The Present and Future Control of Pertussis

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(See the article by Mertsola et al, on pages 656–662.)

Currently, there are 2 tetanus and reduced antigen content diphtheria and acellular pertussis vaccines (Tdap vaccines; called dTpa in Europe) available for the immunization of older children, adolescents, and adults [1]. These vaccines are Boostrix produced by GlaxoSmithKline Biologicals and Adacel produced by Sanofi Pasteur. These vaccines are approved in the United States for only 1 booster dose in older children, adolescents, and adults (Boostrix for those ages 10–64 years and Adacel for those ages 11–64 years). However, because booster doses of diphtheria and tetanus toxoids are currently recommended for decennial administration, it is assumed by most pertussis vaccine and public health experts that after additional studies Tdap will be approved for routine booster doses at 10-year intervals. In this issue of Clinical Infectious Diseases, Mertsola et al [2] examine the immunogenicity and reactogenicity profile of Tdap after a second decennial dose in young adults.

Their data support the need for a decennial booster dose of diphtheria toxoid, whereas some might interpret their teta-
but there is currently no evidence that this has led to an increase in vaccine failures. The development of polymerase chain reaction and the use of single serum serologic testing has also contributed to the increase in reported pertussis [11, 12].

Waning of vaccine-induced immunity has always occurred, so this should not result in an increase in reported pertussis unless present day vaccines have less potency than the past DTP vaccines. This in fact is the case; in 5 vaccine efficacy trials the efficacy of the DTP vaccines was greater than that of the studied DTaP vaccines [13–17]. This fact might be the explanation of the observed outbreaks of pertussis in middle schools because these children would have received predominantly DTaP vaccines.

Clearly, during the past decade, there has been an increased recognition of pertussis in adults. However, pertussis in adults is not new; it was recognized by pertussis experts in the prevaccine era [18, 19]. Also in 5 of the vaccine efficacy studies performed in Sweden and Germany in the 1990s, adults were often noted to have been the primary cases in families [20]. In both of these countries, pertussis was epidemic; in Sweden, they were not vaccinating at all with DTP, and in Germany vaccine use was minimal. So, in essence, it was like the prevaccine era in the United States.

Taking advantage of the fact that immunoglobulin (Ig) A antibody to pertussis antigens occur after infection but not after primary immunization, our group studied the prevalence of IgA antibody in young German and American adults [21]. If B. pertussis organisms were circulating more widely in Germany where pertussis was epidemic than in the United States where pertussis was not epidemic, you would expect to see higher geometric mean antibody titers to B. pertussis antigens in the serum samples collected in Germany. However, this was not the case; the geometric mean antibody titers to pertussis toxin, filamentous hemagglutinin, pertactin, and fimbriae were similar in the 2 groups of serum samples. This indicates that B. pertussis is circulating in young adults in a similar manner in both countries.

Another myth relating to pertussis is that immunity after pertussis cough illness is lifelong, whereas immunity after immunization is relatively short-lived. This is not so; in fact, IgG serum antibody titers to B. pertussis antigens in adults who were previously vaccinated are higher than in adults who were primed by disease [21, 22].

The epidemiology of B. pertussis infections has been studied in 3 types of study: (1) the study of prolonged cough illnesses in adolescents and adults, (2) the study of banked serum samples from the same individuals to determine significant titer rises to pertussis toxin, and (3) the study of B. pertussis cough illnesses in defined populations. Numerous studies of prolonged cough illnesses have been performed in many countries throughout the world [5, 6]. The results of these studies indicate that 13%–20% of these prolonged cough illnesses are due to B. pertussis infection.

In 5 studies in adolescents and adults using banked serum samples from the same individuals, it was noted that B. pertussis yearly infection rates varied from 1% to 6%. More recently, an elegant study by de Melker et al [23] in the Netherlands noted a yearly infection rate of 6.6% for persons 3–79 years of age [23]. The incidence was highest in those 20–24 years old (10.8%); it decreased to 6.5% in those 25–55 years old and then further decreased to ~4% in those 56–79 years of age.

The banked serum sample studies mentioned herein give evidence regarding population infection rates but not B. pertussis illness rates. Prospective studies of cough illnesses in defined populations were performed to determine illness rates. Two such studies have been performed [24, 25]. In the first study, performed in Minneapolis/St Paul, Minnesota, the rate in adolescents and adults was 500 per 100,000 population (1 million cases a year in the United States) [24]. In the second study, controls in an adolescent and adult vaccine efficacy trial were followed up for ~2.5 years. The rate of illness due to B. pertussis was 370 cases per 100,000 population [25].

Pertussis in adolescents and adults is important for 2 reasons. First, it is frequently not a benign illness in adolescents and adults; second, unrecognized pertussis in adults is the major source of pertussis in young infants where the disease is severe and often fatal [4, 11]. In recent years, several excellent studies have looked for the contact cases of pertussis in infants hospitalized with severe pertussis [26–29]. The most common source is the mother who has a cough illness that has not been recognized by her caregivers as pertussis. Most of the other source patients are other family members (fathers, adolescents, and grandparents) who have cough illnesses that have not been recognized as pertussis.

Pertussis in adults is frequently typical, but in other instances it is often difficult to separate its presentation from that of other respiratory illnesses. In a study in Canada of 664 adolescents and adults who sought care, De Serres et al [30] found that most had typical manifestations of pertussis, which consisted of the following: paroxysms, 99%; posttussive apnea, 87%; posttussive vomiting, 65%; whoop, 69%; and sweating episodes, 32% [30]. The following complications were noted: sinusitis, 13%; otitis media, 4%; urinary incontinence, 4%; pneumonia, 4%; weight loss, 3%; rib fracture, 2%; and fainting, 2%. Despite the fact that the clinical presentation is often typical, those who care for adults rarely get the diagnosis correct [31]. It is likely that B. pertussis infection is also the cause of cerebral vascular accidents in older adults. In an institution for elderly patients in the Netherlands, there were 4 B. pertussis–related deaths (5%) due to intracranial bleeding [32]. Presented in Table 1 are 5 clinical vignettes relating to patients that I have been involved with. In adults the misdiagnosis of pertussis has
Table 1. Five Clinical Vignettes of Adults with Pertussis

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, years</th>
<th>Profession</th>
<th>Clinical course</th>
<th>Reference</th>
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<tbody>
<tr>
<td>1</td>
<td>47</td>
<td>Academic physician</td>
<td>On 3 May 1996, the subject presented with mild upper respiratory tract infection with lacrimation; onset of cough occurred on 27 May 1996; from 28 May to 31 May 1996, the subject went on airline trips and experienced severe paroxysmal cough, which worsened at night, and intercostals pain; on 1 June 1996, the subject was treated with prednisone and antitussives; on 6 June 1996, the subject was treated with ofloxacin, and samples were obtained for pertussis culture; on 11 June 1996, culture results became positive, and the subject was treated with azithromycin. The cough lasted 3 months. Forty-seven people at the hospital received antibiotic prophylaxis. The source was the patient’s 13-year-old daughter.</td>
<td>[30]</td>
</tr>
<tr>
<td>2</td>
<td>43</td>
<td>Pediatric anesthesiologist</td>
<td>In 1994, the patient developed a “cold with nasal congestion, sore throat, and myalgia.” Because of worsening symptoms, he took acetaminophen, dextromethorphan, and phenylephrine (Theraflu; Novartis); acetaminophen, dextromethorphan, and doxylamine succinate (Nyquil; Vicks); and pseudoephedrine (Sudafed; McNeil). One week later severe paroxysmal cough occurred, which was so bad that his children thought he was choking and gave him back blows. He was diagnosed as having asthma. Symptoms persisted. He was treated with erythromycin for “mycoplasma.” Diagnosis was eventually made and confirmed by serologic testing after hallway consultation.</td>
<td>[31]</td>
</tr>
<tr>
<td>3</td>
<td>42</td>
<td>Research microbiologist</td>
<td>The patient developed a mild cough in August 1996. After 2 weeks a colleague suggested she see a physician because the cough was annoying him. This began the first of about half a dozen visits to her physician. Her physician thought it was nothing or asthma, but she was concerned about a tumor. Paroxysms were so bad she slept sitting up and outside. She could not catch her breath and had urinary incontinence with paroxysms. Her chest hurt so bad that she suspected a broken rib. After 6 weeks, her research leader called me and I noted classic cough, which was confirmed by serologic testing. Her illness lasted 3 months.</td>
<td>[31]</td>
</tr>
<tr>
<td>4</td>
<td>56</td>
<td>College professor</td>
<td>The patient became ill with an afebrile illness with severe paroxysmal cough in March 2002. He was seen by an otolaryngologist and an internist at UCLA in April. Chest and sinus x-ray findings were normal. His “choking episodes” were severe. He was treated with steroids, and antihistamine, a tranquilizer, and subsequently amoxicillin. The patient was seen by 3 physicians and the diagnoses were “uniformly vague.” The patient’s wife developed the same illness 2 weeks after its onset in the patient. Their 3 children remained well. At the time of a wellchild visit the UCLA pediatrician diagnosed pertussis in the professor and his wife and this diagnosis was confirmed by serologic testing. The patient’s illness lasted 11 weeks.</td>
<td>…</td>
</tr>
<tr>
<td>5</td>
<td>71</td>
<td>Academic physician</td>
<td>At the age of 5 years, the subject developed pertussis, and his wife had pertussis in the late 1980s. The subject was assumed to have been exposed to <em>Bordetella pertussis</em> on an airplane on 5 July 2009. Onset of cough illness occurred on 15 July, and a sweating episode occurred on 18 July. On 29 July, his first whooping episode occurred, and he was treated with azithromycin. An internist diagnosed “cough variant asthma” on 3 August and decided to rule out insulinoma; the patient was treated with prednisone. On 7 August, an otolaryngologist diagnosed Wegener granulomatosis, and the patient underwent CT of the head and neck. Positive PCR results were obtained on 14 August. From August through October, coughing continued, without improvement. Relapse of cough occurred during a cold in November 2009.</td>
<td>…</td>
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**NOTE.** CT, computed tomography; PCR, polymerase chain reaction.
lead to many unnecessary tests (chest radiography and computed tomography) and excessive treatments (steroids). Sweating episodes can lead to unnecessary diagnostic evaluation, as in patient 5 in Table 1. These episodes usually occur between paroxysms and are usually of short duration but can be prolonged as occurred in patient 5.

In contrast, in studies of prolonged cough illness in adolescents and adults, there is often little difference noted in the clinical manifestations between the 2 groups. In a study by our group, the only difference noted was that a productive cough was more likely in the non--B. pertussis infection cases and the non--B. pertussis cases were more likely to be treated with an antibiotic [10].

B. pertussis infection and illness are unique in many ways [33]. B. pertussis illness is the only major infectious illness that is not associated with fever. It is the only respiratory infectious illness in children that is more common in girls and more often fatal in girls. In adults, between paroxysms of cough there are no abnormal physical findings. Finally, infection and illness occur in persons of all ages and immunity after infection or immunization is relatively short-lived, making the ultimate control of pertussis difficult.

Overall, universal immunization programs in children have been successful but have not affected the circulation of B. pertussis [4, 11]. In the new Tdap vaccination era, B. pertussis morbidity and mortality can be further reduced and perhaps eliminated. Currently, several Tdap strategies are being recommended [1]. These strategies include (1) a routine booster dose for preteenagers and teenagers, (2) a routine booster dose for all adults aged <65 years, (3) the use of DTaP rather than diphtheria and tetanus toxoid for wound management, (4) the immunization of health care workers, and (5) the “cocoon” approach to prevent pertussis in infants too young to be immunized (cocooning is the vaccination of the mother immediately post partum or the mother to be in the second or third trimester and the vaccination of other family members who will have contact with the infant after birth).

Although these various approaches are sound, they, even collectively, will not get the job done. To eliminate pertussis and perhaps the circulation of B. pertussis, we need to continue our universal pediatric immunization program with DTaP and implement a universal decennial Tdap program, which starts in preadolescents and continues throughout adulthood, including persons aged ≥65 years. This is a tall order considering the dismal record relating to adult immunization in the United States and in the other countries throughout the world [34].

The question, which will be raised by skeptics, is if this strategy were somehow possible, will it work? The evidence supporting its possible success relates to the serologic correlates data from 2 pediatric DTaP vaccine trials and the antibody decay patterns after adult immunization [35–37]. Antibody to pertactin and fimbriae, both of which have been shown to correlate with protection, and the decay patterns of both of these 2 antigens are such that a decennial booster should be adequate.

Acknowledgments

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