# Combined Tetanus, Diphtheria, and 5-Component Pertussis Vaccine for Use in Adolescents and Adults

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**Context** Increasing reports of pertussis among US adolescents, adults, and their infant contacts have stimulated vaccine development for older age groups.

**Objective** To assess the immunogenicity and reactogenicity of a tetanus-diphtheria 5-component (pertussis toxoid, filamentous hemagglutinin, pertactin, and fimbriae types 2 and 3) acellular pertussis vaccine (Tdap) in adolescents and adults.

**Design, Setting, and Participants** A prospective, randomized, modified double-blind, comparative trial was conducted in healthy adolescents and adults aged 11 through 64 years from August 2001 to August 2002 at 39 US clinical centers.

**Interventions** A single 0.5-mL intramuscular dose of either Tdap or tetanus-diphtheria vaccine (Td).

**Main Outcome Measures** Antibody titers to diphtheria and tetanus toxoids for Tdap and Td were measured in sera collected from subsets of adolescents and adults, before and 28 days after vaccination. For pertussis antigens, titers in sera from Tdap vaccinees were assessed vs those from infants who received analogous pediatric diphtheria-tetanus-acellular pertussis vaccine (DTaP) in a previous efficacy trial. Safety was assessed via solicited local and systemic reactions for 14 days and adverse events for 6 months following vaccination.

**Results** A total of 4480 participants were enrolled. For both Tdap and Td, more than 94% and nearly 100% of vaccinees had protective antibody concentrations of at least 0.1 IU/mL for diphtheria and tetanus, respectively. Geometric mean antibody titers to pertussis toxoid, filamentous hemagglutinin, pertactin, and fimbriae types 2 and 3 exceeded (by 2.1 to 5.4 times) levels in infants following immunization at 2, 4, and 6 months with DTaP. The incidence of solicited local and systemic reactions and adverse events was generally similar between the Tdap and Td groups.

**Conclusions** This Tdap vaccine elicited robust immune responses in adolescents and adults to pertussis, tetanus, and diphtheria antigens, while exhibiting an overall safety profile similar to that of a licensed Td vaccine. These data support the potential routine use of this Tdap vaccine in adolescents and adults.

*JAMA. 2005;293:3003-3011* www.jama.com

In 2003, 11 647 cases of pertussis, many in adolescents and adults, were reported to the US Centers for Disease Control and Prevention (CDC).[1,2] Preliminary CDC data for 2004 indicate an increase to 18 957 cases.[3] Although increased awareness and improved diagnostic methods may increase reporting, factors such as the variable efficacy of whole-cell pertussis vaccines previously used in the United States,[4,5] undervaccination in childhood, and waning immunity in adolescents and adults may also explain an increase in incidence. Incompletely immunized infants and toddlers have the highest susceptibility to pertussis, the most severe disease manifestations, and highest risk of mortality.[6,7] Reported cases of pertussis decline after completion of the primary infant immunization series and remain low until early adolescence, when the number of cases increases. Because no booster pertussis vaccine is currently available for adolescents or adults, these persons become increasingly vulnerable to the disease.[8]

The role of adolescents and adults in the spread of pertussis is critical. Disease may be characterized by nonclassical symptoms, making diagnosis more difficult, particularly given the limitations of available diagnostic tests. However, adolescents and adults who contract pertussis do experience significant morbidity and complications.[9,10] De-

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layed treatment and increased transmission,[8,11] most significantly to unvaccinated or undervaccinated infants, are of concern.[12,13] Vaccination of adolescents and adults with acellular pertussis vaccines might reduce both the morbidity associated with the disease in these populations and transmission to their household and other contacts, especially infants. We describe the immunogenicity and reactogenicity of a new 5-component acellular pertussis vaccine combined with tetanus and diphtheria toxoids (Tdap; Adacel, Sanofi Pasteur Limited, Toronto, Ontario) in adolescents and adults.

## METHODS

We examined the immunogenicity and reactogenicity of booster doses of Tdap vs those of licensed tetanus and diphtheria toxoids adsorbed for adult use (Td, Sanofi Pasteur Inc, Swiftwater, Pa). The trial was conducted following the principles outlined in the Declaration of Helsinki. Written informed consent was obtained from participants, their parents, or guardians before study procedures were initiated. Written informed assents were obtained for underage adolescents, as required by institutional review boards (IRBs). Appropriate IRBs approved study documents at each center. A data and safety monitoring board monitored study data throughout. A contract research organization (CRO) performed some study monitoring under the supervision of the sponsor.

### Participants

Eligible participants were between 11 and 64 years of age, in good health, with a temperature of less than 38.0°C. Exclusion criteria included receipt of any pertussis, diphtheria, or tetanus-containing vaccines within 5 years; diagnosis of pertussis within 2 years; allergy or sensitivity to any vaccine component, including previous vaccine reactions; acute respiratory illness; daily use of oral nonsteroidal, anti-inflammatory drugs; receipt of blood products or immunoglobulins within 3 months; and any immunodeficiency, malignancy, significant underlying disease, neurological impairment, or pregnancy.

### Trial Design

This phase 3, randomized, controlled, modified double-blind trial was conducted at 39 US clinical centers (FIGURE 1). To maintain blinding, study center personnel who administered vaccines did not perform study assessments, while those who performed assessments remained blinded to study vaccines. Study sponsor personnel, who did not participate further in the trial, provided a computer-generated randomization list, including designation of random assignments to provide serum samples, to a central randomization center at the CRO. Vaccine allocation codes were obtained from an interactive voice response system at the CRO; an allocation code list was provided in a sealed envelope by the sponsor. The success of blinding at each site was evaluated during routine monitoring. Participants were randomized to receive Tdap or Td (3:2 for adolescents; 3:1 for adults). To ensure adequate distribution across groups, enrollment was stratified by age (11-13, 14-17, 18-28, 29-48, and 49-64 years; block size was 10 for adolescents and 8 for adults). Serum samples were collected immediately prior to and 28 to 42 days following study vaccination from randomly selected participant subsets representing 50% of Tdap recipients, 75% of adolescent Td recipients, and 100% of adult Td recipients. Participants were observed for 30 minutes following vaccination for immediate reactions; reports of solicited local and systemic reactions were collected for 14 days following vaccination. Unsolicited adverse event reports were collected for 6 months.

### Study Vaccines

Tdap contained 2.5 µg of pertussis toxoid; 5 µg of filamentous hemagglutinin ; 3 µg of pertactin; 5 µg of fimbriae types 2 and 3; 2 Limit of flocculation (Lf) of diphtheria toxoid; 5 Lf of tetanus toxoid; 1.5 mg of aluminum phosphate (0.33 mg aluminum); and 0.6% 2-phenoxyethanol per 0.5-mL dose. The control vaccine, Td, was a licensed product containing 2 Lf of diphtheria toxoid; 5 Lf of tetanus toxoid; 1.5 mg of aluminum phosphate (0.33 mg aluminum); and 0.01% thimerosal as a preservative per 0.5-mL dose.

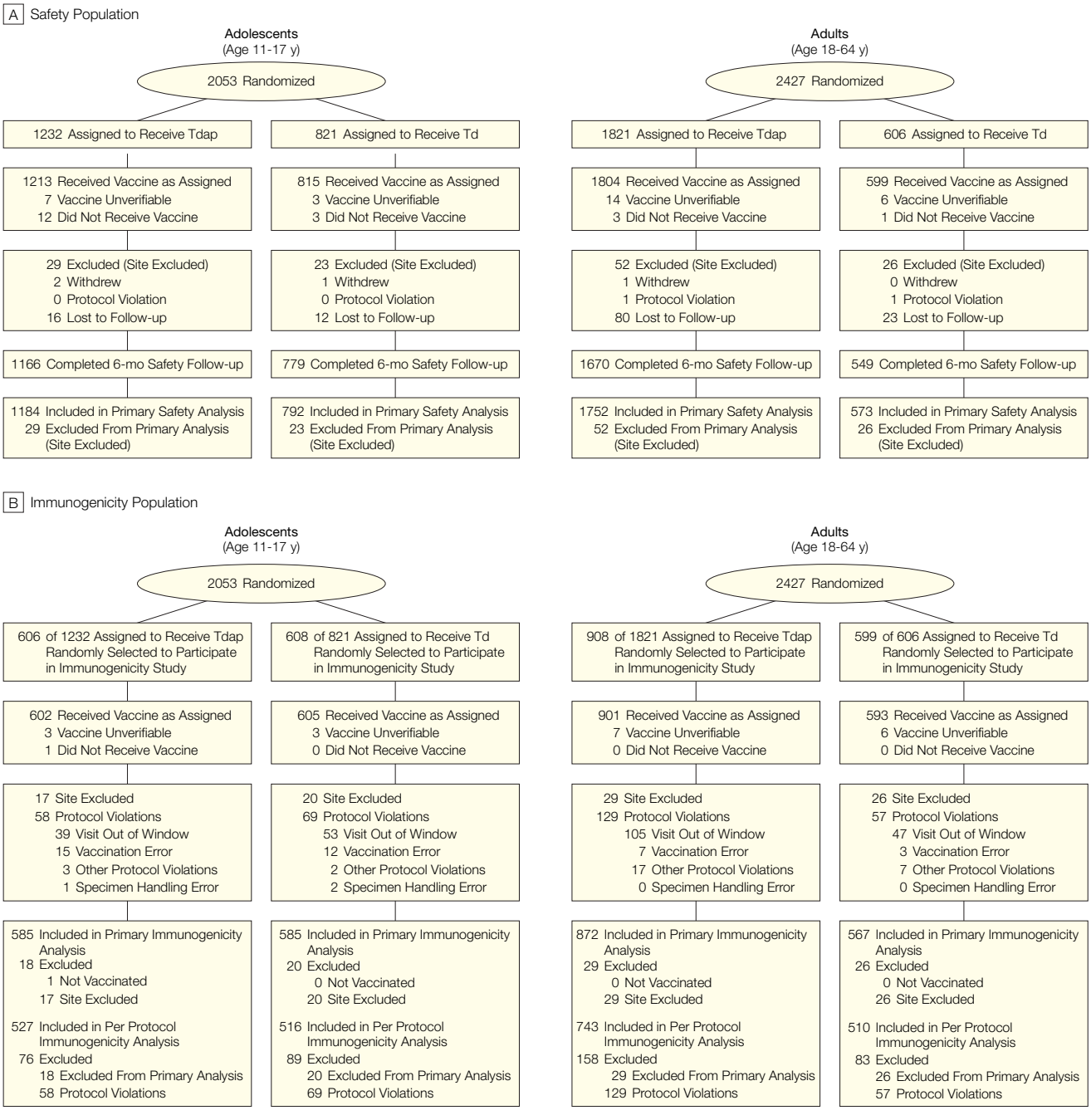
### Laboratory Methods

Antibody assays were performed in a blinded manner at the clinical immunology laboratories of Sanofi Pasteur Limited in Toronto, Ontario (for pertussis antigens) or Sanofi Pasteur Inc in Swiftwater, Pa (for tetanus and diphtheria toxoids) using validated methods.[14-16] Antipertussis, anti–filamentous hemagglutinin, anti–fimbriae types 2 and 3, antipertactin IgG, and antitetanus antibody titers were determined by an enzyme-linked immunosorbent assay (ELISA) method. Results for pertussis antibodies were calculated in ELISA units per milliliter (EU/mL) by comparison with in-house standard antisera of assigned unitage, calibrated to the US Human Reference Lots 3 or 4. Pertussis antibody response comparisons were made using serum samples collected at 7 months of age, following immunization at 2, 4, and 6 months of age, from infant participants in an efficacy trial using analogous pediatric diphtheria-tetanus 5-component-acellular pertussis vaccine (DTaP; Daptacel, Sanofi Pasteur Limited).[4] The infant serum samples from this reference trial were concurrently tested in the same laboratory, under the same conditions, and using the same assay as samples from adolescents and adults. Antitetanus titers were calculated by comparison with an international standard, Lot TE-3, available from the World Health Organization (WHO). Antidiphtheria antibody responses were measured by the ability of test sera to protect Vero cells from a diphtheria toxin challenge. Results were reported by comparison with a calibrated WHO reference serum and were determined by the highest serum dilution that allowed cell metabolism in the presence of the challenge dose of diphtheria toxin.

### Safety and Reactogenicity Outcome Measures

Immediate reaction data were recorded in the clinic. Local solicited reactions of erythema, swelling, pain, axillary node swelling, and limb circumference (at the midpoint between shoulder and elbow of the injected limb) and systemic solicited reactions of fever (temperature ≥38°C), vomiting, headache, diarrhea, nausea, chills, rash, generalized body ache or muscle weakness, tiredness or decrease in energy level, and sore or swollen joints were recorded daily on a study-provided diary card for 14 days. Unsolicited adverse events were recorded for 14 days. Erythema, swelling, and fe-

**Figure 1.** Flow of Patients Through the Trial




A, Participant disposition and safety population. B, Participant disposition and immunogenicity population.

**Table 1.** Demographic Characteristics of the Safety Population*

| | | No. (%) | |
|---|---|---|---|
| | | Tdap | Td |
| Adolescents | | (n = 1184) | (n = 792) |
| Age, mean (SD), y | | 13.8 (1.79) | 13.8 (1.84) |
| | 11-13 | 599 (50.6) | 405 (51.1) |
| | 14-17 | 585 (49.4) | 387 (48.9) |
| Sex | | | |
| | Female | 598 (50.5) | 392 (49.5) |
| | Male | 586 (49.5) | 400 (50.5) |
| Race/ethnicity† | | | |
| | White | 1023 (86.4) | 673 (85.0) |
| | Black | 111 (9.4) | 73 (9.2) |
| | Hispanic | 15 (1.3) | 24 (3.0) |
| | Asian | 16 (1.4) | 8 (1.0) |
| | Other | 19 (1.6) | 14 (1.8) |
| Adults | | (n = 1752) | (n = 573) |
| Age, mean (SD), y | | 39.3 (13.65) | 39.5 (13.32) |
| | 18-28 | 587 (33.5) | 189 (33.0) |
| | 29-48 | 584 (33.3) | 189 (33.0) |
| | 49-64 | 581 (33.2) | 195 (34.0) |
| Sex | | | |
| | Female | 1136 (64.8) | 353 (61.6) |
| | Male | 616 (35.2) | 220 (38.4) |
| Race/ethnicity† | | | |
| | White | 1489 (85.0) | 486 (84.8) |
| | Black | 167 (9.5) | 57 (9.9) |
| | Hispanic | 52 (3.0) | 20 (3.5) |
| | Asian | 25 (1.4) | 6 (1.0) |
| | Other | 19 (1.1) | 4 (0.7) |

Abbreviations: Td, tetanus-diphtheria vaccine; Tdap, tetanus-diphtheria 5-component acellular pertussis vaccine.
*Demographic parameters were similar in both vaccine groups for the immunogenicity population.
†Self-reported.

ver were rated as mild, moderate, or severe, based on size (0-9 mm, 10-34 mm, or ≥35 mm) or temperature (38.0°C-38.7°C, 38.8°C-39.4°C, or ≥39.5°C). Pain was rated as mild to severe, based on the level of incapacitation experienced. After the initial 14-day period, any adverse event that required a medical contact—including change of medication, telephone call, office visit, emergency department visit, or hospitalization—was recorded. Participants were contacted by telephone 6 months after immunization to ensure completeness of reporting. Serious adverse events were recorded throughout the study and rated by investigators for relationship to study vaccine.

### Statistical Analysis

Planned enrollment was 4400 participants, 1000 in each adolescent age stratum (11-13, 14-17 years) and 800 in each adult age stratum (18-28, 29-48, and 49-64 years). The overall population for serum analysis was based on a sample size of 200 participants per stratum for adults receiving Td and 300 per stratum for adolescents in each treatment group and for adults receiving Tdap. Assuming 10% attrition, the power to test each individual immunogenicity hypothesis was at least 80%. The sample size for safety had sufficient power to rule out 2-fold increases of fever occurring at a rate of 3% in the control group among 11- to 17-year-olds. All sample size calculations were performed using nQuery version 3.0 (Statistical Solutions, Sagus, Mass) or in-house SAS version 8.2 (SAS Institute Inc, Cary, NC). Statistical analyses were performed by Red River Statistics Inc of Shreveport, La, and independently by biostatistians at the University of Rochester Medical Center, Rochester, NY.

For tetanus and diphtheria, antibody levels of at least 0.1 IU/mL are widely accepted as protective and are thus a primary outcome measure.[15,16] Consistent with the US Food and Drug Administration (FDA) standards regarding demonstration of noninferiority of new combination products vs licensed or individual products, Tdap was considered to be at least as immunogenic as Td if the lower bound of a 95% confidence interval (CI) around the differences in seroprotection rates in participants vaccinated with Tdap or Td was greater than –10%. For pertussis, Tdap would be considered at least as immunogenic as DTaP if the lower bound of the 95% CI around the postvaccination geometric mean titer (GMT) ratio for Tdap and DTaP was greater than 0.67 (ie, =reciprocal of 1.5, a standard approach required by FDA for demonstrating noninferiority in vaccine trials). For each antigen, booster response was a primary outcome measure, defined as a 4-fold increase if the prevaccination titer was less than or equal to a predefined cut-off value and a 2-fold increase if the prevaccination titer was greater than the cut-off value. The cut-off prevaccination values were based on earlier clinical trial results: 2.56 IU/mL for diphtheria, 2.7 IU/mL for tetanus, 85 EU/mL for pertussis toxoid, 170 EU/mL for filamentous hemagglutinin, 115 EU/mL for pertactin, and 285 EU/mL for fimbriae types 2 and 3.

Baseline variables were compared between groups using the analysis of variance technique for continuous variables and the $\chi^2$ test or Fisher exact test for categorical variables.

Percentages of participants with immediate, local, or systemic reactions and those with adverse events or serious adverse events were tabulated. For the primary safety analysis of erythema, swelling, pain, and fever, Tdap was considered to be at least as safe as Td if the upper bound of the 95% CI of the between-vaccine difference in event rates was less than 10%. A post-hoc analysis for differences in subgroups of vaccinees by sex was performed, as were post-hoc analyses of rate ratios, with 95% CIs, for erythema, swelling, pain, and fever.

All participants randomized to provide sera before and after vaccination who met protocol criteria were included in the per-protocol immunogenicity analysis. The planned modified intention-to-treat analysis for safety was to include all participants who received study vaccine, with a corrected allocation for participants who received the wrong vaccine in error. Data for adolescents (aged 11-17 years) and adults (aged 18-64 years) were evaluated separately. No values were imputed to replace missing data; no adjustments were made for multiplicity. For solicited events, denominators include participants for whom data were available. For all analyses, nonoverlapping 95% CIs were considered to be statistically significant.

## RESULTS

Between August 2001 and August 2002, 4480 participants were randomized and underwent study procedures

at 39 clinical centers across the United States. Of these participants, 2053 were adolescents: 1213 received Tdap and 815 received Td. In the adult group, 2427 enrolled: 1804 received Tdap and 599 received Td (Figure 1). Vaccination errors were reported for 5 participants (eg, randomized to Td but vaccinated with Tdap); these participants were reallocated to the group for which they received vaccine. All data from 1 site (130 participants total) were excluded from the primary safety and immunogenicity analyses due to violations of Good Clinical Practices related to participants' rights, vaccine administration and accountability, documentation, and study blinding (Figure 1). The primary analysis of data omits all data from this study site; for confirmatory purposes, an additional analysis was performed including these data. Results were similar in both analyses; accordingly, primary analysis results are presented. Demographic characteristics by age group are shown in TABLE 1. Data from 80 infants in a reference DTaP efficacy trial were included to evaluate pertussis antibody responses; the 80 infant sera pairs were representative of all 181 pairs tested in the original study, based on GMT ratios.[4]

## Immunogenicity

For tetanus and diphtheria, seroprotection rates of at least 0.1 IU/mL, booster response rates, and 1-month postimmunization GMTs were high and similar between the Tdap and Td groups for both adolescents and adults. Pertussis GMTs and proportions of participants with antibody levels consistent with boosting for each antigen indicated robust responses to Tdap (TABLE 2).

Pertussis antibody GMTs following 1 dose of Tdap were substantially higher than those seen among infants following 3 doses of DTaP for all pertussis antigens in both adults and adolescents (TABLE 3). In both age groups for diphtheria and tetanus, the lower bounds of the CIs around the difference in rates between Tdap and Td were greater than –10%, and for pertussis the lower bounds of the CIs around the GMT ratios between Tdap and DTaP were above 0.67, meeting the noninferiority criteria.

## Safety and Reactogenicity

Safety and reactogenicity evaluation outcomes were comparable between the Tdap and Td groups for both the adolescent and adult populations. Sixteen participants (11 adolescents and 5 adults) reported immediate reactions within 30 minutes of vaccination. Proportions were similar among Tdap and Td recipients: approximately 0.5% for adolescents and 0.2% for adults. Most immediate reactions were nervous system events, such as syncope, dizziness, or vasovagal reaction, or injection site events, such as pain and erythema.

The frequency and maximum intensity of solicited local reactions of erythema and swelling were comparable between the Tdap and Td groups for both adolescents and adults (FIGURE 2). In adolescents, pain occurred slightly more frequently with Tdap vs Td. The onset of solicited local adverse events was highest during days 0 through 3 in both vaccine groups. Reported increases in limb circumference vs baseline were similar between the Tdap and Td groups, and most increases were 2 cm or less. Reported changes from baseline included decreases in limb circum-

**Table 2.** Immunogenicity Findings in the Per-Protocol Population*

| | Adolescents 11-17 y | | Adults 18-64 y | |
|---|---|---|---|---|
| | Tdap (n = 527) | Td (n = 516) | Tdap (n = 743) | Td (n = 510) |
| Seroprotection ≥0.1 IU/mL, No./total (%) | | | | |
| Diphtheria | 526/527 (99.8) | 515/516 (99.8) | 697/741 (94.1) | 482/507 (95.1) |
| Tetanus | 527/527 (100.0) | 516/516 (100.0) | 742/742 (100.0) | 508/509 (99.8) |
| Booster response rates, No./total (%)† | | | | |
| Diphtheria | 501/527 (95.1) | 489/515 (95.0) | 646/739 (87.4) | 422/506 (83.4) |
| Tetanus | 483/527 (91.7) | 471/516 (91.3) | 468/742 (63.1) | 340/509 (66.8) |
| Pertussis toxin | 482/524 (92.0) | | 624/739 (84.4) | |
| Filamentous hemagglutinin | 450/526 (85.6) | | 611/739 (82.7) | |
| Pertactin | 496/525 (94.5) | | 693/739 (93.8) | |
| Fimbriae types 2 and 3 | 499/526 (94.9) | | 635/739 (85.9) | |
| Geometric mean titers (95% CI) | | | | |
| Diphtheria, IU/mL | 8.46 (7.56-9.48) | 7.10 (6.43-7.83) | 2.49 (2.17-2.85) | 2.37 (2.05-2.73) |
| Tetanus, IU/mL | 12.87 (12.28-13.48) | 14.35 (13.64-15.09) | 7.65 (7.28-8.04) | 8.18 (7.64-8.75) |
| Pertussis toxin, EU/mL | 309.26 (283.59-337.25) | 15.61 (13.89-17.54) | 178.84 (164.24-194.74) | 13.16 (11.71-14.79) |
| Filamentous hemagglutinin, EU/mL | 214.83 (200.34-230.37) | 20.85 (18.63-23.34) | 192.91 (180.72-205.93) | 19.28 (17.26-21.54) |
| Pertactin, EU/mL | 344.52 (313.28-378.87) | 11.66 (10.33-13.16) | 341.89 (306.19-381.75) | 11.65 (10.28-13.21) |
| Fimbriae types 2 and 3, EU/mL | 1792.40 (1603.74-2003.24) | 28.84 (25.81-32.23) | 852.72 (762.82-953.20) | 31.68 (28.19-35.61) |

Abbreviations: CI, confidence interval; ELISA, enzyme-linked immunosorbent assay; EU/mL, ELISA units per milliliter; Td, tetanus-diphtheria vaccine; Tdap, tetanus-diphtheria 5-component acellular pertussis vaccine.
*For all comparisons, Tdap vaccine met predefined noninferiority criteria vs Td vaccine based on 95% CIs around the differences in seroprotection rates.
†Percentages based on participants for whom evaluable data were available. Up to 4 participants per group had missing data for an individual measurement.

ference in some participants. No cases of whole-arm swelling were reported in either vaccine group.

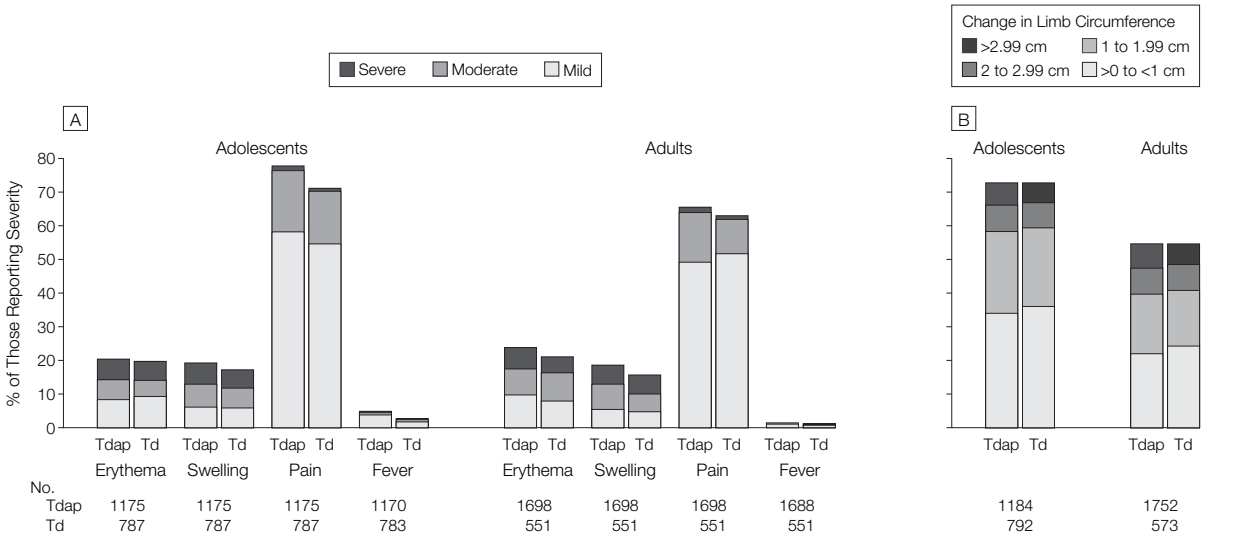
For adolescents and adults, the frequency and maximum intensity of each of the solicited systemic reactions were comparable between the Tdap and Td groups, based on noninferiority testing (TABLE 4). For adolescents and adults, proportions of participants with fever were within predefined comparability bounds. The majority of these fevers were mild, with only 2 of 1170 adolescents in the Tdap group and 1 of 783 adolescents and 1 of 551 adults in the Td group reporting severe fever (temperature ≥39.5°C). Most solicited systemic reactions reported were mild. With the exception of headache, severe adverse events were uncommon for all solicited systemic adverse events, occurring in 1.3% or less of all Tdap and Td participants. Severe headache was reported by 23 of 1175 and 12 of 787 adolescents and 47 of 1698 and 12 of 560 adult Tdap and Td participants for whom severity was reported, respectively, during postvaccination days 0 through 14. A trend for higher per-

**Table 3.** Antibody Responses to Pertussis Antigens*

| Antigens, EU/mL | GMT (95% CI) | | | Tdap/DTaP GMT Ratio (95% CI) | |
|---|---|---|---|---|---|
| | Tdap: Adolescents (n = 527) | Tdap: Adults (n = 741) | DTaP: Infants 2-6 mo (n = 80) | Adolescents | Adults |
| Pertussis toxin | | | | | |
| Prevaccination | 14.46 (12.95-16.14) | 12.54 (11.46-13.73) | 5.24 (4.23-6.48) | 2.76 (2.06-3.70) | 2.39 (1.80-3.18) |
| Postvaccination | 309.26 (283.59-337.25) | 178.84 (164.24-194.74) | 86.55 (71.31-105.04) | 3.57 (2.83-4.52) | 2.07 (1.58-2.70) |
| Filamentous hemagglutinin | | | | | |
| Prevaccination | 19.49 (17.51-21.69) | 18.13 (16.69-19.68) | 5.21 (4.18-6.49) | 3.74 (2.81-4.99) | 3.48 (2.68-4.52) |
| Postvaccination | 214.83 (200.34-230.37) | 192.91 (180.72-205.93) | 39.95 (34.62-46.10) | 5.38 (4.46-6.49) | 4.83 (3.94-5.92) |
| Pertactin | | | | | |
| Prevaccination | 10.01 (8.93-11.24) | 8.45 (7.65-9.34) | 2.15 (1.85-2.49) | 4.67 (3.46-6.30) | 3.94 (2.89-5.36) |
| Postvaccination | 344.52 (313.28-378.87) | 341.89 (306.19-381.75) | 108.12 (91.41-127.88) | 3.19 (2.48-4.10) | 3.16 (2.25-4.44) |
| Fimbriae types 2 and 3 | | | | | |
| Prevaccination | 25.80 (23.49-28.33) | 28.56 (26.12-31.23) | 13.26 (11.23-15.67) | 1.94 (1.52-2.50) | 2.15 (1.63-2.84) |
| Postvaccination | 1792.40 (1603.74-2003.24) | 852.72 (762.82-953.20) | 341.10 (270.23-430.56) | 5.25 (3.90-7.09) | 2.50 (1.77-3.54) |

Abbreviations: CI, confidence interval; ELISA, enzyme-linked immunosorbent assay; EU/mL, ELISA units per milliliter; GMT, geometric mean titer; Td, tetanus-diphtheria vaccine; Tdap, tetanus-diphtheria 5-component acellular pertussis vaccine.
*Based on number of participants with evaluable data for each antigen. For all comparisons, Tdap vaccine met predefined noninferiority criteria.

**Figure 2.** Solicited Reactions of Erythema, Swelling, Pain, and Fever and Change in Limb Circumference Between Tdap and Td for Adolescents and Adults




A, Solicited reactions of erythema, swelling, pain, and fever for adolescents and adults who provided severity measurements of mild to severe. For the percentages of participants reporting these reactions, the upper limit of the 95% confidence interval around the difference between Tdap and Td was less than 10% for all age groups and reactions, except pain in adolescents (10.72%). B, Increases in circumference of the limb injected with Tdap or Td, measured at the midpoint of the upper arm. No differences between the 2 vaccine groups were observed for adolescents or adults.

centages of females vs males with local reactions was observed in the Tdap and Td groups, with greater differences in adults than in adolescents.

No significant between-group differences were observed for unsolicited adverse events (Table 4).

Thirty women, 23 in the Tdap and 7 in the Td group, became pregnant 1 or more times during trial participation; each tested nongravid at study entry. Five miscarriages in the Tdap group, 1 therapeutic abortion in the Td group, and 4 early deliveries (2 in each group) were reported. At birth, 23 newborns, including the 4 early deliveries, were reported to be normal. One Tdap recipient experienced a miscarriage, reconceived, and subsequently delivered a healthy infant.

Sixty-three of 4301 (1.46%) participants reported 1 or more serious adverse events: 44 of 2936 (1.50%) in the Tdap group and 19 of 1365 (1.39%) in the Td group. Only 2 serious adverse events, both in adult Tdap recipients, were considered possibly related to vaccine by the investigator. A 23-year-old woman was hospitalized for a severe migraine with unilateral facial paralysis 1 day after vaccination, recovered without sequelae, and was discharged 2 days later. A 49-year-old woman was hospitalized with a diagnosis of nerve compression 12 days after vaccination; the complaint resolved within 1 day. Two cases of diabetes (1 in each vaccine group) and 2 cases of seizures in adolescents with prior history of seizure disorder (1 in each vaccine group) were among the serious adverse events considered unrelated to study vaccine by investigators.

## COMMENT

In this study, the Tdap vaccine administered was comparable with Td vaccine with respect to reactogenicity and tetanus-diphtheria immunogenicity, while providing robust pertussis antibody responses in both adolescents and adults. The percentages of participants receiving Tdap and having seroprotective antibody levels of at least 0.1 IU/mL to tetanus and diphtheria were high and similar to those among Td recipients. Pertussis GMTs to pertussis toxoid, filamentous hemagglutinin, pertactin, and fimbriae types 2 and 3 after 1 dose of Tdap exceeded those measured in a subset of infants who had received 3 doses of the analogous DTaP vaccine in an efficacy trial that demonstrated 85% protection against classic pertussis and 78% protection against milder pertussis (defined as culture-proven pertussis with ≥1 day of cough).[4] In comparisons between Tdap

**Table 4.** Reactions to Vaccination

| Reactions | No. (%)* Adolescents Tdap (n = 1175) | Adolescents Td (n = 787) | Adults Tdap (n = 1698) | Adults Td (n = 561) |
|---|---|---|---|---|
| **Solicited Reactions** | | | | |
| Local reactions at days 0-3 postimmunization | | | | |
| Erythema | 239 (20.34) | 152 (19.31) | 392 (23.09) | 117 (20.86) |
| Swelling | 245 (20.85) | 136 (17.28) | 336 (19.79) | 92 (16.40) |
| Pain | 912 (77.62) | 555 (70.52) | 1086 (63.96) | 346 (61.68) |
| Axillary node swelling | 676 (5.70) | 37 (4.70) | 86 (5.06) | 18 (3.21) |
| Injection limb circumference increase of ≥1 cm | 391 (33.27) | 237 (30.11) | 502 (29.56) | 146 (26.02) |
| Systemic reactions at days 0-3 postimmunization | | | | |
| Fever (temperature ≥38°C) | 34 (2.91) | 12 (1.53) | 14 (0.83) | 2 (0.36) |
| Vomiting | 32 (2.72) | 8 (1.02) | 16 (0.94) | 3 (0.54) |
| Headache | 373 (31.74) | 223 (28.34) | 392 (23.09) | 128 (22.86) |
| Diarrhea | 58 (4.94) | 37 (4.70) | 107 (6.31) | 35 (6.25) |
| Nausea | 91 (7.74) | 47 (5.97) | 89 (5.24) | 22 (1.30) |
| Chills | 125 (10.64) | 65 (8.26) | 93 (5.48) | 18 (3.21) |
| Rash | 14 (1.19) | 9 (1.14) | 21 (1.24) | 9 (1.61) |
| Generalized body ache/ muscle weakness | 303 (25.79) | 199 (25.29) | 290 (17.09) | 80 (14.29) |
| Tiredness/decreased energy level | 287 (24.43) | 180 (22.87) | 316 (18.61) | 86 (15.36) |
| Sore/swollen joints | 113 (9.62) | 73 (9.28) | 118 (6.95) | 32 (5.71) |
| **Unsolicited Adverse Events†** | | | | |
| Most common adverse events (≥1% in 1 or more groups) at days 0-28 postimmunization | (n = 1184) | (n = 792) | (n = 1752) | (n = 573) |
| Pharyngitis | 40 (3.38) | 27 (3.41) | 34 (1.94) | 7 (1.22) |
| Nasopharyngitis | 36 (3.04) | 34 (4.29) | 33 (1.88) | 11 (1.92) |
| Cough | 25 (2.11) | 20 (2.53) | 17 (0.97) | 6 (1.05) |
| Nasal congestion | 24 (2.03) | 7 (0.88) | 6 (0.34) | 2 (0.35) |
| Upper respiratory tract infection | 15 (1.27) | 11 (1.39) | 18 (1.03) | 5 (0.87) |
| Dizziness | 14 (1.18) | 7 (0.88) | 5 (0.29) | 1 (0.17) |
| Dysmenorrhea | 14 (1.18) | 9 (1.14) | 19 (1.08) | 6 (1.05) |
| Upper abdominal pain | 12 (1.01) | 2 (0.25) | 0 (0.00) | 0 (0.00) |
| Arthralgia | 11 (0.93) | 3 (0.38) | 8 (0.46) | 6 (1.05) |
| Pain in limb | 11 (0.93) | 3 (0.38) | 9 (0.51) | 7 (1.22) |
| Sinusitis | 5 (0.42) | 10 (1.26) | 21 (1.20) | 3 (0.52) |
| Limb injury | 4 (0.34) | 8 (1.01) | 0 (0.00) | 0 (0.00) |

Abbreviations: Td, tetanus-diphtheria vaccine; Tdap, tetanus-diphtheria 5-component acellular pertussis vaccine.
*Based on the number of participants for whom any diary card data was available; no data were imputed for missing values. For formal comparisons, Tdap vaccine met predefined noninferiority criteria vs Td (the upper limit of the 95% confidence interval [CI] around the between-group difference was less than 10%) for erythema, swelling, and fever. For pain in adolescents, the upper limit was 10.72%. In the post-hoc rate ratio (RR) analysis of erythema, swelling, pain, and fever, statistical differences were noted only for pain (RR, 1.10; 95% CI, 1.04-1.16) and fever (RR, 1.85; 95% CI, 1.13-3.02) in adolescents.
†In the intent-to-treat population.

and Td for erythema, swelling, pain, and fever, Tdap was comparable with Td, with the possible exception of pain in adolescents, for which the results were marginally outside of the predefined comparability bound. These results support the use of the Tdap vaccine in adolescents and adults.

The potential benefits of widespread use of an adolescent and adult pertussis booster vaccine include a reduction in pertussis disease. As the overall US case counts have grown, so too has the proportion of pertussis cases in persons at least 10 years old, increasing steadily from 15% in 1977-1979 to 49% in 1997-2000.[2] In 2003, the latest year for which complete data are available, that proportion increased to 64%.[1] Waning immunity to pertussis has been demonstrated in adolescents and adults, indicating increased susceptibility to disease in these age groups. Increased incidence of disease in older patients is of public health significance because they serve as the reservoir for *Bordetella pertussis* infections in infants who are too young to have completed the primary series of immunization. Pertussis may be severe and even life-threatening in very young infants.[11,13,17] Antimicrobial therapy, although effective in eradicating the organism from the respiratory tract,[18] does not alter the progression of disease unless given early, during the catarrhal phase when pertussis is rarely suspected. Therefore, control of the disease must be based on vaccination.

Tolerability is an important consideration in the development of new vaccines. Reactogenicity to pediatric formulation DTaP vaccines is associated with the amount of pertussis or diphtheria toxoid per dose. Formulations with lower diphtheria and pertussis toxoid concentrations elicit less reactogenicity.[19] Therefore, the Tdap studied was formulated to contain lower quantities of diphtheria and pertussis toxoids than the analogous US-licensed pediatric DTaP vaccine. Results of this study show a favorable reactogenicity profile in adolescents and adults, suitable for routine use. Furthermore, differences in reactogenicity between females and males were observed for both vaccines, consistent with observations made with the use of other vaccines, such as influenza vaccine.[20]

Our study had certain limitations. There was insufficient power to detect uncommon adverse events. Also, the use of an infant comparison group to evaluate the immunogenicity of the pertussis component in adolescents and adults may raise some questions. However, no definitive serological correlates of protection are available for pertussis, and the efficacy of the infant formulation in preventing disease is well established. Therefore, this approach has been endorsed by the FDA's Vaccines and Related Biological Products Advisory Committee[21] for the purpose of licensing adolescent and adult acellular pertussis vaccine formulations that are based on infant vaccines of demonstrated efficacy. Additional experience will be needed to further define the profile of this vaccine in larger populations.

Booster vaccination with tetanus and diphtheria toxoids every 10 years has become a standard of care in the United States. Our data indicate that the Tdap vaccine studied could be used to provide protection for tetanus and diphtheria, as recommended, while providing additional protection against pertussis. Evidence to support the introduction of an acellular pertussis booster in the United States includes a recent Canadian National Advisory Committee on Immunization statement recommending that all preadolescents and adolescents be vaccinated with an appropriately formulated acellular pertussis vaccine.[22] The introduction of adolescent and adult Tdap booster immunization in the United States could enhance immunity against pertussis, which would be anticipated to decrease the incidence of pertussis in the population, reduce the reservoir of pertussis, and lessen transmission from adolescents and adults to infants.

**Author Contributions:** Dr Pichichero had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

*Study concept and design:* Pichichero.
*Acquisition of data:* Pichichero, Rennels, Edwards, Blatter, Marshall, Bologa, Wang, Mills.
*Analysis and interpretation of data:* Pichichero, Rennels, Edwards, Blatter, Bologa, Wang, Mills.
*Drafting of the manuscript:* Pichichero, Blatter.
*Critical revision of the manuscript for important intellectual content:* Pichichero, Rennels, Edwards, Marshall, Bologa, Wang, Mills.
*Statistical analysis:* Pichichero.
*Obtained funding:* Pichichero.
*Administrative, technical, or material support:* Rennels, Edwards, Marshall, Bologa.
*Study supervision:* Edwards, Blatter, Marshall, Bologa, Wang, Mills.

**Financial Disclosures:** Drs Pichichero and Edwards have received grants from Aventis, GlaxoSmithKline, and MedImmune. Dr Blatter is on the speakers' bureau for Aventis. Dr Marshall has received research contracts, honoraria, and consultancies from Aventis.

**Funding/Support:** Funding for the study was provided by Aventis Pasteur, now Sanofi Pasteur. Funding went to the academic institutions of the authors.

**Role of the Sponsor:** The authors who are employees of Aventis Pasteur participated in the design, supervision, and conduct of the study; performed interpretation of the data; and provided critical review of the manuscript. The sponsor played a principal role in the design and conduct of the study. A contract research organization, PPD Development, made site visits to ensure accuracy and integrity of the data and managed the study.

**Independent Statistical Analysis:** Jason Roy, PhD, and Shirley Eberly, MS, of the Department of Biostatistics at the University of Rochester Medical Center, Rochester, NY, performed a confirmatory statistical analysis. Shayami Thanabalasundrum and James Trammel of Red River Statistics Inc, Shreveport, La, as well as Aleksandra Kolenc-Saban, MSc, and James Sloan of Aventis Pasteur performed data analyses and management. Aventis Pasteur contracted with Red River Statistics for independent statistical review of the data. Red River Statistics was not employed by Aventis Pasteur, nor were there any other arrangements with Aventis Pasteur other than the contracted arrangement. Analysis of the data was performed by the independent statistics company and guided by the Food and Drug Administration for data requested in association with the Biologics License Application (BLA) (presentations for the BLA occurred on March 15, 2005).

**Study Investigators:** The following physicians enrolled participants into the trial and performed study evaluations: Brian Allen, Onalaska, Wis; Wilson P. Andrews, Jr, Marietta, Ga; Gerald Bader, Vancouver, Wash; Ladan Bakhtari, Plano, Tex; David Bernstein, Cincinnati, Ohio; Mark M. Blatter, Pittsburgh, Pa; Kenneth Bromberg, Brooklyn, NY; Daniel Brune, Peoria, Ill; Timothy Craig, Hershey, Pa; Robert Daum, Chicago, Ill; Cornelia Dekker, Stanford, Calif; Arnold del Pilar, Jr, South Bend, Ind; Kathryn M. Edwards, Nashville, Tenn; Bryan D. Evans, Huntsville, Ala; Stephen M. Fries, Boulder, Colo; David P. Greenberg, Pittsburgh, Pa; Susan A. Keathley, Little Rock, Ark; Donald J. Kennedy, St Louis, Mo; Erik Lamberth, Sellersville, Pa; Thomas Latiolais, Bossier City, La; Joseph Leader, Woburn, Mass; Gary Marshall, Louisville, Ky; Emma E. McCarty, Shreveport, La; Douglas K. Mitchell, Norfolk, Va; Laurie Peterson, Chippewa Falls, Wis; Michael Pichichero, Rochester, NY; Sharon E. Prohaska, Kansas City, Mo; Alfredo Quinonez, San Diego, Calif; Margaret B. Rennels, Baltimore, Md; David Paul Robinson, Columbia, Mo; Kevin G. Rouse, Jonesboro, Ark; Joseph Saponaro, Jupiter, Fla; Shelly David Senders, University Heights, Ohio; Charles Sheaffer, Chapel Hill, NC; Marc R. Shepard, Washington, DC; Peter E. Silas, Layton, Utah; Alex Spyropoulos, Albuquerque, NM; Bradley Sullivan, Marshfield, Wis; Leonard B. Weiner, Syracuse, NY.

**Acknowledgment:** We thank William Bartlett, PhD, and Linda Young, who performed serology analy-

ses; Kathy Heard and Jennifer Kasztejna, who performed and oversaw trial monitoring; Robert Daum, MD, David Johnson, MD, and Michael D. Decker, MD, who provided scientific advice; and Lisa DeTora, PhD, and David Johnson, MD, who are both full-time employees of Sanofi Pasteur in Swiftwater, Pa, and who assisted in the editing of the manuscript.

**Published Online**: June 2, 2005 (doi:10.1001/jama.293.24.3003).

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That approach leaves several critical issues unresolved. First, federal policy actively discourages high-quality research by making access to marijuana by researchers exceedingly difficult. Even when access to marijuana is finally granted, there is substantial variability in the purity and content of the product. Second, researchers need to test the assumption noted by Das that THC is the active ingredient responsible for the perceived beneficial effects. Although that assumption is reasonable, there remains the possibility that marijuana, not THC in isolation, achieves the desirable effects. Third, researchers should test the most efficient delivery system. There may be some added value in smoking that needs to be evaluated.

If research concludes that THC is the beneficial ingredient and that delivery by tablet is safest and most effective, then there is justification for approval of that method only. A synthetic THC oral medication (dronabinol) is already available for prescription with US Food and Drug Administration-approved indications for anorexia associated with weight loss in patients with AIDS and for nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments.

Regulation of the use of marijuana for medical purposes is feasible and socially desirable, but it will require a different way of thinking about the problem. It requires viewing marijuana as a potential medication subject to carefully controlled research, rather than as a drug of strict prohibition.

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**Financial Disclosures:** None reported.

## CORRECTIONS

**Author Contribution Omissions:** In the Original Contribution entitled "High-Dose Atorvastatin vs Usual-Dose Simvastatin for Secondary Prevention After Myocardial Infarction: The IDEAL Study: A Randomized Controlled Trial" published in the November 16, 2005, issue of *JAMA* (2005;294:2437-2445), several contributions were omitted for the author Anders G. Olsson, MD, PhD. In addition to his contributions listed in the article, Dr Olsson contributed to the study concept and design, acquisition of data, drafting of the manuscript, and statistical analysis for the IDEAL trial.

**Duplicated Text:** In the Original Contribution entitled "Neurologic Adverse Events Associated With Smallpox Vaccination in the United States, 2002-2004" published in the December 7, 2005, issue of *JAMA* (2005;294:2744-2750), a section of text was duplicated. The first 4½ lines on the top of page 2747 should be deleted. Thus, the last sentence on the bottom of page 2746 and continuing onto 2747 should read: "Of the remaining 3 cases, one man had probable encephalitis defined by altered mental status, pleocytosis, and multifocal demyelinating lesions on brain MRI 10 days after primary vaccination."

**Incorrect Wording and Data:** In the Original Contribution entitled "Combined Tetanus, Diphtheria, and 5-Component Pertussis Vaccine for Use in Adolescents and Adults" published in the June 22/29, 2005, issue of *JAMA* (2005;293:3003-3011), incorrect wording appeared at the end of the Results section. On page 3009, lines 15-16 of the fourth paragraph, " . . . the complaint resolved within 1 day" should read "the patient was hospitalized for 1 day and the complaint subsequently resolved without sequelae." In addition, in Table 4, for the entry "Axillary node swelling," in column 2 (Tdap Adolescents) 676 should be 67.

**Incorrect Data:** In the Original Contribution entitled "Adverse Events Reported Following Live, Cold-Adapted, Intranasal Influenza Vaccine," published in the December 7, 2005, issue of *JAMA* (2005;294:2720-2725), there were incorrect data in the first full paragraph on page 2724. The corrected paragraph is reprinted below:

Among 11 reports concerning individuals with a prior history of chronic cardiovascular disease, 1 serious case involved a 42-year-old man with a history of uncontrolled hyperlipidemia who was hospitalized with a myocardial infarction 2 days after vaccination. He underwent cardiac catheterization. Among 10 reports from individuals with preexisting metabolic conditions (including 8 with thyroid disease), 1 (a 30-year-old man hospitalized with pneumonia 7 days after vaccination) was serious. There were no other hospitalizations. Among the remaining 15 individuals, 13 had chronic conditions (3 with chronic neurological conditions, 4 with chronic respiratory diseases, 2 with pernicious anemia, 2 with sarcoidosis, 1 with fibromyalgia, and 1 with lupus) and 2 were pregnant; none resulted in hospitalization. One report, in a 48-year-old woman who had a prior history of Bell palsy, was classified as serious.