

Updated treatment and prevention guidelines for pertussis

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ABSTRACT

Pertussis, commonly referred to as whooping cough, is one of the top 10 causes of death in children globally despite vaccine availability. Adhering to vaccination guidelines for both the primary childhood series as well as adolescent and adult boosters is crucial in preventing the spread of disease. However, due to vaccine failure, outbreaks occur every 3 to 5 years. As a result, early recognition and prompt treatment are instrumental in controlling the epidemic.

Keywords: pertussis, whooping cough, DTaP, Tdap, guidelines

Learning objectives

- Recognize the clinical manifestations of pertussis.
- Identify appropriate strategies for diagnosing pertussis based on patient presentation.
- Describe best practices for prevention of pertussis and treatment strategies when prevention fails.

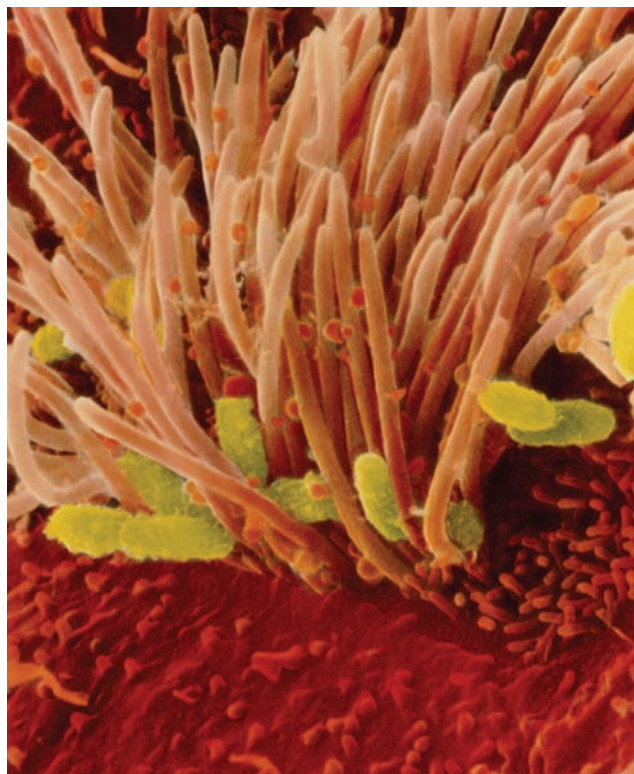
Pertussis, caused by the bacterium *Bordetella pertussis*, and commonly referred to as whooping cough, is one of the top 10 causes of death in children globally.¹ The CDC estimates 30 to 50 million cases of pertussis and 300,000 deaths per year worldwide.² Although the incidence of pertussis is highest in infants, the rate in adolescents and adults is increasing (Figure 1); pertussis is the only vaccine-preventable disease on the rise in the United States.³

Despite vaccine availability, pertussis remains a public health threat in many developed countries.² Epidemics typically occur every 3 to 5 years in the United States.⁴ In 2012, the United States experienced the largest postvaccine pertussis epidemic since the 1940s.⁵

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HISTORY OF THE EPIDEMIC

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 pertussis vaccine became available in the 1940s, more than 200,000 cases of pertussis were reported annually in the United States.⁶ Since widespread use of the vaccine began, incidence has decreased more than 80% compared with the previous era.⁶

Since the 1980s, Canada, Australia, and the United States have seen a resurgence of pertussis.⁷ In 2004 in the United States, 25,827 cases were documented, the most since 1959, with 38% of reported cases among adolescents.^{6,7} In 2012, more than 48,000 pertussis cases were reported in the United States, the most since 1955, when nearly 63,000 cases were reported.⁸

In 2012, the United States faced a crisis similar to that of the prevaccine era. On April 3, 2012, the Washington State Secretary of Health declared a pertussis epidemic. Between January and June, 4,387 cases were reported, a

Key points

- Suspect pertussis in patients with a coughing illness that lasts more than 2 weeks
- Because diagnostic tests have limited sensitivity, treat patients for pertussis if clinical suspicion is high
- Azithromycin and clarithromycin are the first-line antimicrobial agents for treating pertussis.
- All children should be vaccinated with DTaP at ages 2, 4, and 5 months; 15 to 18 months; and 4 to 6 years.
- A one-time booster dose of Tdap is recommended for patients over age 11 years and all pregnant women after 20 weeks gestation.

1,300% increase from the 180 cases reported in the same period in 2011. This outbreak was highest in infants less than 1 year old and children ages 10, 13, and 14 years, despite previous vaccination.⁹ The national incidence of pertussis for the same period in 2012 was lower overall, but increased among infants and children ages 10, 13, and 14 years, consistent with observations in Washington State.⁹

CAUSES AND EPIDEMIOLOGY

Bordetella pertussis, an aerobic, gram-negative coccobacillus, is solely a human pathogen with no known environmental or animal reservoir.¹⁰ The bacterium is transmitted through aerosolized respiratory droplets.¹¹ *B. pertussis* can survive only a few hours in respiratory secretions and requires special media for culture.¹⁰ After *B. pertussis* is inhaled, it adheres to ciliated respiratory epithelial cells in the upper respiratory tract and nasopharynx, destroying protective respiratory cells and causing protein adhesions and coughing episodes.^{6,11}

Pertussis is more severe in infants and young children than in vaccinated adolescents and older adults.^{4,11} Adolescents and adults infected with pertussis serve as reservoirs, transmitting the disease to children and infants, who have the greatest risk of pertussis-related complications.¹¹ The highest incidence of pertussis is found in adolescents. Siblings are the most common source of transmission among adolescents, followed by neighbors and relatives.¹¹

CLINICAL MANIFESTATION

Pertussis is a highly contagious infection with a typical incubation period of 7 to 10 days. However, the incubation period can range from 4 to 21 days and rarely may be as long as 42 days.⁶ The clinical course of the illness is divided into three stages: catarrhal (1 to 2 weeks), paroxysmal (2 to 8 weeks), and convalescence (weeks to months).^{6,12}

The *catarrhal stage* is characterized by onset of a runny nose, low-grade fever, and mild, occasional cough, similar to symptoms of an acute viral upper

respiratory tract infection. The cough gradually becomes more severe. Excessive lacrimation and conjunctival injection are two specific signs that suggest pertussis.

The *paroxysmal stage* is characterized by a persistent cough commonly accompanied by sweats and facial swelling, and in some cases, vomiting.^{12,13} The characteristic whoop, leading clinicians to suspect pertussis, usually is most severe in the nighttime.⁶ Children and infants may vomit or feel weak after coughing outbursts and appear better between outbursts. If untreated, the paroxysmal stage can last up to 3 months, transitioning into the *convalescent stage*, during which the persistent cough declines, although coughing bouts may recur for months, or with subsequent viral infections.⁶

Adult infection ranges from asymptomatic to mild cold symptoms to more severe with classic coughing. Of 19,000 cases that were reported to the US national surveillance system between 1996 and 2004, more than 80% of adults reported having paroxysmal cough and 50% had posttussive vomiting.¹⁴ Symptoms often interfere with daily activities and cause major sleep disturbances.⁶ The most common complication of pertussis is bacterial pneumonia. Neurologic complications are common in infants because coughing leads to hypoxia, resulting in seizures and encephalopathy. Less common complications include otitis media, dehydration, anorexia, pneumothorax, epistaxis, subdural hematoma, hernia, and rectal prolapse.^{6,11}

DIAGNOSIS

According to the CDC and World Health Organization, providers should suspect pertussis in patients with a cough lasting 2 weeks and one of the following symptoms: paroxysms of coughing, inspiratory whoop, or posttussive vomiting. In an outbreak or in patients with a sick contact and a cough lasting more than 2 weeks, providers also can assume a clinical case of pertussis.¹⁵ Various diagnostic

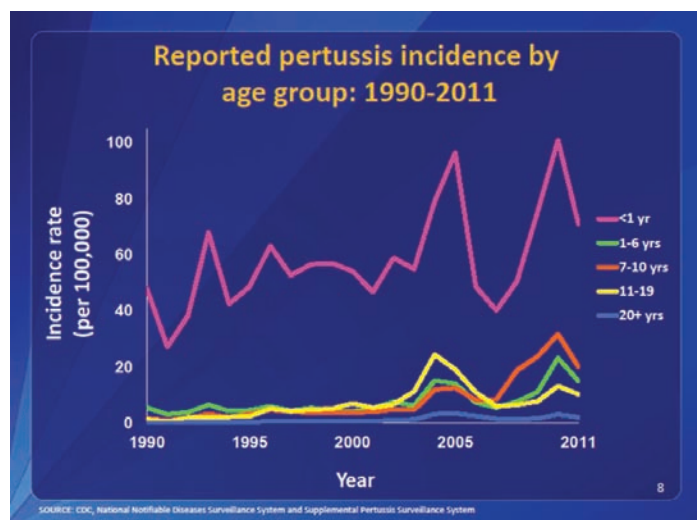


FIGURE 1⁴⁴

TABLE 1. CDC recommended immunization schedule for children age 6 years and younger.⁴⁵

Vaccine ▼	Age ►	Birth	1 month	2 months	4 months	6 months	9 months	12 months	15 months	18 months	19-23 months	2-3 years	4-6 years	
Hepatitis B		HepB	HepB			HepB								Range of recommended ages for all children
Rotavirus			RV	RV	RV									
Diphtheria, tetanus, pertussis				DTaP	DTaP	DTaP			DTaP				DTaP	
Haemophilus influenzae type b				Hib	Hib	Hib		Hib						Range of recommended ages for certain high-risk groups
Pneumococcal				PCV	PCV	PCV		PCV				PPSV		
Inactivated poliovirus				IPV	IPV			IPV					IPV	
Influenza								Influenza (yearly)						
Measles, mumps, rubella								MMR			See footnote ^a		MMR	Range of recommended ages for all children and certain high-risk groups
Varicella								VAR			See footnote ^a		VAR	
Hepatitis A								Dose 1				HepA series		
Meningococcal							MCV4							

measures can aid in confirming pertussis, but depend on the length of time from onset of signs and symptoms.

If the onset of cough is less than 2 weeks, both polymerase chain reaction (PCR) and cultures should be used. Nasopharyngeal aspirate or swab from the posterior portion of the pharynx should be cultured for *B. pertussis*.¹⁵ Culture is the current gold standard for confirming *B. pertussis* infection; this test has a specificity of 100%, but the organism may be difficult to isolate, so a negative culture does not rule out pertussis.^{6,16}

PCR is about 98% specific and 65% sensitive.¹⁷ The higher sensitivity and ability to detect small numbers of viable and nonviable microbes makes it an excellent tool to use in conjunction with bacterial culture.^{6,18} Careful specimen collection and transport and understanding the PCR assays performed will help clinicians obtain accurate diagnostic test results. Because bacterial DNA rapidly decreases after 4 weeks, nasopharyngeal specimens used for PCR should be collected within 3 weeks following cough onset.¹⁸

For adolescents and adults who present more than 3 weeks after cough onset (when cultures and PCR are likely to be negative), serologic testing with pertussis toxin immunoglobulin G (IgG) and immunoglobulin A (IgA) via enzyme-linked immunosorbent assay (ELISA) may be useful in diagnosing pertussis. However, measurement of a single high value of either IgG or IgA antibodies to pertussis toxin suggests pertussis infection.^{6,19} For recently infected patients who have not been immunized recently, ELISA IgG or IgA titers will be higher than the geometric mean titers of healthy adults. Although no FDA-approved

diagnostic test exists for pertussis, detecting a single high value of pertussis toxin IgG or IgA by serology can help in the diagnosis of patients who have not been immunized recently.¹⁹ In clinical practice, due to challenges in diagnosis, implementing antimicrobial treatment is advised when the provider is highly suspicious of pertussis, regardless of the test results.

PREVENTION

DTaP in pediatrics The Advisory Committee on Immunization Practices (ACIP) recommends a five-dose DTaP schedule for all children, including those who are immunocompromised.^{20,21} Infants should receive three doses of DTaP at 2, 4, and 6 months of age. Toddlers should receive the fourth dose between 15 and 18 months. The fifth dose should be administered to children between 4 and 6 years of age (Table 1).²¹ If the ideal vaccine schedule described here was not followed, children can catch up using the vaccination schedule outlined in Table 2.²²

TABLE 2. Catch-up vaccination schedule²¹

	DTaP (4 months to 6 years)	Td or Tdap (6-18 years)
Minimum age for dose 1	6 weeks	7 years
Dose 2	4 weeks after preceding dose	4 weeks after preceding dose
Dose 3	4 weeks after preceding dose	<ul style="list-style-type: none"> • 4 weeks after preceding dose if first administered at age under 12 months • 6 months after preceding dose if first administered at age over 12 months
Dose 4	Minimum age of 1 year; 6 months from preceding dose	6 months
Dose 5	Minimum age of 5 years; 6 months from preceding dose	

In children between the ages of 2 and 8 years, the estimated efficacy of DTaP is 84%.²¹ However, immunity to pertussis wanes 5 to 10 years after the primary childhood vaccination series.^{2,21,23} As a result, adolescents should receive a booster to protect themselves and prevent transmission of the disease.²¹

Adolescent booster Unfortunately, DTaP did not confer the long-lasting immunity that was originally anticipated, resulting in pertussis outbreaks among young adults in highly vaccinated populations since the late 1990s.^{21,24} Although the DTaP vaccine used in the United States yields better levels of seroprotection than the previously used DTaP, several pertussis outbreaks occurred in universities, schools, and other facilities in 2007-2008, with a shift in the peak incidence from infants to school-age children and adults.^{21,24} Other developed countries, including Finland, France, the Netherlands, and Israel, have shown a similar shift in the incidence to adolescents and adults.²

Despite patients' waning immunity after primary vaccination with DTaP, the most promising mode of prevention is providing Tdap boosters to adolescents. Strategies such as enforcing Tdap as a school immunization requirement may improve vaccination rates among this age group.²⁵ Due to the increased rate of pertussis in adolescents, as of 2005, the ACIP recommended a single dose of the Tdap booster for children ages 11 to 18 years, preferably between ages 11 and 12 years.²¹

Recommendation for adults ages 19 to 64 years Similarly, Tdap is recommended by the ACIP for adults ages 19 to 64 years who have not previously received a booster dose (Table 3).^{21,26,27} However, data from studies conducted in Europe and Australia demonstrated a decline in patients' anti-pertussis titers 10 years following vaccination.

Recommendation for adults age 65 years and older From 1999 to 2006, the greatest increase in pertussis incidence was in adults age 65 years and older as a result of waning immunity.²⁸ In addition, pertussis-related morbidity and

mortality increases with age among adults. Grandparents and babysitters can be a source of infection for unvaccinated infants.²⁸ Previously, only Td boosters, lacking pertussis antigens, were recommended in booster doses for adults age 65 years and older.²⁹ As of July 2011, Tdap was approved for use in this population.²⁸

“COCOONING”: VACCINATING THE FAMILY

Cocooning is the practice of vaccinating adults who anticipate household contact with infants.² Infants do not acquire immunity until they receive at least 2 doses of DTaP and are at high risk for pertussis.²³ Providing these infants with herd immunity by vaccinating those around them is the most effective way to protect them. Therefore, the ACIP recommends Tdap administration to adolescents and adults who have not received a booster dose and anticipate close contact with infants.^{21,27,28} Despite this recommendation, only 5% of the adult population with routine contact with susceptible infants received Tdap in 2008.²³

One challenge is the low rate of adult vaccination with Tdap. A study of low-income families revealed barriers to immunization including a lack of insurance and poor access to medical care.²³ One strategy to improve vaccination rates was to offer Tdap to mothers and non-mother caregivers at the infant's 2-week visit to the pediatrician.²³ This intervention significantly increased the vaccination rate, to 69% among this population, and supports the role of routine pediatric care in increasing vaccination rates among multiple adult caregivers.²³

A crucial component of cocooning involves vaccinating mothers, who account for the majority of infant contact. As of August 2012, the ACIP recommends Tdap to all pregnant women after 20 weeks gestation, regardless of their vaccination history.^{30,31} Vaccinating mothers during pregnancy provides the mother with immunity in the postpartum period, therefore cocooning the infant from birth. In addition, maternal antibodies to pertussis are

TABLE 3. Adult vaccination schedule⁴⁶

VACCINE ▼	AGE GROUP ►	19-21 years	22-26 years	27-49 years	50-59 years	60-64 years	≥ 65 years	
Influenza		1 dose annually						
Tetanus, diphtheria, pertussis (Td/Tdap)		Substitute 1-time dose of Tdap for Td booster; then boost with Td every 10 yrs						
Varicella		2 doses						
Human papillomavirus (HPV) Female		3 doses						
Human papillomavirus (HPV) Male		3 doses						
Zoster						1 dose		
Measles, mumps, rubella (MMR)		1 or 2 doses						
Pneumococcal polysaccharide (PPSV23)		1 or 2 doses					1 dose	
Pneumococcal 13-valent conjugate (PCV13)		1 dose						
Meningococcal		1 or more doses						
Hepatitis A		2 doses						
Hepatitis B		3 doses						

Everyone in the category who meets age requirements and lacks evidence of immunity

Recommended if some other risk factor is present

No recommendation

See <http://www.cdc.gov/vaccines/schedules/hcp/adult.html> for recommended vaccinations indicated for adults based on medical and other indications.

transferred across the placenta, providing passive immunity in the neonatal period preceding DTaP vaccination.³⁰ However, the full effectiveness of these antibodies in preventing infant cases of pertussis remains unclear.³⁰

VACCINE FAILURE

Despite the 92% decrease in morbidity and 93% decrease in mortality due to pertussis vaccinations, outbreaks are occurring every 3 to 5 years.^{4,32} The outbreaks may be due to some parents refusing to vaccinate their children, as well as the lack of lifelong immunity acquired from either immunization or infection.

For instance, adolescents have a high rate of waning immunity despite childhood vaccination and recent Tdap booster administration.⁹ Similarly adults who have completed their DTaP series can harbor pertussis and transmit the infection to those susceptible.

Multiple factors likely contribute to vaccine failure and influence the resurgence of pertussis. Improved diagnostic techniques, such as the widespread use of PCR, and increased awareness led to a rise in diagnosed cases but not in true disease incidence.³³ An inappropriate vaccination schedule may also contribute to the failure of the pertussis vaccine. Perhaps adjustments in either the primary vaccination schedule or recommendations for additional booster doses can cause long-lasting pertussis immunity. In addition, genetic variability in the pertussis toxin promoter (*ptxP*) coincides with increased prevalence of the disease in older age groups.²⁴ Similarly, recent research demonstrates *B. pertussis* adaptation to pertactin, a DTaP component, resulting in outbreaks of pertactin-negative variants in the United States.³⁴ DTaP's failure is alarming and requires further research.

TREATMENT

The best treatment for pertussis is primary prevention. To limit the spread of infection, the American Academy of Pediatrics recommends that chemoprophylaxis be administered to all household contacts and other close contacts.³⁵ According to the CDC, postexposure prophylaxis should be targeted toward patients at high risk for developing severe pertussis, and those who anticipate close contact with high-risk groups such as infants, pregnant women in their third trimester, and patients with moderate to severe medically treated asthma.³⁶ Of note, the recommended antimicrobial agents and doses are the same for treatment and chemoprophylaxis.³⁵

When prevention fails, antimicrobial therapy is the treat-

TABLE 4. Pertussis treatment guidelines³⁸

	Dose	Duration of therapy	Patient age	Cost
Azithromycin	10 to 12 mg/kg/day; 10 mg/kg on day 1, then 5 mg/kg on days 2 through 5. Maximum 500 mg/day	5 days	under 1 month	\$25 to \$49
Erythromycin	40 to 50 mg/kg/day in 4 divided doses. Maximum 2 g/day	14 days	over 1 month	under \$25
Clarithromycin	15 to 20 mg/kg/day in 2 divided doses. Maximum 1 g/day.	7 days	over 1 month	\$50 to \$99
TMP/SMX	8 mg/kg/day (TMP), 40 mg/kg/day (SMX) in 2 divided doses	14 days	over 2 months	under \$25

ment of choice. The CDC lists azithromycin and clarithromycin as first-line antimicrobial agents for treating pertussis.^{37,38} Azithromycin has the shortest, simplest course and is approved for infants less than 1 month old (Table 4).^{38,39} Clarithromycin, which causes minimal adverse reactions, may be used in infants 1 month and older. Erythromycin is still used in infants older than 1 month, but studies have shown poor adherence to the antibiotic regimen due to its long course and adverse reactions, most notably infantile hypertrophic pyloric stenosis and gastrointestinal distress.^{40,41} Trimethoprim-sulfamethoxazole (TMP-SMX) may be used in infants older than 2 months who cannot tolerate or have a contraindication to a macrolide, although sulfa allergy and glucose 6-phosphate dehydrogenase deficiency (G6PD) must be considered.^{34,38,42}

Once the diagnosis is made, early treatment during the catarrhal stage may decrease the severity of symptoms and infectivity.¹⁵ Unfortunately, most patients do not seek medical attention until later, during the paroxysmal phase. The ability of antimicrobials to affect the clinical course of pertussis during the paroxysmal stage is unclear but nevertheless recommended by the CDC.^{38,43}

CONCLUSION

Pertussis continues to be a major health problem among children. Recent outbreaks demonstrate the importance of prevention with the primary vaccination series of five DTaP doses. The first three doses are given to infants at ages 2, 4, and 6 months. To ensure protection, a fourth dose is given between ages 15 and 18 months, and a fifth dose to children before starting school between ages 4 and 6 years.²¹ A booster dose of Tdap is recommended for children ages 11 to 12 years who have completed their childhood DTaP series, all pregnant women after 20 weeks, and as a one-time dose for adults older than age 19 years.^{2,21,27-29,31}

If pertussis is diagnosed with high clinical suspicion and positive immunoassays or nasopharyngeal swabs, the patient should be treated with a macrolide, such as azithromycin or clarithromycin, or TMP/SMX as an alternative for patients who have a contraindication to or cannot tolerate a macrolide.^{37,38} **JAAPA**

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