Pertussis

Pertussis, or whooping cough, is an acute infectious disease caused by the bacterium *Bordetella pertussis*. Outbreaks of pertussis were first described in the 16th century, and the organism was first isolated in 1906.

In the 20th century, pertussis was one of the most common childhood diseases and a major cause of childhood mortality in the United States. Before the availability of pertussis vaccine in the 1940s, more than 200,000 cases of pertussis were reported annually. Since widespread use of the vaccine began, incidence has decreased more than 80% compared with the prevaccine era.

Pertussis remains a major health problem among children in developing countries, with an estimated 285,000 deaths resulting from the disease in 2001.

Pertussis

- Highly contagious respiratory infection caused by *Bordetella pertussis*
- Outbreaks first described in 16th century
- *Bordetella pertussis* isolated in 1906
- Estimated 285,000 deaths worldwide in 2001

Bordetella pertussis

B. pertussis is a small, aerobic gram-negative rod. It is fastidious and requires special media for isolation (see Laboratory Diagnosis).

B. pertussis produces multiple antigenic and biologically active products, including pertussis toxin, filamentous hemagglutinin, agglutinogens, adenylate cyclase, pertactin, and tracheal cytotoxin. These products are responsible for the clinical features of pertussis disease, and an immune response to one or more produces immunity to subsequent clinical illness. Recent evidence suggests that immunity from *B. pertussis* infection is not permanent.

Bordetella pertussis

- Fastidious gram-negative bacteria
- Antigenic and biologically active components:
  - pertussis toxin (PT)
  - filamentous hemagglutinin (FHA)
  - agglutinogens
  - adenylate cyclase
  - pertactin
  - tracheal cytotoxin

Pathogenesis

Pertussis is primarily a toxin-mediated disease. The bacteria attach to the respiratory cilia, produce toxins that paralyze the cilia, and cause inflammation of the respiratory tract, which interferes with the clearing of pulmonary secretions. Pertussis antigens appear to allow the organism to evade host defenses, in that lymphocytosis is promoted but chemotaxis is impaired. Until recently it was thought that *B. pertussis* did not invade the tissues. However, recent studies have shown the bacteria to be present in alveolar macrophages.

Pertussis Pathogenesis

- Attachment to cilia of ciliated epithelial cells in respiratory tract
- Pertussis antigens allow evasion of host defenses (lymphocytosis promoted but impaired chemotaxis)
- Local tissue damage in respiratory tract
- Systemic disease may be toxin mediated

Clinical Features

The **incubation period** of pertussis is commonly 7–10 days, with a range of 4–21 days, and rarely may be as long as 42 days. The clinical course of the illness is divided into three stages.

Pertussis Clinical Features

- Incubation period 7-10 days (range 4-21 days)
- Insidious onset, similar to minor upper respiratory infection with nonspecific cough
- Fever usually minimal throughout course of illness

Pertussis Clinical Features

• Catarrhal stage	1-2 weeks
• Paroxysmal cough stage	1-6 weeks
• Convalescence	Weeks to months

The first stage, the **catarrhal stage**, is characterized by the insidious onset of coryza (runny nose), sneezing, low-grade fever, and a mild, occasional cough, similar to the common cold. The cough gradually becomes more severe, and after 1–2 weeks, the second, or paroxysmal stage, begins.

It is during the **paroxysmal stage** that the diagnosis of pertussis is usually suspected. Characteristically, the patient has bursts, or paroxysms, of numerous, rapid coughs, apparently due to difficulty expelling thick mucus from the tracheo-bronchial tree. At the end of the paroxysm, a long inspiratory effort is usually accompanied by a characteristic high-pitched whoop. During such an attack, the patient may become cyanotic (turn blue). Children and young infants, especially, appear very ill and distressed. Vomiting and exhaustion commonly follow the episode. The patient usually appears normal between attacks.

Paroxysmal attacks occur more frequently at night, with an average of 15 attacks per 24 hours. During the first 1 or 2 weeks of this stage, the attacks increase in frequency, remain at the same level for 2 to 3 weeks, and then gradually decrease. The paroxysmal stage usually lasts 1 to 6 weeks but may persist for up to 10 weeks. Infants younger than 6 months of age may not have the strength to have a whoop, but they do have paroxysms of coughing.

In the **convalescent stage**, recovery is gradual. The cough becomes less paroxysmal and disappears in 2 to 3 weeks. However, paroxysms often recur with subsequent respiratory infections for many months after the onset of pertussis. Fever is generally minimal throughout the course of the illness.

Pertussis Among Adolescents and Adults

- Disease often milder than in infants and children
- Infection may be asymptomatic, or may present as classic pertussis
- Adolescents and adults account for more than half of reported cases
- Older persons often source of infection for children

Older persons (i.e., **adolescents and adults**) and those partially protected by the vaccine may become infected with *B. pertussis* but often have milder disease. Pertussis infection in these persons may be asymptomatic, or present as illness ranging from a mild cough illness to classic pertussis with persistent cough (i.e., lasting more than 7 days). Inspiratory whoop is uncommon. Adolescents and adults have accounted for more than half of reported pertussis cases in recent years.

Even though the disease may be milder in older persons, those who are infected may transmit the disease to other susceptible persons, including unimmunized or underimmunized infants. Older persons are often found to have the first case in a household with multiple pertussis cases.

Pertussis Complications*

Condition	Percent reported
Pneumonia	5.2
Seizures	0.8
Encephalopathy	0.1
Hospitalization	20
Death	0.2

*Cases reported to CDC 1997-2000 (N=28,187)

Complications

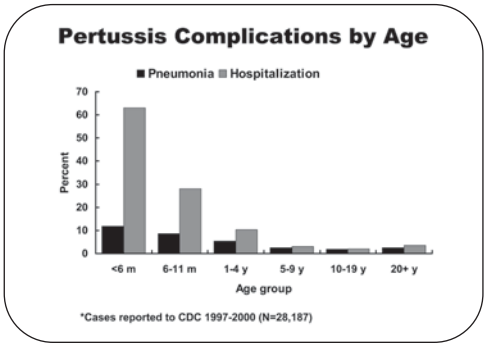
Young infants are at highest risk for acquiring pertussis-associated complications. The most common complication, and the cause of most pertussis-related deaths, is secondary

bacterial pneumonia. Data from 1997–2000 indicate that pneumonia occurred in 5.2% of all reported pertussis cases, and among 11.8% of infants younger than 6 months of age.

Neurologic complications such as seizures and encephalopathy (a diffuse disorder of the brain) may occur as a result of hypoxia (reduction of oxygen supply) from coughing, or possibly from toxin. Neurologic complications of pertussis are more common among infants. Other less serious complications of pertussis include otitis media, anorexia, and dehydration. Complications resulting from pressure effects of severe paroxysms include pneumothorax, epistaxis, subdural hematomas, hernias, and rectal prolapse.

Among persons of all ages with pertussis, 33 cases of encephalopathy and 56 pertussis-related deaths were reported during 2001–2003. Fifty-one (91%) of the deaths were among infants younger than 6 months of age, and 42 (75%) were among infants aged younger than 2 months of age.

Adolescents and adults may also develop complications of pertussis such as difficulty sleeping, urinary incontinence, pneumonia, and rib fracture.



Laboratory Diagnosis

The diagnosis of pertussis is usually based on a characteristic history and physical examination. However, laboratory tests may be useful with young infants, atypical cases, and cases modified by vaccine.

The standard and preferred laboratory test for diagnosis of pertussis is **isolation of *B. pertussis* by culture**. A positive culture for *B. pertussis* confirms the diagnosis. However, fastidious growth requirements make *B. pertussis* difficult to isolate. Isolation of the organism using direct plating is most successful during the catarrhal stage. Specimens from the posterior nasopharynx, not the throat, should be obtained using Dacron® or calcium alginate (not cotton) swabs and should be plated directly onto selective media. Success in isolating the organism declines if the patient has had prior antibiotic therapy effective against pertussis (erythromycin or trimethoprim-sulfamethoxazole), if specimen collection is delayed beyond the first 2 weeks of illness, or if the patient has been vaccinated.

Polymerase chain reaction (PCR) testing of nasopharyngeal swabs or aspirates can be a rapid, sensitive, and specific method for diagnosing pertussis. Currently, it is available only in certain laboratories; the assays vary among laboratories and are not standardized. PCR should be used in addition to culture, not as a replacement for culture, because bacterial isolates may be required for evaluation of antimicrobial resistance or for molecular typing.

Direct fluorescent antibody (DFA) testing of nasopharyngeal specimens may be useful as a screening test for pertussis. Because DFA testing of nasopharyngeal secretions has been shown in some studies to have low sensitivity and variable specificity, it should not be relied on as a criterion for laboratory confirmation.

Serologic testing has proved useful in clinical studies but is not yet standardized. Because of the lack of association between antibody levels and immunity to pertussis, results of serologic testing are difficult to interpret. For these reasons, serologic testing is not widely available. In some areas, it is used for clinical diagnosis and reporting, but in the absence of standardization, serologic test results should not be relied upon for case confirmation for the purpose of national reporting.

An elevated white blood cell count with a lymphocytosis is usually present in classical disease. The absolute lymphocyte count often reaches 20,000 or greater. However, there may be no lymphocytosis in infants and children or in persons with mild or modified cases of pertussis.

More information on the laboratory diagnosis of pertussis is available on the National Immunization Program website.

Medical Management

The medical management of pertussis cases is primarily supportive, although antibiotics are of some value. Erythromycin is the drug of choice. This therapy eradicates the organism from secretions, thereby decreasing communicability and, if initiated early, may modify the course of the illness.

An antibiotic effective against pertussis (such as azithromycin, erythromycin or trimethoprim-sulfamethoxazole) should be administered to all close contacts of persons with pertussis, regardless of age and vaccination status. Revised treatment and postexposure prophylaxis recommendations were published in December 2005 (see selected reference list). All close contacts younger than 7 years of age who have not completed the four-dose primary series should complete the series with the minimal intervals. (minimum age for first dose is 6 weeks; minimum intervals from dose 1 to 2 and from dose 2 to 3 are 4 weeks; minimum interval from dose 3 to 4 is 6 months.) Close contacts who are 4–6 years of age and who have not yet received the second booster dose (usually the fifth dose of DTaP) should be vaccinated.

Epidemiology

Occurrence
Pertussis occurs worldwide.

Reservoir
Pertussis is a human disease. No animal or insect source or vector is known to exist. Adolescents and adults are an important reservoir for *B. pertussis* and are often the source of infection for infants.

Transmission
Transmission most commonly occurs by the respiratory route through contact with respiratory droplets, or by contact with airborne droplets of respiratory secretions. Transmission occurs less frequently by contact with freshly contaminated articles of an infected person. A silent carrier state is thought to exist, but it is infrequent, transient in duration, and probably of little importance in maintaining pertussis organisms in the community.

Temporal Pattern
Pertussis has no distinct seasonal pattern, but it may increase in the summer and fall.

Communicability
Pertussis is highly communicable, as evidenced by secondary attack rates of 80% among susceptible household contacts. Persons with pertussis are most infectious during the catarrhal period and the first 2 weeks after cough onset (i.e., approximately 21 days).

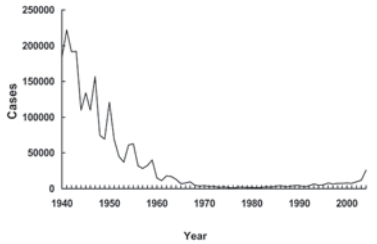
Secular Trends in the United States
Before the availability of vaccine, pertussis was a common cause of morbidity and mortality among children. During the 6-year period from 1940 through 1945, more than 1 million cases of pertussis were reported, an average of 175,000 cases per year (incidence of approximately 150 cases per 100,000 population).

Following introduction of vaccine in the 1940s, pertussis incidence gradually declined, reaching 15,000 reported cases in 1960 (~8 per 100,000 population). By 1970, annual incidence was fewer than 5,000 cases per year, and during 1980–1990, an average of 2,900 cases per year were reported (~1 per 100,000 population).

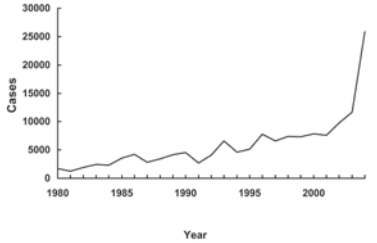
Pertussis Epidemiology

• Reservoir	Human Adolescents and adults
• Transmission	Respiratory droplets
• Communicability	Maximum in catarrhal stage Secondary attack rate up to 80%

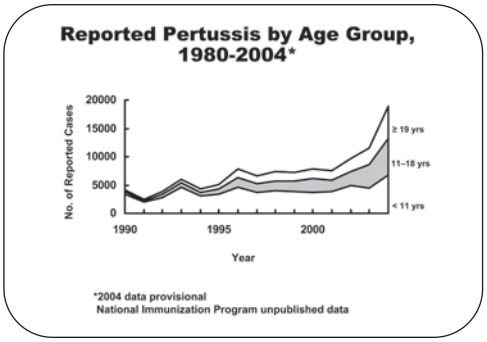
Pertussis—United States, 1940-2004



Pertussis—United States, 1980-2004



Pertussis



Pertussis incidence has been gradually increasing since the early 1980s. A total of 25,827 cases was reported in 2004, the largest number since 1959. The reasons for the increase are not clear but may be a reflection of the 3–5 year cyclicity observed with the disease.

During 2001–2003, the highest average annual pertussis incidence was among infants younger than 1 year of age (55.2 cases per 100,000 population), and particularly among children younger than 6 months of age (98.2 per 100,000 population. In 2002, 24% of all reported cases were in this age group. However, in recent years, adolescents (11–18 years of age) and adults (20 years and older) have accounted for an increasing proportion of cases. During 2001–2003, the annual incidence of pertussis among persons aged 10–19 years increased from 5.5 per 100,000 in 2001, to 6.7 in 2002, and 10.9 in 2003. In 2004, approximately 60% of cases were among persons 11 years of age and older. Increased recognition and diagnosis of pertussis in older age groups probably contributed to this increase of reported cases among adolescents and adults.

Of the 10,650 children 3 months to 4 years of age with reported pertussis during 1990–1996 and known vaccination status, 54% were not age-appropriately vaccinated with DTaP.

Pertussis Surveillance

Pertussis cases are reported to CDC via two systems. States provide information about cases of pertussis, including demographic information, through the National Electronic Transmittal System for Surveillance. More detailed information is reported to CDC through the Supplementary Pertussis Surveillance System. Although many pertussis cases are not reported, the surveillance system is useful for monitoring epidemiologic trends. For instance, although the highest incidence of pertussis occurs in infancy, the age group at greatest risk for severe illness and complications, in recent years, the surveillance system has reflected an increase in the incidence of pertussis in all age groups, most notably among adolescents and adults.

Guidelines on pertussis surveillance and outbreak control are available on the National Immunization Program website at http://www.cdc.gov/nip/publications/pertussis/guide.htm.

Case Definition

The current case definition for pertussis was developed and adopted by the Council of State and Territorial Epidemiologists (CSTE) and CDC. It defines a clinical case of pertussis as an acute cough illness lasting at least 2 weeks

with either paroxysms of coughing, inspiratory "whoop," or posttussive vomiting without other apparent cause (as reported by a health professional).

Case Classification

Probable—Meets the clinical case definition, but is not laboratory confirmed and is not epidemiologically linked to a laboratory-confirmed case.

Confirmed—A clinically compatible case that is laboratory confirmed or epidemiologically linked to a laboratory-confirmed case.

The clinical case definition above is appropriate for endemic or sporadic cases. In outbreak settings, including household exposures, a case can be defined as an acute cough illness lasting at least 2 weeks without other symptoms. See the pertussis chapter of the Manual for the Surveillance of Vaccine-Preventable Diseases (available at http://www.cdc.gov/nip/publications/surv-manual/) for more information on case classification.

Both probable and confirmed cases should be reported to the National Notifiable Diseases Surveillance System (NNDSS).

Pertussis Vaccines

Whole-Cell Pertussis Vaccine

Whole-cell pertussis vaccine is composed of a suspension of formalin-inactivated *B. pertussis* cells. It was developed in the 1930s and used widely in clinical practice by the mid-1940s.

Whole-Cell Pertussis Vaccine

- Developed in mid-1930s and combined as DTP in mid-1940s
- 70%-90% efficacy after 3 doses
- Protection for 5-10 years
- Local adverse reactions common

Based on controlled efficacy trials conducted in the 1940s and on subsequent observational efficacy studies, a primary series of four doses of whole-cell DTP vaccine was 70% to 90% effective in preventing serious pertussis disease. Protection decreased with time, resulting in little or no protection 5 to 10 years following the last dose. Local reactions such as redness, swelling, and pain at the injection site occurred following up to half of doses of whole-cell DTP vaccines. Fever and other mild systemic events were also common. More severe systemic reactions, such as convulsions and hypotonic hyporesponsive episodes occurred less frequently (one case per 1,750 doses administered). Acute encephalopathy occurred even more rarely (0–10.5 cases per million doses administered). Experts disagreed on whether whole-cell pertussis vaccine caused lasting brain damage, but they agreed that if the vaccine caused such damage, it did so only rarely. Concerns about safety led to the development of more purified (acellular) pertussis vaccines that are associated with a lower frequency of adverse reactions.

Acellular Pertussis Vaccines

- Purified "subunit" vaccines
- Pediatric formulations (DTaP) licensed for full series in 1996
- Adolescent and adult formulations (Tdap) licensed in 2005

Acellular Pertussis Vaccine

Characteristics

Acellular pertussis vaccines contain purified, inactivated components of *B. pertussis* cells. Several acellular pertussis vaccines have been developed for different age groups; these contain different pertussis components in varying concentrations. Acellular pertussis vaccines are available only as combinations with tetanus and diphtheria toxoids.

Pediatric Formulation (DTaP)

Pediatric formulations of acellular pertussis vaccines were first licensed for the fourth and fifth doses of the pertussis series in 1991, and for the primary series in 1996. Three pediatric acellular pertussis vaccines are currently available for use in the United States. All three vaccines are combined with diphtheria and tetanus toxoids as DTaP. Infanrix (GlaxoSmithKline) contains three antigens, mostly pertussis toxin (PT) and FHA. Tripedia (sanofi pasteur) contains two components, FHA and PT, in equal amounts. Daptacel (sanofi pasteur) contains five components, PT, FHA, pertacin, and fimbriae types 2 and 3. None of the available DTaP vaccines contains thimerosal as a preservative, although Infanrix and Daptacel contain 2-phenoxyethanol as a preservative. Tripedia does not contain a preservative. All three vaccines are supplied in single-dose vials or syringes.

Adolescent and Adult Formulation (Tdap)

Acellular pertussis-containing vaccines were first licensed for adolescents and adults in 2005. Two vaccines are currently available. Both vaccines are combined with tetanus toxoid and a reduced amount of diphtheria toxoid compared with pediatric DTaP (that is, similar quantities of tetanus and diphtheria toxoid to adult formulation Td). Boostrix (GlaxoSmithKline) was licensed in May 2005 and contains three pertussis antigens (PT, FHA, and pertactin) in a reduced quantity from the GlaxoSmithKline pediatric formulation. The vaccine contains aluminum hydroxide as an adjuvant and does not contain a preservative. Adacel (sanofi pasteur) was licensed in June 2005. It contains same five components as Daptacel but with a reduced quantity of PT. Adacel contains aluminum phosphate as an adjuvant and does not contain a preservative. Both vaccines are supplied as single-dose vials or syringes.

Composition* of Acellular Pertussis Vaccines

Product	PT	FHA	PERT	FIM
Daptacel	10	5	3	5
Infanrix	25	25	8	--
Tripedia	23	23	--	--
Boostrix	8	8	2.5	--
Adacel	2.5	5	3	5

*mcg per dose

Immunogenicity and Vaccine Efficacy

DTaP

Since 1991, several studies conducted in Europe and Africa have evaluated the efficacy of DTaP vaccines administered to infants. These studies varied in type and number of vaccines, design, case definition, and laboratory method

DTaP Clinical Trials

Product	Location	VE (95% CI)
Daptacel	Sweden	85% (80-89)
Tripedia	Germany	80% (59-90)
Infanrix	Italy	84% (76-89)

used to confirm the diagnosis of pertussis, so comparison among studies must be made with caution. Point estimates of vaccine efficacy ranged from 80% to 85% for vaccines currently licensed in the United States. Confidence intervals for vaccine efficacy overlap, suggesting that none of the vaccines is significantly more effective than the others. When studied, the acellular pertussis vaccine was significantly more effective than whole-cell DTP. Mild local and systemic adverse reactions and more serious adverse reactions (such as high fever, persistent crying, hypotonic hyporesponsive episodes, and seizures) occurred less frequently among infants vaccinated with acellular pertussis vaccines than among those vaccinated with whole-cell DTP.

Tdap

Adolescent and adult formulation Tdap vaccines were licensed on the basis of noninferiority of the serologic response to the various components compared with each company's pediatric DTaP formulation (Infanrix and Daptacel) among persons who had received pediatric DTaP or DTP in childhood. For both vaccines, the antibody response to a single dose of Tdap was similar to that following three doses of DTaP in infants. This type of study is known as "bridging." The new vaccines are assumed to have similar clinical efficacy as DTaP vaccine since a similar level of antibody to the components was achieved.

Vaccination Schedule and Use

DTaP

Acellular pertussis vaccine (DTaP) is recommended for all doses of the pertussis schedule. Whole-cell vaccine (DTP) is no longer available in the United States. The primary series of DTaP consists of four doses of vaccine, the first three doses given at 4- to 8-week intervals (minimum of 4 weeks), beginning at 6 weeks to 2 months of age. The fourth dose is given 6–12 months after the third to maintain adequate immunity for the ensuing preschool years. DTaP should be administered simultaneously with all other indicated vaccines.

The **fourth dose** of all brands of DTaP is licensed, and recommended by ACIP, to be administered at 15–18 months of age (17–20 months for Daptacel). However, ACIP recommends that in certain circumstances the fourth dose be given earlier than 15 months of age. The fourth dose of DTaP may be given if the child is *at least 12 months of age*, and *at least 6 months have elapsed since the third dose* of pertussis vaccine was given, and, in the opinion of the immunization provider, *the child is unlikely to return for an additional visit at 15–18 months of age*. All three of these criteria should be met in order to administer the fourth dose of DTaP at 12–14 months of age.

Routine DTaP Primary Vaccination Schedule

Dose	Age	Minimum Interval
Primary 1	2 months	---
Primary 2	4 months	4 wks
Primary 3	6 months	4 wks
Primary 4	15-18 months	6 mos

DTaP Fourth Dose

- Recommended at 15-18 months*
- May be given at 12 months of age if:
  - child is 12 months of age, and
  - 6 months since DTaP3, and
  - unlikely to return at 15-18 months

*17-20 months for Daptacel

School Entry (Fifth) Dose

- Fifth dose recommended when 4th dose given before age 4 years
- Infanrix and Tripedia licensed for 5th dose after DTaP series

Children who received all four primary doses before the fourth birthday should receive a **fifth (booster) dose of DTaP** before entering school. This booster dose is not necessary if the fourth dose in the primary series was given on or after the fourth birthday. The booster dose increases protective antibody levels and may decrease the risk of school-age children transmitting the disease to younger siblings who are not fully vaccinated. Tripedia and Infanrix are approved for the fifth dose following a series of four doses of DTaP.

For children who have started the vaccination series with whole cell-DTP, **DTaP should be substituted for any remaining doses of the pertussis series**.

Interchangeability of Different Brands of DTaP Vaccine

- Series should be completed with same brand of vaccine if possible
- Limited data suggest that "mix and match" DTaP schedules do not adversely affect safety and immunogenicity
- Use different brand of DTaP if necessary

ACIP recommends that the series be completed with the same brand of DTaP vaccine if possible. However, limited data suggest that "mix and match" DTaP schedules do not adversely affect safety and immunogenicity. If the vaccine provider does not know or have available the type of DTaP vaccine previously administered to a child, any available DTaP vaccine should be used to continue or complete the vaccination series. Unavailability of the vaccine used for earlier doses is not a reason for missing the opportunity to administer a dose of acellular pertussis vaccine for which the child is eligible.

Interruption of the recommended schedule or delayed doses does not lead to a reduction in the level of immunity reached on completion of the primary series. **There is no need to restart a series regardless of the time that has elapsed between doses.**

Tdap

Both Tdap vaccines are approved by the Food and Drug Administration for a single (booster) dose for persons who have completed the recommended childhood DTP/DTaP vaccination series. The two vaccines are approved for use in different age groups: Boostrix is approved for persons 10–18 years of age; Adacel is approved for persons 11–64 years of age.

Provisional ACIP Recommendations for Tdap Vaccines

- Adolescents 11-18 years of age should receive a single dose of Tdap instead of Td, preferably at 11-12 years of age*
- Adolescents who received a Td booster should receive a single dose of Tdap to provide protection against pertussis*

*if the person has completed the recommended childhood DTaP/DTP vaccination series

At the time of publication of this book (January 2006) ACIP recommendations for the use of Tdap vaccines for adolescents and adults have not been published. Provisional recommendations are that adolescents 11–18 years of age should receive a single dose of Tdap instead of Td, preferably at 11–12 years of age. Adolescents aged 11–18 years who received Td but not Tdap are encouraged to receive a single dose of Tdap to provide protection against pertussis. A 5-year interval between Td and Tdap is encouraged to reduce the risk of local and systemic adverse reactions. However, Tdap may be given at an interval of less than 5 years if the benefits

of protection from pertussis outweigh the risk of an adverse reaction. An interval of less than 5 years can be considered in situations of increased risk of pertussis, such as during a pertussis outbreak, or if protection is desired because of close contact with an infant younger than 12 months of age or a young child who has not been vaccinated against pertussis.

Provisional recommendations for vaccination of adults are for a single dose of Tdap to replace a single dose of Td for booster immunization against tetanus, diphtheria, and pertussis if the most recent tetanus toxoid-containing vaccine was received at least 10 years earlier. Tdap may be given at an interval shorter than 10 years since receipt of the last tetanus toxoid-containing vaccine if necessary to protect against pertussis. Adults who have or who anticipate having close contact with an infant 12 months of age or younger (e.g., parents, child care providers, healthcare providers) should receive a single dose of Tdap. An interval of 2 years or more since the most recent tetanus toxoid-containing vaccine is suggested for these adults; shorter intervals may be used. Ideally, Tdap should be given at least 1 month before beginning close contact with the infant. Women should receive a dose of Tdap in the immediate postpartum period if they have not previously received Tdap. Any woman who might become pregnant is encouraged to receive a single dose of Tdap.

Provisional ACIP Recommendations for Tdap Vaccines

- Adults should receive a single dose of Tdap to replace a single dose of Td*
- Adults who have or who anticipate having close contact with an infant 12 months of age or younger (e.g., parents, child care providers, healthcare providers) should receive a single dose of Tdap*
- Any woman who might become pregnant is encouraged to receive a single dose of Tdap

*if the person has completed the recommended childhood DTaP/DTP vaccination series

Tdap vaccine may be given at the same visit, or any time before or after any other vaccine.

Immunity following pertussis is not permanent. Persons with a history of pertussis should receive a single dose of Tdap if otherwise indicated.

All adolescents and adults should have documentation of having received a primary series of at least three doses of tetanus and diphtheria toxoids during their lifetime. A person without such documentation should receive a series of three doses of tetanus and diphtheria-containing vaccine. One of these doses, preferably the first, should be Tdap if the person is at least 10 years of age (the minimum age approved for one of the two available Tdap products). The remaining two doses should be adult formulation Td.

No pertussis vaccine is approved for children 7–9 years of age or for persons older than 64 years. ACIP does not recommend the use of Tdap in persons in these age groups.

Combination Vaccines Containing DTaP

TriHIBit

One combination DTaP–Hib (*Haemophilus influenzae* type b) vaccine is available in the United States (TriHIBit,

TriHIBit

- DTaP-Hib combination
- Do not use for primary immunization at 2, 4, or 6 months of age
- May be used as the booster dose of the Hib series at ≥12 months of age following any Hib vaccine*

*booster dose should follow prior dose by ≥2 months

sanofi pasteur). The vaccines are provided in separate vials, and the DTaP component (Tripedia) is used to reconstitute the Hib component (ActHIB). No other brand of DTaP and Hib vaccine may be used to produce this combination (e.g., Infanrix must not be substituted for Tripedia). In addition, when supplied as TriHIBit, the DTaP and Hib components have a single lot number. Providers should generally use only the DTaP and Hib supplied together as TriHIBit. However, it is acceptable to combine Tripedia and ActHIB that have been supplied separately (i.e., not packaged as TriHIBit). In this situation, the lot numbers of both vaccines should be recorded in the child's chart.

Because of evidence of reduced immunogenicity of the Hib component when used as a combination, TriHIBit is not approved by the Food and Drug Administration for use as the primary series at 2, 4, or 6 months of age. It is approved only for the fourth dose of the DTaP and Hib series. If TriHIBit is administered as one or more doses of the primary series at 2, 4, or 6 months of age, the Hib doses should not be counted, and the child should be revaccinated as age-appropriate for Hib. The DTaP doses may be counted as valid and do not need to be repeated.

Although TriHIBit cannot be used in the primary series at 2, 4, or 6 months of age, it may be used as the booster (final) dose following a series of single-antigen Hib vaccine or combination hepatitis B–Hib vaccine (Comvax). Therefore, TriHIBit can be used if the child is 12 months of age or younger, has received at least one prior dose of Hib vaccine 2 or more months earlier, and TriHIBit will be the last dose in the Hib series. For example, TriHIBit can be used for the booster dose at 12–15 months of age in a child who has received Comvax or PedvaxHib at 2 and 4 months of age, or three prior doses of HibTiter or ActHib. TriHIBit can also be used at 15–59 months of age in a child who has received at least one prior dose of any Hib-containing vaccine. TriHIBit should not be used if the child has received no prior Hib doses.

Pediarix

In 2002, the FDA approved Pediarix (GlaxoSmithKline), the first pentavalent (5 component) combination vaccine licensed in the United States. Pediarix contains DTaP (Infanrix), hepatitis B (Engerix-B), and inactivated polio vaccines. In prelicensure studies, the proportion of children who developed a protective level of antibody and the titer of antibody itself were at least as high when the vaccine antigens were given together as Pediarix as when children received separate vaccines.

Pediarix

- DTaP – Hep B – IPV combination
- Approved for 3 doses at 2, 4 and 6 months
- Not approved for booster doses
- Licensed for children 6 weeks to 7 years of age

The minimum age for the first dose of Pediarix is 6 weeks, so it cannot be used for the birth dose of the hepatitis B series. Pediarix is approved for the first three doses of the DTaP and inactivated polio vaccine (IPV) series, which are usually given at about 2, 4, and 6 months of age; it is not approved for fourth or fifth (booster) doses of the DTaP or IPV series. However, Pediarix is approved for use through 6 years of age. A child who is behind schedule can still receive Pediarix as long as it is given for doses 1, 2, or 3 of the series, and the child is younger than 7 years of age.

A dose of Pediarix inadvertently administered as the fourth or fifth dose of the DTaP or IPV series does not need to be repeated.

Pediarix may be used interchangeably with other pertussis-containing vaccines if necessary (although ACIP prefers the use of the same brand of DTaP for all doses of the series, if possible). It can be given at 2, 4, and 6 months to infants who received a birth dose of hepatitis B vaccine (total of four doses of hepatitis B vaccine). Although not labeled for this indication by FDA, Pediarix may be used in infants whose mothers are HBsAg positive or whose HBsAg status is not known.

Pediarix

- May be used interchangeably with other pertussis-containing vaccines if necessary
- Can be given at 2, 4, and 6 months in infants who received a birth dose of hepatitis B vaccine (total of 4 doses)
- May be used in infants whose mothers are HBsAg positive or status unknown

Other DTaP Issues

Infants and children with **underlying neurologic conditions** present a unique problem, whether these conditions are fully recognized or only possible or potential. These children appear to be at increased risk for manifesting the underlying neurologic disorder within 2–3 days after vaccination. However, more prolonged manifestations or increased progression of the disorder or exacerbation of the disorder have not been recognized.

In certain circumstances, vaccination with DTaP vaccine should be delayed until the child has been evaluated, treatment initiated, and the condition stabilized. These conditions include the presence of an evolving neurologic disorder (e.g., uncontrolled epilepsy, infantile spasms, and progressive encephalopathy), a history of seizures that has not been evaluated, or a neurologic event that occurs between doses of pertussis vaccine.

A family history of seizures or other neurologic diseases, or stable or resolved neurologic conditions (e.g., controlled idiopathic epilepsy, cerebral palsy, developmental delay) are not contraindications to pertussis vaccination. Acetaminophen or ibuprofen may be administered to these children at the time of DTaP vaccination and for 24 hours thereafter to reduce the possibility of postvaccination fever.

Pertussis Vaccine Use in Children with Underlying Neurologic Disorders

Underlying Condition	Recommendation
Prior seizure	Delay and assess*
Suspected neurologic disorder	Delay and assess*
Neurologic event between doses	Delay and assess*
Stable/resolved neurologic condition	Vaccinate

*vaccinate after treatment initiated and condition stabilized

Pertussis Vaccination of Children Who Have Recovered From Pertussis

- If documented disease, do not need additional doses of pertussis vaccine
- Satisfactory documentation of disease:
  - —recovery of *B. pertussis* on culture, or
  - —typical symptoms and clinical course when epidemiologically linked to a culture-proven case

DTaP Adverse Reactions

- Local reactions (pain, redness, or swelling at the site of injection)
- Low-grade fever
- More severe adverse reactions not common
- Local reactions more common following 4th and 5th doses

Reducing the dose of whole-cell DTP or DTaP vaccine or giving the full dose in multiple smaller doses may result in an altered immune response and inadequate protection. Furthermore, there is no evidence that the chance of a significant vaccine reaction is likely to be reduced by this practice. The use of multiple reduced doses that together equal a full immunizing dose, or the use of smaller, divided doses is not endorsed or recommended. **Any vaccination using less than the standard dose should not be counted, and the person should be revaccinated according to age**.

Children who have recovered from documented pertussis do not need additional doses of pertussis vaccine. Satisfactory documentation includes recovery of *B. pertussis* on culture or typical symptoms and clinical course when these are epidemiologically linked to a culture-confirmed case, as may occur during outbreaks. When such confirmation of diagnosis is lacking, vaccination should be completed because cough illness may be caused by other other *Bordetella* species, other bacteria, or certain viruses.

Adverse Reactions Following Vaccination

DTaP

As with all injected vaccines, administration of DTaP may cause **local reactions**, such as pain, redness, or swelling. Local reactions have been reported in 20%–40% of children after the first three doses. Local reactions appear to be more frequent after the fourth and/or fifth doses. **Mild systemic reactions** such as drowsiness, fretfulness, and low-grade fever may occur after either whole-cell DTP vaccination or DTaP vaccination. However, mild reactions following the first four doses are less common among children who receive DTaP. For instance, fever of higher than 101oF is reported in 3%–5% of DTaP recipients compared with 16% of recipients of whole-cell DTP. These reactions are self-limited and can be managed with symptomatic treatment with acetaminophen or ibuprofen. **Moderate or severe systemic events** (such as fever [105°F or higher], febrile seizures, persistent crying lasting 3 hours or longer, and hypotonic hyporesponsive episodes) have been reported after administration of DTaP but occur less frequently among children administered DTaP than among children administered whole-cell DTP. Rates of these less common reactions vary by symptom and vaccine but generally occur in fewer than 1 in 10,000 doses. See the pertussis chapter in the textbook *Vaccines* (Plotkin and Orenstein, eds., 2003) for a comprehensive review of DTaP adverse event data.

Information on adverse reactions following a full series of DTaP is also limited. Available data suggest a substantial

increase in the frequency and magnitude of local reactions after the fourth and fifth doses. For example, swelling at the site of injection occurred in 2% of patients after the first dose of Tripedia, and in 29% following the fourth dose. Increases in the frequency of fever after the fourth dose have also been reported, although the increased frequencies of other systemic reactions (e.g., fretfulness, drowsiness, or decreased appetite) have not been observed. Further details on this issue can be found in a supplemental ACIP statement published in 2000 (*MMWR* 2000;49(No RR-13):1–8).

Adverse Reactions Following the 4th and 5th DTaP Dose

- Local adverse reactions and fever increased with 4th and 5th doses of DTaP
- Reports of swelling of entire limb
- Extensive swelling after 4th dose NOT a contraindication to 5th dose

Swelling involving the entire thigh or upper arm has been reported after booster doses of certain acellular pertussis vaccines. The limb swelling may be accompanied by erythema, pain and fever. Although the swelling may interfere with walking, most children have no limitation of activity. The pathogenesis and frequency of substantial local reactions and limb swelling are not known, but these conditions appear to be self-limited and resolve without sequelae.

In the absence of a vaccine supply shortage, ACIP continues to recommend that a fifth dose of DTaP be administered before a child enters school. It is not known whether children who experience entire limb swelling after a fourth dose of DTaP are at increased risk for this reaction after the fifth dose. Because of the importance of this dose in protecting a child during school years, **ACIP recommends that a history of extensive swelling after the fourth dose should not be considered a contraindication to receipt of a fifth dose at school entry**. Parents should be informed of the increase in reactogenicity that has been reported following the fourth and fifth doses of DTaP.

Despite the increased reactogenicity of the fourth and fifth doses, DTaP remains the preferred vaccine for preventing pertussis, diphtheria, and tetanus among children because of the improved safety profile when compared with whole-cell pertussis vaccines.

Tdap

The safety of Tdap vaccines was evaluated as part of prelicensure studies. The most common adverse reaction following both brands of Tdap vaccine is a local reaction, such as pain redness or swelling at the site of injection. Vaccine recipients also reported low-grade fever and a variety of nonspecific systemic events, such as headache, fatigue and gastrointestinal symptoms. Local reactions, fever, and nonspecific systemic symptoms occurred at approximately the same rate in recipients of Tdap and the comparison group that received Td without acellular pertussis vaccine. No serious adverse events have been attributed to Tdap.

Tdap Adverse Reactions

- Local reactions (pain, redness, or swelling at the site of injection)
- Low-grade fever
- Adverse reactions occur at approximately the same rate as Td alone (without acellular pertussis vaccine)

DTaP Contraindications

- Severe allergic reaction to vaccine component or following a prior dose
- Encephalopathy not due to another identifiable cause occurring within 7 days after vaccination

DTaP Precautions*

- Moderate or severe acute illness
- Temperature ≥105°F (40.5°C) or higher within 48 hours with no other identifiable cause
- Collapse or shock-like state (hypotonic hyporesponsive episode) within 48 hours
- Persistent, inconsolable crying lasting ≥3 hours, occurring within 48 hours
- Convulsions with or without fever occurring within 3 days

*may consider use in outbreaks

Tdap Contraindications

- Severe allergic reaction to vaccine component or following a prior dose
- Encephalopathy not due to another identifiable cause occurring within 7 days after vaccination with a pertussis-containing vaccine

Tdap Precautions

- History of Guillain-Barré syndrome within 6 weeks after a previous dose of tetanus toxoid-containing vaccine
- Progressive neurological disorder until the condition has stabilized
- History of a severe local reaction (Arthus reaction) following a prior dose of a tetanus and/or diphtheria toxoid-containing vaccine
- Moderate or severe acute illness

Contraindications and Precautions to Vaccination

DTaP

Contraindications to further vaccination with DTaP are **severe allergic reaction** to a vaccine component or following prior dose of vaccine, and **encephalopathy** not due to another identifiable cause occurring within 7 days after vaccination.

Moderate or severe acute illness is a precaution to vaccination. Children with mild illness, such as otitis media or upper respiratory infection, should be vaccinated. Children for whom vaccination is deferred because of moderate or severe acute illness should be vaccinated when their condition improves.

Certain infrequent adverse reactions following pertussis vaccination are considered to be precautions for subsequent doses of pertussis vaccine. These adverse reactions are **temperature of 105°F (40.5°C) or higher** within 48 hours that is not due to another identifiable cause; **collapse or shock-like state** (hypotonic hyporesponsive episode) within 48 hours; **persistent, inconsolable crying** lasting 3 hours or longer, occurring within 48 hours; and **convulsions with or without fever** occurring within 3 days.

There may be circumstances (e.g., during a communitywide outbreak of pertussis) in which the benefit of vaccination outweighs the risk, even if one of the four precautionary adverse reactions occurred following a prior dose. In these circumstances, one or more additional doses of pertussis vaccine may be considered. DTaP should be used in these circumstances.

Tdap

Tdap is contraindicated for persons with a history of a severe allergic reaction to a vaccine component or following a prior dose of vaccine. Tdap is also contraindicated for persons with a history of encephalopathy not due to another identifiable cause occurring within 7 days after administration of a pertussis-containing vaccine.

Precautions to Tdap include a history of Guillain-Barré syndrome within 6 weeks after a previous dose of tetanus toxoid-containing vaccine, and a progressive neurologic disorder (such as uncontrolled epilepsy or progressive encephalopathy) until the condition has stabilized. Persons with a history of a severe local reaction (Arthus reaction) following a prior dose of a tetanus and/or diphtheria toxoid-containing vaccine should generally not receive Tdap or Td vaccination until at least 10 years have elapsed after the last

Td-containing vaccine. Moderate or severe acute illness is a precaution to vaccination. Persons for whom vaccination is deferred because of moderate or severe acute illness should be vaccinated when their condition improves.

As noted above, certain conditions following DTaP vaccine, such as temperature of 105° F or higher, collapse or shock-like state, persistent crying, or convulsions with or without fever are a precaution to subsequent doses of DTaP. However, occurrence of one of these adverse reactions following DTaP vaccine in childhood is not a contraindication or precaution to administration of Tdap to an adolescent or adult. A history of extensive limb swelling following DTaP is not a contraindication to Tdap vaccination. A stable neurologic disorder (such as controlled seizures or cerebral palsy), pregnancy, breastfeeding, and immunosuppression are not contraindications or precautions to administration of Tdap.

Vaccine Storage and Handling

DTaP and Tdap vaccines should be stored at 35°–46°F (2°–8°C) at all times The vaccines must never be frozen. Vaccine exposed to freezing temperature must not be administered and should be discarded. DTaP and Tdap should not be used after the expiration date printed on the box or label.

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