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Preventing Tetanus, Diphtheria, and Pertussis Among Adolescents: Use of Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccines

Recommendations of the Advisory Committee on Immunization Practices (ACIP)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTERS FOR DISEASE CONTROL AND PREVENTION

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CONTENTS

Disclosure of Relationship

CDC, our planners, and our content experts wish to disclose they have no financial interests or other relationships with the manufacturers of commercial products, suppliers of commercial services, or commercial supporters. This report will not include any discussion of the unlabeled use of a product or a product under investigational use with the exception of the discussion of off-label use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine (Tdap) by all in the following situations:

A. The interval between pediatric DTP/DTaP/DT or Td and Tdap might be shorter than the 5 years indicated in the package insert;
B. Progressive neurologic disorders and uncontrolled epilepsy are considered precautions and not contraindications as indicated in the package insert;
C. Tdap might be used as part of the primary series for tetanus and diphtheria; and
D. Inadvertent administration of Tdap and pediatric DTaP is discussed.

Preventing Tetanus, Diphtheria, and Pertussis Among Adolescents: Use of Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccines

Recommendations of the Advisory Committee on Immunization Practices (ACIP)

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Summary

During spring 2005, two tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine (Tdap) products formulated for use in adolescents (and, for one product, use in adults) were licensed in the United States (BOOSTRIX®, GlaxoSmithKline Biologicals, Rixensart, Belgium [licensed May 3, 2005, for use in persons aged 10–18 years], and ADACEL™, sanofi pasteur, Toronto, Ontario, Canada [licensed June 10, 2005, for use in persons aged 11–64 years]). Prelicensure studies demonstrated safety and efficacy against tetanus, diphtheria, and pertussis when Tdap was administered as a single booster dose to adolescents. To reduce pertussis morbidity in adolescents and maintain the standard of care for tetanus and diphtheria protection, the Advisory Committee on Immunization Practices (ACIP) recommends that: 1) adolescents aged 11–18 years should receive a single dose of Tdap instead of tetanus and diphtheria toxoids vaccine (Td) for booster immunization against tetanus, diphtheria, and pertussis if they have completed the recommended childhood diphtheria and tetanus toxoids and whole cell pertussis vaccine (DTP)/ diphtheria and tetanus toxoids and acellular pertussis vaccine (DTaP) vaccination series (five doses of pediatric DTP/DTaP before the seventh birthday; if the fourth dose was administered on or after the fourth birthday, the fifth dose is not needed) and have not received Td or Tdap. The preferred age for Tdap vaccination is 11–12 years; 2) adolescents aged 11–18 years who received Td, but not Tdap, are encouraged to receive a single dose of Tdap to provide protection against pertussis if they have completed the recommended childhood DTP/DTaP vaccination series. An interval of at least 5 years between Td and Tdap is encouraged to reduce the risk for local and systemic reactions after Tdap vaccination. However, an interval less than 5 years between Td and Tdap can be used; and 3) vaccine providers should administer Tdap and tetravalent meningococcal conjugate vaccine (Menactra®, sanofi pasteur, Swiftwater, Pennsylvania) to adolescents aged 11–18 years during the same visit if both vaccines are indicated and available. This statement 1) reviews tetanus, diphtheria and pertussis vaccination policy in the United States, with emphasis on adolescents; 2) describes the clinical features and epidemiology of pertussis among adolescents; 3) summarizes the immunogenicity, efficacy, and safety data of the two Tdap vaccines licensed for use among adolescents; and 4) presents recommendations for tetanus, diphtheria, and pertussis vaccination among adolescents aged 11–18 years.

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Introduction

Pertussis, an acute, infectious cough illness, remains endemic in the United States despite routine childhood pertussis vaccination for more than half a century and high coverage levels in children for more than a decade (*1–4*). A primary reason for the continued circulation of *Bordetella pertussis* is that immunity to pertussis wanes approximately 5–10 years after completion of childhood pertussis vaccination, leaving adolescents and adults susceptible to pertussis (*5–10*). Among the diseases for which universal childhood vaccination has been

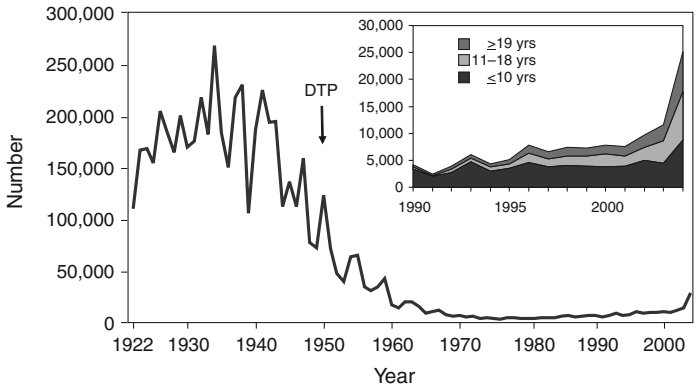
recommended, pertussis is the least well-controlled reportable bacterial vaccine-preventable disease in the United States (*11,12*).

In the United States during 1934–1943, an annual average of 200,752 pertussis cases and 4,034 pertussis-related deaths were reported (*13*). After the introduction of childhood pertussis vaccination during the 1940s, the number of reported pertussis cases declined dramatically, reaching an historic low of 1,010 in 1976 (Figure 1) (*1*). Since the 1980s, the number of reported pertussis cases has been steadily increasing, especially among adolescents and adults (*4,14,15*). Possible reasons for the increase in reported pertussis cases include a true increase in the burden of disease and an increase in the detection and reporting of cases; the relative contribution of each of these factors to the increase observed is unclear (*4,14–17*).

Childhood Pertussis Vaccination Policy in the United States

Whole cell pertussis vaccines became available during the 1920s (*18*), but pediatric diphtheria and tetanus toxoids and whole cell pertussis vaccine (DTP) was not routinely recommended for children until the 1940s and 1950s (*19,20*). In 1991, less reactogenic pediatric acellular pertussis vaccine (diphtheria and tetanus toxoids and acellular pertussis vaccine [DTaP]) was first licensed for use in children for the fourth and fifth doses of the 5-dose childhood vaccination series in the United States (*21,22*), and in 1996, pediatric DTaP was licensed for the first three infant doses (*1*). In 1997, the Advisory Committee on Immunization Practices (ACIP) recommended that pediatric DTaP be used routinely instead of pediatric DTP as a 5-dose DTaP schedule at ages 2, 4, 6, 15–18 months and 4–6 years (*1,23*); pediatric DTP has not been available in the United States since 2002 (CDC, unpublished data, 2005).

FIGURE 1. Number of reported pertussis cases, by year — United States, 1922–2004



SOURCE: 1950–2004, National Notifiable Diseases Surveillance System and 1922–1949, passive reports to the Public Health Service.

Childhood and Adolescent Tetanus and Diphtheria Vaccination Policy in the United States

Vaccination against tetanus and diphtheria has markedly reduced the number of cases and deaths from tetanus and diphtheria in the United States in all age groups (*24*). From 1997 through spring 2005, three vaccine formulations against tetanus and diphtheria were recommended for use in the United States: pediatric DTaP routinely for children aged <7 years, pediatric diphtheria and tetanus toxoids vaccine (DT) for children aged <7 years with contraindications or precautions for pertussis components, and adult tetanus and diphtheria toxoids vaccine (Td) routinely for persons aged ≥7 years (*1,24*) (Appendix A). The formulation of choice for vaccination of persons aged ≥7 years has been Td rather than pediatric DT because the lower diphtheria toxoid antigen content of Td induces an adequate immune response and lower rates of adverse reactions in adults than pediatric DT (*24–28*).

To provide continued protection against tetanus and diphtheria, ACIP recommended a booster dose of Td for adolescents (*24*). Before 1995, the adolescent Td booster was recommended at age 14–16 years, approximately 10 years after completion of the childhood DTP series. In 1995, the first harmonized childhood vaccination schedule endorsed by ACIP, the American Academy of Pediatrics, and the American Academy of Family Physicians recommended lowering the age for Td administration to 11–12 years, but vaccination at age 14–16 years was also acceptable (*29*). In 1996, ACIP, in collaboration with partner organizations, recommended a routine vaccination visit at age 11–12 years to reduce adolescent morbidity associated with vaccine-preventable diseases and to improve vaccine coverage for adolescents (*30*). The 1996 ACIP statement emphasized that the recommended age for Td administration was 11–12 years, if at least 5 years had elapsed since administration of the last pediatric DTP/DTaP dose. Td also was recommended for older adolescents who missed the Td dose at age 11–12 years. In some states, school attendance laws continue to require that adolescents receive the Td dose 10 years after the last tetanus and diphtheria toxoids–containing vaccine, rather than at age 11–12 years (CDC, unpublished data, 2005). After the adolescent Td booster dose, ACIP has recommended Td boosters every 10 years throughout life (*24,31*).

Licensure of Pertussis Vaccines for Use in Adolescents and Adults in the United States

In spring 2005, two tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine (Tdap) products were licensed in the United States for use in adolescents (and, for one product, use in adults) (*32,33*). The pertussis antigen composition of the adolescent and adult Tdap formulations is similar to pediatric DTaP, but some of the pertussis antigens are reduced in quantity. The tetanus and diphtheria toxoid composition of Tdap is similar to licensed adult formulations of Td (Appendix A). No preparation containing pertussis antigens alone is licensed in the United States. Acellular pertussis vaccines formulated for adolescents and adults have been available for use in other countries, including Canada, Australia, and several European countries (e.g., France, Austria and Germany) (*10,34–40*).

Background: Pertussis

General Clinical Characteristics

Pertussis is an acute respiratory infection caused by *Bordetella pertussis*, a fastidious gram-negative coccobacillus. The organism elaborates toxins that damage respiratory epithelial tissue and have systemic effects, including promotion of lymphocytosis (*41,42*). Other species of *Bordetella*, including *B. parapertussis,* and less commonly *B. bronchiseptica* or *B. holmesii*, are associated with cough illness; the clinical presentation of *B. parapertussis* can be similar to that of classic pertussis. Illnesses caused by species of *Bordetella* other than *B. pertussis* are not preventable by pertussis vaccines (*43*).

Factors that affect the clinical presentation of pertussis include age, the level of immunity, and use of antimicrobials early in the course of the illness (*44*). The usual incubation period for pertussis is 7–10 days (range: 5–21 days) (*20,44,45*). Classic pertussis is characterized by three phases of illness: catarrhal, paroxysmal, and convalescent (*20,44,45*). During the catarrhal phase, which generally lasts 1–2 weeks, infected persons experience coryza and an intermittent cough; high fever is uncommon. The paroxysmal phase usually lasts 4–6 weeks and is characterized by spasmodic cough, posttussive vomiting, and inspiratory whoop. Absolute lymphocytosis is common in unvaccinated children (*46*). Symptoms slowly improve during the convalescent phase, which generally lasts 2–6 weeks, but can last months. Complications can occur during the course of pertussis, including hypoxia, pneumonia, weight loss, seizures, encephalopathy, and death (*20,41,44,47*).

Infants aged <12 months with pertussis are more likely than older age groups to have complications or be hospitalized during their illness (*16,47,48*). During 2000–2004, an average of 2,488 cases of pertussis was reported annually among infants aged <12 months. Among these infants, 63% were hospitalized, and the median duration of hospitalization was 5 days (range: 1–152 days) (CDC, unpublished data, 2005). Two to 3 doses of pediatric DTaP (recommended at ages 2, 4, and 6 months) provide protection against severe pertussis (*16,48,49*). Young infants, who can present with symptoms of apnea and bradycardia without cough, are at highest risk for death from pertussis (*16,47,48*). During 1980–2004, a total of 223 pertussis-related deaths in infants aged <4 months were reported to CDC (of 280 in all age groups) (*48*, CDC, unpublished data, 2005). Of the 100 pertussis-related deaths reported during 2000–2004, a total of 90 (90%) were among young infants aged <4 months and 76 (76%) were among infants aged <2 months (CDC, unpublished data, 2005).

B. pertussis is primarily transmitted from person to person through large respiratory droplets generated by coughing or sneezing. Persons with pertussis are most infectious during the catarrhal and early paroxysmal phases of illness (*20,50*). The disease is highly communicable, with attack rates as high as 80%–90% among nonimmune household contacts (*20,24,44*). Adolescents with pertussis can transmit the disease to infants. A study conducted using enhanced pertussis surveillance during 1999–2002 investigated the source of pertussis among infants aged <12 months. On the basis of parental interview, a source was identified among 264 (43%) of 616 infant cases. An adolescent (defined in the study as a person aged 10–19 years) was identified as the source for 43 (7%) of the 616 infants (*51*).

Clinical Features and Morbidity Among Adolescents with Pertussis

The spectrum of disease caused by *B. pertussis* in adolescents ranges from mild cough illness to classic pertussis; infection also can be asymptomatic. When presentation is not classic, pertussis can be clinically indistinguishable from other respiratory illnesses. Adolescents reported with pertussis commonly experience a prolonged cough illness and sometimes have complications (Table 1); rates of certain clinical characteristics and complications in these types of studies probably are higher than among all adolescents with pertussis because the cases with a more classic presentation are more likely to be diagnosed and reported (*52–54;* CDC, unpublished data, 2005). Complications and hospitalizations related to pertussis occur in up to 2% of adolescents reported with pertussis (*52,54;* CDC, unpublished data, 2005). Pertussis-related

TABLE 1. Clinical features and complications in adolescents reported with pertussis

Feature	Proportion of adolescents with clinical feature in study			
	Massachusetts 10–17 yrs (n = 314*)	Massachusetts 10–17 yrs (n = 1,679*)	U.S. without Massachusetts 11–18 yrs (n = 21,174†)§	Quebec, Canada 12–17 yrs (n = 280¶)
Paroxysmal cough	74%	76%	87%	100%
Difficulty sleeping	77%	—**	—	—
Difficulty breathing	72%	—	—	—
Posttussive vomiting	56%	49%	52%	71%
Whoop	—	31%	36%	67%
Weight loss	33%	—	—	—
Apnea	—	27%	28%	86%
Urinary incontinence	3%	—	—	0
Pneumonia	2%	2%	2%††	2%
Hospitalization	0	0.8%	2%	1%
Rib fracture	1%	—	—	1%
Loss of consciousness	1%	—	—	0
Seizure	—	0.2%	0.3%	0

* **SOURCE:** Lee GM, Lett S, Schauer S, et al. Societal costs and morbidity of pertussis in adolescents and adults. Clin Infect Dis 2004;39:1572–80.
† **SOURCE:** National Notifiable Diseases Surveillance System and Supplemental Pertussis Surveillance System, 1996–2004; CDC, unpublished data, 2005.
§ For each factor, the percentage was calculated for cases in which information was available. The percentage of total cases for which data were unavailable is as follows: paroxysmal cough (14%), vomiting (14%), whoop (17%), apnea (17%), pneumonia (25%), hospitalization (18%), and seizure (16%).
¶ **SOURCE:** De Serres G, Shadmani R, Duval B, et al. Morbidity of pertussis in adolescents and adults. J Infect Dis 2000;182:174–9.
** Not available.
†† Radiographically confirmed.

deaths are rarely reported among adolescents; in the United States during 1990–2004, two pertussis-related deaths among adolescents aged 11–18 years were reported to CDC (one adolescent with malignancy and one adolescent with severe neurologic impairment) (CDC, unpublished data, 2005). A prolonged cough is a common feature of pertussis in adolescents. A study in Quebec, Canada, indicated that 97% of adolescents with pertussis coughed for ≥3 weeks, and 47% coughed for >9 weeks (*52*). Massachusetts surveillance data demonstrated that 38% of adolescents with pertussis reported during 1989–2004 had already been coughing for ≥1 month at the time of diagnosis (Massachusetts Department of Public Health [MDPH], unpublished data, 2005).

Adolescents with pertussis often make repeated visits for medical care. Of approximately 7,000 Massachusetts adolescents with pertussis reported during 1989–2004, 41% had one, 32% had two, and 24% had three or more medical visits during their illness (MDPH, unpublished data, 2005). Adolescents with pertussis and their household contacts frequently miss school or work. Of Massachusetts adolescents with pertussis, 83% missed school (mean: 5.5 days; range: 0.4–32 days). In 43% of households with an affected adolescent, one parent or caretaker missed work (mean: 2.4 days, range: 0.1–25), and in 14% of households, a second parent or caretaker missed work (mean: 1.8 days, range: 0.1–11 days) (*54*).

Pertussis Diagnosis

Many factors affect the sensitivity, specificity, and interpretation of diagnostic tests for *B. pertussis*, including the stage of the disease, antimicrobial administration, previous vaccination, the quality of technique used to collect the specimen, transport conditions to the testing laboratory, experience of the laboratory, contamination of the sample, and use of nonstandardized tests (*55,56*). In addition, tests and specimen collection materials might not be readily available to practicing clinicians.

Isolation of *B. pertussis* by culture is 100% specific; however, sensitivity of culture varies because fastidious growth requirements make it difficult to transport and isolate the organism. Although the sensitivity of culture can reach 80%–90% under optimal conditions, in practice, sensitivity typically ranges from 30%–60% (*57*). The yield of *B. pertussis* from culture declines in specimens taken after 2 or more weeks of cough illness, after antimicrobial treatment, or after previous pertussis vaccination (*58*). Within 3 weeks after onset of cough, culture is only 1%–3% sensitive (*59*). Although *B. pertussis* can be isolated in culture as early as 72 hours after plating, it takes 1–2 weeks before a culture result can definitively be called negative (*60*). Culture is essential to isolate *B. pertussis* for antimicrobial susceptibility testing and for molecular subtyping of strains.

Direct fluorescent antibody (DFA) tests provide rapid results (hours), but are generally less sensitive (sensitivity: 10%–50%) than culture. With use of monoclonal reagents, the specificity of DFA should generally be >90%; however, the interpretation of the test is subjective, and interpretation by an inexperienced microbiologist can result in lower specificity (*61*). Because of the limitations of DFA testing, CDC does not recommend its use.

Because of increased sensitivity and shorter turn-around-time, DNA amplification (e.g., polymerase chain reaction [PCR]) is being used more frequently to detect *B. pertussis*. When symptoms of classic pertussis are present (e.g., 2 weeks of paroxysmal cough), PCR typically is 2–3 times more likely than culture to detect a positive *B. pertussis* sample (*56,62,63*). The interpretation of PCR-positive but culture-negative samples as either true positive or false positive is difficult. No U.S. Food and Drug Administration (FDA)–licensed PCR test kit and no national standardized protocols, reagents, and reporting formats are available. Approximately 100 different PCR protocols have been reported. These vary by DNA purification techniques, PCR primers, reaction conditions, and product detection methods (*63*). Laboratories must develop and validate their own PCR tests. As a result, the analytical sensitivity, accuracy, and quality control of PCR-based *B. pertussis* tests might vary widely among laboratories. The majority of laboratory validation studies have not sufficiently established the predictive value of a positive PCR test to diagnose pertussis (*63*). Use of PCR tests with low specificity can result in unnecessary investigation and treatment of persons with false-positive PCR test results and inappropriate chemoprophylaxis of their contacts (*63*). CDC Council of State and Territorial Epidemiologists (CSTE) reporting guidelines support the use of PCR to confirm the diagnosis of pertussis only when the case also meets the clinical case definition (≥2 weeks of cough with paroxysms, inspiratory "whoop," or posttussive vomiting) (Appendix B) (*64,65*).

Diagnosis of pertussis by serology generally requires demonstration of a substantial change in titer for pertussis antigens (usually fourfold) when comparing results from acute (≤2 weeks after cough onset) and convalescent sera (≥4 weeks after the acute sample). The results of serologic tests on paired sera generally become available late in the course of illness and can provide only retrospective diagnosis. A single sample serologic assay with age-specific antibody reference values is used as a diagnostic test for adolescents and adults in Massachusetts but is not available elsewhere (*66*). Other single-sample serologic assays lack standardization and do not clearly differentiate immune responses to pertussis antigens after recent clinical disease, from more remote disease, or from vaccination (*43*). None of these serologic assays, including the Massachusetts assay, is licensed by FDA for routine diagnostic use in the United States. For these reasons, CDC guidelines for laboratory confirmation of pertussis cases do not include serologic testing.

The only pertussis diagnostic tests that the CDC endorses are culture and PCR (when the CDC/CSTE clinical case definition is also met) (Appendix B). CDC-sponsored studies are underway to evaluate both serology and PCR testing. CDC guidance on the use of pertussis diagnostics will be updated as results of these studies become available.

Incidence of Pertussis Among Adolescents

Pertussis is reportable in all 50 states and the District of Columbia. State health departments report confirmed and probable cases of pertussis to CDC through the passive National Notifiable Diseases Surveillance System (NNDSS); additional information for pertussis cases is collected through the Supplemental Pertussis Surveillance System (SPSS) (Appendix B) (*4,16*). During 2004, a total of 8,897 (34%) of the 25,827 reported U.S. cases occurred among adolescents aged 11–18 years (incidence for adolescents: 30 per 100,000 population); 17 states each reported >100 pertussis cases in adolescents (*12*, CDC unpublished data, 2005*). The age distribution of the other pertussis cases reported in 2004 was 3,357 (13%) among infants aged <1 years, 5,441 (21%) among children aged 1–10 years, and 7,481 (29%) among adults aged ≥19 years (the age was unknown for 2.5% of the cases). The incidence of pertussis in adolescents varies widely among states and from year-to-year. During 2000–2004, a total of 11 states had an annual incidence of reported pertussis in adolescents of ≥50 per 100,000 population during at least 1 year (Table 2) (*12*, CDC, unpublished data, 2005).

Data from enhanced surveillance sites and prospective studies indicate that the national passive surveillance data sub-

* Incidence throughout this report was calculated using confirmed and probable cases reported to the NNDSS and population estimates from U.S. Census Bureau, available at http://www.census.gov.

TABLE 2. Reported pertussis cases among adolescents aged 11–18 years in selected states,* 2000–2004

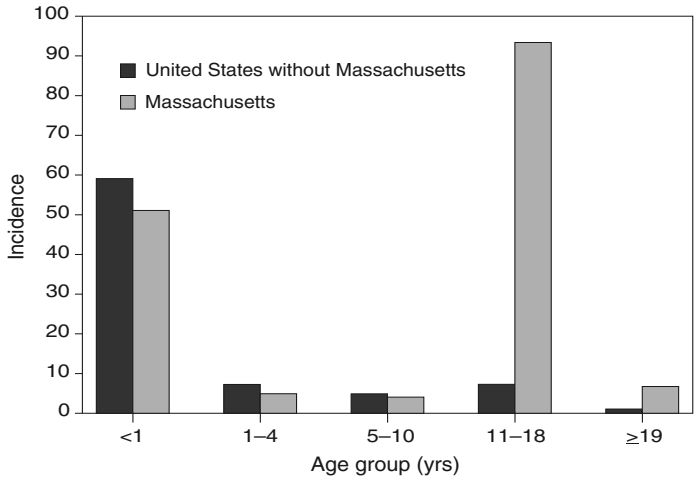
State	High year, no. of cases	High year, annual incidence†	Average annual incidence†
Wisconsin	1,970	305	77
North Dakota	197	246	51
Vermont	157	217	132
Massachusetts	1,060	159	105
Minnesota	690	115	38
Colorado	513	104	44
Arkansas	308	99	28
Iowa	245	71	27
Wyoming	43	66	15
Oregon	250	64	22
South Dakota	56	57	11

SOURCE: CDC, National Notifiable Diseases Surveillance System (NNDSS), unpublished data, 2005.
* States with an annual incidence of ≥50 per 100,000 population for at least one year during 2000-2004.
† Per 100,000 population.

stantially underestimate the burden of pertussis among adolescents. Reliable diagnostic tests are not widely available, and not all diagnosed cases are reported. Since the 1980s, MDPH has conducted enhanced surveillance for pertussis throughout Massachusetts. MDPH uses an in-state, standardized serologic assay for pertussis diagnosis in adolescents and adults; educates health-care providers, public health staff, and the general public about pertussis; and intensifies surveillance around cases, particularly in school settings (*17,66*; MDPH, unpublished data, 2005). During 1996–2004, the average annual incidence of pertussis in Massachusetts adolescents aged 11–18 years was 93 per 100,000 population, approximately 13 times greater than the incidence of 7.3 reported for adolescents in the remainder of the United States (Figure 2); reported rates among children aged <11 years were comparable between Massachusetts and the remainder of the United States (CDC, unpublished data, 2005). Massachusetts data indicated that 62% of reported pertussis cases in adolescents occurred before age 16 years, and 28% of reported cases occurred before age 14 years, suggesting that pertussis booster vaccination early in adolescence could have a substantial impact on the burden of pertussis in adolescents (Figure 3) (CDC, unpublished data, 2005).

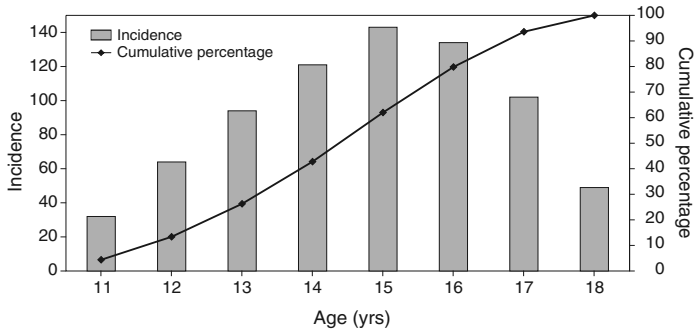
Two prospective studies in the United States have assessed the incidence of pertussis in populations that included adolescents (*67,68*). In a Minnesota health maintenance organization during 1995–1996, persons aged 10–49 years were tested for pertussis if they presented with an acute paroxysmal cough or a persistent cough illness of 7–34 days duration (*67*). Cases were laboratory-confirmed using culture, PCR, and/or serology. On the basis of 27 identified cases, the estimated incidence of laboratory-confirmed pertussis in this study was 507 per 100,000 person-years, and the incidence in adolescents (estimated 997 per 100,000 person-years) was the highest of the age groups studied (*67*). During 1997–2000, a study conducted at sites in eight states estimated the incidence of pertussis among persons aged 15–64 years enrolled in the control arm of an acellular pertussis vaccine trial (*68*). The incidence of pertussis, defined as an acute cough illness of at least 5 days with laboratory confirmation, by culture, PCR, and/or serology, was 370 per 100,000 person-years. Applying less specific case definitions, the study suggested approximately 1,000,000 cases of pertussis occur annually among persons aged ≥15 years in the United States (*68*).

FIGURE 2. Average annual incidence* of reported pertussis cases, by age group — United States without Massachusetts and Massachusetts alone, 1996–2004



SOURCE: CDC, National Notifiable Diseases Surveillance System, unpublished data, 2005.
* Per 100,000 population.

FIGURE 3. Average annual incidence* of reported pertussis cases in adolescents, by age — Massachusetts, 1996–2004



SOURCE: CDC, National Notifiable Diseases Surveillance System, unpublished data, 2005.
* Per 100,000 population.

Pertussis Outbreaks Involving Adolescents

High rates of pertussis in adolescents have been reported during community and statewide outbreaks. For example, in a 1985 outbreak that occurred in a three-county region in semirural central Wisconsin, 32% of 161 cases of pertussis occurred in adolescents aged 10–19 years for an incidence (using only culture-positive cases, the strictest case definition for confirmed cases) of 150 per 100,000 population during the 8-month outbreak period (*69*). Compared with the incidence of pertussis in other age groups, the incidence of pertussis in adolescents was second only to that in infants aged <1 year (496 per 100,000 population) (*69*). In a statewide 1996 outbreak in Vermont, younger adolescents aged 10–14 years accounted for 36% of 280 cases and had the highest incidence (235 per 100,000 population) of all age groups during the outbreak period (*70*).

Reported cases of pertussis in adolescents often occur in outbreaks at middle and high schools, where close interaction occurs among large numbers of students with waning vaccine-

induced immunity to pertussis. Delay in the diagnosis of pertussis contributes to the spread of pertussis in schools. Although the actual number of pertussis outbreaks in schools across the United States is unknown, descriptions of pertussis outbreaks in middle and high schools from several states suggest that these outbreaks are not uncommon. Surveillance data from Massachusetts during 2000–2004 indicated that approximately 90% of the detected pertussis outbreaks (defined in Massachusetts as five or more cases linked in location and time) occurred in schools. During this period, 41% of the reported pertussis cases in adolescents aged 11–19 years were identified through school outbreaks (MDPH, unpublished data, 2005) (Table 3).

Middle and high school outbreaks of pertussis can disrupt usual school functions and result in substantial public health and school efforts to educate families, detect and treat cases, and provide chemoprophylaxis to close contacts. For example, in 2001 in Pike County, Arkansas (population: 11,222), an outbreak of pertussis began among members of a school football team (*71*; CDC, unpublished data, 2005). Among the 242 students in the county's middle and high school, 77 cases (attack rate: 32%) occurred, and the school was temporarily closed because of absenteeism. Of the students in the school, 93% had received at least 4 doses of pediatric DTP/DTaP during childhood. Countywide, 140 cases occurred in 109 households; 64% of the cases were reported among adolescents aged 12–18 years (*71*; CDC, unpublished data, 2005). In July 2003, in Fond du Lac County, Wisconsin (population: 97,296), initial detection of a pertussis outbreak occurred primarily among students who used a high school weight room (*72*; Wisconsin Division of Public Health, unpublished data, 2005). Of the 313 pertussis cases detected in the county over the 8-month outbreak period, 220 (70%) occurred among adolescents aged 10–19 years for an incidence of 1,505 per 100,000 population. A total of 92 cases occurred in six middle schools (range: 1–37 cases per school); 76 cases occurred among high school students (69 cases in one high school). An estimated 5,000 courses of antimicrobials were prescribed during this pertussis outbreak (*72*; Wisconsin Division of Public Health, unpublished data, 2005).

Background: Tetanus and Diphtheria

Tetanus

Tetanus is unique among diseases for which vaccination is routinely recommended in that it is noncommunicable. *Clostridium tetani* spores are ubiquitous in the environment and enter the body through nonintact skin. When inoculated into oxygen-poor sites, such as necrotic tissue that can result from blunt trauma or deep puncture wounds, *C. tetani* spores germinate to vegetative bacilli that multiply and elaborate tetanospasmin, a potent neurotoxin. Generalized tetanus typically presents with trismus (lockjaw), followed by generalized rigidity caused by painful contractions of the skeletal muscles that can impair respiratory function. Glottic spasm, respiratory failure, and autonomic instability can result in death (*73*). During 1998–2000, the case-fatality ratio for reported tetanus was 18% in the United States (*74*).

Following widespread use of tetanus toxoid–containing vaccine during the 1940s, tetanus has become uncommon in the United States, particularly in children and adolescents (*73,75*). During 1990–2004, a total of 624 tetanus cases were reported; 19 (3%) cases were among adolescents aged 11–18 years (*76*; CDC, unpublished data, 2005). A 3-dose primary series of tetanus toxoid–containing vaccine generally induces protective levels of antibody for tetanus that persist for ≥10 years (*73*). Seroprotective rates for tetanus, defined as an antitetanus concentration ≥0.15 IU/mL (international units/milliliter), were obtained from a population-based national serosurvey (National Health and Nutritional Examination Survey [NHANES] III) conducted in the United States during 1988–1994. NHANES III was conducted when Td vaccination was recommended at age 14–16 years, before routine Td vaccination at age 11–12 years was implemented. Results of NHANES III indicated approximately 80% of adolescents aged 12–19 years had protective antitetanus concentrations (*77*).

Neonatal tetanus usually occurs as the result of *C. tetani* infection of the umbilical stump of an infant born to a mother with a maternal antitetanus concentration insufficient to provide protection to the infant (*73*). Neonatal tetanus is extremely

TABLE 3. Number of pertussis outbreaks (>5 cases) identified — Massachusetts, 2000–2004

Category	2000	2001	2002	2003	2004
Total no. of outbreaks	**42**	**12**	**17**	**49**	**22**
No. of outbreaks in schools (% of total outbreaks)	35 (83)	12 (100)	16 (94)	41 (84)	22 (100)
Adolescent cases in school outbreaks/ total adolescent cases (%)	404/869 (46)	160/331 (48)	187/374 (50)	492/1,088 (45)	218/930 (23)

SOURCE: Massachusetts Department of Public Health, unpublished data, 2005.

rare in the United States: three cases were reported during 1990–2004. Two of the cases occurred among children born to mothers who had no dose or 1 dose of a tetanus toxoid–containing vaccine, and the vaccination history of the third mother was unknown (*78,79*; CDC, unpublished data, 2005).

Diphtheria

Respiratory diphtheria is an acute and communicable infectious illness caused by toxigenic strains of *Corynebacterium diphtheriae*, and rarely by toxin-producing *C. ulcerans*; disease is prevented by vaccination with diphtheria toxoid–containing vaccines. Respiratory diphtheria is characterized by a grayish-colored adherent membrane in pharynx, palate, or nasal mucosa that can obstruct the airway. In addition, toxin-mediated cardiac and neurologic complications can occur (*80,81*).

Reports of respiratory diphtheria are rare in the United States in all age groups (*80,82*). During 1998–2004, seven cases of respiratory diphtheria were reported to CDC; one of the cases was imported (*11,12*). The last culture-confirmed case of respiratory diphtheria in a U.S. adolescent was reported in 1996 (*82*). Data obtained from the NHANES III serosurvey during 1988–1994 indicated that the prevalence of immunity to diphtheria, defined as an antidiphtheria concentration of ≥0.1 IU/mL, was approximately 80% among adolescents aged 12–19 years (*77*).

Exposure to diphtheria remains possible during travel to countries where diphtheria is endemic (information available at http://www.cdc.gov/travel/diseases/dtp.htm) or from imported cases. Respiratory diphtheria also can occur following exposure to toxin-producing strains of *C. ulcerans*; some cases have followed contact with dairy animals or consumption of unpasteurized dairy products (*80,83*). Adherence to the ACIP-recommended schedule for tetanus and diphtheria toxoid–containing boosters among adolescents and adults is important to prevent sporadic cases of respiratory diphtheria. Information about the clinical management of diphtheria, including use of diphtheria antitoxin, and the public health response is available at http://www.cdc.gov/nip/vaccine/dat/default.htm and reviewed elsewhere (*24,80,84*).

Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccines for Adolescents

Criteria for Tdap Licensure

In the United States, two Tdap products were licensed for use in adolescents and, for one product, use in adults as a single dose booster immunization against tetanus, diphtheria, and pertussis on the basis of clinical trials demonstrating immunogenicity not inferior to U.S.- licensed Td or pediatric DTaP products and an overall safety profile clinically comparable to U.S.-licensed Td products (*85,86*). In a noninferiority trial, immunogenicity, efficacy, or safety endpoints are demonstrated when a new product is at least as good as a comparator on the basis of a predefined and narrow margin for a clinically acceptable difference between the study groups (*87*). The efficacy of the tetanus and diphtheria toxoid component of each Tdap was based on the immunogenicity of these antigens compared with U.S.-licensed Td using established serologic correlates of protection (*73,81*). The percentage of persons achieving seroprotective antitetanus and antidiphtheria concentrations (≥0.1 IU/mL) and the booster response to each of these antigens 1 month postvaccination were evaluated.

In contrast to tetanus and diphtheria, no well-accepted serologic or laboratory correlate of protection for pertussis exists (*88*). A consensus was reached at the 1997 meeting of the Vaccines and Related Biological Products Advisory Committee that clinical endpoint efficacy studies of acellular pertussis vaccines among adolescents or adults were not required for Tdap licensure in these age groups. Rather, the efficacy of the pertussis components of Tdap administered to adolescents and adults could be inferred using a serologic bridge to infants vaccinated with pediatric DTaP during clinical endpoint efficacy trials for pertussis (*89*). For each Tdap product, the immune response (geometric mean antibody concentration [GMC]) of adolescents to each vaccine pertussis antigen after a single dose of Tdap was compared with the immune response of infants after three doses of pediatric DTaP that included the same pertussis components as the Tdap being assessed (*32,33*). The percentage of adolescents with a booster response to vaccine pertussis antigens exceeding a predefined lower limit for an acceptable booster response also was evaluated.

The safety of Tdap was evaluated by comparing rates of adverse events after vaccination in persons receiving Tdap with those receiving Td. The overall safety profile of Tdap also was assessed.

Tdap Product Information

Data on immunogenicity and safety for the Tdap products licensed in the United States for use in adolescents (and, for one product, use in adults) are presented separately below.

BOOSTRIX®

Indication

BOOSTRIX®, Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine, Adsorbed (Tdap) (GlaxoSmithKline Biologicals [GSK], Rixensart, Belgium), was

licensed on May 3, 2005, for active booster immunization against tetanus, diphtheria, and pertussis as a single dose in persons aged 10–18 years (*33*).

Vaccine Composition

BOOSTRIX® contains the same tetanus toxoid, diphtheria toxoid, and three pertussis antigens (inactivated pertussis toxin [PT], formaldehyde-treated filamentous hemagglutinin [FHA] and pertactin [69 kiloDalton outer membrane protein] [PRN]), as those in INFANRIX® (pediatric DTaP), but BOOSTRIX® is formulated with reduced quantities of these antigens (Appendix A). Each antigen is adsorbed onto aluminum hydroxide. Each dose of BOOSTRIX® (0.5 mL) is formulated to contain 5 Lf [limit of flocculation unit] tetanus toxoid, 2.5 Lf diphtheria toxoid, 8 μg inactivated PT, 8 μg FHA and 2.5 μg PRN. Each dose of BOOSTRIX® also contains aluminum hydroxide (≤0.39 mg aluminum) as the adjuvant, 4.5 mg NaCl, ≤100 μg residual formaldehyde, and ≤100 μg polysorbate 80 (Tween 80) per 0.5–mL dose. BOOSTRIX® contains no thimerosal or other preservative. BOOSTRIX® is available in two presentations: a prefilled disposable syringe without a needle and 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 preparation is latex-free (*33*).

Immunogenicity and Serologic Bridge to Efficacy for Pertussis

A comparative, observer-blinded, multicenter, randomized controlled clinical trial conducted in the United States evaluated the immunogenicity of the tetanus, diphtheria, and pertussis antigens in BOOSTRIX® among adolescents aged 10–18 years (*33,85*). Adolescents were randomized 3:1 to receive a single dose of BOOSTRIX® or a single dose of Td_{MPHBL} (manufactured by the Massachusetts Public Health Biologic Laboratories; contains diphtheria toxoid [2 Lf] and tetanus toxoid [2 Lf]) (*33,85*). Serum samples were obtained before and approximately 1 month after vaccination (*85*). All assays were performed by GlaxoSmithKline Biologicals in Rixensart, Belgium, using validated methods (*90*).

Persons were eligible for enrollment if they were in good health and had completed routine childhood vaccination against diphtheria, tetanus, and pertussis (approximately 98% of persons had received ≥4 doses of pediatric DTP/DTaP). Persons were excluded if they had received the most recent pediatric DTP/DTaP during the preceding 5 years or Td during the preceding 10 years, had a history of pertussis or household exposure to pertussis during the previous 5 years, had any of the ACIP contraindications or precautions for pediatric DTP/DTaP (*91*), had systemic allergic or neurologic reactions or thrombocytopenia after a dose of tetanus or diphtheria toxoid–containing vaccine, had an acute illness, had received blood products or immunoglobulins within 3 months, had any immunodeficiency, had significant underlying disease, had certain neurologic disorders, or were pregnant (*33,85,92*; GSK, unpublished data, 2005).

Tetanus and Diphtheria

Immune responses to tetanus and diphtheria toxoids were compared between the BOOSTRIX® (range: 2,463–2,516 persons) and Td_{MPHBL} (range: 814–834 persons) groups. One month postvaccination, the antitetanus seroprotective (≥0.1 IU/mL) and booster response rates in adolescents who had received a single dose of BOOSTRIX® were noninferior to those who received Td_{MPHBL}. All adolescents had seroprotective antitetanus levels ≥0.1 IU/mL 1 month after vaccination with either BOOSTRIX® (95% confidence interval [CI] = 99.8%–100%) or Td_{MPHBL} (95% CI = 99.6%–100%). The booster response rate to tetanus† in the BOOSTRIX® group was 89.7% (95% CI = 88.4%–90.8%), compared with 92.5% (95% CI = 90.5%–94.2%) in the Td_{MPHBL} group (*33,92*).

One month postvaccination, the antidiphtheria seroprotective (≥0.1 IU/mL) and booster response rates among adolescents who received a single dose of BOOSTRIX® were noninferior to those of adolescents who received Td_{MPHBL}. Among adolescents, 99.9% had seroprotective antidiphtheria levels ≥0.1 IU/mL 1 month postvaccination with either BOOSTRIX® (95% CI = 99.7%–100%) or Td_{MPHBL} (95% CI = 99.3%–100%). The booster response rate to diphtheria† in the BOOSTRIX® group was 90.6% (95% CI = 89.4%–91.7%), compared with 95.9% (95% CI = 94.4%–97.2%) in the Td_{MPHBL} group (*33,92*).

Pertussis

The efficacy of the pertussis components of BOOSTRIX® was evaluated by comparing the immune responses of adolescents vaccinated with a single dose of BOOSTRIX® with the immune responses of infants vaccinated with 3 doses of INFANRIX®. These infants were a subset of those vaccinated with INFANRIX® in a German vaccine efficacy trial during the 1990s (*33,93*). BOOSTRIX® has the same three pertussis antigens as INFANRIX® but in reduced quantities (Appendix A). In the infant trial, the efficacy of 3 doses of INFANRIX® against World Health Organization (WHO)-defined typical pertussis (≥21 days of paroxysmal cough with confirmation of *B. pertussis* infection by culture and/or sero-

† Booster response: In persons with prevaccination antibody concentration <0.1 IU/mL, postvaccination antibody concentration ≥0.4 IU/mL. In persons with prevaccination antibody concentration ≥0.1 IU/mL, an increase of at least four times the prevaccination antibody concentration.

logic testing) was 89% (95% CI = 77%–95%) (*33,93*). The anti-PT, anti-FHA, and anti-PRN GMCs of adolescents 1 month after a single dose of BOOSTRIX® were noninferior to those of infants after 3 doses of INFANRIX® (Table 4) (*33,85,92*).

Booster response rates to the pertussis antigens§ contained in BOOSTRIX® (anti-PT, anti-FHA, and anti-PRN) among adolescents (range: 2,677–2,752 persons) 1 month after administration of BOOSTRIX® met prespecified criteria for an acceptable response. Booster response rates to pertussis antigens were anti-PT, 84.5% (95% CI = 83.0%–85.9%); anti-FHA, 95.1% (95% CI = 94.2%–95.9%), and anti-PRN, 95.4% (95% CI = 94.5%–96.1%) (*33,92*).

Safety

The primary safety study, conducted in the United States, was a randomized, observer-blinded, controlled study in which 3,080 adolescents aged 10–18 years received a single dose of BOOSTRIX®, and 1,034 received Td_{MPHBL} (see BOOSTRIX® Immunogenicity and Serologic Bridge to Efficacy for Pertussis for inclusion and exclusion criteria). Data on solicited local and systemic adverse events were collected using standardized diaries for the day of vaccination and the next 14 consecutive days (i.e., within 15 days following vaccination). Unsolicited and serious adverse events were collected for 6 months following vaccination. No immediate events (within 30 minutes of vaccination) were reported in either vaccination group (*33,85,92*).

Solicited Local Adverse Events

Pain at the injection site was the most frequently reported solicited local adverse event in adolescents vaccinated with BOOSTRIX® or Td_{MPHBL}. Within 15 days after vaccination, 75.3% of persons in the BOOSTRIX® group and 71.7% of persons in the Td_{MPHBL} group reported pain of "any" intensity (Table 5). The rates of any pain and grade 2 or 3 pain combined (but not grade 3 alone) were significantly higher ($p<0.05$) in BOOSTRIX® recipients compared with Td_{MPHBL} recipients (Table 5). However, the rates of grade 3 pain (primary safety endpoint) were similar in each group, and the noninferiority criterion was met for BOOSTRIX® compared with Td_{MPHBL}. No significant differences in the rates of other solicited local adverse events (redness, swelling, and increase in arm circumference above baseline) were observed between the two study groups (*33,85,92*).

Two adolescents in the study reported "large injection-site swelling" after vaccination (predefined as any local swelling with a diameter >100 mm and/or increased circumference of the injected limb >50 mm above baseline measurements and/or any diffuse swelling that interfered with or prevented normal everyday activities). Both persons had onset of symptoms within 3 days of vaccination. One person who had received BOOSTRIX® reported grade 3 pain (Table 5) with functional impairment. This person was evaluated and treated with antimicrobials with symptom resolution within 3 days without sequelae. The second person, who had received Td_{MPHBL}, reported grade 1 pain and did not seek medical attention. The duration of symptoms was unknown, but symptoms resolved without sequelae (*85,90,92*). No cases of whole-arm swelling were reported in either vaccine group (GSK, unpublished data, 2005).

Solicited Systemic Adverse Events

The most frequently reported solicited systemic adverse events within 15 days following vaccination with BOOSTRIX® or Td_{MPHBL} were headache and fatigue (Table 6). A statistically significantly higher rate of grade 2 or grade 3 headache combined (but not grade 3 alone) (Table 6) was reported in the BOOSTRIX® group (15.7%), compared with the Td_{MPHBL} group (12.7%). The proportion of adolescents reporting fever >100.4° F (38.0° C) (5.0% for BOOSTRIX® and 4.7% for Td_{MPHBL}), fatigue, and gastrointestinal systemic events were comparable in both groups (*33,85,92*).

§ Booster responses: In initially seronegative persons (<5 EU/mL [ELISA units per milliliter], postvaccination antibody concentrations ≥20 EU/mL. In initially seropositive persons with prevaccination antibody concentrations ≥5 EU/mL and <20 EU/mL, an increase of at least four times the prevaccination antibody concentration. In initially seropositive persons with a prevaccination antibody concentration of ≥20 EU/mL, an increase at least two times the prevaccination antibody concentration.

TABLE 4. Ratio of pertussis antibody geometric mean concentrations (GMCs) observed in adolescents 1 month after a dose of BOOSTRIX® compared with those observed in infants 1 month after 3 doses of INFANRIX® at ages 3, 4, and 5 months*

Antibody	GMC Ratio: GMC BOOSTRIX®/GMC INFANRIX® (95% CI†)
Anti-pertussis toxin	1.9 (1.8–2.0)§
Anti-filamentous haemagglutinin	7.4 (6.9–7.9)§
Anti-pertactin	4.2 (3.7–4.7)§

SOURCE: Food and Drug Administration. Product approval information—licensing action, package insert: BOOSTRIX®. Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine, Adsorbed. GlaxoSmithKline Biologicals. Rockville, MD: US Department of Health and Human Services, Food and Drug Administration, Center for Biologics Evaluation and Research; 2005. Available at http://www.fda.gov/cber/label/tdapgla122905LB.pdf.

* Populations studied: U.S. adolescents (range: 2,941–2,979) and German infants (range: 631–2,884) from the INFANRIX® vaccine efficacy trial.

† Confidence interval.

§ GMC after BOOSTRIX® was noninferior to GMC after INFANRIX® (lower limit of the 95% CI on the ratio of BOOSTRIX® divided by INFANRIX® >0.67).

TABLE 5. Frequencies of solicited local adverse events among adolescents within 15 days* after a single dose of BOOSTRIX® or Td_{MPHBL}

Event	Description	BOOSTRIX® (%) (N = 3,032)†	Td_{MPHBL} (%) (N = 1,013)†
Pain§	Any	75.3¶	71.7
	Grade ≥2	51.2¶	42.5
	Grade 3	4.6**	4.0
Redness	Any	22.5	19.8
	>20 mm	4.1	3.9
	≥50 mm	1.7	1.6
Swelling	Any	21.1	20.1
	>20 mm	5.3	4.9
	≥50 mm	2.5	3.2
Increased mid-upper arm circumference (vaccinated arm)	Any	28.3	29.5
	>20 mm	2.0	2.2
	>40 mm	0.5	0.3

SOURCES: Food and Drug Administration. Product approval information—licensing action, package insert: BOOSTRIX®. Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine, Adsorbed. GlaxoSmithKline Biologicals. Rockville, MD: US Department of Health and Human Services, Food and Drug Administration, Center for Biologics Evaluation and Research; 2005. Available at http://www.fda.gov/cber/label/tdapgla122905LB.pdf. Food and Drug Administration. Vaccines and Related Biological Products Advisory Committee, March 15, 2005: FDA BOOSTRIX® briefing information. Rockville, MD: US Department of Health and Human Services, Food and Drug Administration; 2005. Available at http://www.fda.gov/ohrms/dockets/ac/05/briefing/2005;4097B1_1.pdf.

* Vaccination day and the following 14 days.
† Number of adolescents in the total vaccinated cohort with local symptom sheets completed.
§ Pain intensity: *Grade 1*: painful on touch (not shown in table); *Grade 2*: painful when limb moved; *Grade 3*: spontaneously painful and/or prevented normal everyday activities; *Any*: Grade 1 + Grade 2 + Grade 3.
¶ Statistically significantly higher ($p<0.05$) after BOOSTRIX® compared with Td_{MPHBL}.
** The rate of Grade 3 injection site pain (primary safety endpoint) after BOOSTRIX® was noninferior to the rate after Td_{MPHBL} (upper limit of two-sided 95% confidence interval on the difference in percentage of adolescents [BOOSTRIX® minus Td groups] ≤4%).

TABLE 6. Frequencies of solicited systemic adverse events among adolescents within 15 days* after a single dose of BOOSTRIX® or Td_{MPHBL}

Event	Description	BOOSTRIX® (%) (N = 3,030)†	Td_{MPHBL} (%) (N = 1,013)†
Fever§	>99.5° F (37.5° C)	13.5	13.1
	>100.4° F (38.0° C)	5.0	4.7
	>102.2° F (39.0° C)	1.4	1.0
Headache¶	Any	43.1	41.5
	Grade ≥2	15.7**	12.7
	Grade 3	3.7	2.7
Fatigue¶	Any	37.0	36.7
	Grade ≥2	14.4	12.9
	Grade 3	3.7	3.2
Gastrointestinal¶††	Any	26.0	25.8
	Grade ≥2	9.8	9.7
	Grade 3	3.0	3.2

SOURCES: Food and Drug Administration. Product approval information—licensing action, package insert: BOOSTRIX®. Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine, Adsorbed. GlaxoSmithKline Biologicals. Rockville, MD: US Department of Health and Human Services, Food and Drug Administration, Center for Biologics Evaluation and Research; 2005. Available at http://www.fda.gov/cber/label/tdapgla122905LB.pdf. Food and Drug Administration. GlaxoSmithKline Biologicals. BOOSTRIX® briefing document. Bethesda, MD: US Department of Health and Human Services, Food and Drug Administration, Center for Biologic Evaluation and Research; March 15, 2005. Available at http://www.fda.gov.ohrms/ac/05/briefing/2005-4097B1_3.pdf.

* Vaccination day and the following 14 days.
† Number of adolescents in the total vaccinated cohort with systemic symptom sheets completed.
§ Oral temperatures or auxillary temperatures.
¶ Headache, fatigue, and gastrointestinal symptoms were each graded as follows: *Grade 1*: easily tolerated (not shown in table); *Grade 2*: interfered with normal activity; *Grade 3*: prevented normal activity; *Any*: Grade 1 + Grade 2 + Grade 3.
** Statistically significantly higher ($p<0.05$) after BOOSTRIX® compared with Td_{MPHBL}.
†† Gastrointestinal symptoms included nausea, vomiting, diarrhea, and/or abdominal pain.

Serious Adverse Events

In the primary U.S. safety study, no serious adverse events (SAEs) occurred within 1 month postvaccination with either BOOSTRIX® or Td_{MPHBL}. During the next 5 months of monitoring, SAEs were reported among 14 (0.4%) of the 3,005 adolescents vaccinated with BOOSTRIX® and two (0.2%) of the 1,003 adolescents vaccinated with Td_{MPHBL}. No SAEs that were of potential autoimmune origin, new onset and chronic in nature, or related to vaccination, as determined by the investigators, were reported (*33,85,90,92*). No seizures, cases of Guillain-Barré syndrome, or physician-diagnosed Arthus reactions were reported (*33,85,90;* GSK, unpublished data, 2005).

Simultaneous Administration with other Vaccines

Safety and immunogenicity of simultaneous administration of BOOSTRIX® with other vaccines were not evaluated during prelicensure studies (*33*).

ADACEL™

Indication

ADACEL™, Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine, Adsorbed (Tdap) (sanofi pasteur, Toronto, Ontario, Canada) was licensed on June 10, 2005, for active booster immunization against tetanus, diphtheria, and pertussis as a single dose in persons aged 11–64 years (*32*).

Vaccine Composition

ADACEL™ contains the same tetanus toxoid, diphtheria toxoid, and five pertussis antigens as those in DAPTACEL® (pediatric DTaP), but ADACEL™ is formulated with reduced quantities of diphtheria toxoid and detoxified PT (Appendix A). Each antigen is adsorbed onto aluminum phosphate. Each dose of ADACEL™ (0.5 mL) is formulated to contain 5 Lf tetanus toxoid, 2 Lf diphtheria toxoid, 2.5 μg detoxified PT, 5 μg FHA, 3 μg PRN, and 5 μg fimbriae types 2 and 3 (FIM). Each dose of ADACEL™ also contains aluminum phosphate (0.33 mg aluminum) as the adjuvant, ≤5 μg residual formaldehyde, <50 ng residual glutaraldehyde, and 3.3 mg 2-phenoxyethanol (not as a preservative) per 0.5–mL dose. ADACEL™ contains no thimerosal. ADACEL™ is available in single dose vials that are latex-free (*32*).

Immunogenicity and Serologic Bridge to Efficacy for Pertussis

A comparative, observer-blinded, multicenter, randomized controlled clinical trial conducted in the United States evaluated the immunogenicity of the tetanus, diphtheria, and pertussis antigens in ADACEL™ among adolescents aged 11–17 years; adults aged 18–64 years were also studied and results are reported elsewhere (*32,86*). Adolescents were randomized 3:2 to receive a single dose of ADACEL™ or a single dose of Td_{sp} (manufactured by sanofi pasteur; contains tetanus toxoid [5 Lf] and diphtheria toxoid [2 Lf]) (*32,86*). Sera from a subset of persons were obtained before and approximately 1 month after vaccination (*32*). All assays were performed at the immunology laboratories of sanofi pasteur in Toronto, Ontario, Canada or Swiftwater, Pennsylvania, using validated methods (*86,94*).

Persons were eligible for enrollment if they were in good health; completion of the childhood DTP/DTaP vaccination series was not required. Persons were excluded if they had received a tetanus, diphtheria, or pertussis vaccine within 5 years; had a diagnosis of pertussis within 2 years; had an allergy or sensitivity to any vaccine component; had a previous reaction to a tetanus, diphtheria or pertussis vaccine, including encephalopathy within 7 days or seizures within 3 days; had an acute respiratory illness on the day of enrollment; had daily use of oral, nonsteroidal anti-inflammatory drugs; had received blood products or immunoglobulins within 3 months; had any immunodeficiency; had significant underlying disease; had neurologic impairment; or were pregnant (*32,94*; sanofi pasteur, unpublished data, 2005).

Tetanus and Diphtheria

Immune responses to tetanus and diphtheria toxoids were compared between the ADACEL™ (N = 527) and Td_{sp} (range: 515–516 persons) groups. One month postvaccination, the antitetanus seroprotective (≥0.1 IU/mL) and booster response rates among adolescents who received ADACEL™ were noninferior to those who received Td_{sp}. All adolescents (95% CI = 99.3%–100% for both groups) had seroprotective antitetanus levels ≥0.1 IU/mL 1 month after vaccination with either ADACEL™ or Td_{sp}. The booster response rate to tetanus[¶] in the ADACEL™ group was 91.7% (95% CI = 89.0%–93.9%) and 91.3% (95% CI = 88.5%–93.6%) in the Td_{sp} group (*32,86,94*). One month postvaccination, the antidiphtheria seroprotective (≥0.1 IU/mL) and booster response rates among adolescents who received a single dose of ADACEL™ were noninferior to those who received Td_{sp}. Among adolescents, 99.8% (95% CI = 98.9%–100%) had protective antidiphtheria levels ≥0.1 IU/mL 1 month after vaccination with either ADACEL™ or Td_{sp}. The booster response rate to diphtheria[¶] in the ADACEL™ group was 95.1% (95% CI = 92.9%–96.8%) and 95.0% (95% CI = 92.7%–96.7%) in the Td_{sp} group (*32,86,94*).

[¶] Booster response was defined as a fourfold rise in antibody concentration, if the prevaccination antibody concentration was equal to or below the cut-off value, and a two-fold rise in antibody concentration if the prevaccination antibody concentration was above the cut-off value. The cut-off value for tetanus was 2.7 IU/mL. The cut-off value for diphtheria was 2.56 IU/mL.

Pertussis

The efficacy of the pertussis components of ADACEL™ was evaluated by comparing the immune responses of adolescents vaccinated with a single dose of ADACEL™ with the immune responses of infants vaccinated with 3 doses of DAPTACEL® in a Swedish vaccine efficacy trial during the 1990s (*32,95*). ADACEL™ and DAPTACEL® contain the same five pertussis antigens, except ADACEL™ contains one fourth the quantity of detoxified PT in DAPTACEL® (*96*) (Appendix A). In the Swedish trial, efficacy of 3 doses of DAPTACEL® against WHO-defined pertussis (≥21 days of paroxysmal cough with confirmation of *B. pertussis* infection by culture and/or serologic testing or an epidemiologic link to a household member with culture-confirmed pertussis) was 85% (95% CI = 80%–89%) (*29,87*). The anti-PT, anti-FHA, anti-PRN, and anti-FIM GMCs of adolescents 1 month after a single dose of ADACEL™ were noninferior to those of infants following three doses of DAPTACEL® (*32,94*) (Table 7).

Booster response rates to the pertussis antigens** contained in ADACEL™ (anti-PT, anti-FHA, anti-PRN, anti-FIM) among adolescents (range: 524–526 persons) 1 month following administration of ADACEL™ met prespecified criteria for an acceptable response. Booster response rates to pertussis antigens were anti-PT, 92.0% (95% CI = 89.3%–94.2%); anti-FHA, 85.6% (95% CI = 82.3%–88.4%); anti-PRN, 94.5% (95% CI = 92.2%–96.3%); and anti-FIM 94.9% (95% CI = 92.6%–96.6%) (*32,94*).

** A booster response for each antigen was defined as a fourfold rise in antibody concentration, if the prevaccination antibody concentration was equal to or below the cut-off value, and a twofold rise in antibody concentration if the prevaccination antibody concentration was above the cut-off value. The cut-off values for pertussis antigens were 85 EU/mL for pertussis toxin, 170 EU/mL for filamentous haemagglutinin, 115 EU/mL for pertactin, and 285 EU/mL for fimbriae.

TABLE 7. Ratio of pertussis antibody geometric mean concentrations (GMCs) observed in adolescents 1 month after a dose of ADACEL™ compared with those observed in infants 1 month after 3 doses of DAPTACEL® at ages 2, 4, and 6 months*

Antibody	GMC Ratio: GMC ADACEL™/ GMC DAPTACEL® (95% CI†)
Anti-pertussis toxin	3.6 (2.8–4.5)§
Anti-filamentous haemagglutinin	5.4 (4.5–6.5)§
Anti-pertactin	3.2 (2.5–4.1)§
Anti-fimbriae	5.3 (3.9–7.1)§

SOURCES: Food and Drug Administration. Product approval information—licensing action, package insert: Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed ADACEL™, sanofi pasteur. Rockville, MD: US Department of Health and Human Services, Food and Drug Administration, Center for Biologics Evaluation and Research; 2006. Available at http://www.fda.gov/cber/label/tdapave012306LB.pdf. Food and Drug Administration. Vaccines and Related Biological Products Advisory Committee, March 15, 2005: FDA ADACEL™ briefing information. Rockville, MD: US Department of Health and Human Services, Food and Drug Administration; 2005. Available at http://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4097B1_4a.pdf. Pichichero ME, Rennels MB, Edwards KM, et al. Combined tetanus, diphtheria, and 5-component pertussis vaccine for use in adolescents and adults. JAMA 2005;293:3003–11.

* Populations studied: U.S. adolescents (range: 524–526) and Swedish infants (N = 80) from DAPTACEL® vaccine efficacy trial (based on number with valuable data for each antigen).

† Confidence interval.

§ GMC after ADACEL™ was noninferior to GMC after DAPTACEL® (lower limit of the 95% CI on the ratio of ADACEL™ divided by DAPTACEL® >0.67).

Safety

The primary adolescent safety study, conducted in the United States, was a randomized, observer-blinded, controlled study in which 1,184 adolescents aged 11–17 years received a single dose of ADACEL™ and 792 received Td_{sp} (see ADACEL™ Immunogenicity and Serologic Bridge to Efficacy for Pertussis for inclusion and exclusion criteria) (*32*). Adults aged 18–64 years were also studied; those results are reported elsewhere (*32*). Data on solicited local and systemic adverse events were collected using standardized diaries for the day of vaccination and the next 14 consecutive days (i.e., within 15 days following vaccination) (*32*).

Immediate Events

Eleven adolescents experienced immediate events within 30 minutes of vaccination (ADACEL™, six persons [0.5%] and Td_{sp}, five persons [0.6%]); all events resolved without sequelae. Immediate events included dizziness, syncope, or vasovagal reactions and pain and erythema at the injection site. No anaphylaxis was reported (*86,94,96*).

Solicited Local Adverse Events

Pain at the injection site was the most frequently reported solicited local adverse event among adolescents in both vaccination groups (Table 8). Within 15 days following vaccination, reports of pain of "any" intensity were more common among adolescents vaccinated with ADACEL™ (77.8%) than among those vaccinated with Td_{sp} (71.0%). The noninferiority criterion was not achieved for the rate of any pain following ADACEL™ compared with the rate following Td_{sp}. Rates of moderate/severe pain, erythema, and swelling following ADACEL™ were comparable to the rates following Td_{sp} (*32,86,94*). No cases of whole-arm swelling were reported in either vaccine group (*94*).

Solicited Systemic Adverse Events

The most frequently reported solicited systemic adverse events within the 15 days following vaccination were headache, generalized body aches, and tiredness (Table 9). The proportion of adolescents reporting fever ≥100.4° F (≥38° C) following vaccination was statistically significantly higher among adolescents vaccinated with ADACEL™ (5.0%) than Td_{sp} (2.7%), but noninferiority criterion for ADACEL™ was

TABLE 8. Frequencies of solicited local adverse events among adolescents within 15 days* after a single dose of ADACEL™ or Td_{sp}

Event	Description	ADACEL™ (%) (N = 1,175)†	Td_{sp} (%) (N = 787)†
Pain§	Any	77.8¶	71.0
	Moderate	18.0	15.6
	Severe	1.5	0.6
Erythema**	Any	20.8	19.7
	Moderate	5.9	4.6
	Severe	6.0	5.3
Swelling**	Any	20.9	18.3
	Moderate	6.5	5.7
	Severe	6.4	5.5
Underarm lymph node swelling§	Any	6.6	5.3
	Moderate	1.0	0.5
	Severe	0.1	0

SOURCES: Food and Drug Administration. Product approval information—licensing action, package insert: Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed ADACEL™, sanofi pasteur. Rockville, MD: US Department of Health and Human Services, Food and Drug Administration, Center for Biologics Evaluation and Research; 2006. Available at http://www.fda.gov/cber/label/tdapave012306LB.pdf. Food and Drug Administration, sanofi pasteur. ADACEL™ briefing document. Bethesda, MD: US Department of Health and Human Services, Food and Drug Administration, Center for Biologic Evaluation and Research; March 15, 2005. Available at http://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4097B1_6.pdf. Food and Drug Administration. Vaccines and Related Biological Products Advisory Committee, March 15, 2005: FDA ADACEL™ briefing information. Rockville, MD: US Department of Health and Human Services, Food and Drug Administration; 2005. Available at http://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4097B1_4a.pdf.

* Vaccination day and the following 14 days.

† Number of persons with available data.

§ Pain at injection site and lymph node swelling each defined as *Mild*: noticeable but did not interfere with activities (not shown in table); *Moderate*: interfered with activities but did not require medical attention/absenteeism; *Severe*: incapacitating, unable to perform usual activities, may have or did necessitate medical care or absenteeism; *Any*: Mild + Moderate + Severe.

¶ The noninferiority criterion was not achieved for the rate of "Any" pain following ADACEL™ compared with the rate following Td_{sp} (upper limit of the 95% confidence interval on the difference in the percentage of persons [ADACEL™ minus Td_{sp}] was 10.7%, whereas the criterion was <10%).

** Erythema and swelling each defined as *Mild*: <10 mm; *Moderate*: 10–34 mm; *Severe*: ≥35mm; *Any*: Mild + Moderate + Severe.

achieved. The rates of the other solicited systemic adverse events were comparable between the ADACEL™ and Td_{sp} groups (*32,94*).

Serious Adverse Events

In the primary adolescent safety study, SAEs within 6 months after vaccination were reported among 11 (0.9%) of the 1,184 adolescents aged 11–17 years vaccinated with ADACEL™ and eight (1.0%) of the 792 adolescents vaccinated with Td_{sp}. Two adolescents (one ADACEL™ recipient and one Td_{sp} recipient) reported seizure events after vaccination; both persons had a history of seizure disorder. SAEs in adolescents were reported by the study investigators to be unrelated to the study vaccine (*94*).

The safety of ADACEL™ among adults also was studied. In the primary adult safety study, SAEs within 6 months after vaccination were reported among 33 (1.9%) of the 1,752 adults aged 18–64 years vaccinated with ADACEL™ and 11 (1.9%) of the 573 adults vaccinated with Td_{sp}. Two of these SAEs were neuropathic events in ADACEL™ recipients and were assessed by the investigators as possibly related to the study vaccine; in both cases, the symptoms resolved completely over several days (*32,86,94,96*). No physician-diagnosed Arthus reactions or cases of Guillain-Barré syndrome were reported in any adolescent or adult (*32,86,96*; sanofi pasteur, unpublished data, 2005).

Simultaneous Administration with Other Vaccines

Hepatitis B Vaccine

Safety and immunogenicity of ADACEL™ co-administered with hepatitis B vaccine (Recombivax HB®, Merck and Co., Inc., White House Station, New Jersey) was evaluated in adolescents aged 11–14 years using methods similar to the primary ADACEL™ studies. Adolescents were randomized to one of two groups. In one group, ADACEL™ and hepatitis B vaccine were administered simultaneously in different arms (simultaneous group; N = 206). In the other group, ADACEL™ was administered first, followed by hepatitis B vaccine 4–6 weeks later (sequential group; N = 204) (*32*; sanofi pasteur, unpublished data, 2005). No interference was observed in the immune responses to any of the vaccine antigens when ADACEL™ and hepatitis B vaccine were administered simultaneously or sequentially†† (*32*).

Adverse events were solicited only after ADACEL™ vaccination (not hepatitis B vaccination) (*86*). Within 15 days of vaccination, the reported rates of injection site pain (at the

†† An antihepatitis B surface antigen level ≥10 mIU/mL was considered seroprotective.

TABLE 9. Frequencies of solicited systemic adverse events among adolescents within 15 days* after a single dose of ADACEL™ or Td_{sp}

Event†	Description	ADACEL™ (%) (N = 1,170–1,175)§	Td_{sp} (%) (N = 783–787)§
Fever	Any	5.0¶	2.7
	Moderate	0.9	0.6
	Severe	0.2	0.1
Chills	Any	15.1	12.6
	Moderate	3.2	2.5
	Severe	0.5	0.1
Headache	Any	43.7	40.4
	Moderate	14.2	11.1
	Severe	2.0	1.5
Generalized body ache	Any	30.4	29.9
	Moderate	8.5	6.9
	Severe	1.3	0.9
Tiredness	Any	30.2	27.3
	Moderate	9.8	7.5
	Severe	1.2	1.0
Nausea	Any	13.3	12.3
	Moderate	3.2	3.2
	Severe	1.0	0.6
Vomiting	Any	4.6	2.8
	Moderate	1.2	1.1
	Severe	0.5	0.3
Diarrhea	Any	10.3	10.2
	Moderate	1.9	2.0
	Severe	0.3	0
Sore and/or swollen joints	Any	11.3	11.7
	Moderate	2.6	2.5
	Severe	0.3	0.1
Rash	Any	2.7	2.0

SOURCES: Food and Drug Administration. Product approval information—licensing action, package insert: Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed ADACEL™, sanofi pasteur. Rockville, MD: US Department of Health and Human Services, Food and Drug Administration, Center for Biologics Evaluation and Research; 2006. Available at http://www.fda.gov/cber/label/tdapave012306LB.pdf. Food and Drug Administration, sanofi pasteur. ADACEL™ briefing document. Bethesda, MD: US Department of Health and Human Services, Food and Drug Administration, Center for Biologic Evaluation and Research; March 15, 2005. Available at http://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4097B1_6.pdf. Food and Drug Administration. Vaccines and Related Biological Products Advisory Committee, March 15, 2005: FDA ADACEL™ briefing information. Rockville, MD: US Department of Health and Human Services, Food and Drug Administration; 2005. Available at http://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4097B1_4a.pdf.

* Vaccination day and the following 14 days.

† Fever: *Mild*: ≥100.4° F (≥38° C) to ≤101.9° F (≤38.8° C); *Moderate*: ≥102.0° F (≥38.9° C) to ≤103.0° F (≤39.4° C); *Severe*: ≥103.1° F (≥39.5° C). Chills, headache, generalized body ache, tiredness, nausea, vomiting, diarrhea, sore (and/or swollen) joints each defined as *Mild*: noticeable but did not interfere with activities (not shown in table); *Moderate*: interfered with activities but did not require medical attention/absenteeism; *Severe*: incapacitating, unable to perform usual activities, may have or did necessitate medical care or absenteeism; *Any*: Mild + Moderate + Severe. Rash defined as any or none.

§ Number of adolescents with available data.

¶ The rate of "Any" fever following ADACEL™ was statistically higher than the rate following Td_{sp} in the adolescents; however, the noninferiority criterion was achieved for ADACEL™ (upper limit of the 95% confidence interval on the difference in the percentage of persons [ADACEL™ minus Td_{sp}] was <10%).

ADACEL™ site) and fever were comparable when ADACEL™ and hepatitis B vaccine were administered simultaneously or sequentially (Table 10). However, rates of erythema and swelling at the ADACEL™ injection site were higher in the simultaneous group than the sequential group, and noninferiority criteria for simultaneous vaccination were not achieved (Table 10) (*86*). Swollen and/or sore joints were reported in 22.5% of persons in the simultaneous group and 17.9% of persons in the sequential group. Most joint complaints were mild in intensity and the mean duration was 1.8 days (*86*).

Trivalent Inactivated Influenza Vaccine

Safety and immunogenicity of ADACEL™ co-administered with trivalent inactivated influenza vaccine ([TIV] Fluzone®, sanofi pasteur, Swiftwater, Pennsylvania) was evaluated in adults aged 19–64 years using methods similar to the primary ADACEL™ studies (*32*). The immunogenicity data are presented elsewhere (*32*). The adults were randomized to one of

TABLE 10. Frequencies of selected solicited local and systemic adverse events among adolescents aged 11–14 years after simultaneous and sequential administration of ADACEL™ and hepatitis B vaccine

Type of adverse event	Simultaneous group ADACEL™ and hepatitis B vaccine (%) (N = 201–202)*	Sequential group ADACEL™ followed by hepatitis B vaccine 4–6 weeks later (%) (N = 200–201)*
Immediate event	0.5	2.0
Solicited local event at the ADACEL™ injections site†	88.1	86.6
Erythema, any	23.4§	21.4
Swelling, any	23.9§	17.9
Pain, any¶	85.6	85.1
Pain, moderate/severe¶	19.9	23.4
Any solicited systemic event*	79.2	74.6
Sore and/or swollen joints	22.5	17.9
Fever ≥100.4° F (≥38° C)	5.5	6.0

SOURCE: Food and Drug Administration. Vaccines and Related Biological Products Advisory Committee, March 15, 2005: FDA ADACEL™ briefing information. Rockville, MD: US Department of Health and Human Services, Food and Drug Administration; 2005. Available at http://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4097B1_4a.pdf.

* Number of persons with available data.

† Vaccination day and the following 14 days.

§ The noninferiority criteria were not achieved for rates of erythema and swelling following simultaneous vaccination compared with the rates following sequential vaccination. The upper limit of the 95% confidence interval on the difference in the percentage of persons (simultaneous vaccination minus sequential vaccination) was 10.1% (erythema) and 13.9% (swelling), whereas the criteria were <10%.

¶ Pain at injection site defined as *Mild*: noticeable but did not interfere with activities (not shown in table); *Moderate*: interfered with activities but did not require medical attention/absenteeism; *Severe*: incapacitating, unable to perform usual activities, may have or did necessitate medical care or absenteeism; *Any*: Mild + Moderate + Severe.

two groups. In one group, ADACEL™ and TIV were administered simultaneously in different arms (simultaneous group; N = 359). In the other group, TIV was administered first, followed by ADACEL™ 4–6 weeks later (sequential group; N = 361) (*32;* sanofi pasteur, unpublished data, 2005). Adverse events were solicited only after ADACEL™ vaccination (not TIV) (*86*). Within 15 days of vaccination, rates of erythema, swelling, and fever were comparable in both vaccination groups. However, the rate of pain at the ADACEL™ injection site was higher in the simultaneous group (66.6%) than the sequential group (60.8%), and did not meet the noninferiority criterion (upper limit of the 95% CI on the difference in percentage of persons [the rate following simultaneous vaccination minus the rate following sequential vaccination] was 13.0%, and the criterion was <10%) (*86*).

Other Vaccines

Safety and immunogenicity of simultaneous administration of ADACEL™ with other vaccines were not evaluated during prelicensure studies (*32*).

Studies of Adolescent Acellular Pertussis Vaccine Impact

Clinical Efficacy Trial

The efficacy against pertussis of an adolescent and adult acellular pertussis (ap) vaccine with the same pertussis antigens included in BOOSTRIX® (without tetanus and diphtheria toxoids) was evaluated in 2,781 adolescents and adults in a prospective, randomized trial (*68*). Results of this study were not considered as part of Tdap licensure in the United States (see Criteria for Tdap Licensure). Persons aged 15–64 years were randomized to receive one dose of ap vaccine or hepatitis A vaccine (Havrix®, GlaxoSmithKline Biologicals, Rixensart, Belgium). The primary outcome measure was confirmed pertussis, defined by a cough illness lasting ≥5 days with laboratory evidence of *B. pertussis* infection by culture, PCR, and/or serologic testing results (acute and convalescent). Nine persons in the hepatitis A vaccine control group and one person in the ap vaccine group had confirmed pertussis during the study period; vaccine efficacy against confirmed pertussis was 92% (95% CI = 32%–99%) (*68*).

Economic Studies

The societal costs of pertussis are important, and universally vaccinating adolescents against pertussis is likely to be cost effective. In one study, the economic impact of pertussis among Massachusetts adolescents aged 10–17 years was evaluated using the state's enhanced pertussis surveillance system (*54*). The mean medical cost per adolescent case of pertussis was an estimated $201 and $256 for mild and severe cases of cough illness, respectively (in 2004 dollars), excluding the cost of providing antimicrobials to close contacts of the case-adolescents (*53,54*). The largest proportion of this cost was for medical office visits and antimicrobial therapy (*54*). When indirect, nonmedical costs (e.g., missed time from work for

parents of adolescents) were included, total societal cost of an adolescent case of pertussis was $361 and $416 for mild and severe cough illness, respectively (in 2004 dollars) (*53,54*).

Two U.S. economic studies have compared adolescent vaccination with other pertussis vaccination strategies (*53,97*). Both studies identified a single dose of Tdap during adolescence as the most cost-effective strategy, under different assumptions about pertussis incidence, waning immunity, vaccine efficacy, vaccine coverage, and infant transmission. In the first study, a cost-benefit analysis was conducted to compare seven adolescent and/or adult pertussis vaccination strategies during a 10-year interval (2001–2010), using a single dose of a Tdap. In this analysis, the incidence of pertussis among adolescents and adults was estimated from prospective studies to be 450–507 cases per 100,000 population. Strategies included vaccinating all adolescents aged 10–19 years, vaccinating all persons aged ≥10 years (i.e., universal adolescent and adult vaccination), vaccinating adolescents and adults aged ≥15 years that were the primary care-takers of infants, and four other adult vaccination strategies. Among these strategies, vaccinating all adolescents was identified as the most cost-effective strategy. Universal adolescent Tdap vaccination was cost-saving to society when the Tdap vaccine and program costs were ≤$37 (2002 dollars) per adolescent vaccinated (*97*).

In a second study, six adolescent and/or adult Tdap vaccination strategies were compared by modeling health outcomes over the course of a lifetime for hypothetical cohort of 4 million adolescents (*53*). Incidence rates of pertussis among adolescents and adults were estimated from Massachusetts surveillance data; baseline estimates were 155 and 11 per 100,000 population for adolescents and adults, respectively. The six strategies included no adolescent or adult vaccination, one-time adolescent vaccination at age 11 years, one-time adult vaccination, adult vaccination with decennial Tdap boosters, adolescent and adult vaccination with decennial Tdap boosters, and postpartum vaccination. The study assumed an incremental increase in Tdap price of $15 compared with Td, with a Tdap vaccination cost of $25 per person vaccinated. Universal adolescent vaccination was the most cost-effective strategy. Vaccinating all adolescents once would cost $1,100 per pertussis case prevented or $20,000 per quality adjusted life year (QALY) saved, both in 2004 dollars. By contrast with the cost-benefit analysis (*97*), which estimated the incidence of pertussis in adolescents to be approximately 3 times higher, Tdap vaccination was not cost-saving under the second study's baseline assumptions (*53*). In a sensitivity analysis, results from the second study found that if the incidence of adolescent and adult pertussis was four times the base-case estimates, universal adolescent Tdap vaccination would be cost-saving to society (*53*).

Other Tetanus and Diphtheria Toxoids Vaccine Preparations for Adolescents

Four Td (Tetanus and Diphtheria Toxoids, Adsorbed for Adult Use) vaccines are licensed in the United States for active immunization against tetanus and diphtheria among persons aged ≥7 years (*98–101*). Two tetanus toxoid vaccines (TT) also are licensed for use in this age group (*102,103*). Of the two TT products, one is adsorbed and is licensed for use in situations in which the combined antigen preparation (Td) is not indicated (*102*). The second TT preparation is a fluid vaccine (not adsorbed) and is indicated only for booster doses, not for primary immunization (*103*). Although TT is licensed in the United States for persons aged ≥7 years, Td has been preferred for routine use to provide dual protection against tetanus and diphtheria (*24*) (Appendix A).

Safety Considerations for Adolescent Vaccination with Tdap or Td

Prelicensure Tdap studies support the safety of these vaccines (*32,33*). However, sample sizes were insufficient to detect rare adverse events, a limitation of prelicensure trials. Enrollment criteria excluded persons who had received vaccines containing tetanus toxoid, diphtheria toxoid, or pertussis components during the preceding 5 or 10 years (*85,86,92,94*). In addition, persons with certain neurologic conditions or events following pediatric DTP/DTaP vaccination were excluded from these studies (*85,92,94*). Therefore, in making recommendations on the spacing and administration sequence of vaccines containing tetanus toxoid, diphtheria toxoid, and/or pertussis components and on vaccination of adolescents with a history of certain neurologic conditions or adverse events after vaccination, ACIP considered data from a range of pre- and postlicensure studies of Tdap and other vaccines containing these components. Safety data being collected from the Vaccine Adverse Event Reporting System (VAERS) and postlicensure studies will facilitate detection of potential adverse reactions following widespread use of Tdap in adolescents (see Reporting of Adverse Events after Vaccination) (*104,105*).

Spacing and Administration Sequence of Vaccines Containing Tetanus Toxoid, Diphtheria Toxoid, and Pertussis Antigens

Historically, moderate and severe local reactions following tetanus and diphtheria toxoid–containing vaccines have been

associated with older, less purified vaccines, larger doses of toxoid, and frequent dosing at short intervals (*106–111*). In addition, high pre-existing antibody titers to tetanus or diphtheria toxoids in children, adolescents, and adults primed with these antigens might be associated with increased rates of local reactions to booster doses of tetanus or diphtheria toxoid–containing vaccines (*26,108,111,112*). Two adverse events of particular clinical interest have been associated with vaccines containing tetanus toxoid, diphtheria toxoid, and/or pertussis antigens, extensive limb swelling (ELS), and Arthus reactions.

Extensive Limb Swelling

ELS reactions have been described following doses of pediatric DTaP and other vaccines (*28,91,113–117*). In retrospective analyses, 2%–3% of children receiving the fourth or fifth booster doses of pediatric DTaP experienced extensive proximal limb swelling; swelling is usually greatest by 48 hours after vaccination (*28,118*). ELS is generally not disabling, is not often brought to medical attention, and resolves without complication within 4–7 days (*118*). ELS has been reported to VAERS almost as frequently following Td as following pediatric DTaP; among adolescents, the majority of reported cases of ELS have involved either Td or hepatitis B vaccine (*117*). The pathogenesis of ELS is not well understood; this reaction has not consistently been related to the content of tetanus toxoids, diphtheria toxoids, pertussis antigens, or aluminum adjuvants in vaccines (*28,118,119*). Whether children who experience ELS after receipt of pediatric DTaP are at increased risk for ELS after receipt of Tdap is unknown. Because these reactions typically resolve without sequelae, ACIP does not consider a history of ELS following pediatric DTaP or any other vaccine to be a precaution or contraindication for pediatric DTaP (*91,113*).

Arthus Reactions

Arthus reactions (type III hypersensitivity reactions) are rarely reported after vaccination and can occur after tetanus toxoid–containing or diphtheria toxoid–containing vaccines (*24,111,120–124*; CDC, unpublished data, 2005). An Arthus reaction is a local vasculitis associated with deposition of immune complexes and activation of complement. Immune complexes form in the setting of high local concentration of vaccine antigens and high circulating antibody concentration (*111,120,121,125*). Arthus reactions are characterized by severe pain, swelling, induration, edema, hemorrhage, and occasionally by necrosis. These symptoms and signs usually occur 4–12 hours after vaccination; by contrast, anaphylaxis (immediate type I hypersensitivity reactions) usually occur within minutes of vaccination. As with ELS, Arthus reactions usually resolve without sequelae. ACIP has recommended that persons who experienced an Arthus reaction after a 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 (*24*).

Interval between Td and Tdap

ACIP has recommended a 10-year interval for routine administration of Td and a 5-year minimum interval between the last pediatric DTaP and the adolescent Td dose (*24,30*). Administration of Td at short intervals might increase the risk for adverse events (*108,109*). Prelicensure clinical trials of Tdap excluded persons who had received doses of a diphtheria or tetanus toxoid–containing vaccine during the preceding 5 or 10 years (see BOOSTRIX® and ADACEL™ sections on Immunogenicity and Serologic Bridge to Efficacy for Pertussis for exclusion criteria) (*90,94,96*). Although administering Td more often than every 10 years (5 years for a tetanus-prone wound) is not necessary to provide protection against tetanus or diphtheria, administering a dose of Tdap less than 5 years after Td could provide a health benefit by protecting against pertussis.

The safety of administering a dose of Tdap at intervals less than 5 years after pediatric DTP/DTaP or Td was evaluated in Canada following the country's licensure of Tdap (ADACEL™) (*126*). The largest Canadian study was a nonrandomized, open-label study of 7,001 students aged 7–19 years residing in Prince Edward Island. This study assessed the rates of adverse events after Tdap and compared reactogenicity of Tdap administered at year intervals of 2–9 years (eight cohorts) versus ≥10 years after the last tetanus and diphtheria toxoid–containing vaccine (Td, or pediatric DTP or DTaP). A year interval was defined as the integer year ±0.5 years (e.g., the 2-year interval was defined as >18 months to ≤30 months). Vaccination history for type of pertussis vaccine(s) received (pediatric DTP and DTaP) also was assessed. The number of persons assigned to cohorts ranged from 464 in the 2-year to 925 in the 8-year cohorts. Among the persons in the 2-year cohort, 214 (46%) received the last tetanus and diphtheria toxoid–containing vaccine 18–23 months before Tdap. Adverse event diary cards were returned for 85% of study participants with a known interval; 90% of persons in the 2-year interval cohort provided safety data (*126*).

Four SAEs were reported in the Prince Edward Island study; none were assessed by the investigators to be related to vaccine. No Arthus reaction was reported. Rates of reported severe local adverse reactions, fever, and any pain were not increased in persons who received Tdap at intervals less than 10 years. Rates of local reactions were not increased among persons who received 5 doses of pediatric DTP, with or without Td (intervals of 2–3 years or 8–9 years). Rates of any

erythema and any swelling were reported more frequently in cohorts that had received at least 1 or 2 doses of pediatric DTaP (intervals of 4–7 years), suggesting that increased rates of local reactions might occur more commonly among adolescents who received pediatric DTaP vaccines, compared with those who received a 5-dose pediatric DTP series. Limb swelling (>100 mm) was reported in 0.2% of participants and was unrelated to the interval since the last tetanus and diphtheria toxoid–containing vaccine (*126*).

A study was conducted in Germany to evaluate the safety of Tdap (BOOSTRIX®) in persons aged 9–13 years who received a 5-dose all acellular pertussis vaccine schedule (5 doses of INFANRIX®, N = 193 or 4 doses of INFANRIX® plus another acellular pertussis vaccine, N = 126); the interval from the fifth to sixth dose of the acellular pertussis vaccines ranged from approximately 5–6 years (GSK, unpublished data, 2005). Within 15 days after vaccination, any pain (63.6%), erythema (51.7%), and swelling (41.4%) were frequently reported symptoms, but the rate of "large injection site swelling" (see BOOSTRIX®, solicited local adverse events for definition) was low (0.9%). Following their sixth consecutive dose of an acellular pertussis vaccine, persons reported more pain, less redness, and less swelling compared with their fifth dose of pediatric DTaP (INFANRIX®) (*127*).

Two smaller Canadian postlicensure safety studies in adolescents also showed acceptable safety when Tdap (ADACEL™) was administered at intervals less than 5 years after tetanus and diphtheria toxoid–containing vaccines (*128,129*). Taken together, these three Canadian studies support the safety of using Tdap after Td at intervals less than 5 years. The largest study suggests intervals as short as approximately 2 years are acceptably safe (*126*).

Simultaneous and Nonsimultaneous Vaccination with Tdap/Td and Diphtheria-Containing Tetravalent Meningococcal Conjugate Vaccine

Tdap, Td, and tetravalent meningococcal conjugate vaccine ([MCV4] Menactra®, sanofi pasteur, Swiftwater, Pennsylvania) contain diphtheria toxoid (*32,33,130,131*). Each of these vaccines is licensed for use in adolescents, but MCV4 is not indicated for active immunization against diphtheria (*131*). During 2005, MCV4 was recommended for routine use among adolescents (*130,132*). In MCV4, the diphtheria toxoid (approximately 48 μg) serves as the carrier protein that improves immune responses to meningococcal antigens. Precise comparisons cannot be made between the quantity of diphtheria toxoid in the vaccines; however, the amount in a dose of MCV4 is estimated to be comparable with the average quantity in a dose of pediatric DTaP (*133*).

No prelicensure studies of simultaneous or sequential vaccination with Tdap and MCV4 were done. None of the persons in the Canadian safety studies described above had received MCV4. Persons who recently received one diphtheria toxoid–containing vaccine might have increased rates of adverse reactions after a subsequent diphtheria toxoid–containing vaccine when diphtheria antibody titers remain elevated from the previous vaccination (*26,108,111,112*). The diphtheria GMCs were comparable or lower following Tdap compared with Td[§§]; therefore, results of a co-administration trial of Td and MCV4 might be informative to infer the effect of co-administration of Tdap and MCV4. A randomized, controlled prelicensure trial assessed the safety of simultaneous versus sequential administration of Td and MCV4.

In this co-administration trial, administration of Td (approximately 8 μg of diphtheria toxoid) with MCV4 first, then placebo 28 days later (simultaneous group), or administration of Td with placebo first, then MCV4 28 days later (sequential group) was studied among 1,021 healthy adolescents aged 11–17 years (Table 11) (*89,131,133*). Serum samples from a subset of adolescents vaccinated with MCV4 from a different clinical trial were used for comparison.

[§§] One month after vaccination, the antidiphtheria GMCs were ADACEL™ 8.5 IU/mL (95% confidence interval [CI] =7.6–9.5) compared with Td_{sp} 7.1 IU/mL (95% CI = 6.4–7.8) and BOOSTRIX® 7.4 IU/mL (95% CI = 7.1–7.6) compared with Td_{MPHBL} 14.0 IU/mL (95% CI = 13.2–14.9); the antidiphtheria seroprotective and booster response rates in the adolescents vaccinated with Tdap (ADACEL™ and BOOSTRIX®) were noninferior to the those vaccinated with Td (see sections on Immunogenicity and Serologic Bridge to Pertussis Efficacy).

TABLE 11. Anti-diphtheria geometric mean titers (GMTs) observed in adolescents 28 days following vaccination in tetravalent meningococcal conjugate vaccine (MCV4) studies

Vaccine sequence	Anti-diphtheria GMT 28 days after vaccination, IU/mL (95% CI*)	
Group A: simultaneous†		
Day 0: Td + MCV4	120.9	(104.6–139.8)
Group B: nonsimultaneous†		
Day 0: Td (and placebo)	8.4	(7.6–9.2)
Day 28: MCV4	16.9	(15.3–18.6)
MCV4 alone§	46.5	(35.1–61.6)

SOURCES: Food and Drug Administration. Vaccines and Related Biological Products Advisory Committee, September 22, 2004: FDA Menactra® briefing information. Rockville, MD: US Department of Health and Human Services, Food and Drug Administration; 2004. Available at http://www.fda.gov/ohrms/dockets/ac/04/briefing/4072B1_2a.pdf. Food and Drug Administration. Aventis Pasteur. Menactra® briefing document. Bethesda, MD: US Department of Health and Human Services, Center for Biologic Evaluation and Research; September 22, 2004. Available at http://www.fda.gov/ohrms/dockets/ac/04/briefing/4072B1_1.pdf.

* Confidence interval.

† Study MTA12 (group A, N = 465; group B, N = 473).

§ MTA02 subset of adolescents (N = 49).

Administration of MCV4 first followed by Td was not studied. Both simultaneous and sequential administration of Td and MCV4 induced immune responses to all antigens. One month postvaccination, the immune responses to diphtheria toxoid were higher when MCV4 was administered simultaneously with Td (GMT 120.9 IU/mL) than when Td was administered with placebo (GMT 8.4 IU/mL). Adolescents vaccinated with MCV4 alone also had high antidiphtheria responses 1 month following vaccination (GMT 46.5 IU/mL) (Table 11) (*89,131,133*).

Adverse events on vaccination day and during the following 7 days were assessed among adolescents in the simultaneous and sequential groups. The overall rates of solicited local reactions were similar for the two groups: 58.0% reported local reactions at the MCV4 injection site in the simultaneous group versus 57.0% in the sequential group, and 74.7% reported local reactions at the Td injection site in the simultaneous group versus 73.3% in the sequential group. Pain was the most frequently reported reaction and pain rates were similar between groups; severe pain was uncommon (<1% of persons). Fever ≥99.5° F (≥37.5° C) and high fever ≥104° F (≥40° C) were reported in ≤5% and <0.5% of persons, respectively (*133–135*). The safety of simultaneous vaccination of MCV4 with Tdap and sequential administration of Tdap first followed by MCV4 1 month later has been inferred from results of this study.

When Tdap or Td is administered after MCV4, rates of adverse reactions might be higher than when the dose is administered before MCV4 because pre-existing diphtheria antibody levels might be higher *(26,108,111,112,133,135)*. Rates of adverse reactions were assessed in a small prelicensure study for MCV4 among 76 adolescents aged 15–17 years who received 2 doses of MCV4 spaced 3 years apart. After the second dose of MCV4, no SAEs, fever ≥102.2° F (≥39° C), or severe local reactions were reported with the exception of one person, who reported severe pain at the injection site that lasted for 1 day (sanofi pasteur, unpublished data, 2005). No other available data exist on the safety of intervals between MCV4 and other diphtheria toxoid–containing vaccines. Postlicensure studies to provide additional information are under way (*104,105*).

Neurologic and Systemic Events Associated with Vaccines with Pertussis Components or Tetanus Toxoid–Containing Vaccines

Vaccines with Pertussis Components

Concerns about the possible role of vaccines with pertussis components in causing neurologic reactions or exacerbating underlying neurologic conditions are long-standing (*20,136*). ACIP recommendations to defer pertussis vaccines in infants with suspected or evolving neurologic disease, including seizures, have been based primarily on concerns that neurologic events after vaccination (with whole cell preparations in particular) might interfere with the subsequent evaluation of the infant's neurologic status (*1,136*).

In 1991, the Institute of Medicine (IOM) concluded that evidence favored acceptance of a causal relation between pediatric DTP and acute encephalopathy; the IOM has not evaluated associations between pediatric DTaP and neurologic events (*123*). Pediatric DTaP is contraindicated for children with a history of encephalopathy not attributable to another identifiable cause occurring within 7 days after pediatric DTP/DTaP vaccination. Though active surveillance in Canada during 1993–2002 failed to ascertain any acute encephalopathy cases causally related to whole cell or acellular pertussis vaccines among a population administered 6.5 million doses of pertussis vaccines (*137*), research conducted in Japan during the introduction of acellular pertussis vaccines yielded rates of 1.0–1.3 attributable encephalopathy cases within 7 days of vaccination per 10 million doses (*138*).

ACIP has recommended that infants with evolving neurologic conditions should not be vaccinated with pediatric DTaP until a treatment regimen has been established and the condition has stabilized (*1*). Concerns about vaccinating adolescents with progressive or uncontrolled underlying neurologic disease must be weighed against the potential for morbidity from pertussis. Adolescents with severe neurologic conditions might be at risk for severe pertussis (*48*; CDC, unpublished data, 2005). ACIP does not consider a history of well-controlled seizures in the vaccinee or a family history of seizures (febrile or afebrile) or other neurologic disorder to be a contraindication or precaution to vaccination with pertussis components (*1*).

ACIP has recommended that vaccine providers and parents evaluate the risks for and benefits of administering subsequent doses of vaccines with pertussis components to young children who experienced these events after pediatric DTP/DTaP: temperature ≥105° F (≥40.5° C) within 48 hours after pediatric DTP/DTaP, not attributable to another cause; collapse or shock-like state (hypotonic hyporesponsive episode) within 48 hours after pediatric DTP/DTaP; persistent crying lasting ≥3 hours, occurring within 48 hours after pediatric DTP/DTaP; or convulsions with or without fever, occurring within 3 days after pediatric DTP/DTaP. All of these events were documented more frequently following whole cell pertussis vaccines than they have been following acellular vaccines (*1,139–142*). VAERS data have documented decreased reports of fever and other systemic events in infants and children fol-

lowing pediatric DTaP in comparison with pediatric DTP (*143*). These events either do not occur in adolescents or are of less clinical concern in this age group than in infants and children (e.g., febrile seizures and hypotonic-hyporesponsive episodes). Taken together, this information supports administering Tdap to adolescents with a history of the events listed above after pediatric DTaP/DTP.

Tetanus Toxoid–Containing Vaccines

ACIP has recommended that Guillain-Barré syndrome occurring ≤6 weeks after receipt of a tetanus toxoid–containing vaccine is a precaution for subsequent tetanus toxoid–containing vaccines (*91*). IOM concluded that evidence favored acceptance of a causal relation between tetanus toxoid–containing vaccines and Guillain-Barré syndrome (*123*). Evidence is based primarily on a well-documented case report (*123,144*). However, a subsequent analysis of active surveillance data in both adult and pediatric populations failed to demonstrate an association between receipt of a tetanus toxoid–containing vaccine and onset of Guillain-Barré syndrome within 6 weeks following vaccination (*145*).

IOM also has concluded that evidence from case reports and uncontrolled studies involving tetanus toxoid–containing vaccines favored a causal relation between tetanus toxoid–containing vaccines and brachial neuritis. Brachial neuritis is considered to be a compensable event through the Vaccine Injury Compensation Program (*123*). However, ACIP does not consider a history of brachial neuritis to be a precaution or contraindication for administration of tetanus toxoid–containing vaccines; brachial neuritis is usually self-limited (*91,143,146*).

Considerations for Vaccinating Pregnant Adolescents with Td or Tdap

ACIP has recommended Td routinely for pregnant women who received the last tetanus toxoid–containing vaccine ≥10 years earlier. This recommendation is primarily to prevent neonatal tetanus (*24,31*). In women adequately vaccinated against tetanus, passive transfer of antibodies across the placenta during pregnancy protects their newborns from neonatal tetanus (*147–149*). During 1999, a global maternal and neonatal tetanus elimination goal was recommended by the WHO, the United Nations Children's Fund, and the United Nations Population Fund (*150*).

As with tetanus, antibodies to pertussis antigens are passively transferred during pregnancy (*151,152*); however, serologic correlates of protection against pertussis are not known (*88*). Whether or not passive transfer of maternal antibodies to pertussis antigens protects neonates against pertussis is also unclear (*88,153*).

All licensed Td and Tdap vaccines are categorized as Pregnancy Category C agents by FDA.[¶¶] Pregnant women were excluded from prelicensure trials, and no animal reproduction studies have been conducted for Td or Tdap (*32,33,98–101*). Td has been used extensively in pregnant women worldwide, and no evidence indicates use of tetanus and diphtheria toxoids administered during pregnancy are teratogenic (*24,154,155*).

Summary of the Rationale for Adolescent Tdap Recommendations

The availability of Tdap, the first pertussis vaccines formulated for use in adolescents and adults in the United States, offers a new opportunity to reduce the burden of pertussis in this country. The primary objective of vaccinating adolescents with Tdap is to protect the vaccinated adolescent against pertussis while maintaining the standard of care for protection against tetanus and diphtheria. A secondary objective of adolescent Tdap vaccination is to reduce the reservoir of pertussis within the U.S. population at large and potentially reduce the incidence of pertussis in other age groups, including infants who have the highest risk for complications from pertussis (*16,48*). The extent to which the secondary objective can be achieved through adolescent vaccination is unknown.

The decision to recommend routine Tdap vaccination for adolescents is based on evidence regarding the burden of pertussis among adolescents; negative effects of pertussis outbreaks involving adolescents on the community and the public health system; studies suggesting use of Tdap among adolescents will likely be safe, effective, and economical; and the established infrastructure for adolescent vaccination (*30,32,33,52–54,68*).

To protect against pertussis, Tdap will be introduced into an adolescent vaccination schedule that already includes two other tetanus and/or diphtheria toxoid–containing vaccines, Td, and MCV4 (*23,130*). Frequent doses of tetanus and diphtheria toxoid–containing vaccines can be associated with increased local and systemic reactogenicity (*108,109*). ACIP has considered issues related to spacing and administration sequence of these three vaccines to develop recommendations for Tdap use in adolescents.

[¶¶] U.S. Food and Drug Administration Pregnancy Category C: Animal studies have documented an adverse effect and no adequate and well-controlled studies in pregnant women have been conducted or no animal studies and no adequate and well-controlled studies in pregnant women have been conducted

Recommendations for Use of Tdap and Td Among Adolescents

The following sections present recommendations for use of Tdap and Td among adolescents aged 11–18 years and include routine Tdap vaccination, contraindications and precautions, and special situations (Appendix C).

1. Routine Tdap Vaccination

1-A. Recommendations for Use (Table 12)

1) Adolescents aged 11–18 years should receive a single dose of Tdap instead of Td for booster immunization against tetanus, diphtheria, and pertussis if they have completed the recommended childhood DTP/DTaP vaccination series*** and have not received Td or Tdap. The preferred age for Tdap vaccination is 11–12 years; routinely administering Tdap to young adolescents will reduce the morbidity associated with pertussis in adolescents.
2) Adolescents aged 11–18 years who received Td, but not Tdap, are encouraged to receive a single dose of Tdap to provide protection against pertussis if they have completed the recommended childhood DTP/DTaP vaccination series.*** An interval of at least 5 years between Td and Tdap is encouraged to reduce the risk for local and systemic reactions after Tdap vaccination. However, an interval less than 5 years between Td and Tdap can be used. The benefit of using Tdap at a shorter interval to protect against pertussis generally outweighs the risk for local and systemic reactions after vaccination in settings with increased risk for pertussis or its complications (See Pertussis Outbreaks and Other Settings with Increased Risk for Pertussis or its Complications [section 3-C]).
3) Vaccine providers should administer Tdap and tetravalent meningococcal conjugate vaccine ([MCV4] Menactra®) (which both contain diphtheria toxoid) to adolescents aged 11–18 years during the same visit if both vaccines are indicated and available (*130,132*).

*** Five doses of pediatric DTP/DTaP before the seventh birthday; if the fourth dose was administered on or after the fourth birthday, the fifth dose is not needed.

TABLE 12. Summary of evidence for routine adolescent tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccination*

Number	Evidence
1-A:1	Efficacy against and tetanus, diphtheria, and pertussis is supported by immunogenicity results of randomized, controlled clinical trials among adolescents; safety is supported by results of randomized, controlled clinical trials among adolescents.
1-A:2	Safety of an interval of at least 5 years between tetanus and diphtheria toxoids vaccine (Td) and Tdap is supported by randomized, controlled clinical trials among adolescents.
1-A:3	Safety of simultaneous vaccination with Tdap and tetravalent meningococcal conjugate vaccine (MCV4) has not been directly studied, but is inferred from results of a randomized, controlled clinical trial among adolescents vaccinated with Td and MCV4.

* For details, see the following sections: BOOSTRIX®, ADACEL™, and Safety Considerations for Adolescent Vaccination with Tdap or Td.

1-B. Dosage and Administration

The dose of Tdap is 0.5 mL, administered intramuscularly (IM), preferably into the deltoid muscle.

1-C. Simultaneous Vaccination with Tdap and Other Vaccines

If two or more vaccines are indicated, they should be administered during the same visit (i.e., simultaneous vaccination). Each vaccine should be administered using a separate syringe at a different anatomic site. Some experts recommend administering no more than two injections per muscle, separated by at least one inch.

Administering all indicated vaccines during a single visit increases the likelihood that adolescents will receive each of the vaccines on schedule (*91*). Vaccine providers should administer MCV4 and Tdap (or Td) during the same visit if both vaccines are indicated and available. MCV4 contains diphtheria toxoid as a carrier protein (*131*) (see Safety Considerations for Adolescent Vaccination with Tdap or Td).

1-D. Interchangeable Use of Tdap Vaccines

A single dose of either Tdap product (BOOSTRIX® or ADACEL™) can be administered to adolescents regardless of the type or manufacturer of pediatric DTP/DTaP used for childhood vaccination.

1-E. Preventing Adverse Events

Syncope can occur after vaccination, might be more common among adolescents and young adults than among other age groups, and has rarely resulted in serious injury (*91,156,157*). Certain experts suggest a 15–20 minute observation period following vaccination (*91,158*). If syncope occurs, patients should be observed until symptoms resolve.

The potential for administration errors involving tetanus toxoid–containing vaccines and other products is well documented (*159–161*). For example, Td and TT have been inadvertently administered

instead of tuberculin purified protein derivative (PPD) (*159*). Attention to proper vaccination technique, including use of an appropriate needle length and standard routes of administration (i.e., IM for Tdap) might minimize the risk for adverse events (*91*). Adverse events associated with inadvertent vaccine administration can be reported to the Vaccine Adverse Event Reporting System (VAERS) (see Reporting of Adverse Events after Vaccination).

1-F. Record Keeping

Health-care providers who administer vaccines are required to keep permanent vaccination records of vaccines covered under the National Childhood Vaccine Injury Act in the vaccinee's medical record; ACIP has recommended that this practice include all vaccines (*91*). Because documentation of tetanus toxoid–containing vaccine administration is frequently required for school or camp entry and as part of wound management, encouraging adolescents to maintain a personal vaccination record is important to minimize administration of unnecessary vaccinations. Vaccine providers can record the type of the vaccine, manufacturer, anatomic site, route, and date of administration and name of the administering facility on the personal record.

2. Contraindications and Precautions for Use of Tdap and Td Among Adolescents Aged 11–18 Years

2-A. Contraindications

- Tdap or Td is contraindicated for persons with a history of serious allergic reaction (i.e., anaphylaxis) to any component of the vaccine. Because of the importance of tetanus vaccination, persons with a history of anaphylaxis to components included in all Tdap and Td vaccines should be referred to an allergist to determine whether they have a specific allergy to tetanus toxoid, can be desensitized to tetanus toxoid, and can safely receive TT vaccinations.
- Tdap is contraindicated for adolescents with a history of encephalopathy (e.g., coma or prolonged seizures) not attributable to an identifiable cause within 7 days of administration of a vaccine with pertussis components. This contraindication is for the pertussis components and these persons should receive Td instead of Tdap.

2-B. Precautions and Reasons to Defer Tdap and/or Td

A precaution is a condition in a vaccine recipient that might increase the risk for a serious reaction (*91*). The following are precautions for Tdap and/or Td. In these situations, vaccine providers should evaluate the risks for and benefits of administering Tdap or Td.

- Guillain-Barré syndrome ≤6 weeks after a previous dose of a tetanus toxoid–containing vaccine. If a decision is made to continue vaccination with tetanus toxoid, Tdap is preferred to Td if otherwise indicated.
- Progressive neurologic disorder, including progressive encephalopathy, or uncontrolled epilepsy, until the condition has stabilized. These precautions are for pertussis components.[†††] If a decision is made to provide protection against pertussis, Tdap is preferred if otherwise indicated. If a decision is made to withhold pertussis vaccination, Td can be used instead of Tdap.

Tdap or Td vaccination should generally be deferred during the following situations.

- Moderate or severe acute illness with or without fever. Defer Tdap or Td vaccination until the acute illness resolves.
- History of an Arthus reaction following a previous dose of a tetanus toxoid–containing and/or diphtheria toxoid–containing vaccine, including MCV4 (see Safety Considerations for Adolescent Vaccination with Tdap or Td section for a description of an Arthus reaction). Vaccine providers should carefully review the medical history to verify the diagnosis of an Arthus reaction, and can consult with an allergist or immunologist. If an Arthus reaction was likely, vaccine providers should consider deferring Tdap or Td vaccination until at least 10 years have elapsed since the last tetanus toxoid–containing and/or diphtheria toxoid–containing vaccine was received. If the Arthus reaction was associated with a vaccine that contained diphtheria toxoid without tetanus toxoid (e.g., MCV4), deferring Tdap or Td might leave the adolescent inadequately protected against tetanus. In this situation, if the last tetanus toxoid–containing vaccine was ≥10 years earlier, vaccine providers can obtain a serum antitetanus level to

[†††] These conditions are precautions for use of Tdap among adolescents but are contraindications for use of pediatric DTaP among infants and children.

evaluate the need for tetanus vaccination (antitetanus levels ≥0.1 IU/mL are considered protective) or administer TT.

2-C. Not Contraindications or Precautions

The following conditions are not contraindications or precautions for Tdap or Td, and adolescents with these conditions can receive a dose of Tdap or Td if otherwise indicated. The conditions in italics are precautions for pediatric DTP/DTaP but are not contraindications or precautions for Tdap vaccination in adolescents (*1*).

- *Temperature ≥105° F (≥40.5° C) within 48 hours after pediatric DTP/DTaP not attributable to another cause;*
- *Collapse or shock-like state (hypotonic hyporesponsive episode) within 48 hours after pediatric DTP/DTaP;*
- *Persistent crying lasting ≥3 hours, occurring within 48 hours after pediatric DTP/DTaP;*
- *Convulsions with or without fever, occurring within 3 days after pediatric DTP/DTaP;*
- History of an extensive limb swelling reaction following pediatric DTP/DTaP or Td that was not an Arthus reaction (see Safety Considerations for Adolescent Vaccination with Tdap or Td section for descriptions of ELS and Arthus reactions);
- Stable neurologic disorder including well-controlled seizures, a history of seizure disorder that has resolved, and cerebral palsy;
- Brachial neuritis;
- Latex allergies other than anaphylactic allergies (e.g., a history of contact allergy to latex gloves) (*162*). The tip and rubber plunger of the BOOSTRIX® needleless syringe contain latex. The BOOSTRIX® single dose vial and ADACEL™ preparations contain no latex. Some Td products contain latex (consult package inserts for details);
- Breastfeeding;
- Immunosuppression, including persons with human immunodeficiency virus (HIV). The immunogenicity of Tdap in persons with immunosuppression has not been studied and could be suboptimal;
- Intercurrent minor illness; and
- Use of antimicrobials.

3. Special Situations for Use of Tdap and Td

3-A. General Principles

This section addresses special situations for Tdap and Td use. As with the routine situations, only a single dose of Tdap should be administered to an adolescent aged 11–18 years. For most, but not all, of the special situations, Tdap is preferred to Td. In some special situations or when contraindications or precautions are present, Td rather than Tdap might be indicated. The dose of Td is 0.5 mL, administered IM.

Tdap (or Td) and MCV4 should be administered at the same visit during special situations if both vaccines are indicated and available, although this might not always be feasible (e.g., wound management). Simultaneous administration of Tdap (or Td) and MCV4 and an interval of at least 5 years between Td and Tdap can reduce the risk for local and systemic reactions. In certain special situations listed below, the benefit of protection against disease probably outweighs this risk.

3-B. Nonsimultaneous Vaccination with Tdap and Other Vaccines, Including MCV4

ACIP has recommended that inactivated vaccines can be administered at any time before or after a different inactivated or live vaccine (i.e., nonsimultaneous vaccination), unless a contraindication exists (*91*). Simultaneous administration of Tdap (or Td) and MCV4 (which all contain diphtheria toxoid) during the same visit is preferred when both Tdap (or Td) and MCV4 are indicated. If simultaneous vaccination is not feasible (e.g., a vaccine is not available), MCV4 and Tdap (or Td) can be administered using any sequence. Persons who recently received one diphtheria toxoid–containing vaccine might have increased rates of adverse reactions after a subsequent diphtheria toxoid–containing vaccine when diphtheria antibody titers remain elevated from the previous vaccination (*26,108,111,112*) (see Safety Considerations for Adolescent Vaccination with Tdap or Td section for a discussion of nonsimultaneous vaccination).

3-C. Pertussis Outbreaks and Other Settings with Increased Risk for Pertussis or its Complications

Vaccine providers can administer Tdap to adolescents aged 11–18 years at an interval less than 5 years after Td, particularly when the benefit of providing protection against pertussis is likely to be increased. The safety of an interval as short as approximately 2 years between Td and Tdap is supported by a Canadian study among children and adolescents (see Spacing and Sequence Administration of Vaccines Containing Tetanus Toxoid, Diphtheria Toxoid, and Pertussis Antigens) (*126*).

The benefit of using Tdap at an interval less than 5 years after Td is likely to be increased among adolescents when the adolescent is at increased risk for acquiring pertussis (e.g., during outbreaks or periods of increased pertussis activity in the community). Postexposure chemoprophylaxis and other pertussis control guidelines are described elsewhere (*64,158,163*). The benefit of using a shorter interval also might be increased for adolescents with severe underlying medical conditions (e.g., chronic pulmonary disease or neurologic disorders) because these adolescents might be at increased risk for pertussis-related complications.

Infants aged <12 months are at highest risk for pertussis-related complications and hospitalizations compared with older age groups; young infants have the highest risk for death from pertussis. Administering Tdap at an interval less than 5 years after Td to an adolescent who has or anticipates having close contact with an infant aged <12 months might reduce the risk for transmitting pertussis to the infant. Infants should be vaccinated on time with pediatric DTaP (*1,23*).

3-D. Lack of Availability of Tdap or MCV4

If Tdap and MCV4 are both indicated but only one vaccine is available, the available vaccine generally should be administered. When Tdap is indicated but not available, vaccine providers should administer Td or temporarily defer Tdap/Td vaccination. Td should be administered to provide protection against tetanus and diphtheria if the adolescent received the last pediatric DTP/DTaP/DT or Td ≥10 years earlier. Recommendations for use of Tdap among adolescents who already received Td would apply to these adolescents when Tdap becomes available (see Routine Tdap Vaccination [section 1-A]). Tdap/Td vaccination can be deferred temporarily if the adolescent completed the childhood DTP/DTaP vaccination series***, received the last pediatric DTP/DTaP/DT or Td <10 years earlier, and is likely to return for follow-up. If the vaccine provider defers Td in order to administer Tdap when it becomes available, a system to recall the adolescent should be maintained. The adolescent also can be referred to another facility for Tdap administration.

3-E. Tetanus Prophylaxis in Wound Management

ACIP has recommended administering tetanus toxoid–containing vaccine and tetanus immune globulin (TIG) as part of standard wound management to prevent tetanus (Table 13) (*24*). Tdap is preferred to Td for adolescents aged 11–18 years who were vaccinated against tetanus ≥5 years earlier, require a tetanus toxoid–containing vaccine as part of wound management, and have not previously received Tdap. Adolescents who have completed the 3-dose primary tetanus vaccination series and have received a tetanus toxoid–containing vaccine <5 years earlier are protected against tetanus and do not require a tetanus toxoid–containing vaccine as part of wound management. Although MCV4 and Tdap (or Td) should be administered at the same visit during routine situations if both vaccines are indicated, this might not be feasible for wound management.

A thorough attempt must be made to determine whether an adolescent has completed the 3-dose primary tetanus vaccination series. Persons with unknown or uncertain tetanus vaccination histories should be considered to have had no previous doses of a tetanus toxoid–containing vaccine (see Adolescents with History of Incomplete Pediatric DTP/DTaP/DT or Td Vaccination [section 3-H]). Persons who have not completed the primary series might require a tetanus toxoid–containing vaccine and passive immunization with TIG at the time of wound management (Table 13). When both TIG and a tetanus toxoid–containing vaccine are indicated, each product should be administered using a separate syringe at different anatomic sites (*24*).

Adolescents with a history of an Arthus reaction after a previous dose of a tetanus toxoid–containing

TABLE 13. Guide to tetanus prophylaxis in routine wound management among adolescents aged 11–18 years

History of adsorbed tetanus toxoid (doses)	Clean, minor wound		All other wounds*	
	Tdap or Td†	TIG	Tdap or Td†	TIG
Unknown or <3	Yes	No	Yes	Yes
≥3	No§	No	No¶	No

* Such as, but not limited to, wounds contaminated with dirt, feces, soil, and saliva; puncture wounds; avulsions; and wounds resulting from missiles, crushing, burns and frostbite.
† Tdap is preferred to Td for adolescents who have never received Tdap. Td is preferred to TT for adolescents who received Tdap previously or when Tdap is not available (If TT and TIG are both used, Tetanus Toxoid Adsorbed rather than Tetanus Toxoid for Booster Use Only [fluid vaccine] should be used).
§ Yes, if ≥10 years since the last tetanus toxoid–containing vaccine dose.
¶ Yes, if ≥5 years since the last tetanus toxoid–containing vaccine dose (see text for discussion of Arthus reactions).

vaccine should not receive a tetanus toxoid–containing vaccine until ≥10 years after the most recent dose, even if they have a wound that is neither clean nor minor (Table 13). If the Arthus reaction was associated with a vaccine that contained diphtheria toxoid without tetanus toxoid (e.g., MCV4), deferring Tdap or Td might leave the adolescent inadequately protected against tetanus and TT should be administered. In all circumstances, the decision to administer TIG is based on the primary vaccination history for tetanus (Table 13).

3-F. History of Pertussis

Adolescents aged 11–18 years who have a history of pertussis generally should receive Tdap according to the routine recommendations. This practice is preferred because duration of protection induced by pertussis is unknown (waning immunity might begin as early as 7 years after infection) and because the diagnosis of pertussis can be difficult to confirm, particularly with test results other than positive culture for *B. pertussis* (*164*). Administering pertussis vaccines to persons with a history of pertussis presents no theoretical safety concern.

3-G. Adolescents with History of Incomplete Pertussis Vaccination (Received Pediatric DT or Td Instead of Pediatric DTP/DTaP)

Adolescents who received pediatric DT or Td vaccination instead of one or more doses of pediatric DTP/DTaP in the series during childhood should generally receive a single dose of Tdap to provide protection against pertussis if they completed the recommended childhood vaccination series for tetanus and diphtheria[§§§] and have no contraindications to the pertussis components. In routine situations, an interval of at least 5 years between Td and Tdap is encouraged (see Routine Tdap Vaccination [section 1-A]).

3-H. Adolescents with History of Incomplete Pediatric DTP/DTaP/DT or Td Vaccination

Adolescents aged 11–18 years who have never been vaccinated against tetanus, diphtheria, or pertussis (no doses of pediatric DTP/DTaP/DT or Td) should receive a series of three tetanus and diphtheria toxoid–containing vaccinations. The preferred schedule is a single Tdap dose, followed by a dose of Td ≥4 weeks after the Tdap dose, and a second dose of Td 6–12 months after the earlier Td dose. Tdap can be substituted for any one of the three Td doses in the series.

Adolescents who received other incomplete vaccination schedules for tetanus and diphtheria should be vaccinated with Tdap and/or Td according to guidance for catch-up vaccination (Appendix D). A single dose of Tdap can be used to substitute for any one of the Td doses in the series.

In situations in which the adolescent probably has received vaccination against tetanus and diphtheria but cannot produce records, vaccine providers can obtain serologic testing for antibodies to tetanus and diphtheria to avoid unnecessary vaccination. If antitetanus and antidiphtheria levels are each ≥0.1 IU/mL, previous vaccination with tetanus and diphtheria toxoid–containing vaccines is likely and a single dose of Tdap is indicated; this Tdap dose counts as the adolescent booster dose.

3-I. Children Aged 7–10 Years with Incomplete Pediatric DTP/DTaP Vaccination History

Neither Tdap vaccine is licensed for use in children aged <10 years (*32,33*). Children aged 7–10 years who never received a pediatric DTP/DTaP/DT dose or a Td dose generally should receive 3 doses of Td[¶¶¶]: dose 2 is administered ≥4 weeks after dose 1 and dose 3 is administered 6–12 months after dose 2. Children aged 7–10 years who received other incomplete vaccination schedules against tetanus, diphtheria, and pertussis should be vaccinated according to catch-up guidance (Appendix E). When these children become adolescents (aged 11–18 years), they should receive Tdap according to the routine recommendations and interval guidance used for adolescents who completed the childhood DTP/DTaP series (see Routine Tdap Vaccination [section 1-A]).

In situations in which the child probably has received vaccination against tetanus and diphtheria but cannot produce records, vaccine providers can obtain serologic testing for antibodies to tetanus and diphtheria to avoid unnecessary vaccination. If antitetanus and antidiphtheria levels are each ≥0.1 IU/mL, previous vaccination with tetanus and diphtheria toxoid–containing vaccines is likely. In this

[§§§] Five doses of pediatric DTP/DTaP/DT before the seventh birthday; if the fourth dose was administered on or after the fourth birthday, the fifth dose is not needed. Children who began the tetanus and diphtheria vaccination series at age ≥7 years required 3 doses of Td to complete the primary series.

[¶¶¶] A single dose of BOOSTRIX® Tdap is licensed for persons aged 10 years and can be used instead of Td for one of the doses in children aged 10 years; if BOOSTRIX® is administered early to a child aged 10 years, the dose counts as the adolescent Tdap dose usually administered at age 11–12 years.

situation, Td vaccination can be deferred until the child is aged 11–12 years and eligible to receive Tdap.

3-J. Inadvertent Administration of Tdap or Pediatric DTaP

To help prevent inadvertent administration of Tdap when pediatric DTaP is indicated or pediatric DTaP when Tdap is indicated, vaccine providers should review product labels before administering these vaccines; the packaging might appear similar. Tdap is not indicated for children aged <10 years. Tdap contains lower amounts of diphtheria toxoid and lower amounts of some pertussis antigens compared with pediatric DTaP. Studies of the immune responses to Tdap among infants have not been conducted. Pediatric DTaP is not indicated for persons aged ≥7 years; the increased diphtheria toxoid content is associated with higher rates of adverse reactions in older persons (*24–28*).

Guidance on the best approach to vaccination following inadvertent administration of Tdap or pediatric DTaP is based primarily on expert opinion. The family should be informed of any inadvertent vaccine administration. Adverse events associated with inadvertent vaccine administration can be reported to VAERS (see Reporting of Adverse Events after Vaccination). If Tdap is inadvertently administered instead of pediatric DTaP to a child aged <7 years as any one of the first three doses of the tetanus-diphtheria-pertussis vaccination series, the Tdap dose should not be counted as valid, and a replacement dose of pediatric DTaP should be administered. If the inadvertent administration is discovered while the child is in the office, the pediatric DTaP can be administered during the same visit. If the child has left the office, some experts suggest administering the replacement dose of pediatric DTaP within approximately 72 hours, or administering it 4 weeks later to optimize the child's immune response to the antigens in pediatric DTaP. This practice helps ensure that the child stays on the primary series schedule and has adequate protection against diphtheria and pertussis. However, the replacement dose of pediatric DTaP can be administered as soon as feasible at any interval after the inadvertent Tdap dose. The remaining doses of the pediatric DTaP series should be administered on the routine schedule, with at least a 4 week interval between the replacement dose of pediatric DTaP and the next dose of pediatric DTaP. For example, if an 8-week-old infant inadvertently received a dose of Tdap instead of the first dose of pediatric DTaP and does not receive a replacement dose of pediatric DTaP within about 72 hours, a replacement dose of pediatric DTaP can be administered 4 weeks after the inadvertent Tdap dose (age 12 weeks). The routine schedule of pediatric DTaP can then be resumed 4 weeks after the pediatric DTaP replacement dose (age 16 weeks) with the other recommended vaccines (*1,23*).

If Tdap is inadvertently administered as the fourth or the fifth dose in the tetanus-diphtheria-pertussis vaccination series to a child aged <7 years, the Tdap dose should be counted as valid and does not need to be repeated; the child who received Tdap as a fourth dose should complete the pediatric DTaP schedule (*23*). The routine adolescent Tdap vaccination recommendations would apply when this child becomes an adolescent. For example, a child who inadvertently receives Tdap at age 5 years instead of the fifth dose of pediatric DTaP should receive a second dose of Tdap at age 11–12 years.

If Tdap or pediatric DTaP is inadvertently administered to a child aged 7-9 years instead of Td as part of catch-up vaccination or for wound management, this dose can be counted as the adolescent Tdap dose, or the child can later receive an adolescent booster dose of Tdap according to the interval guidance used for Td to Tdap (see Routine Tdap Vaccination [section 1-A] and Pertussis Outbreaks and Other Settings with Increased Risk for Pertussis or its Complications [section 3-C]). In either case, the child should receive a dose of vaccine containing tetanus and diphtheria toxoids no longer than 10 years after the inadvertent Tdap or pediatric DTaP dose or according to the guidance for catch-up vaccination (Appendix E).

If pediatric DTaP is inadvertently administered to an adolescent aged 11–18 years, the dose should be counted as the adolescent Tdap booster. The adolescent should receive the next dose of a vaccine containing tetanus and diphtheria toxoids 10 years after the inadvertent pediatric DTaP dose or according to the guidance for catch-up vaccination (Appendix D).

3-K. Vaccination during Pregnancy

As with other inactivated vaccines and toxoids (*91,165*), pregnancy is not considered a contraindication for Tdap vaccination. Guidance on the use of

Tdap during pregnancy to protect against pertussis is under consideration by ACIP. Pregnant adolescents who received the last tetanus toxoid–containing vaccine <10 years previously should generally receive Tdap after delivery, if otherwise indicated (see Post-Partum Vaccination [section 3-L]).

To prevent neonatal tetanus, pregnant adolescents who received the last tetanus toxoid–containing vaccine ≥10 years previously should generally receive Td in preference to Tdap. ACIP has recommended that pregnant women receive Td if the last tetanus toxoid–containing vaccine was administered ≥10 years previously (*24,31,91,165*). If Td is indicated, vaccinating during the second or third trimester is preferred when feasible to minimize a perception of an association of vaccine with adverse pregnancy outcomes, which are more common during the first trimester. A pregnant adolescent who has not received the 3-dose primary tetanus vaccination series should begin this series during pregnancy, using Td. (see Adolescents with History of Incomplete Pediatric DTP/DTaP/DT or Td Vaccination [section 3-H]).

Because of lack of data on the use of Tdap in pregnant women, both Tdap manufacturers have established pregnancy registries. Health-care providers are encouraged to report Tdap vaccination during pregnancy to the following registries: BOOSTRIX® to GlaxoSmithKline Biologicals at 1-888-825-5249 and ADACEL™ to sanofi pasteur at 1-800-822-2463 (1-800-VACCINE) (*32,33*).

3-L. Post-Partum Vaccination

Adolescents aged 11–18 years, including those who are breastfeeding, should receive a single dose of Tdap as soon as feasible in the postpartum period, according to the routine Tdap recommendations and interval guidance (see Routine Tdap Vaccination [section 1-A] and Pertussis Outbreaks and Other Settings with Increased Risk for Pertussis or its Complications [section 3-C]). For adolescent mothers who have not already received Tdap, vaccinating the mother with Tdap during the postpartum period might reduce the risk for pertussis transmission to the infant. Protection of the mother against pertussis requires an estimated 1 to 2 weeks after vaccination.

3-M. Older Adolescents and Adults Aged >18 Years

To maintain protection against tetanus and diphtheria, ACIP has recommended decennial Td boosters for adults beginning 10 years after the adolescent dose (*24,30*). The safety and efficacy of Tdap (ADACEL™) as a single dose booster immunization against tetanus, diphtheria, and pertussis has been demonstrated for persons aged 19–64 years (*32*). In October 2005, ACIP recommended a single dose of Tdap (ADACEL™)for adults aged 19–64 years who have not received Tdap; recommendations for the use of Tdap among adults will be published separately.****

Reporting of Adverse Events After Vaccination

As with any newly licensed vaccine, surveillance for rare adverse events associated with administration of Tdap is important for assessing its safety in large-scale use. The National Childhood Vaccine Injury Act of 1986 requires health-care providers to report specific adverse events that follow tetanus, diphtheria, or pertussis vaccination (http://vaers.hhs.gov/reportable.htm). All clinically significant adverse events should be reported to VAERS, even if causal relation to vaccination is not certain. VAERS reporting forms and information are available electronically at http://www.vaers.hhs.gov/ or by telephone, (800) 822-7967. Web-based reporting is available and providers are encouraged to report electronically at https://secure.vaers.org/VaersDataEntryintro.htm to promote better timeliness and quality of safety data.

Safety surveillance for adolescent Tdap, MCV4, and other vaccines is being conducted on an ongoing basis in cooperation with FDA. Previously published safety data for Td and for tetravalent meningococcal polyscaccharide vaccine will provide some of the basis for comparison with postlicensure safety surveillance for Tdap and MCV4, respectively (*130,166*).

Vaccine Injury Compensation

The National Vaccine Injury Compensation Program (VICP), established by the National Childhood Vaccine Injury Act of 1986, is a system under which compensation can 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. Anyone receiving a covered vaccine, regardless of age, can file a petition under VICP. The program is intended as an alternative to civil litigation under the traditional tort system because negligence need not be proven.

The Act establishes 1) a Vaccine Injury Table that lists the vaccines covered by the program; 2) the injuries, disabilities,

**** Provisional ACIP recommendations are available at http://www.cdc.gov/nip/recs/provisional_recs/default.htm; final ACIP recommendations are available at http://www.cdc.gov/nip/publications/acip-list.htm.

and conditions (including death) for which compensation might be paid without proof of causation; and 3) the period after vaccination during which the first symptom or substantial aggravation of the injury must appear. Persons might be compensated for an injury listed in the table or one that can be demonstrated to result from administration of a listed vaccine. All tetanus toxoid–containing vaccines and vaccines with pertussis components (e.g., Tdap, Td, and pediatric DTaP) are covered under the Act. Additional information about the program is available at http://www.hrsa.gov/osp/vicp or by calling 1-800-338-2382.

Areas for Future Research Related to Tdap and Adolescents

With recent licensure and introduction of Tdap for adolescents, close monitoring of pertussis disease trends and vaccine safety will be high priorities for public health organizations and health-care providers. Active surveillance sites in Massachusetts and Minnesota, supported by CDC, are being established to provide additional data on the burden of pertussis in adolescents and other age groups and the impact of adolescent Tdap vaccination recommendations. Postlicensure studies and surveillance activities are planned or under way to evaluate

- changes in the incidence of pertussis;
- physicians' uptake of Tdap;
- safety and immunogenicity of simultaneous and nonsimultaneous administration of Tdap and MCV4 in adolescents (*104,105*); and
- the prevalence of and risk factors for ELS in adolescents, including studies of adolescents who were vaccinated with 5 doses of pediatric DTaP series (during 2008, the first birth cohort for which an all-pediatric DTaP 5-dose schedule was recommended will turn 11 years of age and become eligible for adolescent vaccination with Tdap).

Research is needed to evaluate and define

- immunologic correlates of protection for pertussis;
- improved diagnostic tests for pertussis;
- methods to enhance coverage and delivery of Tdap to adolescents; and
- safety and effectiveness of repeated Tdap doses.

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Appendix A

Composition of selected vaccines with tetanus toxoid, diphtheria toxoid, and acellular pertussis components licensed in the United States, 2006*

Vaccines for persons aged <7 years	Trade name	Manufacturer	Pertussis antigens (μg)†				Diphtheria toxoid†	Tetanus toxoid†
			PT	FHA	PRN	FIM		
DTaP	INFANRIX®	GlaxoSmithKline Biologicals (GSK)	25	25	8	—	25 Limit of flocculation unit (Lf)	10 Lf
DTaP-IPV-HepB§	PEDIARIX™	GSK	25	25	8	—	25 Lf	10 Lf
DTaP	DAPTACEL®	sanofi pasteur	10	5	3	5¶	15 Lf	5 Lf
DTaP	Tripedia®	sanofi pasteur	23.4	23.4	—	—	6.7 Lf	5 Lf
DTaP+HIB (Tripedia + ActHIB)**	TriHIBit®	sanofi pasteur	23.4	23.4	—	—	6.7 Lf	5 Lf
DT	No trade name	sanofi pasteur	—	—	—	—	6.7 Lf	5 Lf
Vaccines for persons aged ≥7 years								
Tdap	BOOSTRIX®††	GSK	8	8	2.5	—	2.5 Lf	5 Lf
Tdap	ADACEL™§§	sanofi pasteur	2.5	5	3	5¶	2 Lf	5 Lf
Td	No trade name	Massachusetts Public Health Biologics Laboratory	—	—	—	—	2 Lf	2 Lf
Td	DECAVAC™	sanofi pasteur	—	—	—	—	2 Lf	5 Lf
Td	TENIVAC™	sanofi pasteur	—	—	—	—	2 Lf	5 Lf
Td	No trade name	sanofi pasteur	—	—	—	—	2 Lf	5 Lf
TT (adsorbed)	No trade name	sanofi pasteur	—	—	—	—	—	5 Lf
TT (booster) (fluid)	No trade name	sanofi pasteur	—	—	—	—	—	4 Lf

* Consult package inserts for prescribing information, age indication, and additional product information; package inserts are routinely updated. Some vaccines are licensed but no longer available in the Untied States. See Appendix F for a complete list of abbreviations.
† Per recommended dose of 0.5 mL. PT=pertussis toxin (vaccine component is inactivated/detoxified), FHA=filamentous haemagglutinin, PRN=pertactin, FIM=fimbriae.
§ The tetanus, diphtheria, and pertussis components are the same as those in INFANRIX®: also contains hepatitis B surface antigen, plus poliovirus Type 1 (Mahoney), Type 2 (MEF-1), and Type 3 (Saukett).
¶ Types 2 and 3.
** The tetanus, diphtheria, and pertussis components are the same as those in Tripedia®: also contains *Haemophilus influenzae* type b (Tetanus Toxoid Conjugate).
†† BOOSTRIX® – indicated as a single dose for persons aged 10–18 years.
§§ ADACEL™ – indicated as a single dose for persons aged 11–64 years.

Appendix B

CDC and Council of State and Territorial Epidemiologists (CSTE) pertussis case definition*

Clinical Case Definition

- a cough illness lasting at least 2 weeks with one of the following: paroxysms of coughing, inspiratory "whoop," or posttussive vomiting, and without other apparent cause (as reported by a health-care professional)

Laboratory Criteria for Diagnosis

- isolation of *Bordetella pertussis* from a clinical specimen, or
- positive polymerase chain reaction (PCR) assay for *B. pertussis*

Case Classification

Confirmed

- an acute cough illness of any duration associated with *B. pertussis* isolation, or
- a case that meets the clinical case definition and is confirmed by PCR, or
- a case that meets the clinical definition and is epidemiologically linked directly to a case confirmed by either culture or PCR

Probable

- a case that meets the clinical case definition, is not laboratory confirmed by culture or PCR, and is not epidemiologically linked directly to a laboratory-confirmed case.

SOURCES: Guidelines for the control of pertussis outbreaks. Atlanta, GA: CDC. Available at http://www.cdc.gov/nip/publications/pertussis/guide.htm. Council of State and Territorial Epidemiologists. CSTE position statement, 1997-ID-9: Public health surveillance control and prevention of pertussis, available at http://www.cste.org/ps/1997/1997-id-09.htm.

* Both probable and confirmed cases should be reported to the National Notifiable Diseases Surveillance System (http://www.cdc.gov/epo/dphsi/nndsshis.htm).

Appendix C

Summary of recommendations for tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine (Tdap) and tetanus and diphtheria toxoids (Td) use among adolescents aged 11–18 years*

Routine Tdap vaccination for adolescents aged 11–18 years

- Adolescents aged 11–18 years should receive a single dose of Tdap instead of Td for booster immunization against tetanus, diphtheria, and pertussis if they have completed the recommended childhood DTP/DTaP vaccination series† and have not received Td or Tdap. The preferred age for Tdap vaccination is 11–12 years; routinely administering Tdap to young adolescents will reduce the morbidity associated with pertussis in adolescents [1-A].
- Adolescents aged 11–18 years who received Td, but not Tdap, are encouraged to receive a single dose of Tdap to provide protection against pertussis if they have completed the recommended childhood DTP/DTaP vaccination series.† An interval of at least 5 years between Td and Tdap is encouraged to reduce the risk for local and systemic reactions after Tdap vaccination. However, an interval less than 5 years between Td and Tdap can be used. The benefit of using Tdap at a shorter interval to protect against pertussis generally outweighs the risk for local and systemic reactions after vaccination in settings with increased risk for pertussis or its complications (see Pertussis Outbreaks and Other Settings with Increased Risk for Pertussis or its Complications) [1-A].
- Vaccine providers should administer Tdap (or Td) and tetravalent meningococcal conjugate vaccine ([MCV4] Menactra®) (which both contain diphtheria toxoid) during the same visit if both vaccines are indicated and available (MCV4 recommendations available at http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5407a1.htm and http://www.cdc.gov/mmwr/preview/mmwrhtml/mm54d1006a1.htm)§ [1-A].
- Tdap (or Td) should be administered with other vaccines that are indicated during the same visit when feasible. Each vaccine should be administered using a separate syringe at different anatomic sites. Some experts recommend administering no more than two injections per muscle, separated by at least one inch [1-C].

Contraindications, precautions, and reasons to defer Tdap or Td among adolescents aged 11–18 years

- **Contraindications**: History of serious allergic reaction (i.e., anaphylaxis) to vaccine components or encephalopathy (e.g., coma or prolonged seizures) not attributable to an identifiable cause within 7 days of administration of a vaccine with pertussis components (this is a contraindication for the pertussis components; Td can be used) [2-A].
- **Precautions and Reasons to Defer Vaccination:** Guillain-Barré syndrome ≤6 weeks after a previous dose of a tetanus toxoid–containing vaccine; progressive neurologic disorder, including progressive encephalopathy, or uncontrolled epilepsy, until the condition has stabilized (these conditions are precautions for the pertussis components; Td can be used); acute illness; and history of an Arthus reaction after a tetanus toxoid–containing and/or diphtheria toxoid–containing vaccine administered <10 years previously [2-B].

Reporting of adverse events after vaccination

- All clinically significant adverse events should be reported to the Vaccine Adverse Event Reporting System (VAERS), even if causal relation to vaccination is not certain. VAERS reporting forms and information are available electronically at http://www.vaers.org or by telephone, 800-822-7967. Providers are encouraged to report electronically at https://secure.vaers.org/VaersDataEntryintro.htm.

* Consult recommendations in text for details.

† Five doses of pediatric DTP/DTaP before the seventh birthday; if the fourth dose was administered on or after the fourth birthday, the fifth dose is not needed.

§ A prelicensure study demonstrated that simultaneous vaccination with Td and MCV4 was acceptably safe; the safety of simultaneous vaccination with Tdap and MCV4 has been inferred from this study. Td followed 1 month later by MCV4 was studied, and rates of local reactions were comparable to simultaneous vaccination. Other schedules of MCV4 and Td and MCV4 and Tdap have not been studied (http://www.fda.gov/cber/label/mpdtave011405LB.pdf).

Special situations for Tdap (single dose) and Td use among adolescents aged 11–18 years

- **Nonsimultaneous vaccination:** If simultaneous vaccination is not feasible, inactivated vaccines can be administered at any time before or after a different inactivated or live vaccine. Tdap (or Td) and MCV4 vaccines (which all contain diphtheria toxoid) can be administered using any sequence. Persons who recently received one diphtheria toxoid–containing vaccine might have increased rates of adverse reactions after a subsequent diphtheria toxoid–containing vaccine when diphtheria antibody titers remain elevated from the previous vaccination[§] [3-B].
- **Pertussis Outbreaks and Other Settings with Increased Risk for Pertussis or its Complications:** Vaccine providers can administer Tdap to adolescents aged 11–18 years at an interval less than 5 years after Td, particularly when the benefit of providing protection against pertussis is likely to be increased (e.g., pertussis outbreaks and close contact with an infant aged <12 months). The safety of an interval as short as approximately 2 years between Td and Tdap is supported by a Canadian study among children and adolescents. Postexposure chemoprophylaxis and other pertussis control guidelines are available at http://www.cdc.gov/nip/publications/pertussis/guide.htm and http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5414a1.htm [3-C].
- **Lack of Availability of Tdap or MCV4:** If Tdap and MCV4 are both indicated for adolescents but only one vaccine is available, the available vaccine should generally be administered [3-D].
- **Use of Td when Tdap is Not Available:** When Tdap is indicated but not available, vaccine providers should administer Td if the last pediatric DTP/DTaP/DT or Td dose was ≥10 years earlier to provide protection against tetanus and diphtheria. Td can be deferred temporarily when the last pediatric DTP/DTaP/DT or Td was administered <10 years earlier and the adolescent is likely to return for follow-up. Vaccine providers should maintain a system to recall adolescents when Tdap/Td vaccination is deferred [3-D].
- **Tetanus Prophylaxis in Wound Management:** Adolescents who require a tetanus toxoid–containing vaccine as part of wound management should receive a single dose of Tdap instead of Td if they have not previously received Tdap; if Tdap is not available or was previously administered, adolescents who need a tetanus toxoid–containing vaccine should receive Td [3-E].
- **History of Pertussis:** Adolescents who have a history of pertussis generally should receive Tdap according to the routine recommendations [3-F].
- **No History of Pertussis Vaccination:** Adolescents who have not received vaccines with pertussis components but completed the recommended tetanus and diphtheria vaccination series[¶] with pediatric DT or Td generally should receive Tdap according to the routine recommendations if they do not have a contraindication to the pertussis components [3-G].
- **No History of Pediatric DTP/DTaP or Td/Tdap Vaccination:** Adolescents who have never received tetanus-diphtheria-pertussis vaccination should receive a series of three vaccinations. The preferred schedule is a single Tdap dose, followed by a dose of Td ≥4 weeks after the Tdap dose and a second dose of Td 6–12 months after the earlier Td dose. Tdap can be substituted for any one of the 3 Td doses in the series [3-H].
- **Vaccination during Pregnancy:** Pregnancy is not considered a contraindication for Tdap or Td vaccination. Guidance on the use of Tdap during pregnancy is under consideration by the Advisory Committee on Immunization Practices. Pregnant adolescents who received the last tetanus toxoid–containing vaccine <10 years previously should generally receive Tdap in the postpartum period, according to the routine vaccination recommendations and interval guidance, and pregnant adolescents who received the last tetanus toxoid–containing vaccine ≥10 years previously should generally receive Td in preference to Tdap (during the second or third trimester) [3-K, 3-L].

[¶] Five doses of pediatric DT before the seventh birthday; if the fourth dose was administered on or after the fourth birthday, the fifth dose is not needed. Children who began the tetanus and diphtheria vaccination series at age ≥7 years required 3 doses of Td to complete the primary series.

Appendix D

Guide to catch-up vaccination with Td and Tdap for adolescents aged 11–18 years*

Vaccination history before catch-up: number of pediatric DTP/DTaP/DT or Td doses administered before age 11 years		No. of Td/Tdap doses needed to catch-up*†	Minimum interval between doses of tetanus and diphtheria toxoid–containing vaccines*†			
No. doses at age <1 year	No. doses at age 1–10 years		Last dose administered at age <11 years to adolescent dose 1	Adolescent dose 1 to dose 2	Adolescent dose 2 to dose 3	Adolescent dose 3 to dose 4
Unknown	Unknown	3	NA§	4 weeks	6 months	—¶
0	0	3	NA	4 weeks	6 months	—¶
0	1	2	4 weeks	6 months	—¶	NA
0	2	1	6 months	—¶	NA	NA
0	3	0	—¶**	NA	NA	NA
1	0	3	NA: administer now	4 weeks	6 months	—¶
1	1	2	4 weeks	6 months	—¶	NA
1	2	1	6 months	—¶	NA	NA
1	3	0	—¶**	N/A	NA	NA
2	0	2	NA: administer now	6 months	—¶	NA
2	1	1	6 months	—¶	NA	NA
2	2	0	—¶**	NA	NA	NA
3	0	1	NA: administer now	—¶	NA	NA
3	1	0	—¶**	NA	NA	NA

* Adolescents aged 11–18 years with incomplete vaccination schedules for tetanus and diphtheria should receive a single dose of Tdap as part of catch-up vaccination if they have not received Tdap to add protection against pertussis; Td should be used for other doses if indicated (see text, Routine Tdap Vaccination [1-A]). Pediatric DTaP/DTP/DT vaccines are not indicated for persons aged ≥7 years. See Appendix F for a complete list of vaccine abbreviations.

† Number of doses and the minimum intervals between the last dose administered and the next dose of tetanus and diphtheria toxoid–containing vaccine needed to provide protection against tetanus and diphtheria.

§ Not applicable.

¶ To maintain protection against tetanus and diphtheria, a tetanus and diphtheria toxoid–containing vaccine is indicated 10 years after the last adolescent dose.

** If the adolescent has not received Tdap as one of the doses, a single dose of Tdap is encouraged to add protection against pertussis; an interval of at least 5 years between Td and Tdap is encouraged but shorter intervals can be used (see text, Routine Tdap Vaccination [1-A]).

Appendix E

Guide to catch-up vaccination with Td for children aged 7–10 years*

Vaccination history before catch-up: number of pediatric DTP/DTaP/DT or Td doses administered before age 7 years		No. of Td/ doses needed to catch-up*†	Minimum interval between doses of tetanus and diphtheria toxoid–containing vaccines*†			
No. doses at age <1 year	No. doses at age 1–6 years		Last pediatric DTP/DTaP/DT dose to Td dose 1 at age ≥7 years	Td dose 1 to Td dose 2	Td dose 2 to Td dose 3	Td dose 3 to Td dose 4
Unknown	Unknown	3	NA§	4 weeks	6 months	—¶
0	0	3	NA	4 weeks	6 months	—¶
0	1	2	4 weeks	6 months	—¶	NA
0	2	1	6 months	—¶	NA	NA
0	3	0	—¶**	NA	NA	NA
1	0	3	NA: administer now	4 weeks	6 months	—¶
1	1	2	4 weeks	6 months	—¶	NA
1	2	1	6 months	—¶	NA	NA
1	3	0	—¶**	NA	NA	NA
2	0	2	NA: administer now	6 months	—¶	NA
2	1	1	6 months	—¶	NA	NA
2	2	0	—¶**	NA	NA	NA
3	0	1	NA: administer now	—¶	NA	NA
3	1	0	—¶**	NA	NA	NA

* Td is recommended for children aged 7–10 years; a single dose of BOOSTRIX® Tdap vaccine is licensed for persons aged 10 years and can be used instead of Td for one of the doses in children aged 10 years. If BOOSTRIX® is administered to a child aged 10 years, the dose counts as the adolescent Tdap dose. Pediatric DTaP/DTP/DT vaccines are not indicated for persons aged ≥7 years. See Appendix F for a complete list of vaccine abbreviations.

† Number of doses and the minimum intervals between the last dose administered and the next dose of tetanus and diphtheria toxoid–containing vaccine needed to provide protection against tetanus and diphtheria.

§ Not applicable.

¶ These children should receive Tdap to provide protection against tetanus, diphtheria and pertussis according to the routine vaccination recommendations for adolescents who completed the pediatric DTP/DTaP series, when they become adolescents aged 11–18 years; an interval of at least 5 years between Td and Tdap is encouraged, but shorter intervals can be used (see text, Routine Tdap Vaccination [1-A]).

** Some experts suggest administering a dose of Td now to children aged 7–10 years with this vaccination history if no dose of a tetanus and diphtheria toxoid–containing vaccine was administered at age ≥4 years.

Appendix F

Abbreviations used in this report

ACIP	Advisory Committee on Immunization Practices
ap	acellular pertussis vaccine (without tetanus and diphtheria toxoids)
B. bronchiseptica	*Bordetella bronchiseptica*
B. holmesii	*Bordetella holmesii*
B. parapertussis	*Bordetella parapertussis*
B. pertussis	*Bordetella pertussis*
C. diphtheriae	*Corynebacterium diphtheriae*
C. tetani	*Clostridium tetani*
C. ulcerans	*Corynebacterium ulcerans*
CI	confidence interval
CSTE	Council of State and Territorial Epidemiologists
DFA	direct fluorescent antibody
DT	pediatric diphtheria and tetanus toxoids vaccine
DTaP	pediatric diphtheria and tetanus toxoids and acellular pertussis vaccine
DTP	pediatric diphtheria and tetanus toxoids and whole cell pertussis vaccine
EU	ELISA units
ELISA	enzyme-linked immunosorbent assay
ELS	extensive limb swelling
FDA	Food and Drug Administration
FHA	filamentous hemagglutinin
FIM	fimbriae
GMC	geometric mean antibody concentration
GMT	geometric mean titer
GSK	GlaxoSmithKline Biologicals
HAI	haemagglutinin inhibition
HIV	human immunodeficiency virus
IM	intramuscularly
IOM	Institute of Medicine
IU	international units
Lf	limit of flocculation unit
MCV4	tetravalent meningococcal conjugate vaccine
MDPH	Massachusetts Department of Public Health
mIU	milli-international unit
mL	milliliter
MPHBL	Massachusetts Public Health Biologic Laboratories
ng	nanogram
NNDSS	National Notifiable Diseases Surveillance System
NHANES	National Health and Nutritional Examination Survey
PCR	polymerase chain reaction
2-PE	2-phenoxyethanol
PRN	pertactin
PPD	tuberculin purified protein derivative
PT	pertussis toxin
QALY	quality adjusted life year
SAE	serious adverse event

sp	sanofi pasteur
SPSS	Supplemental Pertussis Surveillance System
Tdap	tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine
Td	adult tetanus and diphtheria toxoids vaccine
TIG	tetanus immune globulin
TIV	trivalent inactivated influenza vaccine
TT	tetanus toxoid vaccine
VAERS	Vaccine Adverse Event Reporting System
VICP	Vaccine Injury Compensation Program
μg	microgram

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