olds. Children who had received 5 previous doses of any diphtheria-tetanus-acellular pertussis (DTaP) vaccine were enrolled in a phase IV clinical trial; 646 10-year-olds and 645 11-year-olds completed the study, which involved a single intramuscular dose of Tdap5 along with pre- and postvaccination serologies. Postvaccination geometric mean concentrations (GMCs) of antibody to pertussis antigens (pertussis toxoid, filamentous hemagglutinin, pertactin, and fimbria types 2 and 3) of 10-year-olds were noninferior to those of 11-year-olds, as were booster response rates for all pertussis antibodies, except for those to fimbrial antigens (94% and 97%, respectively). Seroprotection rates among 10-year-olds for tetanus and diphtheria were noninferior to those in 11-year-olds. Rates of injection site reactions, solicited systemic reactions, and unsolicited adverse events, adverse reactions, and serious adverse events were similar in the two groups. These data support the conclusion that Tdap5 is safe and immunogenic in 10-year-olds. (This study has been registered at ClinicalTrials.gov under registration no. NCT01311557.)

Tetanus-diphtheria-acellular pertussis vaccine (Tdap) is used to boost immunity against the respective diseases in adolescents and adults. The Advisory Committee on Immunization Practices recommends that all adolescents 11 through 18 years of age receive a single dose of Tdap, with preferred vaccination at 11 through 12 years of age (1). Several U.S. states have instituted a requirement that children receive Tdap before entering 6th grade or middle school; some of these students are 10 years of age at school entry. Adacel, a Tdap that contains 5 pertussis antigens (Tdap5; Sanofi Pasteur, Swiftwater, PA), is indicated in the United States for persons 11 through 64 years of age and thus cannot be used on-label for some children entering middle school. This study was conducted to evaluate the safety and immunogenicity of Tdap5 in 10-year-olds.

MATERIALS AND METHODS

Study design. This was a phase IV, open-label, two-arm clinical trial performed at 36 sites in the United States from March through June 2011 (study Td519; ClinicalTrials.gov registration no. NCT01311557). The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice, as defined by the International Conference on Harmonisation (http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/EP6/EP6_R1_Guideline.pdf), and the protocol was approved by the appropriate institutional review board at each site. Parents or legal representatives provided written informed consent, and the participants provided written informed assent prior to the initiation of study-specific procedures.

Participants had a blood sample obtained on visit 1 and then received a single dose of Tdap5. A second blood sample was obtained at visit 2, 25 to 35 days later. Solicited adverse events (AEs) were collected for 7 days postvaccination, and unsolicited and serious adverse events (SAEs) were collected up to visit 2 (see “Reactogenicity and safety” below).

Participants. Children 10 and 11 years of age who had received 5 previous doses of any diphtheria–tetanus–acellular pertussis (DTaP) vaccine (3 doses in the first year of life, a fourth dose in the second year of life, and a fifth dose at 4 through 6 years of age) were eligible to participate in the study. Exclusion criteria included the following: primary or acquired immunodeficiency states; receipt of pertussis-, diphtheria-, or tetanus-containing vaccines within the preceding 5 years; confirmed pertussis disease within the past 2 years; history of serious reaction to previous doses of diphtheria-, tetanus-, or pertussis-containing vaccines; receipt of blood products in the past 3 months; receipt of any vaccine in the 30 days prior to receiving the study vaccine or planned receipt of any other vaccine before visit 2 (influenza vaccine was allowed between 30 and 15 days prior to receipt of the study vaccine); history of HIV, hepatitis B virus, or hepatitis C virus infection; thrombocytopenia, bleeding disorder, or receipt of anticoagulants within 3 weeks prior to vaccination; pregnancy; history of Guillain–Barre syndrome; and moderate or severe acute febrile illness on the day of vaccination.

An interactive voice response system was used to ensure that equal numbers of 10-year-olds (group 1; from the 10th birthday to the day before the 11th birthday) and 11-year-olds (group 2; from the 11th birthday to the day before the 12th birthday), as well as equal numbers of boys and girls, were enrolled at each site.

Vaccine. Tdap5 was administered intramuscularly into the deltoid muscle at visit 1. Each 0.5-ml dose, supplied in prefilled syringes, contained 5 limit of flocculation units (Lf) tetanus toxoid, 2 Lf diphtheria toxoid, 2.5 μg detoxified pertussis toxin (PT), 5 μg filamentous hemagglutinin (FHA), 3 μg pertactin (PRN), and 5 μg fimbria types 2 and 3 (FIM), with 1.5 mg aluminum phosphate as the adjuvant (2).
Serology. Serological testing was conducted at the Global Clinical Immunology Laboratory of Sanofi Pasteur (Swiftwater, PA) without knowledge of group assignment. Anti-diphtheria toxin antibody was measured by the ability of test sera to protect Vero cells from diphtheria toxin challenge (microneutralization assay) in comparison to a World Health Organization (WHO) reference serum and expressed as international units per milliliter (IU/ml) (3). The lower limit of quantitation (LLOQ) was 0.0005 IU/ml. Anti-tetanus toxoid antibody was measured by IgG enzyme-linked immunosorbent assay (ELISA) by using a WHO international reference serum, with purified tetanus toxoid as the coating antigen; the LLOQ was 0.01 IU/ml. Antibodies to PT, FHA, PRN, and FIM were measured by standardized IgG ELISAs, expressed in ELISA units per milliliter (EU/ml) (4). The LLOQ was 3 EU/ml for FHA and 4 EU/ml for PT, PRN, and FIM.

Reactogenicity and safety. Children were monitored at the study site for 20 min following vaccination in order to observe immediate reactions. Parents or legal representatives then recorded solicited injection site reactions (pain, erythema, and swelling) and systemic reactions (fever, headache, malaise, and myalgia) for the 7 days following vaccination. Intensity was graded as follows. For injection site pain: grade 1, easily tolerated; grade 2, discomforting enough to interfere with normal behavior; grade 3, incapacitating, unable to perform usual activities. For erythema and swelling: grade 1, <2.5 cm; grade 2, 2.5 to 4.9 cm; grade 3, ≥5 cm. For headache, malaise, and myalgia: grade 1, no interference with activity; grade 2, some interference with activity; grade 3, significant, prevents daily activity.

Unsolicited AEs, unsolicited adverse reactions (ARs; defined as AEs that were considered by the investigator to be related to the study vaccine), and SAEs were recorded for approximately 1 month postvaccination (from date of vaccination until visit 2) and were coded for analysis using the Medical Dictionary for Regulatory Activities, version 13.0.

Statistical analysis. A sample size of 1,300 participants (650 per group) was estimated to allow an assumed dropout rate of 10% and provide 91% overall power to demonstrate noninferiority for all prespecified hypotheses (as outlined below).

Statistical analyses were performed using SAS software version 9.1 (SAS Institute, Cary, NC, USA). It was hypothesized that 10-year-olds would have serological responses that were noninferior to those of 11-year-olds, as assessed by the following endpoints: postvaccination anti-pertussis geometric mean concentrations (GMCs); booster response rates to pertussis, tetanus, and diphtheria antigens; and postvaccination seroprotection rates to tetanus and diphtheria (serologic correlates of protection are not established for pertussis). Hypotheses were tested separately for each vaccine antigen. To test the pertussis GMC hypotheses, a two-sided 95% confidence interval (CI) was constructed around the ratio of GMCs in group 1 divided by the GMCs in group 2 for each antigen; noninferiority was achieved if the lower bound of the 95% CI of the ratio was >0.67.

To maintain comparability with original licensure studies, a booster response to pertussis, tetanus, or diphtheria antigen was defined as a 4-fold increase in prevaccination to postvaccination concentrations for participants with a prevaccination concentration of ≤93 EU/ml for PT,

TABLE 1 Antibody response to pertussis antigens (per-protocol analysis set)†

| Antibody     | Group 1 (10 yrs of age), 613 participants | Group 2 (11 yrs of age), 608 participants | Noninferiority comparison |
|--------------|------------------------------------------|------------------------------------------|---------------------------|
|              | n (GMC (95% CI))                         | n (GMC (95% CI))                         | GMC ratio of group 1/group 2 (95% CI) | Noninferiority criteria met |
| Anti-PT (EU/ml) |                                            |                                          |                           |                           |
| Prevaccination | 590 (4.96 (4.54, 5.42))                   | 591 (4.85 (4.41, 5.34))                  | 0.94 (0.84, 1.05)         | Yes                       |
| Postvaccination | 577 (30.1 (28.0, 32.4))                   | 566 (32.0 (29.6, 34.7))                  |                           |                           |
| Anti-FHA (EU/ml) |                                            |                                          |                           |                           |
| Prevaccination | 609 (22.1 (20.1, 24.2))                   | 605 (20.3 (18.5, 22.3))                  | 1.03 (0.94, 1.13)         | Yes                       |
| Postvaccination | 613 (232 (218, 247))                     | 608 (225 (211, 239))                    |                           |                           |
| Anti-PRN (EU/ml) |                                            |                                          |                           |                           |
| Prevaccination | 600 (15.6 (14.2, 17.1))                   | 601 (14.8 (13.5, 16.2))                  | 1.05 (0.93, 1.18)         | Yes                       |
| Postvaccination | 613 (464 (426, 506))                     | 607 (444 (408, 482))                    |                           |                           |
| Anti-FIM (EU/ml) |                                            |                                          |                           |                           |
| Prevaccination | 590 (6.77 (6.05, 7.57))                   | 587 (7.07 (6.33, 7.89))                  | 0.88 (0.73, 1.06)         | Yes                       |
| Postvaccination | 606 (477 (413, 550))                     | 605 (540 (478, 611))                    |                           |                           |

† n, number of participants with available data; GMC, geometric mean concentration; CI, confidence interval; PT, pertussis toxoid; FHA, filamentous hemagglutinin; PRN, pertactin; FIM, limbria types 2 and 3.
those in group 2 (Table 1). Postvaccination booster response rates for tigens (PT, FHA, PRN, and FIM) in group 1 were noninferior to those in group 2. The noninferiority criterion was met for FIM (Table 2), because the difference in booster response or seroprotection rates in the two groups; noninferiority was achieved if the lower bound of this 95% CI was >−10% (or >−5% if the rate was >95% in group 2). These calculations were the equivalent of testing the null hypothesis using a one-sided type I error rate of 0.025.

RESULTS

Participants. A total of 1,302 participants were enrolled, 651 to each group. The median age of group 1 was 10.5 years, and that of group 2 was 11.3 years. The groups were similar with respect to sex (overall, 52% male) or self-identified racial/ethnic group (overall, 79.0% Caucasian, 8.8% black, 5.5% Hispanic, 6.7% other). As shown in Fig. 1, 1,299 participants were vaccinated and included in the safety analysis set, 1,282 were included in the full analysis set (all vaccinated participants with at least one valid postvaccination serology result), and 1,221 were included in the per-protocol analysis set (participants with no relevant protocol deviations).

Immunogenicity. Postvaccination GMCs to the pertussis antigens (PT, FHA, PRN, and FIM) in group 1 were noninferior to those in group 2 (Table 1). Postvaccination booster response rates against diphtheria, tetanus, PT, FHA, and PRN in group 1 were noninferior to those in group 2. The noninferiority criterion was not met for FIM (Table 2), because the difference in booster response rates for FIM was −3.4%, with a lower bound of the 95% CI of −5.96%, which was slightly below the noninferiority criterion of −5% prespecified for booster response rates of >95%. Postvaccination seroprotection rates (antibody concentration of ≥0.1 IU/ml) against tetanus and diphtheria in group 1 were noninferior to those in group 2 (Table 3).

Reactogenicity and safety. (i) Immediate reactions. Two immediate unsolicited AEs were reported within 20 min of vaccination. One group 1 participant developed diaphoresis that lasted 1 day and was considered by the investigator to be unrelated to vaccination. A participant in group 2 developed a right parieto-occipital cerebrovascular event and was discontinued from the study. On the day of enrollment, the girl presented to her pediatrician with hyponatremia. This was later interpreted by the investigator as a possible early symptom of stroke. On the day after vaccination, she developed right eye drooping and 2 days later experienced right-sided facial weakness, ptosis, slurred speech, altered mental status, and symptoms of cerebral salt wasting. She was diagnosed with right parieto-occipital cerebral vascular accident due to an arterial malformation, likely present since birth. This SAE, which resulted in ongoing disability, was considered by the investigator to be unrelated to the study vaccine.

(ii) Solicited injection site reactions. Solicited injection site reactions were reported by 546 (84.8%) participants in group 1 and 547 (84.8%) in group 2 (Table 4). Injection site pain, reported to be unrelated to the study vaccine.

{| Antibody | Group 1 (10 yrs of age), 613 participants | Group 2 (11 yrs of age), 608 participants | Noninferiority comparison |
|---|---|---|---|
| | % | n/N | % | n/N | Difference between group 1 and group 2 (95% CI) | Noninferiority criteria met |
| Anti-PT (EU/ml) | 56.7 | 314/554 | 56.1 | 308/549 | 0.6 (−5.26, 6.41) | Yes |
| Anti-FHA (EU/ml) | 84.2 | 513/609 | 84.9 | 513/605 | −0.6 (−4.64, 3.52) | Yes |
| Anti-PRN (EU/ml) | 98.0 | 588/600 | 97.5 | 585/600 | 0.5 (−1.26, 2.30) | Yes |
| Anti-FIM (EU/ml) | 93.7 | 546/583 | 97.1 | 568/585 | −3.4 (−5.96, −1.03) | No |
| Anti-tetanus (IU/ml) | 98.5 | 601/610 | 98.8 | 596/603 | −0.3 (−1.75, 1.09) | Yes |
| Anti-diphtheria (IU/ml) | 97.7 | 595/609 | 98.0 | 593/605 | −0.3 (−2.06, 1.41) | Yes |

a n, number of participants with booster response; N, number of participants with available data; CI, confidence interval; PT, pertussis toxoid; FHA, filamentous hemagglutinin; PRN, pertactin; FIM, fimbria types 2 and 3. See Materials and Methods for definition of a booster response.

TABLE 3 Seroprotection rates for tetanus and diphtheria (per-protocol analysis set)*

| Antibody | Group 1 (10 yrs of age), 613 participants | Group 2 (11 yrs of age), 608 participants | Noninferiority comparison |
|---|---|---|---|
| | % | n/N | % | n/N | Difference between group 1 and group 2 (95% CI) | Noninferiority criteria met |
| Anti-tetanus of ≥0.1 IU/ml | | | | | | |
| Prevac. | 90.3 | 551/610 | 91.2 | 551/604 | −0.3 (−1.18, 0.35) | Yes |
| Postvac. | 99.7 | 611/613 | 100 | 607/607 | | |
| Anti-diphtheria of ≥0.1 IU/ml | | | | | | |
| Prevac. | 83.6 | 510/610 | 75.9 | 459/605 | −0.3 (−1.18, 0.34) | Yes |
| Postvac. | 99.7 | 610/612 | 100 | 608/608 | | |

* n, number of participants who met seroprotection criterion; N, number of participants with available data.
were grade 1 in intensity, started within 3 days of vaccination, and lasted 1 to 3 days.

(iii) Solicited systemic reactions. Solicited systemic reactions were reported by 395 (61.3%) participants in group 1 and 450 (69.7%) participants in group 2 (Table 4). Myalgia was the most frequently reported solicited systemic reaction (52.8% of all participants), followed by headache (35.5%) and malaise (27.8%) (Fig. 2). Most solicited systemic reactions were grade 1 in intensity, started within 3 days of vaccination, and lasted 1 to 3 days.

(iv) Unsolicited AEs, ARs, and SAEs. Unsolicited AEs were reported by 31.8% of participants in group 1 and 33.1% of participants in group 2 (Table 4). The most commonly reported unsolicited AEs were cough (4.0%) and headache (3.5%) in group 1 and headache (3.4%) and oropharyngeal pain (2.8%) in group 2. The majority of unsolicited nonserious AEs were grade 1 or 2 in intensity.

At least 1 unsolicited AR was reported by 6.0% of participants in group 1 and 7.9% of participants in group 2. The most commonly reported unsolicited ARs were injection site reactions: pruritus (1.5%) and hematoma (0.9%) in group 1 and pruritus (2.0%) and rash (1.4%) in group 2. The majority of unsolicited nonserious ARs were grade 1 or 2 in intensity. Only one unsolicited AR, an injection site hematoma, was still ongoing at the time of visit 2.

### DISCUSSION
In this study, antibody responses to all antigens met statistical noninferiority in 10-year-olds compared to 11-year-olds, except for the proportion of children with booster responses to FIM. Booster response rates were as expected for adolescents who had received 5 prior doses of vaccine, with the most recent dose 4 to 6 years previously. Given that the FIM GMC was noninferior among the 10-year-olds compared to the 11-year-olds, and given that the slightly inferior FIM booster response rate nonetheless was >90%, this failure to meet 1 of 12 immunogenicity criteria is very unlikely to be of any clinical significance. Safety results were consistent with those seen in other studies of Tdap boosters among young adolescents.

Nearly 96% of children in the United States have received at least 3 doses of pertussis-containing vaccines (5); despite this, pertussis remains endemic and outbreaks are common. In fact, the number of reported cases increased from a historic low of 1,010 in 1976 to a total of 48,277 in 2012 (6), the highest number of reported cases since 1955. Increased awareness of the disease, vaccine hesitancy, pockets of underimmunization, and improved detection play a role in this increase. It could also be attributable in
part to the waning of immunity following childhood immunization with acellular vaccines (7–9).

Booster vaccination with Tdap at 11 to 12 years of age has been recommended since 2005 (1). The increasing prevalence of disease among 7- to 10-year-olds raises the possibility that a booster dose may be needed sooner than adolescence. In fact, there is already a recommendation to administer Tdap to children between 7 and 10 years of age who are not fully vaccinated (fully vaccinated being defined as 5 doses of DTaP or 4 doses of DTaP if the fourth dose was administered on or after the fourth birthday) (10). In this regard, it is notable that only 2 Tdap vaccines are licensed for use in the United States: Boostrix (Tdap3; GlaxoSmithKline), indicated at ≥10 years of age, and Adacel (Tdap5; Sanofi Pasteur), indicated at 11 through 64 years of age. Administration of Tdap to children 7, 8, and 9 years of age is off-label for both products, and administration of Tdap5 to 10-year-olds is currently off-label. Because administration of Tdap is recommended or required for some 10-year-olds, it is appropriate to seek incorporation of such children in the Tdap5 label indication. Should recommendations or requirements indicate a need to extend Tdap administration to younger children, such studies could be undertaken.

In summary, this study demonstrates that Tdap5 is safe and immunogenic for children 10 years of age.

ACKNOWLEDGMENTS

This study was funded by Sanofi Pasteur, the employer of V. Pool, D. P. Greenberg, D. R. Johnson, and M. D. Decker. G. S. Marshall has received study support funding through the University of Louisville from Sanofi Pasteur, GlaxoSmithKline, Merck, and Novartis and has served as a consultant for each of those companies as well as for Pfizer.

Helpful statistical comments were provided by Amitabha Bhaumik. We thank Julia R. Gage, contractor to Sanofi Pasteur, for assistance with writing the manuscript, and we thank all the investigators, nurses, support staff, and participants, without whom the study could not have been accomplished.

REFERENCES
1. Broder KR, Cortese MM, Iskander JK, Kretsinger K, Slade BA, Brown KH, Mijalski CM, Tiwari T, Weston EJ, Cohn AC, Srivastava PU, Moran JS, Schwartz B, Murphy TV, Advisory Committee on Immunization Practices. 2006. Preventing tetanus, diphtheria, and pertussis among adolescents: use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm. Rep. 55:31–34.
2. Sanofi Pasteur. 12 March 2014. Adacel® full prescribing information. Sanofi Pasteur, Lyon, France. https://www.vaccineshoppe.com/image.cfm?doc_id=10438&image_type=product_pdf.
3. Langleby JM, Predy G, Guasparini R, Law B, Diaz-Mitoma F, Whitstit P, Tapiero B, Dionne M, Tomovici A, Mills E, Halperin SA. 2007. An adolescent-adult formulation tetanus and diphtheria toxoids adsorbed combined with acellular pertussis vaccine has comparable immunogenicity but less reactogenicity in children 4–6 years of age than a pediatric formulation acellular pertussis vaccine and diphtheria and tetanus toxoids adsorbed combined with inactivated poliomyelitis vaccine. Vaccine 25: 1121–1125. http://dx.doi.org/10.1016/j.vaccine.2006.09.053.
4. Kapasi A, Meade BD, Plikaytis B, Pawloski L, Martin MD, Yoder S, Rock MT, Coddens S, Haezbroeck V, Fievet-Groyne F, Bixler G, Jones C, Hildreth S, Edwards KM, Messonnier NE, Tondella ML. 2012. Comparative study of different sources of pertussis toxin (PT) as coating antigens in IgG anti-PT enzyme-linked immunosorbent assays. Clin. Vaccine Immunol. 19:64–72. http://dx.doi.org/10.1128/CVI.05460-11.
5. Centers for Disease Control and Prevention. 2012. National, state, and local area vaccination coverage among children aged 19-35 months—United States, 2011. MMWR 61:689–696.
6. Centers for Disease Control and Prevention. 2013. Notice to readers: final 2012 reports of nationally notifiable infectious diseases. MMWR 62: 669–682.
7. Misegades LK, Winter K, Harriman K, Talarico J, Messonnier NE, Clark TA, Martin SW. 2012. Association of childhood pertussis with receipt of 5 doses of pertussis vaccine by time since last vaccine dose, California, 2010. JAMA 308:2126–2132. http://dx.doi.org/10.1001/jama.2012.14939.
8. Kuczmarek MC, Valenti L, Kelly HA, Ware RS, Britt HC, Lambert SB. 2013. Sevenfold rise in likelihood of pertussis test requests in a stable set of Australian general practice encounters, 2000-2011. Med. J. Australia 198: 624–628. http://dx.doi.org/10.5694/mja13.10044.
9. Tartof SY, Lewis M, Kenyon C, White K, Osborn A, Liko J, Zell E, Martin S, Messonnier NE, Clark TA, Skoff TH. 2013. Waning immunity to pertussis following 5 doses of DTaP. Pediatrics 131:e1047–e1052. http://dx.doi.org/10.1542/peds.2012-1928.
10. Centers for Disease Control and Prevention. 2011. Updated recommendations for use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis (Tdap) vaccine from the Advisory Committee on Immunization Practices, 2010. MMWR 60:13–15.