Pertussis: Is Eradication Achievable?

Russell W. Steele, MD

The World Health Organization has identified a number of infectious diseases for global eradication. Surprisingly, pertussis, or whooping cough, is not one of them, even though it fulfills the usual criteria for potential elimination: availability of an effective vaccine, identification of practical control measures, and no animal reservoir.1

A major shortcoming of preventive strategies previously was the reactogenicity of whole-cell pertussis (DTP) vaccine (Table 1, see page 526),2 which contains the entire bacterium, a great concern of parents and a primary reason for noncompliance in children receiving the vaccine. Another drawback of the current preventive program resides in the nature of the vaccine schedules for all pertussis vaccines. Immunization requires a three-dose primary series and two additional boosters during childhood for continued protection. Another booster dose is currently being considered for older children and adults. Any multidose immunization program is impractical in developing countries and difficult to achieve even where public health clinics are readily available and services are free of charge.

The Vaccines for Children program in the United States, federally mandated and implemented nationally in October 1994, was a major attempt to resolve missed opportunities for vaccine administration by creating approaches that are individualized for each region. Unfortunately, Congress has periodically con-
sidered eliminating this vital program and substituting block grants to individual states. This would place responsibility at the local level for determining methods of preventive intervention.

Eradication efforts are also limited by the efficacy of the vaccine. At 80%, this is well below that achieved by vaccines for polio, tetanus, diphtheria, and measles, as well as many other current immunizations. Development of a more effective pertussis vaccine has been hampered by the inability to identify with certainty major immunogenic components of the organism. With 80% protection representing the maximum threshold for a fully immunized population, the disease is likely to continue. However, epidemiologic data are encouraging because an immunization rate of only 40% has been shown to prevent major outbreaks.1

It is now apparent that adults, usually parents or other household members but also hospital personnel, are the contact sources for most pediatric cases. Illness in adults is often undetected because it is so mild, yet may result in severe disease among young infant contacts. The recently reported increase in deaths among neonates and young infants emphasizes this epidemiologic circumstance.4

Although active whooping cough during childhood usually confers immunity for 15 years, protection from vaccine wanes by age 11 to 15; the last booster dose is given just before age 6.5,6 To control pertussis more effectively, a safe and effective booster vaccine for adolescents and adults is needed. Recent studies have indicated that the current acellular products using extractions of specific proteins from bacteria may fulfill these requirements, and no anaphylactic reactions have been observed with any diphtheria, tetanus, and acellular pertussis (DtaP) combined vaccine products.

The primary concern is, of course, reactogenicity to the vaccine in older recipients. Additional safety data are being generated and appear promising. If the vaccine is approved for adults, health-care workers most likely will be the first group targeted for immunization, but booster doses given to parents of young children also would significantly reduce transmission, an approach referred to as the "cocoon strategy." Researchers are therefore in a position to take a major step toward controlling pertussis, if not eradicating it completely.

**HISTORICAL ASPECTS**

Whooping cough was first described as an epidemic of pediatric respiratory disease in 1578 that began in Paris, France, and subsequently spread throughout Europe.8 It is unclear whether this represented an emerging infectious disease at that point, or whether the author of the report, Guillaume de Baillou,8 simply had an interest in this disease, which resulted in a careful recording of clinical observations for the first time.

Subsequently, outbreaks of pertussis were observed throughout the world, and this disease was recognized as the leading cause of death in children from communicable diseases in the United States at the beginning of the 20th century. The continued morbidity and mortality associated with disease in young children eventually led to the development of DTP vaccines in the 1940s.

During the 30 years following introduction of vaccine in the United States, a 220-fold reduction in the incidence of pertussis was evident, with rates dropping from 110 per 100,000 children to 0.5 per 100,000 per year.9 Currently, fewer than 10 reported deaths are reported in the United States each year.9

Despite the potential availability of vaccines, they are not adequately used in many developing countries. The disease therefore continues, with approximately 50 million cases of pertussis occurring annually throughout the world, associated with 300,000 deaths. Pertussis is the fifth leading cause of vaccine-preventable deaths, following hepatitis B, measles, tetanus, and *Haemophilus influenzae* type B.

**MICROBIOLOGY**

The genus *Bordetella* currently contains six species: *B. pertussis*, *B. parapertussis*, *B. hinzii*, *B. holmesii*, *B. bronchiseptica*, and *B. avium*. The first four have host species specificity for humans, but *B. bronchiseptica* can infect dogs, causing severe respiratory disease, occasionally associated with a high mortality in these animals. *B. avium* can cause respiratory illness in turkeys and other birds. The live *B. bronchiseptica* vaccine used to immunize dogs has been shown to cause severe illness in young children exposed to recently vaccinated dogs and milder symptoms in adults exposed directly to the aerosolized vaccine.10
Epidemiology

*B. pertussis* is one of the most contagious of all bacterial infections, with an incidence of secondary cases as high as 80% in nonimmune household contacts. Rapid preventive interventions are necessary once a primary case is identified. The disease is seen worldwide, with a significantly higher incidence observed in those countries where a vaccine is not routinely given. Significant increases in disease have also been seen in countries following changes in immunization policies, often a result of concern about adverse events related to the previously used DTP vaccine. Such epidemics have been documented in the United Kingdom, Sweden, and Japan.11

Humans, the only reservoir of *B. pertussis*, transmit disease by aerosolization of respiratory secretions. This is much more likely to occur in infants and toddlers who put things in their mouths and subsequently expose their playmates to contaminated objects. Close face-to-face contact for young children in daycare centers is also a common circumstance leading to outbreaks of pertussis.

Whooping cough follows a consistent epidemiologic pattern, with increased outbreaks every 3 to 5 years related to the cycling of susceptible people in a population. This periodicity does offer an opportunity to introduce immunization programs at times predicted to have the greatest effects on disease incidence.

It is now apparent that young adults and children older than 10 represent index cases in households and the source of infection for most susceptible infants and young children. Because older people are likely to have mild symptoms, their illnesses often go undiagnosed. For those reasons, a booster dose of vaccine is now being considered for older children, adolescents, and adults in the United States.
Transmission of pertussis is much more likely during the catarrhal stage (discussed later in this article) and during the first 1 or 2 weeks of paroxysmal cough, when 85% of infected children are culture or fluorescent stain positive. Later in the paroxysmal stage, fewer than 20% have pertussis bacteria in the posterior nasopharynx. Immunized individuals who later acquire disease are contagious for a shorter period of time.

Erythromycin therapy is highly effective in eradicating organisms and renders patients noninfectious within 4 days of onset of treatment.12 At diagnosis of an index case, it is recommended that all household members, immunized or unimmunized, receive 14 days of prophylactic erythromycin therapy. The vaccine is not effective in preventing disease in exposed contacts but should be given to unimmunized children to prevent disease in the future.

**Clinical Manifestations**

Pertussis is a chronic disease, referred to in China as “the cough lasting 100 days,” which can result in malnutrition and failure to thrive in infants secondary to reduced oral intake during the prolonged disease process. Illness is classically divided into three stages: catarrhal, lasting approximately 2 weeks; paroxysmal, lasting 4 to 6 weeks; and convalescent, which can continue for as long as 2 months. Duration of each stage is somewhat dependent on the patient’s age; young infants have a briefer catarrhal stage with a longer convalescence, while partially or fully immunized older children and adults may exhibit only paroxysmal coughing for a few weeks.

This infection is unique in that patients are generally afebrile and do not show an elevation in the erythrocyte sedimentation rate or increases in other classic acute phase reactants. Most characteristic is a marked lymphocytosis of both T and B cells. Pertussis is one of the more common causes of a leukemoid reaction, with leukocyte counts often exceeding 50,000 cells/mm³. The classic chest radiographic finding is a “shaggy heart” produced by bilateral perihilar infiltrates, interstitial edema, and atelectasis. The presence of fever, neutrophilia, or consolidated pneumonia should suggest a secondary bacterial infection in the lungs, and antibiotics should be selected to cover pneumococcus and *Staphylococcus aureus* empirically.

**Diagnosis**

Cultures for *B. pertussis* or fluorescent stain of posterior nasopharyngeal secretions are equally sensitive for confirmation of diagnosis. The culture requires special media, such as Regan-Lowe or Bordet-Gengou. Fluorescent stains are preferred because cultures may require incubation for as long as 2 weeks.
**TABLE 5.**

<table>
<thead>
<tr>
<th></th>
<th>DTaP</th>
<th>Not Available in US Tdap</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Product Name</strong></td>
<td>Tripedia</td>
<td>Boostrix Tdap</td>
</tr>
<tr>
<td><strong>Manufacturer</strong></td>
<td>Aventis</td>
<td>Adacel</td>
</tr>
<tr>
<td><strong>Indicated Age</strong></td>
<td>Infants</td>
<td>GlaxoSmithKline</td>
</tr>
<tr>
<td><strong>Group</strong></td>
<td>Children**</td>
<td>Aventis</td>
</tr>
<tr>
<td><strong>Antigenic Components</strong></td>
<td></td>
<td>Adults</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adolescents**</td>
</tr>
<tr>
<td>PT</td>
<td>23.4 μg</td>
<td>8 μg</td>
</tr>
<tr>
<td></td>
<td>25 μg</td>
<td>2.5 μg</td>
</tr>
<tr>
<td>FHA</td>
<td>23.4 μg</td>
<td>8 μg</td>
</tr>
<tr>
<td></td>
<td>5 μg</td>
<td>5 μg</td>
</tr>
<tr>
<td>PRN</td>
<td>8 μg</td>
<td>2.5 μg</td>
</tr>
<tr>
<td></td>
<td>3 μg</td>
<td>3 μg</td>
</tr>
<tr>
<td>Fim 2+3</td>
<td>8 μg</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>5 μg</td>
<td>5 μg</td>
</tr>
<tr>
<td>D</td>
<td>6.7 Lf</td>
<td>2.5 Lf</td>
</tr>
<tr>
<td></td>
<td>15 Lf</td>
<td>2 Lf</td>
</tr>
<tr>
<td>T</td>
<td>5 Lf</td>
<td>5 Lf</td>
</tr>
</tbody>
</table>

* Pedialrix also contains these DTaP components.
** Ages 6 weeks to 7 years.
*** Boostrix is indicated for ages 10 years or older in Australia, Adacel is indicated for ages 12 to 54 in Canada.

PT = pertussis toxin, FHA = filamentous hemagglutinin, PRN = pertucin, FIM 2+3 = fimbrial agglutinogen 2 and 3, D = diphtheria toxoid, T = tetanus toxoid

Unfortunately, the direct immunofluorescent assay has relative low specificity, thereby yielding a high percent of false-positive results. Many experts, therefore, recommend culture when accurate epidemiologic information is being sought. Future immunization is contraindicated in children who have laboratory-confirmed disease only because a few case reports suggested higher reactogenicity to DTP vaccine in these children. This association has not been observed with acellular vaccine products.

Serologic tests, which rely on measurement of immunoglobulin antibody to pertussis toxin, are available commercially. However, these have highly variable sensitivity and specificity. Most cases of pertussis are, therefore, diagnosed clinically in afebrile infants with a prolonged cough, the characteristic respiratory whoop, posttussive vomiting, or cyanosis along with lymphocytosis. Apnea in young infants occurring in a household where older individuals have had a chronic cough is also strongly suggestive of this diagnosis. For cases diagnosed only on clinical grounds, subsequent administration of acellular pertussis vaccine is not contraindicated.

**DIFFERENTIAL DIAGNOSIS**

Other organisms that produce chronic cough without fever include respiratory adenoviruses, Mycoplasma pneumoniae, Chlamydia pneumoniae, Chlamydia trachomatis, B. bronchiseptica, and B. parapertussis. Because adenoviruses tend to circulate at the same time cases of pertussis are seen (ie, September and October), combined infection is relatively common. Obviously, illness with any of these pathogens makes it difficult to accurately determine clinical effectiveness in any vaccine trial.

**TREATMENT**

Infants younger than 6 months with pertussis generally require hospitalization to manage potential apneic episodes and to provide nutritional support. Once the paroxysms of cough occur less frequently than every 6 hours, discharge may be considered. During the time in the hospital, young infants should undergo minimal stimulation (ie, infrequent examinations and bathing) to reduce the likelihood of prolonged coughing episodes.

Erythromycin is highly effective in eliminating B. pertussis but has no effect on the duration or severity of the clinical course. This drug should be given at a dosage of 40 to 50 mg/kg per day in four divided doses for 14 days. Equally effective is azithromycin given at a daily dose of 10 to 12 mg/kg per day for 5 days and clarithromycin at 15 to 20 mg/kg per day in two divided doses for 7 days. Treatment does not differ for previously immunized children or adults.

Neonates younger than 13 days should not receive erythromycin because of its association with hypertrophic pyloric stenosis, a result of increased gastric motility produced by erythromycin. Azithromycin and clarithromycin do not produce this physiologic change in the gastrointestinal tract. Although treatment and preventive studies are not available in this young age
group, it would be prudent to substitute a newer macrolide for erythromycin.

PROGNOSIS

Most mortality from pertussis occurs in neonates and infants younger than 3 months. In the United States, case fatality rates are 0.8% in infants younger than 60 days, but less than half of this in infants ages 2 months to 1 year. Therefore, many of these deaths occur before adequate immunization is normally completed. Apneic episodes are also seen in these young children and can be fatal if unattended. Pertussis is a well-described cause of sudden infant death syndrome, found in 16% to 25% of published cases where postmortem cultures or identification of pertussis in tissue was undertaken.

Progression of respiratory infection or secondary pneumonia with other bacterial pathogens accounts for 90% of all deaths from pertussis, and central nervous system complications produce the remainder. Pertussis may also cause encephalopathy with retardation or seizures. In infants younger than 1 year, pneumonia has been reported in 22%, seizures in 2%, and encephalopathy in 0.1% to 0.5%.

PREVENTION

DTaP vaccines have totally replaced DTP products in the United States, and are, therefore, the only vaccines discussed in detail in this article. It should be remembered, however, that the older DTP vaccines had a major effect on disease and were not discarded primarily because DTaP vaccines are more effective. Rather, the major issue was adverse events related to the DTP products (Table 1, see page 526).

There are at least eight major antigenic and biologically active components of B. pertussis, each of which exhibits virulence capability but also represents a potential target for protective antibodies (Table 2, see page 527). Up to five antigens are contained in available vaccine products: pertussis toxin (PT), filamentous hemagglutinin (FHA), pertactin (PRN), and the fimbrial subunit genes Fim2 and Fim3. A major challenge in developing improved vaccines centers around determining the relative importance for each of these various components and its role in stimulating protective immunity. Currently, most vaccine clinical studies have used antibodies to PT, FHA, and PRN as surrogate markers of protective efficacy.

Acellular pertussis vaccines vary by total number of antigen components, component mixture, and amount of each antigen. A trend suggests vaccines with more components confer higher protection, and many experts recommend their preferred selection. Clinical trials have suggested greater protection from mild disease by the five-component vaccine, but this conclusion remains debatable. The 2003 Red Book states, “although licensed vaccines differ in their formulation of pertussis antigens, their efficacy seems similar.”

IN VITRO STUDIES

Pertussis Toxin (Lymphocytosis-Promoting Factor)

The biological effects of PT, summarized in Table 2 (see page 527), are numerous. In fact, PT was thought to be the single component responsible for clinical disease at one time. However, the important virulence activities of other B. pertussis antigens, along with the observation that B. parapertussis does not produce PT but can cause similar illness, largely have discredited this hypothesis.

Perhaps the best in vitro evidence of anti-PT antibody as an important protective factor is its ability to inhibit the adhesion of B. pertussis to Vero cells, a marker for attachment of this pathogen to respiratory epithelial cells early in the infectious process. A recent study determined that anti-PT antibodies did not promote phagocytosis and subsequent killing of microorganisms, so control of disease does not appear to be enhanced by immunization with PT antigen.

Filamentous Hemagglutinin

FHA is considered the major factor for adhesion of B. pertussis, promoting attachment of organisms to the upper respiratory tract and trachea but not the lungs. Anti-FHA antibodies almost completely inhibit adhesion of organisms to Vero cells. Interestingly, preincubation of Vero cells with purified FHA antigen causes an enhanced adherence of virulent strains but has no effect on related nonviral bacteria.

Pertactin

Many studies have suggested antibodies to PRN best correlate with protective efficacy. The mechanism by which anti-PRN humoral immunity provides protection appears to be through enhanced opsonophagocytosis because killing of organisms in vitro is seen to a much lower extent with anti-PT, anti-FHA and anti-fimbriae (Fim) antibodies.
Lipooligosaccharide exhibits properties characteristic of other endotoxins produced by Gram-negative bacteria. Local inflammation produced by lipooligosaccharide likely contributes to clinical illness and was a major contributor to DTP adverse events.

Fimbriae

The two fimbril filaments, Fim 2 and Fim 3, can independently induce protection against respiratory infection with *B. pertussis*. Similar to other Gram-negative bacteria, these Fim were assumed to promote adhesion to mammalian cells. Studies, however, have indicated that FHA is the major adhesion of *B. pertussis* and that Fim do not mediate adhesion to Vero cells. In fact, Fim may reduce the adhesion effects of FHA. However, antibodies to Fim do inhibit the adhesion of pathogenic organisms to Vero cells. This correlates with the ability of anti-Fim to protect mice against lower respiratory infection with *B. pertussis*, perhaps by preventing attachment to beating cilia and mucus-producing cells. Agglutination of pathogenic organisms by anti-Fim antibody is another likely mechanism of protection.

Adenylate cyclase Toxin

The extracytoplasmic enzyme adenylate cyclase toxin (AC) disrupts host cyclic 3',5'-adenosine monophosphate metabolism and exhibits direct toxic effects on respiratory epithelial cells causing tissue damage with resulting inflammation and transudation of edema fluid. These events are postulated to contribute significantly to clinical symptoms. In addition, AC inhibits opsonophagocytosis of neutrophils, monocytes, and killing mediated by natural killer cells, thereby impairing host efforts to eliminate infecting bacteria. *B. pertussis* strains that do not contain AC do not produce clinical disease in laboratory animals.

Heat-labile Toxin (Dermonecrotic Toxin)

The first virulence factor identified, heat-labile toxin (HLT), was purified by Bordet and Gengou and observed to produce skin necrosis in animal models. Later studies identified similar damage to respiratory epithelial cells.

Lipooligosaccharide

Lipooligosaccharide exhibits properties characteristic of other endotoxins produced by Gram-negative bacteria. Local inflammation produced by lipooligosaccharide likely contributes to clinical illness and was a major contributor to DTP adverse events. Similar to fimbriae, lipooligosaccharide can agglutinate human cells; it also appears to enhance colonization of bacteria in the lower respiratory tract of animals following aerosol challenge.

Tracheal Cytotoxin

Similar to AC, tracheal cytotoxin exhibits the dual properties of direct tissue destruction along with inhibition of neutrophil function. Damage to respiratory epithelial cells accounts for the prolonged cough and interference with the host’s efforts to eliminate the bacterial pathogen, prolonging the illness.

IN-VIVO ANIMAL STUDIES

Although *B. pertussis* produces natural clinical disease only in humans, animals can be infected with wild strains of organisms, resulting in inflammatory changes of the respiratory tract. Obviously, results from such studies may not be fully applicable to human disease.

A mouse aerosol-challenge model has been used to evaluate the protective effects of various purified immunization materials. Animals are first immunized with specific antigens by intraperitoneal injection at least 3 weeks before infection. For these studies, strains of *B. pertussis* are grown on charcoal agar plates and suspended in liquid media at a concentration of $1 \times 10^7$ to $2 \times 10^7$ organisms per milliliter; $10^6$ organisms have usually been used in the challenge of young mice age 5 to 7 weeks.

Animals are anesthetized and bacterial suspension placed on the tips of their noses where material is inhaled into the lungs. In some studies, bacterial suspensions have been injected directly into the
trachea. Following this aerosol challenge, animals are sacrificed and the respiratory tract examined for evidence of bacterial colonization and damage.

With this model, immunization with three B. pertussis antigens — FHA, PRN, and Fim — has been shown to protect against histologically confirmed infections, and lipooligosaccharide was shown to reduce bacterial colonization in the lungs and trachea. This aerosol challenge was also used to show that mutant strains of B. pertussis without AC do not produce infection, indirect evidence that this enzyme is essential for clinical disease. Additional studies have shown PT produces an increase in histamine release, peripheral blood lymphocytosis, increased insulin secretion, and augmentation of lymphocyte responses to mitogens.

**DTaP Vaccines**

The relatively common and sometimes serious adverse events associated with DTP vaccines led to the development of DTaP vaccines for children, which contain substantially less endotoxin than DTP vaccines. Such products were first used in Japan in 1981 for primary immunization of 2-year-old children. Two DTaP vaccines, Acet-Imune and Tripedia, were licensed in the United States 10 years later but only approved for the fourth and fifth doses in children ages 15 months to 6 years who had previously received three or more doses of DTP vaccine.

By 1991, a number of studies had shown immunization of infants at ages 2, 4, and 6 months with DTaP was effective in preventing pertussis and associated with significantly fewer local and serious systemic reactions. This led to approval by the Food and Drug Administration of these two vaccines to be given as the initial four doses and Acet-Imune to be given for all five doses. In 2002, Tripedia was approved for the fifth dose, and a third vaccine, Infanrix, was licensed in January 1997 for the initial four doses and was approved in 2003 for the fifth dose.

Unfortunately, production of Acet-Imune was discontinued in June 2000 because of manufacturing difficulties, leaving only two vaccines for immunization of young children. Subsequently, a five-component DTaP vaccine, Daptacel, was approved for routine use in primary immunization in 2003. Daptacel is a combination vaccine containing DTaP (Infanrix), hepatitis B, and inactivated polio vaccines.

**Vaccine Efficacy**

From 1991-2004, seven studies (Table 5, see page 529) evaluated the clinical efficacy of eight different DTaP vaccines in infants. These vaccines contained a varying number and quantity of antigens and were produced by different manufacturers. Some studies looked at a primary series of four doses and others used three doses. Some studies were randomized placebo-controlled clinical trials but others compared various vaccine products. Case definitions also differed in these trials particularly pertaining to the inclusion of mild clinical disease with a lower probability of these truly being caused by B. pertussis. Because of significant differences in the design of these clinical trials and a dramatic range in efficacy results (59% to 89%), it is difficult to draw clear conclusions as to the comparative efficacy of the various products.

Two controlled clinical trials studied Infanrix and Daptacel individually in 1996, with one trial conducted in Italy and the other in Sweden. The Italian study examined two DTaP vaccines, including Infanrix, and compared these with DTP vaccine. The efficacy of each vaccine given in three doses was determined for 14,751 children during an average of 17 months, with cases defined as an illness with 21 days or more of paroxysmal cough and evidence of B. pertussis infection on culture or diagnostic serologic testing. The efficacy of Infanrix was 76% to 89%, whereas the efficacy for DTP vaccine was 36%. Efficacy of Infanrix for mild disease, defined as 7 days of cough, was 71%. Antibody responses for the other DTaP studied were also shown to be greater than those with DTP. Local and systemic adverse events were significantly less frequent with Infanrix.

The clinical trial conducted in Sweden compared the five-componentacellular vaccine Daptacel with DTP vaccine and a two-component vaccine that subsequently was never marketed. Case definitions were similar to the Italian study in that a confirmed case included the presence of at least 21 consecutive days of paroxysmal cough plus culture-confirmed B. pertussis, serologic antibody titer rise, or documented contact with an infected household member with culture-confirmed B. pertussis who began to cough within 28 days before or after the onset of the study participant’s cough. There also was a secondary case definition where the diagnosis was established by the presence of laboratory-confirmed pertussis by culture, serologic analysis, or polymerase chain reaction and a cough of shorter duration.

In the study, after three doses, the efficacy of Daptacel was 85.2%, compared with 58.9% for the two-component DTaP and 48.3% for the DTP vaccine. Daptacel also showed protection against mild disease, defined as 1 day of cough, with an efficacy of 78% in short duration. The DTP vaccine was also associated with significantly higher rates of adverse events such as protracted crying, cyanosis, fever, and local reactions. The authors’ conclusion was that Daptacel should be recommended for general use before other products because of its
favorable safety profile and superior protection against pertussis.

The two European studies were similar enough in design to draw some comparisons with the currently available vaccines, which appear equally efficacious, at 84% protection for Infanrix and 85% for Daptace.17,39

ACELULAR PERTUSSIS VACCINES FOR OLDER CHILDREN AND ADULTS

On July 6, 2004 manufacturer GlaxoSmithKline sought Food and Drug Administration (FDA) approval to sell Boostrix, their booster to include tetanus (T), diphtheria (d) and acellular pertussis (aP) for older children and teens (ages 11 to 18) and another manufacturer, Aventis Pasteur, is not far behind. This combination for adults and older children is abbreviated Tdap. Both the American Academy of Pediatrics and Advisory Committee on Immunization Practices are publishing documents supporting routine booster immunization for these age groups.43

Documentation of low reactogenicity accompanied by significant serologic antibody titer rises following Tdap administration has supported approval.44,47 These studies have included vaccines containing one to five components and using concentrations of antigen that were equal to or as low as one-tenth of the combination in pediatric products. Vaccines were well tolerated in all studies, with systemic reactions occurring no more frequently among subjects given the vaccine than among those who received placebo or control vaccines48 (Table 6, see page 530). Minor reactions, such as pain or tenderness at the injection site, were common and similar in frequency for all acellular pertussis vaccines studied. Late-onset injection site reactions also were seen in all groups.46

Responses to pertussis antigens showed significant increases in mean antibody titers in the majority of subjects, including those who received low doses of antigen.49 This included antibody responses to PT, FHA, and PRN antigens. After 1 year, levels of antibody declined by approximately 50% but were still substantially higher than pre-immunization levels. The authors concluded routine re-immunization of adults with Tdap vaccine can substantially enhance pertussis antibody levels without an increase in adverse reactions or diminution in response to the diphtheria and tetanus components. Interestingly, there were also significant antibody responses to antigens not present in these vaccines. This is not a new observation, as similar increases were noted in children receiving booster doses of acellular pertussis vaccine.48

All data support a strategy of booster doses of vaccine as our next step in an effort to reduce the incidence of disease in children. This recommendation has already been implemented in France, Germany, and Canada.49 However, it should be pointed out that clinical efficacy studies of this approach have not been undertaken, nor are there data showing that re-immunization of older people actually reduces the incidence of pertussis in these vaccine recipients.

Another potentially vital benefit to immunizing young adults includes women of childbearing age. Very young infants who have not completed immunization for pertussis are those at highest risk both for acquiring disease following exposure and for the mortality associated with progressive pulmonary infection. Higher serum concentrations of antibody, passively acquired from mothers, are protective. Studies have shown that cord blood anti-pertussis immunoglobulin concentrations are equal to maternal levels.50 Therefore, boosting antibody titers in mothers would assure optimal protection in neonates and young infants until their immunizations can be completed. This appears to be the most prudent approach to minimizing mortality. Additional evidence supporting this approach is that maternal immunization for tetanus and influenza protects neonates and young infants from these diseases.50 In the case of tetanus, immunization offers almost absolute prevention among neonates.50

SUMMARY

We are now on the threshold of a major step in reducing the incidence of pertussis and its associated mortality and morbidity in young children. Assuring that vaccines are received in a timely fashion by all children and correcting the "missed opportunities" for providing this highly effective intervention are most critical. A plan for booster immunizations must be developed for older children and adults to offer further protection of young infants through the cocoon effect that this would create for them.

REFERENCES


