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# Pertussis: Old foe, persistent problem

## ■ ABSTRACT

Although a safe and effective vaccine is available, pertussis continues to be an important cause of morbidity and mortality. Immunity acquired from natural infection or vaccination wanes within 5 years, making older children, adolescents, and adults important reservoirs of infection. Many neonates and infants contract pertussis from older people with mild symptoms and are at risk for developing severe, life-threatening illness. Immunization programs are being considered for adolescents and for adults who live with or care for infants.

## ■ KEY POINTS

Since the early 1980s, pertussis has steadily increased in the United States, with epidemic peaks every 3 to 5 years. Several large outbreaks have occurred in the past several years.

Infection is common in adults, despite previous vaccination or prior infection. Those with unrecognized pertussis place susceptible contacts, especially infants, at high risk.

Pertussis is difficult to definitively diagnose: culture and polymerase chain reaction testing of nasopharyngeal secretions are insensitive, and serologic testing is sensitive but impractical for clinical use.

Trials of acellular pertussis vaccines have shown that they are safe and effective in adults and adolescents.

**V**ACCINATION for pertussis (whooping cough) may soon be done in teenagers and adults, not just in infants, even if they were already immunized as infants. The reason is that immunity wanes quickly after vaccination or natural infection, and infected family members can spread the disease to unimmunized infants, in whom the disease is more severe. New acellular vaccines should be safer for older people than the cellular vaccine.

This review examines the epidemiologic and clinical features of pertussis, as well as current and future prevention strategies.

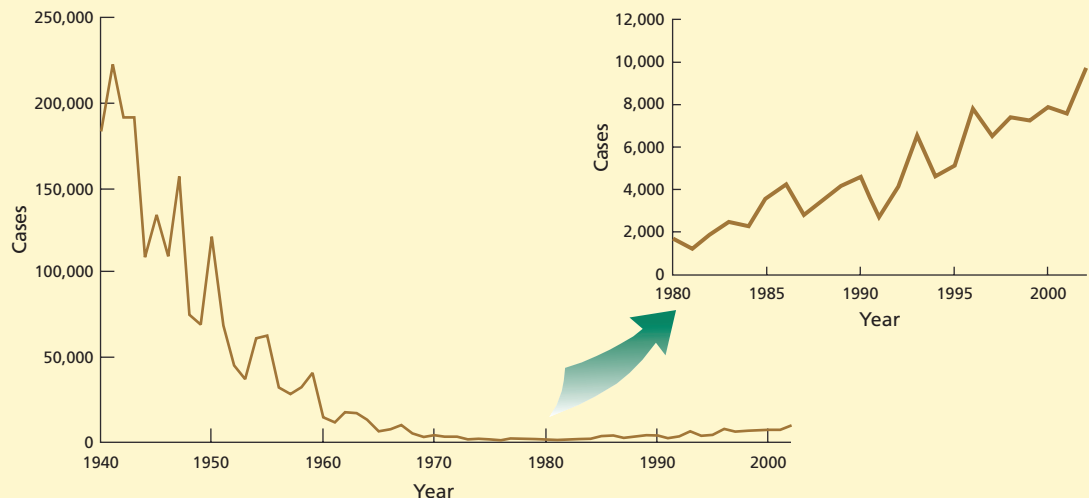
## ■ INCIDENCE IS REBOUNDED

Pertussis is an acute upper respiratory tract infection characterized by spasms of intense coughing and a protracted clinical course.

*Bordetella pertussis*, a nonmotile gram-negative coccobacillus, is the major cause of epidemic and sporadic pertussis. (Other *Bordetella* species, such as *B parapertussis*, can cause a mild pertussis illness, but this is not common.) Before the vaccine against this organism became widely used in the late 1940s, pertussis was a leading cause of illness and death in the United States, accounting for up to 270,000 cases and 10,000 deaths each year.<sup>1</sup> By the early 1970s, the incidence had declined by 99% compared with the prevaccine years, with a nadir of 1,010 reported cases in 1976 (FIGURE 1).<sup>2</sup>

Since the early 1980s, however, pertussis has steadily increased in the United States, with epidemic peaks every 3 to 5 years. Several large outbreaks have occurred in the past several years<sup>3-5</sup>: in 2003, more cases

### The incidence of pertussis has declined since the start of vaccination...but is starting to rebound



**FIGURE 1.** Incidence of pertussis in the United States, 1940–2002.

DATA FROM THE US CENTERS FOR DISEASE CONTROL AND PREVENTION.<sup>1</sup>

**Immunity to pertussis wanes within 5 years of vaccination or infection**

(11,647) in the United States were reported than in nearly 4 decades, and this likely underestimates the true incidence.<sup>6</sup>

Worldwide, pertussis continues to be an important killer of children. The World Health Organization estimates that 294,000 pertussis-related deaths occurred in 2002.<sup>7</sup>

*B pertussis* is extremely contagious via direct transmission from close respiratory contact: the secondary attack rate among susceptible household contacts is 80%.<sup>6</sup> Most cases in the United States occur between June and October.<sup>8,9</sup>

#### Common in older children and adults

Neither vaccination nor natural infection provides long-lasting immunity: subclinical or mild illness occurs commonly in those who are fully or partially immunized or who are naturally immune.<sup>10,11</sup> Immunity wanes within 3 to 5 years of vaccination or natural infection and is often undetectable at 12 years.<sup>12</sup> Fortunately, people do not become chronic carriers of the organism.

In the prevaccine era, the highest incidence was in children 1 to 5 years old. However, in the 1980s, 70% of reported cases were in infants younger than 6 months (peak

age 4–8 weeks).<sup>13</sup> Since the early 1990s, reported cases in children 10 years and older have dramatically increased (FIGURE 2),<sup>14</sup> a trend that may, however, reflect better reporting due to heightened awareness rather than a true increase in disease incidence.

Many studies show that pertussis is a common cause of prolonged cough in adolescents and adults, accounting for 12% to 32% of cases. A prospective, population-based study with active surveillance in the United States found that 13% of participants 10 to 49 years old who presented to a community clinic with an acute paroxysmal cough or a cough illness lasting at least 2 weeks had evidence of an acute pertussis infection.<sup>15</sup> A prospective study from Canada found that 20% of 442 adolescents and adults with a cough lasting 7 to 56 days had pertussis, based on a combination of diagnostic techniques, including culture, polymerase chain reaction (PCR), and serologic testing.<sup>16</sup> (The difference in prevalence between the two studies was likely due to the different durations of cough.)

#### Older people pass pertussis to younger

Adults and adolescents with mild or subclinical disease are important reservoirs of infec-

tion and are often index cases for infants and children.<sup>11</sup> In an outbreak in Chicago in 1993, mothers were an important source of pertussis in their infants.<sup>3</sup>

Long et al<sup>11</sup> studied 18 family members of four infants who had culture-proven pertussis. Fifteen had evidence of a recent pertussis infection by culture, antigen testing, and serology. Only five contacts had symptoms 2 to 4 weeks before the infants were diagnosed; the rest were completely without symptoms. Sixteen of the contacts had been vaccinated early in life.

Deen et al<sup>17</sup> investigated 255 exposed contacts of 40 infants and children with bacteriologically proven pertussis and found that 145 had evidence of recent pertussis infection. Of these, 45% were without symptoms, 21% had mild respiratory symptoms, and 34% had clinical evidence of pertussis.

## ■ MOST OLDER PATIENTS HAVE Milder Disease

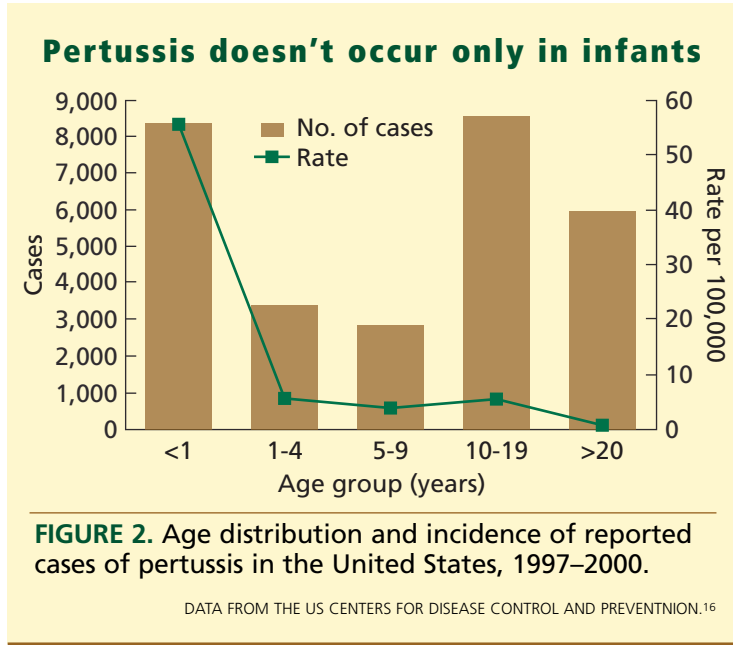
The classic description of pertussis—an incubation period of 7 to 10 days, followed by three stages, each lasting at least 2 weeks—is based on nonimmunized young children. In partially or totally immunized children, the stages are shorter and may be atypical.

**The catarrhal stage** consists of nonspecific upper respiratory tract symptoms: rhinorrhea, lacrimation, mild cough, and conjunctival injection. Neonates do not have an apparent catarrhal stage.

**The paroxysmal stage** is characterized by an intermittent dry hacking cough, consisting of a repetitive series of forceful coughs within a single expiration. A sudden massive inspiration often occurs at the end of the cough paroxysm, resulting in a high-pitched “whoop.” Associated findings include choking, gagging, cyanosis, and apnea in the very young. Between attacks, patients appear comfortable without apparent distress.

**The convalescent stage.** Paroxysms diminish in severity and frequency but it is common for patients to continue intermittent coughing for weeks to months, exacerbated by respiratory illness.

Adolescents and adults usually have



milder disease without distinct phases. A persistent cough (> 21 days), which is indistinguishable from other respiratory infections, may be the only symptom. About 70% of patients have a paroxysmal cough, and about one third of patients have an inspiratory whoop. Other symptoms may include posttussive emesis, choking, and sleep disturbed by cough.<sup>18</sup>

In the large Canadian surveillance study of adolescents and adults,<sup>16</sup> predictors of confirmed pertussis infection included a history of prolonged violent cough (median 43 days), a longer cough illness (median 56 days), and posttussive emesis. Posttussive emesis is common at all ages and serves as a clue to the diagnosis in older children and adults.

Fever is characteristically absent at all stages in children and adults; if fever is present, secondary bacterial infection should be suspected.<sup>19</sup>

## Physical examination is usually normal

The physical examination is usually normal. Some patients have conjunctival hemorrhage and upper-body petechial lesions from the force of the cough and the posttussive emesis.

## Elevated WBCs in unimmunized children

Leukocytosis secondary to absolute lymphocytosis is common in unimmunized infants and

**Fever is absent in pertussis unless there is secondary bacterial infection**

TABLE 1

### Differential diagnosis of pertussis

#### Infants

Adenovirus infection  
Respiratory syncytial virus infection  
Viral bronchiolitis  
Cystic fibrosis  
Bacterial pneumonia

#### Older children and adults

Reactive airway disease  
*Mycoplasma pneumoniae* infection  
*Chlamydia pneumoniae* infection  
Upper respiratory tract infection  
Adenovirus infection  
Bronchitis  
Gastroesophageal reflux

children during the paroxysmal or late catarrhal stage. The degree of lymphocytosis parallels the severity of disease, and total white blood cell concentrations between 50 and 100 × 10<sup>9</sup>/L are typical.

Leukocytosis and lymphocytosis are uncommon in adults and in partially immunized children.

#### Chest radiographs are often normal

Chest radiography is commonly normal, although perihilar infiltrates, pneumothorax, or pneumomediastinum may be present.

#### ■ DIAGNOSIS IS DIFFICULT

Pertussis is difficult to definitively diagnose: culture and PCR testing of nasopharyngeal secretions are insensitive, and serologic testing is sensitive but impractical for clinical use. The differential diagnosis is listed in TABLE 1.

#### Culture: The (insensitive) gold standard

Isolation of *B pertussis* by culture is the diagnostic standard. However, the organism is fastidious, so proper technique is essential. The specimen should be obtained from the posterior nasopharynx using a calcium alginate or Dacron-tipped (not cotton) swab. The specimen should be immediately inoculated onto Regan-Lowe medium and incubated for 7

days. A semisolid transport medium is available if a specimen cannot be immediately inoculated onto a solid medium.

Even under ideal conditions, sensitivity is low. Cultures are only likely to be positive in unimmunized children, those who have not been treated with macrolides or sulfonamides, and early in the illness (the catarrhal and early paroxysmal phases).<sup>20</sup> Thus, an adult with pertussis who has been coughing for 3 weeks is very unlikely to have a positive culture.

#### PCR testing becoming more available

PCR testing of nasopharyngeal specimens has recently been developed and has become more widely available. PCR is more sensitive than culture, including for patients with mild symptoms or who have been treated with macrolides.<sup>21,22</sup>

However, compared with serologic tests (used for research purposes), the sensitivity of PCR is highly dependent on patient age: PCR is 60% to 70% sensitive in infants and young children, but less than 10% sensitive in older children and adults,<sup>23</sup> probably reflecting past immunization and immune responses.

#### Direct fluorescent antibody testing is also insensitive

Direct fluorescent antibody testing of nasopharyngeal specimens for pertussis antigens was used in the past but was even less sensitive than culture and required experienced laboratories for accurate results. This test is rarely used today.

#### Serologic testing is sensitive, but impractical

Serologic testing to detect antibodies to components of *B pertussis* in samples from patients in the acute and convalescent stages is the most sensitive diagnostic method. It is used extensively in epidemiologic studies and vaccine trials and has led to the current understanding of the role of pertussis in adolescents and adults with prolonged cough illness.<sup>24</sup> Unfortunately, these tests are not readily available, are difficult to interpret in immunized patients, and are not helpful for diagnosing acute disease.

**Adults with pertussis who have been coughing for 3 weeks are unlikely to have a positive culture**

**TABLE 2****Pertussis-related hospitalizations and complications by age group—United States, 1997–2000**

AGE GROUP	PERCENT OF PATIENTS				
	HOSPITALIZED	PNEUMONIA	SEIZURES	ENCEPHALOPATHY	DEATHS
< 2 months	90	20	2–4	1	0.5–1.0
< 6 months	63.1	11.8	1.4	0.2	0.8
6–11 months	28.1	8.6	0.7	0.1	0.1
1–4 years	10.3	5.4	1.2	0.1	< 0.1
5–9 years	3.1	2.5	0.5	0	0.1
10–19 years	2.1	1.9	0.3	0.1	0
≥ 20 years	3.5	2.6	0.6	0.1	< 0.1
Total	20.0	5.2	0.8	0.1	0.2

ADAPTED FROM PERTUSSIS—UNITED STATES, 1997–2000. MMWR MORB MORTAL WKLY REP 2002; 51:73–76.

**■ INFANTS HAVE THE HIGHEST MORTALITY RATE**

Infants have the highest incidence of morbidity and mortality (TABLE 2): 90% of pertussis-related deaths occur in those younger than 6 months.<sup>14</sup> Secondary bacterial pneumonia occurs in about 5% of reported cases and is the most common complication, as well as the cause of most deaths (FIGURE 3). Other important complications include apnea, bradycardia, dehydration, pulmonary hypertension, pneumothorax, seizures, hypoxia, and retinal hemorrhages.

Although complications are much more common in infants, pertussis also causes significant morbidity in adults, including pneumonia, otitis media, rib fracture, pneumothorax, pneumomediastinum, and urinary incontinence.<sup>19</sup>

**■ MANAGEMENT: SUPPORTIVE CARE, MACROLIDES**

**Supportive care** is the mainstay of management. Hospitalization is indicated for most infants younger than 6 months old to assess for life-threatening events associated with paroxysms, such as apnea, bradycardia, and hypoxia. Hospitalization also allows continuous cardiorespiratory monitoring, vigilant suctioning of the nasopharynx, oxygen therapy if needed, careful attention to feeding and hydration, and monitoring and treatment of acute complications.

**Antimicrobial therapy** is always indicated for proven or suspected pertussis to eliminate the organism from the nasopharynx and thereby limit the spread to others. However, it has little influence on the clinical course unless started early in the catarrhal phase.<sup>25</sup>

Because clinical symptoms, microbiologic studies, and lymphocytosis are of limited value in diagnosing pertussis in adults, antimicrobial therapy should be given to any adult with a suspected infection.

Standard antimicrobial therapy is erythromycin estolate 40 to 50 mg/kg/day (maximum 2 g/day) in four divided doses for 14 days.

The newer macrolides may be as effective as erythromycin. A large, multicenter, randomized trial of children 6 months to 16 years old with suspected or confirmed pertussis found that once-daily azithromycin (10 mg/kg on day 1 and 5 mg/kg on days 2–5) was as effective as erythromycin estolate (40 mg/kg per day in three divided doses for 10 days) and was associated with improved compliance.<sup>26</sup>

Trimethoprim-sulfamethoxazole is the recommended alternative for patients who cannot tolerate macrolides, although few data exist to confirm its efficacy.

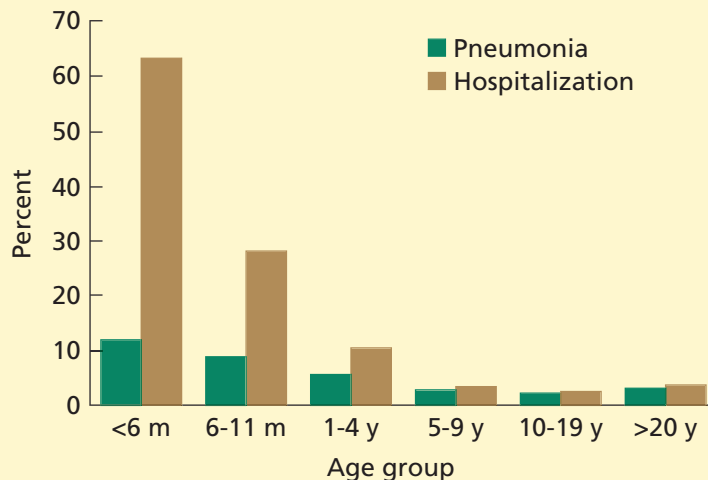
**Care of close contacts**

Chemoprophylaxis significantly reduces but does not eliminate the risk of pertussis. Erythromycin (for 14 days) should be given promptly to all household and close contacts (eg, those in child care) of infected individu-

**The newer macrolides may be as effective as erythromycin for pertussis**



### Infants are at greatest risk of pertussis complications



**FIGURE 3.** Pertussis complications by age in cases reported to the US Centers for Disease Control and Prevention, 1997–2000 (N = 28,187)

**The FDA is considering approval of acellular pertussis vaccine for adolescents and adults**

als<sup>27,28</sup> as well as exposed health care workers,<sup>29</sup> regardless of immunization status. Other macrolides are potential but unproven alternatives for chemoprophylaxis.

#### ■ VACCINATE OLDER AGE GROUPS?

Universal vaccination is the mainstay of prevention. The currently available acellular vaccines are from 75% to 90% effective and are well tolerated. Nevertheless, pertussis persists, resulting in significant morbidity and mortality, apparently due to waning immunity after vaccination and natural infection, underdiagnosis of mild disease, and an ever-renewing population of susceptible infants who have not completed their primary immunization series.

Because of the role of adolescents and adults in transmitting infection, recent interest has focused on vaccinating older age groups. Currently, pertussis vaccine is not recommended for those 7 years old and older because of concerns about the safety of the previously used whole-cell vaccines.<sup>30,31</sup> With the introduction of the less reactogenic acellular vaccines over the last decade, great interest has been generated in studying these vac-

cines for use in adolescents and adults.

Several studies have shown that these vaccines are safe and immunogenic in adults.<sup>32,33</sup> Adverse reactions have been mild, with local swelling and redness as the most commonly reported events, which occurred equally among vaccine and placebo recipients.

In a prospective, multicenter National Institutes of Health trial, 2,781 healthy subjects aged from 15 to 65 years were randomized to receive acellular pertussis vaccine or hepatitis A vaccine. The pertussis vaccine was immunogenic, prevented clinical pertussis, and provided sustained immune responses.<sup>34,35</sup> It was also well tolerated: fewer than 5% of subjects reported minor local or systemic adverse reactions.

A recent European trial of 265 adolescents immunized with acellular pertussis booster vaccines found that after 3 years, humoral immunity persisted in 82% to 100% of subjects and cell-mediated immunity persisted in 92%.<sup>36</sup>

Although acellular vaccines were well tolerated in trials, vaccinating with booster doses of acellular vaccines after primary immunization with these vaccines may result in more severe limb swelling, as has occurred in children.<sup>37</sup> Limb swelling has not been a problem in those who received whole-cell pertussis vaccine for their primary immunization. Adolescents and adults who previously received acellular vaccines will need to be closely observed when given booster doses of diphtheria-tetanus-acellular pertussis vaccines to determine the frequency and severity of such reactions.

Given the immunogenicity and safety of acellular vaccines in adolescents and adults, it is likely that a vaccination program in these age groups will soon be implemented. These vaccines are routinely used in Canada, France, Australia, and Germany for immunization of adolescents and adults. Purdy et al<sup>38</sup> estimated that a program of vaccinating everyone aged 10 years and older would prevent 1.3 million to 6.5 million cases of pertussis over a 10-year span. Assuming that 70% of infants acquire infection from older household contacts, such a program would prevent from 3,000 to 15,000 cases among infants younger than 1 year. Immunizing adolescents 10 to 19 years old

appears to be the most economical strategy and would be the easiest to implement, particularly if the acellular vaccine is added to the currently available and recommended diphtheria-tetanus vaccine. In addition, vaccinating special subgroups, including older adults, household contacts and caretakers of young infants, and health care workers, would provide significant health and economic benefits.

The US Food and Drug Administration's Vaccines and Related Biologic Products Advisory Committee recently voted unanimously to recommend two acellular pertussis vaccines, in combination with booster tetanus toxoid and adult diphtheria toxoid

for active immunization of adolescents and adults. While the Advisory Committee on Immunization Practices of the US Centers for Disease Control and Prevention has yet to issue formal recommendations, these vaccines will likely replace tetanus and diphtheria vaccines on the routine childhood immunization schedule. They will likely be given universally to adolescents at 11 to 12 year of age, with "catch-up" immunization for those between 13 and 18 years of age. Discussions are ongoing about whether pertussis vaccination of adults will be universal or directed against high-risk groups, such as health care workers and adults who have contacts with infants.

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