Pertussis

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Pertussis, also known as whooping cough, is an acute upper respiratory tract illness that is characterized by a severe cough followed by a gasp for air that may sound like a "whoop." Prior to the introduction of vaccine against pertussis, whooping cough was a leading cause of death in children. With the introduction of whole-cell pertussis vaccine in the mid-1940s, rates of reported illness and death dropped dramatically.[1] However, the incidence of pertussis has increased recently in both adults and children, despite high vaccination rates. This article reviews the epidemiology, clinical presentation, and treatment of pertussis. In addition, it discusses the effects of vaccination in prevention and control of pertussis, particularly in light of the recent increased incidence of pertussis.

EPIDEMIOLOGY

Pertussis is endemic in the United States, even in populations with high levels of vaccination. The illness is extremely contagious and resurges in epidemic cycles that occur at intervals of 2 to 5 years. Typically, the caseload peaks in July through October, with the earlier peak occurring in the southern United States and a later peak in the northern states.

For many years after the first pertussis vaccine was introduced, the incidence of cases of pertussis decreased, but by the 1980s, the numbers again began to gradually increase. In 1950, the annual reported number of cases of pertussis in the United States was 120,718. By 1970, the number had dropped to 4249 cases. From the 1980s through the 1990s, rates began to increase, particularly in infants younger than 6 months.[2] Between 1998 and 2001, the rates were steady, with an average of 7535 cases per year.[3] In 2002, the rates increased again, with a total of 9771 cases. Preliminary data for 2003 indicate another jump in the number of cases to 11,647,[4] continuing the recent upward trend (**Figure 1**). In 2001, 22% of cases were infants younger than 6 months, and 52% were aged 10 years or older.[5] The distribution of cases by age-group remained similar to the distribution in 2001; 21% patients were infants younger than 6 months, and affected patients aged 10 years or older remained the same at 52%.[6] The age distribution of pertussis cases in 2001 and 2002 is shown in **Figure 2**. In adults, infection is more common among women, particularly those who care for young children. There is general agreement among infectious disease experts that cases of adult pertussis are underreported, making epidemiologic studies in adults more difficult to interpret.

The persistence of this disease is interesting, particularly considering that vaccination coverage with the primary pertussis series of 3 shots has been greater than 94% in the United States since 1995.[7] Some researchers have suggested that a genetic adaptation of *Bordetella pertussis* to the vaccine is responsible for the persistence and reemergence of infection.[8] Others have proposed that as immunity diminishes over time, individuals become more susceptible to infection, thus creating a reservoir in adolescents and adults.[9]

ETIOLOGY

B. pertussis, a strictly human pathogen, is the primary cause of whooping cough. Of the various *Bordetella* species, only *B. pertussis* produces the major virulence protein, pertussis toxin (PT). *B. pertussis* also causes the most severe disease, most likely due to the presence of PT. Other *Bordetella* species are less frequently pathogenic in humans. *B. parapertussis* usually causes infection in animals (eg, kennel cough in dogs) but can cause a milder form of whooping cough in humans. Other species that have been isolated from humans include *B. holmesii* and *B. bronchiseptica,* both of which have been documented causes of infection in immunocompromised patients. *B. holmesii* has also been found in asplenic patients.[10] Various *Bordetella* species are very closely related and are being studied for their role in human infection, including an isolate that has been identified as *B. holmesii,* but unlike other previously described *B. holmesii* infections, this isolate produces the cough characteristic of pertussis.[11]

Bordetella species are fastidious, immotile, aerobic, gram-negative bacteria that colonize and infect the ciliated respiratory epithelium of mammals. They require special media and handling for culture and do not survive

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long in the environment. They produce various biologically active proteins that contribute to the disease process, and these can be grouped based on their actions in the pathogenesis of the disease.

Infection with pertussis occurs in 4 steps: (1) attachment to the ciliated cells, (2) local damage to the epithelium, (3) interference with host defenses, and (4) systemic infection. Filamentous hemagglutinin, fimbriae agglutinin (Fim) types 1 and 2, and the surface antigen pertactin are responsible for attachment. Dermonecrotic factor, tracheal cytotoxin, and adenylate cyclase cause local damage to the ciliated epithelium, allowing better uptake of the other proteins and preventing the normal clearing function of the cilia. PT, produced only by *B. pertussis,* interferes with normal leukocyte function, causing leukocytosis and impaired chemotaxis. In addition, it causes histamine sensitivity and insulin secretion. The result of these processes is local damage and systemic involvement, producing the clinical findings of pertussis infection.

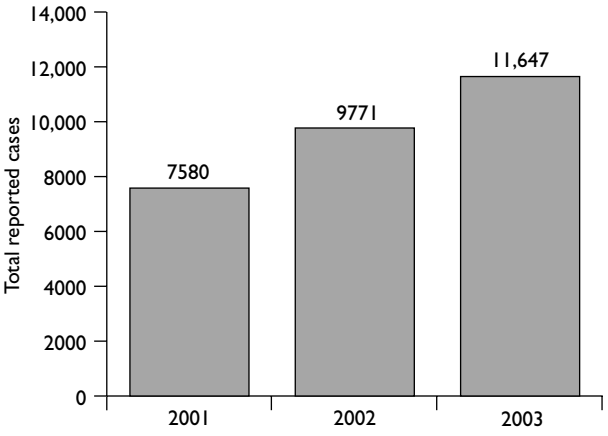

Figure 1. Distribution of pertussis cases by age in 2001 and 2002. (Data from Summaries of notifiable diseases in the United States, 2001. Centers for Disease Control and Prevention [CDC]. MMWR Morb Mortal Wkly Rep 2003;50:1–21; *and* Groseclose SL, Brathwaite WS, Hall PA, et al. Summary of notifiable diseases—United States, 2002. Centers for Disease Control and Prevention [CDC]. MMWR Morb Mortal Wkly Rep 2004; 51:1–84.)

CLINICAL DISEASE

Clinical Course

Bordetella infection is transmitted by respiratory droplets and usually has an incubation period of 7 to 21 days. As the illness progresses, it develops in 3 stages. Initial infection is characterized by a mild illness that appears to be a typical cold with symptoms of low-grade fever, mild cough, and nasal congestion; this is referred to as the *catarrhal stage.* This stage lasts roughly 1 to 2 weeks before progressing to the symptoms of the *paroxysmal stage.*

During the paroxysmal stage, symptoms characteristic of whooping cough develop. Patients experience episodes of abrupt, rapid, severe coughing and are unable to draw a breath between the short coughs; they may even become cyanotic. The cough may be severe enough to cause tongue protrusion, lacrimation, and post-tussive emesis. Although the cough is usually nonproductive, at times plugs of mucus may be expelled. After prolonged coughing without a deep breath, the patient gasps for air, causing a high pitched "whoop" sound against the inflamed trachea. Following the coughing episode, the patient is visibly fatigued. Paroxysmal episodes gradually increase in frequency from just a few to daily averages of 13 or more; after about 2 weeks, the paroxysms begin to decrease in frequency and severity. The paroxysmal stage lasts between 2 and 6 weeks, sometimes longer. The only systemic sign that typically develops during this time is a leukocytosis characterized by a lymphocytosis,[12] which may not occur in milder infections. There is no fever, and between paroxysms, the patient feels well and results of physical examination are usually normal.

As the cough improves, the patient enters the convalescent stage. A gradual resolution of the paroxysms is noted over several weeks, with decreasing frequency and severity of attacks. Occasional paroxysms of cough may continue for months, particularly during subsequent upper respiratory tract infections.

Children and adults who are not immunized have similar symptoms, but the clinical picture is less clear in patients who have been immunized or have had the illness before. These patients will develop a milder infection: shortened duration of symptoms, a milder cough that may or may not produce paroxysms, little or no whooping, and no leukocytosis. In addition, very young infants do not have a typical presentation because they are not yet strong enough to have the full paroxysms and whooping. Atypical infection in either children or adults may also be caused by *B. parapertussis.* In these cases, the illness is less severe and does not produce the lymphocytosis that is seen with *B. pertussis* because *B. parapertussis* does not produce the PT toxin. Although the illness is milder, the cough can be persistent and troublesome.

Complications

Complications associated with pertussis can be loosely classed into 3 groups: cough-related, secondary infections, and neurologic abnormalities. Cough-related

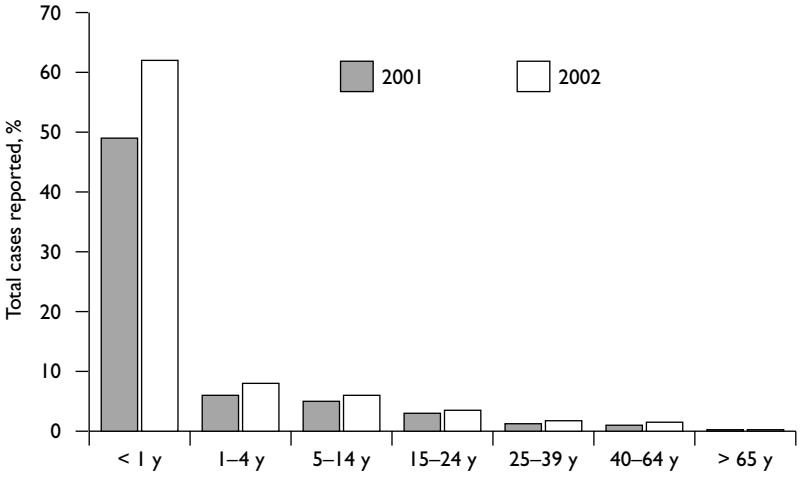

Figure 2. Reported cases of pertussis in the United States from 2001 to 2003. (Data from Summaries of notifiable diseases in the United States, 2001. Centers for Disease Control and Prevention [CDC]. MMWR Morb Mortal Wkly Rep 2003;50:1–21; *and* Groseclose SL, Brathwaite WS, Hall PA, et al. Summary of notifiable diseases—United States, 2002. Centers for Disease Control and Prevention [CDC]. MMWR Morb Mortal Wkly Rep 2004;51:1–84.)

problems are the result of pressure effects from the tremendous force produced. Petechiae on the upper body, post-tussive vomiting, subconjunctival hemorrhages, and epistaxis frequently develop. In severe cases, pneumothorax, subdural hematoma, rib fractures, apnea, hypoxia resulting in neurologic damage, and inguinal hernias can result. Adults may develop urinary incontinence and cases of unusual complications such as unilateral hearing loss,[13] carotid artery dissection,[14] and a herniated disc[15] have been reported.

Secondary infections include pneumonia and otitis media, which are common complications in both children and adults. Pneumonia is the primary complication leading to death in both children and adults and should be suspected in a patient who develops fever and other systemic symptoms, such as tachypnea and tachycardia. Pulmonary hypertension commonly occurs in infants who have developed pneumonia and is, along with a marked leukocytosis, an ominous finding.[16] Adults who are smokers or have asthma are more likely to develop secondary infection and have a prolonged cough.[17]

Seizures, blindness, deafness, mental retardation, behavioral changes, and other permanent neurologic sequelae can result from encephalopathy. Cerebellar ataxia is a rare complication and may be due to a direct effect of pertussis exotoxins.[18]

Most severe complications and death occur in very young infants who have not yet received their full primary immunization series against pertussis. Between 1997 and 2000, 63% of infants in the United States younger than age 6 months infected with pertussis required hospitalization, 12% developed pneumonia, and 1% developed seizures. This age-group also had the greatest mortality, accounting for 90% of the reported 62 deaths during that time.[19] In 2000 alone, there were 17 pertussis-related deaths among infants younger than 4 months.[20] While great progress has been made in protecting children and adults from pertussis infection, the lack of protective immunity in very young infants remains a serious problem.

DIAGNOSIS

Clinical Diagnosis

The Centers for Disease Control and Prevention defines pertussis as an illness with a cough that lasts at least 2 weeks with at least one of the following symptoms that cannot be attributed to another cause: paroxysms of cough, the characteristic "whoop," or post-tussive emesis.[1] A case is "probable" if it is not confirmed by culture or the patient's infection cannot be traced to a culture-proven case. The case is considered "confirmed" if it is confirmed by laboratory testing or the patient was directly exposed to a culture-proven pertussis-infected person.

Even if the characteristic symptoms are not present, pertussis should be considered a possibility in patients who have a severe cough that persists for more than 14 days. Between 10% and 20% of adults with persistent severe cough have been found to have pertussis infection.[21] These results, however, are at odds with the absolute numbers of pertussis cases reported each year, suggesting that pertussis is underdiagnosed, particularly in adults with milder infections.

Laboratory Testing

Pertussis is usually diagnosed clinically, but bacterial culture can help confirm the diagnosis, particularly if the illness is atypical or is suspected in an infant. However, *B. pertussis* is fastidious and difficult to grow in

culture. For this reason, culture is less sensitive than other available testing methods but is very specific and allows detection of any antibiotic resistance. Culture is most likely to be successful if the nasopharyngeal specimen is obtained during the catarrhal stage before any antibiotic therapy is given. The specimen should be obtained from the posterior nasopharynx with a calcium alginate (or Dacron) swab and plated directly onto selective media. Half-strength Regan-Lowe agar can be used for transport to the laboratory.[22]

Because culture is less sensitive for diagnosing pertussis infection, additional laboratory testing should be performed. Polymerase chain reaction (PCR) is both sensitive and specific. PCR provides rapid results but is not widely available and is not standardized. Direct fluorescent antibody testing is not as sensitive as PCR and not as specific as culture[23] but may be useful for screening. Serologic testing for IgG to pertussis is not standardized and is used for clinical studies only. Despite these drawbacks, these additional laboratory tests are helpful in confirming that culture has correctly identified *Bordetella* species as the infectious agent.

TREATMENT

Antibiotic Therapy

Treatment of pertussis can control the spread of the disease as well as reduce the severity and duration of symptoms if treatment is begun early in the course of the illness. The preferred treatment for *Bordetella* species is erythromycin. For children, 40 mg/kg daily in 4 divided doses is given orally for a full 14 days.[24] In adults, the dosing schedule is 500 mg orally in 4 divided doses per day for 14 days. Erythromycin resistance among *B. pertussis* isolates has been reported but occurred in fewer than 1% of patients in one study.[25] Trimethoprim-sulfamethoxazole is an alternative to erythromycin but has variable degrees of activity against *B. pertussis*. Erythromycin or other macrolides may also be preferred because *B. parapertussis* has a poor response to antibiotics other than the macrolides.

Erythromycin remains the drug of choice, but because of its side effects, which include a possible relationship with infantile hypertrophic pyloric stenosis,[26] a shorter 7-day course of treatment with erythromycin[27] and treatment with other macrolides have been studied for efficacy. These appear to be excellent alternatives for treating pertussis infection in adults and children. A 5-day course of azithromycin or treatment with clarithromycin appears to be just as effective as erythromycin and has fewer side effects in adults and children.[28] Fluoroquinolones have also been studied for possible use in treatment of adults. As a group, the fluoroquinolones have shown excellent activity against *B. pertussis* and some activity against *B. parapertussis*.[29] They are useful against erythromycin-resistant strains but are not first-line choices for treatment, as they are broad-spectrum drugs.

Household and other close contacts to a person diagnosed with pertussis should be treated prophylactically with antibiotics to prevent the spread of the infection. Erythromycin treatment for a full 14 days appears to offer adequate protection,[20] although Halperin et al[31] found no benefit. Additionally, appropriate respiratory isolation (in the hospital for inpatients or at home for outpatients) until the sixth day of therapy is ideal. Any household members who have not had a full series of immunizations should resume the series or receive a booster.

Supportive Therapy

Very young infants often require hospitalization to manage severe symptoms such as apnea and to monitor for pneumonia and dehydration from post-tussive vomiting. Older children can usually be managed as outpatients but should be watched closely for development of complications.

Symptomatic treatment for the cough is difficult and of unproven efficacy. Treatments such as immunoglobulin to pertussis, dexamethasone, diphenhydramine, and salbutamol have been tried with minimal success.[32]

VACCINATION

Vaccine Formulations

Dramatic reductions in the incidence of *B. pertussis* infection and, subsequently, pertussis-related morbidity and mortality in the United States would not have occurred without immunization of virtually all children. Vaccination produces an antibody response, thereby providing immunity; however, there is also evidence that cell-mediated immunity is induced by vaccine as well.[33]

Two pertussis vaccine formulations are used worldwide: the original whole-cell vaccine and the acellular vaccine; both are effective in reducing the frequency and severity of pertussis infection. The original whole-cell vaccine is prepared as a suspension of inactivated *B. pertussis* cells that is adsorbed to aluminum salts and combined with the vaccines for diphtheria and tetanus (DTP). The DTP vaccine is up to 95% effective in preventing or reducing the severity of infection.[34] Although DTP is still used in many parts of the world, it is no longer licensed for use in the United States because whole-cell pertussis vaccine is more likely than acellular

Table 1. Contents of Licensed Pertussis Vaccine Formulations

Vaccine	Immunogenic Components	Adjuvant	Preservatives
Certiva DtaP[38]*	PT	Aluminum	Thimerosal†
Daptacel DtaP[39]	PT, FHA, Pn, Fim2, Fim3	Aluminum	2-Phenoxyethanol
Infanrix DtaP[40]	PT, FHA, Pn	Aluminum	2-Phenoxyethanol
Pediarix DtaP, HepB, IPVC[41]	PT, FHA, Pn	Aluminum	2-Phenoxyethanol
Tripedia DtaP[42]	PT, FHA	Aluminum	Thimerosal

DtaP = diphtheria, tetanus, acellular pertussis; FHA = filamentous hemagglutinin; Fim2/Fim3 = fimbriae agglutinin type 1 and 2; HepB = hepatitis B; IPVC = inactivated poliovirus vaccine combined; Pn = pertactin; PT = pertussis toxin.

*This product is no longer manufactured but is currently licensed.

†Thimerosal is a mercury compound used as a preservative. It is present in trace amounts in vaccines produced since 2001 and is not considered a risk.[43]

vaccine to cause fever and injection-site reactions after immunization. In addition, there is a possible but unproven increase in the risk for encephalopathy following vaccination with the whole-cell vaccine.[35]

The acellular pertussis vaccines, which became available in the mid-1990s, are at least as immunogenic as the whole-cell vaccine but with fewer side effects.[36,37] These vaccine formulations contain bacterial component(s) rather than the deactivated cells (**Table 1**). All acellular vaccines contain deactivated PT; some may also contain other components, such as filamentous hemagglutinin, pertactin, Fim2, and Fim3. Numerous studies have been performed in an effort to determine the best combination of components to ensure the greatest efficacy and the fewest side effects. To date, it appears that a single-component vaccine is adequate, but this efficacy improves as more components are added.[44] Some studies have found that only formulations with PT and pertactin offer significant protection.[45,46] The acellular vaccine may provide immunity to *B. parapertussis* as well.[47]

Newer vaccine combinations with hepatitis B and *Haemophilus influenzae* type B vaccines appear to be safe and well tolerated.[48,49] The availability of combined vaccines reduces the total number of injections an infant has to receive at one time.

Side Effects of Vaccination

Side effects are less frequent and less severe with the acellular vaccine than with DTP. The most common side effects with the acellular vaccine are local redness, swelling, and pain at the site of the injection. Significant limb swelling may also occur. Local reactions are more likely to occur after the fifth dose.[50,51] Other side effects, such as fever, nausea, vomiting, prolonged crying, and malaise, may occur but are less common.

There has been considerable interest in long-term outcomes following pertussis vaccination, but many concerns that were initially voiced have proven unfounded. Some researchers have speculated on a relationship between type 1 diabetes and vaccination, but studies have not supported this speculation.[52,53] There is also no apparent relationship between asthma and atopy or childhood vaccination with pertussis.[54]

Severe (but very rare) adverse effects include seizures, encephalopathy, neuropathies, and hypotonic-hyporesponsive episodes. These rare side effects are thought to occur more often in patients already predisposed to them by another medical condition, and most studies found that the events were so rare that it was difficult to determine whether they were statistically significant.[35,55] Other studies suggest that the more severe reactions were more common with the original whole-cell vaccine.[56,57] Overall, the acellular vaccine is safe, and the benefits clearly outweigh the risks.

Contraindications to Vaccination

There are few contraindications to pertussis vaccination. A relative contraindication for vaccine administration indicates that the vaccine recipient may be at increased risk for a serious adverse reaction. Family history of seizures or reaction to pertussis vaccine has been cited in the past as a relative contraindication, but the Advisory Committee on Immunization Practices does not recommend withholding vaccine unless the patient himself had a reaction.[43] There is an increased risk of febrile seizures on the day of vaccination, but this does not appear to cause any long-term problems.[58] Relative contraindications also include the following reactions within 48 hours of a dose: a fever greater than 105°F, inconsolable crying for 3 or more hours, collapse

or a shock-like reaction, or a seizure up to 3 days after a prior dose. In patients with relative contraindications, pertussis vaccine generally should not be given in these cases unless the risk of not receiving the vaccine is greater than the risk of withholding it (eg, during a large local epidemic of pertussis); this decision is left to the discretion of the medical provider.

The absolute contraindications to vaccination are a history of a severe prior allergic reaction to the vaccine or its components and an encephalopathy that cannot be attributed to other causes within 7 days of a prior dose of vaccine.[43] Many also consider an unstable or undiagnosed neurologic condition as a contraindication. In those patients, once the neurologic problem is diagnosed and considered stable, immunization should resume.

Special Considerations

Children who are at high risk for complications from pertussis infection can be started early on immunizations. Preterm infants appear to have less IgG response to PT with immunization, but there is no apparent benefit in waiting to begin the vaccination series.[59] The recommendation is to continue with vaccination based on chronologic age, regardless of degree of prematurity or weight (**Table 2**).

If vaccine status is not recorded, such as with adopted children with an unknown immunization status, revaccination is acceptable. The only concern is that there is some risk for increased local reactions after the fourth and fifth vaccine doses. Because there is no readily available serologic test for immunity to pertussis, serologic testing for response to other vaccines that are usually given concurrently, such as diphtheria, may be a useful way to estimate immunity, particularly if there is a strong injection-site response to vaccine and there is concern about continuing the series.[43]

Immunocompromised patients may not develop a good immune response to the vaccine, but because the vaccine does not contain live bacteria, it can be given safely. Patients who should be considered immunocompromised include those with HIV infection and AIDS, hematopoietic stem cell transplantation, solid organ transplants, cancer, congenital immunodeficiency, leukemia, and lymphoma or those being treated with large doses of corticosteroids.[60]

Patients who have bleeding disorders are at increased risk for hematoma after vaccination, but using a small-gauge needle and applying pressure for a couple minutes after the injection avoids this problem. In addition, if these patients receive therapy, such as fresh frozen plasma for hemophilia, the injection can be postponed until just after treatment.

Table 2. Vaccination Intervals Recommended by the Advisory Committee on Immunization Practices

Dose	Recommended Age	Minimum Age	Interval to Next Dose	Minimum Interval
DtaP1	2 mo	6 wk	2 mo	4 wk
DtaP2	4 mo	10 wk	2 mo	4 wk
DtaP3	6 mo	14 wk	6–12 mo	6 mo
DtaP4	15–18 mo	12 mo	3 y	6 mo
DtaP5	4–6 y	4 y	n/a	n/a

Data from Atkinson WL, Pickering LK, Schwartz B, et al. General recommendations on immunization. Recommendations of the Advisory Committee on Immunization Practices (ACIP) and the American Academy of Family Physicians (AAFP). Centers for Disease Control and Prevention. MMWR Recomm Rep 2002:51:1–35.

DtaP = diphtheria, tetanus, acellular pertussis.

Vaccination should not be withheld due to mild upper respiratory infection, treatment for otitis media, mild gastroenteritis, or other mild illnesses. If the patient has a severe infection, vaccination should be resumed as soon as he or she is well.

Booster Vaccination

Much discussion continues about the potential benefits and risks of giving booster doses to adults and adolescents. Immunity wanes over time after either vaccination or illness. Infected adults and adolescents, in turn, serve as a reservoir for infecting others. Booster vaccination provides a good serologic response, revitalizing the immunity to pertussis,[61] and by giving booster vaccinations to adolescents and adults, it may be possible to decrease the number of people affected by infection.

Booster vaccination after the childhood series is completed appears to be safe and well tolerated. Adults have not had significant morbidity with booster doses of acellular vaccine.[62,63] Purdy et al[63] suggest that it is safe and cost-effective to offer a booster to adolescents between ages 10 and 19 years, thereby preventing pertussis in that age-group.

Initial studies of the use of acellular pertussis vaccine indicate that it is safe and efficacious in adolescents and adults. Because of the encouraging results of these early studies, the US Food and Drug Administration has approved the use of booster doses of acellular pertussis vaccine in adolescents as the next step in the ongoing

effort to minimize pertussis infections in all age-groups in the United States.[63]

CONCLUSION

Pertussis is a common illness that affects both children and adults. Despite often being a mild illness, the symptoms can be severe. Safe, effective vaccines are available to help prevent infection. In the future, booster vaccinations may be given to adolescents and adults in hopes of controlling the increase in incidence of pertussis that has been observed. Currently, vaccination of infants and effective treatment and isolation of infected individuals are our best tools to control the spread of pertussis. **HP**

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