Epidemiological, Clinical, and Laboratory Aspects of Pertussis in Adults

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In populations without immunization, pertussis is a high-incidence, endemic disease with cyclic epidemic peaks occurring every 2–5 years. The universal use of pertussis vaccines in children results in a marked reduction in incidence, but the frequency of disease cycles does not lengthen. This indicates that the organism (Bordetella pertussis) remains prevalent in the population. Studies of prolonged cough illnesses in adolescents and adults indicate that between 12% and 32% are the result of B. pertussis infection. Serological survey data indicate that all adults have been previously infected, and IgA antibody studies suggest that infections in adults are as frequent in the United States, where pertussis has been controlled, as in Germany, where pertussis has been epidemic. Because of the apparent reservoir of B. pertussis infections in adolescents and adults, I believe that B. pertussis circulation cannot be controlled by our present childhood immunization program.

Acellular pertussis vaccines make adolescent and adult booster immunization programs possible, and these could lead to a decrease in the circulation of the organism.

Two decades ago, pertussis in adults was a recognized curiosity, but data relating to its incidence and importance were lacking [1–6]. About 15 years ago, the purification of specific Bordetella pertussis antigens and the development of the ELISA allowed the serological diagnosis of B. pertussis infections in patients in whom the diagnosis previously would have been missed [7]. During the last decade, a number of studies have indicated that B. pertussis is a common cause of prolonged cough illnesses in adults and have suggested an important role of adults in the epidemiology of pertussis [8–15]. Here I review epidemiological, clinical, and laboratory aspects of adult pertussis in the present era.

Epidemiology of Pertussis

During the first half of this century, in the prevaccine era, pertussis was a high-incidence, endemic disease, with cyclic epidemic peaks occurring every 2–5 years [10, 16–18]. Although the incidence of pertussis was dramatically reduced by the introduction and universal use of pertussis vaccines during the third quarter of the present century, the cyclic pattern of pertussis and the frequency of the cycles did not change. This was a surprising finding considering the other diseases that have been controlled by immunization. For example, when measles was first brought under control in the United States, the interepidemic period of time increased. These observations led to the suggestion by Fine and Clarkson [18] that pertussis immunization controls disease but does not control the circulation of B. pertussis in the population.

Since it has been known for 20 years [2] that adolescents and adults with unrecognized pertussis are often the contact cases for severe diseases in infants, we and others considered the possibility that infections in adults were an important reservoir for the continued circulation of B. pertussis [8–15, 19–22].

Clinical Studies of Cough Illnesses in Adults

During the last decade, there have been seven published studies in which adolescents and adults with prolonged cough illnesses have been investigated for B. pertussis infections [9–15]. Summaries of these studies are presented in table 1.

From September 1986 through February 1989, our group studied 130 UCLA students with cough illnesses of ≥6 days’ duration who sought care at the Student Health Service [10]. Laboratory methods included culture and direct fluorescent antibody assay of nasopharyngeal swab specimens, as well as ELISA and agglutinating antibody studies. IgA and IgG antibodies to pertussis toxin (PT) and filamentous hemagglutinin (FHA) as well as agglutinins were determined on single and paired (acute- and convalescent-phase) sera. If a value for a single serum sample was high in comparison with mean values of sera from 108 well students, that was also considered diagnostic of pertussis.

The serological criteria for a case were as follows: an initial or follow-up agglutinin titer ≥3 SD above the control group’s geometric mean titer; a fourfold or greater difference between the agglutinin titers noted in the initial and follow-up serum samples; or an ELISA value for initial or follow-up serum samples ≥3 SD above the control group’s geometric mean titer of IgA and IgG antibodies to PT and FHA or a fourfold or greater difference between the values for IgA and IgG antibody.
**Table 1.** Contemporary studies of *Bordetella pertussis* infections in adults with persistent cough.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Location</th>
<th>Population</th>
<th>Laboratory methods (diagnostic criteria)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>[10]</td>
<td>Los Angeles</td>
<td>130 UCLA students with cough lasting ≥6 d</td>
<td>Culture, DFA, ELISA for IgG and IgA to PT and FHA, agglutinins (single serum, titer ≥3 SD above mean of controls; fourfold rise in titer)</td>
<td>26% positive (1 by DFA, 33 by serology)</td>
</tr>
<tr>
<td>[9]</td>
<td>Sydney, Australia</td>
<td>218 adults (age 18–81 y) with cough lasting &gt;1 mo</td>
<td>ELISA on single serum; IgA to whole organism (&gt;3 SD above mean of controls)</td>
<td>26% positive; all age groups equally involved</td>
</tr>
<tr>
<td>[14]</td>
<td>Chicago</td>
<td>38 adolescents and adults (age 13–81 y) with cough lasting ≥6 d</td>
<td>Culture or ELISA for IgG and IgA to PT and FHA (twofold rise or high single value)</td>
<td>26% positive (1 by culture)</td>
</tr>
<tr>
<td>[13]</td>
<td>Nashville, Tennessee</td>
<td>75 adults (mean age, 32 ± 10 y); emergency room visit with cough lasting ≥14 d</td>
<td>Culture, ELISA for IgG to PT or FHA (fourfold change or single value ≥2 SD above mean of controls)</td>
<td>21% positive (none by culture)</td>
</tr>
<tr>
<td>[15]</td>
<td>Northern California</td>
<td>153 adults (age 24–78 y) with cough lasting ≥2 w</td>
<td>ELISA on single serum sample determining IgG to PT (&gt;2 SD above mean of controls)</td>
<td>12.4% positive; attack rate, 176/100,000</td>
</tr>
<tr>
<td>[12]</td>
<td>Germany</td>
<td>265 adults with cough lasting ≥21 d in families of children in an efficacy study</td>
<td>Culture or ELISA for IgA and IgG to PT, FHA, or pertactin (≥2-fold rise or IgA value ≥2 SD of mean of controls; responses to FHA without response to PT or pertactin ignored)</td>
<td>31% positive (1 by culture)</td>
</tr>
<tr>
<td>[11]</td>
<td>Germany</td>
<td>203 adults with cough lasting ≥7 d in families of children in an efficacy study</td>
<td>Culture, PCR, ELISA for IgG and IgA to PT, FHA, pertactin, and fimbriae-2, agglutinins (in single serum sample, value ≥99th percentile of controls or a change in ELISA titer 99th percentile fold change limit of the assay or a fourfold rise in agglutinin titer)</td>
<td>64 positive (32%) (5 by culture, 8 by PCR, 59 by serologic studies)</td>
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</table>

**NOTE.** DFA = direct fluorescent antibody assay; FHA = filamentous hemagglutinin; PT = pertussis toxin.

To PT and FHA noted for the initial and convalescent-phase sera. Although a high value for a single serum sample had been used in the past for the diagnosis of pertussis, we were able to demonstrate graphically the utility of this method.

In this study, the median age of the participants was 23 years, and 94% had received pertussis vaccine during early childhood. Thirty-four subjects (26%) had laboratory evidence of *Bordetella* infection: none were positive by culture, one was positive by direct fluorescent antibody assay, and 33 were positive by serological tests. During the 2 and 1/2-year study period, our subject recruitment was uneven, but in every 3-month period in which we saw two or more participants, we identified a case.

As noted in table 1, six other studies examined cough illnesses in adults. These studies used different criteria for duration of cough to qualify for study and, most importantly, different serological criteria for the determination of cases. With the exception of the Australian study [9], the percentage of positivity correlated directly with the number of antigens and antibodies (IgG, IgA) used and whether high single values as well as increases in titer were considered. The lowest percentage of positivity (12.4%) occurred in the Northern California study, in which only high single values of serum IgG antibody to PT were determined [15]. In spite of the low percentage of positivity in this study, the authors estimated an adult incidence of 176 cases/100,000 person-years. In the German study carried out by members of our group, we estimated a minimal adult incidence of 133/100,000 person-years [11].

**Serological Survey Data**

*German and American men.* While working in Germany on a pertussis vaccine efficacy trial [23], we were surprised to see several adults with typical pertussis. The reason for this surprise was that pertussis had been epidemic and endemic during the previous 2 decades; therefore, we wondered how these adults escaped previous infection and were now appearing with what we assumed were primary infections. Our group had the opportunity to perform and compare serological studies (IgG and IgA antibodies determined by ELISA and agglutinating antibody studies) on sera from young Germans meeting their obligatory military requirement and on Creighton University students of identical age [19]. When we compared IgG antibodies, as determined by ELISA, to fimbriae-2, FHA, PT, and pertactin and agglutinins we found that the geometric mean...
antibody values were two- to fourfold higher in the sera from the Americans than in the sera from the Germans. All studied subjects (Germans and Americans) had measurable IgG antibody to one or more of the *B. pertussis* antigens evaluated.

In contrast with the ELISA results for IgG antibody, the geometric mean values and the percentages with measurable IgA antibody to the four antigens were similar in the German and American men. Since serum IgA antibodies are relatively short-lived and result from infection and not vaccination, these findings indicated that *B. pertussis* infection in young adults was similarly common in the United States, where pertussis was controlled, and in Germany, where pertussis was not controlled. Since it is likely that most of the American college students had been vaccinated during childhood and most of the Germans had not been, these data suggested that priming by immunization followed by infection resulted in higher IgG antibody values than does priming by infection followed by repeat infection. Since adult infections were found to be common in German adults [11, 12], our data suggest that immunity following infection is not long-lasting.

**Identification of infection by serological data.** As part of a hospital-based epidemiological study relating to AIDS, we prospectively collected sera from female health care workers from 1984 to 1989 [20]. In this cohort, there were six consecutive yearly samples from 51 subjects, and we used ELISA to measure IgA and IgG antibody to PT, FHA, pertactin, and fimbriae-2 on these sera. In this study, a subject was considered to have had a *B. pertussis* infection within a specific year if a significant increase in IgA or IgG antibody to any of the four antigens was demonstrated. A significant increase was an increase in antibody titer that was greater than or equal to the average fold 99.9% limit of controls (the rate of false-positive results per antigen per test would be 1:1,000).

During the 5-year period, 46 (90%) of the 51 subjects had serological evidence of an infection. Fifty-five percent of the subjects had evidence of two infections, 17% had evidence of three infections, and 4% had evidence of four infections. When only antibody (IgG or IgA) to PT was considered, 17 subjects (33%) had one or more infections during the 5-year study period. Infections were noted during all study years, with an average annual rate of 33%.

Cromer et al. [24] carried out a serological study of 156 adolescents in a teenage clinic in Ohio. They used ELISA to examine increases in IgG antibody to PT, FHA, and pertactin in yearly specimens. The criterion for an infection was a ≥50% increase in antibody to two antigens. The annual incidence of infection was 6.1%.

Data from these two studies, plus the finding of IgA antibody to PT, FHA, and pertactin in all age groups of controls in Los Angeles [21], indicate that unrecognized *B. pertussis* infections are common and endemic.

**The reliability of serological data.** The reliance on serological data for the diagnosis of *B. pertussis* infections in adults has been disquieting to many observers [25]. There are three major possible reasons for false-positive serological results: chance because of multiple comparisons, cross-reacting antibodies, and polyclonal antibody responses.

It is clear statistically that multiple comparisons will result in false-positive identification of cases. However, the criteria used by most present investigators have considered this and therefore have been conservative. On the other hand, cross-reacting antibodies due to *Bordetella parapertussis* infection can be a significant problem. In one study, 19 (83%) of 23 children with *B. parapertussis* infection were found to have an antibody response to FHA, and 15 (65%) and 8 (35%) had responses to pertactin and fimbriae-2, respectively [23].

There is a possibility of cross-reactions with nontypeable *Haemophilus influenzae* due to high-molecular-weight surface-exposed proteins that are related to the FHA of *B. pertussis* [26]. However, this had not been demonstrated, and we examined acute- and convalescent-phase sera from three children with otitis media due to nontypeable *H. influenzae* and found no increase in antibody to FHA (H. Faden, J. Cherry, unpublished data).

In our study of UCLA students with cough illnesses, we found four with serological evidence of *Mycoplasma pneumoniae* infection (fourfold increase in titer determined by indirect fluorescent antibody assay) [10]. Three of these four had serological evidence of *B. pertussis* infection. There are no data regarding polyclonal responses.

**Clinical Illness in Adults**

*Adult cough illness studies.* In our UCLA student study, we compared the clinical findings in subjects with *B. pertussis* infections with those in subjects without *B. pertussis* infections [10]. The only significant differences noted were the decreased likelihood of productive cough in *B. pertussis* infections (3% vs. 21%) and the more frequent use of antibiotics at the clinic visit in non-*B. pertussis* infections (39% vs. 64%). The two main clinical diagnoses in the *B. pertussis*-infected subjects were upper respiratory tract infection (39%) and bronchitis (48%). The clinical diagnosis of pertussis was not made in any subject positive for *B. pertussis*.

In our study in Germany, all adults were evaluated by one of three study pediatricians [11]. Of the 64 cases with positive results, 39% were considered to have definite or probably pertussis and 14% were thought not to have pertussis. The clinical diagnoses for the nine cases thought not to be pertussis were three with upper respiratory tract infection, two with nasopharyngitis, and one each with adenoiditis, pharyngitis, sinusitis, and upper respiratory tract infection along with chronic bronchitis. Of the 64 adults with *B. pertussis* infections, 70% had paroxysmal cough, 38% had whooping, 66% had posttussive phlegm, 17% had posttussive vomiting, and 26% had a history...
and severe weight loss [27]. Cough was noted and her illness was diagnosed by ELISA. Her acute hearing loss, rib fracture, inguinal hernia, lumbar pain, broken rib. After 6 weeks, I saw the patient, and the classic lymphadenopathy, and one case each of aspiration, one-sided with paroxysms. Her chest hurt so much that she suspected a transient urinary incontinence, two cases of painful cervical She could not catch her breath and had urinary incontinence four cases of otitis media, three cases of pneumonia, three cases paroxysms were so severe that she slept sitting up and outside.

Complications occurred in 18 patients. These included nothing or asthma, and she was concerned about a tumor. Her pertussis, 33%; and being the primary case in the family, 15% organization. The physicians there thought that it was either pain, 17%; sudden sweating attacks, 15%; a history of previous pertussis. Forty-eight percent of the cases in adults The source of this patient’s illness was thought to be his 13-year-old daughter.

Another Germany study of pertussis in adults that comprised 84 cases, the characteristics were as follows: cough >21 days, 81%; spasmodic cough >21 days, 65%; sleep disturbed by cough, 55%; choking, 56%; sneezing attacks, 23%; sinus pain, 17%; sudden sweating attacks, 15%; a history of previous pertussis, 33%; and being the primary case in the family, 15% [12]. Complications occurred in 18 patients. These included four cases of otitis media, three cases of pneumonia, three cases of transient urinary incontinence, two cases of painful cervical lymphadenopathy, and one case each of aspiration, one-sided acute hearing loss, rib fracture, inguinal hernia, lumbar pain, and severe weight loss [27].

Clinical vignettes. Hewlett reported the following [8]: Five adults with an interest in auto racing traveled from Virginia to Indiana for the Indianapolis 500 in May 1986. Because of a series of rain delays in the race, the group was together indoors for most of the trip, and during that time one person had rhinorrhea and a cough develop which became paroxysmal. Seven to ten days after returning home, the other four persons had the onset of rhinorrhea, watery eyes, and dry cough without fever, which progressed to paroxysmal cough. Their illnesses lasted several months. One who had been fully immunized against pertussis as a child, had cough syncope develop, which persisted for several months. Although one patient wondered whether she might have ‘‘whooping cough,’’ that diagnosis was not considered by the physicians involved. All five adults had high antibody values to PT and FHA determined by ELISA.

Musher and Keitel [28] had the following experience with a patient:

A 49-year-old women presented with severe paroxysmal coughing and disabling pleuritic pain of one week’s duration. Physical examination revealed a haggard, afebrile women who appeared to be exhausted. The physical examination was interrupted by paroxysms of coughing followed by whoop. Chest X-ray revealed a fractured left rib. Paroxysmal cough continued for 4 weeks and was associated with another possible rib fracture. Illness lasted two months. The patient had a significant antibody titer rise to PT by ELISA.

B. A. Lipsky (personal communication) reported a 47-year-old medical school professor who noted a mild upper respiratory tract infection with lacrimation on 23 May 1996. Four days later, the onset of cough occurred. From 28 to 31 May, the professor traveled by air on a lecture tour, and during this time he noted a severe paroxysmal cough, with intercostal pain that was worse at night. On 1 June, he was treated with prednisone and antitussives. Five days later, he was treated with ofloxacin for 3 days and a sample was taken and cultured for Bordetella species. On 11 June, the culture yielded B. pertussis, and the patient was treated with azithromycin. The patient’s cough illness lasted 3 months, and 47 people at the hospital where he worked received prophylactic antibiotics. The source of this patient’s illness was thought to be his 13-year-old daughter.

In recent years, I have seen the following two cases: A 42-year-old research microbiologist 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 a half-dozen visits to her health maintenance organization. The physicians there thought that it was either nothing or asthma, and she was concerned about a tumor. Her paroxysms were so severe that she slept sitting up and outside. She could not catch her breath and had urinary incontinence with paroxysms. Her chest hurt so much that she suspected a broken rib. After 6 weeks, I saw the patient, and the classic cough was noted and her illness was diagnosed by ELISA. Her illness lasted 3 months.

A 43-year-old pediatric anesthesiologist developed a ‘‘cold with nasal congestion, sore throat, and myalgia.’’ Because of worsening symptoms he took over-the-counter cold preparations (Theraflu, Niquil, and Sudafed). One week later, he had a severe paroxysmal cough that caused his children to fear he was choking and slapped him on the back. His illness was diagnosed by his physicians as asthma. His symptoms persisted. Erythromycin was prescribed for ‘‘mycoplasma.’’ The diagnosis was eventually made by serological study in our laboratory.

Recent Epidemiology of Pertussis

In the United States from 1982 to the present, there has been a modest upward trend in the pertussis attack rate (figure 1). A major contribution to this upward trend has been an increased recognition of cases in adults [29, 30]. The number and percentage of pertussis cases by age group from 1992 to 1994 are presented in table 2. As can be seen, 27% of the cases were in persons >10 years of age and 11% in persons ≥20 years of age [29]. In a 1996 outbreak of pertussis in Vermont, 69% of the cases were in persons ≥10 years of age, and 23% were in those ≥20 years of age [30].
Table 2. Number and percentage of pertussis cases by age group in the United States, 1992–1994.

<table>
<thead>
<tr>
<th>Age group</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;6 mo</td>
<td>4,524 (33)</td>
</tr>
<tr>
<td>6–11 mo</td>
<td>1,094 (8)</td>
</tr>
<tr>
<td>1–4 y</td>
<td>2,682 (20)</td>
</tr>
<tr>
<td>5–9 y</td>
<td>1,551 (11)</td>
</tr>
<tr>
<td>10–19 y</td>
<td>2,223 (16)</td>
</tr>
<tr>
<td>≥20 y</td>
<td>1,541 (11)</td>
</tr>
<tr>
<td>Total</td>
<td>13,615</td>
</tr>
</tbody>
</table>

NOTE: Modified from [29].

A popular explanation for this increase is that waning vaccine immunity is responsible [31–33]. This hypothesis assumes that infection results in long-lasting immunity. However, the data presented herein as well as in my historical review [34] suggest that this hypothesis is incorrect.

In my opinion, the recent increase in the rate of reported pertussis in the United States as well as the increased percentage of adolescents and adults are the result of a general increased awareness of the disease and an increase in the availability of diagnostic laboratory services. Also contributing to the increase is the use of one whole-cell pertussis component diphtheria-tetanus-pertussis vaccine that has poor efficacy [35, 36]. Although there are no data available to support my opinion, I believe that this particular vaccine was effective in the past but that it has changed in recent years.

Summary and Conclusions

Illnesses due to *B. pertussis* infections in adolescents and adults are common and endemic. Immunity to *B. pertussis* illness, whether vaccine- or infection-induced, is not long-lasting. The outcome of repeat infection depends on the time that has elapsed since the previous infection. A short time interval results in asymptomatic infection, whereas a longer duration results in symptomatic disease. Endemic disease in adults is responsible for cyclic disease in unvaccinated children.

Since pertussis in adolescents and adults plays a major role in pertussis epidemiology, it is apparent that our present immunization approach will not control the circulation of *B. pertussis*. The present availability of less reactogenic acellular pertussis vaccines makes adolescent and adult booster immunization programs possible. It is my opinion that an immunization program that includes adolescent and adult booster immunizations will decrease the circulation of *B. pertussis* and could lead to its elimination.

References


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