

Continuing Education for Pharmacists

Volume XXIV, No. 3

Pertussis: The Disease and Immunization in Adolescents and Adults

Thomas A. Gossel, R.Ph., Ph.D.
Professor Emeritus
Ohio Northern University
Ada, Ohio

and

J. Richard Wuest, R.Ph., Pharm.D.
Professor Emeritus
University of Cincinnati
Cincinnati, Ohio

Goals. The goals of this lesson are to discuss pertussis infection as a re-emerging health problem in the United States, and emphasize the role of booster immunization of adolescents and adults as a means to curtail infection in infants and children.

Objectives. At the conclusion of this lesson, successful participants should be able to:

1. identify the etiology, incidence, pathophysiology, communicability, transmission, and symptoms of pertussis infection;



Gossel



Wuest

2. describe the economic impact of pertussis infection;

3. compare and contrast early and newer vaccines for pertussis; and

4. select from a list the indications and uses, adverse effects, and therapeutic applications of the pertussis booster vaccines.

Background: A Changing Epidemiology

During the early- to mid-1900s, whooping cough (pertussis) was one of the most common causes of childhood morbidity and a major cause of childhood mortality in the U.S. By 1940, the incidence of pertussis was approximately 150/100,000 population. Between 1940 and 1945, more than one million cases of pertussis were reported worldwide. It is estimated that there are 200,000 to 400,000 deaths worldwide from pertussis each year.

Widespread immunization against pertussis was implemented in the U.S. in 1946 with introduction of diphtheria and tetanus toxoids and whole-cell pertussis (DTP) vaccine. As a result, by the 1970s the average annual incidence of pertussis infection had decreased by 99 percent, reaching a low point for infection in 1976.

Since 1980, however, the number of reported cases each year has again been rising. In 2003, the

Centers for Disease Control and Prevention (CDC) recorded 11,647 cases and nearly 19,000 for 2004. Throughout 2005, CDC counted between 596 and 855 new cases of pertussis each *week*, higher than historic limits; pertussis cases were expected to exceed 37,000 in 2005.

Infection among adolescents and adults now accounts for the bulk of the recent increase in the U.S., with more than half of reported cases now occurring in these age groups. Concurrently, there has been an increase in the number of cases and deaths reported among infants over four months of age. Pertussis is the only disease for which children in the U.S. are routinely vaccinated that is not currently at historically low levels. Thus, the eradication of pertussis remains a challenge for both scientists and clinicians.

The primary goal of pertussis outbreak control is to decrease morbidity and mortality among infants; a secondary goal is to reduce morbidity among persons of all ages.

Pertussis can occur among persons of any age. Children under one year of age are most susceptible to pertussis infection. The increasing number of cases seen in adolescents and adults is of concern because they may serve as a reservoir of pertussis infection for younger children.

Defining Pertussis

The first mention of whooping cough (later called *pertussis*, meaning violent cough) in the medical annals appeared in 1540; the first epidemic was reported in 1578. Widespread epidemics followed around the globe in the 17th and 18th centuries.

This continuing education activity is supported by an educational grant from GlaxoSmithKline.



Table 1
Typical Course of Pertussis Infection*

Symptom	Catarrhal Phase (1-2 weeks)	Paroxysmal Phase (3-6 weeks)	Convalescent Phase (>6weeks)
Cough	++	+++	++
Paroxysmal cough	-/+	+++	-/+
Whooping cough	-	+++	-/+
Vomiting	-	+++	-/+
Cyanosis	-	+++	-
Apnea	-	+++	-

+ = present; - = absent; -/+ = equivocal

*Pertussis. *Epidemiology & Prevention of Vaccine-Preventable Diseases*. "The Pink Book," 8th ed. National Immunization Program (NIP). Atlanta: January 2005:75-87

Pertussis is a highly communicable infectious disease caused by the gram-negative bacterium *Bordetella pertussis*. Characterized by continuous spasms (paroxysms) of severe coughing, the pertussis paroxysms are often followed by a distinctive *whoop* sound and/or post-coughing vomiting. The characteristic whoop occurs when powerful coughs follow quickly one after the other, hindering inspiration.

The incubation period may vary between six and 21 days, but is typically six to 10 days. Rarely, it may last as long as 42 days. Illness onset is often insidious, with initial symptoms mimicking a minor upper respiratory infection (i.e., catarrhal period). During the first one to two weeks of illness (Table 1), coryza (profuse nasal discharge) with an intermittent non-productive cough is common. This period is followed by episodes of paroxysmal coughing that frequently persist several weeks (i.e., paroxysmal period). Attacks occur more frequently at night. Symptoms peak in severity after one or more weeks of paroxysmal coughing, then begin to subside with an extensive convalescent period of more than six weeks that may continue up to three months in some cases.

Pertussis Transmission

B. pertussis is transmitted between persons via aerosolized droplets produced from a cough or sneeze, or by direct contact with secretions from the respiratory tract of infected

individuals. No animal or insect source or vector is known to exist. Pertussis is most infectious during the first two weeks after cough onset. Some individuals, such as infants who remain culture-positive for several weeks, may be infectious for a longer period. Compared to other infectious diseases, less is known about pertussis transmission including extent of bacterial infection required for transmission or length of exposure needed to cause infection in a susceptible individual.

Several studies have documented that household members have been the source of pertussis infection in infants. In one study of confirmed pertussis cases among 430 hospitalized children aged less than two years, the source of pertussis in the child was a sibling in 53 percent, parent in 20 percent, child relative in 12 percent, neighbor in 8 percent, and a daycare contact in 3 percent of cases.

Pathophysiology of Pertussis Infection

The pathophysiology of *B. pertussis* infection is poorly understood. It is believed that following introduction of *B. pertussis* into the respiratory tract, the organisms attach to ciliated cells in the nasopharynx, which are the primary, if not the only, site of infection. Without an active immune response to intercede, the bacteria colonize, then proliferate, spreading into ciliated cells in the trachea and bronchi to result in ciliostasis (paralysis of the

cilia), damage to the respiratory epithelium, induction of mucus release, and an inflammatory influx into the lumen of the respiratory tract. Disruption of normal ciliated mucosal function and associated damage to the respiratory epithelium are primary pathologies associated with many *Bordetella* infections.

B. pertussis is a mucosal pathogen; bacteremia does not occur. *B. pertussis* can enter and survive within phagocytic leukocytes and non-phagocytic cells, but how this affects the pathogenesis and host immune response is unclear. Virulence factors, such as pertussis toxin and perhaps others yet to be identified, are responsible for the clinical characteristics of pertussis. *B. pertussis* infection can cause a primary pertussis pneumonia with subsequent respiratory failure and death.

Infection caused by *B. pertussis* should be differentiated from infections with other etiologic agents of cough illness, including adenoviruses, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and respiratory syncytial virus. Three other *Bordetella* species, *B. parapertussis*, *B. bronchiseptica* and *B. holmesii*, have occasionally been associated with a pertussis-like cough illness. Differentiation between *Bordetella* species is confirmed by culturing with identification of the organism.

Immunity to Pertussis Infection

The observed increase in pertussis infection is not due to ineffective vaccines or immunization programs. The effectiveness of today's pertussis vaccine and immunization coverage among vaccine-eligible age groups remain high. However, pertussis infection continues to afflict susceptible adolescents and adults because of their own waning vaccine-induced immunity, as well as infants who are still too young to have completed the primary vaccination series. Protective immunity to pertussis wanes four to 12 years

following immunization with whole-cell pertussis vaccine. Waning immunity following vaccination with acellular pertussis vaccines, described subsequently, may also occur but definitive data are currently limited.

Contrary to long-held dogma, acquired immunity following natural pertussis infection may also decline over time. A review of the published literature on duration of immunity reveals estimates that infection-acquired immunity against pertussis disease declines after four to 20 years. Why immunity is short-lived remains unknown. Since neonates are susceptible to pertussis, it is suggested that maternal antibodies that cross the placenta do not protect against pertussis.

Symptoms of Pertussis Infection

Apnea (temporary cessation of breathing) may occur and whoop or paroxysms may be absent among infants under six months of age. Leukocytosis and lymphocytosis are common findings during the early paroxysmal stage in young, unimmunized children. Infants are more likely than older children or adults to have severe disease, and are most likely to experience complications, require hospitalization, and die. In infants, choking spells are common.

Compared with unimmunized children, adolescents and adults often experience milder illness. As stated earlier, their symptoms may resemble an upper respiratory infection or an acute cough illness without paroxysms, whoop, or post-coughing vomiting. However, some infections may result in severe illness with significant mortality. Complications occur in one of four adults and include sinusitis, pneumonia, urinary incontinence, intense coughing (mean duration in adults, 12 weeks), fractured ribs, fatigue, encephalitis, seizures, and disturbed sleep. Because pertussis is not commonly considered as a cause of cough illness among adolescents and adults, these patients may be

misdiagnosed as having bronchitis or asthma.

Further complicating the clinical picture is that not all pertussis infections result in a cough illness in adolescents and children. The spectrum of symptoms among adults in 121 families with at least one pertussis case in a child was studied. Among the 121 families, 79 adults showed evidence of infection with *B. pertussis*. Of these adults, 9 percent had no cough. Of the adults with a cough, the cough continued an average of 54 days (median, 49 days).

Economic Impact of Pertussis

Pertussis produces a significant economic burden for children, adolescents, adults, families, hospitals, and communities. One study of 107 confirmed cases found that the average duration of illness was 21 days (range, 12 to 37 days), with an average of three physician visits (range, 1 to 15) before diagnosis. Antibiotics were prescribed for 91 percent of the patients, and all of them received appropriate medications for symptom control. Emergency department visits and hospitalizations occurred in 28 percent and 14 percent of patients, respectively. Most patients missed work as a result of illness or to care for a sick child.

In a second study, 172 individuals representing 130 families developed pertussis during an 18-month surveillance period. The direct medical costs for care averaged \$2,822 for an ill infant, \$308 for a child, \$254 for an adolescent, and \$181 for an adult. Among adults, workdays missed to care for sick children or because of personal illness averaged six days (range, one to 35 days), to result in an associated additional cost of \$767 per family. The financial burden in total averaged \$2,115 per family.

Pertussis Vaccines

Early *B. pertussis* vaccines consisted of inactivated whole cells. These vaccines were effective, although concerns over potential

adverse reactions led to development of a second generation of pertussis vaccines. These acellular vaccines are composed of purified, inactivated components of *B. pertussis*, including pertussis toxin, filamentous hemagglutinin, fimbriae and pertactin protein antigens. With the change from whole-cell to the less problematic acellular pertussis vaccines in the 1990s, excellent pertussis control along with improved safety profiles were achieved. Today, the acellular vaccines are routinely used worldwide.

Acellular booster vaccines.

More recently, the realization that vaccine-induced immunity conferred during childhood is not lifelong led to development of booster formulations of acellular pertussis vaccines combined with an adult formulation of diphtheria and tetanus toxoids (Tdap) intended for administration in adolescents and adults (Table 2). Clinical trials have shown that these vaccines share excellent safety and immunogenicity characteristics.

The Advisory Committee on Immunization Practices (ACIP) has drafted provisional recommendations for Tdap vaccines for use in adolescents and adults. As noted earlier, it is believed that this population harbors the bacteria that can be passed along to susceptible children. Effective control of pertussis will most likely require booster immunization of all adolescents and adults, in addition to active immunization of children.

Although the two new booster vaccines differ slightly in formulation (see Table 2), both are believed to have equivalent immunogenicity and protective efficacy, and both are equally safe. Adacel contains the same components as Daptacel, a vaccine indicated for infants and children. Adacel is recommended for adolescents and adults 11 to 64 years of age. Boostrix has the same components as Infanrix, a DTaP vaccine for infants and young children, and is indicated for use as a single booster dose to adolescents 10 to 18 years of age. An adult

Table 2
Approved Tdap Booster Vaccines for Use in Adolescents and Adults

	Pertussis Antigens*	Indication and Usage
Adacel	PT, FHA, PRN, FIM (5-component acellular pertussis vaccine)	Indicated for active booster immunization against tetanus, diphtheria, and pertussis as a single dose in persons 11 through 64 years
Boostrix	PT, FHA, PRN (3-component acellular pertussis vaccine)	Indicated for active booster immunization against tetanus, diphtheria, and pertussis as a single dose in persons 10 through 18 years

*PT = detoxified pertussis toxin, FHA = filamentous hemagglutinin, PRN = pertactin, FIM = fimbriae, types 2 & 3

booster is likely to soon follow. The adolescent/adult booster vaccines contain one-third the concentration of pertussis antigen that is found in pediatric formulations. A single dose of either vaccine induces an antibody response to *B. pertussis* antigens that is significantly greater in adults than that observed in infants at seven months of age following three doses of the pediatric vaccines. The Tdap vaccines are indicated for active booster immunization against tetanus, diphtheria, and pertussis; neither vaccine is indicated for treatment of active infections.

The most common adverse effects seen in premarketing clinical trials with either vaccine included injection site pain, swelling, and redness; and fever. Headache, fatigue, muscle ache, and gastrointestinal symptoms were also reported.

Healthcare providers should inform patients, parents or guardians of the potential benefits and risks of the vaccine. The vaccine recipient, parent or guardian should be questioned concerning occurrence of any adverse reaction after a previous dose of vaccine. Healthcare providers should inform the patients, parents or guardians about the potential for adverse events that have been temporally associated with administration of the vaccine or other vaccines containing similar components. The patient, or parent or guardian accompanying the recipient, should be told to report

any severe or unusual adverse events to their doctor.

Diagnosis and Treatment Guidelines

The CDC recommends that culture to identify the etiologic agent be performed in all patients with presumed pertussis during the period when patients are likely to be infectious. The culture specimen is obtained from the posterior nasopharynx. Culture should be done regardless of which other diagnostic tests are used. Both the CDC and FDA are currently working on standardization of laboratory testing methods (i.e., polymerase chain reaction [PCR]) for diagnosis of pertussis. Patients seen early in their illness (i.e., during the first three weeks after onset of coughing) 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 in whom cough has persisted beyond four weeks.

The CDC also recommends that patients with presumed or confirmed pertussis be treated with erythromycin (or one of the newer erythromycin analogs, e.g., clarithromycin [Biaxin]), but acknowledges the limitations of this treatment due to adverse effects. For patients who present after onset of paroxysmal cough, antibiotics will unlikely affect the clinical course but will preclude transmission of *B. pertussis* to susceptible hosts

beginning five days after onset of therapy.

Summary and Conclusion

There has been much recent concern over an increasing incidence of pertussis despite an active and effective immunization program for infants and children. Pertussis infection in adolescents and adults is more common than previously recognized and causes significant morbidity. The economic impact of pertussis infection, including time lost from work and school, is substantial. Pertussis vaccines are highly efficacious. Control of pertussis requires an increase in immunity among all age groups. Immunization of adolescents and adults with a booster vaccine may, therefore, be a cost-beneficial strategy. Immunization of adolescents and adults with pertussis booster vaccine will impact the incidence of this disease.