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Recommended Antimicrobial Agents for Treatment and Postexposure Prophylaxis of Pertussis

2005 CDC Guidelines

DEPARTMENT OF HEALTH AND HUMAN SERVICES
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Recommended Antimicrobial Agents for the Treatment and Postexposure Prophylaxis of Pertussis

2005 CDC Guidelines

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Summary

The recommendations in this report were developed to broaden the spectrum of antimicrobial agents that are available for treatment and postexposure prophylaxis of pertussis. They include updated information on macrolide agents other than erythromycin (azithromycin and clarithromycin) and their dosing schedule by age group.

Introduction

Pertussis is an acute bacterial infection of the respiratory tract that is caused by *Bordetella pertussis,* a gram-negative bacterium (Box 1). *B. pertussis* is a uniquely human pathogen that is transmitted from an infected person to susceptible persons, primarily through aerosolized droplets of respiratory secretions or by direct contact with respiratory secretions from the infected person.

Disease Burden

The Council of State and Territorial Epidemiologists (CSTE) reviewed and approved a standard case definition for pertussis in June 1997 (*1,2*) (Box 2). The national pertussis surveillance system is passive and relies on physicians to report cases of pertussis to state and local health departments, which then report cases of pertussis weekly to the National Notifiable Diseases Surveillance System (NNDSS). The reports are transmitted to CDC through the National Electronic Telecommunications System for Surveillance (NETSS) and contain demographic data and supplemental clinical and epidemiologic information for each reported pertussis case.

Despite high childhood vaccination coverage levels for pertussis vaccine (*3,4*), pertussis remains a cause of substantial morbidity in the United States. Pertussis is the only disease for which universal childhood vaccination is recommended that has an increasing trend in reported cases in the United States. The disease is endemic in the United States with epidemic cycles every 3–4 years. In the early vaccine years during 1922–1940, an average annual rate of 150 per 100,000 population was reported (*5,6*). After introduction of universal vaccination during the 1940s, the incidence of reported pertussis declined dramatically to approximately one case per 100,000 population.

During the preceding 3 decades, reports of pertussis steadily increased again in the United States, from a nadir of 1,010 cases in 1976 (*3*) to 25,827 in 2004 (2004 rate: 8.5 cases per 100,000 population) (*7*); the number of reported pertussis cases in 2004 was the highest since 1959. Increased awareness and improved recognition of pertussis among clinicians, greater access to and use of laboratory diagnostics (especially extensive polymerase chain reaction [PCR] testing), and increased surveillance and reporting of pertussis by public health departments could have contributed to the increase in reported cases (*8*). Some of the reported increase might constitute a real increase in the incidence of pertussis (*9*). Although infants have the highest incidence of pertussis of any age group, adolescents and adults account for the majority of reported cases.

Clinical Manifestations

The incubation period of pertussis averages 7–10 days (range: 5–21 days) (*6,10*) and has been reported to be as long as 6 weeks (*11,12*). Pertussis has an insidious onset with catarrhal symptoms (nasal congestion, runny nose, mild sorethroat, mild dry cough, and minimal or no fever) that are indistinguishable from those of minor respiratory tract infec-

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BOX 1. Epidemiology, diagnosis, treatment, and prevention of pertussis (whooping cough)

Epidemiology

- 25,827 cases reported in the United States in 2004, the highest number of reported cases since 1959.
- Approximately 60% of cases are in adolescents (aged 11–18 years) and adults (aged >20 years).
- Transmitted person-to-person through aerosolized droplets from cough or sneeze or by direct contact with secretions from the respiratory tract of infectious persons.
- Incubation period 5–21 days; usually 7–10 days.
- Highly contagious; 80% secondary attack rates among susceptible persons.
- Endemic in the United States; epidemic every 3–4 years.

Clinical findings

- Catarrhal period (1–2 weeks): illness onset insidious (coryza, mild fever, and nonproductive cough); infants can have apnea and respiratory distress.
- Paroxysmal period (2–6 weeks): paroxysmal cough, inspiratory "whoop," posttussive vomiting.
- Convalescent period (≥2 weeks): paroxysms gradually decrease in frequency and intensity.

Laboratory testing

- Culture of nasopharyngeal aspirate or Dacron™ swab for *Bordetella pertussis* on Regan Lowe or Bordet-Gengou culture medium.
- Detection of *B. pertussis* DNA by polymerase chain reaction.
- Not helpful to test contacts without respiratory symptoms.

Recommended treatment

- Macrolide antibiotic
  - 5-day course of azithromycin
  - 7-day course of clarithromycin
  - 14-day course of erythromycin.
- Alternative agent
  - 14-day course of trimethoprim-sulfamethoxazole.
- Treat persons aged >1 year within 3 weeks of cough onset.
- Treat infants aged <1 year within 6 weeks of cough onset.

Postexposure prophylaxis

- Administer course of antibiotic to close contacts within 3 weeks of exposure, especially in high-risk settings; same doses as in treatment schedule.

Prevention and surveillance

- Vaccinate children aged 6 weeks–6 years with diphtheria, tetanus toxoids and acellular pertussis vaccine (DTaP). In 2005, The Advisory Committee on Immunization Practices voted to recommend a single dose of Tetanus Toxoid and Reduced Diphtheria and Acellular Pertussis vaccine (Tdap) for adolescents and adults aged <65 years.
- Report all cases to local and state health departments.

BOX 2. Council of State and Territorial Epidemiologists case definition for pertussis

Clinical case: A cough illness lasting ≥2 weeks with one of the following: paroxysms of coughing, inspiratory "whoop," or posttussive vomiting without other apparent cause.

Laboratory criteria for diagnosis

- Isolation of *Bordetella pertussis* from clinical specimen or
- Positive polymerase chain reaction (PCR) for *B. pertussis* (as qualified in comments)

Case classification

Probable: a case that meets the clinical case definition, is not laboratory confirmed, and is not epidemiologically linked to a laboratory-confirmed case

Confirmed: an acute cough illness of any duration that is laboratory confirmed by culture or one that meets the clinical case definition and is either laboratory confirmed by PCR (as qualified in comments) or epidemiologically linked to a laboratory-confirmed case.

Comment

- The clinical case definition is appropriate for endemic or sporadic cases. In outbreak settings, a case might be defined as a cough illness lasting ≥2 weeks.
- No assay in the United States is validated and standardized. Although these PCR assays might meet the state and CLIA requirements for analytical and clinical validation, no data is available on interlaboratory validation, including clinical sensitivity and specificity. For all these reasons and because in general PCR is less specific than culture, PCR-positive cases with <14 days duration should not be reported as confirmed.
- Because some studies have documented that direct fluorescent antibody (DFA) testing of nasopharyngeal secretions has low sensitivity and variable specificity, DFA testing is not a criteria for laboratory confirmation of a case for national reporting purposes.
- Serologic testing for pertussis is commercially available but is not approved by the U.S. Food and Drug Administration for diagnostic use and, therefore, generally should not be used and relied on as a criterion for laboratory confirmation for national reporting purposes.
- Both probable and confirmed cases should be reported to the National Notifiable Diseases Surveillance System.

tions. Some infants can have atypical disease and initially have apneic spells and minimal cough or other respiratory symptoms. The catarrhal stage last approximately 1–2 weeks. The cough, which is initially intermittent, becomes paroxysmal. A typical paroxysm is characterized by a succession of coughs that follow each other without inspiration. Paroxysms terminate in typical cases with inspiratory "whoop" and can be followed by posttussive vomiting. Although children are often exhausted after a coughing paroxysm, they usually appear relatively well between episodes. Paroxysms of cough usually increase in frequency and severity as the illness progresses and usually persist for 2–6 weeks. Paroxysms can occur more frequently at night. The illness can be milder and the characteristic whoop absent in children, adolescents, and adults who were previously vaccinated.

Convalescence is gradual and protracted. The severity of illness wanes, paroxysms subside, and the frequency of coughing bouts decreases. A nonparoxysmal cough can continue for 2–6 weeks or longer. During the recovery period, superimposed viral respiratory infections can trigger a recurrence of paroxysms.

Patients with pertussis often have substantial weight loss and sleep disturbance (*13*). Conditions resulting from the effects of the pressure generated by severe coughing include pneumothorax, epistaxis, subconjunctival hemorrhage, subdural hematoma, hernia, rectal prolapse, urinary incontinence, and rib fracture (*14*). Some infections are complicated by primary or secondary bacterial pneumonia and otitis media. Infrequent neurologic complications include seizures and hypoxic encephalopathy.

Adolescents and adults with unrecognized or untreated pertussis contribute to the reservoir of *B. pertussis* in the community. Patients with pertussis are most infectious during the catarrhal stage and during the first 3 weeks after cough onset. Pertussis is highly infectious; the secondary attack rate exceeds 80% among susceptible persons (*15,16*). Unvaccinated or incompletely vaccinated infants aged <12 months have the highest risk for severe and life-threatening complications and death (*5,8,17–25*).

Differential Diagnosis

The differential diagnoses of pertussis include infections caused by other etiologic agents, including adenoviruses, respiratory syncytial virus, *Mycoplasma pneumoniae, Chlamydia pneumoniae,* and other *Bordetella* species such as *B. parapertussis,* and rarely *B. bronchoseptica* (*26*) *or B. holmseii* (*27*). Despite increasing awareness and recognition of pertussis as a disease that affects adolescents and adults, pertussis is overlooked in the differential diagnosis of cough illness in this population (*28*).

Prevention

Vaccination of susceptible persons is the most important preventive strategy against pertussis. Universal childhood pertussis vaccine recommendations have been implemented since the mid-1940s. For protection against pertussis during childhood, the Advisory Committee on Immunization Practices (ACIP) recommends 5 doses of diphtheria and tetanus toxoid and acellular pertussis (DTaP) vaccine at ages 2, 4, 6, 15–18 months, and 4–6 years (*29*). Childhood vaccination coverage for pertussis vaccines has been at an all-time high (*4*). However, neither vaccination nor natural disease confers complete or lifelong protective immunity against pertussis or reinfection. Immunity wanes after 5–10 years from the last pertussis vaccine dose (*3,8,30–34*). Older children, adolescents, and adults can become susceptible to pertussis after a complete course of vaccination during childhood.

During spring of 2005, two Tetanus Toxoid and Reduced Diphtheria Toxoid and Acellular Pertussis vaccines adsorbed (Tdap) formulated for adolescents and adults were licensed in the United States (BOOSTRIX®, GlaxoSmithKline Biologicals, Rixensart, Belgium and ADACEL, Sanofi Pasteur, Toronto, Ontario, Canada). ACIP voted to recommend a single dose of Tdap for adolescents aged 11–18 years in June 2005 and adults aged 19–64 years in October 2005.

Treatment of Pertussis

Maintaining high vaccination coverage rates among preschool children, adolescents, and adults and minimizing exposures of infants and persons at high risk for pertussis is the most effective way to prevent pertussis. Antibiotic treatment of pertussis and judicious use of antimicrobial agents for postexposure prophylaxis will eradicate *B. pertussis* from the nasopharynx of infected persons (symptomatic or asymptomatic). A macrolide administered early in the course of illness can reduce the duration and severity of symptoms and lessen the period of communicability (*35*). Approximately 80%–90% of patients with untreated pertussis will spontaneously clear *B. pertussis* from the nasopharynx within 3–4 weeks from onset of cough (*36*); however, untreated and unvaccinated infants can remain culture-positive for >6 weeks (*37*). Close asymptomatic contacts (*38*) (Box 3) can be administered postexposure chemoprophylaxis to prevent secondary cases; symptomatic contacts should be treated as cases.

Erythromycin, a macrolide antibiotic, has been the antimicrobial of choice for treatment or postexposure prophylaxis of pertussis. It is usually administered in 4 divided daily doses for 14 days. Although effective for treatment (Table 1) and postexposure prophylaxis (Table 2), erythromycin is accompanied by uncomfortable to distressing side effects that result in poor adherence to the treatment regimen. During the last decade, in vitro studies have demonstrated the effectiveness against *B. pertussis* of two other macrolide agents (azithromycin and clarithromycin) (*57–64*). Results from in vitro studies are not always replicated in clinical studies and practice. A literature search and review was conducted for in vivo studies

BOX 3. Close contacts and postexposure prophylaxis

- A close contact of a patient with pertussis is a person who had face-to-face exposure within 3 feet of a symptomatic patient. Respiratory droplets (particles >5 μm in size) are generated during coughing, sneezing, or talking and during the performance of certain procedures such as bronchoscopy or suctioning; these particles can be propelled through the air for distances of approximately 3 feet.
  - — Close contacts also can include persons who
    - have direct contact with respiratory, oral, or nasal secretions from a symptomatic patient (e.g., cough, sneeze, sharing food and eating utensils, mouth-to-mouth resuscitation, or performing a medical examination of the mouth, nose, and throat)
    - shared the same confined space in close proximity with a symptomatic patient for ≥1 hour
  - — Some close contacts are at high risk for acquiring severe disease following exposure to pertussis. These contacts include infants aged <1 year, persons with some immunodeficiency conditions, or other underlying medical conditions such as chronic lung disease, respiratory insufficiency, or cystic fibrosis
- Postexposure prophylaxis with an appropriate antimicrobial agent can be administered to close contacts of patients and to persons who are at high risk for having severe or complicated pertussis.

and clinical trials that were conducted during 1970–2004 and used clarithromycin or azithromycin for the treatment and prophylaxis of pertussis (Table 3). On the basis of this review, guidelines were developed to broaden the spectrum of macrolide agents available for pertussis treatment and postexposure prophylaxis and are presented in this report to update previous CDC recommendations (*71*). Treatment and postexposure prophylaxis recommendations are made on the basis of existing scientific evidence and theoretical rationale.

Recommendations

I. General Principles

A. Treatment. The macrolide agents erythromycin, clarithromycin, and azithromycin are preferred for the treatment of pertussis in persons aged ≥1 month. For infants aged <1 month, azithromycin is preferred; erythromycin and clarithromycin are not recommended. For treatment of persons aged ≥2 months, an alternative agent to macrolides is trimethoprim-sulfamethoxazole (TMP–SMZ) (Table 4).

The choice of antimicrobial for treatment or prophylaxis should take into account effectiveness, safety (including the potential for adverse events and drug interactions), tolerability, ease of adherence to the regimen prescribed, and cost. Azithromycin and clarithromycin are as effective as erythromycin for treatment of pertussis in persons aged ≥6 months, are better tolerated, and are associated with fewer and milder side effects than erythromycin. Erythromycin and clarithromycin, but not azithromycin, are inhibitors of the cytochrome P450 enzyme system (CYP3A subclass) and can interact with other drugs that are metabolized by this system. Azithromycin and clarithromycin are more resistant to gastric acid, achieve higher tissue concentrations, and have a longer half-life than erythromycin, allowing less frequent administration (1–2 doses per day) and shorter treatment regimens (5–7 days). Erythromycin is available as generic preparations and is considerably less expensive than azithromycin and clarithromycin.

B. Postexposure prophylaxis. A macrolide can be administered as prophylaxis for close contacts of a person with pertussis if the person has no contraindication to its use. The decision to administer postexposure chemoprophylaxis is made after considering the infectiousness of the patient and the intensity of the exposure, the potential consequences of severe pertussis in the contact, and possibilities for secondary exposure of persons at high risk from the contact (e.g., infants aged <12 months). For postexposure prophylaxis, the benefits of administering an antimicrobial agent to reduce the risk for pertussis and its complications should be weighed against the potential adverse effects of the drug. Administration of postexposure prophylaxis to asymptomatic household contacts within 21 days of onset of cough in the index patient can prevent symptomatic infection. Coughing (symptomatic) household members of a pertussis patient should be treated as if they have pertussis. Because severe and sometimes fatal pertussis-related complications occur in infants aged <12 months, especially among infants aged <4 months, postexposure prophylaxis should be administered in exposure settings that include infants aged <12 months or women in the third trimester of pregnancy. The recommended antimicrobial agents and dosing regimens for postexposure prophylaxis are the same as those for treatment of pertussis (Table 4).

C. Special considerations for infants aged <6 months when using macrolides for treatment or postexposure prophylaxis. The U.S. Food and Drug Administration (FDA) has not licensed any macrolide for use in infants aged <6 months. Data on the safety and efficacy of azithromycin and clarithromycin use among infants aged <6 months are limited.

Data from subsets of infants aged 1–5 months (enrolled in small clinical studies) suggest similar microbiologic effective-

TABLE 1. Results from studies that evaluated the effectiveness of erythromycin treatment on reducing symptoms of pertussis patients

Author and year	Setting	Type of study	Case definition	Comparison groups	Sample size	Erythromycin treatment	Effect of treatment on symptoms	Vaccination status
Bass, 1969 (*39*)	U.S.	Randomized	Clinical pertussis and culture-positive or direct fluorescent antibody (DFA)-positive	Four therapy (erythromycin, chloramphenicol, oxytetracycline, and ampicillin) and one untreated control group	10 patients in each group	50 mg per day, 4 divided doses for 7 days	Duration of catarrhal, paroxysmal, and convalescent stages was similar between the groups	Two children had 3 doses of DTP (both in oxytetracycline group)
Baraff, 1978 (*40*)	U.S.	Experimental	Cough lasting >1 week and cyanosis, vomiting, or whoop, and culture-positive	Those who received erythromycin versus those who were not treated (onset not reported)	Seven untreated, 18 treated patients	Estolate: 40 mg/kg per day (duration not reported)	Mean duration of hospitalization was similar in two groups: 7.3 days in treatment group versus 8.5 days in control group	Not controlled for
Bergquist, 1987 (*41*)	Sweden	Randomized open	Age >1 year, suspected pertussis evident for <14 days; 25 of 38 already had whoops	Same as cases, untreated	17 treated with erythromycin, 21 untreated controls	Ethylsuccinate: 25 mg/kg twice daily for 10 days	Number of whoops between day 1 and 14: 50% reduction in the treatment group (p<0.02) and doubled in the control group (p<0.05)	Not reported
Steketee, 1988 (*42*)	U.S.	Observational, retrospective, cohort	Respiratory illness and culture-, DFA-, or serology-positive in an institutional setting	Treatment within 1 week versus >1 week of any respiratory symptoms in seropositive patients or untreated patients	40 treated <1 week, 43 treatment started >1 week	Erythromycin base or ethylsuccinate: 40 mg/kg per day orally, divided into 4 daily doses for 14 days	43% (17 of 40) of early treated patients and 19% (eight of 43) of late treated patients did not have cough (risk ratio = 2.28; 95% confidence interval = 1.1–4.5). Duration of cough longer and a significantly higher proportion of severe symptoms in late treatment group	Few unvaccinated residents, not controlled for in the analysis
Farizo, 1997 (*43*)	U.S.	Analysis of national surveillance data	Cases of pertussis reported to CDC during 1980–1989	Persons with cases who started prophylaxis <0–7 days, 8–14 days, and >14 days of onset of cough compared with untreated group (controlled for age)	>700 in each group	All treated persons received oral erythromycin therapy for ≥10 days	Percentage of those with cough of ≥28 days was lower in the group treated <0–7 days after cough onset compared with untreated group (p<0.01). The highest percentage of patients with long cough was in the group treated >14 days of cough onset	Not controlled for
Bortolussi, 1995 (*35*)	Canada	Observational prospective, household study	Culture-positive index cases	Persons who began treatment <1 week of cough onset versus >21 days of cough onset	189 patients in all ages	Dosage and duration not reported	Mean duration of cough and paroxysms 38 and 28 days in early treatment group versus 57 and 44 days in late treatment group	>90% of children had 3 doses
Halperin, 1997 (*44*)	Canada	Prospective, randomized, controlled, clinical trial	Nasopharyngeal aspirate culture-positive	Those who received 7 days of erythromycin versus those who received 14 days of erythromycin	87 treated for 7 days, 106 treated for 14 days	7 or 14 days of erythromycin estolate, 40 mg/kg per day in 3 divided doses, maximum: 1 g per day	No difference in the bacteriologic persistence (p=0.98) or bacteriologic relapse (p=0.77) between the 7- and 14-day treatment groups	Not reported

TABLE 2. Results from studies that evaluated the effectiveness of erythromycin treatment and prophylaxis on reducing spread of pertussis

Author and year	Setting	Type of study	Case definition	Treatment of index case	Comparison groups	Erythromycin prophylaxis	Effect of prophylaxis on secondary spread	Vaccination status
Altemeier, 1977 (*45*)	U.S.	Case report	Index patient: culture-positive, hospitalized, symptomatic neonate	Not treated at the time of exposure	Seven neonates exposed to the index patient before his treatment	50 mg/kg per day of erythromycin intramuscularly for 5 days	None had symptoms (two were culture-positive before prophylaxis)	Not available
Halsey, 1980 (*46*)	U.S.	Case report	Index patient: culture-positive, hospitalized, symptomatic neonate	Erythromycin: 55 mg/kg per day. Infant was still culture-positive at the time of exposure	One infant exposed to the index patient for 3 days during culture-positive stage	Ethylsuccinate 55 mg/kg per day	Three days after erythromycin prophylaxis began, contact became symptomatic and culture-positive. After 8 more days of treatment, contact became culture-negative	One dose of DTP
Grob, 1981 (*47*)	Britain	Randomized, placebo-controlled, double blind	Index patient: culture-positive; secondary case: not specified	29 of 40 index patients treated with erythromycin, dosage and duration not reported	Household contacts (31unvaccinated,60 vaccinated) prophylaxed or received placebo	50 mg/kg per day, 4 divided doses for 14 days. Prophylaxis began 13 days (±8 days)	Unvaccinated contacts: 20% (four of 20) treated versus 18% (two of 11) untreated contacts had pertussis. Could not separate effect of treatment of index patient from effect of prophylaxis	None of the vaccinated children had pertussis
Spencely, 1981 (*48*)	Britain	Randomized	Diagnosed pertussis; secondary case: respiratory symptoms of more than trivial duration	17 patients: eight received erythromycin, two received other antibiotics; dosage and duration not reported	Household contacts prophylaxed (11) or received placebo (nine)	125 mg or 250 mg 4 times a day for 10 days for children aged <2 years or $\geq$2 years, respectively	82% (nine of 11) treated and 22% (two of nine) untreated children had pertussis. More of erythromycin group was already experiencing symptoms at trial onset	Nine contacts were unvaccinated, five had 2 doses
Granstrom, 1987 (*49*)	Sweden	Retrospective review of cases	Index patient: pregnant women with serology- or culture-positive pertussis	250–500 mg for 3 doses a day for 10 days. Received 3 (±3 days) before delivery	28 newborns prophylaxed with erythromycin; four did not receive	Erythromycin 40 mg/kg per day, 3 times a day; 22 for 10 days, six for 5 days. All mothers nursed their infants.	None of the infants had symptoms or laboratory evidence of pertussis	Not available
Biellik, 1988 (*50*)	U.S.	Case-control, household study	Acute cough illness $\geq$14 days or $\geq$7 days and paroxysms or paroxysmal cough causing sleep disturbance on $\geq$2 nights	Not reported	Households with secondary cases versus households without secondary cases	Erythromycin, dosage and duration not reported	Average interval between onset of illness in first patient and initiation of therapy: 24 days (households with secondary cases) versus 11 days (households with no secondary cases) ($p<0.001$). Average interval between onset of illness in first patient and initiation of prophylaxis: 23 days (household with secondary cases) versus 14 days (household with no secondary cases) ($p<0.02$). Similar number of contacts administered prophylaxis, number of contacts and first patients completed $\geq$10 days of treatment	Similar vaccination status

TABLE 2. (*Continued*) Results from studies that evaluated the effectiveness of erythromycin treatment and prophylaxis on reducing spread of pertussis

Author and year	Setting	Type of study	Case definition	Treatment of index case	Comparison groups	Erythromycin prophylaxis	Effect of prophylaxis on secondary spread	Vaccination status
Steketee, 1988 (*42*)	U.S.	Observational, retrospective cohort	Respiratory illness and culture-, direct fluorescent antibody (DFA)- or serology-positive in an institutional setting	Erythromycin base or ethylsuccinate: 40 mg/kg per day orally, divided into 4 daily doses for 14 days	Wards whose residents prophylaxed within <2 weeks of cough onset of first case versus wards prophylaxed within 4 weeks of first case	Same as treatment for all residents of exposed wards	Attack rates in wards prophylaxed early: 16% (13 of 125 residents) versus 75% late (85 of 113)	Few unvaccinated residents; in the analysis, vaccination status not controlled for
Sprauer, 1988 (*51*)	U.S.	Observational, retrospective cohort	Culture-positive, ≥14 days cough or paroxysmal cough of ≥7 days.; secondary case: onset 7–28 days after first case	Received 5 days of continuous erythromycin, dosage not reported	Households (17) with secondary cases versus households (20) without secondary cases	≥10 days of erythromycin after exposure	More first patients in households with no secondary transmission received treatment (100% versus 76%) (p<0.05). Median interval to treatment of first patient: 11 days in households with no secondary cases, 21 days in households with secondary cases (p = 0.057). Percentage of contacts receiving prophylaxis <3 weeks of first patient: 97% in households with no secondary cases, 47% in households with secondary cases (p<0.001). Median interval from first patients to prophylaxis: 16 days in households with no secondary cases, 22 days in households with secondary cases (p<0.001)	Vaccination status similar between groups
Fisher, 1989 (*52*)	U.S.	Observational	Culture-, DFA-, or serology-positive	Erythromycin, 14 days	None. Results from culture specimens taken on three occasions (0 and 18 days and 2 months later) were compared	Erythromycin, 14 days	Administration of erythromy-cin to all residents eliminated culture-positive cases and stopped the spread of infection. No resident had a positive culture or DFA test result at the end of 14 days of treatment or 2 months later	
Wirsing von Konig, 1995 (*53*)	Germany	Household study, nested in a vaccine efficacy trial	Primary case: 21-day paroxysmal cough and laboratory (culture, serology) confirmation; secondary case: ≥7-day paroxysmal cough and laboratory confirmation, onset ≥7 days after primary case	Erythromycin, dosage and duration not reported	Household contacts whose index patients have been treated (265) or not treated (151)	Erythromycin, dosage and duration not reported	Attack rate in child contacts (6–47 months, unvacci-nated) of treated first patients: 51% (55 of 109) versus untreated first patients: 64% (41 of 64) (p>0.05). Attack rate in adult contacts of treated first patients: 20% (31 of 156) versus untreated first patients: 36% (31 of 87) (p<0.05)	Not reported for contacts

TABLE 2. (*Continued*) Results from studies that evaluated the effectiveness of erythromycin treatment and prophylaxis on reducing spread of pertussis

Author and year	Setting	Type of study	Case definition	Treatment of index case	Comparison groups	Erythromycin prophylaxis	Effect of prophylaxis on secondary spread	Vaccination status
DeSerres, 1995 (*54*)	Canada	Retrospective cohort, household study	Primary case: culture-positive or CDC case definition; secondary case: ≥2 weeks cough	Not reported	Contacts (940) in households with prophylaxis versus those without prophylaxis	Varied. Adults: 250–500 mg 3 times a day; children 40–50 mg/kg per day for 10–14 days	Secondary attack rate: households with prophylaxis: 17%; households without prophylaxis: 25% (risk ratio = 0.69; 95% confidence interval = 0.5–0.9). Secondary attack rate: prophylaxis used before onset of secondary case: 4% versus 35% after secondary case (p<0.001). Compared with secondary attack rates among households prophylaxed within 21 days, secondary attack rates doubled when prophylaxis was administered >21 days after onset of cough in the primary patient or not administered at all	Vaccination status was not a factor in secondary AR
Schmitt, 1996 (*55*)	Germany	Blinded, prospective follow-up of household contacts	Index case: ≥21 day spasmodic cough and culture- or serology-positive; secondary case: onset 7–28 days after onset of cough in the first patient	Erythromycin, dosage not reported	Unvaccinated contacts whose index patients have been treated versus those not treated	Erythromycin, dosage and duration not reported	Attack rates in unvaccinated household contacts whose index patients have been treated: 51% versus 64% in index patient not treated (p=0.08)	67% of unvaccinated contacts received prophylaxis
Halperin, 1999 (*56*)	Canada	Randomized, double-blind, placebo controlled	a) culture-positive, b) culture-positive or paroxysmal cough of ≥2 weeks, or c) culture-positive or cough ≥2 weeks and whoop, paroxysm, vomiting, apnea, or cyanosis	Erythromycin for 7 or 14 days	Household contacts of randomly selected culture-confirmed cases. Contacts were administered placebo	10 days of erythromycin estolate, 40 mg/kg per day in 3 divided doses; maximum: 1 g per day	Fewer posttussive vomiting or whoop in the erythromycin treatment group; respiratory symptoms, nasal congestion, cough, or paroxysmal cough similar in both groups. Efficacy in preventing culture-positive pertussis was 67.5% (95% confidence interval = 7.6%–88.7%). No significant difference in secondary attack rates when only contacts who were asymptomatic before prophylaxis were examined	Not reported

TABLE 3. Results from studies that evaluated the effectiveness of azithromycin or clarithromycin for treatment of pertussis patients

Author and year	Setting	Type of study	Participants (positive cultures)	Comparison treatment groups	Sample size	Microbiologic eradication rate at end of treatment and follow-up	Vaccination status
Ayoma, 1996 (*65*)	Japan	Prospective, randomized during June 1993–March 1995	Cases matched with historical erythromycin group by age, sex, vaccination status, and recent onset of disease before June 1993	10 mg/kg per day twice daily for 5 days (maximum: 500 mg)	Azithromycin N = 8	100% at 1 week post-treatment for azithromycin and 81% in erythromycin group; no relapse at 2 weeks in both groups	Five unvaccinated children aged <1 year
			Age <2 years (10 of 17) 2 –13 years (seven of 17)	Clarithromycin 10 mg/kg once daily (maximum: 400 mg) for 7 days	N = 9	100% at 1 week post treatment for clarithromycin and 89% in erythromycin group; no relapse at 2 weeks in both groups	Six unvaccinated children aged <1 year
			Mean duration of illness Azithromycin = 14.1 (±3 days) Clarithromycin = 11.8 (±7.2 days) Erythromycin = 11.2 (±7.1 days)	Historical control group: Erythromycin 40–50 mg per day three times daily for 14 days	N = 34		
Bace, 1999 (*66*)	Croatia	Prospective, open	Age 1–18 months (Mean: 7.5 months)	Azithromycin: 10 mg/kg once daily on day 1 then 5 mg/kg once daily for 4 days	N = 17	100% at days 7, 14, and 21 from start of treatment	Not reported
		Noncomparative to assess efficacy and safety of two azithromycin regimens	Duration of illness: 3–30 days (mean: 12.5 days)	Azithromycin 10 mg/kg once daily for 3 days	N = 20	89.5%, 100%, and 7.1 % at days 7, 14, 21 from start of treatment	
Bace, 2000 (*67*)	Croatia	Prospective, open, randomized, comparative	Age 1–15 months Duration of illness: 2–37 days	Azithromycin 10 mg/kg once daily for 3 days	A = 9	100% at days 7, 14, and 21 in all groups	Groups similar
				Erythromycin for 14 days	E = 15		Not reported
Langley, 2004 (*68*)	Canada	Prospective, open, multicenter, comparative	Age 6 months–16 years	Azithromycin 10 mg/kg once on day 1 then 5mg/kg once daily for 4 days	N = 58	100% at end of treatment and 7 days after completion in both groups for participants with available cultures	Groups similar
				Erythromycin estolate 40 mg/kg per day three times daily for 10 days	N = 56		Not reported
Lebel and Mehra, 2001 (*69*)	Canada	Prospective, single-blind, parallel group trial	Age 1 month–16 years	Clarithromycin 15 mg/kg per day twice per day for 7 days	N = 76	100% for clarithromycin group and 96% for erythromycin group at end of treatment	89% vaccinated in clarithromycin group and 90% for erythromycin
				Erythromycin 40 mg/kg per day three times daily for 14 days	N = 77		
Pichichero, 2003 (*70*)	U.S.	Prospective, open label, noncomparative	Age 6 months–20 years	Azithromycin 10 mg/kg once on day 1 then 5mg/kg once daily for 4 days	N = 29	100% at days 3 and 21 from start of treatment	Not reported

TABLE 4. Recommended antimicrobial treatment and postexposure prophylaxis for pertussis, by age group

	Primary agents			Alternate agent*
Age group	**Azithromycin**	**Erythromycin**	**Clarithromycin**	**TMP-SMZ**
<1 month	Recommended agent. 10 mg/kg per day in a single dose for 5 days (only limited safety data available.)	Not preferred. Erythromycin is associated with infantile hypertrophic pyloric stenosis. Use if azithromycin is unavailable; 40–50 mg/kg per day in 4 divided doses for 14 days	Not recommended (safety data unavailable)	Contraindicated for infants aged <2 months (risk for kernicterus)
1–5 months	10 mg/kg per day in a single dose for 5 days	40–50 mg/kg per day in 4 divided doses for 14 days	15 mg/kg per day in 2 divided doses for 7 days	Contraindicated at age <2 months. For infants aged ≥2 months, TMP 8 mg/kg per day, SMZ 40 mg/kg per day in 2 divided doses for 14 days
Infants (aged ≥6 months) and children	10 mg/kg in a single dose on day 1 then 5 mg/kg per day (maximum: 500 mg) on days 2–5	40–50 mg/kg per day (maximum: 2 g per day) in 4 divided doses for 14 days	15 mg/kg per day in 2 divided doses (maximum: 1 g per day) for 7 days	TMP 8 mg/kg per day, SMZ 40 mg/kg per day in 2 divided doses for 14 days
Adults	500 mg in a single dose on day 1 then 250 mg per day on days 2–5	2 g per day in 4 divided doses for 14 days	1 g per day in 2 divided doses for 7 days	TMP 320 mg per day, SMZ 1,600 mg per day in 2 divided doses for 14 days

* Trimethoprim sulfamethoxazole (TMP–SMZ) can be used as an alternative agent to macrolides in patients aged ≥2 months who are allergic to macrolides, who cannot tolerate macrolides, or who are infected with a rare macrolide-resistant strain of *Bordetella pertussis.*

ness of azithromycin and clarithromycin against pertussis as with older infants and children. If not treated, infants with pertussis remain culture-positive for longer periods than older children and adults (*36,72*). These limited data support the use of azithromycin and clarithromycin as first-line agents among infants aged 1–5 months, based on their in vitro effectiveness against *B. pertussis*, their demonstrated safety and effectiveness in older children and adults, and more convenient dosing schedule.

For treatment of pertussis among infants aged <1 month (neonates), no data are available on the effectiveness of azithromycin and clarithromycin. Abstracts and published case series describing use of azithromycin among infants aged <1 month report fewer adverse events compared with erythromycin (*73*); to date, use of azithromycin in infants aged <1 month has not been associated with infantile hypertrophic pyloric stenosis (IHPS). Therefore, for pertussis, azithromycin is the preferred macrolide for postexposure prophylaxis and treatment of infants aged <1 month. In this age group, the risk for acquiring severe pertussis and its life-threatening complications outweigh the potential risk for IHPS that has been associated with erythromycin (*74*). Infants aged <1 month who receive a macrolide should be monitored for IHPS and other serious adverse events.

D. Safety. A comprehensive description of the safety of the recommended antimicrobials is available in the package insert, or in the latest edition of the *Red Book: Pharmacy's Fundamental Reference*. A macrolide is contraindicated if there is history of hypersensitivity to any macrolide agent (Table 5). Neither erythromycin nor clarithromycin should be administered concomitantly with astemizole, cisapride, pimazole, or terfenadine. The most commonly reported side effects of oral macrolides are gastrointestinal (e.g., nausea, vomiting, abdominal pain and cramps, diarrhea, and anorexia) and rashes; side effects are more frequent and severe with erythromycin use.

II. Specific Antimicrobial Agents

1. Azithromycin. Azithromycin is available in the United States for oral administration as azithromycin dihydrate (suspension, tablets, and capsules). It is administered as a single daily dose.

Recommended regimen:

- Infants aged <6 months: 10 mg/kg per day for 5 days.
- Infants and children aged ≥6 months: 10 mg/kg (maximum: 500 mg) on day 1, followed by 5 mg/kg per day (maximum: 250 mg) on days 2–5.
- Adults: 500 mg on day 1, followed by 250 mg per day on days 2–5.
- Side effects include abdominal discomfort or pain, diarrhea, nausea, vomiting, headache, and dizziness. Azithromycin should be prescribed with caution to patients with impaired hepatic function. All patients should be cautioned not to take azithromycin and aluminum- or magnesium-containing antacids simultaneously because

TABLE 5. Preparation and adverse events of antimicrobial agents used for treatment and postexposure prophylaxis of pertussis

		Major adverse events		
Drug	**Preparation**	**Indicating need for medical attention**	**Indicating need for medical attention if persistent or bothersome**	**Special instructions**
Azithromycin	**Oral suspension:** 20 mg/mL 40 mg/mL **Capsules:** 250 mg, 600 mg	**Rare:** Acute interstitial nephritis Hypersensitivity/anaphylaxis (dyspnea, hives, and rash) Pseudomembranous colitis	Gastrointestinal disturbances (abdominal discomfort or pain, diarrhea, (nausea, and vomiting) Headache, dizziness	Administer 1 hour before or 2 hours after a meal; do not use with aluminum- or magnesium-containing antacids Use with caution in patients with impaired hepatic function Potential drug interactions
Clarithromycin	**Oral suspension:** 25 mg/mL, 50 mg/mL **Tablets:** 250 mg, 500 mg	**Rare:** Hepatotoxicity Hypersensitivity reaction (rash, pruritis, and dyspnea) Pseudomembranous colitis Thrombocytopenia	**Frequent:** Gastrointestinal disturbances (abdominal discomfort or pain, diarrhea, (nausea, and vomiting) **Infrequent:** Abnormal taste sensation Headache	Dose should be adjusted for patients with impaired renal function Can be administered without regard to meals Reconstituted suspensions should not be refrigerated Potential drug reactions
Erythromycin	**Oral suspension and tablets** (many preparation strengths)	Hypersensitivity/anaphylaxis (dyspnea, hives, rash) **Rare:** Hepatic dysfunction Infantile hypertrophic pyloric stenosis in neonates aged <l month Torsade de pointes Pseudomembranous colitis	**Frequent:** Gastrointestinal disturbances (anorexia, nausea, vomiting, and diarrhea)	Dose should be adjusted for patients with impaired renal function Potential drug reactions
Trimethoprim-sulfamethoxazole (TMP/SMZ)	**Oral suspension:** TMP 8 mg/mL and SMZ 40mg/ mL **Tablets:** Single Strength TMP 80 mg and SMZ 400 mg **Double Strength:** TMP 160 mg SMZ 800 mg	**More frequent:** Skin rash **Less frequent:** Hypersensitivity reactions (skin rash, and fever) Hematologic toxicity (leucopenia, neutropenia, thrombocytopenia, and anemia) **Rare:** Exfoliative skin disorders (including Stevens-Johnsons syndrome), Hemolytic anemia (with G6-PD deficiency) Methhemoglobinemia Renal toxicity (crystaluria, nephritis, and tubular necrosis) Central nervous system toxicity (aseptic meningitis) Pseudomembranous colitis Cholestatic hepatitis Thyroid function disturbance	Gastrointestinal disturbances (anorexia, nausea, vomiting, and diarrhea	Dose should be adjusted for patients with impaired renal function Maintain adequate fluid intake to prevent crystaluria and stone formation (take with full glass of water) Potential for photosensitivity skin reaction with sun exposure

the latter reduces the rate of absorption of azithromycin. Monitoring of patients is advised when azithromycin is used concomitantly with agents metabolized by the cytochrome P450 enzyme system and with other drugs for which the pharmacokinetics change (e.g., digoxin, triazolam, and ergot alkaloids). Drug interactions reactions similar to those observed for erythromycin and clarithromycin have not been reported. Azithromycin is classified as an FDA Pregnancy Category B drug (*75*).

2. **Erythromycin.** Erythromycin is available in the United States for oral administration as erythromycin base (tablets and capsules), erythromycin stearate (tablets), and erythromycin ethylsuccinate (tablets, powders, and liquids). Because relapses have been reported after completion of 7–10 days of treatment with erythromycin, a 14-day course of erythromycin is recommended for treatment of patients with pertussis or for postexposure prophylaxis of close contacts of pertussis patients (*76*).

Recommended regimen:

- Infants aged <1 month: not preferred because of risk for IHPS. Azithromycin is the recommended antimicrobial agent. If azithromycin is unavailable and erythromycin is used, the dose is 40–50 mg/kg per day in 4 divided doses. These infants should be monitored for IHPS.
- Infants aged ≥1 month and older children: 40–50 mg/kg per day (maximum: 2 g per day) in 4 divided doses for 14 days.
- Adults: 2 g per day in 4 divided doses for 14 days

Gastrointestinal irritation, including epigastric distress, abdominal cramps, nausea, vomiting, and diarrhea, are the most common adverse effects associated with oral administration of erythromycin. Symptoms are dose-related. Some formulations with enteric-coated tablets and the ester derivatives (e.g., ethylsuccinate) can be taken with food to minimize these side effects. Hypersensitivity reactions (e.g., skin rashes, drug fever, or eosinophilia), cholestatic hepatitis, and sensorineural hearing loss have occurred after administration of macrolides; severe reactions such as anaphylaxis are rare.

An increased risk for IHPS has been reported in neonates during the month after erythromycin administration. In one case, pyloric stenosis occurred in a breastfeeding infant whose mother took erythromycin. In 1999, a cluster of seven cases of IHPS were reported among neonates (all aged <3 weeks when prophylaxis was started) who had taken erythromycin after exposure to a pertussis patient. In a cohort study, erythromycin prophylaxis was causally associated with IHPS (seven cases out of 157 erythromycin exposed infants versus zero cases out of 125 infants with no erythromycin exposure (relative risk: infinity [95% confidence interval = 1.7–infinity]).

The high case-fatality ratio of pertussis in neonates underscores the importance of preventing pertussis among exposed infants. Health-care providers who prescribe erythromycin rather than azithromycin to newborns should inform parents about the possible risks for IHPS and counsel them about signs of IHPS.

Erythromycin is contraindicated if there is history of hypersensitivity to any macrolide agent. Erythromycin should not be administered concomitantly with astemizole, cisapride, pimazole, or terfenadine. Rare cases of serious cardiovascular adverse events, including electrocardiographic QT/QT_c interval prolongation, cardiac arrest, torsades de pointes, and other ventricular arrhythmias, have been observed after concomitant use of erythromycin with these drugs.

Erythromycin is an inhibitor of the cytochrome P450 enzyme system (CYP3A subclass). Coadministration of erythromycin and a drug that is primarily metabolized by CYP3A can result in elevations in drug concentrations that could increase or prolong both the therapeutic and adverse effects of the concomitant drug. Drugs that are metabolized by CYP3A include alfentanil, bromocriptine, cyclosporine, carbamazepine, cilostazol, disopyramide, dihydroergotamine, ergotamine, lovastatin and simvastatin, methylprednisolone, quinidine, rifabutin, vinblastine, tacrolimus, triazolo-benzodiazepines (e.g., triazolam and alprazolam) and related benzodiazepines, and sildenafil. In addition, reports exists of drug interactions of erythromycin with drugs not thought to be metabolized by CYP3A, including zidovudine, hexobarbital, phenytoin, and valproate, theophylline, digoxin, and oral anticoagulants.

Erythromycin is classified as an FDA Pregnancy Category B drug (*76*). Animal reproduction studies have failed to demonstrate a risk to the fetus, but no adequate or well-controlled studies in humans exist.

3. **Clarithromycin.** Clarithromycin is available in the United States for oral administration as granules for oral suspension and tablets.

Recommended regimen:

- Infants aged <1 month: not recommended.
- Infants and children aged ≥1 month: 15 mg/kg per day (maximum: 1 g per day) in 2 divided doses each day for 7 days.
- Adults: 1 g per day in two divided doses for 7 days.

The most common adverse effects associated with clarithromycin include epigastric distress, abdominal cramps, nausea, vomiting, and diarrhea. Hypersensitivity reactions (e.g., skin rashes, drug fever, or eosinophilia), hepatotoxicity, and severe reactions such as anaphylaxis are rare. Because of its similarity to erythromycin, both chemically and metabolically, clarithromycin should not be administered to infants aged <1 month because it is unknown if the drug can be similarly associated with IHPS. The drug is contraindicated if there is history of hypersensitivity to any macrolide agent. Similar to erythromycin, clarithromycin should not be administered concomitantly with astemizole, cisapride, pimazole, or terfenadine. Clarithromycin inhibits the cytochrome P450 enzyme system (CYP3A subclass), and coadministration of clarithromycin and a drug that is primarily metabolized by CYP3A can result in elevations in drug concentrations that could increase or prolong both the therapeutic and adverse effects of the concomitant drug. Clarithromycin can be administered without dosage adjustment in patients with impaired hepatic function and normal renal function; however, drug dosage and interval between doses should be reassessed in the presence of impaired renal function. Clarithromycin is classified by FDA as a Pregnancy Category C drug (*76*). Animal reproduction studies have shown an adverse effect on the fetus; no adequate or well-controlled studies in humans exist.

4. Alternate agent (TMP–SMZ). Data from clinical studies indicate that TMP–SMZ is effective in eradicating *B. pertussis* from the nasopharynx (*64,77,78*). TMP–SMZ is used as an alternative to a macrolide antibiotic in patients aged ≥2 months who have contraindication to or cannot tolerate macrolide agents, or who are infected with a macrolide-resistant strain of *B. pertussis*. Macrolide-resistant *B. pertussis* is rare. Because of the potential risk for kernicterus among infants, TMP–SMZ should not be administered to pregnant women, nursing mothers, or infants aged <2 months.

Recommended regimen (*79*):

- Infants aged <2 months: contraindicated.
- Infants aged ≥2 months and children: trimethoprim 8 mg/kg per day, sulfamethoxazole 40 mg/kg per day in 2 divided doses for 14 days.
- Adults: trimethoprim 320 mg per day, sulfamethoxazole 1,600 mg per day in 2 divided doses for 14 days.

Patients receiving TMP-SMZ might experience gastrointestinal adverse effects, hypersensitivity skin reactions, and rarely, Stevens-Johnson syndrome, toxic epidermal necrolysis, blood dyscrasias, and hepatic necrosis. TMP–SMZ is contraindicated if there is known hypersensitivity to trimethoprim or sulfonamides. TMP–SMZ should be prescribed with caution to patients with impaired hepatic and renal functions, folate deficiency, blood dyscrasias, and in older adults because of the higher incidence of severe adverse events. Patients taking TMP–SMZ should be instructed to maintain an adequate fluid intake to prevent crystalluria and renal stones. Drug interactions must be considered when TMP–SMZ is used concomitantly with drugs, including methotrexate, oral anticoagulants, antidiabetic agents, thiazide diuretics, anticonvulsants, and other antiretroviral drugs. TMP–SMZ is classified by FDA as a Pregnancy Category C drug (*76*). Animal reproduction studies have indicated an adverse effect on the fetus; no adequate or well-controlled studies in humans exist.

5. Other antimicrobial agents. Although in vitro activity against *B. pertussis* has been demonstrated for other macrolides such as roxithromycin and ketolides (e.g., telithromycin) (*60*), no published data exist on the clinical effectiveness of these agents.

Other antimicrobial agents such as ampicillin, amoxicillin, tetracycline, chloramphenicol, fluoroquinolones (e.g., ciprofloxacin, levofloxacin, ofloxacin, moxifloxacin), and cephalosporins exhibit various levels of in vitro inhibitory activity against *B. pertussis,* but in vitro inhibitory activity does not predict clinical effectiveness. The clinical effectiveness of these agents for treatment of pertussis has not been demonstrated. For example, both ampicillin and amoxicillin were ineffective in clearing *B. pertussis* from nasopharynx (*80*). Poor penetration into respiratory secretions was proposed as a possible mechanism for failure to clear *B. pertussis* from the nasopharynx (*81*). The minimum inhibitory concentration of *B. pertussis* to the cephalosporins is unacceptably high (*82*). In addition, tetracyclines, chloramphenicol, and fluoroquinolones have potentially harmful side effects in children. Therefore, none of the above antimicrobial agents are recommended for treatment or postexposure prophylaxis of pertussis.

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