Pertussis (Whooping Cough)

CLINICAL MANIFESTATIONS: Pertussis begins with mild upper respiratory tract symptoms similar to the common cold (catarrhal stage) and progresses to cough, usually paroxysms of cough (paroxysmal stage), characterized by inspiratory whoop (gasping) after repeated cough on the same breath, which commonly is followed by vomiting. Fever is absent or minimal. Symptoms wane gradually over weeks to months (convalescent stage). Cough illness in immunized children and adults can range from typical to mild and unrecognized. The duration of classic pertussis is 6 to 10 weeks. Approximately half of adolescents with pertussis cough for 10 weeks or longer. Complications among adolescents and adults include syncope, weight loss, sleep disturbance, incontinence, rib fractures, and pneumonia; among adults, complications increase with age. Pertussis is most severe when it occurs during the first 6 months of life, particularly in preterm and unimmunized infants. Disease in infants younger than 6 months can be atypical with a short catarrhal stage, followed by gagging, gasping, bradycardia, or apnea (67%) as prominent early manifestations; absence of whoop; and prolonged convalescence. Sudden unexpected death can be caused by pertussis. Complications among infants include pneumonia (23%) and pulmonary hypertension as well as complications related to severe coughing spells, such as conjunctival bleeding, hernia, and severe coughing spells leading to hypoxia and complications such as seizures (2%), encephalopathy (less than 0.5%), apnea, and death. More than two thirds of infants with pertussis are hospitalized. Case-fatality rates are approximately 1% in infants younger than 2 months and less than 0.5% in infants 2 through 11 months of age. Maternal immunization during pregnancy and an infant's previous immunization reduce morbidity and mortality in young infants.

ETIOLOGY: Pertussis is caused by a fastidious, gram-negative, pleomorphic bacillus, *Bordetella pertussis*. Other causes of sporadic prolonged cough illness include *Bordetella parapertussis, Mycoplasma pneumoniae, Chlamydia trachomatis, Chlamydia pneumoniae, Bordetella bronchiseptica* (the cause of kennel cough), *Bordetella holmesii,* and certain respiratory tract viruses, particularly adenoviruses and respiratory syncytial viruses.

EPIDEMIOLOGY: Humans are the only known hosts of *B pertussis*. Transmission occurs by close contact with cases via large respiratory droplets generated by coughing or sneezing.

Cases occur year-round, typically with a late summer-autumn peak. Neither infection nor immunization provides lifelong immunity. Waning immunity, particularly when acellular pertussis vaccine is used for the entire immunization series, is predominantly responsible for increased cases reported in school-aged children, adolescents, and adults. Additionally, waning maternal immunity of mothers who have not received Tdap vaccine during that pregnancy results in low concentrations of transplacentally transmitted antibody and an increase in pertussis in very young infants. Reports of pertussis increased in the United States in recent years with notable epidemic peaks in disease; more than 48 000 cases of pertussis were reported in 2012, the highest number in over 50 years. Pertussis is highly contagious. As many as 80% of previously immunized household contacts of symptomatic infant cases are infected with *B pertussis,* with symptoms in these contacts varying from mild to classic pertussis. Siblings and adults with cough illness are important sources of pertussis infection for young infants. Infected people are most contagious during the catarrhal stage through the third week after onset of paroxysms. Factors affecting the length of communicability include age, immunization status or previous infection, and receipt of appropriate antimicrobial therapy.

The **incubation period** is 7 to 10 days, with a range of 5 to 21 days.

DIAGNOSTIC TESTS: Culture was considered the "gold standard" for laboratory diagnosis of pertussis but is not optimally sensitive, because *B pertussis* is a fastidious organism. Culture requires collection of an appropriate nasopharyngeal specimen, obtained either by aspiration or with polyester or flocked rayon swabs or calcium alginate swabs. Specimens must be placed into special transport media (such as Regan-Lowe) immediately and not allowed to dry during prompt transport to the laboratory. Culture results can be negative if taken from a previously immunized person, if antimicrobial therapy has been started, if more than 2 weeks has elapsed since cough onset, or if the specimen is not collected or handled appropriately.

Nucleic acid amplification tests (NAATs), including polymerase chain reaction (PCR) assay, now are commercially available and cleared by the FDA as standalone tests or as multiplex assays, and are the most commonly used laboratory method for detection of *B pertussis* because of greater sensitivity and more rapid turnaround time. The PCR test requires collection of an adequate nasopharyngeal specimen using a Dacron swab or nasopharyngeal wash or aspirate. Calcium alginate swabs can be inhibitory to PCR and should not be used for PCR tests. The PCR test has optimal sensitivity during the first 3 weeks of cough, is unlikely to be useful if antimicrobial therapy has been given for more than 5 days, and has lower sensitivity in previously immunized people, but still is more sensitive than culture. The Centers for Disease Control and Prevention (CDC) has released a "best practices" document to guide pertussis PCR assays (**www.cdc.gov/pertussis/clinical/diagnostic-testing/diagnosis-pcr-bestpractices.html**) as well as a video demonstrating optimal specimen collection. Some PCR assays target only a multicopy insertion gene sequence (IS 481) found in *B pertussis* as well as the less commonly encountered *B holmesii* and some strains of *B bronchiseptica*. Multiple DNA target sequences are required to distinguish among *Bordetella* species. Direct fluorescent antibody (DFA) testing no longer is recommended.

Commercial serologic tests for pertussis infection can be helpful for diagnosis, especially late in illness and in adolescents and adults in whom antibody concentrations from prior immunization have waned. Most assays are formulated as enzyme immunoassays.

However, no commercial kit is cleared by the FDA for diagnostic use, and little is understood about the clinical accuracy of these kits. In the absence of recent immunization, an elevated serum immunoglobulin (Ig) G antibody to pertussis toxin (PT) present 2 to 8 weeks after onset of cough is suggestive of recent *B pertussis* infection. For single serum specimens, an IgG anti-PT value of approximately 100 IU/mL or greater (using standard reference sera as a comparator) has been recommended. Positive paired serologic results based on the World Health Organization pertussis case definition may also be considered diagnostic. IgA and IgM assays lack adequate sensitivity and specificity and should not be used for the diagnosis of pertussis.

An increased white blood cell count attributable to absolute lymphocytosis is suggestive of pertussis in infants and young children but often is absent in older people with pertussis and can be only mildly abnormal in some young infants at the time of presentation. A markedly elevated white blood cell count is associated with a poor prognosis in young infants.

TREATMENT: Antimicrobial therapy administered during the catarrhal stage may ameliorate the disease. Antimicrobial therapy is indicated before test results are received if the clinical history is strongly suggestive of pertussis or the patient is at high risk of severe or complicated disease (eg, is an infant). A 5-day course of azithromycin is the appropriate first-line choice for treatment and for postexposure prophylaxis (PEP [see Table 3.52, p 625]).[1] After the paroxysmal cough is established, antimicrobial agents have no discernible effect on the course of illness but are recommended to limit spread of organisms to others. Resistance of *B pertussis* to macrolide antimicrobial agents has been reported, but rarely. Penicillins and first- and second-generation cephalosporins are not effective against *B pertussis*.

Azithromycin should be used with caution in people with prolonged QT interval and proarrhythmic conditions. An association between orally administered erythromycin and azithromycin with infantile hypertrophic pyloric stenosis (IHPS) has been reported,[2] but azithromycin remains the drug of choice for treatment or prophylaxis of pertussis in very young infants because the risk of developing severe pertussis and life-threatening complications outweighs the potential risk of pyloric stenosis (odds ratio, 2.9–8.3), and azithromycin has a lower odds ratio than erythromycin for pyloric stenosis. Health care providers should be alert to the possible development of pyloric stenosis in infants from birth up to 6 weeks of age who have received azithromycin or erythromycin. Cases of IHPS should be reported to MedWatch (see MedWatch, p 1026).

Trimethoprim-sulfamethoxazole is an alternative for patients older than 2 months who cannot tolerate macrolides or who are infected with a macrolide-resistant strain, but studies evaluating trimethoprim-sulfamethoxazole as treatment for pertussis are limited.

Young infants are at increased risk of respiratory failure attributable to apnea or secondary bacterial pneumonia and are at risk of cardiopulmonary failure and death from severe pulmonary hypertension. Hospitalized young infants with pertussis should be managed in a setting/facility where these complications can be recognized and managed ur-

[1]Centers for Disease Control and Prevention. Recommended antimicrobial agents for the treatment and postexposure prophylaxis of pertussis: 2005 CDC guidelines. *MMWR Recomm Rep.* 2005;54(RR–14):1–16

[2]Eberly MD, Eide MB, Thompson JL, Nylund CM. Azithromycin in early infancy and pyloric stenosis. *Pediatrics.* 2015;135(3):483–486

gently. Exchange transfusions or leukopheresis have been reported to be life-saving in infants with progressive pulmonary hypertension and markedly elevated lymphocyte counts.

Because data on the clinical effectiveness of antibiotic treatment on *B parapertussis* are limited, treatment decisions should be based on clinical judgment, with particular attention toward special populations that may be at increased risk for severe *B parapertussis* disease, including infants, elderly, and immunocompromised people. Treatment may be warranted to prevent severe outcomes and decrease duration of illness in these patients. Limited available data suggest that *B parapertussis* is less susceptible to antimicrobial agents than *B pertussis,* although some studies indicate that macrolides, trimethoprim-sulfamethoxazole, and ciprofloxacin generally have activity against *B parapertussis.*

ISOLATION OF THE HOSPITALIZED PATIENT: In addition to standard precautions, droplet precautions are recommended for 21 days from onset of cough if appropriate antimicrobial therapy is not administered or for 5 days after initiation of effective therapy.

CONTROL MEASURES: Pertussis is a nationally notifiable disease in the United States.

Care of Exposed People

Household and Other Close Contacts. Close contacts who are unimmunized or underimmunized should have pertussis immunization initiated or continued using age-appropriate products according to the recommended schedule as soon as possible; this includes off-label use of tetanus toxoid, reduced-content diphtheria toxoid, and acellular pertussis vaccine (Tdap) in children 7 through 9 years of age who did not complete the diphtheria and tetanus toxoids and acellular pertussis vaccine (DTaP) series (see Table 3.53, p 626).

PEP is recommended for all household contacts of the index case and other close contacts, including children in child care, regardless of immunization status. **(www.cdc.gov/pertussis/outbreaks/pep.html).** When considering borderline degree of exposure for a nonhousehold contact, PEP should be administered if the contact personally is at high risk or lives in a household with a person at high risk of severe pertussis (eg, young infant, pregnant woman, person who has contact with infants). If 21 days have elapsed since onset of cough in the index case, PEP has limited value but should be considered for households with high-risk contacts. The agents, doses, and duration of PEP are the same as for treatment of pertussis (see Table 3.52). Prophylaxis for people exposed to *B parapertussis* is not recommended currently.

People who have been in contact with an infected person should be monitored closely for respiratory tract symptoms for 21 days after last contact with the infected person. Close contacts with cough should be evaluated.

Child Care. Pertussis vaccine and chemoprophylaxis should be administered as recommended for household and other close contacts. Child care providers and exposed children, especially incompletely immunized children, should be observed for respiratory tract symptoms for 21 days after last contact with the index case while infectious. Children and child care providers who are symptomatic or who have confirmed pertussis should be excluded from child care pending physician evaluation and completion of 5 days of the recommended course of antimicrobial therapy. Untreated children and providers should be excluded until 21 days have elapsed from cough onset.

Schools. Students and staff members with pertussis should be excluded from school until they have completed 5 days of the recommended course of antimicrobial therapy. People who do not receive appropriate antimicrobial therapy should be excluded from school for 21 days after onset of symptoms. Use of PEP for large groups of students usually is not

recommended, especially in the setting of widespread community transmission, but exceptions for individuals can be considered. This occurs when close contact simulates a household exposure or when pertussis in the exposed person would have severe medical consequences. Public health officials should be consulted for recommendations to control pertussis transmission in schools; their additional recommendations could include use of Tdap in children after their 4- to 6-year DTaP booster but before they are 10 years of age (off label), Tdap administration at 10 years of age, and institution of the DTaP series in siblings who are 6 weeks of age. The immunization status of close contacts should be reviewed, and appropriate vaccines administered when indicated. Parents and teachers should be notified about possible exposures to pertussis. Exclusion of exposed people with cough illness should be considered pending evaluation by a physician.

Health Care Settings.[1] Health care facilities should maximize efforts to immunize all health care personnel (HCP) with Tdap. All HCP should observe respiratory precautions when examining a patient with a cough illness. People exposed to a patient with pertussis should be evaluated by infection-control personnel for postexposure management and follow-up. Data on the need for PEP in Tdap-immunized HCP are inconclusive. Some immunized HCP still are at risk of *B pertussis* infection. Receipt of Tdap may not preclude the need to administer PEP.

Recommendations of the CDC are as follows:

- PEP is recommended for all HCP (even if immunized with Tdap) who have been exposed to pertussis and are likely to expose other patients at risk of severe pertussis (eg, hospitalized neonates and pregnant women). Other exposed HCP either should receive PEP or should be monitored daily for 21 days after exposure and treated at the onset of signs and symptoms of pertussis.
- Other people (patients, caregivers) defined as close contacts or high-risk contacts of a patient or HCP with pertussis should receive chemoprophylaxis (and immunization when indicated), as recommended for household contacts (see Table 3.52, p 625).
- HCP with symptoms of pertussis (or HCP with any respiratory illness within 21 days of exposure to pertussis who did not receive PEP) should be excluded from work for at least the first 5 days of the recommended antimicrobial therapy. HCP with symptoms of pertussis who do not accept antimicrobial therapy should be excluded from work for 21 days from onset of cough. Use of a respiratory mask is not sufficient protection during this time.

Immunization

Vaccine Products. Purified acellular-component pertussis vaccines (DTaP) replaced previously used diphtheria, tetanus, and whole-cell pertussis vaccine (DTwP or DTP) exclusively in 1997 and contain 3 or more immunogens derived from *B pertussis* organisms: inactivated pertussis toxin (toxoid), filamentous hemagglutinin, fimbrial proteins (agglutinogens), and pertactin (an outer membrane 69-kd protein); see Table 3.53 (p 627) for products. Acellular pertussis vaccines are adsorbed onto aluminum salts and must be administered intramuscularly. All pertussis vaccines in the United States are combined with diphtheria and tetanus toxoids; none contains thimerosal as a preservative. DTaP products may be formulated as combination vaccines containing one or more of inactivated

[1]Centers for Disease Control and Prevention. Immunization of health-care personnel. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep.* 2011;60(RR-07):1–45

Table 3.52. Recommended Antimicrobial Therapy and Postexposure Prophylaxis for Pertussis in Infants, Children, Adolescents, and Adults[a]

Age	Recommended Drugs			Alternative
	Azithromycin	Erythromycin	Clarithromycin	TMP-SMX
Younger than 1 mo	10 mg/kg/day as a single dose daily for 5 days[b,c]	40 mg/kg/day in 4 divided doses for 14 days	Not recommended	Contraindicated at younger than 2 mo
1 through 5 mo	10 mg/kg/day as a single dose daily for 5 days[b]	40 mg/kg/day in 4 divided doses for 14 days	15 mg/kg/day in 2 divided doses for 7 days	2 mo or older: TMP, 8 mg/kg/day; SMX, 40 mg/kg/day in 2 doses for 14 days
6 mo or older and children	10 mg/kg as a single dose on day 1 (maximum 500 mg), then 5 mg/kg/day as a single dose on days 2 through 5 (maximum 250 mg/day)[b,d]	40 mg/kg/day in 4 divided doses for 7–14 days (maximum 1–2 g/day)	15 mg/kg/day in 2 divided doses for 7 days (maximum 1 g/day)	2 mo or older: TMP, 8 mg/kg/day; SMX, 40 mg/kg/day in 2 doses for 14 days
Adolescents and adults	500 mg as a single dose on day 1, then 250 mg as a single dose on days 2 through 5[b,d]	2 g/day in 4 divided doses for 7–14 days	1 g/day in 2 divided doses for 7 days	TMP, 320 mg/day; SMX, 1600 mg/day in 2 divided doses for 14 days

TMP indicates trimethoprim; SMX, sulfamethoxazole.

[a]Centers for Disease Control and Prevention. Recommended antimicrobial agents for the treatment and postexposure prophylaxis of pertussis: 2005 CDC guidelines. *MMWR Recomm Rep*. 2005;54(RR-14):1–16

[b]Azithromycin should be used with caution in people with prolonged QT interval and certain proarrhythmic conditions.

[c]Preferred macrolide for this age because of risk of idiopathic hypertrophic pyloric stenosis associated with erythromycin.

[d]A 3-day course of azithromycin for PEP or treatment has not been validated and is not recommended.

Table 3.53. Composition and Recommended Use of Vaccines With Tetanus Toxoid, Diphtheria Toxoid, and Acellular Pertussis Components Licensed and Available in the United States[a,b]

Pharmaceutical	Manufacturer	Pertussis Antigens	Recommended Use
DTaP Vaccine for Children Younger Than 7 Years			
DTaP (Infanrix)	GlaxoSmithKline Biologicals	PT, FHA, pertactin	**All 5 doses**, children 6 wk through 6 y of age
DTaP (Daptacel)	Sanofi Pasteur	PT, FHA, pertactin, fimbriae types 2 and 3	**All 5 doses**, children 6 wk through 6 y of age
DTaP-hepatitis B-IPV (Pediarix)	GlaxoSmithKline Biologicals	PT, FHA, pertactin	**First 3 doses, children 6 wk through 6 y of age; usual use** at 6- to 8-wk intervals beginning at 2 mo of age; then 2 doses of DTaP are needed to complete the 5-dose series before 7 y of age
DTaP-IPV/Hib (Pentacel)	Sanofi Pasteur	PT, FHA, pertactin, fimbriae types 2 and 3	**First 4 doses, children 6 wk through 4 y of age; usual use** at 2, 4, 6, and 15 through 18 mo of age; then 1 dose of DTaP is needed to complete the 5-dose series before 7 y of age
DTaP-IPV (Kinrix)	GlaxoSmithKline Biologicals	PT, FHA, pertactin	**Booster dose** for **fifth dose** of DTaP and **fourth dose** of IPV at 4 through 6 y of age
DTaP-IPV (Quadracel)	Sanofi Pasteur	PT, FHA, pertactin, fimbriae types 2 and 3	**Booster dose** for **fifth dose** of DTaP and **fourth dose** of IPV at 4 through 6 y of age
Tdap Vaccines for Adolescents			
Tdap (Boostrix)	GlaxoSmithKline Biologicals	PT, FHA, pertactin	**Single dose** at 11 through 12 y of age
Tdap (Adacel)	Sanofi Pasteur	PT, FHA, pertactin, fimbriae types 2 and 3	**Single dose** at 11 through 12 y of age

DTaP indicates pediatric formulation of diphtheria and tetanus toxoids and acellular pertussis vaccines; PT, pertussis toxoid; FHA, filamentous hemagglutinin; Hib, *Haemophilus influenzae* type b vaccine; IPV, inactivated poliovirus; Tdap, adolescent/adult formulation of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine; Td, tetanus and reduced diphtheria toxoids (for children 7 years of age or older and adults).

[a]DTaP recommended schedule is 2, 4, 6, and 15 through 18 months and 4 through 6 years of age. The fourth dose can be administered as early as 12 months of age, provided 6 months have elapsed since the third dose was administered. The fifth dose is not necessary if the fourth dose was administered on or after the fourth birthday. Refer to manufacturers' product information for comprehensive product information regarding indications and use of the vaccines listed.

[b]Tripedia and TriHibit are licensed but no longer are available in the United States.

poliovirus vaccine, hepatitis B vaccine, and *Haemophilus influenzae* type b vaccine. Recommendations for the series of DTaP for children younger than 7 years are provided in the annual immunization schedule for children and adolescents **(https://redbook.solutions.aap.org/SS/Immunization_Schedules.aspx).** Adolescent and adult formulations, known as Tdap vaccines, contain reduced quantities of diphtheria toxoid and some pertussis antigens compared with DTaP. A single dose is recommended universally for people 11 years and older, including adults of any age, in place of a decennial tetanus and diphtheria vaccine (Td). The preferred schedule is to administer Tdap at the 11- or 12- year-old preventive visit, with catch-up of older adolescents. Booster doses of Tdap are not recommended for any group of people except pregnant women (see subsequent sections).

Dose and Route. Each 0.5-mL dose of DTaP or Tdap is administered intramuscularly. Use of a decreased volume of individual doses of pertussis vaccines or multiple doses of decreased-volume (fractional) doses is not recommended.

Interchangeability of Acellular Pertussis Vaccines. Insufficient data exist on the safety, immunogenicity, and efficacy of DTaP vaccines from different manufacturers when administered interchangeably for the primary series in infants. In circumstances in which the type of DTaP product(s) received previously is unknown or the previously administered product(s) is not readily available, any DTaP vaccine licensed for use in the primary series may be used. There is no need to match Tdap vaccine manufacturer with DTaP vaccine manufacturer used for earlier doses.

Recommendations for Routine Childhood Immunization With DTaP. Five doses of pertussis-containing vaccine are recommended prior to entering school: 4 doses of DTaP before 2 years of age and 1 dose of DTaP before school entry. The first dose of DTaP may be administered as early as 6 weeks of age, followed by 2 additional doses at intervals of approximately 2 months. The fourth dose of DTaP is recommended at 15 through 18 months of age, and the fifth dose of DTaP is administered before school entry (kindergarten or elementary school) at 4 through 6 years of age. The fourth dose can be administered as early as 12 months of age, provided 6 months have elapsed since the third dose was administered. If the fourth dose of pertussis vaccine is delayed until after the fourth birthday, the fifth dose is not recommended.

Other recommendations are as follows:

- Simultaneous administration of DTaP and all other recommended vaccines is acceptable. Vaccines should not be mixed in the same syringe unless the specific combination is licensed by the FDA (see Simultaneous Administration of Multiple Vaccines, p 35, and *Haemophilus influenzae* Infections, p 367).
- Inadvertent administration of Tdap instead of DTaP to a child younger than 7 years as either dose 1, 2, or 3 of DTaP does not count as a valid dose; DTaP should be administered as soon as is feasible.
- Inadvertent administration of Tdap instead of DTaP to a child younger than 7 years of age as either dose 4 or 5 can be counted as valid for DTaP dose 4 or 5.
- During a pertussis outbreak in the community, public health authorities may recommend starting DTaP immunization as early as 6 weeks of age, with doses 2 and 3 in the primary series administered at intervals as short as 4 weeks.
- Children younger than 7 years who have begun but not completed their primary immunization schedule with DTwP outside the United States should receive DTaP to complete the pertussis immunization schedule.

- DTaP is not licensed or recommended for people 7 years or older.
- Children between 7 and 10 years of age who have not completed their primary immunization schedule or have an unknown vaccine history should receive a single dose of Tdap. If they require additional tetanus and diphtheria toxoid doses, Td should be used.

Combined Vaccines. Several pertussis-containing combination vaccines are licensed for use (see Table 3.53, p 626) and may be used when feasible and when any components are indicated and none is contraindicated.

Recommendations for Scheduling Pertussis Immunization for Children Younger Than 7 Years in Special Circumstances

- For children whose pertussis immunization schedule is resumed after deferral or interruption of the recommended schedule, the next dose in the sequence should be administered, regardless of the interval since the last dose—that is, the schedule is not restarted (see Lapsed Immunizations, p 38).
- For children who have received fewer than the recommended number of doses of pertussis vaccine but who have received the recommended number of diphtheria and tetanus toxoid (DT) vaccine doses for their age, DTaP should be administered to complete the recommended pertussis immunization schedule.
- The total number of doses of diphtheria and tetanus toxoids (as DT, DTaP, or DTwP) should not exceed 6 before the seventh birthday.
- Although *B pertussis* infection confers protection against recurrent infection, the duration of protection is unknown. Age-appropriate DTaP dose(s) or a Tdap dose should be administered to complete the standard or catch-up immunization series on schedule in people who have had pertussis infection. No interval between disease and immunization is needed.

Medical Records. Charts of children for whom pertussis immunization has been deferred should be flagged, and the immunization status of these children should be assessed periodically to ensure that they are immunized appropriately.

Adverse Events After DTaP Immunization in Children Younger Than 7 Years

- **Local and febrile reactions.** Reactions to DTaP can occur within several hours of immunization and subside spontaneously within 48 hours without sequelae. Most commonly, these include redness, swelling, induration, and tenderness at the injection site as well as drowsiness. Less common reactions include fretfulness, anorexia, vomiting, crying, and slight to moderate fever.

  Swelling involving the entire thigh or upper arm has been reported in 2% to 3% of vaccine recipients after administration of the fourth and fifth doses of DTaP. Limb swelling can be accompanied by erythema, pain, and fever; it is not an infection. Although thigh swelling may interfere with walking, most children have no limitation of activity; the condition resolves spontaneously and has no sequelae. Entire limb swelling after a fourth dose of DTaP is associated with a modestly increased risk of a similar reaction or an injection-site reaction >5 cm after the fifth dose. Entire limb swelling is not a contraindication to further DTaP, Tdap, or Td immunization.

  A review by the Institute of Medicine (IOM) based on case-series reports found evidence of a rare yet likely causal relationship between receipt of tetanus toxoid-containing vaccines and brachial neuritis. However, the frequency of this event has not been determined. Brachial neuritis is listed in the Vaccine Injury Table.

- **Other reactions.** The rate of anaphylaxis following DTwP was estimated to be approximately 2 cases per 100 000 injections; the incidence of anaphylaxis after immunization with DTaP or Tdap is unknown. The Institute of Medicine report titled "Adverse Effects of Vaccines: Evidence and Causality" links tetanus-containing vaccines to anaphylaxis.[1] Severe anaphylactic reactions and resulting deaths, if any, are rare after pertussis immunization. Transient urticarial rashes that occur occasionally after pertussis immunization, unless appearing immediately (ie, within minutes), are unlikely to be anaphylactic (IgE mediated) in origin.
- **Seizures.** The incidence of seizures occurring within 48 hours of administration of DTwP was estimated to be 1 case per 1750 doses administered. These usually are simple febrile seizures and have not been demonstrated to result in recurrent afebrile seizures (ie, epilepsy) or other neurologic sequelae.

  Seizures have been reported substantially less often after DTaP, and a postlicensure study of children 6 to 23 months of age who received DTaP during 1997–2001 did not show an increased risk for seizures. A small increased risk for febrile seizures after DTaP when administered simultaneously with inactivated influenza vaccine was observed in a study in the Vaccine Safety Datalink. However, neither the CDC Advisory Committee on Immunization Practices (ACIP) nor the American Academy of Pediatrics recommends administering vaccines on separate days.
- **Hypotonic-hyporesponsive episode.** A hypotonic-hyporesponsive episode (HHE) (also termed "collapse" or "shock-like state") was reported to occur at a frequency of 1 per 1750 doses of DTwP administered, although reported rates varied widely. A follow-up study of a group of children who experienced an HHE following DTwP immunization demonstrated no evidence of subsequent serious neurologic sequelae or intellectual impairment. HHEs occur significantly less often after immunization with DTaP than with DTwP and are not a contraindication to subsequent dose(s).
- **Temperature 40.5°C (104.8°F) or higher.** The rate of temperature to 40.5°C (104.8°F) or higher after administration of DTaP is less than 0.1%.
- **Prolonged crying.** The frequency of inconsolable crying for 3 or more hours within 48 hours of receipt of DTaP is 0.2% or less. The significance of persistent crying is unknown, has been noted after receipt of vaccinations other than pertussis vaccine, is not known to be associated with sequelae, and is not a contraindication to subsequent dose(s).

Evaluation of Adverse Events Temporally Associated With Pertussis Immunization. Appropriate diagnostic studies should be performed to establish the cause of serious adverse events occurring temporally after immunization, rather than assuming that they are caused by the vaccine.[2] The CDC has established independent Clinical Immunization Safety Assessment (CISA) centers to assess people with selected adverse events and offer recommendations for management. Genetic testing of several cases of encephalopathy temporally associated with DTwP revealed a genetic defect in neuronal sodium channels (Dravet syndrome); fever associated with DTwP likely unmasked the genetic condition and was not the cause of encephalopathy. The cause of events temporally related to immunization,

---

[1]Institute of Medicine. *Adverse Effects of Vaccines: Evidence and Causality*. Washington, DC: The National Academies Press; 2011

[2]Williams SE, Edwards KM, Baxter RP, et.al. Comprehensive assessment of serious adverse events following immunization by health care providers. *J Pediatr*. 2013;162(6):1276–1281

even when unrelated to the immunization received, cannot always be established, even after extensive diagnostic and investigative studies.

The preponderance of evidence does not support a causal relationship between immunization with DTwP and sudden infant death syndrome, infantile spasms, or serious acute neurologic illness resulting in permanent neurologic injury. Active surveillance performed by the IMPACT network of Canadian pediatric centers screening more than 12 000 admissions for neurologic disorders between 1993 and 2002 found no case of encephalopathy attributable to DTaP after administration of more than 6.5 million doses.

Contraindications and Precautions to DTaP Immunization.

Contraindications to DTaP and Tdap:

- **Severe allergic reaction (eg, anaphylaxis)** to a dose of DTaP or to a vaccine component. (DT or Td) is a contraindication to DTaP, DT, or Td. Because of the importance of tetanus vaccination, people who experience anaphylactic reactions should be referred to an allergist to determine whether they have a specific allergy to tetanus toxoid and can be desensitized to tetanus toxoid.
- Encephalopathy (eg, coma, decreased level of consciousness, or prolonged seizures) not attributable to another identifiable cause within 7 days after administration of a previous dose of diphtheria and tetanus toxoids and pertussis vaccine (DTwP, DTaP, or Tdap) is a contraindication to the pertussis component.

Precautions:

- **Guillain-Barré syndrome** within 6 weeks after a previous dose of tetanus toxoid-containing vaccine is a **precaution** to further doses of DTaP, Tdap, DT, or Td.
- Moderate or severe acute illness with or without a fever is a reason to defer administration of any vaccine until the person has recovered.
- **Evolving neurologic disorder** generally is a reason to defer DTaP or Tdap immunization temporarily to reduce confusion about reason(s) for a change in the clinical course. If deferred in the first year of life, DT should not be administered, because in the United States, the risk of acquiring diphtheria or tetanus by children younger than 1 year is remote. The decision to administer DTaP should be revisited, and if deferral is chosen after 1 year of age, DT immunization should be completed according to the recommended schedule (see Diphtheria, p 319, and/or Tetanus, p 793).

Recommendations for Routine Adolescent Immunization With Tdap.[1] Adolescents 10 years and older should receive a single dose of Tdap instead of Td for booster immunization against tetanus, diphtheria, and pertussis. The preferred age for Tdap immunizations is 11 through 12 years of age.

- Adolescents who received Td but not Tdap should receive a single dose of Tdap to provide protection against pertussis regardless of time since receipt of Td.
- Simultaneous administration of Tdap and all other recommended vaccines is recommended when feasible. Vaccines should not be mixed in the same syringe. Other indicated vaccine(s) that are not available and, therefore, cannot be administered at the time of administration of Tdap, can be administered anytime thereafter.
- Inadvertent administration of DTaP instead of Tdap in people 7 years and older is counted as a valid dose of Tdap

[1]Centers for Disease Control and Prevention. Updated recommendations for the use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis (Tdap) vaccine from the Advisory Committee on Immunization Practices, 2010. *MMWR Morb Mortal Wkly Rep.* 2011;60(1):13–15

- Outside of pregnancy, a second dose of Tdap is not recommended. See the following sections for special situations.

Recommendations for Scheduling Tdap in Children 7 Years and Older Who Did Not Complete Recommended DTaP Doses Before 7 Years of Age. Children 7 through 10 years of age who have not completed their immunization schedule with DTaP before 7 years of age (see previous section) or who have an unknown vaccine history should receive a single dose of Tdap. If further dose(s) of tetanus and diphtheria toxoids are needed in a catch-up schedule, Td is used. The preferred schedule is Tdap followed by Td (if needed) at 2 months and 6 to 12 months, but a single dose of Tdap could be substituted for any dose in the series. Children who receive Tdap at 7 through 10 years of age may receive the standard Tdap booster at 11 or 12 years of age.

Recommendations for Adolescent and Adult Immunization With Tdap in Special Situations. Currently, Tdap vaccines are licensed for only a single dose. Special situations for use of Tdap, or repeated use of Tdap off label, are provided in the following sections.

Use of Tdap in Pregnancy.[1] Providers of prenatal care should implement a Tdap immunization program for all pregnant women. The ACIP recommends that a dose of Tdap be administered during **each** pregnancy, irrespective of the mother's prior history of receiving Tdap. Tdap should be administered preferably early in the interval between 27 and 36 weeks' gestation, although Tdap may be administered at any time during pregnancy. Current evidence suggests that immunization early in the interval between 27 and 36 weeks' gestation will maximize passive antibody transfer to the infant. For women not previously vaccinated with Tdap and in whom Tdap was not administered during pregnancy, Tdap should be administered immediately postpartum. Postpartum Tdap is not recommended for women who previously received Tdap at any time.

Protection of Young Infants: The Cocoon Strategy. Tdap vaccination during each pregnancy is the preferred strategy for protecting young infants from pertussis in the early months of life. In addition, the AAP, CDC, American College of Obstetricians and Gynecologists, and American Academy of Family Physicians recommend the "cocoon" strategy to help protect infants from pertussis. This strategy may offer indirect protection through immunization of their family members to decrease their likelihood of acquisition and subsequent transmission of *B pertussis* to young infants, who have high risk of severe or fatal pertussis. Immunizing parents or other adult family contacts in the pediatric office setting could increase immunization coverage for this population.[2]

- Underimmunized children younger than 7 years should receive DTaP, and underimmunized children 7 years and older should receive Tdap (see previous discussion).
- All adolescents and adults should have received a single dose of Tdap. To ensure receipt, all adolescents and adults who have or anticipate having close contact with an infant younger than 12 months (eg, parents, siblings, grandparents, child care providers, and HCP) and who previously have not received Tdap should receive a single dose of Tdap, ideally at least 2 weeks before beginning close contact with the infant.

---

[1]Centers for Disease Control and Prevention. Updated recommendations for use of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine (Tdap) in pregnant women--Advisory Committee on Immunization Practices (ACIP), 2012. *MMWR.* 2013;62(7):131–135

[2]Lessin HR; Edwards KM; American Academy of Pediatrics, Committee on Practice and Ambulatory Medicine, Committee on Infectious Diseases. Immunizing parents and other close family contacts in the pediatric office setting. *Pediatrics.* 2012;129(2):e247-e253

There is no minimum interval required between Tdap and prior Td.

- Cough illness in contacts of neonates should be investigated and managed aggressively, with consideration given for azithromycin prophylaxis for the neonate if pertussis contact is likely (see Control Measures).

Special Situations.

- **Wound management in people who previously received Tdap.** In the setting when tetanus prophylaxis is required following a wound in a person who previously received Tdap ≥5 years earlier or in whom Tdap history is uncertain, Tdap can be used if Td is not readily available.
- **Wound management for pregnant women.** As part of standard wound management care to prevent tetanus, if a tetanus toxoid-containing vaccine is indicated in a pregnant woman who has not received at Td-containing vaccine within 5 years, Tdap should be administered.
- **Pregnant women for whom tetanus booster is due.** If Td booster immunization is indicated during pregnancy (ie, more than 10 years since previous Td), Tdap should be administered, preferably between weeks 27 and 36 of gestation.
- **Pregnant women with unknown or incomplete tetanus vaccination.** To ensure protection against maternal and neonatal tetanus, pregnant women who never have been immunized against tetanus should receive 3 doses of Td-containing vaccines during pregnancy. The recommended schedule is 0, 4 weeks, and 6 to 12 months. Tdap should replace 1 dose of Td, preferably between weeks 27 and 36 of gestation.

Health Care Professionals. The CDC recommends a single dose of Tdap as soon as is feasible for HCP of any age who previously have not received Tdap. There is no minimum interval suggested or required between Tdap and prior Td. After receipt of Tdap, HCP should receive routine decennial Td booster immunization. The decision not to recommend decennial Tdap for HCP is not related to safety concerns but rather to poor cost effectiveness.

In certain cases (eg, documented transmission in the health care setting), revaccination of HCP with Tdap may be considered **(www.cdc.gov/vaccines/vpd/pertussis/tdap-revac-hcp.html).** In such a case, Tdap is not a substitute for infection prevention and control measures, including postexposure antimicrobial prophylaxis for exposed HCP. If implemented, HCP who work with infants or pregnant women should be prioritized for revaccination.

Hospitals and ambulatory care facilities should provide Tdap for HCP and maximize immunization rates (eg, education about the benefits of immunization or mandatory requirement, convenient access, and provision of Tdap at no charge).

Recommendations for Adult Immunization With Tdap. The CDC recommends administration of a single dose of Tdap universally for adults of any age who previously have not received Tdap, with no minimum interval required between Tdap and prior dose of Td.

When available, Boostrix (GlaxoSmithKline, Research Triangle Park, NC) is the preferred Tdap vaccine for adults 65 years and older, because Boostrix is FDA approved for this indication; however, providers should not miss an opportunity to vaccinate and can use any available Tdap product. A dose of either vaccine is considered valid.

Adverse Events After Administration of Tdap. Local adverse events after administration of Tdap in adolescents and adults are common but usually are mild. Systemic adverse events also are common but usually are mild (eg, any fever, 3%–14%; any headache, 40%–44%;

tiredness, 27%–37%). Postmarketing data suggest that these events occur at approximately the same rate and severity as following receipt of Td.

Syncope can occur after immunization, is more common among adolescents and young adults, and can result in serious injury. Vaccine recipients should be seated and observed for 15 minutes after immunization. If syncope occurs, patients should be observed until symptoms resolve.

Contraindications, Precautions, and Deferral of Use of Tdap in Adolescents and Adults. Anaphylaxis that occurred after any component of the vaccine is a **contraindication** to Tdap (see Tetanus, p 793, for additional recommendations regarding tetanus immunization). In **latex-allergic** individuals, package inserts should be consulted regarding latex content.

History of **Guillain-Barré** syndrome within 6 weeks of a dose of a tetanus toxoid vaccine is a **precaution** to Tdap immunization. If the decision is made to continue tetanus toxoid immunization, Tdap is preferred if indicated. A history of severe **Arthus hypersensitivity reaction** after a previous dose of a tetanus or diphtheria toxoid-containing vaccine administered less than 10 years previously should lead to **deferral** of Tdap or Td immunization for 10 years after administration of the tetanus or diphtheria toxoid-containing vaccine.