CLINICAL PRACTICE

Pertussis — Not Just for Kids

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This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.*

Six weeks ago, a 45-year-old woman noticed a scratchy feeling in her throat that has now progressed to more than 20 episodes of severe, spasmodic coughing per day. Her coughing spells are worse at night and are sometimes associated with gagging and vomiting. Her adolescent son and several of his friends, who received all of their childhood immunizations on schedule, had similar illnesses involving cough several weeks before the onset of her symptoms, and they continue to cough. How should the patient be assessed for possible pertussis? Should she be treated and, if so, how? Could this illness have been prevented?

THE CLINICAL PROBLEM

Despite rates of immunization for pertussis of more than 80 percent among young children, the number of cases of pertussis reported annually in the United States has increased by a factor of six since 1980, with 11,647 cases reported in 2003 (Fig. 1). The reported incidence rates probably substantially underestimate the true burden of disease because of incomplete reporting and a lack of recognition of the illness on the part of physicians.[1-4] The diagnosis of pertussis is frequently missed, often because of misconceptions that whooping cough is solely a pediatric illness that has been controlled by routine childhood immunizations and that immunity resulting from pertussis disease or immunization is lifelong. In addition, residual immunity from prior vaccination may modify the clinical presentation of pertussis in adolescents and adults and make the diagnosis even more difficult.
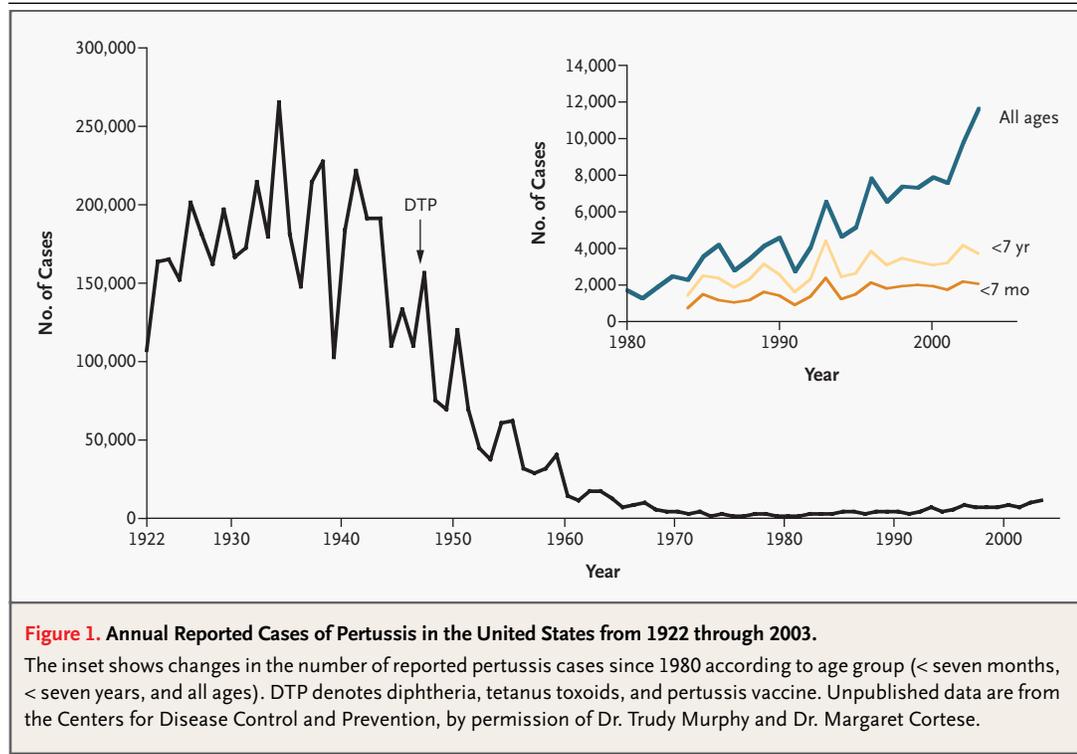
CLINICAL PRESENTATION AND COMPLICATIONS

Anyone who has heard the frightening paroxysmal cough of a child with classic pertussis would question how the diagnosis of pertussis could be overlooked. The illness begins, however, less dramatically, with the catarrhal phase, which consists of nonspecific symptoms such as coryza, conjunctival irritation, and, occasionally, a slight cough, none of which suggest pertussis as the primary diagnosis. After 7 to 10 days, the characteristic cough heralds the onset of the paroxysmal phase. After several weeks, the intensity and frequency of the cough may begin to decrease, but the convalescent phase, which can include episodes of exacerbated paroxysmal coughing brought on by unrelated upper airway infections, can last for weeks to months.

The typical paroxysmal cough in a child who is not immunized consists of a series of rapid, forced expirations, followed by gasping inhalation, which can result in the typical whooping sound. Post-tussive vomiting is common. These symptoms often occur in the absence of fever. Asymptomatic intervals occur between coughing spells. Very young infants may present with apnea or cyanosis in the absence of cough and are at greater risk than are older children for death or severe complications, including

1215

Figure 1. Annual Reported Cases of Pertussis in the United States from 1922 through 2003.
The inset shows changes in the number of reported pertussis cases since 1980 according to age group (< seven months, < seven years, and all ages). DTP denotes diphtheria, tetanus toxoids, and pertussis vaccine. Unpublished data are from the Centers for Disease Control and Prevention, by permission of Dr. Trudy Murphy and Dr. Margaret Cortese.

pneumonia (*Bordetella pertussis* infection or infection with another pathogen), pneumothorax, severe pulmonary hypertension, seizures, or encephalopathy.[5-9]

The current pertussis-related mortality rate among infants in the United States is 2.4 deaths per 1 million, and fatal cases in infants account for more than 90 percent of all deaths from pertussis. These numbers highlight the need for new approaches to protect infants, who are too young to be immunized according to the current vaccination schedule.[2,10,11]

Among immunized patients, especially adolescents and adults, a prolonged cough may be the only manifestation of pertussis.[3] A number of studies have documented that between 13 and 32 percent of adolescents and adults with an illness involving a cough of six days' duration or longer have serologic evidence of infection with *B. pertussis*.[12-17] The symptoms and complications of pertussis infection reported in these studies are often quite different from those seen in children.[14-18] For example, scratchy throat and other pharyngeal symptoms occur in about one third of adults with pertussis, and episodes of sweating are reported by 40 to 50 percent of persons over the age of 30 years. Although

70 to 99 percent of adolescents and adults with pertussis are reported to have paroxysmal cough, the reported frequencies of other symptoms are more variable, with whoop in 8 to 82 percent and posttussive vomiting in 17 to 50 percent.[6] Because adolescents and adults often do not seek medical care until several weeks after the onset of their illness, the differential diagnosis includes other causes of chronic cough, such as asthma, gastroesophageal reflux disease, postviral bronchospasm, chronic sinusitis with postnasal drip, tuberculosis, chlamydia or mycoplasma infections, other chronic lung diseases, and malignant conditions. Almost 80 percent of adults with confirmed pertussis have an illness involving a cough of at least 3 weeks' duration, and 27 percent still had a cough after 90 days.[18,19] Complications of pertussis, which are similar in adolescents and adults, include pneumonia (in 2.1 to 3.5 percent of patients), seizures (0.3 to 0.6 percent), and encephalopathy (0.1 percent). Some complications, such as cough-induced urinary incontinence, increase with age. Unusual complications that have been reported anecdotally in older patients include a herniated intervertebral disc, the sudden onset of hearing loss, angina, and carotid-artery dissection.[6,18-24]

EPIDEMIOLOGY, INCIDENCE, AND BURDEN OF DISEASE

Although multiple reports have highlighted the role of pertussis as an important cause of persistent cough in adolescents and adults, the actual burden of disease in these groups is difficult to determine.[4,6,12-25] This seemingly simple task is complicated by the biology of *B. pertussis* and the difficulty in detecting the organism.[4] Most pathogens of the respiratory tract have short incubation periods, are easy to culture, cause illness for a relatively short period, and are rapidly eliminated. *B. pertussis* is different in that the incubation period is measured in days to weeks, the organism exhibits fastidious behavior in culture, and it has the ability to cause, as the Chinese term it, a "cough of 100 days." The organism can be recovered from patients only during the first three to four weeks of illness and is particularly difficult to isolate in previously immunized persons.[25] These factors result in outbreaks that span months and that can be difficult to track epidemiologically.[26]

Before vaccination was available, pertussis was responsible for more than 270,000 cases of severe illness involving cough and 10,000 deaths annually in the United States.[27] The introduction of whole-cell pertussis vaccine into the general population during the 1940s was associated with a 99 percent reduction in the incidence of the disease, with a nadir of 1010 reported cases in 1976. Since that time, the absolute number of reported cases has increased, with the 11,647 cases in 2003 approaching the highest total since 1964 (Fig. 1).[1] The routine immunization of young children in the United States according to the schedule shown in Table 1 has markedly reduced the rates of reported pertussis in children. However, striking increases in rates of disease have been seen among adolescents and adults during the past 10 years (Fig. 1 and 2). In the United States, from 1997 to 2000 there were 8273 cases of pertussis reported in patients 10 to 19 years of age and 5745 cases in those older than 19 years.[1] There are probably multiple reasons for this increase, and they include the increased recognition of the disease (with the use of serologic testing for diagnosis) and the limited duration of protection from vaccine.[28]

STRATEGIES AND EVIDENCE

The critical elements involved in the diagnosis and treatment of pertussis, as with other infectious dis-

Table 1. Recommended Immunization Schedules for Pertussis in Canada, France, Germany, and the United States.

Country	Type of Vaccine*	Ages at Vaccination	Ages at Booster†
Canada	DTaP†	2, 4, and 6 mo	18 mo; 4–6 and 14–16 yr
France	DTP‡	2, 3, and 4 mo	
	DTaP		16–18 mo; 11–13 yr
Germany	DTaP	3, 4, and 5 mo	11–14 mo; 9–17 yr
United States	DTaP	2, 4, and 6 mo	18 mo; 4–6 yr

* DTaP denotes diphtheria, tetanus toxoids, and acellular pertussis vaccine. There are multiple formulations of this vaccine, with each formulation containing one to four antigens, and multiple manufacturers; therefore, no two vaccines are identical. Commonly recognized side effects include swelling, redness, and tenderness at the site of injection; fever; and secondary febrile convulsions.
† Canada, France, and Germany have initiated the use of a booster dose in adolescents at the ages indicated. In France, a DTaP booster is used after the primary series with DTP. In Canada and Germany, the adolescent booster is dTap, reflecting a reduced dose of diphtheria and acellular pertussis.
‡ DTP denotes diphtheria, tetanus toxoids, and pertussis vaccine. Side effects include anaphylaxis; swelling, redness, and tenderness at the site of injection; prolonged or inconsolable crying; fever; and secondary febrile convulsions.

eases, are its inclusion in the differential diagnosis, the availability of reliable and rapid laboratory tests for confirmation, and the prompt and appropriate use of the resultant information.
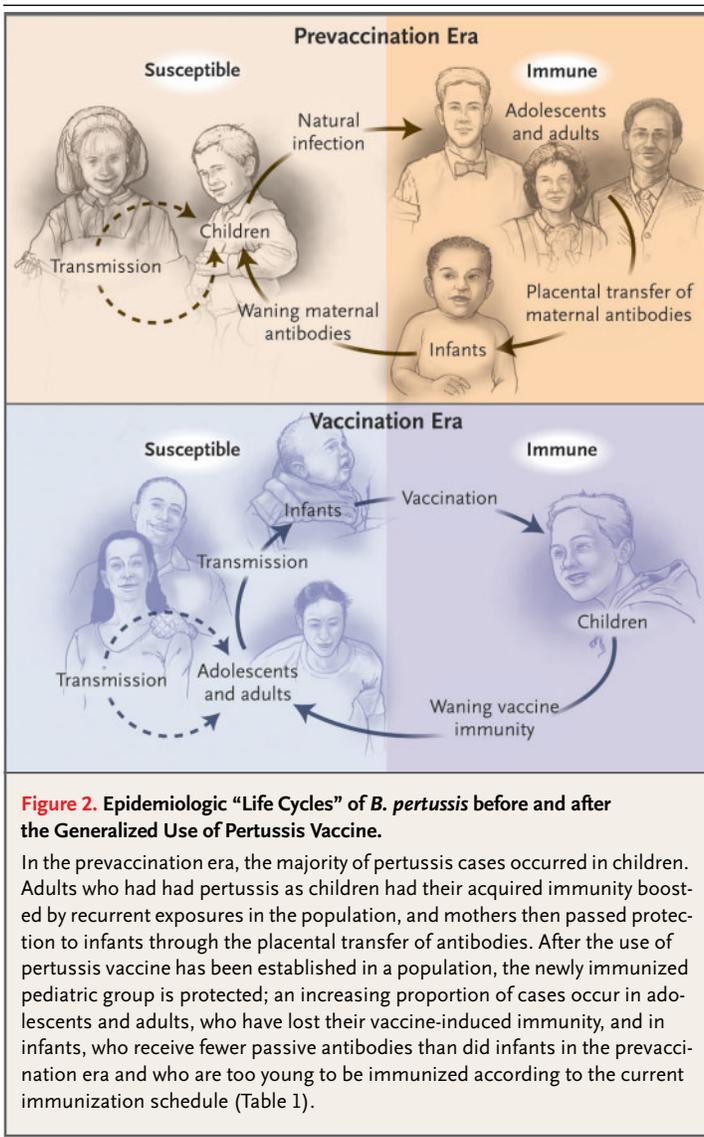
DIAGNOSTIC METHODS

Three laboratory tests have been used to detect *B. pertussis* or related bordetella species in the respiratory secretions of patients suspected of having pertussis: direct fluorescent antibody staining, bacterial culture, and polymerase chain reaction (PCR).[29] Because the direct fluorescent antibody technique has low sensitivity and specificity in comparison with culture and PCR, this method is not currently recommended.[29,30] A positive culture of nasopharyngeal secretions (preferably an aspirate) on selective Regan–Lowe medium is the gold standard for the diagnosis of pertussis. The sensitivity of culture is limited by the fastidious nature of *B. pertussis* and the loss of viability between the site of collection and the clinical laboratory. The yield is lower from dilute specimens, specimens from patients who have had a long duration of illness, and specimens obtained after antibiotic therapy. Nonetheless, when carried out appropriately, culture continues to be recommended in patients who present within three weeks after the onset of cough. Although antibiotic resistance is rare, isolation of the causative

organism, as recommended by the Centers for Disease Control and Prevention (CDC), allows for characterization of antigenic variation and antibiotic sensitivity.[31]

The use of PCR-based diagnostic assays with one or more primers, available in many health departments and clinical laboratories, is an alternative approach. These assays have been reported to detect fewer than 10 organisms, which do not need to be viable to be detected, and thus the tests have significantly greater sensitivity than does culture.[29,32] PCR assays with multiple primers can be used to identify and distinguish among several bordetella species (i.e., *B. pertussis*, *B. parapertussis*, and *B. bronchisepti-*

ca).[29,33,34] Although the period during which the organism can be identified is longer with PCR than for culture, false positive PCR results have been a problem.[35] For these reasons, the National Immunization Program of the CDC recommends the use of culture and PCR assays during the period in which patients could be infectious — at least three weeks after the onset of cough or four weeks after the appearance of any symptoms.[36] Standardized procedures and reagents and rigid quality control of PCR assays are needed to ensure accurate diagnoses and to minimize false positive results.[35,37,38]

An alternative method of diagnosing pertussis in adolescents and adults is the measurement of antibody to specific components of *B. pertussis* with the use of enzyme-linked immunosorbent assays. Since the diagnosis of pertussis is often not considered during the period when organisms can still be detected, the demonstration of increased antibody titers between the acute phase of illness (i.e., in serum obtained within the first week after the onset of symptoms) and the convalescent phase (in serum collected four to six weeks later) may be necessary. Alternatively, a single serum antibody titer (that exceeds a diagnostic cutoff point for the level of IgG against pertussis toxin or another antigen) obtained at least three weeks into the illness may be required to confirm the diagnosis.[29,38-40] However, the lack of a widely available serologic test with an established cutoff point, the limited diagnostic value of commercial tests, and the delay in obtaining results limit the usefulness of serologic testing in practice.[6,41] As a result, the CDC recommends that combinations of diagnostic tests be used to identify persons with pertussis more effectively.[29,38] Within the first four weeks after the onset of symptoms (when cough has been present for three weeks), the use of culture and PCR is appropriate for diagnosis; when cough has been present for three to four weeks, PCR and serologic tests can both be used; and after four weeks of cough, serologic tests alone are most likely to provide a diagnosis.

Figure 2. Epidemiologic "Life Cycles" of *B. pertussis* before and after the Generalized Use of Pertussis Vaccine.

In the prevaccination era, the majority of pertussis cases occurred in children. Adults who had had pertussis as children had their acquired immunity boosted by recurrent exposures in the population, and mothers then passed protection to infants through the placental transfer of antibodies. After the use of pertussis vaccine has been established in a population, the newly immunized pediatric group is protected; an increasing proportion of cases occur in adolescents and adults, who have lost their vaccine-induced immunity, and in infants, who receive fewer passive antibodies than did infants in the prevaccination era and who are too young to be immunized according to the current immunization schedule (Table 1).

TREATMENT

Antibiotics should be administered to patients with pertussis to hasten clearance of the organism and to limit transmission to susceptible contacts. Although controversial, it appears that treatment can sometimes reduce the duration or severity of symptoms, or both, but a benefit is unlikely when treatment is initiated after the first week of symptoms.[36] Adolescents and adults with sporadic cases fre-

quently present during the paroxysmal phase, which occurs at least a week after the onset of symptoms, and in such cases, antibiotics rarely affect the course of the disease. However, viable organisms can be recovered from untreated patients for three weeks after the onset of the cough. Thus, the routine administration of antibiotics during the first four weeks of illness is justified. For patients who are likely to be in contact with high-risk persons, such as infants, women in the third trimester of pregnancy (who might continue to be infectious after delivery), and health care workers, treatment is recommended even six to eight weeks after the onset of illness.[36]

The National Immunization Program recommends erythromycin for the treatment of pertussis.[42] However, the newer macrolides azithromycin and clarithromycin have been demonstrated in head-to-head trials to be similar in efficacy to erythromycin, with fewer side effects and more convenient administration.[43-45] Dosages, common side effects, and contraindications are summarized in Table 2.[46,47] An alternative treatment for patients who cannot tolerate macrolides is trimethoprim–sulfamethoxazole. Although *B. pertussis* strains are sensitive in vitro to fluoroquinolones and ketolides, there are no clinical data to support the use of these agents.[48]

Treatment also involves supportive care, which is most important for infants and small children, since they are vulnerable to dehydration and malnutrition from post-tussive vomiting and an inability to eat. None of the pharmacologic or immunologic interventions that have been tested, such as corticosteroids, salbutamol, diphenhydramine, and pertussis immune globulin, have been documented to be effective in reducing the symptoms or controlling the cough of pertussis.[49]

PROPHYLAXIS AFTER EXPOSURE

The same agents and regimens used for the treatment of patients with established pertussis are recommended for chemoprophylaxis in contacts. These modes of treatment are expected to be effective in the protection of persons exposed to patients with active pertussis, when administered before the onset of symptoms in the contact. Because infectiousness declines with the increasing duration of illness, prophylaxis for contacts needs to be initiated only if the interval since the onset of cough in the index case is three weeks or less. Prophylaxis is generally recommended only if the contact was

exposed within the previous three weeks,[50] but for persons at high risk or those who are likely to come into contact with high-risk persons, prophylaxis may be warranted for up to six to eight weeks after exposure.

PREVENTION

The mainstay for control of pertussis is vaccination, and this is recommended routinely for infants and young children according to the schedules shown for several countries in Table 1. Whole-cell vaccines consisting of killed organisms are highly effective but have been associated with frequent local and systemic reactions.[27] In the 1980s and early 1990s, new acellular vaccines, which contain one or more purified pertussis components, were demonstrated to be immunogenic, associated with fewer local and systemic reactions than whole-cell vaccines, and efficacious in the prevention of culture-confirmed pertussis disease in infants and young children.[51] These acellular vaccines have replaced whole-cell vaccines in the United States and elsewhere.

Given the recognition that immunity wanes after vaccination early in life, repeated vaccination in adolescence or adulthood has been proposed. A large, randomized clinical trial evaluated the efficacy of a three-component acellular pertussis vaccine (containing pertussis toxoids, filamentous hemagglutinin, and pertactin) in nearly 3000 healthy subjects 15 to 65 years of age. Active surveillance for pertussis was conducted every two weeks for two years. With the use of culture or PCR and serologically confirmed disease as end points, preliminary data from this study indicated that there was a 92 percent efficacy rate for the vaccine (95 percent confidence interval, 32 to 99 percent).[52]

A recently published cost-benefit analysis that assumed that the incidence of pertussis was the same as that observed in the above-mentioned trial led to the conclusion that an additional booster dose of pertussis vaccine would be cost-effective.[53] Of the scenarios considered in the analysis, vaccination of adolescents was considered to be the least expensive, the easiest to implement, and the most acceptable. In light of the greater recognition of disease in adolescents and adults, some countries, such as Germany, France, and Canada, now recommend the routine vaccination of adolescents with acellular pertussis vaccine boosters (Table 1). Although there are no formulations of pertussis vaccine currently licensed in the United States for use in persons over the age of six years, advisory groups

Table 2. Choice of Antibiotic Agents for the Treatment of Pertussis.

Drug	Dosage	Regimen	Side Effects	Contraindications
Erythromycin	Children, 40–50 mg/kg/day Adults, 1–2 g/day	4 divided doses for 14 days*	Gastrointestinal irritation, abdominal cramps, nausea, vomiting; hypertrophic pyloric stenosis has been reported in infants	Known sensitivity to any macrolide antibiotic; should be used with caution in infants because of association with hypertrophic pyloric stenosis[46]
Azithromycin	10 mg/kg (maximum, 500 mg) as a single dose on day 1; 5 mg/kg (maximum, 250 mg) thereafter[43]‡	Lower dose once daily for 4 additional days	Allergic reaction and hepatic toxicity	Known sensitivity to any macrolide antibiotic
Clarithromycin	20 mg/kg/day (maximum, 1 g/day)	Two divided doses daily for 7 days	Allergic reaction and hepatic toxicity	Known sensitivity to any macrolide antibiotic
Trimethoprim–sulfamethoxazole†	Trimethoprim, 8 mg/kg/day (maximum, 320 mg/day); sulfamethoxazole, 40 mg/kg/day (maximum, 1600 mg/day)	Two divided doses daily for 7 days	Rash, kernicterus in newborns	Known allergy to sulfonamides or trimethoprim; should not be given to pregnant women shortly before delivery, breast-feeding mothers, or infants <2 mo old, because of the risk of kernicterus

* A 7-day regimen has been shown to be similar in efficacy to a 14-day regimen.[54]

† Trimethoprim–sulfamethoxazole should be prescribed as an alternative to the macrolides in patients who cannot tolerate them.

‡ The *2003 Red Book* recommendation is for 10 to 12 mg per kilogram per day once daily for five days.

are considering the routine use of acellular vaccines in this population once vaccines are approved and become available.

AREAS OF UNCERTAINTY

Despite extensive research on the toxins, adhesions, and other factors related to the virulence of *B. pertussis*, little is known about the mechanisms by which these factors cause the illness of pertussis. For example, although it is clear that pertussis toxin causes the characteristic lymphocytosis and other abnormalities associated with the disease, the mechanism responsible for the severe and prolonged cough remains unknown.

Vaccination of pregnant women has been proposed as a strategy to protect infants from pertussis passively before they receive active vaccination. The potential for such a strategy to work is based on observations that maternal antibody titers to pertussis antigens are low but that, when present, antibodies are actively transported in cord blood.[55] However, data to support the safety and efficacy of maternal vaccination are lacking. An alternative or complementary approach would be the active immunization of newborns with acellular pertussis vaccines; such approaches are being studied.

GUIDELINES

The CDC recommends that for all patients with presumed pertussis, culture be performed to identify the etiologic agent during the time when patients are likely to be infectious, regardless of which other diagnostic tests are used.[36] The CDC and the Food and Drug Administration are currently working on standardization of PCR and serologic methods for the diagnosis of pertussis. Patients seen early in the course of their illness (i.e., during the first three weeks after cough begins) should be evaluated with the use of culture and PCR; PCR and serologic tests can be used when cough has been present for three to four weeks; and serologic tests should be used for patients who present with cough that has persisted for longer than four weeks.

The CDC also recommends the treatment of presumed or confirmed cases of pertussis with erythromycin but acknowledges the limitations of this treatment due to side effects. In cases in which the patient presents after the onset of paroxysmal cough, antibiotic treatment is unlikely to affect the clinical course but will preclude transmission to susceptible hosts beginning five days after the onset of therapy.

CONCLUSIONS AND RECOMMENDATIONS

For the patient described in the vignette, whose symptoms started six weeks ago, single-sample serologic testing is the only method that could yield the diagnosis. Given the duration of the symptoms, treatment with antibiotics would not affect the course of the patient's illness, and we would not recommend it at this point. If, however, the diagnosis of pertussis had been made two or more weeks earlier, it would have been appropriate to treat the patient in order to prevent further spread of the infection. If pertussis had been documented (by culture, PCR, or both) in the patient's son during the first three weeks of his illness, it would have been appropriate to consider her a contact and to treat her, whether or not she became symptomatic, with either azithromycin or clarithromycin, according to the regimen in Table 2. With this approach, even if her condition did progress to clinical pertussis, the antibiotic treatment would have the potential to reduce the duration and severity of her illness.

Pertussis vaccines are highly efficacious, but in many countries, including the United States, they are administered only to a small subgroup of the population — namely, children younger than six years of age. The control of pertussis requires an increase in the immunity of all age groups. We believe that the vaccination of adolescents (with a suitable formulation of acellular pertussis vaccine) should be added to the current immunization schedule for pertussis in order to reduce the risk of the disease later in life as well as the transmission to infants.

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1221

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