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Prevention of Pertussis, Tetanus, and Diphtheria Among Pregnant and Postpartum Women and Their Infants

Recommendations of The Advisory Committee on Immunization Practices (ACIP)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
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Disclosure of Relationship

CDC and content experts have no financial interest or other relationship with the manufacturers of commercial products or suppliers of commercial services mentioned herein. This report includes discussions of the use of Td and Tdap in the following situations in which Td or Tdap is not indicated according to current FDA labeling:

A. when the interval between Td and Tdap might be <5 years as specified in the package inserts;
B. when progressive or unstable neurological disorders (e.g., cerebrovascular events, acute encephalopathic conditions) exist that are considered precautions and a reason to defer Td and/or Tdap;
C. when Tdap is used as part of the primary series for tetanus and diphtheria; and
D. when Tdap or pediatric DTaP is administered inadvertently outside the licensed age indications.

Prevention of Pertussis, Tetanus, and Diphtheria Among Pregnant and Postpartum Women and Their Infants

Recommendations of the Advisory Committee on Immunization Practices (ACIP)

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Summary

In 2005, two tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccines were licensed and recommended for use in adults and adolescents in the United States: ADACEL® (sanofi pasteur, Swiftwater, Pennsylvania), which is licensed for use in persons aged 11–64 years, and BOOSTRIX® (GlaxoSmithKline Biologicals, Rixensart, Belgium), which is licensed for use in persons aged 10–18 years. Both Tdap vaccines are licensed for single-dose use to add protection against pertussis and to replace the next dose of tetanus and diphtheria toxoids vaccine (Td). Available evidence does not address the safety of Tdap for pregnant women, their fetuses, or pregnancy outcomes sufficiently. Available data also do not indicate whether Tdap-induced transplacental maternal antibodies provide early protection against pertussis to infants or interfere with an infant's immune responses to routinely administered pediatric vaccines. Until additional information is available, CDC's Advisory Committee on Immunization Practices recommends that pregnant women who were not vaccinated previously with Tdap: 1) receive Tdap in the immediate postpartum period before discharge from hospital or birthing center, 2) may receive Tdap at an interval as short as 2 years since the most recent Td vaccine, 3) receive Td during pregnancy for tetanus and diphtheria protection when indicated, or 4) defer the Td vaccine indicated during pregnancy to substitute Tdap vaccine in the immediate postpartum period if the woman is likely to have sufficient protection against tetanus and diphtheria. Although pregnancy is not a contraindication for receiving Tdap vaccine, health-care providers should weigh the theoretical risks and benefits before choosing to administer Tdap vaccine to a pregnant woman. This report 1) describes the clinical features of pertussis, tetanus, and diphtheria among pregnant and postpartum women and their infants, 2) reviews available evidence of pertussis vaccination during pregnancy as a strategy to prevent infant pertussis, 3) summarizes Tdap vaccination policy in the United States, and 4) presents recommendations for use of Td and Tdap vaccines among pregnant and postpartum women.

Introduction

Pertussis is an acute and prolonged infectious cough illness caused by *Bordetella pertussis*, a fastidious gram-negative coccobacillus. Pertussis results in substantial morbidity among adults and adolescents whose immunity to past childhood vaccination or *B. pertussis* infection might have waned and who have not received booster immunization for pertussis with adult tetanus, reduced diphtheria, and acellular pertussis (Tdap) vaccine (*1*,*2*). In 2004, women aged 15–39 years accounted for 97% of all live births in the United States (*3*). During 2000–2006, a total of 103,940 cases of pertussis were reported to CDC's National Notifiable Diseases Surveillance System (NNDSS); 27,759 (27%) of these cases occurred among persons aged 15–39 years (CDC, unpublished data, 2007). Parents with pertussis, including new mothers, are the identified source of *B. pertussis* infection in ≥25% of pertussis

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cases in early infancy, when rates for complications and fatalities are highest (*4–8*). Infants aged <12 months accounted for 145 (93%) of 156 pertussis-related deaths reported to CDC for 2000–2006 (CDC, unpublished data, 2007). Decennial booster vaccination with adult tetanus toxoid and reduced diphtheria toxoid (Td) vaccine has been largely responsible for reducing the average annual number of tetanus and respiratory diphtheria cases reported during 2000–2006 to 31 and less than one, respectively. In contrast, the average annual number of pertussis cases was 14,849 during the same period (*9–15*; CDC, unpublished data, 2007).

In 2005, two Tdap vaccines were licensed in the United States: ADACEL® (sanofi pasteur, Swiftwater, Pennsylvania) for use in persons aged 11–64 years (*16*) and BOOSTRIX® (GlaxoSmithKline Biologicals, Rixensart, Belgium) for persons aged 10–18 years (*17*) (Table 1). Both vaccines are licensed for single-dose administration. Acellular pertussis vaccines formulated with tetanus and diphtheria toxoids also are available for adults and adolescents in other countries, including an increasing number of European countries (e.g., France, Austria, and Germany), Canada, and Australia (*18–20*). No vaccine containing acellular pertussis antigens without tetanus and diphtheria toxoids is available in the United States.

Vaccinating adults and adolescents using Tdap reduces the burden of pertussis among vaccine recipients and might prevent transmission of *B. pertussis* to infants (*1,2*). Statements and recommendations by CDC's Advisory Committee for Immunization Practices (ACIP) regarding use of Tdap by adults, including health-care personnel, and adolescents (Table 2) provide background information on pertussis and extensive discussion regarding the safety and immunogenicity of Tdap in prelicensure trials. These recommendations encourage adult and adolescent women of childbearing age to receive Tdap at a routine health assessment before conception to prevent the morbidity of pertussis that could occur during pregnancy and encourage use of Tdap among adults and adolescents who anticipate contact with an infant aged <12 months both for personal protection and to reduce the risk for transmitting *B. pertussis* to the infants (*1,2*).

In 2006, ACIP recommended routine administration of Tdap for postpartum women who were not vaccinated previously with Tdap to provide personal protection and reduce the risk for transmitting pertussis to their infants (*1,2*) . After careful consideration, in June 2006, ACIP voted to reaffirm its recommendation for use of Td in pregnant women who have urgent indication for tetanus toxoid or diphtheria toxoid vaccination to prevent maternal or neonatal tetanus, or to prevent diphtheria. Pregnant women not vaccinated previously with Tdap will receive a measure of protection against pertussis by ensuring that children in the household are up-to-date with recommended doses of pediatric diphtheria and tetanus toxoids and acellular pertussis vaccine (DTaP)* (*21–23*) and that adult and adolescent household contacts have received a dose of Tdap (Table 2) (*1,2*). Health-care providers can monitor pregnant women who have not received a dose of Tdap for exposures to pertussis or to respiratory illness consistent with pertussis, and they can administer antimicrobials for postexposure prophylaxis or treatment of pertussis, if needed, to reduce the risk for transmitting pertussis to their infants.

This report provides the background and rationale for routine administration of Tdap in postpartum women who were not vaccinated previously with Tdap and for maintaining the previous recommendation for use of Td in pregnant women if indicated. The safety and efficacy of using Tdap in pregnant women has not been demonstrated, and Tdap is not recommended for use in pregnant women in any country. No evidence exists of excess morbidity or any fatality among pregnant women ascribed to pertussis. No evidence exists demonstrating whether

- Tdap in pregnant women harms the fetus or increases risk for adverse pregnancy outcomes,
- transplacental antibody induced by Tdap administered during pregnancy will protect infants against pertussis, or
- Tdap-induced transplacental maternal antibody will have a negative impact on an infant's protective immune response to later-administered routine pediatric DTaP or to conjugate vaccines containing tetanus toxoid or diphtheria toxoid.

This report discusses certain situations in which health-care providers might choose to administer Tdap to a pregnant woman. Health-care providers should weigh the theoretical risks and benefits before choosing to administer Tdap vaccine to a pregnant woman.

Methods

During June 2006, ACIP evaluated the limited evidence available concerning safety, immunogenicity, and pregnancy outcomes after administration of Tdap; evidence from historic use of pertussis, tetanus, and diphtheria vaccines in pregnant women; and the potential effects of transplacental maternal antibody on the infant's immune response to active immunization with pediatric diphtheria and tetanus toxoids and whole-cell pertussis (DTP) or DTaP vaccines, or to con-

* The recommended childhood schedule of pediatric DTaP is a dose at ages 6–8 weeks, at 4 months, and at 6 months and a booster dose at age 15–18 months and at age 4–6 years (*23*).

jugate vaccines containing tetanus toxoid or diphtheria toxoid. The evaluation included a synthesis of information from scientific literature published in English, unpublished sources of information, consultations, analyses, and extensive discussion by an ACIP working group[†] during 2005–2006. The working group comprised persons with expertise in pertussis, tetanus, and diphtheria; obstetrics and gynecology; pediatrics, family practice, internal medicine, immunology, public health, and vaccine regulation; and liaison members from partner organizations.

The workgroup considered multiple diverse views on the adequacy of evidence needed to form a recommendation for use of Tdap in pregnant and postpartum women. A minority view held that available data from nonpregnant women and men, and experience with the use of Td in pregnant women to prevent neonatal and maternal tetanus, were sufficient to support a recommendation for the safe use of Tdap in pregnant women for individual protection from pertussis. The majority view, while acknowledging the desirability of preventing pertussis in pregnant women and the substantial body of information demonstrating the usefulness of Td to prevent maternal and neonatal tetanus, held that the evidence was insufficient at this time to support a recommendation for routine administration of Tdap in pregnant women. The specific issues for pertussis differ from those for tetanus and diphtheria. Important among these is the limited understanding of immunity and correlates of protection for pertussis. In addition, data supporting the safety of vaccinating pregnant women with Tdap to prevent pertussis are scarce for women, their fetuses, and pregnancy outcomes. Whether transplacental maternal antibody exerts an inhibitory or other effect on the infant-protective immune response to active immunization with pediatric DTaP or conjugate vaccines containing tetanus toxoid or diphtheria toxoid has not been studied. Protection against infant pertussis through Tdap-induced transplacental maternal antibody has not been demonstrated. Until additional information is available, the majority view of the working group held that Tdap administered to women in the immediate postpartum period, in addition to ensuring pertussis vaccination of close contacts, would likely provide a measure of protection for mother and infant.

Pertussis

B. pertussis, the organism that causes pertussis, elaborates multiple toxins, including tracheal cytotoxin, which damages the respiratory epithelial tissue in vitro (*24*), and pertussis toxin, which has systemic effects (e.g., promoting lymphocytosis) (*25*). Illnesses caused by other species of Bordetella are not considered preventable by available pertussis vaccines (*26,27*).

Clinical Features

B. pertussis infections and reinfections among adults and adolescents can be asymptomatic or range from a mild cough illness to the severe, prolonged cough illness of classic pertussis (*28*). The clinical presentation of pertussis can be similar to that for respiratory illness caused by *B. parapertussis, B. bronchiseptica, B. holmseii, Mycoplasma pneumoniae, Chlamydia* (*Chlamydophila*) *pneumoniae*, and multiple viral agents (e.g., adenovirus, parainfluenza virus, human metapneumovirus, influenza virus, rhinovirus, and coronavirus). The incubation period for pertussis typically is 7–10 days (range: 5–21 days) (*29,30*).

Classic pertussis is characterized by three phases: catarrhal, paroxysmal, and convalescent (*28,29*). The catarrhal phase lasts 1–2 weeks and consists of a watery nasal discharge and frequent cough, frequent sneezing, and injection of the conjunctiva, often with lacrimation. The cough typically suggests tracheal irritation (e.g., a tickle in the throat) and is short, sharp, hacking, and isolated (as distinguished from paroxysmal). The cough is equally persistent during day and night and rarely croupy or hoarse. Fever is uncommon during any phase unless the illness is complicated by secondary infection or coinfection (*28*). The paroxysmal phase lasts 2–6 weeks. The patient has intermittent periods of intense coughing (paroxysms) alternating with periods of appearing relatively well with a normal respiratory rate. The paroxysms are characterized by spasms of coughing, choking, posttussive vomiting, and inspiratory whoop (*29,31*). Adults experience greater severity of illness than adolescents, including cough-related incontinence in 28% of cases in women; in up to 5% of cases, adults and adolescents experience one or more rib fracture, syncope, or pneumonia, or they require hospitalizations (*1,2,31,32*). Approximately one third of adults and adolescents lose weight during the illness (*31,33*). Anecdotal reports of pneumothorax, seizures, stroke, and other complications have been summarized previously (*1,34*). The convalescent phase of pertussis typically lasts 2–6 weeks (*35*). Symptoms can persist for ≥6 months (*1,2*). Factors that can lessen the severity of *B. pertussis* infection include residual immunity from previous infection or vaccination and use of macrolide antimicrobials in the catarrhal (early) phase of the illness (*36*).

Adults and adolescents with pertussis make repeated medical visits and miss work and school. During 1998–2000 in Massachusetts, among 936 adults and 1,679 adolescents reported with confirmed pertussis, the median number of

[†] A list of members appears on inside back cover of this report.

TABLE 1. Disease-specific composition of vaccines containing tetanus toxoid, with and without diphtheria toxoid and acellular pertussis antigens, by age and vaccine type — United States, 2008*

Age and vaccine type	Trade name	Manufacturer	Pertussis antigens (μg)†				Diphtheria toxoid† (DT) (Lf§)	Tetanus toxoid† (TT) (Lf)
			PT¶	FHA**	PRN††	FIM§§		
For age <7 yrs								
DTaP¶¶	INFANRIX®	GlaxoSmithKline Biologicals (GSK)	25	25	8		25	10
DTaP-IPV-Hep B§§§	PEDIARIX™	GSK	25	25	8		25	10
DTaP	DAPTACEL™	sanofi pasteur	10	5	3	5¶¶¶	15	5
DTaP, DTaP-Hib	Tripedia,® TriHIBit® (Tripedia® + ActHIB®)††††	sanofi pasteur sanofi pasteur	23.4	23.4			6.7	5
DT§§§§	No trade name	sanofi pasteur					6.7	5
For age ≥7 yrs								
Tdap¶¶¶¶	BOOSTRIX®*****	GSK	8	8	2.5		2.5	5
Tdap	ADACEL®†††††	sanofi pasteur	2.5	5	3		2	5
Td§§§§§	No trade name	Massachusetts Public Health Biologic Laboratory					2	2
Td	No trade name	MassBioLogics					2	2
Td	DECAVAC™	sanofi pasteur					2	5
TT¶¶¶¶¶ (adsorbed)	No trade name	sanofi pasteur						5

* Limited to vaccines licensed and marketed in the United States. Consult package inserts for prescribing information, age indication, and additional product information: package inserts are routinely updated. Additional information is available at http://www.fda.gov/cber/index.html.
† Per recommended dose of 0.5 mL.
§ Limit of flocculation
¶ Inactivated/detoxified pertussis toxin.
** Filamentous haemagglutinin.
†† Pertactin.
§§ Fimbriae.
¶¶ Pediatric diphtheria and tetanus toxoids and acellular pertussis vaccine.
*** Residual 2-phenoxyethanol, not used as a preservative.
††† The tip cap and rubber plunger of the needleless prefilled syringes contain dry natural latex rubber; the vial stopper is latex-free.
§§§ Tetanus, diphtheria, and pertussis components are the same as those in INFANRIX®; also contains hepatitis B surface antigen, and inactivated polioviruses Type 1 (Mahoney), Type 2 (MEF-1), and Type 3 (Saukett).
¶¶¶ Fimbriae types 2 and 3.
**** The stopper to the vial contains dry natural rubber that might cause allergic reactions in latex-sensitive person
†††† Tripedia® reconstituted with ActHIB.® The tetanus, diphtheria, and pertussis components are the same as those in Tripedia®; ActHIB® contains *Haemophilus influenzae* type b polysaccharide–tetanus toxoid conjugate.
§§§§ Pediatric diphtheria and tetanus toxoids.
¶¶¶¶ Tetanus toxoid and reduced diphtheria toxoid and accellular pertussis vaccine.
***** Indicated as a single dose for persons aged 10–18 years.
††††† Indicated as a single dose for persons aged 11–64 years.
§§§§§ Tetanus and reduced diphtheria toxoids.
¶¶¶¶¶ Tetanus toxoid.

TABLE 1. (*Continued*) Disease-specific composition of vaccines containing tetanus toxoid, with and without diphtheria toxoid and acellular pertussis antigens, by age and vaccine type — United States, 2008*

How supplied	Adjuvant: aluminum (Al) salt (mg Al/dose)	Thimerosal (methyl mercury per 0.5 mL dose)	Preservative: Other (content per dose)	Preservative: Latex	Other inactive components†
Single dose	Hydroxide (0.625 mg Al)	0	No*** (2.5 mg)	Yes†††	≤100 μg residual formaldehyde ≤100 μg Tween 80
Single dose	Hydroxide (DTaP), Phosphate (Hep B) (≤0.85 mg Al total)	0	None	Yes†††	≤100 μg residual formaldehyde ≤100 μg Tween 80 ≤0.05 ng neomycin sulfate ≤0.01ng polymyxin B ≤5% yeast protein
Single dose	Phosphate (0.33 mg Al)	0	No*** (3.3 mg)	Yes****	≤5 μg residual formaldehyde <50 ng glutaraldehyde
Single dose	Sulfate (≤0.17 mg Al)	≤0.3 μg (trace)	None	Yes****	≤100 μg residual formaldehyde Tween 80 Gelatin
Single dose	Sulfate (≤0.17 mg Al)	<0.3 μg (trace)	None	Yes****	≤100 μg residual formaldehyde
Single dose	Hydroxide (≤0.39 mg Al)	0	None	Yes†††	≤100 μg residual formaldehyde ≤100 μg Tween 80
Single dose	Phosphate (0.33 mg Al)	0	No*** (3.3 mg)	No	≤5 μg residual formaldehyde <50 ng glutaraldehyde
Multidose	Phosphate (0.45 mg Al)	8.3 μg	None	Yes****	<100 μg residual formaldehyde
Single dose	Phosphate (0.45 mg Al)	≤0.3 μg (trace)	None	No	<100 μg residual formaldehyde
Single dose	Sulfate (0.28 mg Al)	≤0.3 μg (trace)	None	No	≤100 μg residual formaldehyde
Single dose	Sulfate (0.25 mg Al)	≤0.3 μg (trace)	None	No	≤100 μg residual formaldehyde

TABLE 2. Summary of recommendations of the Advisory Committee on Immunization Practices (ACIP) for vaccination to prevent pertussis, tetanus, and diphtheria among adults and adolescents,* with recommended intervals for vaccination from the most recent tetanus and diphtheria toxoids-containing vaccine† — United States, 2006–2008

Setting	March 2006 Adolescents (aged 11–18 yrs)	December 2006 Adults (aged 19–64 yrs)	May 2008 Women of childbearing age, including pregnant and postpartum women
Routine*	Tdap at age 11–12 yrs; Tdap catch-up ages 11-18 yrs§	Tdap to replace the next decennial Td¶; ideally, women will receive Tdap before becoming pregnant	Tdap to replace the next decennial Td¶; Tdap is encouraged during preconception wellness visits
Special situations*			
Pregnant women			
Interval <10 yrs	Tdap as soon as feasible in the postpartum period§	Tdap postpartum before leaving hospital or birthing center; interval as short as 2 yrs¶	Tdap postpartum before leaving hospital or birthing center; interval as short as 2 yrs¶**††
Interval ≥10 yrs	Td recommended during pregnancy	Td recommended during pregnancy	• Td recommended during pregnancy,†† or • Tdap-postpartum before leaving hospital or birthing center instead of Td during pregnancy, if sufficient tetanus and diphtheria protection is likely until delivery
Nonpregnant adults and adolescents who anticipate having, or will have contact with an infant aged <12 mos	Tdap at age 11–12 yrs; Tdap catch-up ages 11–18 yrs§	Tdap ideally administered at least 2 wks before contact with the infant; interval as short as 2 yrs suggested¶	Tdap, ideally administered at least 2 wks before contact with the infant; interval as short as 2 yrs suggested¶
Increased risk for pertussis or its complications, e.g., health-care personnel with direct patient contact and persons in settings with a pertussis outbreak	Tdap ages 11–18 yrs§	Tdap; interval as short as 2 yrs¶	Tdap-postpartum before leaving hospital or birthing center; interval as short as 2 yrs¶**††; pregnant women should be advised of symptoms of pertussis and the benefits of treatment and early prophylaxis for household contacts exposed to pertussis
Increased risk for diphtheria	Tdap, when indicated§	Tdap to replace the next Td when indicated*	Td for urgent protection during pregnancy††; Tdap postpartum before leaving hospital or birthing center
Tetanus wound management	Tdap instead of Td when indicated§§	Tdap instead of Td when indicated§§	Td when indicated for pregnant women††§§
No tetanus and diphtheria toxoids vaccination, or vaccination history incomplete or unknown	1 dose Tdap, followed by Td ≥4 wks later and dose 2 Td 6–12 mos later	1 dose Tdap, followed by Td ≥4 wks later and dose 2 Td 6–12 mos later	1 dose Td during pregnancy followed by dose 2 Td ≥4 wks later†† and dose 3 as Tdap 6–12 mos later (postpartum)

Sources: CDC. Preventing tetanus, diphtheria, and pertussis among adolescents: use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccines. Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2006;55(No. RR-3). CDC. Preventing tetanus, diphtheria, and pertussis among adults: use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine (Tdap). Recommendations of the Advisory Committee on Immunization Practices (ACIP) MMWR 2006;55 (No. RR-17).

* ACIP recommends routine vaccination with tetanus and diphtheria toxoids every 10 years to boost tetanus and diphtheria protection. In 2006, ACIP recommended that adults and adolescents who have not been vaccinated previously with tetanus and reduced diphtheria toxoids and acellular pertussis (Tdap), including persons with a history of pertussis, receive a dose of Tdap to boost pertussis protection in addition to tetanus and diphtheria protection. Tdap is licensed for single-dose administration. In persons who have received Tdap, tetanus and reduced diphtheria toxoids (Td) vaccine should be administered when subsequent decennial booster vaccination is indicated for tetanus or diphtheria protection.

† For adults and adolescents, tetanus and diphtheria toxoids–containing vaccines include tetanus toxoid (TT), Tdap, and Td; for infants and children, tetanus toxoid and diphtheria toxoids–containing vaccines include pediatric diphtheria and tetanus toxoids and whole-cell pertussis (DTP), pediatric diphtheria and tetanus toxoids and acellular pertussis (DTaP), pediatric diphtheria and tetanus toxoids and acellular pertussis, inactivated poliovirus and hepatitis B (DTaP-IPV-Hep B), and pediatric diphtheria and tetanus toxoids (DT).

§ During 2000–2006, U.S. adolescents aged 10–19 years had the highest incidence of reported pertussis outside of infancy (CDC, unpublished data, 2008). For this reason, a catch-up dose of Tdap is recommended for adolescents aged 11–18 years to add protection against pertussis if they have received Td but not Tdap. For catch-up Tdap, an interval of at least 5 years from the most recent tetanus and/or diphtheria toxoids–containing vaccine is encouraged to reduce the risk for local and systemic reactions that could result when concentration of tetanus and/or diphtheria antitoxin is high. An interval less than 5 years after Td may be used, particularly when the benefit of providing pertussis protection is likely to be increased. Adolescents who have received a childhood series of pediatric DTP or DTaP and Td or Tdap are protected against tetanus and diphtheria.

¶ A shorter interval may be used.

** Limited evidence informs the risk of local and systemic reactions after Tdap at intervals of <2 years. Higher rates of local and systemic reactions and more severe reactions can occur with high preexisting serum titers of tetanus or diphtheria antitoxin. Providers may choose to administer Tdap in postpartum women who received a tetanus toxoid– and/or diphtheria toxoid–containing vaccine (e.g., Td or TT) less than 2 years previously if the women have no history of serious adverse reaction after the most recent dose of tetanus and/or diphtheria toxoid–containing vaccine.

†† In special situations, a dose of Tdap might be warranted during pregnancy. Health-care providers who choose to administer Tdap to pregnant women should discuss with the women the lack of evidence of safety and effectiveness for the mother, fetus, pregnancy outcome, and effectiveness of transplacental maternal antibodies to provide early pertussis protection to the infant. These women should be informed that no study has examined the effectiveness of transplacental pertussis antibodies induced by Tdap on the adequacy of the infant immune response to pediatric DTaP and conjugate vaccines containing tetanus toxoid or diphtheria toxoid. Because adverse outcomes of pregnancy are most common in the first trimester, vaccinating these pregnant women with Tdap during the second or third trimester is preferred to minimize the perception of an association of Tdap with an adverse outcome, unless vaccine is needed urgently.

§§ A Td booster might be recommended for wound management if ≥5 years have elapsed since the previous Td. Persons who have completed the 3-dose primary tetanus vaccination series and have received a tetanus toxoid–containing vaccine within the preceding 5 years are protected against tetanus and do not require a tetanus toxoid–containing vaccine as part of wound management.

medical visits was two (range: 0–15) (*31*). Among 203 adults and 314 adolescents with confirmed pertussis who were interviewed during 2001–2003, 158 (78%) adults were employed. Of these employed adults, 123 (78%) missed work (mean: 9.8 days; range: 0.1–180 days); 261 of the 314 (83%) adolescents missed school (mean: 5.5 days; range: 0.4–32 days). Among primary caregivers for adolescents, 136 of 314 (43%) missed work (mean: 2.4 days; range: 0.1–25 days); a second caregiver in 53 families also missed work (mean: 1.8 days; range: 0.1–11 days) (*31*).

Pertussis is transmitted from person to person via large respiratory droplets generated by coughing or sneezing; early reports suggested that *B. pertussis* can be recovered from dried mucus for up to 3 days (*28*,*30*). Pertussis is highly infectious, with attack rates among exposed, nonimmune household contacts as high as 80%–90% (*29*,*37*,*38*). The most infectious periods are the catarrhal and early paroxysmal phases (*28*). Untreated patients, particularly infants, remain infectious for 6 weeks or longer (*29*). Among older children and adults with previous vaccination or infection, the infectious period typically is ≤21 days (*29*).

In a Canadian study conducted in 1999, a source was identified in 60%–70% of adults and adolescents with pertussis. Among adults aged 18–39 years, the source was a person in the household in 25%–44% of cases or at work or school in 17%–25% of cases. Among adolescents aged 12–17 years, the source was a person in the household in 9% of cases and a friend or person at school or work in 51% of cases (*39*).

Pertussis During Pregnancy

Case reports suggest that the morbidity of pertussis is not increased among pregnant women compared with nonpregnant women. In a general medical practice during 1979–1980, four pregnant women had onset of cough during the 12th, 14th, 14th, and 36th week of gestation and cough that lasted 36, 6, 8, and 6 weeks, respectively; two women had vomiting after coughing and worsening cough paroxysms at night; and one woman developed hemoptysis and subconjunctival hemorrhage after repeated and forceful coughing paroxysms (*40*). A 1993 case report described a pregnant woman who was hospitalized 6 days before delivery for severe paroxysms and posttussive emesis (*41*). In a series of 32 women who had pertussis during pregnancy or at term, the illness was characterized as "a very tiresome disease"; no obstetric complication was reported, and no infant was premature (*42*). No pertussis-related deaths have been reported in pregnant women. The source of pertussis in infected pregnant women has not been examined systematically.

Reports of fetal morbidity among pregnant women with pertussis are rare, and no causal relationship with abnormal fetal development, fetal morbidity, or adverse outcome of pregnancy has been confirmed. One fetus of a mother who had severe paroxysmal coughing early in pregnancy had an extradural hematoma that was identified by ultrasonography and magnetic resonance at 31 weeks' gestation; studies had been normal at 12 and 22 weeks' gestation (*43*). Another fetus of a mother who had pertussis during the first trimester had prenatal diagnosis of laryngotracheal obstruction (*44*).

Infantile Pertussis

Infants aged <12 months typically have the most severe pertussis, often requiring hospitalization for respiratory or other complications (Table 3) (*8*,*45*–*49*). The risk for pertussis death or severe pertussis is highest among infants in the first 6 months of life and remains elevated until infants have received 1–2 doses of pediatric DTaP (*8*,*50*,*51*). During 2000–2006, the average annual incidence of pertussis among infants aged <6 months was 111 cases per 100,000 population; for infants aged 6–11 months, incidence was 19 cases per 100,000 population (CDC, unpublished data, 2007).

Complications and deaths from infant pertussis have been characterized by necrotizing bronchiolitis (*52*) and high rates of primary or secondary pneumonia and/or coinfection with bacterial and viral pathogens (*8*,*28*,*47*,*53*). Since 1993, pulmonary hypertension has been increasingly recognized among fatal infant cases (*47*,*52*,*54*–*58*). The majority of all infant deaths have occurred among unvaccinated infants (*47*,*53*,*58*; CDC, unpublished data, 2007). Hispanic infants and infants born at estimated gestational age <37 weeks or with low birth weight have comprised a larger proportion of pertussis deaths than would have been expected on the basis of population

TABLE 3. Number* and percentage of hospitalizations and complications among infants aged <12 months with reported pertussis — United States, 2000–2006

Hospitalization/Complication	No.	(%)†
Hospitalization	9,078	(61.0)
Complication		
Apnea	8,348	(56.0)
Pneumonia§	1,578	(12.8)
Seizure	186	(1.3)
Death	145	(0.8)

Source: CDC's National Notifiable Diseases Surveillance System and Supplemental Pertussis Surveillance System, 2000–2006.

* N = 18,564.

† Percentages are based on total number with information. For 20% of cases, no information was available on hospitalization or apnea; for 21%, no information was available on seizure; and for 33%, no information was available on pneumonia. Because multiple complications might have been reported, totals do not add to 100%.

§ Confirmed radiographically.

estimates (*47,53,58*). Compared with the prevaccine era, during 2000–2006, the proportion of reported pertussis deaths among infants aged <3 months increased from 37% to 83% (Figure 1) (*38,47*; CDC, unpublished data, 2007).

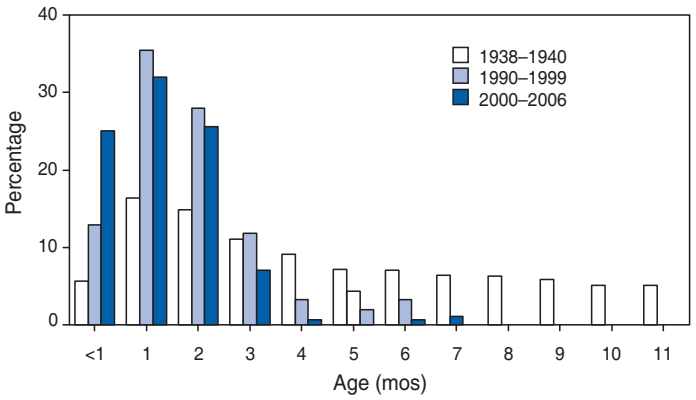
Since the 1970s, parents, especially mothers, have been identified as the most important source of infant pertussis; however, a source has been identified in only 30%–60% of cases investigated (*5–7,34,38,42,48,59–68*). One or more household contact with pertussis is the source of pertussis in approximately 75% of cases among infants aged ≤6 months for whom the source is identified. A parent is implicated in approximately 25% of cases in infants, including the mother in 16%–19% of cases. A sibling is implicated as the source of transmission in <10% of cases (*5,7,34*).

Mathematical modeling evaluating different vaccine strategies for the United States has suggested that pertussis vaccination of 90% of household contacts (children, adolescents, and adults) of newborns, in addition to pertussis vaccination of 75% of adolescents generally in the population, might prevent approximately 75% of pertussis cases among infants aged 0–23 months (*69*). Another model estimated vaccination of both parents of an infant before discharge from the hospital could prevent 38% of infant cases and deaths (*70*). However, the efficacy of these strategies in practice has not been evaluated.

Disease Burden

Although pertussis is a nationally notifiable disease in the United States (*71*), data on the pregnancy status of women with pertussis have not been collected. However, the burden of pertussis among pregnant women is likely to be similar to the burden among other adults in the population. Pertussis reports typically demonstrate increases in activity every 3–4 years (*72*); aside from these cycles of activity, the number of reported cases of pertussis in the United States has increased gradually since 1976. During 2004–2005, more than 25,000 cases were reported per year (Figure 2). During 2006, a total of 15,632 pertussis cases were reported, including 2,029 (13%) cases among infants, 5,045 (32%) cases among children aged 1–14 years, 5,148 (33%) cases among persons aged 15–39 years, and 3,331 (21%) cases among adults aged ≥40 years. A total of 40 pertussis-related deaths were reported in 2005 and 16 in 2006; 39 (98%) of these deaths occurred among infants in 2005 and 14 (88%) in 2006 (CDC unpublished data, 2007). Prospective and serologic studies suggest that pertussis infection and reinfection are underrecognized among adults and adolescents (*29,73–75*). The pertussis burden is believed to be substantially more than the number of reported cases; approximately 600,000 cases are estimated to occur annually just among adults (*1,34,76*).

FIGURE 1. Proportion of reported infant pertussis deaths, by age — United States, 1938–1940,* 1990–1999,† and 2000–2006§



* **Source:** Sako W, Treuting WL, Witt DB, Nichamin SJ. Early immunization against pertussis with alum precipitated vaccine. JAMA 1945;127:379–84. N = 7,123 reported infant pertussis deaths.

† **Source:** Vitek CR, Pascual FB, Baughman AL, Murphy TV. Increase in deaths from pertussis among young infants in the United States in the 1990s. Pediatr Infect Dis J 2003; 22:628–34. N = 93 reported infant pertussis deaths.

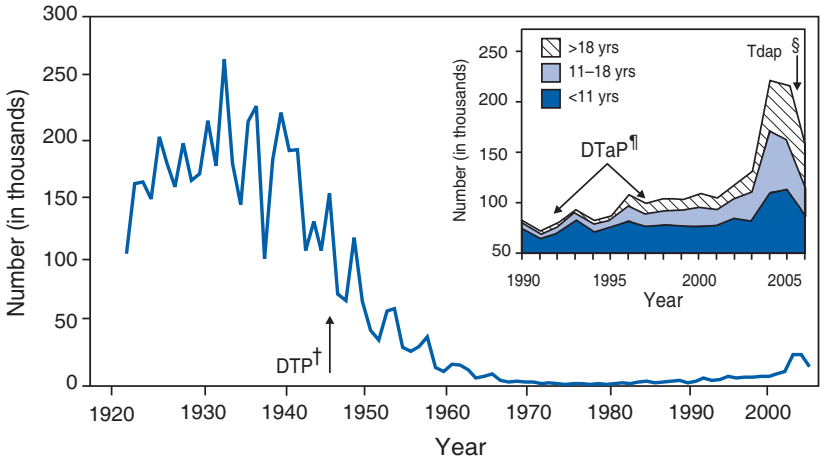
§ **Source:** CDC, unpublished data, 2007. N = 145 reported infant pertussis deaths.

Transmission in Obstetric and Neonatal Health-Care Settings

Health-care personnel can transmit *B. pertussis* in health-care settings if pertussis has not been considered by hospital staff (*1,77,78*). Outbreaks have been documented in prenatal and postnatal clinics (*79,80*), maternity wards (*51,62,81–83*), neonatal nurseries, and neonatal intensive-care services (*62,81,84–90*). Ongoing transmission is facilitated by delay in isolation and treatment of patients and in prophylaxis of contacts and by inconsistent use of face or nose and mouth protection (*1,85,87,91*). Unprotected exposures to pertussis in health-care settings can result in labor-intensive, disruptive, and costly investigations and control measures, particularly when the number of contacts is substantial (*80,92*). Pertussis transmitted to health-care personnel or patients can result in substantial morbidity (and on rare occasions in fatal disease) among hospitalized infants (*79,80,85–88,93,94*).

Health-care personnel who have not been vaccinated with Tdap (Table 2) can be an important source of pertussis and pertussis outbreaks in obstetric and neonatal settings. A wide range of health-care disciplines have been implicated, including physicians, resident physicians, and students (*80,82,85,95*); nurses and nurse midwives (*51,81,85,87,96–98*); and aides, medical assistants, and educators (*1,51,78,79,81,82,85,87*). Pregnant and postpartum women with unrecognized pertussis and visitors to prenatal, obstetric, and neonatal units, including fathers and other close relatives, pose a substantial

FIGURE 2. Number of reported pertussis cases, by year — United States, 1922–2006*



* **Sources:** For 1950–2006, CDC, National Notifiable Diseases Surveillance System; for 1922–1949, passive reports to the U.S. Public Health Service.
† Universal pediatric diphtheria and tetanus toxoids and whole-cell pertussis (DTP) vaccine was recommended in the United States in the late 1940s.
§ Adolescent (ages 11–18 years) and adult (ages 19–64 years) single-dose tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccine was available in the United States in 2005 and was recommended in 2006 for use in adults aged 19–64 years and adolescents aged 11–18 years.
¶ Universal pediatric diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccine was recommended in the United States for doses 4 and 5 in1991 and for doses 1–5 in 1997.

risk for transmission to infants, pregnant women, and health-care personnel and have been associated with outbreaks in these settings (*6,41,62,80,81,84–86,93,98*). Early recognition and treatment of pertussis in pregnant and postpartum women and prophylaxis of household contacts who visit health-care settings is critical to prevent continuing transmission. Antimicrobial treatment for women who have pertussis near term or at delivery and prophylaxis for their newborns and household contacts are effective in preventing further transmission (*42,99*).

Diagnosis

The diagnosis of pertussis is complicated by the limitations of currently available diagnostic tests. The only pertussis diagnostic tests that are accepted to confirm a case for purposes of national reporting are culture and polymerase chain reaction (PCR) (when the clinical case definition also is met) (*100*; Box 1). Multiple factors affect the sensitivity, specificity, and interpretation of diagnostic tests for pertussis (*101,102*).

Culture

Culture to isolate *B. pertussis* is essential for identifying the organism early in the course of disease (*103*) and for antimicrobial susceptibility testing, if indicated. Isolation of *B. pertussis* by culture is 100% specific; for optimal yield, culture requires specimens that contain nasopharyngeal cells obtained by aspirate or nasopharyngeal swab and special medium for growth. The sensitivity of culture early in pertussis varies (range: 30%–60%) (*103–105*). Outside of infancy, the yield of *B. pertussis* declines to 1%–3% in specimens taken in the third week of cough illness or later, after starting antimicrobial treatment, or in a patient who was vaccinated previously (*106,107*). *B. pertussis* can be isolated in culture as early as 72 hours after plating but requires 1–2 weeks before a result can definitively be called negative (*108*).

Polymerase Chain Reaction

DNA amplification (e.g., PCR) to detect *B. pertussis* has increased sensitivity and more rapid turnaround time (*109–111*). When symptoms of classic pertussis are present (e.g., ≥2 weeks of paroxysmal cough), PCR can be two to three times more likely than culture to detect *B. pertussis* in a known positive sample (*101,103,112,113*). As with culture, the PCR result is affected by the technique used to collect the specimen; a poorly taken nasopharyngeal swab is more likely to be negative by both culture and PCR. PCR is less affected than culture by antimicrobial therapy because the organism does not need to be viable for the test to be positive. Adults and adolescents who have specimens taken later in the course of illness, who have started antibiotic treatment, or who were vaccinated previously tend to have PCR-positive, culture-negative test results (*103,114*).

Although PCR testing for pertussis has been available for nearly 20 years (*115*), no U.S. Food and Drug Administration (FDA)–licensed PCR test kit is available. The analytical sensitivity, accuracy, and quality control of PCR-based *B. pertussis* tests vary widely among laboratories. PCR assays used by the majority of laboratories amplify a single gene sequence, typically within the insertion sequence IS481. Both false-positive and false-negative results have been reported with these assays; reported outbreaks of respiratory illness mistakenly attributed to pertussis have resulted in unnecessary investigation and treatment, and unnecessary chemoprophylaxis of contacts (*112,116–119*). Using more than one genetic target and consensus interpretation criteria for PCR diagnosis of pertussis (*120,121*) has been suggested as a way to provide increased assurance of specificity (*122*) and to allow discrimination between Bordetella species.

BOX 1. CDC and the Council of State and Territorial Epidemiologists (CSTE) Pertussis Case Definitions*

Clinical Case Definition

- A cough illness lasting ≥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 directly linked epidemiologically to a laboratory-confirmed case.

Sources: Guidelines for the control of pertussis outbreaks. Atlanta, GA: US Department of Health and Human Services, CDC; 2006. 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).

Other Diagnostic Tests

Direct fluorescent antibody (DFA) tests provide rapid results (within hours), but sensitivity (10%–50%) is less than with culture (*123*). With use of monoclonal reagents, the specificity of DFA should be >90%. However, interpretation of the test is subjective, and, when interpreted by an inexperienced microbiologist, the specificity can be lower (*110*). Diagnosis of pertussis by serology requires a substantial change in titer for pertussis antigens (typically fourfold) from acute (<2 weeks after cough onset) to convalescent sera (≥4 weeks after the acute sample). The results typically become available too late in the course of the illness to be useful clinically. Single-sample serologic tests for antipertussis toxin (anti-PT) IgG have been developed for research purposes; sera must be collected at least 2 weeks after the onset of symptoms (*124*). Pertussis serology assays using commercial reagents are available, but these assays are not validated clinically and do not differentiate between recent and remote infection and vaccination (*125,126*). No serologic assay is licensed by FDA for routine diagnostic use in the United States.

Postexposure Prophylaxis and Treatment

A macrolide (erythromycin, azithromycin, or clarithromycin) is the preferred antimicrobial for postexposure prophylaxis and treatment of pertussis (*127*). Antimicrobial treatment administered in the early (catarrhal) phase of the illness can modify the severity of the symptoms (*36,128,129*). An antimicrobial generally does not modify the severity or the course of the illness after paroxysmal cough is established but is used to eliminate *B. pertussis* and halt transmission (*36,127–129*). Without use of an effective antimicrobial, *B. pertussis* can be recovered for 6 weeks or longer from infant patients and for 21 days or longer from adult and adolescent patients. Detailed recommendations, indications, and schedules for postexposure antimicrobial prophylaxis and treatment of pertussis have been published previously (*127*).

Pregnant women with pertussis near term and other household contacts with pertussis are an important source of pertussis for newborn infants (*6,41,42,62,64,99*). Antimicrobial treatment and prophylaxis are effective in preventing transmission of pertussis to neonates. A macrolide is administered to a woman with pertussis that is acquired late in pregnancy or shortly before delivery, her household contacts, and the neonate. Early recognition of pertussis in a pregnant woman is necessary to ensure the effectiveness of this approach (*42,99*).

Pregnancy is not a contraindication for use of erythromycin, azithromycin, or clarithromycin. Erythromycin and azithromycin are listed as FDA Category B drugs, and clarithromycin is listed as a Category C drug (*130–132*). Macrolides can interact with a variety of other therapeutic agents, precluding concurrent use. Although macrolides can have gastrointestional side effects (e.g., nausea and vomiting), serious side effects (e.g., hepatic dysfunction or pseudomembranous colitis) are rare (*127*). Infants aged <1 month who receive erythromycin are at increased risk for infantile hypertrophic pyloric stenosis (*83,133–136*). For this reason, and because azithromycin is associated with fewer adverse effects than erythromycin, azithromycin is the preferred antimicrobial for prophylaxis of neonates exposed to pertussis (*127*). Infantile hypertrophic pyloric stenosis has been reported in two preterm infants who received azithromycin for postexposure prophylaxis (*137*); however, a causal association

between infantile hypertrophic pyloric stenosis and azithromycin has not been established.

Immunity to Pertussis

The mechanisms of protection against pertussis are incompletely understood. On the basis of studies in animals and humans, both humoral and cellular immunity are believed to play a complementary role (*138–143*). The protection that results from *B. pertussis* infection or pertussis vaccines persists for an estimated 5–10 years or more. Protection wanes over time, leaving persons susceptible to infection or reinfection (*4,75,144–150*).

Humoral Immunity to Pertussis Vaccine Antigens

Immune responses to *B. pertussis* can be directed variably against a range of pertussis toxins and antigens. No level of antibody, presence of specific antibodies, or antibody profile has been accepted universally as a quantifiable serologic measure of protection (*139,141,151–158*). Studies of parenterally administered immune globulins for postexposure prophylaxis (*159,160*) or for treatment of pertussis (*28,161–165*) report mixed results and do not clarify the role of passive antibodies in prevention or treatment of pertussis. By extrapolation, these results do not help predict the role of transplacental maternal antibodies in infant protection.

Pertussis toxin (PT), previously called lymphocytosis promoting factor (LPF), is considered one of the most important of a range of clinically relevant toxins and virulence factors of *B. pertussis* (including pertactin or 69-kDa protein [PRN], fimbriae types 2 and 3 [FIM], filamentous hemagglutinin [FHA]) (*140,142,152,157,166–169*). Detoxified PT is a component of all pertussis vaccines. The preventive efficacy of a pediatric DTaP vaccine containing detoxified PT as the only immunizing antigen was 71% (95% confidence interval [CI] = 63%–78%) against classical pertussis (*170*). However, the contribution to protection by anti-PT varied in analyses of the humoral immune responses to specific vaccine antigens when evaluated in two household studies. Elevated concentrations of anti-PRN and anti-FIM were associated most closely with protection in these (*152,157*) and other studies (*171*). Evidence of added protection from anti-FHA has been mixed (*152,156,157,172,173*).

Cellular Immunity to Pertussis Vaccine Antigens

Cell-mediated immune mechanisms clear *B. pertussis* from within macrophages and other cells (*52,139,174–177*). In addition to humoral immune responses, *B. pertussis* antigens in acellular pertussis vaccines induce cell-mediated immune responses (*178*) after primary immunization with pediatric DTaP among infants (*158,179*), after booster vaccination among children (*140,141,149*), and after booster vaccination with reduced pertussis antigen content vaccines among adolescents (*178,180–183*) and adults (*183,184*). Protection is maintained among children whose antibody levels drop below the level of detection over time (*185*) suggesting that cell-mediated immunity is an important component of protection. Cell-mediated immune responses remain measurable substantially longer than antibodies to the same antigens, particularly PT, and the cell-mediated immune responses to initial doses of pertussis vaccines are believed to correlate better with long-term immunity than antibody responses (*140,141,149,158,178,180,181,183,185*).

Prevalence of Pertussis-Specific Antibodies: Pregnant Women and their Infants

Although the importance of antipertussis activity in sera relative to protection remains uncertain, studies conducted since the 1930s have determined the prevalence of antipertussis activity in sera from mothers and infants using multiple assays (Tables 4–8) (*37,154,186–199*). Detectable pertussis-specific antibodies have been identified in unvaccinated women without a history of pertussis (*28,187,190,192*), women with a past history of pertussis (*28,187,190,192*), women who likely received whole-cell pertussis vaccine during childhood (*195,196,198–200*), and women with a recent history of pertussis (*99*). With the exception of women with recent pertussis, the majority of pregnant women have low geometric mean concentrations (GMCs) of anti-PT and antibodies to other pertussis antigens (Tables 4–8) (*159*), consistent with generally low concentrations of antipertussis antibodies among adults surveyed in the general population (*147,201–205*). GMCs of pertussis-specific antibodies among pregnant women typically have been low regardless of age, as demonstrated in a predominantly (80%) African-American population reported in 2005 (*199*). A 2006 study of pregnant Hispanics found lower GMCs among adolescents than among women aged ≥20 years (*198*).

The efficiency of maternal-fetal transfer of IgG antibodies to pertussis-specific antigens varies; the majority of investigators report similar antigen-specific concentrations in cord or neonatal infant sera and in maternal sera measured late in pregnancy or at delivery (*195–200*), but higher concentrations in cord or neonatal sera than in maternal sera have been reported, which might indicate active transport in certain settings (Tables 7 and 8) (*195,197,199*). In a 2005 survey of mothers and their infants, anti-PT, anti-FHA, and anti-PRN were detected in maternal sera from 35%, 95%, and 80% of women, respectively, and in cord sera from 45%, 93%, and

TABLE 4. Pertussis immune responses in unvaccinated and vaccinated pregnant women and their newborn infants, measured by opsonocytophagic assay — selected studies,* United States, 1937–1945

Study	No. mother/ infant pairs	No. pregnant women vaccinated	No. women with any history of pertussis	Immune response to *Bordetella pertussis*	
				Mother's specimen	Neonatal or cord specimen
				Average no. leukocytes with ≥20 organisms among 25 leukocytes counted	
1	12	0	0	9.3	3.3
	8	0	8	17.6	9.1
2	11	0	0	18.0	9.0
	11	0	11	20.4	15.7
	11	11	0	18.3	13.7
	17	17	17	20.2	17.8
3	17	0	NR†	6.5§	4.1§¶
4				"Moderate to strong" and "strong" responses**	
				No. (%)	No. (%)
	42	0	NR	21 (50)	4 (5)
	57	57	NR	53 (93)	36 (63)

* Study 1 = Bradford WL, Slavin B. Opsono-cytophagic reaction of blood in pertussis. J Clin Invest 1937;16:825–8. Study 2 = Lichty JA Jr, Slavin B, Bradford WL. An attempt to increase resistance to pertussis in newborn infants by immunizing their mothers during pregnancy. J Clin Invest 1938;17:613–21. Study 3 = Rambar AC, Howell K, Denenholz EJ, Goldman M, Stanard R. Studies in immunity to pertussis; an evaluation of pertussis vaccination by clinical means and by the opsonocytophagic test. JAMA 1941;117:79–85. Study 4 = Kendrick P, Thompson M, Eldering G. Immunity response of mothers and babies to injections of pertussis vaccine during pregnancy. Am J Dis Child 1945;70:25–8. No infants were vaccinated in these studies.

† Not reported.

§ Average is for ≥21 organisms per cell.

¶ Infants were all of "premature" birth, and their specimens were obtained at age 2–9 wks.

** Infant cells were obtained at age 6–29 days (median age of immunized and nonimmunized infant groups was 10 and 11 days, respectively). The opsonic titer was calculated as the product of an arbitrary factor: 0, 1, 3, 8, and 12, respectively, for 0, 0–5, 6–20, 21–40, and ≥41 organisms per cell. The sum of the products defined the "opsonic titer" as "negative to weak"(0–50), "weak to moderate" (51–100), "moderate to strong" (101–200), and "strong" (201–300).

TABLE 5. Pertussis immune responses in unvaccinated and vaccinated pregnant women and their newborn infants, by assay used — selected studies,* United States, 1937–1943

Study	Assay	No. mother/ infant pairs	No. pregnant women vaccinated	No. women with any history of pertussis	Immune response to *Bordetella pertussis*			
					Mother's specimen positive		Neonatal or cord specimen positive	
					No.	%	No.	%
1	Complement fixation	20	0	NR†	3	15	3	15
2 and 3	Complement fixation	3§	0	0	0	0	0	0
		—	29¶	18	2	7	—	—
		29	29**	18	22	76	21	70
2 and 3	Mouse protection††	3§	0	0	0	0	2	22
		—	29¶	18	10	34	—	—
		29	29**	18	29	100	28§§	100

* Study 1 = Weichsel M, Douglas HS. Complement fixation tests in pertussis. J Clin Invest 1937;15:15–22. Study 2 = Mishulow L, Leifer L, Sherwood C, Schlesinger SL, Berkey SR. Pertussis antibodies in pregnant women. Protective, agglutinating and complement-fixing antibodies before and after vaccination. Am J Dis Child 1942;64:608–17. Study 3 = Cohen P, Scadron SJ. The placental transmission of protective antibodies against whooping cough by inoculation of the pregnant mother. JAMA 1943;121:656–62. No infants were vaccinated in these studies.

† Not reported

§ Three maternal/infant pairs and six additional infants (nine total) were studied.

¶ Specimen collected before pregnant woman was vaccinated.

** Postvaccination.

†† Mice received intramuscular injection of 0.2 cc of patient serum 19–24 hours before peritoneal injection of a "multiple killing dose" of virulent *B. pertussis*. Protection was defined by survival of ≥30% of mice at 7–8 days after challenge.

§§ Results were available from 28 of 29 infants.

TABLE 6. Pertussis immune responses in unvaccinated and vaccinated pregnant women and their newborn infants, measured by agglutinin antibody titer — selected studies,* United States, 1941–1990

Study	No. mother/ infant pairs	No. pregnant women vaccinated	No. women with any history of pertussis	Agglutinin antibody titer to *Bordetella pertussis*†					
				Mother specimen positive			Neonate or cord specimen positive		
				No.	%	Titer	No.	%	Titer
1–3									
	3§	0	0	0	0	>1:10	0	0	>1:10
		29¶	18	4	14	>1:10			
	29	29**	18	27	93	>1:10	25	83	>1:10
4	142	0	NR††	30	21	1:20–1:320	30	21	<1:10–1:160
				3	2	<1:10–1:80	3	2	1:40–1:80
				109	77	<1:10	109	77	<1:10
	16	16	NR	16	100	>1:40 (mean: 1:320)	12	75	>1:40 (mean 1:160)
5	108	0	NR	0	0	≥1:320	0	0	≥1:320
				54	50	Any detectable titer	34	63	Any detectable titer
6	144	0	NR	NR	NR	NR	1	<1	≥1:320
							2	1	1:200
							141	98	Negative
7	106	106	NR	88	83	≥1:300	88	83	≥1:300
8	93	0	NR	0	0	≥1:320	1	2	≥1:320
				50	54	>1:10	22	52	>1:10
9	34	0	NR			GMT (CI)§§			GMT (CI)
						34.0 (23.3–49.7)			34.7 (23.5–51.3)

* Study 1 = Mishulow L, Wilkes ET, Liss MM, Lewis E, Berkey SR, Leifer L. Stimulation of pertussis-protective antibodies by vaccination. A comparative study of protective, agglutinating and complement-fixing antibodies. Am J Dis Child 1941;62:1205–16. Study 2 = Mishulow L, Leifer L, Sherwood C, Schlesinger SL, Berkey SR. Pertussis antibodies in pregnant women. Protective, agglutinating and complement-fixing antibodies before and after vaccination. Am J Dis Child 1942;64:608–17. Study 3 = Cohen P, Scadron SJ. The placental transmission of protective antibodies against whooping cough by inoculation of the pregnant mother. JAMA 1943;121:656–62. Study 4 = Adams JM, Kimball AC, Adams FH. Early immunization against pertussis. Am J Dis Child 1947;74:10–8. Study 5 = Miller JJ Jr, Faber HK, Ryan ML, Silverberg RJ, Lew E. Immunization against pertussis during the first four months of life. Pediatrics 1949;4:468–78. Study 6 = Di Sant'Agnese PA. Combined immunization against diphtheria, tetanus and pertussis in newborn infants. I. Production of antibodies in early infancy. Pediatrics 1949;3;20–33. Study 7 = Cohen P, Schneck H, Dubow E. Prenatal multiple immunization. J Pediatr 1951;38:696–704. Study 8 = Goerke LS, Roberts P, Chapman JM. Neonatal response to DTP vaccines. Publ Health Rep 1958;73:511–9. Study 9 = Van Savage J, Decker MD, Edwards KM, Sell SH, Karzon DT. Natural history of pertussis antibody in the infant and effect on vaccine response. J Infect Dis 1990;161:487–92. No infants were vaccinated before specimens were obtained for these results.

† Number and percentage positive of number tested.

§ Three maternal infant pairs and six additional infants (nine total) were studied.

¶ Specimen collected before the pregnant woman was vaccinated.

** Postvaccination.

†† Not reported.

§§ Geometric mean titer (95% confidence interval).

81% of infants, respectively (*199*). Among 17 infants studied in 1990, the half-life of transplacental maternal antibody was 36.3 days for anti-PT, 40.3 days for anti-FHA, and 55.0 days for pertussis agglutinins (*195*). Transplacental maternal antibody was not detectable or was negligible in the majority of infants by age 6–8 weeks (*195,197*) or by age 4 months (*195*), consistent with the results of early studies (*186*). By contrast, in a study of 23 unvaccinated Swedish infants whose mothers had pertussis late in pregnancy, five infants had neutralizing antibody detectable as long as 14 months and detectable anti-PT for 5 months or longer (*99*).

Kinetics of Pertussis Booster Vaccination in Nonpregnant Adults and Adolescents

The majority of adults and adolescents have had exposure to *B. pertussis*, pertussis antigen–containing vaccines, or both, and they will have a booster response to vaccination with pertussis antigens (*184,206*). A rise in antibodies is measurable by 7 days after vaccination (*207*), and GMCs reach near-peak levels by 2 weeks after booster vaccination (*207–210*). Antibody concentrations decline rapidly in the first few months following vaccination, after which the rate of decline slows (*157,181,209,211*). Anti-PT levels decline more rapidly than anti-PRN or anti-FHA levels. Among adults who received a booster dose of an acellular pertussis vaccine without tetanus

TABLE 7. Antibodies to pertussis toxin (PT)* among women and their newborn infants, measured by enzyme-linked immunosorbent assay (ELISA) — selected studies, † United States, 1990–2006 and Italy, 2003

Study	No. mother/ infant pairs	Antibodies to pertussis toxin IgG-specific geometric mean concentration (GMC) or titer (GMT) and 95% confidence interval [CI] or standard deviation [SD]), EU/mL§				Cord sample to maternal sample ratio
		Mother at delivery		Cord		
		GMC or GMT	CI or SD	GMC or GMT	CI or SD	
1	34¶	4.9	CI = 1.8–13.4	14.0	CI = 6.1–32.1	NR**
2	45††	NR	NR	4.5	CI = 3.3–5.9	DNSS§§
	46	NR	NR	5.5	CI = 3.9–7.8	NR
3	64¶¶	2.4 (range: 1–33)	CI = 1.9–3.1	4.1 (range: 1–114)	CI = 3.0–5.5	169%
4	101***	4.4	SD = 2.6	5.6	SD = 3.0	r††† = 0.98
5	55§§§	6.0 (range: 1–60)	CI = 4.6–7.8	6.5 (range: 1–43)	CI = 5.0–8.5	1.08
	220 infants	NR	NR	8.45 (range: 1–493)	CI = 7.24–9.86	NR

* Pertussis toxin (previously known as lymphocytosis promoting factor [LPF]).

† Study 1 = Van Savage J, Decker MD, Edwards KM, Sell SH, Karzon DT. Natural history of pertussis antibody in the infant and effect on vaccine response. J Infect Dis 1990;161:487–92. Study 2 = Belloni C, De Silvestri A, Tinelli C, et al. Immunogenicity of a three-component acellular pertussis vaccine administered at birth. Pediatrics 2003;111:1042–5. Study 3 = Healy CM, Munoz FM, Rench MA, Halasa NB, Edwards KM, Baker CJ. Prevalence of pertussis antibodies in maternal delivery, cord, and infant serum. J Infect Dis 2004;190:335–40. Study 4 = Gonik B, Puder KS, Gonik N, Kruger M. Seroprevalence of *Bordetella pertussis* antibodies in mothers and their newborns. Infect Dis Obstet Gynecol 2005;13:59–61. Study 5 = Healy CM, Rench MA, Edwards KM, Baker CJ. Pertussis serostatus among neonates born to Hispanic women. Clin Infect Dis 2006;42:1439–42.

§ ELISA units/milliliter.

¶ Subjects were women who delivered infants at Nashville General Hospital, Nashville, Tennessee in 1988. Assays were performed by Vanderbilt University School of Medicine, Nashville, Tennessee. Results were reported as antibody concentrations to LPF and not specifically as IgG antibody concentrations.

** Not reported.

†† Subjects were healthy term infants in 1999 in Pavia, Italy, enrolled in a clinical trial of neonatal versus standard schedule DTaP (Biocine, Emeryville, California). Gestational age was 37–42 weeks. The mean age of the women was 30 years (±4 years) (range: 17–37 years). Assays were performed in the research laboratories for Pediatric Oncohematology IRCCS Policlinico San Matteo, Pavia, Italy.

§§ Difference not statistically significant.

¶¶ Predominantly (81%) white women studied during 1999–2000 in Houston, Texas (mean maternal age: 29.7 years [range: 19–42 years]; mean infant gestational age: 39 weeks [range: 36–41 weeks]). Assays performed by Vanderbilt University School of Medicine, Nashville, Tennessee.

*** Predominantly (80%) African-American women (mean age: 26.8 years [SD = 6.8]); mean infant gestational age was 38.9 (SD = 1.4 wks); 101 maternal sera, 103 cord sera. Assays were performed by Glaxo SmithKline Biologicals Laboratory, Rixensart, Belgium.

††† Pearson's correlation coefficient.

§§§ Hispanic women delivering infants in 2004 in Houston, Texas; the mean maternal age (standard deviation) was 26.2 years (SD = ±6 years). Assays were performed by Vanderbilt University School of Medicine, Nashville, Tennessee.

or diphtheria toxoids, concentrations of IgG anti-PT and anti-PRN declined 58% and 39%, respectively, after 6 months. By 18 months after vaccination, concentrations declined 73% and 56%, respectively (*209*).

Vaccinating Pregnant Women against Pertussis

Tdap

No prelicensure studies were conducted with Tdap in pregnant women. In 2005, to increase understanding of the safety of Tdap in relationship to pregnancy, both Tdap manufacturers established registries to solicit voluntary reports of pregnant women who received Tdap during pregnancy or who received Tdap and were determined subsequently to be pregnant (*212,213*). The main utility of the registries is to signal the possibility and nature of any risk (*214*). All women who are vaccinated with Tdap at any time during pregnancy should be reported to the registry as early as possible during the pregnancy. Information from pregnancy registries differs from surveillance reports, which are used to evaluate outcomes among women when an adverse outcome of pregnancy already might have occurred (e.g., an infant born with a birth defect) (*214*).

As of December 31, 2007, GlaxoSmithKline had received five reports of pregnancy exposure to BOOSTRIX® within 28 days before conception or during any trimester of pregnancy, including two in the first trimester, one in the second trimester, and two during an unknown trimester. Among the two first-trimester exposures, one subject delivered a normal infant at 33 weeks' gestation, and one subject was lost to follow-up. Of the remaining exposures, information on the outcome of two pregnancies was not yet available, and one subject was lost to follow-up (GlaxoSmithKline, unreported data, 2008).

As of November 23, 2007, sanofi pasteur had received 107 spontaneous reports and 47 reports from postlicensing surveillance studies of exposure to ADACEL® during pregnancy. For these 154 reports, pregnancy outcomes were 68 live infants (including 64 term deliveries [one with a congenital

TABLE 8. Antibodies to antigens in pertussis vaccines among women and their newborn infants, measured by enzyme-linked immunosorbent assay (ELISA) — selected studies, United States,* 1990–2006 and Italy, 2003

Study	No. mother/ infant pairs	Antigen	IgG-specific geometric mean concentration (GMC) and 95% confidence interval [CI] or standard deviation [SD]), EU/mL†				Cord sample to maternal sample ratio
			Mother at delivery		Cord		
			GMC	CI or SD	GMC	CI or SD	
1	45§	PRN¶	NR**	NR	4.6	CI = 3.1–6.8	NR
	46	PRN	NR	NR	4.5	CI = 2.6–6.9	NR
2	101††	PRN	12.3	SD = 2.9	10.2	SD = 3.2	r§§ = 0.96
3	64¶¶	FIM***	13.0 (range: 2.5–869.0)	CI = 9.2–18.5	20.4 (range: 2.5–1,231.0)	CI = 14.0–29.6	157%
4	33†††	FHA	41.4	CI = 26.1–65.6	26.8	CI = 14.5–49.4	NR
1	45	FHA	NR	NR	16.6	CI = 12.4–22.3	NR
	46	FHA	NR	NR	23.4	CI = 16.1–33.5	NR
3	64	FHA	6.9 (range: 1.5–137.0)	CI = 5.0–9.5	12.3 (range: 1.5–377.0)	CI = 8.8–17.3	178%
2	101	FHA	26.6	SD = 3.1	32.0	SD = 3.2	r = 0.90

* Study 1 = Belloni C, De Silvestri A, Tinelli C, et al. Immunogenicity of a three-component acellular pertussis vaccine administered at birth. Pediatrics 2003;111:1042–5. Study 2 = Gonik B, Puder KS, Gonik N, Kruger M. Seroprevalence of *Bordetella pertussis* antibodies in mothers and their newborns. Infect Dis Obstet Gynecol 2005;13:59—61. Study 3 = Healy CM, Munoz FM, Rench MA Halasa NB, Edwards KM, Baker CJ,. Prevalence of pertussis antibodies in maternal delivery, cord, and infant serum. J Infect Dis 2004;190:335–40. Study 4 = Van Savage J, Decker MD, Edwards KM, Sell SH, Karzon DT . Natural history of pertussis antibody in the infant and effect on vaccine response. J Infect Dis 1990;161:487–92.

† ELISA units/milliliter.

§ Subjects were healthy term infants in 1999 in Pavia, Italy, enrolled in a clinical trial of neonatal versus standard schedule DTaP (Biocine, Emeryville, California). Gestational age was 37–42 weeks. The mean age of the women was 29.8 years (±4.3 years) (range: 17–37 years). Assays were performed in the research laboratories for Pediatric Oncohematology IRCCS Policlinico San Matteo, Pavia, Italy.

¶ 69kDa protein, pertactin.

** Not reported.

†† Predominantly (80%) African-American women (mean age: 26.8 years (SD = 6.8); mean infant gestational age was 38.9 (SD = 1.4 wks); 101 maternal sera, 103 cord sera. Assays were performed by Glaxo SmithKline Biologicals Laboratory, Rixensart, Belgium.

§§ Pearson's correlation coefficient.

¶¶ Predominantly (81%) white women studied during 1999–2000 in Houston, Texas (mean maternal age: 29.7 years [range: 19–42 years]; mean infant gestational age: 39 weeks [range: 36–41 weeks]). Assays performed by Vanderbilt University School of Medicine, Nashville, Tennessee.

*** Fimbrial proteins.

††† Subjects were women who delivered infants at Nashville General Hospital, Nashville, Tennessee in 1988. Assays were performed by Vanderbilt University School of Medicine, Nashville, Tennessee. Results were reported as antibody to filamentous hemagglutinin (FHA), not specifically to IgG antibody concentrations.

anomaly] and four preterm deliveries [one at 28 weeks after complications of pregnancy, labor, and delivery; two at 35 weeks for preeclampsia; and one at 35 weeks for breech presentation]); three spontaneous abortions (at 9, 51, and 99 days postvaccination); three induced abortions; and one fetal demise (at 35 days postvaccination). For 32 reports, either the outcome of pregnancy was unknown or the patient was lost to follow-up, and for 47 reports, information on outcome of pregnancy was not yet available (sanofi pasteur, unreported data, 2008).

A retrospective survey of 4,524 health-care personnel vaccinated in a mass vaccination campaign conducted in 2006 provides additional information regarding adverse reactions in pregnant women within 14 days of receiving Tdap (ADACEL®) (*215,216*). Pregnancy was not an exclusion criterion for Tdap; 24 health-care personnel who received Tdap identified themselves as pregnant at the time of vaccination. Among 2,676 (59%) survey respondents, 1,792 (67%) received Tdap at an interval of ≥2 years after their most recent dose of Td; 17 of these respondents identified themselves as pregnant. Adverse reactions reported by the 17 pregnant women were compared with reactions reported by 472 nonpregnant female personnel aged 18–44 years. The frequencies of injection-site pain, redness, and swelling of moderate to severe intensity were not greater among the pregnant women than among the nonpregnant women. Three of the pregnant women reported feeling "feverish" after receiving Tdap. None of the 17 pregnant women reported seeking nonroutine medical attention for the adverse reaction (*215,216*). Among the pregnant women vaccinated with Tdap, results of the outcome of pregnancy were known for 10 women; no pregnancy resulted in premature birth or abnormality in the infant when assessed shortly after birth (Elizabeth A. Talbot, Dartmouth College, Lebanon, New Hampshire, personal communication, 2007).

Whole-Cell Pertussis Vaccine

Five clinical trials conducted during the 1930s and 1940s evaluated vaccinating pregnant women with whole-cell per-

tussis vaccine as a strategy to increase the levels of maternal pertussis-specific antibodies transferred to their infants via the placenta (Table 9) (*186,189,190,192,193,217*). The protective efficacy of the vaccine against pertussis in the women was not a consideration. Whole-cell pertussis vaccine was prepared from sterile extracts of killed *B. pertussis*. To maximize the passive transfer of maternal antibody, pregnant women were vaccinated with 2–6 doses at 1- to 2-week intervals during the third trimester.

Local reactions to vaccination in the pregnant women were common, some of which were severe. Systemic reactions were uncommon, adverse pregnancy outcomes were not reported (Table 9) (*190,192,193,217*).

The majority of women had substantial rise in titer to *B. pertussis* antigens in postvaccination sera compared with prevaccine titers (Tables 4–6) (*186,189,190,192,193,217*). Neither history of pertussis (*190,192*) nor preexisting titers of antibodies in the women correlated with maternal titers after vaccination (*193*). The majority of infant antibody titers were lower than (*186*) or similar to maternal titers (*37,150,186,187,189–193*). Infant titers exceeded maternal titers in certain cases although higher titers might have been within the range of assay variation (*37,186–191,193*).

In subsets of infants in two studies, the duration of detectable transplacental pertussis antibodies was followed among unvaccinated infants (*186,217*). The mothers in both studies

TABLE 9. Clinical trials in pregnant women using killed, whole-cell pertussis vaccines — selected studies*, United States, 1938–1951

Study	No. pregnant women vaccinated	Total dose (cfu† of killed *Bordetella pertussis*)	Vaccine				Adverse reactions
			Inactivation (manufacturer)	Timing	Doses (route)	Interval between doses	
1	42	0.15–2.5 mL (15–25 billion cfu)	0.5% phenol§ (Eli Lilly & Co.)	"Last 6 wks of pregnancy"	3 (SC¶ or IM**)	2 wks	"Many" complained of sore arm; four refused third injection; and one had systemic reaction (nausea and vomiting).
2–5	167 (170)	80– or 90–150 billion cfu	"Phenolized"§ (New York City Department of Health)	Starting in fifth or sixth mo of pregnancy	6 (SC)	2 wks	• All vaccinees reported arm soreness and tenderness; some could not move arm for 2–3 days. • Common: persistent lump for "days" • Two of 100, fever • No ill effects on the babies or mothers during course of pregnancy††
6	57	25 billion cfu	Merthiolate (thimerosal) 1:10,000 (Michigan Department of Health)	Most recent dose administered approximately 1 mo before delivery	3 (SC)	1 week	NR§§
7	16	100 billion cfu	NR (Cutter Laboratories, Berkeley, CA)	Third trimester (most recent dose administered ≥1 mo before term)	3	2 wks	NR
8	106	Two preparations¶¶ • 97 billion cfu, alum-precipitated • 120 billion cfu, fluid	NR	Seventh mo of pregnancy (completed 6 wks before delivery)	3	4 wks	• Great majority of reactions were mild (pertussis-tetanus mixtures) • Less severe reactions with alum-precipitated than fluid preparations • No adverse effects on mothers or babies

* Study 1 = Lichty JA Jr, Slavin B, Bradford WL. An attempt to increase resistance to pertussis in newborn infants by immunizing their mothers during pregnancy. J Clin Invest 1938;17:613–21. Study 2 = Cohen P, Scadron SJ. The placental transmission of protective antibodies against whooping cough by inoculation of the pregnant mother. JAMA 1943;121:656–62. Study 3 = Cohen P, Scadron SJ. The effects of active immunization of the mother upon the offspring. J Pediatrics 1946;29:609–19. Study 4 = Mishulow L, Wilkes ET, Liss MM, Lewis E, Berkey SR, Leifer L. Stimulation of pertussis-protective antibodies by vaccination. A comparative study of protective, agglutinating and complement-fixing antibodies. Am J Dis Child 1941;62:1205–16. Study 5 = Mishulow L, Leifer L, Sherwood C, Schlesinger SL, Berkey SR. Pertussis antibodies in pregnant women. Protective, agglutinating and complement-fixing antibodies before and after vaccination. Am J Dis Child 1942;64:608–17. Study 6 = Kendrick P, Thompson M, Eldering G. Immunity response of mothers and babies to injections of pertussis vaccine during pregnancy. Am J Dis Child 1945;70:25–8. Study 7 = Adams JM, Kimball AC, Adams FH. Early immunization against pertussis. Am J Dis Child 1947;74;10–18. Study 8 = Cohen P, Schneck H, Dubow E. Prenatal multiple immunization. J Pediatr 1951;38:696–704.

† Colony forming units.

§ Killed phase I *Bordetella pertussis* diluted to 10 billion cfu per 1.0 cubic milliliter (**Source:** Saur LW. Immunization with *Bacillus pertussis* vaccine. JAMA 1933;101:1449–53).

¶ Subcutaneous.

** Intramuscular.

†† No premature births occurred, and no postpartum complications were attributed to vaccination.

§§ Not reported.

¶¶ Two pertussis vaccine preparations were used during the trials. The number of subjects allocated to each vaccine group, and the details of the protocol were not reported. Certain women might have received separate injections of diphtheria toxoid, inactivated influenza vaccine and or tetanus toxoid.

had received 3 doses of whole-cell pertussis vaccine during the third trimester. The mean of the agglutinin titers among 13 infants in one study dropped from 1:160[§] at birth to 1:80 at age 2 months; titers no longer were measurable at "a few months of age" (*186*). Of 36 infants with high agglutinin titers at birth in the other study, 16 (44%) had titers of ≥1:300 at age 3 months. None of 9 infants followed to age 6 months had a titer of 1:300 (*217*).

Infant Protection by Transplacental Maternal Antibody

The role of transplacental maternal antibody in infant protection against pertussis remains uncertain. Prevaccine era observations concluded that infants have no "congenital immunity" and are susceptible to pertussis from the "day of birth," with the possible exception of an infant whose mother had pertussis during pregnancy (*35*,*189*,*190*,*192*,*193*,*219*). Transplacental maternal antibodies might explain the smaller proportion of infant pertussis deaths observed in the first month of life compared with the second and third months of life (Figure 1) (*35,45*). An alternative explanation might be that parents avoid exposing newborn infants to ill contacts (*99,219*).

Two retrospective surveys were conducted after early vaccine trials in pregnant women to assess infant protection (*217,220*). In one survey conducted during the 1940s, a subset of 100 (59%) of 170 women who received 6 doses of whole-cell pertussis vaccine during the third trimester and 100 women who were not vaccinated were questioned regarding pertussis in their infants during the first year of life. During the first 6 months of life, eight exposures (three of which were "close exposures") and no cases of pertussis were reported among infants whose mothers had been vaccinated, and six exposures and three cases of infant pertussis were reported among infants whose mothers had not been vaccinated. From age 6–11 months, two cases of infant pertussis were reported in each group (*220*). In a second survey by the same investigators, a subset of 66 (62%) of 106 women who received 3 doses of whole-cell pertussis vaccine during the third trimester reported two exposures and no case of pertussis among their infants during the first 6 months of life (*217*). The results of these surveys suggested that high concentration of transplacental pertussis antibodies might provide a degree of infant protection against pertussis in the first 6 months of life (*217,220*).

[§] Titers of ≥1:320 have been reported to correlate with protection in some studies (*218*).

Inhibitory Effect of Transplacental Maternal Antibody on Infant Immunization

Transplacental maternal antibodies to pertussis antigens can interfere with the infant's response to active immunization with the pertussis components of pediatric DTP and pediatric DTaP (*221*). A proposed mechanism for the interference with pertussis and other vaccine antigens is maternal antibody binding to vaccine antigens, masking the vaccine antigens from the infant's B cells. Infant antigen-presenting cells also might take up maternal antibody-vaccine antigen complexes stimulating selective T-cell responses without humoral immune responses to the vaccine antigens (*221–223*). The concentrations and specificities of the maternal antibodies for vaccine-antigen epitopes contributes to the degree of interference (*221,223–225*). The inhibitory effect of transplacental maternal antibody can be detectable for a few weeks or for more than 1 year (*221,222,224–228*). As transplacental maternal antibody declines over time, a threshold is reached when the infant's immune system responds to vaccine antigens in subsequent doses. In theory, the threshold concentration of residual maternal antibody could be lower than the concentration of antibody needed for infant protection, but this concentration is not known for pertussis. In this setting, a theoretical window of "relative susceptibility" exists for the infant until the infant mounts a humoral immune response to a subsequent dose of vaccine (*222,229*).

Interference with Pertussis Responses to Pediatric DTP

Substantially lower concentrations of infant IgG anti-PT result after 3 doses of pediatric DTP among infants with "high" (variably defined) prevaccination levels of maternal IgG anti-PT, than among infants with "low" or no measurable prevaccination level of maternal IgG anti-PT (*195, 230–233*). The post-dose 3 concentrations of infant anti-PT in one study were 28% or 56% lower with each doubling of the concentration of transplacental maternal anti-PT, respectively, for the two DTP products studied ($p \leq 0.05$) (*233*). The reductions in post–dose 3 concentrations also were significant for anti-FIM (18% lower) and agglutinins (15% lower) for one DTP product, and for anti-FHA (16% lower) for the other DTP product, with each doubling of the concentration of the specific transplacental maternal antibodies ($p \leq 0.05$) (*233*).

Interference with Pertussis Responses to Pediatric DTaP

Transplacental maternal IgG anti-PT might interfere less with infant responses after 3 doses of pediatric DTaP than

after pediatric DTP (*195,196,230,233*). The percentage decrease in post–dose 3 infant antibody response with each doubling of the concentration of maternal antibodies was 3% for anti-PT (not statistically significant), but was 13% for anti-PRN, 17% for anti-FIM, 10% for agglutinins, and 8% for anti-FHA (all statistically significant; $p \leq 0.05$) when results from several DTaP products were combined in one study (*233*). The difference between interference by maternal antibody with infant responses to DTP and DTaP might result from the higher content of pertussis-specific antigens in pediatric DTaP than in pediatric DTP relative to the concentration of transplacental maternal antibody (*159,222*). In addition, the maternal antibodies induced by the mothers' childhood DTP vaccinations might have less specificity for the pertussis vaccine antigens in acellular pertussis vaccines (*222,234–236*).

Noninterference with Pertussis Cellular Immune Responses to Pediatric DTP or DTaP

Infants who have relatively poor humoral immune responses to active immunization with whole-cell or acellular pertussis vaccine in the presence of inhibitory concentrations of transplacental maternal antibody have evidence of T-cell priming for booster (anamestic) responses (*158,237*). Protection against pertussis in T-cell primed infants in the absence of specific humoral antibodies has not been established (*158,238–241*).

Lactation

Existing data do not provide evidence that human colostral pertussis antibodies contribute to infant protection, although pertussis-specific antibodies present in the mother are found in colostral milk (*186,190,242*). Protection studies in animal models suggest human and animal colostral-derived pertussis antibodies can protect animals when the antibodies are absorbed or injected parenterally (*243–245*); however, the relevance of these studies for human infants is uncertain (*190,246,247*). Human breast milk antibodies do not enter the human neonatal circulation from the intestine in substantial amounts. In contrast, infant pigs, horses, ruminants, dogs, and cats acquire the majority of neonatal protection through intestinal uptake of colostral antibodies (*245,248–250*). Maternal antibodies in human milk do not interfere with the infant immune response to pediatric vaccines (*23*).

Tetanus

Tetanus is caused by *Clostridium tetani* spores, which are ubiquitous in the environment. Spores enter the body through disrupted skin or mucus membranes. When inoculated into oxygen-poor sites (e.g., necrotic tissue or wounds), *C. tetani* spores germinate to vegetative bacilli that elaborate tetanospasmin, a potent neurotoxin. More than 80% of cases of tetanus are of the generalized syndrome; the remaining cases are localized or cephalic. Persons with generalized cases typically have trismus (lockjaw), followed by rigidity and painful contractions of the skeletal muscles that can impair respiratory function. Glottic spasm, respiratory failure, and autonomic instability can result in death. The onset of tetanus typically is within 7 days of the injury (range: 0–112 days) The course of tetanus is up to 4 weeks or longer, followed by a prolonged period of convalescence (*251,252*).

Obstetric and Neonatal Tetanus

Obstetric tetanus is defined as tetanus during pregnancy or with onset within 6 weeks after the termination of pregnancy (*253*). Obstetric tetanus occurs after contamination of wounds or abrasions during pregnancy or after unclean deliveries or abortions. In a review covering 1941–1990, an estimated 65%–80% of cases of obstetric tetanus occurred in the puerperal or postpartum period; the majority of the other cases occurred after surgical or spontaneous abortions (*254*).

Obstetric tetanus has the highest mortality when the incubation period is short and respiratory complications are present (*255*). Cases can be complicated by gram-negative sepsis (*256*). Case-fatality rates vary (range: 16%–>50%); higher fatality rates are reported from places where access to medical intensive care is limited (*255,257,258*). Case-fatality rates historically have been higher for postabortal than for postpartum obstetric tetanus (*254*).

Neonatal tetanus (tetanus neonatorum) is associated with contamination of the umbilical stump. In nearly all cases of infant tetanus, onset occurs in the first month of life. Symptoms commonly begin at 3–14 days of life and are characterized by increasing irritability and difficulty feeding. Signs of neonatal tetanus are similar to tetanus in older age groups. Case-fatality rates vary (range: 10%–100%) (*252,259*). Infants who survive can have residual neurologic injury (e.g., cerebral palsy and psychomotor retardation) (*252*).

Burden

Tetanus is a nationally notifiable disease in the United States (*260*). In 2006, a total of 41 cases were reported. No cases occurred among women aged 15–19 years or those aged 30–39 years. One case occurred among women aged 20–29 years, and three cases occurred among women aged 40–49 years. None of the women died. During 1972–2006, case reporting forms did not collect information regarding pregnancy; however, no case of obstetric tetanus was identified

among more than 1,000 reports to NNDSS (CDC, unpublished data, 2006). In 1999, tetanus-specific coding became available in CDC's mortality database; no case of tetanus-associated obstetric death was reported through 2005, the most recent year for which data are available (CDC, unpublished data, 2008).

During the 1950s, approximately 100 neonatal tetanus deaths were reported annually in the United States, and neonates comprised more than one third of tetanus deaths in all age groups (*261,262*). During 1972–2006, the cumulative number of reported neonatal tetanus cases decreased to 32; the most recent cases were reported in 1989, 1995, 1998, and 2001 (*263*). Among these 32 neonatal cases, 27 (84%) births occurred in a nonhospital setting; 30 of 31 mothers with available history reported never having received a dose of tetanus toxoid vaccine (*264–266*; CDC, unpublished data, 2006).

Diagnosis and Treatment

The diagnosis of tetanus is clinical and is supported by a compatible setting, immunization history, and exclusion of other possible diseases. Anaerobic cultures of tissues or aspirates for *C. tetani* typically are not positive. Low or undetectable levels of serum antitoxin at the time of onset are compatible with the diagnosis of tetanus, but higher levels of antitoxin do not exclude the diagnosis (*252,267*). Electromyography might aid in the diagnosis of certain cases (*268*). Postpartum eclampsia, which typically occurs within the first few days after delivery, was the most important disease in the differential diagnosis in community-based studies (*254*).

Treatment of tetanus is directed at neutralizing unbound toxin with administration of human tetanus immune globulin, removing the source of infection through debridement, and use of an antimicrobial (e.g., metronidazole). The control of rigidity and spasms, attendant respiratory and autonomic dysfunction and their complications, and maintaining nutrition require careful and sustained attention that is best provided in intensive-care settings with specialty consultation (*251,252,269*).

Immunity to Tetanus

The level of antitoxin that protects against obstetric and neonatal tetanus can vary with the wound characteristics, the degree of contamination, the specificity of the antitoxin, and the type of assay employed to measure the antitoxin level (*270*). The minimum level of antitoxin correlating with protection is 0.01 IU/mL as measured by in vivo neutralization assay. An antitoxin concentration at ≥0.1 IU/mL is the preferred correlate of protection based on the results of other assays (e.g., enzyme-linked immunoabsorbant assay [ELISA]), and because higher concentrations of antitoxin might be necessary to protect in certain circumstances (*252,270*). The serum level of tetanus antitoxin achieved in response to vaccination is determined by the number of doses of tetanus toxoid, the type of tetanus toxoid administered (adjuvanted toxoid, which is more immunogenic, has replaced fluid toxoid), the interval since the most recent dose, and individual variation in the response to vaccination (*270*).

Deferring Td During Pregnancy to Substitute Tdap in the Immediate Postpartum Period

Ensuring maternal and neonatal tetanus protection as part of prenatal care is a priority for women who are due for a recommended decennial tetanus and diphtheria toxoids booster dose. For women who have not received a dose of Tdap previously, administering Td during pregnancy, followed in a few months by Tdap postpartum, theoretically could increase the risk or severity of adverse reaction, which typically is local. Moderate to severe local reactions have been associated with high levels of tetanus and diphtheria antitoxin (see Interval Between Td and Tdap). In these women, deferring the Td booster during pregnancy to substitute Tdap in the immediate postpartum period may be considered to boost protection against pertussis as well as tetanus and diphtheria. The majority of women of childbearing age who have lived in the United States since infancy or childhood have received 4–5 infant and childhood doses of tetanus toxoid with pediatric DTP or DTaP and ≥1 booster dose of Td (or tetanus toxoid without diphtheria toxoid [TT]) in accordance with national recommendations (*1,2,271*). The recommended schedule of vaccination to prevent tetanus is intended to maintain levels of antitoxin considerably higher than the minimum level required for protection against the majority of cases of tetanus, including protection among persons with intrinsically lower responses to vaccination (*1,2,252,271–273*).

In 2004, women aged 15–39 years accounted for 97% of all births in the United States (*3*). Data from a population-based serosurvey conducted nationwide in the United States during 1988–1994 documented tetanus antitoxin concentrations at ≥0.15 IU/mL among >80% of women aged 12–39 years (*274,275*). The proportion of women with antitoxin at ≥0.15 IU/mL declined with increasing age to 62% among women aged 40–49 years (*274,275*). Slightly lower prevalence of this titer was found among women aged 20–59 years who were not born in the United States (*276*). A 1999–2000 study evaluated 2,134 adult patients in an emergency department for wound management and measurement of their antitoxin titer (*277*). Antitoxin concentrations of ≥0.15 IU/mL were

present among 1,051 (95%) of 1,106 adults aged 18–39 years. Among adults of all ages studied, approximately 95% of those with up-to-date vaccination histories and approximately 86% of those whose vaccinations were not up-to-date had antitoxin titers ≥0.15 IU/mL. The rates of a protective titer were lower for immigrants, persons with less education, and persons aged >70 years (*277*). Limitations of these studies are that one study did not report any connection between vaccination histories and antitoxin concentrations (*274–276*), and the other study included subjects who might not be representative of the U.S. population (*277*). However, when combined with the small number of tetanus cases among women of childbearing age in the United States, these studies suggest that when pregnant women have previously received the recommended schedule of tetanus and diphtheria toxoids vaccinations, a routine decennial Td booster during pregnancy typically can be deferred so Tdap can be substituted at delivery or before discharge from the hospital or birthing center.

Vaccinating to Prevent Obstetric and Neonatal Tetanus

Success in preventing obstetric and neonatal tetanus relies on antitoxin being present at delivery (*254*). In countries where access to childhood vaccines is limited, neonatal tetanus constitutes a major cause of infant mortality; during 1978–1985, an estimated 800,000 neonatal tetanus deaths occurred annually worldwide (*278*). In 1974, worldwide elimination of neonatal tetanus (less than one case per 1,000 live births) through vaccine initiatives became a major focus of the Expanded Program of Immunization of the World Health Organization (WHO) (*259,279*). The initiative promoted clean deliveries and tetanus toxoid vaccination for pregnant women. Nonpregnant women of childbearing age also were targeted for at least 3 doses of tetanus toxoid vaccine in supplemental immunization activities.

The strategy of targeting pregnant women for vaccination to prevent neonatal tetanus was based on reports published in the 1960s concerning two vaccine trials that demonstrated that ≥2 doses of tetanus toxoid administered during pregnancy were >95% effective in preventing neonatal tetanus (Table 10) (*280,281*). Subsequent studies confirmed that 3 doses of aluminum phosphate-adjuvanted tetanus toxoid (rather than fluid toxoid) administered during pregnancy induced antitoxin levels that would protect the mother and prevent neonatal tetanus for ≥10 years. Adjuvanted vaccine also lowered the rates of local reactions in pregnant women (*282–284*).

Although the burden of obstetric tetanus has not been characterized as well as the burden of neonatal tetanus, the annual worldwide burden of obstetric tetanus deaths has been estimated at 15,000–30,000, accounting for approximately 5% of all maternal deaths in the 1990s (*254,259*). In April 2006, WHO's Strategic Advisory Group of Experts (SAGE) reported on the success of the maternal and neonatal tetanus elimination initiatives and the plan to transition from vaccination goals for women of childbearing age to universal tetanus control, to be achieved through sustained high coverage with pediatric DTP starting in infancy and childhood and booster doses to prevent tetanus throughout life (*259,285,286*).

Safety of Tetanus Vaccination During Pregnancy

No evidence suggests that adverse outcomes for a mother or fetus increase after tetanus toxoid is administered to a pregnant woman (*1,2,23*). Tetanus toxoid administered during any trimester of pregnancy was evaluated for association with congenital abnormalities at birth during 1980–1994 in Budapest, Hungary. The rate of tetanus toxoid vaccination among 21,563 mothers of infants with congenital abnormalities was not significantly different than the rate of tetanus toxoid vaccination among 35,727 mothers of infants who were normal (0.12% and 0.09%, respectively; p = 0.39) (*287*). In a similar study conducted in nine countries in South America starting in 1977, approximately one half of the women had received tetanus toxoid during the first trimester of pregnancy. The rate of early tetanus toxoid vaccination among the mothers of 34,293 newborns with congenital malformations (9.2 [CI = 8.2–10.3] per 1,000 mothers) was not substantially different than the rate among the mothers of 34,477 newborns who were normal (7.6 [CI = 6.6–8.5] per 1,000 mothers) (*288*).

Infant Protection by Transplacental Maternal Antibody

Tetanus toxoid is one of the most immunogenic protein antigens in any vaccine. Administration of 2 doses of tetanus toxoid to pregnant women at least 4–6 weeks before delivery stimulates antitoxin that protects the mother and readily crosses the placenta, thereby protecting the newborn against tetanus when the risk is highest (*289*). Pregnant women who receive a booster dose of tetanus toxoid have a measurable immune response within 5 days and a peak response in <2 weeks. The response to vaccination might be slower after a first (primary) dose or when the interval after the most recent booster dose is long (*252,272*). Placental transport of maternal IgG antitoxin is efficient; cord blood levels generally are similar to maternal levels (*290,291*). After the neonatal period, the infant is at little risk for tetanus until becoming self-mobile, typically at an age when sustained protection has been induced by 3 infant doses of pediatric DTP or DTaP (*252*).

TABLE 10. Number and percentage of neonatal tetanus cases, by number of doses of tetanus toxoid vaccine administered to the pregnant woman — selected studies, New Guinea, 1961 and Columbia, 1966

Study*	Trial design	Vaccine	No. of doses					
			0–1 dose		2 doses		3 doses	
			No.	(%)	No.	(%)	No.	(%)
1	62 villages	Fluid toxoid	16/160	(10.0)	8/234	(3.4)	1/175	(0.6)
			0 dose		1 dose		2–3 doses	
			No.	(%)	No.	(%)	No.	(%)
2	Double-blind, controlled	Al PO_3-adsorbed toxoid	46/617	(7.5)	9/224	(4.0)	0/341	(0)

* Study 1 = Schofield FD, Tucker VM, Westbrook GR. Neonatal tetanus in New Guinea: effect of active immunization in pregnancy. Br Med J 1961;2:735–9. Study 2 = Newell KW, Dueñas Lehmann AD, LeBlanc DR, Garces Osorio NG. The use of toxoid for the prevention of tetanus neonatorum: final report of a double-blind controlled field trial. Bull World Health Org 1966;35:863–71.

Inhibitory Effect of Transplacental Maternal Antibody on Infant Immunization

Transplacental maternal tetanus antitoxin can interfere with the infant response to active immunization after up to 3 doses of tetanus toxoid (e.g., in pediatric DTP, DTaP, or DT) (*222,230,292–297*). Certain studies (*296,297*), but not all (*298*), indicate that antitoxin inhibits the response to tetanus toxoid after vaccination with *Haemophilus influenzae* type b polysaccharide conjugated to tetanus toxoid. An age-accelerated schedule results in further decrease in infant responses in the presence of maternal antitoxin (*295*). When levels of transplacental maternal antitoxin wane sufficiently, infants respond to subsequent doses of vaccine (*229,293,294,299–301*). T-cell priming for a booster response is not substantially affected by maternal antitoxin (*222,302, 303*). Typically, infants respond to the second dose of tetanus toxoid–containing vaccine with a protective level of antitoxin, even when the initial levels of maternal antitoxin are high; 3 doses of tetanus toxoid are required to achieve antitoxin concentrations that persist above protective levels (*292,304*).

Lactation

No substantial difference in the infant immune response to tetanus toxoid (in DTP) has been identified with consumption of human milk compared with consumption of cow milk (*305*).

Diphtheria

Respiratory diphtheria is an acute, severe infection caused by strains of *Corynebacterium diphtheriae* that produce diphtheria toxin. Rarely, toxin-producing strains of *C. ulcerans* cause a diphtheria-like illness (*306*). Respiratory diphtheria is characterized by a grayish-colored adherent membrane on the pharynx, palate, or nasal mucosa that can obstruct the airway with fatal outcome. The disease can be complicated by toxin-mediated cardiac, neurologic, or renal dysfunction. Case-fatality rates are ≥10% (*307,308*).

Obstetric and Neonatal Diphtheria

Respiratory diphtheria (*309–312*) or vulvovaginal infection (*313,314*) can occur during any trimester of pregnancy, at term, or in the postpartum period. The mortality rate of obstetric respiratory diphtheria is high (estimated at 50%) without infusion of diphtheria antitoxin, even with tracheostomy or intubation, and is accompanied by fetal loss or premature birth in approximately one third of survivors. Early treatment with serum diphtheria antitoxin improves survival and pregnancy outcomes, although complications of the disease might require prolonged supportive care (*309–312*). Postpartum women with respiratory diphtheria can transmit *C. diphtheriae* to their neonates (*310*).

Burden

Respiratory diphtheria is a nationally notifiable disease in the United States. Rare cases occur in the United States after infection with diphtheria toxin–producing strains of *C. diphtheriae* or other corynebacteria (*315,316*). During 1998–2006, seven cases of respiratory diphtheria were reported to CDC. The most recent culture-confirmed adult case of respiratory diphtheria caused by *C. diphtheriae* was reported in 2000, and an adult case of respiratory diphtheria caused by *C. ulcerans* was reported in 2005 (*306*). The risk for diphtheria can be increased during travel to areas in which diphtheria is endemic; a list of these areas is available at http://www.cdc.gov/travel/default.aspx. Diphtheria also can be acquired from persons with imported cases or from carriers (i.e., asymptomatic persons who are colonized with toxin-producing *C. diphtheriae*) (*315,316*).

Diagnosis and Treatment

The diagnosis of diphtheria is confirmed by isolation of *C. diphtheriae* in culture of the adherent membrane and by testing the isolate for toxin production (*317*). The mainstay of treatment in respiratory diphtheria is early administration of diphtheria antitoxin (equine), which is available to physicians in the United States from CDC through an FDA-Investigational New Drug protocol (24-hour telephone, 770-488-7100). Additional information is available at http://www.cdc.gov/vaccines/vpd-vac/diphtheria/dat/dat-main.htm. No human-derived serum diphtheria antitoxin is available. Antibiotics are administered to limit transmission and to prevent continuing production of diphtheria toxin (*318*). Prompt reporting of suspect cases, investigation, culture, and antimicrobial prophylaxis of contacts and immunization of the affected community (*317,318*) is of critical importance. Because respiratory diphtheria does not always confer protection against future illness, patients should complete active immunization with diphtheria toxoid after recovery (*286*).

Diphtheria Immunity

Protection against respiratory diphtheria is predominantly from IgG antibody to diphtheria toxin (antitoxin) induced after infection with toxin-producing *C. diphtheriae* or after vaccination with diphtheria toxoid. In areas with little or no endemic exposure to toxin-producing *C. diphtheriae*, periodic vaccination is required to maintain immunity (*237,286,307, 319–321*). Although the immune responses to infection and vaccination vary, antitoxin concentrations of ≥0.1 IU/mL typically are considered protective. Concentrations of 0.01 IU/mL–0.1 IU/mL might provide protection against severe disease; concentrations <0.01 IU/mL do not protect against diphtheria (*286,307,322*).

Td Booster During Pregnancy for Diphtheria Protection

Data from a national population-based serosurvey conducted during 1988–1994 that evaluated the prevalence of immunity to diphtheria (defined as a diphtheria antitoxin concentration of ≥0.1 IU/mL) among women in the United States determined immunity to diphtheria to be lower than immunity to tetanus (see Tetanus: Deferring Td During Pregnancy to Substitute Tdap in the Immediate Postpartum Period). The prevalence of immunity to diphtheria decreased with increasing age (77% among women aged 12–19 years, 74% among women aged 20–29 years, 65% among women aged 30–39 years, and ≤45% among women aged ≥40 years) and with birth outside the United States or less formal education (*274,276*).

Vaccinating Pregnant Women, Infant Protection by Transplacental Antibody

Diphtheria toxoid vaccine trials conducted among pregnant women in the 1940s demonstrated quantitative increases in diphtheria antitoxin after the women were vaccinated. Maternal antitoxin was transferred efficiently to the fetus (*217,226,320,323,324*). Several studies indicate transplacental maternal antitoxin provides newborn infants with protection against diphtheria at birth if their mother is immune (*226,250,321,325*).

Safety

The safety of diphtheria toxoid (without tetanus toxoid) vaccination in pregnant women was examined during the 1970s (*326*). After diphtheria toxoid was administered during the first 4 months of pregnancy, 75 mother-child pairs were followed for malformations until the child reached age 7 years. Although the number of vaccinated pregnant women studied was small, the risk for malformations in their children was lower than the risk among children in a much larger group of mother-child pairs in which the women were not vaccinated with diphtheria toxoid during pregnancy (survival- and race-standardized relative risk: 0.88) (*327*).

Inhibitory Effect of Transplacental Maternal Antibody on Infant Immunization

Transplacental maternal diphtheria antitoxin concentrations of ≤0.1 IU/mL can interfere with primary diphtheria toxoid immunization in infancy (*237,292,321,328–331*). The duration of interference is affected by the concentration of maternal antitoxin, the formulation and toxoid content of the infant vaccine (e.g., the limit of flocculation [Lf] units of diphtheria toxoid, aluminum hydroxide-adsorbed, or fluid preparation), and the length of the interval between doses (*229,237,292,293,295,299,321,328–331*). Infants typically respond with increases in antitoxin after 2 doses of high-content diphtheria toxoid vaccine when maternal antitoxin concentrations are 0.1 IU/mL in cord sera but not until after ≥3 infant doses of high-content diphtheria toxoid vaccine when maternal antitoxin concentrations are ≥1.0 IU/mL in cord sera (*225,229,292,299,321,329,331,332*). When infants receive subsequent doses of diphtheria toxoid, the responses are rapid, often within 2 weeks (*330*), suggesting that T-cell priming occurs in the absence of an infant antibody response to previous doses of vaccine (*229,237,324,329,330*).

Lactation

Consumption of human milk does not affect the infant immune response to diphtheria toxoid–containing vaccines (*292,332*). Ingestion of colostrum from an immune mother does not result in an increase in the concentration of diphtheria antitoxin in infant sera (*250*).

Adult and Adolescent Acellular Pertussis Combined with Tetanus and Reduced Diphtheria Toxoids (Tdap) Vaccines and Tetanus and Reduced Diphtheria Toxoids (Td) Vaccines

Both Tdap vaccines used in the United States (ADACEL® and BOOSTRIX®) were licensed on the basis of clinical trials in the United States demonstrating immunogenicity not inferior to that of U.S.-licensed Td (*333,334*) and the pertussis components of pediatric DTaP made by the same manufacturer and an acceptable safety profile (*212,213*). Adsorbed Td products for adults and adolescents have been licensed in the United States since the 1950s (*335*). Components of these and other diphtheria and tetanus toxoids–containing vaccines have been listed (Table 1) and are available at http://www.fda.gov/cber/vaccines.htm.

In prelicensure trials, data on local and systemic adverse events were collected using standard diaries for the day of vaccination and the next 14 consecutive days (*212,213,336–338*). The efficacies of the tetanus toxoid and the diphtheria toxoid components of Tdap were inferred from the immunogenicity of the antigens in Tdap compared with Td using established serologic correlates of protection in sera obtained before and approximately 1 month after vaccination. Because no well-accepted serologic or laboratory correlate of protection is available for pertussis, the efficacy of the pertussis components of Tdap was inferred using a serologic bridge (comparison) to the immune response to vaccine antigens among infants who received 3 doses of pediatric DTaP (made by the same manufacturer) during clinical efficacy trials for pertussis during the 1990s (*339*). The efficacy against pertussis of an acellular pertussis vaccine without tetanus and diphtheria toxoids was 92% (CI = 32%–99%) for adults and adolescents in a randomized, controlled trial (*340*); these results were not considered in the evaluation of Tdap for licensure in the United States.

Selected results from the prelicensure trials are summarized below. Additional information can be found in previous ACIP statements discussing use of Tdap among adults and adolescents and in the package labels of the specific products (*1,2,212,213*).

ADACEL®

ADACEL® contains the same tetanus toxoid, diphtheria toxoid, and five pertussis antigens as those in DAPTACEL® (pediatric DTaP, also made by sanofi pasteur), but ADACEL® is formulated with reduced quantities of diphtheria toxoid and detoxified PT. Prelicensure trials in the United States evaluated the immunogenicity and the safety of ADACEL® among adults aged 18–64 years and among adolescents aged 11–17 years, randomized to receive a single dose of ADACEL® or a single dose of Td made by the same manufacturer (Table 1) (*1,2,212,333*). Pregnant women were excluded.

Immunogenicity

Tetanus and Diphtheria Toxoids. The rates of seroprotection and booster response for both antitetanus and antidiphtheria among adults and adolescents who received a single dose of ADACEL® were noninferior to rates among those who received Td. Nearly all (>99%) subjects in the ADACEL® and Td groups achieved seroprotective antitetanus levels (≥0.1 IU/mL), and >94% of adults and >99% of adolescents achieved seroprotective antidiphtheria levels (≥0.1 IU/mL) in ADACEL® and Td groups (*212,341*).

Pertussis Antigens. The efficacy of the pertussis components was inferred by comparing the immune responses (GMCs) of adults and adolescents vaccinated with a single dose of ADACEL® to those of infants vaccinated with 3 doses of DAPTACEL® in a Swedish vaccine efficacy trial (*338,342*). The efficacy of 3 doses of pediatric DAPTACEL® against WHO-defined pertussis (≥21 days of paroxysmal cough with confirmation of *B. pertussis* infection by culture or serologic testing, or an epidemiologic link to a household member with culture-confirmed pertussis) was 85% (CI = 80%–89%) (*338,342*). The GMCs of anti-PT, anti-FHA, anti-PRN, and anti-FIM among adults and adolescents after a single dose of ADACEL® were noninferior to those of infants after 3 doses of DAPTACEL.® The prespecified criteria for booster responses also were met (*1,2,212,336,341*).

Safety

The safety of ADACEL® was evaluated in four clinical studies with data from 2,448 adults aged 18–64 years and 3,393 adolescents aged 11–17 years (*212*).

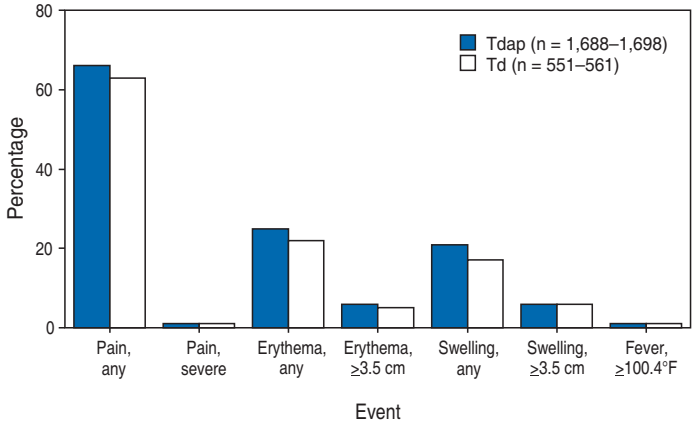
Immediate Events. No anaphylaxis was reported. Five adults reported an immediate event within 30 minutes of vaccination (four persons [0.2%] for ADACEL® and one person [0.2%] for Td); three of these five events were classified as nervous system disorders (hypoesthesia/paresthesia). Eleven adolescents reported an immediate event (six persons [0.5%] for ADACEL® and five persons [0.6%] for Td); these events included dizziness, syncope, or vasovagal reactions in addi-

tion to pain and erythema at the injection site. All events resolved without sequelae (*338,341,343*).

Solicited Local and Systemic Adverse Events. Rates of erythema and swelling (Figures 3 and 4), or systemic (headache, generalized body aches, and tiredness [data not presented]) adverse events reported to occur during 0–14 days following vaccination with Td or Tdap were similar (*1,2,212,338,341*). Fever ≥100.4°F (≥38°C) was reported with the same frequency by adults vaccinated with Td and with Tdap (Figure 3) (*212*); the rate of any fever reported by adolescents vaccinated with Tdap (5%) was higher than the rate for those vaccinated with Td (3%) but met the noninferiority criterion (Figure 4) (*212,341*). No case of whole-arm swelling was reported (*341*).

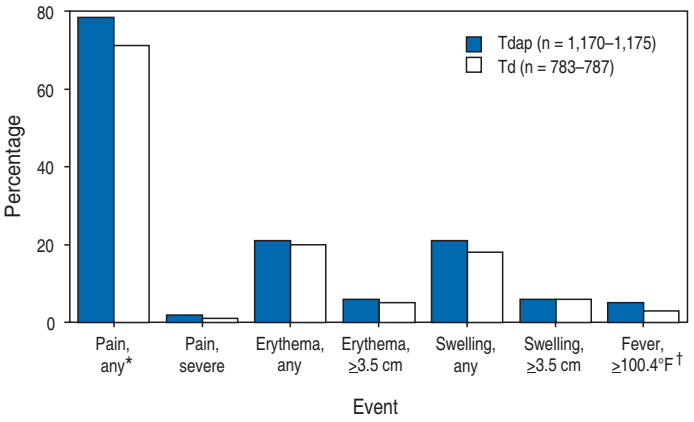
Serious Adverse Events. Among adults, serious adverse events (e.g., appendicitis) within 6 months after vaccination were reported for 33 (2%) of 1,752 persons in the ADACEL® group and for 11 (2%) of 573 persons in the Td group (*338,341*). Two serious adverse events in ADACEL® recipients were neuropathic and were assessed by the investigators as possibly related to vaccination. In both cases, the symptoms resolved completely over several days (*1,212,338, 341,343*). Among adolescents, serious adverse events within 6 months after vaccination were reported for 11 (1%) of 1,184 persons in the ADACEL® group and for eight (1%) of 792 persons in the Td group. All events were reported by investigators to be unrelated to the study vaccine (*341*). No physician-diagnosed Arthus reaction (see Important Local Reactions) or case of Guillain-Barré syndrome (see Neurologic and Systemic Events) was reported (*1*).

FIGURE 3. Frequencies of selected solicited adverse events in adults aged 18–64 years within 15 days after a single dose of ADACEL® tetanus, reduced diphtheria, and acellular pertussis (Tdap) vaccine or tetanus and reduced diphtheria toxoids (Td) vaccine — United States, 2001–2002



Source: Product label available at http://www.fda.gov/cber/index.html.

FIGURE 4. Frequencies of selected solicited adverse events in adolescents aged 11–17 years within 15 days after a single dose of ADACEL® tetanus, reduced diphtheria, and acellular pertussis (Tdap) vaccine or tetanus and reduced diphtheria toxoids (Td) vaccine — United States, 2001–2002



Source: Product label available at http://www.fda.gov/cber/index.html.

* Tdap did not meet the noninferiority criteria for the rate of "any" injection-site pain compared with the Td rate (upper limit of two-sided confidence interval on the difference in the percentage of adolescents [Tdap minus Td] was 10.7% whereas the noninferiority criterion was <10%).

† The rate of "any" fever was higher after Tdap than after Td ($p<0.05$); however, the noninferiority criterion was met for Tdap.

Simultaneous Administration of Tdap with Other Vaccines

Trivalent Inactivated Influenza Vaccine. The safety and immunogenicity of ADACEL® co-administered with trivalent inactivated influenza vaccine ([TIV] Fluzone,® sanofi pasteur, Swiftwater, Pennsylvania) were evaluated in nonpregnant adults aged 19–64 years randomized to simultaneous administration in different arms (n = 359), or to TIV administered first, followed by ADACEL® 4–6 weeks later (n = 361). Rates of fever and injection site erythema and swelling were similar following ADACEL® administered concurrently with TIV or separately. Pain at the ADACEL® injection site occurred more frequently after simultaneous administration than after separate administration (67% and 61%, respectively) (*338*). Immunogenicity criteria were met with the following exceptions: the GMC of anti-PRN was lower in the simultaneous group than in the sequential group (*338,344*), and the tetanus booster response rates were lower after simultaneous administration than after sequential administration (79% and 83%, respectively). However, more than 98% of subjects in both groups achieved seroprotective levels (≥0.1 IU/mL) of tetanus antitoxin (*338,344*).

Hepatitis B Vaccine. The safety and immunogenicity of ADACEL® administered with hepatitis B (Hep B) vaccine (Recombivax HB,® Merck and Co., White House Station, New Jersey) were evaluated among nonpregnant adolescents

aged 11–14 years randomized to simultaneous administration (n = 206) or to ADACEL® administered first, followed by hepatitis B vaccine 4–6 weeks later (n = 204). Rates of solicited erythema and swelling at the ADACEL® injection site were higher in the simultaneous group than in the sequential group, and noninferiority was not achieved (*1,338*). No interference was observed in the immune responses to any of the vaccine antigens when ADACEL® and hepatitis B vaccine were administered concurrently or separately (*212*).

BOOSTRIX®

BOOSTRIX® contains the same tetanus toxoid, diphtheria toxoid, and three pertussis antigens as those in INFANRIX® (pediatric DTaP, also made by GlaxoSmithKline), but BOOSTRIX® is formulated with reduced quantities of antigens. Prelicensure trials conducted in the United States evaluated the immunogenicity and safety of BOOSTRIX® among adolescents aged 10–18 years (*213,337*), randomized to receive a single dose of BOOSTRIX® or a single dose of Td (Massachusetts Public Health Biologic Laboratory, Mattapan, Massachusetts) (Table 1) (*213,334,337*). Pregnant adolescents were excluded.

Immunogenicity

Tetanus and Diphtheria Toxoids. The rates of seroprotection and booster response for both antitetanus and antidiphtheria among adolescents who received a single dose of BOOSTRIX® were noninferior to those who received Td. All adolescents had seroprotective antitetanus levels (≥0.1 IU/mL); >99% of adolescents had seroprotective antidiphtheria levels (≥0.1 IU/mL) (*1,213,336*).

Pertussis Antigens. The efficacy of the pertussis components was inferred 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® in a German vaccine efficacy trial (*213,336, 345*). The efficacy of 3 doses of pediatric INFANRIX® against WHO-defined pertussis was 89% (CI = 77%–95%) (*213,345*). The GMCs of anti-PT, anti-FHA, and anti-PRN after a single dose of BOOSTRIX® were noninferior to those of infants after 3 doses of INFANRIX.® The prespecified criteria for booster responses also were met (*1,213,336,337*).

Safety

A total of 3,080 adolescents aged 10–18 years received BOOSTRIX® in the primary safety study (*213*). No immediate events (i.e., those occurring within 30 minutes of vaccination) were reported (*1,213,336,337*).

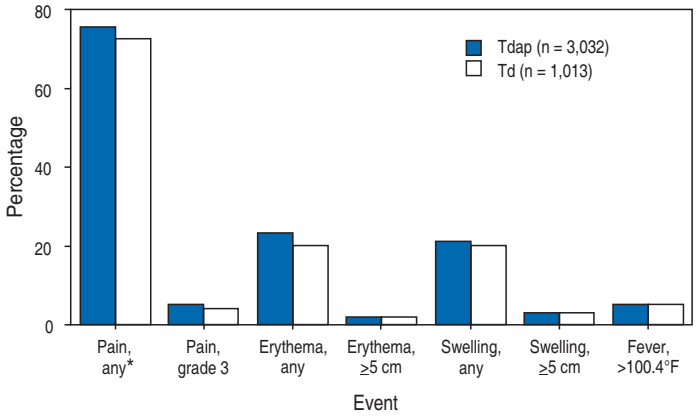
Solicited Local and Systemic Adverse Events. No substantial differences were observed between the BOOSTRIX® and Td recipients in the rates of solicited local (redness, swelling, and increase in arm circumference above baseline) (Figure 5) or systemic (headache, fatigue, gastrointestinal systemic events, fever >100.4°F [>38.0°C] [data not presented]) adverse events (*1,213,336,337*). No case of whole-arm swelling was reported (*1*).

Serious Adverse Events. Serious adverse events within 6 months after vaccination were reported among 14 (0.4%) of 3,005 adolescents vaccinated with BOOSTRIX® and two (0.2%) of 1,003 adolescents vaccinated with Td. All events were reported by the investigators to be unrelated to the study vaccine (*213,336,337,346*). No physician-diagnosed Arthus reaction or case of Guillain-Barré syndrome was reported (*1,213,337,346*).

Pregnant Women Vaccinated with Tdap

Pregnant women were excluded from prelicensure trials of Tdap. The outcome of pregnancy among six women who were administered ADACEL® inadvertently during or within 1 month of conception was a healthy full-term infant (n = 3), a preterm infant (n = 1), or a miscarriage (n = 2). No infant was born with a congenital anomaly (sanofi-pasteur, unreported data, 2007). Two pregnancies occurred in BOOSTRIX® recipients ≥4 months postvaccination; one subject experienced a spontaneous abortion within the first trimester, and the other subject delivered a healthy infant (*337*).

FIGURE 5. Frequencies of selected solicited adverse events in adolescents aged 10–18 years within 15 days after a single dose of BOOSTRIX® tetanus, reduced diphtheria, and acellular pertussis (Tdap) vaccine or tetanus and diphtheria toxoids (Td) vaccine — United States, 2002–2003



Source: Product label available at http://www.fda.gov/cber/index.html.
* The rate of "any" injection-site pain was higher after Tdap compared with Td (p<0.05).

Regulatory Considerations for Tdap in Pregnant Women

As with the majority of vaccines, Tdap is labeled pregnancy category C. This designation indicates that no adequate and well-controlled studies have been conducted with the vaccine in pregnant women to determine the product's safety (*347,348*).

Safety Considerations for Adult and Adolescent Use of Td or Tdap

Prelicensure studies in nonpregnant adults and adolescents evaluated the safety of Tdap with respect to local and systemic adverse events (*212,213*). The sample sizes were insufficient to detect rare adverse events. Enrollment criteria excluded persons who were pregnant; had received vaccines containing tetanus toxoid, diphtheria toxoid, or pertussis components more recently than either the preceding 5 years for ADACEL® (*212*) or the preceding 10 years for BOOSTRIX® (*213*); or had certain neurologic conditions or events (*336–338,341,346*). Safety data are being collected by the Vaccine Adverse Event Reporting System (VAERS), and postlicensure studies continue to monitor for potential adverse reactions following widespread use of Tdap in adults and adolescents (*16,17*). Registries have been established by both Tdap manufacturers for reporting women vaccinated with Tdap during pregnancy.

Interval between Td and Tdap

ACIP has made several recommendations for intervals between tetanus toxoid– and diphtheria toxoid–containing vaccines that balance the benefits of protection against the risks of moderate and severe local reactions. Moderate and severe local reactions, including Arthus reaction, are associated with frequent dosing at short intervals and larger doses of toxoid. High antitoxin levels are more likely to result when the interval between doses is short and the number of doses increases (*349–354*). High preexisting antibody titers to tetanus or diphtheria toxoids also are associated with increased rates and severity of local reactions to booster doses in adults (*349,354–356*).

ACIP recommends a 10-year interval for routine administration of Td (e.g., decennial Td booster), and a 5-year interval for Td when indicated for wounds management (*1,2,357*). Administering Td more often than every 10 years (5 years for certain nonclean, nonminor wounds) is not necessary to provide protection against tetanus or diphtheria; however, administering a single dose of Tdap at an interval shorter than 5 years after Td could provide a health benefit by adding protection against pertussis (Table 2) (*1,2*). When Tdap is administered to add protection against pertussis, ACIP encourages an interval of ≥5 years between the most recent Td and the Tdap dose for adolescents because they might receive other recommended vaccines containing tetanus or diphtheria toxoids (including quadrivalent meningococcal conjugate vaccine [MCV4] [Menactra,® sanofi pasteur, Swiftwater, Pennsylvania]) (*2*). An interval as short as 2 years is recommended between the most recent Td and the single dose of Tdap for health-care personnel with direct patient contact, and a 2-year interval between the most recent Td and Tdap is suggested for adults in close contact with infants (*1*). ACIP allows for a shorter interval between the most recent Td and administration of Tdap in certain circumstances that might require urgent protection (*1,2*).

Several studies have suggested that an interval as short as 2 years between Td and a single dose of Tdap is acceptably safe. Three studies conducted among Canadian children and adolescents evaluated the safety of Tdap (ADACEL®) at an interval shorter than 5 years after Td or after pediatric DTP or DTaP (*358–360*). The largest was an open-label study of 7,001 students aged 7–19 years. Rates of local reactions were not increased among students who had received the most recent of 5 pediatric DTP or DTaP doses, or a Td dose, ≥2 years before Tdap, compared with ≥10 years before Tdap (*358*). The other Canadian studies demonstrated similar safety when Tdap was administered at an interval of <5 years after the previous tetanus toxoid– and diphtheria toxoid–containing vaccine (*359,360*).

Adverse reactions after Tdap (ADACEL®) administered at an interval of <2 years from the most recent Td were evaluated in a retrospective survey of 4,524 health-care personnel who received Tdap at a median age of 46 years during an outbreak of pertussis-like illness in New Hampshire in 2006 (*118,215,361*). For the 2,676 (59%) responses, the rates of reactions were analyzed by interval from Td to Tdap as either ≥2 years (n = 1,792) or <2 years (n = 370). The rates of pain, redness, or swelling of moderate or severe intensity, subjective fever, and medical visits were not higher among respondents with an interval of <2 years between administration of Td and that of Tdap. Three serious adverse events were reported among adults who received Tdap at an interval ≥2 years after the most recent dose of Td; causality was not assessed. The events were a case of Guillain-Barré syndrome (not requiring hospitalization) with onset 11 days after Tdap, a case of anaphylaxis-like reaction with onset 6 days after Tdap, and a case of eosinophilic nephritis with onset 6 days after Tdap in a health-care worker with a history of a renal transplant (*215,216*).

Important Local Reactions

Arthus Reaction

Arthus reaction (type III hypersensitivity reaction) can occur after tetanus toxoid– or diphtheria toxoid–containing vaccines (*354,357,362–366*; CDC, unpublished data, 2005). Arthus reaction is a local vasculitis with deposition of immune complexes and activation of complement; it occurs in the setting of high local concentration of vaccine antigens and high circulating antibody concentration (*354,362, 363,367*). The reaction is characterized by severe pain, swelling, induration, edema, and hemorrhage, and occasionally by local necrosis. Vaccine-related arthus reaction typically resolves without sequelae. The onset of symptoms and signs is 4–12 hours after vaccination, compared with anaphylaxis (immediate type I hypersensitivity reaction), which has onset within minutes after vaccination. ACIP recommends that persons who experience an Arthus reaction after administration of a tetanus toxoid–containing vaccine not receive Td or other tetanus toxoid–containing vaccine more frequently than every 10 years, even for tetanus prophylaxis as part of wound management (*1,357*).

Extensive Limb Swelling

Extensive limb swelling reactions have been reported to VAERS following administration of Td (*368,369*) and are described following dose 4 or dose 5 of pediatric DTaP (*23,208,368,370–373*). Extensive limb swelling after pediatric DTaP resolves without complication within 4–7 days (*370*), and is not considered a precaution or contraindication for Tdap (*23*).

Neurologic and Systemic Events

Pertussis Components

Concerns regarding a possible role of pertussis vaccine components in causing neurologic reactions or exacerbating underlying neurologic conditions in infants and children are long-standing (*29,374*). In 1991, the Institute of Medicine (IOM) concluded that evidence favored acceptance of a causal relation between pediatric DTP vaccine and acute encephalopathy (*365*). A subsequent retrospective analysis of >2 million children in the United States did not demonstrate that pediatric DTP was associated with an increased risk for encephalopathy after vaccination (*375*). Active surveillance in Canada during 1993–2002 also failed to identify any acute encephalopathy cases causally related to whole-cell or acellular pertussis vaccines among a population administered 6.5 million doses of pertussis-containing vaccines (*376*). Results of one recent investigation suggested that some acute encephalopathies attributed previously to pertussis-containing vaccines could be the result of genetically determined epileptic encephalopathies related to mutations in the sodium channel gene SCN1A (*377,378*). 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 remains a contraindication for Tdap (but not Td) in adults and adolescents.

The possibility that Tdap would complicate neurologic evaluation of chronic progressive neurologic disorders that are stable in adults (e.g., dementia) is of limited clinical concern and does not constitute a reason to delay administration of Tdap (*1*). Unstable or evolving neurologic conditions (e.g., cerebrovascular events or acute encephalopathic conditions) would be reason to delay administration of Tdap until the condition has stabilized (*1*). Among adolescents who have progressive or uncontrolled underlying neurologic disease, concerns regarding administering Tdap must be weighed against the morbidity from pertussis, which could be severe (*2*). ACIP does not consider a history of well-controlled seizures or a family history of seizures (febrile or afebrile) or other neurologic disorder to be a contraindication or precaution to vaccination with pertussis components (*22*).

Tetanus Toxoid Component

ACIP considers Guillain-Barré syndrome within 6 weeks after receipt of a tetanus toxoid–containing vaccine to be a precaution (see Precautions and Reasons to Defer Td or Tdap) for administration of subsequent tetanus toxoid–containing vaccines (*23*). Although IOM concluded that evidence favored acceptance of a causal relation between tetanus toxoid–containing vaccines and Guillain-Barré syndrome on the basis of a single well-documented case (*365,379*), subsequent analysis of data from both adult and pediatric populations failed to demonstrate an association (*380*). As of January 29, 2007, eight patients with Guillain-Barré syndrome temporally associated with receipt of Tdap or of Tdap administered on the same day with other vaccines had been reported to VAERS. The onsets were not clustered by the interval since vaccination or by a single pattern of vaccine exposure (*361*).

ACIP does not consider a history of brachial neuritis to be a precaution or contraindication for administration of tetanus toxoid–containing vaccines (*23,381*). IOM concluded that evidence from case reports and uncontrolled studies involving tetanus toxoid–containing vaccines did favor a causal relation between tetanus toxoid–containing vaccines and brachial neuritis (*365*); however, brachial neuritis typically is self-limited (*23,381*). Brachial neuritis is a compensable event through the Vaccine Injury Compensation Program (VICP) (*365*).

Economic Considerations

No study has evaluated the disease morbidity and societal costs associated with pertussis among pregnant women or modeled the cost benefit or cost effectiveness of a Tdap strategy that includes vaccination of pregnant women. The morbidity and societal cost of pertussis in adults is substantial (*1*,*2*). A retrospective assessment of medical costs of confirmed pertussis in 936 adults in Massachusetts during 1998–2000, and a prospective assessment of nonmedical costs in 203 adults during 2001–2003 (*31*) indicated that the mean medical and nonmedical cost per case was $326 and $447, respectively, for a societal cost of $773. If the cost of antimicrobials to treat contacts and the cost of personal time were included, the societal cost could be as high as $1,952 per adult case *(31)*.

Cost-benefit and cost-effectiveness analyses of adult Tdap vaccination have varied in their results (*382,383*). When discrepancies in the models were addressed, an adult Tdap vaccination program was cost-effective when incidence of pertussis exceeded 120 cases per 100,000 population, using a benchmark of $50,000 per quality-adjusted life year saved (*384–386*). After adjusting for the severity of the illness at high disease incidence, little effect was observed on the overall cost effectiveness of a vaccination program. Similar results were obtained when program costs and benefits were analyzed over the lifetime of the adult cohort for decennial booster strategies (*1,387*).

Implementing Tdap

Preconception Assessments

Administering a dose of Tdap during routine wellness visits of adult and adolescent women of childbearing age, if indicated, is the most effective programmatic strategy to ensure that women are protected against pertussis in addition to tetanus and diphtheria and minimizes any theoretical effect of vaccination on infant immune responses should the woman become pregnant (see Immunity to Pertussis and Kinetics of Pertussis Booster Vaccination in Nonpregnant Adults and Adolescents) (*1,388–392*). Because Tdap contains only toxoids and purified bacterial components, women who receive Tdap do not need to wait after vaccination to become pregnant (*23*). Assessments provide repeated opportunities for documenting the history of past doses of Td (or TT) and any serious adverse reactions to tetanus, diphtheria, and pertussis vaccines. To access and maintain immunization records, state-based immunization information systems (IIS) are increasingly becoming available to clinicians and public health officials. These confidential, computerized information systems, which consolidate vaccination data from multiple health-care providers, can generate reminder and recall notifications, assist with vaccine management and adverse events reporting, and capture lifespan vaccination histories (*393)*. Additional guidance regarding administration of vaccines during routine assessments, record keeping, vaccine storage, and related topics has been published previously (*23*).

Prenatal Visits: Deferring Td During Pregnancy to Substitute Tdap in the Immediate Postpartum Period

In 2004, a total of 96% of pregnant women started prenatal care in the first or second trimester (*394)*. Prenatal visits provide additional opportunities for assessing the history of past vaccination with Tdap, Td, or TT and any serious adverse reactions to tetanus, diphtheria, and pertussis vaccines. Women who have not received a previous dose of Tdap can be advised that ACIP recommends Tdap postpartum before discharge from the hospital or birthing center to provide personal protection and reduce the risk for transmitting pertussis to their infants.

Health-care providers can monitor pregnant women for respiratory illness consistent with pertussis or for recent exposure to pertussis, either to themselves or to family members, and prescribe a macrolide antimicrobial for treatment of pertussis or postexposure prophylaxis, if indicated. Women and their partners should receive counseling regarding the severity of infant pertussis and ACIP's recommendation for a single dose of Tdap for adults and adolescents who anticipate contact with an infant (*1,2*). In a 2005 national survey of obstetricians, 72% of respondents affirmed the belief that obstetricians, pediatricians, adult primary care providers, and public health providers share responsibility to promote administration of Tdap for adults who anticipate contact with an infant, including fathers and close relatives (*395*). Ideally, health-care providers delivering prenatal care will encourage persons likely to have contact with an infant, including child care providers, to receive Tdap first.

When pregnant women who have not received Tdap have indications for tetanus or diphtheria booster protection (≥10 years since the most recent Td), ACIP recommends receipt of Td during pregnancy (Table 2). ACIP has developed criteria for safely deferring administration of Td until delivery among women who have received past tetanus toxoid–containing vaccinations, so the majority of these women can substitute Tdap in the immediate postpartum period for Td during pregnancy (see Deferring Td During Pregnancy to Substitute Tdap in the Immediate Postpartum Period). When the history of tetanus toxoid vaccination for the women is uncertain or lacking, health-care providers can determine the con-

centration of tetanus antitoxin to ensure protective concentrations of tetanus antitoxin (≥0.1 IU/mL by ELISA). Because diphtheria is rare in the United States, serologic screening for diphtheria antitoxin typically is not necessary. A woman who anticipates travel to an area in which diphtheria is endemic can improve protection against diphtheria by receiving a booster dose of Td during pregnancy or a dose of Tdap postpartum. Serologic screening to establish immunity to pertussis is not useful.

In special situations in which a pregnant woman has increased risk for tetanus, diphtheria, or pertussis, ACIP acknowledges that health-care providers may choose to administer Tdap instead of Td during pregnancy to add protection against pertussis, after discussing the theoretical benefits and risks for her, her fetus, and the pregnancy outcome with the woman before vaccination (see Considerations for Use of Tdap in Pregnant Women in Special Situations). Data to inform this decision are scarce. No theoretical risk for harm to the mother or fetus exists from Tdap, and administration of Tdap in the pregnant woman might provide a degree of early protection to the infant against pertussis. However, a theoretical risk for the infant is that the dose of Tdap in pregnancy might not result in early protection against pertussis or could increase transplacental pertussis-specific antibodies to levels that would have a negative effect on the infant's response to immunization with pediatric DTaP or with conjugate vaccines containing tetanus toxoid or diphtheria toxoid (e.g., *Haemophilus influenzae* type b pneumococcal conjugate vaccine) (*222*). Health-care providers who choose to vaccinate pregnant women with Tdap are encouraged to report such administration to the manufacturers' pregnancy registry.

Postpartum Tdap

In 2004, a reported 99% of live births in the United States occurred in a hospital. Of out-of-hospital live births, 27% occurred at a free-standing birthing center and 65% at a residence (*394*). In these settings, attendants can implement protocols to ensure that postpartum women who have not received Tdap previously receive it before discharge. They also can encourage previously unvaccinated adults and adolescents who anticipate contact with an infant to receive Tdap. Tdap vaccination of the women and potential contacts before discharge rather than at a follow-up visit has the advantage of decreasing the time when new mothers and contacts of the newborns could acquire and transmit pertussis to the infants (*1*,*2*). Standing orders for postpartum Tdap vaccination before discharge have successfully raised vaccination rates to more than 80% of eligible women (*396*). Although obtaining a history of the most recent Td vaccination was anticipated to be a barrier to postpartum vaccination with Tdap, in practice it was not identified as a barrier (*395*,*396*).

Vaccination of parents and household contacts of premature infants has been advocated to ensure that such persons receive Tdap (*397*). Premature and low birth weight infants are at increased risk for severe and complicated pertussis. The case-fatality rate for pertussis is increased compared with term infants, and premature infants might respond less well than term infants to initial doses of DTaP vaccine because of comorbidities or treatments (e.g., dexamethasone) (*47*,*53*, *398–403*).

Parents should be reminded of other measures to protect infants from pertussis. To the extent feasible, parents can limit infant exposures to persons who have respiratory illness until they are determined to be noninfectious (*99*,*219*,*321*). When pertussis exposure occurs, antimicrobial prophylaxis of exposed contacts can be effective in preventing transmission of pertussis (*42*,*99*,*404*,*405*). Ensuring that infants begin the pediatric DTaP vaccination series at the recommended chronologic age of 6–8 weeks is critical to protection and reducing the severity of pertussis (*8*,*45*,*397*,*406*). Administration of 2 or 3 doses of pediatric DTP or DTaP can prevent hospitalization for pertussis and its complications (*5*,*8*,*407–409*).

Recommendations

Recommendations for routine use of Td and Tdap among women of childbearing age who might become pregnant have been published previously (*1*,*2*) and have been summarized (Table 2). Women are encouraged to receive a single dose of Tdap either as ADACEL® (adults and adolescents aged 11–64 years) or as BOOSTRIX® (adolescents aged 11–18 years) before conception (e.g., during routine wellness visits) if they have not already received Tdap. Recommendations for adults and adolescents who anticipate or have household contact with an infant aged <12 months also have been published previously (*1*,*2*) and summarized (Table 2). The dose of Tdap will provide active booster immunization against tetanus, diphtheria, and pertussis and will replace the next dose of Td according to routine recommendations. A single preconception dose of Tdap will prevent pertussis, reduce morbidity associated with pertussis, and might prevent exposing persons at increased risk for pertussis and its complications, including infants. The risk for pertussis death and severe pertussis is highest among infants in the first months of life and remains elevated until an infant has received 1–2 doses of pediatric DTaP (*8*,*45*,*47*).

The following sections present recommendations for use of Td and Tdap among pregnant and postpartum women,

including routine vaccination, contraindications, precautions, and special situations. As with most inactivated vaccines and toxoids, pregnancy is not a contraindication for use of Tdap. Although the safety and immunogenicity of Tdap is expected to be similar in pregnant and nonpregnant women, few data on the safety of Tdap for women, fetuses, and pregnancy outcomes are available, and no information is available on the immunogenicity of Tdap in pregnant women. Vaccinating pregnant women with a single dose of Tdap might provide a degree of protection against pertussis to the infant in early life through transplacental maternal antibody, but evidence supporting this hypothesis is lacking. A concern is the unknown effect of potential interference by maternal antibody on the ability of the infant to mount an adequate immune response when the infant receives pediatric DTaP or conjugate vaccines containing tetanus toxoid or diphtheria toxoid.

In special situations, administration of Tdap during pregnancy might be warranted for pregnant women who were not vaccinated previously with Tdap. Health-care providers who choose to administer Tdap to pregnant women should discuss with the women the potential risks and benefits of immunization including the lack of data on Tdap administered during pregnancy or its unknown effects on active immunization of their infant. The following recommendations are intended to provide guidance to clinicians until additional information is available.

1. Routine Tdap Vaccination

1-A. Recommendations for Use of Postpartum Tdap

For women who have not received Tdap previously (including women who are breastfeeding), Tdap is recommended as soon as feasible in the immediate postpartum period to protect the women from pertussis and reduce the risk for exposing their infants to pertussis. The postpartum Tdap should be administered before discharge from the hospital or birthing center. If Tdap cannot be administered at or before discharge, the dose should be administered as soon as feasible thereafter. Elevated levels of pertussis antibodies in the mother are likely within 1–2 weeks after vaccination.

Although an interval of 10 years since receipt of the most recent Td dose is recommended for the next routine Td booster, to reduce the risk for women exposing their infants to pertussis, an interval as short as 2 years between the most recent Td and administering Tdap[¶] is suggested for postpartum women. The safety of such an interval is supported by three Canadian studies among adolescents and by a study among nonpregnant adult health-care personnel (*215,358–360*), an interval shorter than 2 years may be used (see Postpartum Tdap When <2 Years Have Elapsed Since the Most Recent Td). In this setting, the benefit of Tdap to protect against pertussis typically outweighs the risk for local and systemic reactions after vaccination. Routine postpartum Tdap recommendations are supported by evidence from randomized controlled clinical trials, nonrandomized open-label trials and a retrospective survey, observational studies, and expert opinion (Box 2).

[¶] An interval of 5 years since the most recent tetanus and diphtheria toxoids–containing vaccine is encouraged for routine vaccination of adolescents who are not pregnant (*2*).

1-B. Dosage and Administration

The dose of Tdap or, if indicated, the dose of Td 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 typically 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. Certain 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 pregnant and postpartum women will receive recommended vaccinations (*23*).

1-D. Interchangeable Use of Tdap Vaccines

A single dose of ADACEL® may be used for adults aged 19–64 years, and a single dose of either ADACEL® or BOOSTRIX® may be used for adolescents aged 11–18 years, regardless of the type or manufacturer of pediatric DTP or pediatric DTaP used for childhood vaccination.

1-E. Preventing Adverse Events

Attention to proper immunization technique, including use of an appropriate needle length and standard routes of administration (i.e., IM for Td and Tdap) might minimize the risk for adverse events. Guidance for administration of vaccines is available (*23*).

Syncope can occur after vaccination and might be more common among young adults and adolescents than among other age groups. Syncope rarely has resulted in serious injury (*23,410–412*). Vaccine providers should strongly consider observing patients for 15 minutes after they are vaccinated (*23,412*). If syncope occurs, patients should be observed until symptoms resolve.

BOX 2. Summary of evidence for routine adult tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccination

- Efficacy against tetanus, diphtheria, and pertussis is supported by immunogenicity results from randomized, controlled clinical trials among nonpregnant adults and adolescents.
- Safety is supported by the results of randomized, controlled clinical trials among nonpregnant adults and adolescents; limited data are available from a retrospective survey of a small group of vaccinated pregnant women.
- The safety of an interval of approximately 2 years between adult tetanus and reduced diphtheria toxoids vaccine (Td) and Tdap is supported by three nonrandomized, open-label clinical trials among children and nonpregnant adolescents and by preliminary results from a retrospective survey of vaccinated adult healthcare personnel.

1-F. Inadvertent Administration of Pediatric DTaP, BOOSTRIX® Tdap, or Purified Protein Derivative (PPD)

The potential for administration errors involving tetanus toxoid–containing vaccines (*413*) and other vaccines is well-documented (*414–416*). Pediatric DTaP and pediatric diphtheria toxoid and tetanus toxoid vaccine (DT) formulations indicated for use in children aged 6 weeks–6 years should not be administered to adults or adolescents; these vaccines can be associated with more severe local reactions than adult formulations (*350,417*). Packaging of adult and adolescent Tdap vaccines, pediatric DTaP, and purified protein derivative (PPD) might appear similar. Only one formulation of Tdap, ADACEL,® is licensed and recommended for adults aged 19–64 years. Both formulations of Tdap (BOOSTRIX® and ADACEL®) are licensed and recommended for adolescents aged 11–18 years. Providers should review product labels before administering these vaccines. If pediatric DTaP is administered inadvertently to an adult or adolescent, or if BOOSTRIX® is administered inadvertently to an adult aged ≥19 years, the dose should be counted as the Tdap dose, and the person should not receive an additional dose of Tdap. Adults or adolescents who receive PPD instead of Tdap should receive a dose of Tdap.

1-G. Record Keeping

Health-care providers who administer vaccines to adults and adolescents are required to keep permanent vaccination records of vaccines covered under the National Childhood Vaccine Injury Compensation Act. ACIP has recommended that this practice include all vaccines (*23*). Encouraging adults and adolescents to maintain a personal vaccination record is important to minimize administration of unnecessary vaccinations. Ideally, the personal vaccine record will document the type of the vaccine, manufacturer, anatomic site, route, and date of administration, and the name of the administering facility (*23*).

2. Contraindications and Precautions for Use of Td and Tdap

2-A. Contraindications

The following conditions are contraindications for Td or Tdap:

- Td and Tdap are 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 any Td or Tdap vaccines should be referred to an allergist to determine whether they have a specific allergy to tetanus toxoid and whether they can safely receive TT vaccination.
- Tdap (but not Td) is contraindicated for adults and 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 Td or Tdap

A precaution is a condition in a vaccine recipient that might increase the risk for a serious adverse reaction (*23*). In the following situations, vaccine providers should evaluate the risks and benefits of administering Td or Tdap:

- Guillain-Barré syndrome with onset ≤6 weeks after previous dose of a tetanus toxoid–containing vaccine;
- moderate or severe acute illness with or without fever until the acute illness resolves;
- history of an Arthus reaction (see Important Local Reactions) after a previous dose of a tetanus toxoid–containing and/or diphtheria toxoid–containing vaccine, including MCV4. The vaccine provider should review the patient's medical history to verify the diagnosis of Arthus reaction and consult with an allergist or immunologist. If an Arthus reaction was likely, vaccine providers should consider deferring Td or Tdap vaccination until at least

10 years have elapsed since the last tetanus toxoid– 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 Td or Tdap might leave the adult or adolescent woman and her neonate unprotected against tetanus. In this situation, if the last tetanus toxoid–containing vaccine was administered ≥10 years previously, vaccine providers may obtain a serum tetanus antitoxin level to evaluate the need for tetanus vaccination (tetanus antitoxin levels ≥0.1 IU/mL by ELISA are considered protective) or administer TT; and

- Tdap (but not Td) for adults aged 19–64 years with unstable neurologic conditions (e.g., cerebrovascular events or acute encephalopathic conditions) (*1*) and adolescents aged 11–18 years with any progressive neurologic disorder including progressive encephalopathy, or uncontrolled epilepsy (until the condition has stabilized) (*2*) (see Neurologic and Systemic Events).

2-C. Conditions Under Which Td or Tdap May Be Administered If Otherwise Indicated

The following conditions are not contraindications or precautions for Td or Tdap:

- stable neurologic disorder, including well-controlled seizures, a history of a seizure disorder that has resolved, or cerebral palsy;
- brachial neuritis after a previous dose of tetanus toxoid– or diphtheria toxoid– containing vaccine;
- a history of an extensive limb swelling reaction that was not an Arthus hypersensitivity reaction after pediatric DTP or DTaP or after Td;
- immunosuppression, including persons with human immunodeficiency virus (HIV) (the immunogenicity of Tdap in persons with immunosuppression has not been studied and could be suboptimal);
- breastfeeding;
- intercurrent minor illness; and
- use of antimicrobials.

Latex allergies other than anaphylactic allergies (e.g., a history of contact allergy to latex gloves) are not a contraindication or precaution to Tdap (*417*). The tip and rubber plunger of the BOOSTRIX® needleless syringe contain latex. The BOOSTRIX® single dose vial and ADACEL® preparations contain no latex. Certain Td products contain latex. The package inserts should be consulted for details (Table 1).

3. Special Situations

3-A. Deferring Td during Pregnancy to Substitute Tdap in the Immediate Postpartum Period

Tetanus and diphtheria booster vaccination is recommended for pregnant women if ≥10 years have elapsed since the previous Td vaccination (*1,2*). To add protection against pertussis, health-care providers may defer the Td vaccination during pregnancy to substitute Tdap as soon as feasible postpartum if the woman is likely to have sufficient tetanus and diphtheria protection until delivery.

Sufficient tetanus protection is likely if:

- a pregnant woman aged <31 years has received a complete childhood series of immunization (4–5 doses of pediatric DTP, DTaP, and DT) and ≥1 Td booster dose during adolescence or as an adult (a primary series consisting of 3 doses of Td (or TT) administered during adolescence or as an adult substitutes for the childhood series of immunization),**
- a pregnant woman aged ≥31 years has received a complete childhood series of immunization (4–5 doses of pediatric DTP, DTaP, and/or DT) and ≥2 Td booster doses,
- a primary series consisting of 3 doses of Td (or TT) was administered during adolescence or as an adult substitute for the childhood series of immunization,** or
- a pregnant woman has a protective level of serum tetanus antitoxin (≥0.1 IU/mL by ELISA).

A woman should receive Td during pregnancy if she

- does not have sufficient tetanus immunity to protect against maternal and neonatal tetanus, or
- requires urgent booster protection against diphtheria (e.g., for travel to an area in which diphtheria is endemic††).

Alternatively, health-care providers may choose to administer Tdap instead of Td during pregnancy (see Considerations for Use of Tdap in Pregnant Women in Special Situations).

3-B. Postpartum Tdap When <2 Years Have Elapsed Since the Most Recent Td

Certain postpartum women (e.g., those who have received Td or TT within 2 years of the immediate postpartum period) might benefit from Tdap for pertussis protection. Few subjects have been evaluated to determine the risk for adverse local and systemic reactions after Tdap at intervals <2 years

** Women who have had a 3-dose series as TT instead of Td will likely have protection against tetanus but might not be protected against diphtheria. A protective titer of diphtheria antitoxin is ≥0.1 IU/mL by ELISA.

†† A list of areas in which diphtheria is endemic is available at www.cdc.gov/travel/diseases/dtp.htm.

since the most recent Td (or other tetanus toxoid– or diphtheria toxoid–containing vaccine) (*215*). After obtaining a history to exclude women with moderate or severe adverse reactions following previous doses, health-care providers may choose to administer Tdap in postpartum women who received tetanus toxoid– or diphtheria toxoid–containing vaccine[§§] <2 years previously (see Precautions and Reasons to Defer Td and Tdap).

Health-care providers should encourage vaccination of household and child care provider contacts of infants aged <12 months for protection against pertussis, according to current recommendations (Table 2) (*1,2*). Women should be advised of the symptoms of pertussis and the effectiveness of early antimicrobial prophylaxis for themselves, their infant, and members of their household, if pertussis is suspected (*127*).

3-C. History of Pertussis

Postpartum women who have a history of pertussis should receive Tdap according to the routine recommendation (see Recommendations for Use of Postpartum Tdap). This practice is preferred because the duration of protection induced by pertussis is unknown (waning might begin as early as 5–10 years after infection) (*4*), and a diagnosis of pertussis often is not reliably confirmed. Administering pertussis vaccine to persons with a history of pertussis presents no theoretical safety concern.

3-D. Considerations for Use of Tdap in Pregnant Women in Special Situations

ACIP recommends administration of Td for booster protection against tetanus and diphtheria in pregnant women. However, health-care providers may choose to administer Tdap instead of Td during pregnancy to add protection against pertussis in special situations. In these situations, the pregnant woman should be informed of the lack of data confirming the safety and immunogenicity of Tdap in pregnant women, the unknown potential for early protection of the infant against pertussis by transplacental maternal antibodies, and the possible adverse effect of maternal antibodies on the ability of the infant to mount an adequate immune response to antigens in pediatric DTaP or conjugate vaccines containing tetanus toxoid or diphtheria toxoid.

Special situations in which Tdap might be used might include instances when

- a pregnant woman has insufficient tetanus or diphtheria protection until delivery, or
- a pregnant woman is at increased risk for pertussis.

Persons at increased risk for pertussis might include adolescents aged 11–18 years, health-care personnel, and women employed in institutions in which a pertussis outbreak is occurring or living in a community in which a pertussis outbreak is occurring.

Adverse pregnancy outcomes are most common in the first trimester (*418*). To minimize the perception of an association of vaccine with an adverse outcome, vaccinating with tetanus toxoid–containing vaccines during the second or third trimester is preferred.

Because information on the use of Tdap in pregnant women is lacking, both manufacturers of Tdap have established a pregnancy registry. Health-care providers are encouraged to report vaccination of pregnant women with Tdap, regardless of trimester, to the appropriate manufacturer's registry. For ADACEL,® vaccination should be reported to sanofi pasteur, telephone 1-800-822-2463 (1-800-VACCINE), and for BOOSTRIX,® vaccination should be reported to GlaxoSmithKline Biologicals, telephone 1-888-825-5249.

3-E. Tetanus Prophylaxis for 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 11) (*357*). A Td booster might be recommended for wound management in pregnant women if 5 years or more have elapsed since the previous Td (*1,2*). Health-care providers may choose to substitute Tdap for Td during pregnancy in these women (see Considerations for Use of Tdap in Pregnant Women in Special Situations). For pregnant women vaccinated previously with Tdap, Td should be used if a tetanus toxoid–containing vaccine is indicated for wound care. Pregnant women who have completed the 3-dose primary tetanus vaccination series and have received a tetanus toxoid–containing vaccine within the preceding 5 years are protected against tetanus and do not require a tetanus toxoid–containing vaccine as part of wound management.

To avoid unnecessary vaccination, health-care providers should attempt to determine whether the woman has completed the 3-dose primary tetanus vaccination series. Pregnant women with unknown or uncertain previous tetanus vaccination histories should be considered to have had no prior tetanus toxoid–containing vaccine and they should complete a 3-dose primary series of immunization to prevent maternal and neonatal tetanus (see Pregnant Women with Unknown

[§§] Tetanus toxoid– and/or diphtheria toxoid–containing vaccines include pediatric DTP, DTaP, DT, other pediatric combination vaccines including any of these components (e.g., pediatric DTaP–inactivated poliovirus vaccine–Hep B and pediatric DTaP–*Haemophilus influenzae* type b), and adult and adolescent Td, Tdap, and TT). MCV4 contains diphtheria toxoid but not tetanus toxoid (*2*).

TABLE 11. Guide to tetanus prophylaxis in routine wound management among pregnant women aged 11–64 years

No. doses of adsorbed, tetanus toxoid–containing vaccine	Clean, minor wound		All other wounds*	
	Td†	TIG	Td	TIG
Unknown number or <3 doses	Yes	No	Yes	Yes
≥3 doses				
≥10 yrs since most recent dose	Yes	No	Yes	No
5–9 yrs since most recent dose	No	No	Yes	No
<5 yrs since most recent dose	No	No	No	No

* For example, wounds contaminated with dirt, feces, soil, and saliva; puncture wounds; avulsions; and wounds resulting from missiles, crushing, burns, and frostbite.

† Adult tetanus and diphtheria toxoids vaccine (Td) is preferred to tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine (Tdap) for pregnant women who have never received Tdap. Tdap is preferred to Td for nonpregnant adults and adolescents who have never received Tdap. In special situations, use of Tdap during pregnancy might be warranted. Health-care providers who choose to administer Tdap during pregnancy should discuss with the women the lack of evidence of safety and effectiveness for the mother, fetus, pregnancy outcome, and the lack of evidence of the effectiveness of transplacental maternal antibodies to provide early pertussis protection to the infant. In addition, no study has examined the effectiveness of transplacental pertussis antibodies induced by Tdap on the adequacy of the infant immune response to pediatric DTaP and conjugate vaccines containing tetanus toxoid or diphtheria toxoid. Because adverse outcomes of pregnancy are most common in the first trimester, vaccinating pregnant women with Tdap during the second or third trimester is preferred to minimize the perception of an association of Tdap with an adverse outcome, unless vaccine is needed urgently. Td is preferred to tetanus toxoid vaccine (TT) for adults who received Tdap previously or who require tetanus protection when Tdap is not available. If TT and tetanus immune globulin (TIG) are both used, tetanus toxoid adsorbed rather than tetanus toxoid (fluid vaccine) should be administered.

or Incomplete Tetanus Vaccination). Pregnant women who have not completed the primary series might require tetanus toxoid and passive vaccination with TIG at the time of wound management (Table 11). When both TIG and a tetanus toxoid–containing vaccine are indicated, each product should be administered using a separate syringe at different anatomic sites. Pregnant women with a history of Arthus reaction after a previous dose of a tetanus toxoid–containing vaccine should not receive a tetanus toxoid–containing vaccine until 10 years or more after the most recent dose, even if they have a wound that is neither clean nor minor. If the Arthus reaction was associated with a vaccine that contained diphtheria toxoid without tetanus toxoid (e.g., MCV4), deferring Td or Tdap might leave the pregnant women inadequately protected against tetanus, and TT should be administered (see Precautions and Reasons to Defer Td or Tdap). In all circumstances, the decision to administer TIG is based on the primary vaccination history for tetanus (Table 11).

3-F. Pregnant Women with Unknown or Incomplete Tetanus Vaccination

Pregnant women who never have been vaccinated against tetanus (i.e., have received no dose of pediatric DTP, DTaP, or DT or of adult Td or TT) should receive a series of three vaccinations containing tetanus and diphtheria toxoids starting during pregnancy to ensure protection against maternal and neonatal tetanus. A primary series consists of a first dose administered as soon as feasible, a second dose at least 4 weeks later, and a third dose 6 calendar months after the second dose. If feasible, pregnant women who have received fewer than 3 doses of tetanus toxoid–containing vaccine should complete the 3-dose primary series during pregnancy. Td is preferred for the doses during pregnancy. Health-care providers may choose to substitute a single dose of Tdap for 1 dose of Td during pregnancy and complete the series with Td. In such cases, the women should be informed of the lack of data on safety, immunogenicity, and pregnancy outcomes for pregnant women who receive Tdap (see Considerations for Use of Tdap in Pregnant Women in Special Situations).

Reporting 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. A table of reportable events following vaccination is available from VAERS at 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, 1-800-822-7967. To promote better timeliness and quality of safety data, providers are encouraged to report electronically by using web-based reporting (https://secure.vaers.orgVaersDataEntryintro.htm).

Vaccine Injury Compensation Program

VICP is a system established by the National Childhood Vaccine Injury Act of 1986 that enables compensation to be paid on behalf of a person thought to have been injured or 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, 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 regarding the program is available at http://www.hrsa.gov/vaccinecompensation or by telephone, 1-800-338-2382.

Areas for Future Research

Interest in vaccinating pregnant women to prevent infant pertussis declined in the late 1940s when whole-cell vaccine trials demonstrated pertussis-specific antibodies in as many as 75% of infants vaccinated starting at birth or in the first few months of life (*38,186,188,218,237*) and infant and childhood vaccination was adopted as the primary national strategy for protection against childhood diseases (*419,420*). Aside from initiatives to eliminate neonatal tetanus and more recently to prevent influenza during pregnancy, limited attention has been focused on vaccinating pregnant women as a strategy to prevent disease in the women and their infants during the first few months of life (*290,421–430*). A major barrier to conducting vaccine trials in pregnant women is the potential liability from expected adverse pregnancy outcomes that might be related temporally to vaccination (*388,431,432)*. However, the high morbidity and mortality of certain infections that affect pregnant women and neonates warrant renewed consideration of the strategy of vaccinating pregnant women.

Ensuring the safety of vaccination for mother and fetus and for pregnancy outcomes is a public health priority. In addition, important considerations include understanding whether a degree of protection might be achieved for the mother and for her newborn by vaccinating during pregnancy, whether maternal vaccination would be required with each pregnancy to achieve these benefits (if any), and whether change in the levels of transplacental maternal antibody might affect infant responses to routine vaccination (*159,222,224,228*). Because few vaccines are currently recommended for pregnant women (e.g., Td and influenza), the effects of the transplacental maternal antibodies on the subsequent infant responses to routine vaccination with the same antigens are not known for most vaccines. Change in the levels of transplacental antibody can affect infant susceptibility to disease at a population level. For example, a decrease over time in the level of transplacental maternal antibody from women who were immunized with measles vaccine during childhood (rather than by measles disease) resulted in susceptibility to measles among their infants at an earlier age, and to the decision to recommend infant measles vaccination at age 12 months rather than age 15–18 months in the United States (*228,433,434*).

Major gaps exist in the knowledge of how best to prevent pertussis in early infancy. These include 1) the safety of pertussis vaccines for pregnant women, their fetuses, and pregnancy outcomes; 2) the immunogenicity of acellular pertussis vaccines in pregnant women and transplacental maternal antibodies with respect to the timing of immunization during pregnancy; 3) the degree and duration of protection against pertussis in early infancy through transplacental maternal antibodies; and 4) the effects of transplacental maternal antibodies (induced by pertussis, DTP, DTaP, and/or Tdap) on the infant responses to active immunization with pediatric DTaP and conjugate vaccines containing tetanus toxoid or diphtheria toxoid (*159,222,234,235,435*). To understand the range of options for protecting women and infants from pertussis, studies are needed to determine the safety and any benefits of accelerated infant pertussis vaccination schedules or dosing (e.g., pertussis vaccination starting at birth or employing acellular vaccines that do not contain diphtheria toxoid and tetanus toxoid) (*221,436,437*). Alternative infant vaccination strategies examined independently or in conjunction with vaccinating pregnant women will determine the most effective and practical approaches to reduce the morbidity and mortality of pertussis.

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Appendix A

Summary of ACIP Recommendations for Prevention of Pertussis, Tetanus and Diphtheria Among Pregnant and Postpartum Women and Their Infants

Use of Td or Tdap in Women Who Have Not Received Tdap Previously

- **Routine postpartum Tdap.** Pregnant women (including women who are breastfeeding) who have not received a dose of Tdap previously should receive Tdap after delivery and before discharge from the hospital or birthing center if 2 years or more have elapsed since the most recent administration of Td; shorter intervals may be used (see Special Situations). If Tdap cannot be administered before discharge, it should be administered as soon as feasible thereafter. The dose of Tdap substitutes for the next decennial dose of Td.
- **Simultaneous administration.** Tdap should be administered with other vaccines that are indicated. Each vaccine should be administered using a separate syringe at a different anatomic site.

Contraindications to Administration of Td and Tdap

The following conditions are contraindications to administration of Td and Tdap:

- a history of serious allergic reaction (i.e., anaphylaxis) to any component of the vaccine, or
- for Tdap (but not Td), 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.

Precautions and Reasons to Defer Administration of Td or Tdap

The following conditions are reasons to defer administration of Td or Tdap:

- Guillain-Barré syndrome with onset 6 weeks or less after a previous dose of tetanus toxoid–containing vaccine;
- moderate or severe acute illness;
- a history of an Arthus reaction to tetanus toxoid– and/or diphtheria toxoid–containing vaccine less than 10 years previously;
- for adults, unstable neurologic conditions (e.g., cerebrovascular events or acute encephalopathic conditions); or
- for adolescents, any progressive neurologic disorder, including progressive encephalopathy or uncontrolled epilepsy (until the condition has stabilized).

Special Situations

Deferring Td During Pregnancy to Substitute Tdap in the Immediate Postpartum Period

ACIP recommends administration of Td for booster vaccination during pregnancy if 10 years or more have elapsed since a previous Td booster. To add protection against pertussis, health-care providers may defer the Td vaccination during pregnancy and substitute Tdap as soon as feasible after delivery if the woman is likely to have sufficient tetanus and diphtheria protection until delivery. Sufficient tetanus protection is likely if:

- a pregnant woman aged <31 years has received a complete childhood series of immunization (4–5 doses of pediatric DTP, DTaP, and/or DT) and ≥1 Td booster dose during adolescence or as an adult (a primary series consisting of 3 doses of Td (or TT) administered during adolescence or as an adult substitutes for the childhood series of immunization),*
- a pregnant woman aged ≥31 years has received a complete childhood series of immunization (4–5 doses of pediatric DTP, DTaP, and/or DT) and ≥2 Td booster doses,
- a primary series consisting of 3 doses of Td (or TT) was administered during adolescence or as an adult substitute for the childhood series of immunization,* or
- a pregnant woman has a protective level of serum tetanus antitoxin (≥0.1 IU/mL by ELISA).

A woman should receive Td during pregnancy if she

- does not have sufficient tetanus immunity to protect against maternal and neonatal tetanus, or
- requires booster protection against diphtheria (e.g., for travel to an area in which diphtheria is endemic†).

* Women who have had a 3-dose series as TT instead of Td will likely have protection against tetanus but might not be protected against diphtheria. A protective titer of diphtheria antitoxin is ≥0.1 IU/mL by ELISA.

† A list of areas in which diphtheria is endemic is available at www.cdc.gov/travel/diseases/dtp.htm.

Alternatively, health-care providers may choose to administer Tdap instead of Td during pregnancy (see Considerations for Use of Tdap in Pregnant Women in Special Situations).

Postpartum Tdap When <2 Years Have Elapsed Since the Most Recent Dose of Td

Health-care providers should obtain a history of adverse reaction after previous doses of vaccines containing tetanus and diphtheria toxoids. Limited information is available concerning the risk for local and systemic reactions after Tdap at intervals of <2 years. Providers may choose to administer Tdap to these women postpartum for protection against pertussis after excluding a history of moderate to severe adverse reactions following previous tetanus and diphtheria-toxoids–containing vaccines.

Health-care providers should encourage vaccination of household and child care provider contacts of infants aged <12 months. Women should be advised of the symptoms of pertussis and the effectiveness of early antimicrobial prophylaxis, if pertussis is suspected.

Considerations for Use of Tdap in Pregnant Women in Special Situations

ACIP recommends that Td be administered when booster protection is indicated during pregnancy. Health-care providers may choose to administer Tdap instead of Td during pregnancy to add protection against pertussis in situations when Td cannot be delayed until delivery or when the risk for pertussis is increased. In such cases, the women should be informed of the lack of data on safety, immunogenicity, and pregnancy outcomes for pregnant women who receive Tdap. Whether administration of Tdap to pregnant women results in protection of the infant against pertussis through transplacental maternal antibodies is unknown. Maternal antibodies might interfere with the infant's immune response to infant doses of DTaP or conjugate vaccines containing tetanus toxoid or diphtheria toxoid.

If Tdap is administered, the second or third trimester is preferred unless protection is needed urgently. Providers are encouraged to report Tdap administrations regardless of trimester to the appropriate manufacturers' pregnancy registry: for ADACEL,® to sanofi pasteur, telephone 1-800-822-2463 (1-800-VACCINE) and for BOOSTRIX,® to GlaxoSmithKline Biologicals, telephone 1-888-825-5249.

Tetanus Prophylaxis for Wound Management

ACIP recommends administration of a Td booster for wound management in pregnant women in certain situations if ≥5 years have elapsed since the previous Td. Health-care providers may choose to administer Tdap instead of Td during pregnancy to add protection against pertussis in these situations. In such cases, the women should be informed of the lack of data on safety, immunogenicity, and pregnancy outcomes for pregnant women who receive Tdap (see Considerations for Use of Tdap in Pregnant Women in Special Situations).

Pregnant Women with Unknown or Incomplete Vaccination

Pregnant women who have not received 3 doses of a vaccine containing tetanus and diphtheria toxoids should complete a series of three vaccinations, including 2 doses of Td during pregnancy, to ensure protection against maternal and neonatal tetanus. The preferred schedule in pregnant women is 2 doses of Td separated by 4 weeks and 1 dose of Tdap administered 6 months after the second dose (postpartum). Health-care providers may choose to substitute a single dose of Tdap for a dose of Td during pregnancy. In such cases, the women should be informed of the lack of data on safety, immunogenicity, and pregnancy outcomes for pregnant women who receive Tdap (see Considerations for Use of Tdap in Pregnant Women in Special Situations).

Reporting Adverse Events after Vaccination

All clinically significant adverse events should be reported to VAERS even if a causal relation to vaccination is uncertain. VAERS reporting forms and information are available at http://www.vaers.hhs.gov or by telephone, 1-800-822-7967. Providers are encouraged to report adverse events electronically at https://secure.vaers.org/VaersDataEntryintro.htm.

Appendix B

Abbreviations Used in This Report

ACIP	Advisory Committee on Immunization Practices
Anti-FHA	Antibody directed against filamentous hemagglutinin
Anti-FIM	Antibody directed against fimbrial proteins
Anti-PRN	Antibody directed against pertactin
Anti-PT	Antibody directed against pertussis toxin
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
ELISA	Enzyme-linked immunoabsorbant assay
FDA	Food and Drug Administration
FHA	filamentous hemagglutinin
FIM	Fimbriae
GMC	geometric mean antibody concentration
Hep B	Hepatitis B vaccine
Hib	*Haemophilus influenzae* type b
IIS	Immunization Information Systems
IPV	Inactivated poliovirus vaccine
IM	intramuscularly
IOM	Institute of Medicine
IU	international units
Lf	limit of flocculation unit
MCV4	Quadrivalent meningococcal conjugate vaccine
mL	Milliliter
NNDSS	National Notifiable Disease surveillance System
PCR	polymerase chain reaction
PRN	pertactin, 69kDa protein
PPD	tuberculin purified protein derivative
PT	pertussis toxin, lymphocytosis promoting factor
Tdap	adult tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine
Td	adult tetanus and reduced 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
WHO	World Health Organization

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