



Prevention of Pertussis Among Adolescents: Recommendations for Use of Tetanus Toxoid, Reduced Diphtheria Toxoid, and Acellular Pertussis (Tdap) Vaccine

Committee on Infectious Diseases

Organizational Principles to Guide and Define the Child Health Care System and / or Improve the Health of All Children

ABSTRACT

The purpose of this statement is to provide the rationale and recommendations for adolescent use of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccines. Despite universal immunization of children with multiple doses of pediatric diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccine, pertussis remains endemic with a steady increase in the number of reported cases. Two peaks in the incidence of pertussis occur in pediatric patients: infants younger than 6 months of age who are inadequately protected by the current immunization schedule and adolescents 11 through 18 years of age whose vaccine-induced immunity has waned. Significant medical and public health resources are being consumed in postexposure management of adolescent cases, contacts, and outbreaks with little beneficial effect on individuals or the epidemiology of disease. Two Tdap products were licensed in 2005 for use in people 10 through 18 years of age (Boostrix) and 11 through 64 years of age (Adacel). The American Academy of Pediatrics recommends the following:

1. Adolescents 11 to 18 years of age should receive a single dose of Tdap instead of tetanus and diphtheria toxoids (Td) vaccine for booster immunization. The preferred age for Tdap immunization is 11 to 12 years.
2. Adolescents 11 to 18 years of age who have received Td but not Tdap are encouraged to receive a single dose of Tdap. An interval of at least 5 years between Td and Tdap is suggested to reduce the risk of local and systemic reactions; however, intervals of less than 5 years can be used, particularly in settings of increased risk of acquiring pertussis, having complicated disease, or transmitting infection to vulnerable contacts. Data support acceptable safety with an interval as short as approximately 2 years.
3. Tdap and tetavalent meningococcal conjugate vaccine (MCV4 [Menactra]) should be administered during the same visit if both vaccines are indicated. If this is not feasible, MCV4 and Tdap can be administered using either sequence. When not administered simultaneously, the American Academy of Pediatrics suggests a minimum interval of 1 month between vaccines.

The rationale for this strategy is to provide direct protection of immunized adolescents. With implementation of vaccine recommendations, indirect benefit

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Key Words

pertussis

Abbreviations

FDA—US Food and Drug Administration
Tdap—tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis
DTaP—pediatric diphtheria and tetanus toxoids and acellular pertussis
GMCs—geometric mean antibody concentrations
Td—adult-type tetanus and diphtheria toxoid
Lf—limit of flocculation units
DTP—diphtheria and tetanus and whole-cell pertussis
MPHBL—Massachusetts Public Health Biological Laboratory
sp—Sanofi Pasteur
ELS—entire or extensive limb swelling
VAERS—Vaccine Adverse Events Reporting System
CDC—Centers for Disease Control and Prevention
AAP—American Academy of Pediatrics
MCV4—tetavalent meningococcal conjugate vaccine
CI—confidence interval
GMT—geometric mean titer
TT—tetanus toxoid
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also is likely to extend to unimmunized peers and other age groups. The strategy of universal Tdap immunization at 11 to 12 years of age is cost-effective.

CLINICAL CHARACTERISTICS OF PERTUSSIS IN ADOLESCENTS

Pertussis is an acute respiratory tract infection caused by *Bordetella pertussis*, a fastidious Gram-negative coccobacillus. The organism elaborates toxins that damage respiratory epithelial tissue and have systemic effects. *B pertussis* causes a spectrum of disease in previously immunized people. Morbidity of pertussis in adolescents is significant. When pertussis is recognized and confirmed in adolescents,^{1,2} 72% to 100% report paroxysmal cough, difficulty breathing, and difficulty sleeping; 50% to 70% have posttussive vomiting; 30% to 65% have whoop; 1% to 2% are hospitalized, have pneumonia, or have a rib fracture; and 0.2% to 1% have a seizure or lose consciousness. In a study in Quebec, Canada,² 97% of adolescents with pertussis coughed for 3 weeks or longer, and 47% coughed for more than 9 weeks. In a study in Massachusetts,¹ 38% were still coughing, at the final interview, for a mean of 3.4 months after cough onset. A long delay in diagnosis also is typical in adolescents and results in an unsuspected and uninterrupted prolonged period of infectiousness.

Multiple prospective studies of adolescents and young adults who seek medical attention for a nonspecific cough illness lasting more than 1 week show that 13% to 20% have pertussis.³ In adolescents in Massachusetts confirmed to have pertussis in 1989–1998, almost 20% did not have paroxysms, whooping, or posttussive vomiting.⁴ The vast majority of contagious cases of pertussis in adolescents do not come to medical attention or are not recognized and treated to render them noncontagious, and their contacts are not provided postexposure prophylaxis. Even when recognized, delayed treatment and postexposure prophylaxis have little to no effect.⁵

EPIDEMIOLOGY OF PERTUSSIS IN ADOLESCENTS

In the prevaccine era, pertussis was a disease of preschool-aged children. Less than 10% of cases occurred among infants younger than 1 year of age, and pertussis was rare among adolescents and adults.⁶ After introduction of childhood pertussis immunization in the 1940s, the rate of pertussis decreased dramatically from a prevaccine rate of almost 200 000 cases annually to a historic low of 1010 cases in 1976 (Fig 1).⁷ Because of the paucity of pertussis cases in school-aged children and adults in the prevaccine and early vaccine era, the belief that immunization conferred lifelong immunity, and the reactogenicity of whole-cell pertussis vaccine in young children, no pertussis-containing vaccine was licensed in the United States for use in people 7 years of age or older. Since the 1980s, despite high levels of routine childhood immunization for pertussis, the number of reported cases has increased steadily among young infants and among 11- to 18-year-old people (referred to hereafter as adolescents) and adults (Fig 1).^{7–11} With the changing epidemiology of pertussis in recent decades, the tenet of lifelong protection after pertussis or childhood immunization has been dismissed. Some increase in reported pertussis cases undoubtedly is the result of increased recognition. However, the age-specific burden of cases suggests a changing incidence, and the magnitude of the problem documents an undeniable burden of pertussis currently and the expectation of a growing burden in the future unless booster immunization is undertaken. Pertussis is unique in this regard among diseases for which universal childhood immunization has been implemented.

In 2004, 25 827 cases of pertussis were reported in the United States—the highest number since the 1950s. Thirty-four percent of cases occurred in adolescents 11 to 18 years of age (incidence: 30 per 100 000).⁷ Data from enhanced surveillance and prospective studies show that passive surveillance exponentially underesti-

FIGURE 1
Reported cases of pertussis: United States, 1922–2004⁷ (courtesy of Kristin Brown).

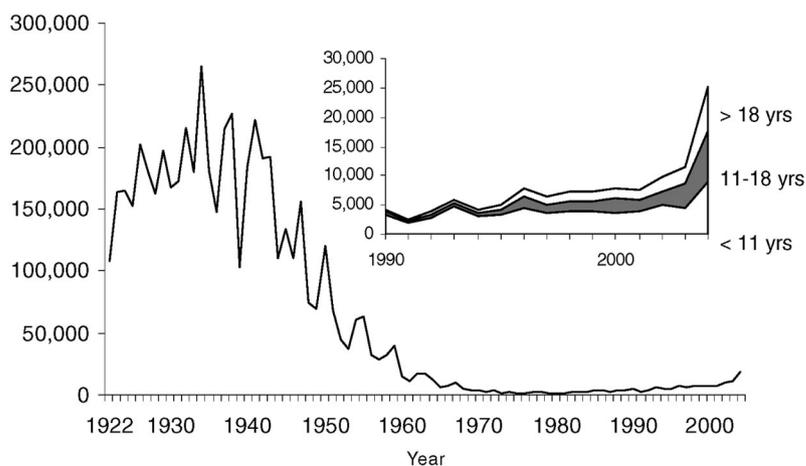
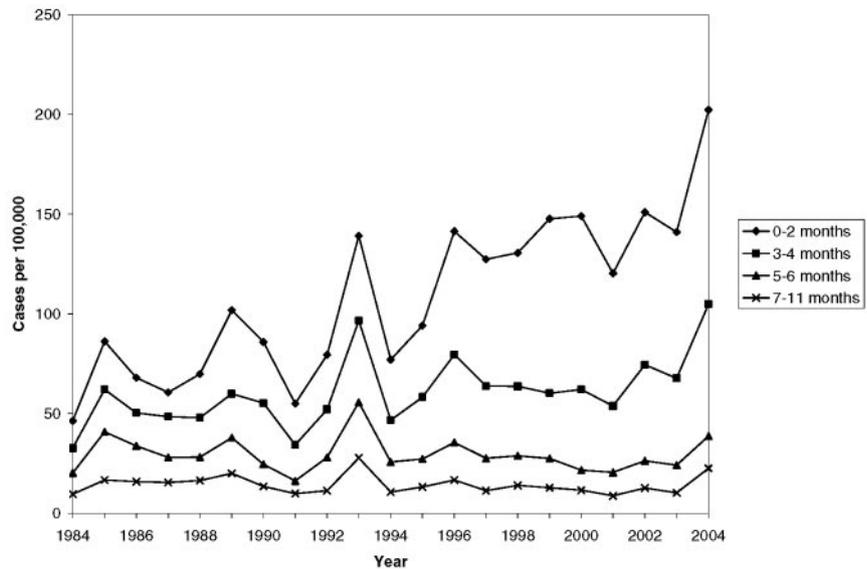


FIGURE 2

Incidence of reported cases of pertussis per 100 000 in infants according to month of age: United States, 1984–2004^{7,18} (courtesy of Pamela Srivastava).



mates the burden of pertussis in adolescents. In Massachusetts, where enhanced pertussis surveillance is conducted and serologic diagnosis is available, the average annual rate of pertussis reported from 1996–2004 in adolescents 11 to 18 years of age (93 per 100 000) was 13 times that reported for adolescents in the remainder of the United States (7.3 per 100 000; data from National Notifiable Disease Surveillance, 1996–2003). Reported rates in those aged 11 years and younger in Massachusetts were comparable with rates for the remainder of the United States, which is under passive surveillance. Younger adolescents accounted for the majority of adolescent cases in Massachusetts, with 62% being younger than 16 years of age and 28% being younger than 14 years of age.⁷

Two prospective studies using extensive methods for evaluation and diagnosis assessed pertussis in US populations including adolescents. In a Minnesota health maintenance organization study, individuals 10 to 49 years of age were evaluated for acute paroxysmal cough or persistent cough illness of 7 or more days' duration; the estimated annual incidence of pertussis in adolescents was estimated to be 997 per 100 000 people.¹² In a second prospective study, individuals 15 to 64 years of age in the control arm of an acellular pertussis vaccine trial were evaluated for cough illness of 5 or more days' duration; the estimated annual incidence of pertussis was 370 to 450 per 100 000 people. Data from the latter study suggest that approximately 1 million cases of pertussis occur annually in the United States in people 15 years of age or older.¹³

Outbreaks involving adolescents occur in a variety of settings including middle and high schools, residences for disabled individuals, and entire communities.¹⁴ In 1996 in Massachusetts, 20 distinct outbreaks of pertussis were reported, 18 of which occurred in school settings;

67% of the cases were in 10- to 19-year-old individuals.¹⁵ In a 6-community outbreak in Arizona in 2002–2003, 42% of 485 cases were associated with schools; eighth-grade students had the highest attack rate.¹⁶ In an outbreak of pertussis in Fond du Lac County, Wisconsin, during 2003–2004, 70% of 313 cases of pertussis in county residents were in 10- to 19-year-old people. At least 1 reported case occurred among students at 24 different schools; 55% of initial cases were linked to a single high school weight room.¹⁷ Intensive control measures during this outbreak included an estimated 5000 courses of antimicrobial agents prescribed for case-patients and their close contacts.

Adolescents are reservoirs of *B pertussis* and can be sources of pertussis for young infants, who have the highest risk of pertussis-related complications, hospitalization, and death (Fig 2).^{18,19} In a case-control study of risk factors for pertussis among infants during a Chicago outbreak, the odds ratio was 7.4 for maternal age 15 to 19 years old and 13.6 for maternal cough illness of more than 7 days' duration; older maternal age or having children younger than 5 years of age in the household were not identified as risk factors.²⁰

TETANUS TOXOID, REDUCED DIPHTHERIA TOXOID, AND ACCELLULAR PERTUSSIS VACCINES

In spring 2005, the US Food and Drug Administration (FDA) approved 2 tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccine products. Each Tdap product was licensed as a single-dose booster immunization against tetanus, diphtheria, and pertussis on the basis of clinical trials that demonstrated safety and immunogenicity in adolescents (and adults for 1 product) that were not inferior to currently licensed comparator vaccines. Boostrix (GlaxoSmithKline

TABLE 1 Diphtheria and Tetanus Toxoid and Acellular Pertussis Antigen Content per 0.5-mL Dose of Vaccine

Antigens	GlaxoSmithKline		Sanofi Pasteur		
	Infanrix (6 wk to 6 y) ^a	Boostrix (10 to 18 y)	Tripedia (6 wk to 6 y)	Daptacel (6 wk to 6 y)	Adacel (11 to 64 y)
T, Lf	10	5	5	5	5
D, Lf	25	2.5	6.7	15	2
PT, μg	25	8	23.4	10	2.5
FHA, μg	25	8	23.4	5	5
PRN, μg	8	2.5	—	3	3
FIM 2 + 3, μg	—	—	—	5	5

T indicates tetanus toxoid; D, diphtheria toxoid; PT, pertussis toxoid; FHA, filamentous hemagglutinin; PRN, pertactin; FIM, fimbrial agglutinogens.

^a Pediarix also contains these DTaP components.

Biologicals, Rixensart, Belgium) was licensed May 3, 2005, for use in people 10 through 18 years of age,²¹ and Adacel (Sanofi Pasteur, Toronto, Ontario, Canada) was licensed on June 10, 2005, for use in people 11 through 64 years of age.²² Content of relevant diphtheria and tetanus toxoids and acellular pertussis (DTaP) and Tdap vaccines is shown in Table 1. No preparation containing pertussis antigens alone is licensed in the United States.

Efficacy of the pertussis components in each Tdap vaccine was demonstrated by comparing the immune response in adolescents (and adults for Adacel) immunized with a single dose of Tdap to the immune response in infants immunized in clinical efficacy trials with 3 doses of pediatric DTaP with the same pertussis antigens as the Tdap being assessed, except that infants had received the pediatric formulation with greater amounts of all or some acellular pertussis antigens and with greater amounts of diphtheria toxoid. The geometric mean antibody concentrations (GMCs) to all vaccine pertussis antigens in adolescents 1 month after a single dose of Boostrix were noninferior to those of infants immunized with 3 doses of pediatric Infanrix in a German clinical efficacy trial during the 1990s.^{21,23} The GMCs to all vaccine pertussis antigens in adolescents 1 month after a single dose of Adacel were noninferior to those of infants immunized with 3 doses of pediatric Daptacel in a Swedish infant vaccine-efficacy trial during the 1990s.^{24,25} In addition, booster response rates to the pertussis antigens contained in Tdap in adolescents met the prespecified criteria for an acceptable response for both vaccines.^{21,22} The efficacy of the tetanus and diphtheria toxoid components of each Tdap vaccine was based on comparative immunogenicity studies with US-licensed adult-type tetanus and diphtheria toxoid (Td) vaccines using established correlates of protection and booster responses. One month after immunization, the antitetanus and antidiphtheria toxoid seroprotective (≥ 0.1 IU/mL) and booster response rates among adolescents who received Tdap were noninferior to those who received Td.^{21,22}

Vaccines

Boostrix

Boostrix^{7,21,26} contains the same tetanus toxoid, diphtheria toxoid, and pertussis antigens as those in Infanrix (pediatric DTaP) but with reduced quantities of these antigens (Table 1). Boostrix contains aluminum as the adjuvant and no thimerosal. Boostrix is available either in a prefilled disposable syringe without needles or in a single-dose vial. The tip cap and rubber plunger of the needleless prefilled syringe contain dry natural latex rubber; the single-dose vial stopper is latex-free.

The primary safety study for Boostrix was conducted among healthy adolescents 10 to 18 years of age in the United States. In this randomized, observer-blinded, controlled study, 3080 adolescents 10 to 18 years of age received a single dose of Boostrix and 1034 received Td_{MPHBL} vaccine (manufactured by the Massachusetts Public Health Biological Laboratory; contains tetanus toxoid 2 limit of flocculation units [Lf] and diphtheria toxoid 2 Lf). The primary exclusion criterion was receipt of whole-cell diphtheria and tetanus and pertussis (DTP)/DTaP vaccine within the previous 5 years or Td vaccine within the previous 10 years. Data on solicited local and systemic adverse events were collected by using standardized diaries on the day of immunization and during the next 14 consecutive days (ie, within 15 days of immunization). Unsolicited and serious adverse events were collected for 6 months after immunization. There were no immediate reactions. There were also no seizures, physician-diagnosed Arthus reactions, or other serious adverse events considered by the investigator to be related to immunization reported in either vaccine group (ref 21; GlaxoSmithKline Biologicals, unpublished data, 2005).

Pain at the injection site was the most frequently reported solicited local adverse event in both vaccine groups, and any pain was reported more frequently in adolescents immunized with Boostrix, compared with Td_{MPHBL}; 75% of subjects in the Boostrix group and 72% of subjects in the Td_{MPHBL} group reported some degree of

pain. The rate of severe pain (primary safety end point), defined as pain on rest or pain that prevented everyday activities, in the Boostrix group (4.6%) was similar to that in the Td_{MPHBL} group (4.0%). Some degree of redness, swelling, or increased mid–upper arm circumference each occurred in 20% to 30% of individuals who received Boostrix or Td_{MPHBL}; severe degrees of each occurred in less than 4% of vaccine recipients. The frequency of these events was similar among Boostrix and Td_{MPHBL} recipients. One subject who received Boostrix and 1 who received the Td_{MPHBL} vaccine had self-resolving “large injection site swelling” within 3 days.

The most frequently reported solicited systemic adverse events within 15 days of immunization with Boostrix or Td_{MPHBL} were headache (42–43%) and fatigue (37%), which occurred similarly in vaccine groups and was severe in less than 4% of subjects. The proportion of adolescents reporting fever higher than 100.4°F (5%) and gastrointestinal systemic events (26%) was also similar in vaccine groups.²⁶

Adacel

Adacel^{7,22,24,27} contains the same tetanus toxoid, diphtheria toxoid, and pertussis antigens as those in pediatric Daptacel (pediatric DTaP) but with reduced quantities of diphtheria toxoid and inactivated pertussis toxin (Table 1). Adacel contains aluminum as the adjuvant and no thimerosal. Adacel is available in single-dose vials that are latex-free.

The primary safety study was conducted among adolescents in the United States (adults 18–64 years of age were studied also; results in adults are reported elsewhere).²² In this randomized, observer-blinded, controlled study, 1184 adolescents 11 to 17 years of age received a single dose of Adacel, and 792 adolescents received Td_{sp} vaccine (manufactured by Sanofi Pasteur; contains tetanus toxoid [5 Lf] and diphtheria toxoid [2 Lf]). The primary exclusion criterion was receipt of any tetanus-, diphtheria- or pertussis-containing vaccine within 5 years.

Data on solicited local and systemic adverse events were collected by using standardized diaries on the day of immunization and during the next 14 consecutive days (ie, within 15 days of immunization). Eleven adolescents experienced immediate reactions within 30 minutes of immunization (Adacel, 6 subjects; Td_{sp}, 5 subjects); all incidents resolved without sequelae. Immediate reactions included dizziness, syncope, or vasovagal reactions as well as pain and erythema at the injection site. No incident of anaphylaxis was reported. One Adacel and 1 Td_{sp} recipient, each with a history of seizure disorder, reported a seizure after immunization; neither was assessed by the investigators to be related to the study vaccine. No physician-diagnosed Arthus reaction or serious adverse event considered by the investigators to be related to immunization was reported in either

adolescent group (refs 7 and 24; Sanofi Pasteur, unpublished data, 2005).

Pain at the injection site was the most frequently reported solicited local adverse event among adolescents in both vaccine groups, and any pain was reported more frequently among adolescents immunized with Adacel compared with Td_{sp}; 78% of subjects in the Adacel group and 71% of those in the Td_{sp} group reported some degree of pain at the injection site. Moderate and severe pain (incapacitating, unable to perform usual activities, or associated with medical care/absenteeism) were reported in 18% and 1.5%, respectively, of Adacel recipients, and in 16% and 0.6%, respectively, of Td_{sp} recipients. Some degree of redness or swelling each occurred in 19% to 21% of individuals who received Adacel or Td_{sp}; severe degrees of each occurred in less than 7% of vaccine recipients. Rates of moderate and severe pain, erythema, and swelling after receipt of Adacel were similar to those after receipt of Td_{sp}. No case of whole-arm swelling was reported in either vaccine group.

The most frequently reported systemic adverse events within 15 days after immunization were headache (40–44%), generalized body aches (30%), and tiredness (27–30%). A greater proportion of adolescents in the Adacel group reported fever of 100.4°F or higher compared with the Td_{sp} group (5.0% Adacel vs 2.7% Td_{sp}), but the noninferiority criterion for Adacel was achieved. Rates of the solicited systemic adverse events, other than fever, were similar between the Adacel and Td_{sp} groups.

Safety Considerations for Adolescent Tdap and Other Diphtheria and Tetanus Toxoid–Containing Vaccines

Three types of local adverse events can follow tetanus-diphtheria-pertussis immunization: (1) typical reactions (local pain, redness, and induration, sometimes associated with fever, headache, and other systemic symptoms); (2) entire or extensive limb swelling (ELS); and (3) Arthus type III hypersensitivity reactions.

Mild typical local reactions occur in up to 80% of individuals after receipt of tetanus and diphtheria toxoid–containing vaccines without pertussis components. Moderate and severe local reactions historically have been associated with older, less purified vaccines; larger doses of toxoid; and frequent dosing. High levels of preexisting antibody in tetanus- and diphtheria-primed children, adolescents, and adults may be associated with increased rates of local reactions to tetanus and diphtheria toxoids.^{28–30}

In retrospective analysis, ELS occurred in 2% to 6% of children receiving fourth or fifth doses of DTaP^{31,32}; ELS is self-limited and usually does not require medical attention. ELS has been reported to the Vaccine Adverse Events Reporting Systems (VAERS) almost as frequently after Td immunization as after pediatric DTaP immunization. Among adolescents, most reported cases of ELS have involved Td or hepatitis B vaccine.³³ The pathogen-

esis is not understood fully, and the reaction is not consistently related to diphtheria or tetanus toxoid content, pertussis proteins, or aluminum content of vaccines.^{34,35} It is unknown whether children who received pediatric DTaP exclusively for their primary immunization series (anticipated cohort achieving age for Tdap immunization in 2008) or those who experienced ELS after receipt of pediatric DTaP immunization are at increased risk of ELS after receipt of a Tdap vaccine. A history of ELS after receipt of pediatric DTaP or any other vaccine is not considered a precaution or contraindication for DTaP immunization in children younger than 7 years of age.³⁶

Arthus reaction is a local inflammatory vasculitis that develops after formation and deposition of immune complexes and activation of complement. Immune complexes form in the setting of high local concentration of vaccine components and high circulating antibody concentration.³⁷ Arthus reactions are characterized by severe pain, swelling, induration, edema, hemorrhage, and, occasionally, necrosis at the injection site. These symptoms and signs usually develop 4 to 12 hours after immunization; by contrast, immediate type I hypersensitivity reactions (anaphylaxis) usually occur within minutes of immunization. The Centers for Disease Control and Prevention (CDC) has recommended that persons who experienced an Arthus reaction after a previous dose of tetanus toxoid-containing vaccine should not receive Td more frequently than every 10 years even for tetanus prophylaxis as part of wound management.³⁸

Reactogenicity Considerations of Tdap After DTP/DTaP/Td Immunization

For routine administration, both the American Academy of Pediatrics (AAP) and the CDC have recommended an adolescent booster dose of Td vaccine at the 11- to 12-year visit.^{38,39} The CDC also has recommended at least a 5-year interval between the last dose of pediatric DTaP and the adolescent Td dose. Both the AAP and CDC have recommended a 10-year interval between subsequent, routine booster Td doses and a 5-year interval for wound management. Administering frequent doses of Td at short intervals may increase reactogenicity of Td vaccine.^{40,41} Prelicensure trials for Tdap excluded subjects who had received pediatric DTaP/DTP vaccine within 5 years or Td vaccine within 10 years (Boostrix)²⁶ or 5 years (Adacel).²⁷ Although administering Td at intervals shorter than 5 years is not necessary to prevent tetanus and diphtheria, using Tdap at shorter intervals from Td to protect against pertussis might be desirable.

The safety of administering Tdap vaccine at intervals less than 5 years after a dose of DTP/DTaP or Td vaccine was evaluated in Canada.⁴² An open-label, nonrandomized study of 7001 students 7 to 19 years of age assessed the rates of adverse events after administration of Tdap

vaccine (Adacel) according to the type of event and interval from the last dose of Td or pediatric DTP or DTaP vaccine. Reports of severe local reactions were not increased in subjects who received Tdap vaccine at intervals less than 10 years; there was no signal of increased reactogenicity at the shortest 2-year interval group (464 subjects younger than 18 months to 30 months of age or younger) versus the longest interval of more than 10 years. No vaccine-related serious adverse event or Arthus reaction was reported. Another Canadian study of 260 students 14 to 17 years of age also showed acceptable safety when Tdap (Adacel) was administered at intervals less than 5 years after Td.⁴³ No individual in these Canadian studies had received tetravalent meningococcal conjugate vaccine (MCV4 [Menactra]).

Reactogenicity Considerations of Tdap/Td Immunization Simultaneously and Nonsimultaneously With MCV4

Tdap, Td, and MCV4 (Menactra) all contain diphtheria toxoid.^{21,22,44} No prelicensure immunogenicity or safety study of simultaneous or sequential administration of MCV4 with either Tdap vaccine was performed. The diphtheria toxoid GMCs were comparable or lower after receipt of Tdap compared with Td in prelicensure trials*; therefore, studies of Td and MCV4 may be informative. Simultaneous administration of Td and MCV4 or sequential administration of Td and placebo followed 28 days later by administration of MCV4 was studied among 1021 adolescents 11 to 17 years of age in a prelicensure trial of MCV4. No prelicensure trial examined administration of Td after administration of MCV4. The Td vaccine, manufactured by Sanofi Pasteur, contains approximately 8 μ g of diphtheria toxoid per dose, and MCV4 contains approximately 48 μ g of diphtheria toxoid per dose.⁴⁵ Simultaneous- and sequential-administration schedules studied induced immune responses to all antigens. One month after immunization, the immune responses to diphtheria toxoid were higher when MCV4 was administered simultaneously with Td (geometric mean titer [GMT]: 120.9 IU/mL; 95% CI: 104.6–139.8) than when Td was administered with placebo (GMT: 8.4 IU/mL; 95% CI: 7.6–9.2) or when MCV4 was given alone in another prelicensure study (GMT: 46.5 IU/mL; 95% CI: not available). The GMT was intermediate when MCV4 was administered 28 days after Td (GMT 1 month after receipt of MCV4: 16.9 IU/mL; 95% CI: not available). The overall rates of solicited adverse local and systemic events were similar for the simultaneous- and sequential-administration study groups. Acceptable safety of simultaneous immunization of MCV4 with Tdap and sequential administration of Tdap first

* One month after immunization, the antidiphtheria toxoid GMCs were: Adacel, 8.5 IU/mL (95% confidence interval [CI]: 7.6–9.5), compared with Tdsp, 7.1 IU/mL (95% CI: 6.4–7.8); and Boostrix, 7.3 IU/mL (95% CI: 7.1–7.6), compared with TdMPHBL, 14.0 IU/mL (95% CI: 13.2–14.9). The antidiphtheria toxoid seroprotective and booster response rates in the adolescents immunized with Tdap (Adacel and Boostrix) were noninferior to the those immunized with Td.^{21,22}

followed by MCV4 1 month later can be inferred from results of this study. Postlicensure studies are underway to address reactogenicity of simultaneous and sequential administration of Tdap vaccines and the MCV4 vaccine.^{21,22}

Economic Studies

Two US economic studies have compared adolescent immunization with other pertussis immunization strategies.^{46,47} Both studies identified universal, single-dose Tdap during adolescence as the most cost-effective strategy, considering a variety of assumptions regarding incidence of pertussis, waning immunity, vaccine efficacy, vaccine coverage, and infant transmission. Purdy et al⁴⁷ compared 7 potential adolescent/adult pertussis immunization strategies during a 10-year interval, estimating the incidence of pertussis (from prospective studies) to be 450 to 507 cases per 100 000 population. Universal immunization of adolescents was cost-saving to society when the Tdap and program costs were \$37 or less (2002 dollars) per adolescent immunization. Lee et al⁴⁶ compared 6 potential adolescent/adult Tdap immunization strategies over the course of a lifetime for the hypothetical cohort of 4 million US adolescents and estimated the incidence of pertussis (from Massachusetts surveillance data) to be 155 per 100 000 for adolescents and 11 per 100 000 for adults. The study assumed a Tdap immunization cost of \$25 per person immunized (ie, an incremental cost of \$15 for Tdap over Td). In this model, immunizing all adolescents would cost \$1100 per pertussis case prevented or \$20 000 per quality-adjusted life-year saved (in 2004 dollars). In a sensitivity analysis, Lee et al⁴⁶ estimated that universal adolescent Tdap would be cost-saving to society if the incidence of adolescent and adult pertussis was at least 4 times greater than their base case estimates (which would be similar to Purdy et al⁴⁷ base case estimates).

Rationale for Adolescent Tdap Recommendations

The primary objective of immunizing adolescents with Tdap is to protect immunized adolescents against pertussis.^{7,48} A secondary objective is to reduce the reservoir of pertussis within the population at large and potentially to reduce the incidence of pertussis in nonimmunized peers and those in other age groups, including infants, who have the highest risk of complications from pertussis.^{7,8,49} The extent to which the secondary objective can be achieved through adolescent immunization is unknown, but high penetration of vaccine among susceptible individuals (eg, >70%) may be required before an effect might be anticipated.

The decision to recommend Tdap immunization for adolescents is based on several considerations: the burden of pertussis among adolescents; attendant disruption of families, schools, and communities; consumption of primary medical and public health resources in post-

exposure management of contacts, with little benefit; studies suggesting that adolescent pertussis immunization would be safe, effective, and economical; and the established infrastructure for adolescent immunization.^{46,47,50–55}

A simple exchange of Tdap for Td in the immunization schedule at the 11- to 12-year visit and during wound management to protect against pertussis has some caveats of uncertain importance. Frequent doses of tetanus and diphtheria toxoid-containing vaccines can be associated with heightened local and systemic reactogenicity. Therefore, in making recommendations on the spacing and sequencing of vaccines containing tetanus toxoid, diphtheria toxoid, and/or pertussis components, the AAP considered data from a range of prelicensure and postlicensure studies of Tdap and other vaccines containing these components.

RECOMMENDATIONS

Routine Adolescent Immunization With Tdap Vaccine

1. Adolescents 11 to 18 years of age should receive a single dose of Tdap instead of Td vaccine for booster immunization against tetanus, diphtheria, and pertussis if they have completed the recommended childhood DTP/DTaP immunization series† and have not received Td; the preferred age for Tdap immunization is 11 to 12 years (both evidence grade I [see Appendix]).
2. Adolescents 11 to 18 years of age who received Td but not Tdap vaccine are encouraged to receive a single dose of Tdap to provide protection against pertussis if they completed the recommended childhood DTP/DTaP immunization series† (evidence grade I). An interval of at least 5 years between Td and Tdap immunization is suggested to reduce the risk of local and systemic reactions after Tdap immunization. However, Tdap can be given at shorter intervals, particularly in settings of increased risk of pertussis (see “Adolescent Immunization With Tdap Vaccine in Special Situations”), because benefits of protection from pertussis outweigh possible increased local and systemic reactions (evidence grade II-3). The safety of intervals as short as approximately 2 years between Td and Tdap is supported by a Canadian study of children and adolescents.
3. Health care professionals should administer Tdap and MCV4 vaccines to adolescents 11 to 18 years of age during the same visit if both vaccines are indicated (evidence grade I, Td and MCV4).⁵⁶ If simultaneous immunization is not feasible, MCV4 and Tdap vaccine can be administered using either sequence. The AAP

† Five doses of DTP/DTaP before the seventh birthday; if dose 4 was administered on or after the fourth birthday, dose 5 was not required. Children who begin the tetanus and diphtheria immunization series at 7 years of age or older required 3 doses of Td to complete the primary series.

suggests a minimum interval of 1 month between Tdap and MCV4 (evidence grade III).

Dosage and Administration

The dose of Tdap (Boostrix or Adacel) is 0.5 mL, administered intramuscularly. The deltoid muscle of the upper arm generally should be used.

Interchangeable Use of Tdap Products

A single dose of either Boostrix or Adacel may be administered to adolescents who have or have not completed the childhood DTP/DTaP immunization series regardless of the type or manufacturer of DTP/DTaP vaccines used to complete childhood immunization.

Simultaneous Immunization With Tdap and Other Vaccines

Administering all indicated vaccines during a single visit increases the likelihood that adolescents will receive each of the immunizations on schedule. Each vaccine should be administered by using a separate syringe at different anatomic sites. Some experts recommend administering no more than 2 injections per deltoid, separated by 1 inch during 1 visit.

Adolescent Immunization With Tdap Vaccine in Special Situations

Only 1 dose of Tdap should be administered to an adolescent. In most special situations, a single dose of Tdap is preferred to Td. Simultaneous administration of Tdap and MCV4, as well as a 5-year or greater interval between Td and Tdap, may limit the risk of increased local injection-site reactions. In certain settings, benefits of immunization to protect against disease outweigh risks of reactions.

Situations of Increased Risk of Acquiring Pertussis

4. Adolescents 11 to 18 years of age are encouraged to receive a single dose of Tdap, if they previously have not received Tdap, during situations of increased risk of acquiring pertussis even if they have received Td within 5 years. Situations of increased risk of acquiring pertussis include living in a community in which there is an increased rate of pertussis or an outbreak or having close direct contact with a case of pertussis, such as in a family, residential facility, a school, or school-related activity.

Situations of Increased Risk of Complications From Pertussis

5. Adolescents 11 to 18 years of age are encouraged to receive a single dose of Tdap, if they previously have not received Tdap, if they or their close contacts have increased risk of complications from pertussis even if they have received Td within 5 years. Situations of increased risk from pertussis include (1) having an underlying medical condition for which pertussis would have increased morbidity or possible mortality

(eg, neurologic, muscular, or cardiac disorder; airway or pulmonary disorder) and (2) having close contact (eg, household member or out-of-home caregiver) with an infant younger than 12 months of age.

Tetanus Prophylaxis in Wound Management

6. Adolescents 11 to 18 years of age who require tetanus toxoid vaccine as part of wound management³⁹ should receive a single dose of Tdap instead of Td if they have not previously received Tdap. A history of earlier MCV4 immunization should not be factored into management decisions for wound prophylaxis.

- MCV4 should be given concurrently with Tdap vaccine, if feasible, if not given previously.
- If Tdap is not available or if Tdap was administered more than 5 years previously, adolescents who need a tetanus toxoid vaccine as part of wound management should receive Td vaccine; tetanus toxoid (TT) can be administered if Td is not available or the adolescent has a contraindication or precaution to Td.
- A thorough attempt must be made to determine if an adolescent has completed the 3-dose primary immunization series against tetanus. Persons with unknown or uncertain tetanus-immunization histories should be considered to have had no previous doses of a tetanus toxoid-containing vaccine (see "History of Incomplete DTP/DTaP/DT or Td Immunization").
- Persons who have not completed the primary series may require a tetanus toxoid-containing vaccine and passive immunization with tetanus immune globulin at the time of wound management. If tetanus immune globulin and a tetanus toxoid-containing vaccine are both indicated, each product should be administered using a separate syringe at different anatomic sites.

History of Pertussis

7. Adolescents 11 to 18 years of age who have a history of pertussis generally should receive Tdap according to the routine recommendation. The duration of protection after *B pertussis* infection is unknown (waning may begin as early as 7 years after infection), and the diagnosis of pertussis can be difficult to confirm, particularly with test results other than a positive culture for *B pertussis*.⁵⁷ Administering pertussis vaccines to persons with a history of pertussis presents no theoretic safety concerns.

History of Receipt of DT or Td but Incomplete Pertussis Immunization

8. Adolescents 11 to 18 years of age who received DT or Td vaccine(s) instead of 1 or more doses of DTP/DTaP

vaccine(s) generally should receive a single dose of Tdap vaccine to provide protection against pertussis if they completed the recommended childhood immunization series for tetanus and diphtheria toxoids† and have no contraindication to a pertussis vaccine. In routine situations, an interval of at least 5 years between the most recent Td dose and Tdap vaccine is suggested (see “Situations of Increased Risk of Acquiring Pertussis” and “Situations of Increased Risk of Complications From Pertussis”).

History of Incomplete DTP/DTaP/DT or Td Immunization

9. Adolescents 11 to 18 years of age who have never been immunized against tetanus, diphtheria, or pertussis should receive a series of 3 tetanus and diphtheria toxoid-containing vaccines, 1 of which is Tdap. The preferred schedule is a single Tdap dose, followed by a dose of Td vaccine 4 weeks or more after the Tdap dose, and a second dose of Td vaccine 6 to 12 months after the Td dose. Tdap may substitute for any 1 of the 3 doses in the series. Adolescents who received other incomplete immunization schedules against tetanus and diphtheria should be immunized with Tdap and/or Td according to catch-up recommendations.³⁹ A single dose of Tdap may be used to substitute for any 1 of the Td doses.

History of Receipt of DTP/DTaP/DT or Td Vaccine but Incomplete Records

10. In situations in which adolescents 11 to 18 years of age are likely to have received immunization against tetanus and diphtheria but cannot produce records, health care professionals can obtain serologic testing for antibodies to tetanus and diphtheria toxoids to avoid unnecessary immunizations. If antitetanus and antidiphtheria toxoid concentrations are each ≥ 0.1 IU/mL, previous immunization with tetanus and diphtheria toxoid-containing vaccines is presumed, and a single dose of Tdap vaccine is indicated; this Tdap dose is considered the adolescent booster dose.

Pregnancy

11. Pregnancy is not a contraindication to Tdap (or Td) immunization. The AAP recommends that pregnant adolescents be given the same considerations for immunization as nonpregnant adolescents. If Tdap or Td vaccine is indicated, administration in the second or third trimester (before 36 weeks of gestation) is preferred, when feasible, to minimize a perception of an association of immunization with

adverse pregnancy outcomes, which are more common during the first trimester. No evidence exists of a risk of immunizing pregnant women with inactivated bacterial vaccines or toxoids or inactivated viral vaccines.³⁶ Both Tdap and Td vaccines are categorized as pregnancy category C agents by the FDA. FDA-acceptable well-controlled human studies and animal reproduction studies have not been conducted for Tdap.^{21,22} Because of lack of data on use of Tdap vaccine in pregnant women, both Tdap manufacturers have established pregnancy registries for women immunized with Tdap during pregnancy. Health care professionals are encouraged to report Tdap immunization during pregnancy (Boostrix, GlaxoSmithKline Biologicals, 888-825-5249; or Adacel, Sanofi Pasteur, 800-822-2463).

Health care professionals should consider immunizing adolescents 11 to 18 years of age as soon as feasible in the immediate postpartum period, if the adolescent has not previously received Tdap, to reduce the risk of becoming infected and then transmitting pertussis to the infant (see “Situations of Increased Risk of Complications From Pertussis”). Protection of the adolescent mother against pertussis may develop 1 to 2 weeks after immunization. AAP recommendations for use of Tdap vaccines in pregnant adolescents may differ from those of the CDC.

Lack of Availability of Tdap or MCV4

12. If Tdap (or Td) vaccine and MCV4 are both indicated for adolescents but only 1 vaccine is available, the available vaccine generally should be administered and the other administered when the missed vaccine becomes available. If simultaneous immunization is not feasible, the AAP suggests a minimum interval of 1 month between administration of Tdap and MCV4.

Use of Td When Tdap Is Not Available

13. Health care professionals should administer a dose of Td when Tdap is indicated but not available if the last DTP/DTaP/DT/Td dose was administered 10 or more years earlier. After completion of childhood DTaP/DTP immunization, most adolescents are adequately protected against tetanus and diphtheria for at least 10 years. Immunization can be deferred temporarily when the last tetanus- and diphtheria-containing vaccine was administered less than 10 years earlier and the adolescent is likely to return for follow-up. If immunization is deferred, health care professionals should maintain a system to recall the adolescent when vaccine becomes available or should refer the adolescent to another facility for immunization.

† Five doses of DTP/DTaP before the seventh birthday; if dose 4 was administered on or after the fourth birthday, dose 5 was not required. Children who begin the tetanus and diphtheria immunization series at 7 years of age or older required 3 doses of Td to complete the primary series.

Children 7 to 10 Years of Age With History of Incomplete Childhood DTP/DTaP Immunization

14. Neither Tdap vaccine is licensed for use in children younger than 10 years of age. Boostrix is licensed for children beginning at 10 years of age,²¹ and Adacel is licensed for children beginning at 11 years of age.²² Children 7 through 9 years of age who never received any pediatric DTP/DTaP/DT or Td dose generally should receive 3 doses of Td: dose 2 is administered 4 weeks or more after dose 1, and dose 3 is administered 6 to 12 months or longer after dose 2. A 10-year-old child could receive Boostrix for 1 of these doses. A single dose of Tdap is recommended for adolescents 11 to 18 years of age who have completed a 3-dose Td series if the series did not include Boostrix during the 10th year; an interval of at least 5 years between the most recent Td dose and Tdap is suggested (see “Situations of Increased Risk of Acquiring Pertussis” and “Situations of Increased Risk of Complications From Pertussis”). Children 7 to 10 years of age who received other incomplete immunization schedules against tetanus, diphtheria, and pertussis should be immunized against tetanus and diphtheria according to catch-up recommendations³⁹ using an all-Td schedule (except children in their 10th year, who could receive a single dose of Boostrix substituted for 1 dose of Td).

Children with no history or an incomplete history of pediatric DTP/DTaP/DT or Td immunization could have received doses. Health care professionals can obtain serologic testing for antibodies against tetanus and diphtheria toxoids in these children. If tetanus and diphtheria toxoid antibody concentrations are each protective at ≥ 0.1 IU/mL, then the child can be presumed to have been immunized against tetanus, diphtheria, and possibly pertussis, and Td immunization may be deferred until the child is 11 to 12 years of age, when Tdap vaccine should be given.

Inadvertent Administration of Tdap or Pediatric DTaP Vaccine

15. Tdap vaccine is not indicated for children younger than 10 years of age. The family should be informed of any error in vaccine administration. If Tdap vaccine is administered inadvertently instead of DTaP to a child younger than 7 years of age as the first, second, or third dose of the immunization series, the Tdap dose should not be counted and DTaP should be given on the same day or as soon as possible, to keep the child on schedule for all vaccines. The remaining doses of the DTaP series should be administered on the usual schedule. If Tdap vaccine is administered inadvertently instead of DTaP to a child younger than 7 years of age as the fourth or

fifth dose in the series, the dose should be counted as valid. If Tdap was administered as the fourth dose, the child should receive a fifth dose of the series using DTaP vaccine on the usual schedule. The routine recommendations for adolescent Tdap immunization would apply to children who inadvertently received Tdap instead of DTaP vaccine at an age younger than 7 years.

If Tdap is administered inadvertently instead of Td vaccine to a child 7 to 9 years of age, the Tdap dose should be counted as the adolescent Tdap booster. The child should receive a vaccine containing tetanus and diphtheria toxoids 10 years after the inadvertent Tdap dose.

DTaP is not indicated for people 7 years of age or older. If DTaP is administered inadvertently to a child 7 years of age or older or to an adolescent, the dose should be counted as the adolescent Tdap booster. The child or adolescent should receive a vaccine containing tetanus and diphtheria toxoids 10 years after the inadvertent DTaP dose.

Individuals Older Than 18 Years and Adults

16. To maintain protection against tetanus and diphtheria, the CDC has recommended decennial Td boosters for adults, beginning 10 years after the adolescent dose.³⁸ The safety and immunogenicity of 1 Tdap (Adacel) as a single booster immunization against tetanus, diphtheria, and pertussis have been demonstrated for people 19 to 64 years of age.²² CDC recommendations for the use of Tdap (Adacel) in persons older than 18 years will be published.

Contraindications and Precautions for Tdap and Td Vaccine Use

Contraindications to Administration of Tdap or Td

- Tdap or Td is contraindicated among people with a history of serious allergic reaction (ie, anaphylaxis) to any component of the vaccines. Because of the importance of tetanus immunization, individuals with a history of anaphylaxis to components included in all Tdap and Td vaccines should be referred to an allergist to determine if they have a specific allergy to tetanus toxoid, can be desensitized to tetanus toxoid, and can safely receive TT vaccine.
- Tdap is contraindicated among people with a history of encephalopathy (eg, coma, prolonged seizures) within 7 days of administration of a pertussis vaccine that is not attributable to another identifiable cause. These people should receive Td instead of Tdap.

Precautions to Administration of Tdap or Td or Both Vaccines

A precaution is a condition in a recipient that might increase the risk of a serious reaction. In these situations,

health care professionals should evaluate the risks and benefits of administering Tdap or Td. Precautions include the following.

- Guillain-Barré syndrome 6 weeks or less after the previous dose of a tetanus toxoid vaccine. If a decision is made to continue tetanus toxoid immunization, Tdap is preferred if otherwise indicated.
- Progressive neurologic disorder, uncontrolled epilepsy, or progressive encephalopathy until the condition has stabilized. This precaution is for vaccines with pertussis components. If a decision is made to withhold pertussis immunization, Td may be used instead of Tdap.

Deferral of Administration of Tdap or Td or Both Vaccines

Reasons for deferral include the following.

- Moderate or severe acute illness with or without fever: immunization should be deferred until the acute illness resolves.
- History of a severe Arthus hypersensitivity reaction after a previous dose of a tetanus and diphtheria toxoid-containing vaccine or a diphtheria toxoid vaccine that does not contain tetanus toxoid, such as MCV4 (which contains diphtheria toxoid as a carrier protein); if a true Arthus reaction is likely, vaccine providers should defer Tdap or Td immunization for at least 10 years after the tetanus or diphtheria toxoid-containing vaccine. If the Arthus reaction was associated with a vaccine that contained diphtheria toxoid without tetanus toxoid, deferring Tdap or Td vaccine might leave the adolescent inadequately protected against tetanus. In this situation, if the last tetanus toxoid vaccine was administered 10 or more years earlier, providers may administer TT vaccine or consider measuring tetanus antibody concentrations to evaluate the need for tetanus immunization; tetanus antibody concentrations of ≥ 0.1 IU/mL are considered protective.

Conditions That Are Not Contraindications or Precautions to Administration of Tdap

The following conditions are not contraindications or precautions for Tdap. Adolescents with these conditions can receive a dose of Tdap if otherwise indicated. The first 4 conditions listed are precautions for pediatric DTaP/DTP but are not contraindications or precautions for Tdap immunization in adolescents.

- Temperature $\geq 105^{\circ}\text{F}$ ($\geq 40.5^{\circ}\text{C}$) within 48 hours after DTP/DTaP immunization not attributable to another cause;
- Collapse or shock-like state (hypotonic hyporesponsive episode) within 48 hours after DTP/DTaP immunization;

- Persistent crying lasting 3 hours or longer occurring within 48 hours after DTP/DTaP immunization;
- Convulsions with or without fever, occurring within 3 days after DTP/DTaP immunization;
- History of ELS reaction after pediatric DTP/DTaP or Td immunization that was not an Arthus hypersensitivity reaction;
- Stable neurologic disorder, including well-controlled seizures, history of seizure disorder, and cerebral palsy;
- Brachial neuritis;
- Latex allergy other than anaphylactic allergies (eg, a history of contact to latex gloves) (The tip and rubber plunger of the Boostrix needleless syringe contain latex; this Boostrix product should not be administered to adolescents with a history of a severe [anaphylactic] allergy to latex but may be administered to people with less severe allergies [eg, contact allergy to latex gloves]. The Boostrix single-dose vial and Adacel preparations do not contain latex.);
- Pregnancy;
- Breastfeeding;
- Immunosuppression, including people with human immunodeficiency virus infection (Tdap poses no known safety concern for immunosuppressed people; the immunogenicity of Tdap in people with immunosuppression has not been studied and could be suboptimal);
- Intercurrent minor illness; and
- Antibiotic use.

Reporting of Adverse Events After Immunization

As with any newly licensed vaccine, surveillance for rare adverse events associated with administration of Tdap vaccine is important for assessing safety in large-scale use. The National Childhood Vaccine Injury Act of 1986 requires health care professionals to report specific adverse events that follow tetanus, diphtheria, or pertussis immunization. All clinically significant adverse events should be reported to VAERS⁵⁸ even if a causal relationship to immunization is uncertain. VAERS reporting forms and information are available on the Internet at <http://vaers.hhs.gov> or by calling 800-822-7967. Web-based reporting is available, and health care professionals are encouraged to report electronically to promote better timeliness and quality of safety data.

Vaccine Injury Compensation

The National Childhood Vaccine Injury Compensation Program, established by the National Childhood Vaccine Injury Act of 1986, is a system under which compensation may be paid on behalf of a person thought to have been injured or to have died as a result of receiving a

vaccine covered by the program. All pertussis-containing vaccines, including Tdap, are covered under the act. The program is intended as an alternative to civil litigation under the traditional tort system, because negligence need not be proven. Additional information is available on the Internet at www.hrsa.gov/osp/vicp or by calling 800-338-2382. An interim Tdap vaccine information statement (VIS) is available at www.cdc.gov/nip/publications/VIS/default.htm#tdap.

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APPENDIX US Preventive Services Task Force Rating System of Quality of Scientific Evidence

I	Evidence obtained from at least 1 properly designed, randomized, controlled trial
II-1	Evidence obtained from well-designed controlled trials without randomization
II-2	Evidence obtained from well-designed cohort or case-control analytic studies, preferentially from >1 center or group
II-3	Evidence obtained from multiple time series with or without the intervention or dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s)
III	Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

Source: US Preventive Services Task Force. *Guide to Clinical Preventive Services*. 2nd ed. Alexandria, VA: International Medical Publishing; 1996:861–865.

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