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Pertussis in Childhood

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Drs Snyder and Fisher have disclosed no financial relationships relevant to this article. This commentary does contain a discussion of an unapproved/investigative use of a commercial product/device.

Educational Gap

The incidence in the United States of pertussis, a potentially fatal disease, has increased during the past decade and new recommendations for vaccination have been made in recent years.

Objectives After reading this article, readers should be able to:

1. Understand the pathophysiology of pertussis.
2. Describe the clinical presentation, natural history, and potential complications of pertussis infection.
3. Appreciate the changing epidemiology of pertussis.
4. Master the laboratory diagnosis and medical management of pertussis infection.
5. Describe the vaccination strategies for the prevention of pertussis infection.

Introduction

Pertussis, commonly known as “whooping cough,” is a respiratory illness caused by the bacterium *Bordetella pertussis*. The classic clinical syndrome causes morbidity by affecting the upper respiratory tract in patients of all ages. The disease can be modified greatly and prevented by primary vaccination. An ongoing resurgence of clinical pertussis has been seen in the United States over the past decade, with increasing numbers of young infants affected despite the availability of effective vaccines. It is important to understand the biological properties of the bacterium, the clinical presentation, and the factors contributing to the continuing burden of this disease.

The Organism and Pathophysiology

B pertussis is a small Gram-negative coccobacillus that infects only humans. It is aerobic and grows best at 35°C to 37°C. *Bordetella* species, including *B pertussis* and *B parapertussis*, are fastidious and difficult to grow on media usually used in the laboratory to grow respiratory pathogens; *B pertussis* requires supplemental growth factors including charcoal, blood, and starch. Media such as Bordet-Gengou, which contains potato starch, and charcoal-based Regan-Lowe media typically are used in microbiology laboratories for culturing the organism.

B pertussis causes irritation and inflammation by infecting the ciliated respiratory tract epithelium. The ensuing tissue necrosis and epithelial cell damage recruits macrophages, and reactive lymphoid hyperplasia of peribronchial and tracheobronchial lymph nodes occurs.

The bacterium has several virulence factors and toxins that are important in the pathogenesis of the disease and also play a role in inducing protective immune responses. Filamentous hemagglutinin and fimbriae are adhesins required for tracheal colonization. These substances are highly immunogenic and are major components of acellular vaccines.

Abbreviations

CDC: Centers for Disease Control and Prevention
DTP: diphtheria, tetanus, and whole cell pertussis vaccine
DTaP: diphtheria, tetanus, and acellular pertussis vaccine
PCR: polymerase chain reaction
PT: pertussis toxin
RSV: respiratory syncytial virus
Tdap: diphtheria, tetanus, and acellular pertussis vaccine (reduced diphtheria component)

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Other virulence factors such as pertactin and pertussis toxin (PT) can act as adhesins as well. PT can inactivate or suppress signaling pathways of the immune system in the lung, which delays recruitment of neutrophils. The role of pertussis toxin in the pathogenesis of pertussis is not fully understood. The toxin has been shown to cause leukocytosis with lymphocytosis and possibly the rare encephalopathy seen in the clinical disease. Other direct systemic effects of PT include sensitization of the beta-islet cells of the pancreas. This effect can lead to hyperinsulinemia with a resistant hypoglycemia, and sometimes occurs in young infants who have poor feeding, which exacerbates the symptoms. Adenylate cyclase toxin inhibits migration and activation of phagocytes and T cells.

Epidemiology

Worldwide, an estimated 50 million cases and 300,000 deaths due to pertussis occur annually. (1) In the United States, pertussis is an endemic disease, with periodic epidemics every 3 to 5 years and frequent outbreaks. The last peak in the incidence of pertussis occurred in 2005, when ~25,000 cases were reported nationally. Increasing incidence has been noted in the United States and other countries despite widespread immunization. In 2009, nearly 17,000 cases of pertussis were reported in the United States, with many more going unreported. (2)

In the past year, 9,477 cases of pertussis (including 10 infant deaths) were reported in California, the highest incidence in the state since the cyclical peak in 2005. (3) According to the Centers for Disease Control and Prevention (CDC), 50% of infants under age 1 year who are infected with pertussis will require hospitalization. Of these, 50% will develop pneumonia and 1% will die of complications from their infection. Pertussis morbidity and mortality is most significant in infants younger than age 3 months. Infants in this age group have the highest incidence of hospitalization, admission to intensive care units, and death from pertussis.

In a review of a national pediatric inpatient database from 2000 to 2003, 86% of all hospitalizations for pertussis were in infants age <3 months. (4) In the United States and other industrialized countries, the resurgence of pertussis is being

seen in very young infants who are not fully immunized, and in children and adolescents aged 10 years and older. Waning vaccine-induced immunity and lack of natural booster events may account for many of those cases in this older age group. Other factors that might be contributing to the increase in reported cases of pertussis are heightened awareness and reporting among health-care providers, increased use of polymerase chain reaction (PCR) testing for diagnosis, and decreased pertussis vaccination rates in some areas (Fig 1).

Pertussis in developing countries is still the source of the highest disease burdens, primarily in Asia, Africa, and South America. Pertussis worldwide remains one of the top 10 causes of mortality in infants younger than age 1 year. Varying case definitions make comparisons of incidence between countries difficult. Hospitalization rates sometimes are used to follow incidence and the severity of outbreaks.

A clinical case is defined commonly as a cough illness lasting at least 2 weeks with one of the following: paroxysms of coughing, inspiratory "whoop," or post-tussive vomiting without other apparent cause (as reported by a health professional). A confirmed case is defined as any cough illness in which *B pertussis* is isolated by culture. A case that satisfies the clinical case definition and is confirmed by PCR, or that has an epidemiological link to a laboratory-confirmed case,

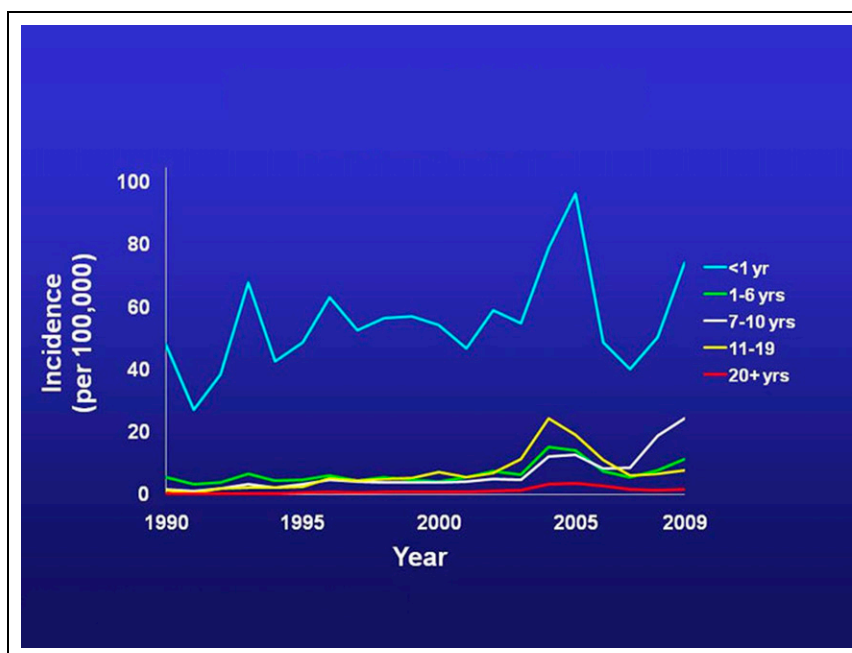


Figure 1. Reported pertussis incidence by age group 1990–2008. Source: Centers for Disease Control and Prevention, National Notifiable Diseases Surveillance System; 2009.

also may be considered a true case, particularly in outbreak situations.

Clinical Presentation and Natural History

Pertussis is spread by aerosol droplets expelled while coughing or sneezing in proximity to others. Many infants who get pertussis are infected by older siblings, parents, or caregivers who may have only mild symptoms. After an incubation period of 7 to 14 days, the natural history of pertussis tends to follow a relatively predictable clinical course, although disease severity and prognosis are quite variable. Because of this variability, a high degree of suspicion is necessary to make a timely diagnosis. A child suspected of having pertussis should be placed in appropriate isolation until the infection is confirmed or ruled out. A patient suspected of having pertussis should be masked in waiting rooms and when sent for ancillary testing.

Catarrhal Phase

The catarrhal phase of pertussis lasts from 1 to 2 weeks and includes nonspecific complaints. The mild fever, cough, and nasal signs and symptoms associated with this early phase of the illness are similar to those seen in many viral upper respiratory tract infections, which often leads to a delay in identifying suspected cases. During this phase of the illness, the cough worsens as the patient progresses to the paroxysmal phase.

Paroxysmal Phase

The paroxysmal phase of the illness lasts from weeks 2 to 6. This phase is characterized by paroxysms of cough, often described as “rapid fire” or “staccato.” Classically, as many as 5 to 10 uninterrupted coughs occur in succession, followed by a “whoop” as the patient rapidly draws in a breath. An audio file of the cough and whoop can be accessed online through the following link: <http://www.pkids.org/diseases/pertussis.html>. This classic whooping sound is heard less commonly in adolescents and adults.

The paroxysms may occur several times per hour and can be associated with cyanosis, salivation, lacrimation, and post-tussive emesis. These paroxysms can be exhausting and often interfere with sleep and nutritional intake. Despite the severe

spells, patients often appear relatively well between episodes.

Infants younger than age 6 months often have a less typical presentation. The classic “whoop” may be absent, and gasping, gagging, and apnea can occur. Sudden death has been reported. As the cough gradually improves, the patient enters the convalescent phase of the illness.

Convalescent Phase

Following the peak of the paroxysmal phase, improvement in respiratory tract integrity and function is associated with decreasing frequency and severity of the coughing episodes. The duration of this convalescent phase is highly variable, lasting from weeks to months.

Complications

Pertussis is most severe in infants under age 6 months, for whom the mortality rate is ~1%. Greater than 80% of deaths related to pertussis infection occur in infants under age 1 year, with more than half of these deaths occurring in infants age <2 months. (5) The disease tends to be milder or even subclinical in those protected by immunization.

Complications of pertussis include apnea, pneumonia, seizures, encephalopathy, and death. Pneumonia may be primary or secondary to coinfection. Concomitant infection with other organisms such as influenza or respiratory syncytial virus (RSV) can lead to a more severe clinical course.

The paroxysms themselves can result in pressure-related complications such as pneumothorax or

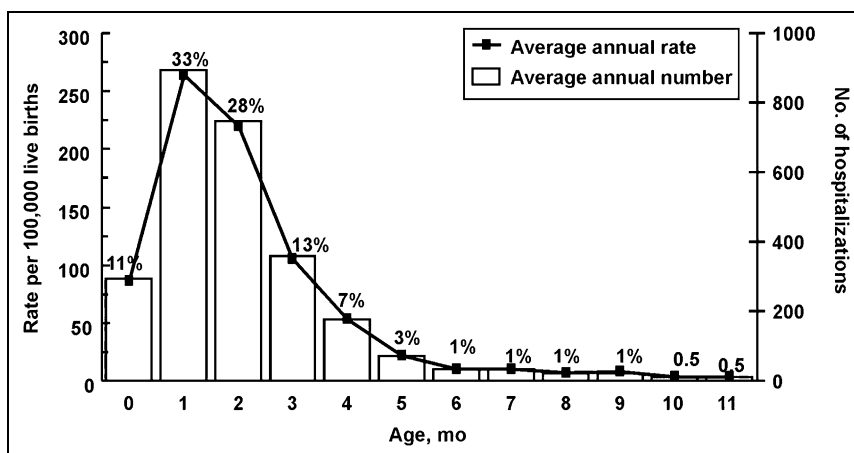


Figure 2. Average annual incidence of pertussis hospitalizations and number (percent) of hospitalizations according to age group in the KID (2000 and 2003). Reprinted, with permission, from Shinall MC et al. “Potential impact of acceleration of the pertussis vaccine primary series for infants.” *Pediatrics*. 2008;121:484–492.

pneumomediastinum, subcutaneous emphysema, superficial petechial hemorrhage, rib fracture, rectal prolapse, and even intracranial hemorrhage.

Infants afflicted with pertussis often require hospitalization for fluid, nutritional, and respiratory support. During the years 1999–2003, the hospitalization rate for infants age ≤ 6 months was 78%. (6) In a recent review that used the Kids' Inpatient Database, 86% of children under age 1 year who were hospitalized with pertussis were age ≤ 3 months (Fig 2). (4)

Diagnosis by Laboratory Studies

Isolation of *B pertussis* from nasopharyngeal swab or aspirate cultured on specialized media used to be the gold standard for detecting the organism. Because the organism is variably present only in the early stage of the illness, yield from cultures done later, when clinical symptoms are more evident, is low. Specimens obtained 3 weeks after the onset of cough produces yields as low as 1% to 3%. Adolescents and adults tend to present later in the course of the illness, and the culture rate in this population is very low. Culture time generally is 2 weeks. In unimmunized infants with a high bacterial load who are cultured early in the illness, cultures may be positive in as little as

72 hours. Culture also will identify cases that are caused by *B parapertussis*.

Although culture remains the gold standard laboratory test to confirm the diagnosis of *B pertussis*, PCR is beginning to replace culture as the diagnostic test of choice for *B pertussis* in many clinical settings. PCR for *B pertussis* is a rapid, specific, and sensitive diagnostic test that will remain positive late in the course of the illness. Even in the presence of antibiotic treatment, PCR often will remain positive for as long as 7 days. Many laboratories perform only PCR and do not use culture for identifying *B pertussis*, although most state public health laboratories do maintain the ability to perform both culture and PCR testing.

The PCR test also has been adopted as an acceptable method for diagnostic case surveillance in the United States. However, because there are still no nationally standardized assays, sensitivity and specificity vary among laboratories. Since the advent of PCR testing for identifying pertussis, the number of confirmed cases has increased. Culturing for *B pertussis* still may have a role in some special circumstances, such as during an outbreak. In several instances, cases detected solely on the basis of PCR in hospital settings have proven to be "pseudo-outbreaks" due to false-positive PCR results. (7)

Table 1. Laboratory Methods for Diagnosing Pertussis Infection

Test	Sensitivity, %	Specificity, %	Optimal Timing	Advantages	Disadvantages
Culture	12–60	100	<2 wk postcough onset	Very specific (100%)	Low sensitivity; 7–10 day delay between specimen collection and diagnosis
Polymerase chain reaction	70–99	86–100	<4 wk postcough onset	Rapid test; more sensitive than culture; organisms do not need to be viable; positive postantibiotics.	No FDA approved tests or standardization; potential for false positives; DNA cross-contamination can be problematic
Paired sera	90–92	72–100	At symptom onset and 4–6 wk later	Effective indication of mounting antibody titers	Late diagnosis; no FDA-approved tests or standardization
Single sera	36–76	99	At least 2 wk postcough onset; ideally 4–8 wk postcough	Useful for late diagnosis or postantibiotics	No FDA-approved test or standardization; possibly confounded by recent vaccination; diagnostic cutoffs not validated

FDA=Food and Drug Administration.
Adapted from Centers for Disease Control and Prevention (CDC) Pertussis and Diphtheria Laboratory.

Because direct fluorescent antibody testing of nasopharyngeal secretions has been demonstrated in some studies to have low sensitivity and variable specificity, such testing should not be relied upon as a criterion for laboratory confirmation. Most laboratories therefore have discontinued use of the fluorescent antibody testing of nasal secretions for pertussis.

Serological testing for pertussis is available in some areas, but it is not standardized and, therefore, also should not be relied upon as a criterion for laboratory confirmation. Antibodies to PT are the most common serological test performed, generally utilizing an enzyme-linked immunosorbent assay. Pertussis-specific immunoglobulin M testing is not available routinely. In a nonimmune child, a single positive immunoglobulin G assay done during the second phase of the illness is considered diagnostic. In the presence of pre-existing immunity, a rise in titer using paired specimens 2 to 3 weeks after onset of clinical illness is necessary and is considered the gold standard for serologic diagnosis (Table 1).

Leukocytosis, together with an absolute lymphocytosis on a peripheral complete blood count, is another laboratory finding supportive of *B pertussis* infection. This finding often correlates with disease severity, especially in very young infants. White blood cell counts as high as 30 to $60 \times 10^3/\mu\text{L}$ can be seen. Monitoring of fluids and electrolytes is necessary in infants with severe disease. Laboratory evaluation to rule out other respiratory illness may be necessary.

Differential Diagnosis

Other respiratory pathogens causing a cough illness can mimic pertussis. Because very young infants can present only with apnea episodes without the typical whoop or spasms of cough, RSV infection should be considered. Rapid viral antigen testing by various methods, including direct fluorescent antibody panels, direct enzyme immunoassays, and multiplex PCR panels, may help differentiate among RSV, influenza, and adenoviruses. *Chlamydia trachomatis* can present as a cough illness in neonates, but usually creates an interstitial pneumonitis pattern and lower respiratory tract findings. Other causes of prolonged cough illness in older children and adolescents include *Chlamydia pneumoniae* and *Mycoplasma pneumoniae*. Specific serologies can be sent for these atypical organisms.

Management

If left untreated, most individuals will clear *B pertussis* spontaneously from the nasopharynx within 2 to 4 weeks of infection. However, nasopharyngeal carriage can

persist for 6 weeks or more. During this period, individuals remain contagious and can spread the illness to others. When started early in the course of the illness, during the catarrhal stage, antibiotics can shorten the course and attenuate the severity of pertussis. Once the paroxysmal phase has started, however, antibiotics are not effective in altering the course of the disease. By this stage, clinical manifestations of the illness are due to toxin-mediated effects, and thus are not affected by antimicrobial therapy. Unfortunately, because the catarrhal phase of pertussis is nonspecific, resembling many benign upper respiratory tract infections, most cases are not yet diagnosed by this point in the illness.

Although the clinical course of pertussis is not readily affected by treatment, the use of an appropriate antibiotic is indicated, even in the catarrhal phase, because this therapy results in rapid clearance of the organism from the nasopharynx (usually within 5 days of the start of therapy) and thus can greatly shorten the period of contagiousness.

For many years, the standard regimen for the treatment of pertussis in children has been administration of oral erythromycin. Recent studies have demonstrated equal efficacy and improved tolerability of other macrolides, such as azithromycin. (8) Azithromycin is associated with fewer adverse gastrointestinal events, may be dosed once daily, and does not inhibit the cytochrome P450 system, and therefore may be preferable. In addition, erythromycin has been associated with an increased risk of pyloric stenosis when administered to infants in the first 2 weeks after birth. (9)

The use of trimethoprim-sulfamethoxazole also has been shown to be effective in eliminating the nasopharyngeal carriage of *B pertussis* and may be an appropriate alternative for individuals age >2 months who are unable to take a macrolide. A recent Cochrane review of 13 clinical trials showed that a 7-day course of therapy is equally effective as a 14-day course and is associated with fewer adverse effects (Table 2). (10)

Prophylaxis

Antibiotics may prevent infection with *B pertussis* in exposed individuals if given within 21 days of symptom onset in the index case. The CDC and the American Academy of Pediatrics currently recommend prophylaxis of high-risk close contacts, as well as close contacts who may have contact with high-risk individuals. The recommended antibiotics and dosing regimens for pertussis prophylaxis are the same as for treatment. Because an individual's previous vaccination status may not always reliably predict his susceptibility to infection, this status

Table 2. Antibiotic Regimens for Treatment and Prophylaxis of Pertussis

Agent	Dose and Regimen
Azithromycin*	<ul style="list-style-type: none"> • Infants age <6 mo: 10 mg/kg for 5 days • Infants and children age ≥6 mo: 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/day on days 2–5
Clarithromycin*	<ul style="list-style-type: none"> • Infants aged <1 mo: not recommended • Infants and children aged >1 mo: 15 mg/kg per day (maximum 1 g/day) in 2 divided doses each day for 7 days • Adults: 1 g/day in 2 divided doses for 7 days
Erythromycin*	<ul style="list-style-type: none"> • Infants aged <1 mo: Azithromycin is preferred because of risk for pyloric stenosis with erythromycin. If erythromycin is used, the dose is 40–50 mg/kg per day in 4 divided doses. These infants should be closely monitored for pyloric stenosis. • Infants aged >1 mo and older children: 40–50 mg/kg per day (maximum 2 g/day) in 4 divided doses for 14 days • Adults: 2 g/day in 4 divided doses for 14 days
TMP-SMX	<ul style="list-style-type: none"> • Infants aged <2 mo: contraindicated • Infants aged >2 mo and children: TMP 8 mg/kg per day, SMX 40 mg/kg per day in 2 divided doses for 14 days • Adults: TMP 320 mg/day, SMX 1,600 mg/day in 2 divided doses for 14 days

TMP=trimethoprim; SMX=sulfamethoxazole.
 *Infants aged <1mo should be monitored closely for pyloric stenosis when treated with a macrolide.
 Adapted from CDC. Recommended antimicrobial agents for the treatment and postexposure prophylaxis of pertussis. *MMWR*. 2005;54(RR14):1–16.

should not be a factor when determining the need for prophylaxis (Table 3).

Individuals with confirmed or suspected pertussis should be excluded from school or child care settings pending evaluation and completion of 5 days of an appropriate antibiotic. If not appropriately treated, individuals with pertussis should be kept from school or child care settings until 21 days have elapsed from the onset of cough. (11)

Prevention

Infection with *B pertussis* can be prevented through appropriate immunization. Available vaccines are 80% to 85% effective at preventing disease after completion of the primary series. Children who do become infected with *B pertussis* after immunization are more likely to have subclinical or less severe illness. All currently available pertussis vaccines are combined with tetanus (T)

and diphtheria (D) toxoids, as either DTaP or Tdap (diphtheria, tetanus, and acellular pertussis vaccine-reduced diphtheria and pertussis components) (Table 4).

The pertussis component of the vaccine designated ap or aP is acellular, containing varying amounts of PT, filamentous hemagglutinin, pertactin, and fimbriae antigens, depending on the vaccine type. The American Academy of Pediatrics and the CDC's Advisory Committee on Immunization Practices currently recommend a primary series of 3 DTaP doses to be given at age 2, 4, and 6 months, followed by boosters at age 15 to 18 months and 4 to 6 years. The fifth dose is not recommended if the fourth dose is administered at age ≥4 years. Children who have confirmed cases of pertussis also should complete the immunization series against pertussis.

Because immunity to pertussis from the DTaP series wanes over time, a booster dose is recommended at age

Table 3. Pertussis Prophylaxis: Definition of Close Contact and High Risk

Close Contact	High Risk
<ul style="list-style-type: none"> • Close sharing of confined space with infected individual for >1 h • Direct contact with respiratory, oral, or nasal secretions from infected patient • Face-to-face exposure within 3 ft of infected patient 	<ul style="list-style-type: none"> • Infants age <1 y • Pregnant women in third trimester
	<ul style="list-style-type: none"> • Immunocompromised • Underlying lung disease

Adapted from CDC. Recommended antimicrobial agents for the treatment and postexposure prophylaxis of pertussis. *MMWR*. 2005;54(RR14):1–16.

Table 4. Pertussis-Containing Vaccines

Pertussis-Containing Vaccines for Children	Brand	Licensed Date and Used For
DTaP	INFANRIX®* DAPTACEL®†	First licensed in 1991; used for all childhood doses
DTaP+IPV+HepB	PEDIARIX®*	Used for the first 3 doses
DTaP+IPV+Hib	PENTACEL™†	Approved in 2008; used for primary 4-dose series
DTaP+IPV	KINRIX™*	Approved in 2008; used for booster dose at 4–6 y
Pertussis-Containing Vaccines for Adolescents and Adults	Brand	Licensed Date
Tdap	ADACEL®† BOOSTRIX®*	First available in 2005
Other Vaccines	Brand	Licensed Date
Pertussis only DT/Td	DECAVAC™† TENIVAC™†	Not available in the United States Do not contain pertussis; DT used for primary series when pertussis vaccination was not desired; Td used in persons aged ≥7 y

D=diphtheria toxoid; d=diphtheria toxoid reduced dose; T=tetanus toxoid; P=pertussis vaccine; aP=acellular pertussis vaccine; ap=acellular pertussis vaccine reduced dose.
*GlaxoSmithKline, Research Triangle Park, NC.
†Sanofi Pasteur Inc., Swiftwater PA.
Adapted from CDC, Manual for the Surveillance of Vaccine-Preventable Diseases (5th Edition, 2011).

11 to 18 years, and preferably between age 11 and 12 years. This booster is administered by using the Tdap formulation of the vaccine, which contains a reduced dose of both the diphtheria and pertussis components to minimize local reactions.

Although it is not Food and Drug Administration-approved for children age 7 through 9 years, the Advisory Committee on Immunization Practices recommends a single dose of Tdap for children age 7 through 9 years who are not fully immunized against pertussis. This group includes children who have received fewer than 4 doses of DTaP, children who have received 4 doses of DTaP with the last dose given before age 4 years, and children whose immunization status is unknown. The booster is recommended also for adults aged 19 and older.

The incidence of pertussis in infants and children declined dramatically following the introduction of widespread immunization in this country. In the past decade, however, pertussis rates have been climbing. There has been a shift also in the age distribution of disease. Although infants younger than age 6 months still account for the majority of reported cases of pertussis, older children and adolescents represent an increasingly large proportion of the clinical cases.

In addition, many cases of pertussis remain undiagnosed in the United States, because illness often goes unrecognized in adolescents and adults who may not have typical symptoms. In adults, pertussis illness may not be

recognized because it is a subclinical disease at least 40% of the time. (12)

Evaluation of pertussis-specific serological responses after illness indicates that prolonged cough illness in adolescents and adults often is diagnosed incorrectly as bronchitis or a viral upper respiratory tract infection.

Adults who have these clinical syndromes may be important reservoirs for spread of infection to infants. (13) Many studies have shown that the rates of interfamilial and household transmission to unimmunized infants are high. When the source can be identified in these studies of newborns with pertussis, family members are the source of transmission in up to 83% of cases. In one study, parents accounted for 55% of sources, siblings for 16%, and other family members and friends for another 18% when a source was identified. (14) Another study identified household contacts of infants younger than age 6 months age with pertussis and attributed the source to be mothers 38% of the time and siblings 41% of the time. (15)

Although the explanation for the changing epidemiology of pertussis infection is unclear, it is believed to be due both to an increased awareness and recognition of cases and to waning vaccine efficacy over time. Recent evidence suggests that at least some of this waning vaccine efficacy may be due to antigenic divergence between circulating and vaccine strains of *B pertussis*. (16)

With an adolescent Tdap vaccination rate of only 56%, and an adult rate of <6%, an increased effort at vaccinating

this older population is an important step in breaking the cycle of infection. Recent outbreaks of pertussis in infants and young children in populations with high vaccine refusal have raised the concern that pockets of underimmunization also may be contributing to the increase in pertussis cases. Recent evidence has confirmed higher rates of pertussis infection in populations of vaccine refusers. (17)

Infants, particularly those under age 3 months, are most vulnerable to the serious complications of pertussis infection. These infants typically become infected from adolescents and adults whose immunity has waned over time, making the Tdap booster an extremely important element of the overall pertussis prevention strategy. Because immunization with Tdap during pregnancy confers protection to the newborn as a result of transplacental antibodies, the CDC also recommends Tdap for pregnant women after 20 weeks' gestation who have not already received it, or whose vaccination status is unknown. If Tdap is not given during pregnancy, it should be given in the immediate postpartum period.

DTaP or Tdap (depending on age) is also recommended by the CDC for all family members and caregivers of the infant, including adults age ≥ 65 years, for whom Tdap is not US Food and Drug Administration-approved. This "cocooning" strategy can effectively shield the susceptible newborn from exposure to pertussis infection. Recent evidence suggests that newborns themselves may be able to mount an adequate antibody response to pertussis vaccine. Further research on infant immunization against pertussis may lead the way to improved protection for this most vulnerable population. (18)(19)

Vaccine Safety

An effective pertussis vaccine has been in use in the United States since the introduction of the original whole cell pertussis vaccine in the mid-1940s. This vaccine was combined with diphtheria and tetanus toxoids as the diphtheria, tetanus, and whole cell pertussis vaccine (DTP) vaccine in 1947. Although this vaccine was effective, it was associated with a high frequency of significant but nonlife-threatening adverse events, ranging from high fever to hypotonic-hyporesponsive episodes. These reactions were a consequence of the large number of proteins present in this whole cell preparation.

Fear of these sometimes frightening reactions led some parents and clinicians to link the vaccine to brain damage and other conditions that were seen following vaccination with DTP. Antivaccine groups and negative media coverage surrounding this alleged linkage created a backlash against the vaccine, resulting in a wave of

successful litigation against the manufacturers of DTP. In the United States, pharmaceutical companies stopped producing the vaccine, requiring action from the federal government to safeguard the nation's supply by enacting the National Childhood Vaccine Injury Act of 1986. This act included the Vaccine Injury Compensation Program, which established a fund supported by an excise tax on each vaccine component to compensate parents of children who developed any condition listed on its compensable injury table.

Despite the long history of concern over the DTP vaccine, multiple well-designed studies have repeatedly failed to link the vaccine to brain injury. (20)(21)(22)(23)(24)(25) In 1990, the acellular pertussis vaccine (DTaP) was introduced, which is associated with a significantly reduced incidence of adverse events. Local reactions still are relatively common, with 20% to 40% of children experiencing some combination of local redness, swelling, and pain. Systemic reactions are uncommon, with 3% to 5% experiencing a fever ($\geq 101^\circ\text{F}$). These reactions are seen most often following the fourth and fifth doses.

Summary

- Pertussis is a serious and potentially fatal disease caused by the bacterium *Bordetella pertussis*. In infants under age 6 months, who are too young to be adequately protected by the vaccine, pertussis is associated with a hospitalization rate of almost 80% and a mortality rate of nearly 1%.
- Complications of pertussis include encephalopathy, pneumonia, apnea, seizures, and death. The course of the illness is more severe in young children, with infants under age 6 months most at risk for hospitalization and severe complications.
- A high degree of suspicion is important. Treatment usually is initiated too late in the illness to alter the course, but can prevent transmission of the disease to others.
- An effective vaccine is available and recommended for all children. Because of waning vaccine immunity over time, an additional dose of vaccine is recommended for older children and adults.
- Women whose pregnancy has passed 20 weeks or who are in the postpartum period who were not vaccinated previously or whose vaccination status is unknown, and other individuals who may come in contact with a newborn, should be vaccinated as part of a strategy to "cocoon" the newborn from infection.
- Enlarging pockets of underimmunization may be a contributing factor to the current upswing in pertussis cases, reminding us of the importance of maintaining high vaccination rates for the prevention of disease outbreaks.

References

1. World Health Organization. WHO –Recommended standards for surveillance of selected vaccine-preventable diseases. 2003. WHO/V&B/02.01, 28–30
2. Centers for Disease Control and Prevention. In: Roush S, McIntyre L, Baldy L, eds. 5th ed. Atlanta, GA: Manual for the Surveillance of Vaccine-Preventable Diseases; 2011
3. Centers for Disease Control and Prevention. Pertussis. (Whooping Cough) Outbreaks. Available at: <http://www.cdc.gov/pertussis/outbreaks.html>. Accessed January 4, 2012
4. Cortese MM, Baughman AL, Zhang R, Srivastava PU, Wallace GS. Pertussis hospitalizations among infants in the United States, 1993 to 2004. *Pediatrics*. 2008;121(3):484–492
5. Haberling DL, Holman RC, Paddock CD, Murphy TV. Infant and maternal risk factors for pertussis-related infant mortality in the United States, 1999 to 2004. *Pediatr Infect Dis J*. 2009;28(3):194–198
6. Centers for Disease Control and Prevention. QuickStats: rate of hospitalizations for pertussis among infants aged <6 months—United States, 1994–1998 and 1999–2003. *MMWR*. 2005;54(40):1027
7. Weber DJ, Miller MB, Brooks RH, Brown VM, Rutala WA. Healthcare worker with “pertussis”: consequences of a false-positive polymerase chain reaction test result. *Infect Control Hosp Epidemiol*. 2010;31(3):306–307
8. Langley JM, Halperin SA, Boucher FD, Smith B; Pediatric Investigators Collaborative Network on Infections in Canada (PICNIC). Azithromycin is as effective as and better tolerated than erythromycin estolate for the treatment of pertussis. *Pediatrics*. 2004;114(1):e96–e101
9. Cooper WO, Griffin MR, Arbogast P, Hickson GB, Gautam S, Ray WA. Very early exposure to erythromycin and infantile hypertrophic pyloric stenosis. *Arch Pediatr Adolesc Med*. 2002;156(7):647–650
10. Altunajji S, Kukuruzovic R, Curtis N, Massie J. Antibiotics for whooping cough (pertussis). *Cochrane Database Syst Rev*. 2007;(3):CD004404
11. American Academy of Pediatrics. Pertussis (whooping cough). In: Pickering LK, Baker CJ, Kimberlin DW, Long SS, eds. *Red Book: 2009. Report of the Committee on Infectious Diseases*. 28th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2009:504–519
12. Farizo KM, Cochi SL, Zell ER, Brink EW, Wassilak SG, Patriarca PA. Epidemiological features of pertussis in the United States, 1980–1989. *Clin Infect Dis*. 1992;14(3):708–719
13. Cherry J. Epidemiological, clinical, and laboratory aspects of pertussis in adults. *Clin Infect Dis*. 1999;28:S112–S117
14. Wendelboe AM, Njamkepo E, Bourillon A, et al; Infant Pertussis Study Group. Transmission of *Bordetella pertussis* to young infants. *Pediatr Infect Dis J*. 2007;26(4):293–299
15. De Greeff S, Mooi F, Westerhoff A, et al. Pertussis disease burden in the household: how to protect young infants. *Clin Infect Dis*. 2010;50(10):1339–1345
16. He Q, Mäkinen J, Berbers G, et al. Bordetella pertussis protein pertactin induces type-specific antibodies: one possible explanation for the emergence of antigenic variants? *J Infect Dis*. 2003;187(8):1200–1205
17. Glanz JM, McClure DL, Magid DJ, et al. Parental refusal of pertussis vaccination is associated with an increased risk of pertussis infection in children. *Pediatrics*. 2009;123(6):1446–1451
18. Wood N, Siegrist C. Neonatal immunization: where do we stand? *Curr Opin Infect Dis*. 2011;24(3):190–195
19. Wood N, McIntyre P, Marshall H, Robertson D. Acellular pertussis vaccine at birth and one month induces antibody responses by two months of age. *Pediatr Infect Dis J*. 2010;29(3):209–215
20. Pollock TM, Morris J. A 7-year survey of disorders attributed to vaccination in North West Thames Region. *Lancet*. 1983;1(8327):753–757
21. Shields WD, Nielsen C, Buch D, et al. Relationship of pertussis immunization to the onset of neurologic disorders: a retrospective epidemiologic study. *J Pediatr*. 1988;113(5):801–805
22. Walker AM, Jick H, Perera DR, Knauss TA, Thompson RS. Neurologic events following diphtheria-tetanus-pertussis immunization. *Pediatrics*. 1988;81(3):345–349
23. Griffin MR, Ray WA, Mortimer EA, Fenichel GM, Schaffner W. Risk of seizures and encephalopathy after immunization with the diphtheria-tetanus-pertussis vaccine. *JAMA*. 1990;263(12):1641–1645
24. Gale JL, Thapa PB, Wassilak SG, Bobo JK, Mendelman PM, Foy HM. Risk of serious acute neurological illness after immunization with diphtheria-tetanus-pertussis vaccine. A population-based case-control study. *JAMA*. 1994;271(1):37–41
25. Ray P, Hayward J, Michelson D, et al; Vaccine Safety Datalink Group. Encephalopathy after whole-cell pertussis or measles vaccination: lack of evidence for a causal association in a retrospective case-control study. *Pediatr Infect Dis J*. 2006;25(9):768–773

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1. An obstetrical resident asks you when to administer the pertussis vaccine to a 25-year-old pregnant woman whose immunization status is unknown. You tell the resident that, among the following, the soonest recommended time would be after
 - A. 16 weeks
 - B. 20 weeks
 - C. 24 weeks
 - D. 28 weeks
 - E. 32 weeks
2. The woman delivers before the vaccine is administered. You recommend that the following people who live in the household be vaccinated:
 - A. Both parents
 - B. Mother
 - C. Parents and siblings over 10 years
 - D. Parents, siblings over 10 years, and grandparents
 - E. Parents, siblings over 10 years, grandparents, and nanny
3. A 4-month-old infant boy has had a fever (100.6°F), a persistent cough, and nasal discharge for the past week. You are considering a diagnosis of pertussis. The most practical and rapid laboratory study to confirm the diagnosis is
 - A. Complete blood count with differential
 - B. Culture on Regan-Lowe medium
 - C. Fluorescent antibody testing
 - D. Polymerase chain reaction testing
 - E. Serum antibody titer
4. The diagnosis of pertussis is confirmed. The antibiotic of choice for an infant this age is
 - A. Azithromycin
 - B. Erythromycin
 - C. Penicillin
 - D. Trimethoprim-sulfamethoxazole
 - E. Vancomycin
5. The infant is begun on appropriate treatment. The parents ask when he can return to child care. You tell them that their son will no longer be contagious after receiving antibiotic therapy for
 - A. 24 hours
 - B. 48 hours
 - C. 72 hours
 - D. 5 days
 - E. 10 days

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