Pertussis

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INTRODUCTION

Pertussis, or whooping cough, is an upper respiratory tract infection (URI) caused by *Bordetella pertussis*. The classic clinical syndrome is a prolonged illness characterized by severe coughing paroxysms, inspiratory whooping, and posttussive emesis. Many classic features of pertussis infection are absent or less prominent in previously immunized adolescents and adults.1

After the widespread introduction of the pertussis vaccine in the 1940s, the incidence of pertussis declined dramatically.2 Despite vaccination strategies, however,
B. pertussis is far from eradicated, even in developed nations, and remains a significant cause of morbidity and mortality worldwide. Unimmunized infants and partially immunized children are at greatest risk for complications and death from pertussis. In the past 2 decades, there has been a resurgence of reported cases of pertussis worldwide, including in the United States. As a result of more sensitive diagnostic techniques, it is increasingly recognized that pertussis immunity (once believed to be lifelong after both natural infection and immunization) wanes over a period 7 to 10 years, resulting in subclinical infection in those previously immunized and subsequent spread of pertussis to unimmunized or partially immunized infants and children.

Diagnosis of pertussis requires a high index of suspicion for the disease and prompt nasopharyngeal sampling for laboratory confirmation. Numerous diagnostic modalities, including traditional culture, polymerase chain reaction (PCR) assays, and serologic-based tests, are available to confirm diagnosis of pertussis. Treatment and postexposure prophylaxis must be initiated early to be effective. Guidelines for pertussis vaccination are updated frequently, with increased attention to provision of booster vaccines to adolescents and adults to prevent transmission of pertussis to at-risk populations.

This article provides clinically relevant information about pertussis and:

- Reviews the microbiology, transmission, pathogenesis, and epidemiology of pertussis
- Describes both classic and atypical clinical presentations of pertussis infection and how these vary based on host factors
- Compares available diagnostic methods and describes appropriate use of these tests and
- Summarizes current treatment, postexposure prophylaxis, and vaccination guidelines.

**MICROBIOLOGY**

Pertussis or whooping cough is caused by the small gram-negative, strictly aerobic coccobacillus B. pertussis. B. pertussis is 1 of 9 known *Bordetella* species, many of which are known for causing illnesses in animal species, including *B. bronchoseptica* (the cause of kennel cough in cats and dogs). B. pertussis, conversely, is a strict human pathogen without an animal reservoir. Most human respiratory infections caused by *Bordetella* species are caused by *B. pertussis or B. parapertussis*, which causes a clinically similar, although usually less severe respiratory illness. *Bordetella* species are highly fastidious organisms, the growth of which is inhibited by many components of common laboratory media; isolation of the organism, therefore, requires a high index of suspicion and preparation on appropriate media (see section on laboratory diagnosis).

**TRANSMISSION**

Pertussis is transmitted from person to person via respiratory droplets spread by coughing. The incubation period is approximately 7 to 10 days. Pertussis is highly contagious; on contact with an infected patient, up to 34% of household contacts develop clinical pertussis and as many as 46% of asymptomatic household contacts show laboratory evidence of nasopharyngeal colonization, suggesting that asymptomatic individuals or carriers can serve as a reservoir of disease. Unimmunized infants are particularly at risk for complications from pertussis, and epidemiologic studies have shown that infants most commonly contract pertussis from a household source.
PATHOGENESIS

Once droplets of *B. pertussis* are inhaled, infection occurs through a 4-step process, each mediated by specific virulence factors. These steps are attachment, evasion of host defenses, local tissue damage, and systemic manifestations.\(^1\)

*B. pertussis* attaches to ciliated epithelial cells of the upper respiratory tract via at least 8 different adhesion factors. The most important of these adhesins are filamentous hemagglutinin and fimbriae, highly immunogenic proteins required for airway colonization and included in most acellular pertussis vaccines.\(^1\)

Two virulence factors are primarily responsible for evasion of host defenses: adenylylate cyclase toxin (ACT) and pertussis toxin (PT). ACT inhibits neutrophil chemotaxis and phagocytosis by catalyzing excessive amounts of cyclic adenosine monophosphate from adenosine triphosphate. PT, the major virulence determinant of *B. pertussis*, comprises 2 interdependent components: the active (A) and binding (B) subunits. The B subunit is responsible for binding to cell membranes, facilitating entry of the A subunit, which acts via G-protein coupled receptor pathways to alter cell function\(^13\) and to inhibit migration of neutrophils, lymphocytes, and macrophages, preventing them from reaching areas of infection.\(^1\) PT, a major component of most pertussis vaccines, is also responsible for many of the systemic manifestations caused by alterations in signaling pathways.\(^1\)

Local damage to respiratory tract tissue is mediated by several virulence factors, the most important of which is tracheal cytotoxin, which specifically damages and kills ciliated respiratory epithelial cells via local nitric oxide production, causing epithelial sloughing. This damage is believed to contribute to the characteristic paroxysmal cough, although additional unidentified toxins may also be responsible.\(^1\)

Systemic manifestations of pertussis infection, though uncommon, are mediated primarily through PT, which is responsible for a lymphocyte-predominant leukocytosis and pancreatic islet cell sensitization and hyperinsulinemia, which can lead to hypoglycemia, particularly among young infants.\(^1,14\)

EPIDEMIOLOGY

Despite routine vaccination strategies, pertussis remains an important global public health problem, with an estimated 30 to 50 million cases annually; it is responsible for an estimated 300,000 attributable deaths per year. More than 90% of cases occur in developing countries where infant and childhood vaccination rates remain low.\(^3,15\)

Pertussis outbreaks occur in a cyclical pattern, with peaks occurring every 2 to 5 years.\(^2\) Unlike influenza and other respiratory infections, pertussis has no clear seasonal pattern.\(^2\) Before the widespread introduction of the whole-cell pertussis vaccine in the late 1940s, pertussis was a leading cause of death among children worldwide. In the prevaccination period, the average incidence of pertussis in the United States was 157 cases per 100,000 persons, with more than 90% of reported cases occurring in children younger than 10 years. In contrast to current trends, infants younger than 1 year accounted for fewer than 10% of cases.\(^2\) After implementation of vaccination strategies, rates of pertussis infection decreased substantially for several decades, reaching a nadir in the late 1970s. In 1976, only 1010 cases of pertussis were reported in the United States.\(^2,16\)

Since the early 1980s, there has been an increase in the overall annual incidence of pertussis worldwide, particularly among adolescents and adults.\(^17\) Although this increase may reflect a true increase in the number of cases as a result of waning immunity, it also likely reflects increased awareness of pertussis as a cause of prolonged
cough in these populations, newer diagnostic testing methods, and improved reporting via national surveillance systems.\textsuperscript{18}

Although the incidence of pertussis has increased among adolescents and adults, it has also increased among infants younger than 1 year, in whom rates of hospitalization, serious complications, and mortality are the highest. Recent estimates indicate that up to 90\% of pertussis-related hospitalizations\textsuperscript{19} and 79\% to 90\% of pertussis-related deaths occur in infants younger than 1 year (Fig. 1).\textsuperscript{20,21}

**Recent US Trends**

In 2010, more than 27,550 cases of pertussis were reported to the Centers for Disease Control (CDC). This number decreased to 18,719 cases in 2011, but increased dramatically in 2012, with greater than 40,000 provisional cases reported and incidence estimates of 11.6 cases per 100,000 persons.\textsuperscript{5} Consistent with recent trends, nearly 50\% of these cases occurred in adolescents and adults. US pertussis outbreaks affecting children as well as adolescents and adults have been described in many states and small residential communities, including college campuses.\textsuperscript{22,23} Case-fatality rates remain highest among infants younger than 3 months.\textsuperscript{5}

**CLINICAL MANIFESTATIONS**

The clinical presentation of \textit{B pertussis} infection varies by host age, immune status, and coexistent conditions. Children and those not previously immunized are more likely to present with classic symptoms than are adults and children with previous immunity.

![Reported NNDSS pertussis cases: 1922-2011](http://www.cdc.gov/media/Pertussis Cases_1922_2011_accessed July 5 2012[1].pdf)

**Classic Presentation**

The classic presentation is characterized by 3 well-differentiated phases: the catarrhal (or prodromal) phase, the paroxysmal phase, and the convalescent phase. The catarrhal phase typically begins 7 to 14 days after contact with an infected individual and is marked by signs and symptoms of URI, including rhinorrhea and lacrimation. A low-grade fever may be present and cough, when present, is generally mild. During this stage, affected individuals are highly contagious. The catarrhal stage lasts 1 to 2 weeks; toward the end of these 2 weeks, the cough begins to worsen in both frequency and intensity, and the patient enters the paroxysmal phase, a period marked by coughing fits or paroxysms (average of 15 per 24 hours). These spells of 5 to 10 forceful coughs during a single expiration are frequently followed by a vigorous inspiratory effort with associated whoop, caused by inspiration against a partially closed glottis. Posttussive emesis is common and the cough tends to be worse at night. This prolonged period of cough is a distinguishing feature of pertussis (known as 100-day cough in China), but duration can be highly variable (typically lasting 1–6 weeks). The convalescent phase follows the paroxysmal phase and can last up to 8 weeks; it is characterized by decreased frequency and severity of coughing paroxysms. However, episodic paroxysmal coughing may return, with recurrent upper respiratory infections for up to 1 year (Table 1).

**Physical Examination, Laboratory, and Radiology Findings**

The physical examination is usually normal, without specific findings to differentiate pertussis from other common viral respiratory tract infections. The white blood cell count is often normal. Lymphocytosis can be present, most often between stages 1 and 2, with total lymphocyte count greater than 10,000/mL and is associated with poorer outcomes. Chest imaging is usually normal. The lack of specific examination, laboratory, and imaging findings emphasizes why it is important for clinicians to have a high clinical suspicion for pertussis based on symptoms alone.

**Presentation in Infants, Adolescents, and Adults**

Infants represent the most vulnerable population to severe pertussis infection, because of lack of previous or complete immunity through vaccination. Clinical features are often atypical in infants, who are more likely to present with apnea, cyanosis, and poor feeding, as well as shorter duration of cough.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Classic phases of pertussis infection</th>
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<tr>
<td><strong>Onset</strong></td>
<td><strong>Catarrhal</strong></td>
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<tr>
<td>After exposure.</td>
<td></td>
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<td></td>
<td>7–14 d</td>
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<tr>
<td><strong>Clinical features</strong></td>
<td>Rhinorrhea</td>
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<tr>
<td></td>
<td>Mild cough</td>
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<tr>
<td></td>
<td>Lacrimation</td>
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<tr>
<td></td>
<td>Fever absent or low grade</td>
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<tr>
<td></td>
<td>Cough later worsens in frequency and intensity</td>
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<tr>
<td><strong>Duration</strong></td>
<td>1–2 wk</td>
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a After exposure.
Because most adolescents and adults are immunized against pertussis during childhood, clinical presentation can be atypical, often marked by a prolonged cough in isolation of other symptoms. Most infected adults report a cough of greater than 3 weeks’ duration (mean 36–48 days). They may also have episodes of diaphoresis and syncope. Characteristic whoop and posttussive emesis are less common; however, the presence of these symptoms is highly predictive of pertussis in this subset of patients. Because of the atypical features of infection in these patients, many cases of pertussis remain unrecognized. It is estimated that 12% to 32% of cases of cough lasting greater than 1 week in adults are caused by pertussis. Furthermore, adult patients tend to present later, at times when standard diagnostic methods such as culture and PCR are less likely to be positive. The implications of unrecognized infection in this population as a source of ongoing exposure to susceptible individuals have been identified and have influenced immunization schedules in many countries.

Complications

Pneumonia (either primary or secondary) is the most common and most severe complication of pertussis infection, disproportionately affecting infants younger than 6 months of age. Respiratory syncytial virus is a common copathogen, with coinfection rates as high as 33% of hospitalized infants. Other complications include neurologic sequelae (seizures and encephalopathy), weight loss, and complications of severe cough, including incontinence, rib fractures, hernias, conjunctival hemorrhage, cerebral artery dissection, and syncope. Pertussis is associated with higher rates of other concurrent infections, such as sinusitis and otitis media. Case-fatality rates approach 1% of infected infants.

DIFFERENTIAL DIAGNOSIS

Because of a lack of specific symptoms, particularly among hosts who present with atypical features, the differential diagnosis of pertussis infection can be refined by duration of cough, as presented in Table 2. In the early phase, pertussis is generally indistinguishable from common viral URIs and atypical bacterial pneumonias caused by Mycoplasma pneumoniae and Chlamydia pneumoniae, all of which

<table>
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<th>Differential diagnosis of pertussis by duration of cough</th>
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<tr>
<td><strong>Acute (&lt;3 wk)</strong></td>
</tr>
<tr>
<td>Viral URI</td>
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<tr>
<td>Atypical pneumonia</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease exacerbation</td>
</tr>
<tr>
<td>Congestive heart failure</td>
</tr>
<tr>
<td>Bacterial sinusitis</td>
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<tr>
<td>Allergic rhinitis</td>
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<tr>
<td>Bacterial pneumonia</td>
</tr>
<tr>
<td>Asthma exacerbation</td>
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<tr>
<td><strong>Subacute (3–8 wk)</strong></td>
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<tr>
<td>Postinfectious cough</td>
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<tr>
<td>Bacterial sinusitis</td>
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<tr>
<td>Asthma</td>
</tr>
<tr>
<td><strong>Chronic (&gt;8 wk)</strong></td>
</tr>
<tr>
<td>Postnasal drip</td>
</tr>
<tr>
<td>Asthma</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
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<tr>
<td>Angiotensin-converting enzyme inhibitors</td>
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<td>Gastroesophageal reflux disease</td>
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manifest primarily by rhinorrhea, mild cough, and absent or low-grade fever. Infectious considerations decrease dramatically as the duration of cough increases. Host factors, detailed history taking, and empirical trial of agents such as proton-pump inhibitors for gastroesophageal reflux disease and bronchodilators for asthma can help distinguish pertussis from other common causes of chronic cough (see Table 2).

**DIAGNOSIS**

**Clinical Case Definitions**

Both the CDC and World Health Organization (WHO) have developed similar case definitions for pertussis for surveillance purposes. WHO defines a clinical case as an individual with cough lasting at least 2 weeks, in addition to at least 1 of the following symptoms: coughing paroxysms, inspiratory whooping, or posttussive vomiting without other apparent cause.31

WHO defines a confirmed case as an individual satisfying the above clinical case definition in combination with at least 1 of the following laboratory findings: isolation of *B pertussis* in culture, detection of genomic sequences by PCR, or positive paired serology (see section on laboratory diagnosis).31

The CDC definition for a confirmed case is similar, but does not include paired serology and does include epidemiologic link with a culture-confirmed case of pertussis.32 The WHO clinical definition is estimated to be 95.2% sensitive and 15.0% specific when compared with laboratory-confirmed cases.33 With increased number of positive symptoms, the clinical case definition increases in specificity at the expense of decreased sensitivity.

The clinical diagnosis of pertussis is limited by variable disease presentation across age groups, modification of presenting symptoms influenced by previous immunization, and low clinical suspicion by physicians.1,33 The clinical case definitions described earlier have been criticized as outdated and not universally applicable to all age groups. To more accurately capture the variable clinical presentation, age-specific clinical case definitions for pertussis have been proposed.34 Based on consensus recommendations developed at the 2011 Global Pertussis Initiative Conference, pertussis should be clinically suspected in patients presenting with cough without fever, and 1 or more age group-specific symptoms (Fig. 2).

![Fig. 2. Clinical case definition of pertussis for surveillance purposes. (From Cherry JD, Tan T, Wirsing von Konig CH, et al. Clinical definitions of pertussis: summary of a global pertussis initiative roundtable meeting, February 2011. Clin Infect Dis 2012;54:1762; with permission.)](image-url)
Laboratory Diagnosis

Once pertussis is clinically suspected based on the criteria described earlier, confirmation may be made via multiple laboratory techniques. There is no universally agreed gold standard for the laboratory diagnosis of pertussis, although traditionally culture has been used because of its high specificity. Several methods exist, each with its own benefits and limitations.

Specimen Collection

Among suspected cases, samples tested for *B. pertussis* require proper technique and timing as well as special handling to optimize diagnostic yield. Specimens can be obtained via nasal swab or aspiration. Swabs should be obtained from the posterior nasopharynx, rather than the anterior nasopharynx or throat, to optimize yield of live bacteria or DNA from ciliated respiratory epithelial cells for diagnosis. Nasopharyngeal aspiration with saline yields better results than swabs, but aspiration is not always practical in clinical settings. Swabs with Dacron or rayon tips should be used for collection; calcium-alginate and cotton-tipped swabs can inhibit PCR analysis and kill pertussis organisms, respectively. Specimens obtained for culture should be transported in Regan-Lowe agar, a charcoal medium that contains cephalexin to inhibit the growth of other oropharyngeal organisms, then plated on either Borget-Genou or Regan-Lowe agar.

Culture

*B. pertussis* can grow on culture media in as little as 2 to 4 days, but growth often takes up to 5 to 7 days, limiting the timeliness for acute management. The specificity of culture for detection of *B. pertussis* approaches 100%, but sensitivity ranges from 30% to 70%. Sensitivity is limited by improper collection and culturing technique, time delay between specimen collection and culture, previous administration of antibiotics, and previous vaccination status. Cultures tend to be most sensitive in younger patients and if collected early in the disease course, ideally within 2 weeks of symptom onset. Advantages include confirmation and strain identification in outbreak settings as well as the ability to perform antimicrobial susceptibility testing.

Molecular Testing

Molecular-based tests offer several advantages over traditional culture techniques, including more rapid diagnosis and improved sensitivity, and are widely used in the diagnosis of pertussis. Many PCR assays are available to detect DNA from various chromosomal regions specific to *B. pertussis*. PCR has become an increasingly popular diagnostic technique because of its rapid turnaround time (1–2 days), ability to diagnose pertussis up to 4 weeks after symptom onset (when yield of culture-based techniques is limited), and ability to detect pertussis in patients who have been previously immunized or have already received treatment with up to 5 days of antibiotics. Sensitivity of PCR-based testing ranges from 70% to 99%, with a specificity of 88% to 94%. Limitations of PCR testing include availability of laboratory space and properly trained technicians, limited availability of commercial kits, lack of standardized methods, absence of universal thresholds for positivity, and expense of testing. The CDC recommends that PCR be used in conjunction with culture for diagnosis of pertussis, particularly in outbreak situations.
Serology

Serologic methods can also be used for the diagnosis of pertussis. Exposure to *B pertussis* results in rapid production of IgA, IgG, and IgM antibodies to various pertussis antigens that can be detected with enzyme-linked immunosorbent assay techniques. These antibodies are typically apparent by the time clinical symptoms manifest. Immune response to pertussis persists for weeks after initial exposure, therefore serology can be useful in diagnosing pertussis in patients with greater than 2 to 4 weeks of symptoms, an advantage over traditional culture-based techniques. Antibodies to the pertussis toxin antigen (anti-PT antibodies) are the most widely used, because the PT antigen is highly immunogenic and specific to *B pertussis*. Immune response to pertussis persists for weeks after initial exposure, therefore serology can be useful in diagnosing pertussis in patients with greater than 2 to 4 weeks of symptoms, an advantage over traditional culture-based techniques. Antibodies to the pertussis toxin antigen (anti-PT antibodies) are the most widely used, because the PT antigen is highly immunogenic and specific to *B pertussis*. Immunization results in the production of both IgG and IgM antibodies; therefore, use of serologic testing is more difficult to interpret in patients who have been immunized, particularly in children who have completed the full series or in adolescents and adults who have received a booster in the past year.

Dual-sample serology, based on increase in antibody titer from acute to convalescent samples, is not used clinically because of the high number of previously immunized patients and the usual timing of presentation late in the course of illness. In practice, single-sample serology of anti-PT IgG is used, with a cutoff value based on healthy age-matched controls, to determine a positive test result. There is no universally agreed cutoff value for a positive result, but the European Union reference laboratories suggest a value between 65 and 125 IU/mL. This cutoff range results in a sensitivity of 70% to 80% and a specificity of 95% to 99%.

Serologic diagnosis suffers from a lack of standardized commercially available testing kits and lack of universally agreed cutoff values for interpreting positive results. Further, serologic evaluation is limited in infants, whose ability to generate an antibody response may be limited, and among adolescents and adults, whose booster immunizations may be less remote because of newer vaccination schedules.

Direct Fluorescent Antibody Testing

Direct fluorescent antibody (DFA) testing, which uses fluorochrome-conjugated antibodies to antigens of *B pertussis*, was once widely used for rapid diagnosis of pertussis. This modality has largely been replaced by other diagnostic tests because of limited sensitivity and specificity, with high rates of false-positive results attributable to cross-reactivity with other oropharyngeal flora such as *Haemophilus influenzae*. The use of DFA is not recommended for the laboratory diagnosis of pertussis.

Guidance regarding optimal testing strategies based on host and timing of presentation is available in Box 1 and Fig. 3.

**Box 1**

**Summary of diagnosis recommendations**

- PCR and culture should be performed in all patients with high clinical suspicion of pertussis and cough of less than 2 weeks’ duration
- PCR and serology should be performed for adolescent and adult patients with cough of greater than 2 weeks’ duration
- Single-sample serology alone should be considered in patients with symptoms for greater than 4 weeks
Antimicrobial Therapy

Efficacy of antimicrobial therapy during the various stages of pertussis infection has been the subject of much debate. Antibiotics are believed to be most effective in limiting symptom severity and duration when administered early in the course of illness.

Macrolides are the treatment of choice for *B. pertussis*. Antibiotics such as erythromycin, clarithromycin, and azithromycin have all been found to be effective at treating pertussis, with choice of agent primarily based on side effect profile and ease of dosing:

- Azithromycin 500 mg × 1 day, then 250 mg × 4 days
- Clarithromycin 500 mg 2 times/d × 7 days
- Erythromycin 500 mg 4 times/d × 14 days

Newer macrolides including azithromycin and clarithromycin are as effective as erythromycin at eradicating *B. pertussis* from nasopharyngeal secretions and are generally preferred because of less frequent dosing and fewer gastrointestinal side effects, which can be particularly severe with erythromycin and can decrease adherence rates. Azithromycin is the preferred agent in infants younger than 1 month because of associations between erythromycin use and development of hypertrophic pyloric stenosis. Azithromycin is preferable to clarithromycin and erythromycin in patients on multiple medications, because it has far fewer drug interactions. Resistance to macrolides, although it has been described, is rare, and routine antimicrobial susceptibility testing is not generally performed.

Trimethoprim-sulfamethoxazole can be used as an alternative agent in patients with contraindications or allergies to macrolides. The recommended regimen is:

- Trimethoprim-sulfamethoxazole 1 double-strength tablet 2 times/d × 14 days.

Timing of Treatment

Treatment is most effective at reducing the severity or duration of cough if administered within the first 7 days of symptoms, often before the onset of coughing paroxysms. Treatment initiated after this period has limited impact on symptom duration, but does lead to faster eradication of the organism from the nasopharynx, thus reducing rates of transmission. The CDC recommends treating patients older than 1 year within 21 days of symptom onset. Treatment within 6 weeks of symptom onset is recommended for pregnant women in the third trimester, infants younger than 1 year, and those in close contact with infants. If clinical suspicion for pertussis is high, antibiotic therapy should be initiated at the same time that diagnostic testing is performed.
Symptomatic Treatment of Cough

A Cochrane database systematic review examined the impact of various adjunctive therapies for symptomatic treatment of cough related to pertussis, including corticosteroids, $\beta_2$ agonists, leukotriene receptor antagonists, and antihistamines. None of these agents was found to have a significant impact on reducing the frequency or severity of coughing episodes or length of hospital stay.49

Postexposure Prophylaxis

The CDC recommends postexposure prophylaxis for all household contacts of an infected patient within 3 weeks of symptom onset in the index patient.42 The dose and duration of prophylactic antibiotics are the same as those used for treatment. However, a Cochrane review found that postexposure prophylaxis was only marginally effective in preventing development of pertussis in household contacts, and that prophylactic treatment was associated with significant side effects. This study concluded that prophylactic treatment should be instituted only in households with infants younger than 6 months.43 Clinicians should evaluate on a case-by-case basis the risks and benefits of postexposure prophylaxis. Postexposure prophylaxis should be administered to exposed individuals who have (or are in contact with others with) high-risk characteristics for developing complications from pertussis, including infants younger than 1 year, immunocompromised patients, or patients with chronic pulmonary conditions such as cystic fibrosis or chronic obstructive pulmonary disease.

PREVENTION

Immunization

Routine immunization is recommended to prevent pertussis infection. Historical vaccines using killed whole $B$ pertussis organisms in various preparations, in combination with diphtheria and tetanus toxoids, were developed shortly after the cause was identified1 and were released in the United States in the mid-1940s for routine vaccination of children.24 Whole-cell vaccines were widely used for many years and resulted in a dramatic decrease in pertussis incidence.1 Three of the 4 available whole-cell vaccines, evaluated 5 decades after their widespread implementation, were found to be 89% to 96% effective in preventing pertussis infection.1,24 However, concerns regarding the reactogenicity of whole-cell vaccines, including greater propensity toward both local and systemic reactions as well as controversy surrounding serious neurologic sequelae (now largely refuted), led to the introduction of acellular vaccines in the 1990s.1 Clinical efficacy of acellular vaccines ranges from 59% to 93%.1,24

Vaccination Formulations and Schedules

Current vaccine formulations include DTaP (diphtheria, tetanus, and acellular pertussis), used for the initial childhood vaccine series, and Tdap (which contains reduced doses of diphtheria and pertussis antigens), used for adolescent and adult booster immunizations. Two formulations of Tdap booster are available: Adacel (manufactured by Sanofi Pasteur) and Boostrix (manufactured by GlaxoSmithKline).50

Before 2006, infants and children were the only populations routinely immunized against pertussis. As data accumulated supporting the notion of waning immunity after pertussis vaccination5,51 and the importance of older patients as sources of pertussis transmission to unimmunized infants and children,10,11 expanded immunization strategies to include adolescents and adults have been investigated. Based on results of the Adult Pertussis Trial, in which the acellular pertussis vaccine was found to be 92%
effective among adolescents and adults, \(^5^2\) revised vaccination guidelines now include recommendations for pertussis boosters for both adolescents and adults.

The CDC’s Advisory Committee of Immunization Practices (ACIP) recommended vaccine schedule for pertussis is summarized in Box 2. \(^8^, ^5^3\) Tdap boosters can be administered at any time, irrespective of timing of the most recent tetanus-containing or diphtheria-containing vaccine. \(^8\) A recent study reported that a Tdap booster in adulthood, 10 years after a previous booster, was safe and elicited a robust immune response. \(^5^4\) Further refinement of ACIP guidelines may include recommendations for routine decennial Tdap boosters for all adults. \(^5^5\)

**Vaccine Side Effects**

The DTaP and Tdap vaccines are generally well tolerated and associated with fewer local and systemic reactions than historical whole-cell vaccines. The most common side effects (and their relative frequency) include \(^6^6\): injection site pain (67%–75%) or redness (20%); headache (30%–40%) and fatigue (25%–33%); and mild fever less than 100.4°F (1%–4%). Moderate to severe reactions are rare but include: moderate to severe arm pain/swelling (4%–6%); fever greater than 102°F (0.4–1%); seizure (less than 1/14,000); and severe allergic reaction, prolonged seizure, coma, brain damage (less than 1/1,000,000).

**Special Populations: Pregnant Women**

Pregnant women and those in close contact with infants warrant special consideration. A strategy of vaccinating pregnant women and other household contacts of a neonate to provide partial protection from infection is known as a cocooning strategy. \(^5^5\) The ACIP, in conjunction with the American College of Obstetrics and Gynecology, recommends that pregnant women who have not previously received a Tdap booster should receive 1 dose of Tdap during the third trimester or late second trimester, or in the immediate postpartum period if it is not administered during pregnancy. \(^5^7, ^5^8\) As noted earlier, all adults, including those aged 65 and older, who anticipate close contact with an infant and who have not received a Tdap booster, are advised to receive 1 dose of Tdap at least 2 weeks before contact with the infant. \(^8\)

Studies have reported detectable levels of antibodies to \(B\) pertussis antigens in neonates of women immunized during pregnancy, with detectable antibody levels

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**Box 2**

**Summary recommendations for use of tetanus, diphtheria, and acellular pertussis vaccines**

**Infants and Children**
- Five-dose primary immunization series with DTaP recommended at ages 2, 4, 6, and 18 months, with booster at age 4 to 6 years

**Adolescents**
- Adolescents 11 to 18 years of age who have completed the recommended childhood DTaP series should receive a single Tdap booster, preferably at their 11-year-old to 12-year-old preventive health visit

**Adults**
- Adults aged 19 to 64 years should receive a single Tdap booster in lieu of 1 Td booster
- Adults aged 65 and older who have not previously received a Tdap booster should receive 1 booster dose, particularly if contact with infants is anticipated
persisting for up to 6 weeks post partum\textsuperscript{59,60} and likely providing partial protection against pertussis initiation of the primary immunization series at age 2 months.

**Special Populations: Health Care Workers**

Health care workers are at increased risk of exposure to pertussis and have been implicated in nosocomial outbreaks of pertussis.\textsuperscript{61} The ACIP recommends that all adult health care workers with direct patient contact receive a Tdap booster.\textsuperscript{29}

**SUMMARY**

- Incidence of pertussis has increased in recent years, particularly among adolescents and adults, as a result of waning immunity and increased recognition/reporting of the disease.
- Infected adults and adolescents serve as a reservoir to transmit pertussis to infants and children, who are at greater risk for morbidity and mortality.
- Previously immunized adolescents and adults are more likely to present with a prolonged cough illness than the classic symptoms of inspiratory whooping and posttussive emesis; they often have no specific examination, laboratory, or radiographic evidence that can distinguish pertussis from other respiratory infections.
- Physicians must have a high level of clinical suspicion to avoid missing the diagnosis of pertussis.
- If pertussis is suspected clinically, attempts should be made to confirm diagnosis. The diagnostic method of choice (culture, PCR, or serology) depends largely on time from symptom onset.
- Prompt initiation of treatment with a macrolide antibiotic may decrease the severity and duration of symptoms, and may also reduce rates of transmission. Treatment should be initiated at the same time that diagnostic testing is performed.
- Routine completion of infant and childhood vaccination series is still critical to prevent pertussis; because of waning immunity over time, booster immunizations are now also necessary for adolescents, adults, pregnant women, and health care workers.

**REFERENCES**


57. Centers for Disease Control and Prevention. Updated recommendations for use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine (Tdap) in pregnant women and persons who have or anticipate having close contact with an infant aged <12 months–Advisory Committee on Immunization Practices (ACIP). 2011. MMWR Morb Mortal Wkly Rep 2011;60(41):1424–6.


