The Epidemiology of Pertussis: A Comparison of the Epidemiology of the Disease Pertussis With the Epidemiology of *Bordetella pertussis* Infection

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James D. Cherry, MD, MSc

ABSTRACT. In the prevaccine era pertussis epidemics followed a cyclic pattern, with peaks every 2 to 5 years. With the marked reduction of pertussis by vaccination, the same cyclic pattern still occurs. Studies relating to reported pertussis and Bordetella pertussis infection have been reviewed and analyzed. The increase in reported pertussis over the last 2 decades is mainly due to a greater awareness of pertussis and perhaps to the use of several less efficacious vaccines.

Studies of prolonged cough illnesses in adolescents and adults reveal that 13% to 20% are a result of B pertussis infection. Serologic studies suggest that the rate of B pertussis infection in adolescents and adults is ~2.0% per year. The rate of cough illnesses (pertussis) caused by B pertussis infection in adolescents and adults is between 370 and 1500 per 100 000 population. These data suggest that there are between ~800 000 and 3.3 million cases per year in the United States.

The coming availability of adolescent- and adult-formulated diphtheria and tetanus toxoids and acellular pertussis vaccines for adolescents and adults and their widespread use should reduce the reservoir of B pertussis disease. It is suggested that a universal program of adolescent and adult boosters would decrease the circulation of B pertussis in these age groups and possibly could lead to the elimination of the organism from the population. Pediatrics 2005;115:1422–1427; pertussis, Bordetella pertussis, adult pertussis, adolescent pertussis, pertussis epidemiology.

ABBREVIATIONS. DTaP, adolescent- and adult-formulated diphtheria and tetanus toxoids and acellular pertussis; ELISA, enzyme-linked immunosorbent assay; PCR, polymerase chain reaction; PT, pertussis toxin; FHA, filamentous hemagglutinin; PRN, pertactin; FIM, fimbriae; DTP, diphtheria and tetanus toxoids and pertussis; APERT, adult acellular pertussis vaccine efficacy trial.

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and other \(B\) pertussis proteins (filamentous hemagglutinin [FHA], pertactin [PRN], and fimbriae [FIM]) by ELISA or agglutination.

**RESULTS**

### The Epidemiology of Reported Pertussis

The number of cases of pertussis reported each year from 1922 to 2003 is presented in Fig 1, and the percent distribution of reported pertussis according to age group is presented in Fig 2. In the prevaccine era pertussis was a universally present disease with cyclic peaks every 2 to 5 years.\(^1\)\(^4\) The average yearly rate of reported pertussis was 157 per 100,000 population.\(^4\) Significant underreporting of pertussis was known to occur; thus, an estimated corrected yearly attack rate for the United States was 872 cases per 100,000 population.\(^4\)

In the prevaccine era reported cases occurred almost exclusively in children; \(>93\%\) of reported cases occurred in children <10 years old.\(^1\)\(^4\)\(^8\) Pertussis immunization commenced in the United States in the 1940s, and by 1960 there were \(<10\) cases of reported pertussis per 100,000 population.\(^4\) A decade later (1970) the rate had fallen to \(<1\) per 100,000 population.

In contrast with the prevaccine and early vaccine era, the reporting of pertussis in adolescents and adults has increased dramatically.\(^1\)\(^8\) As noted in Fig 2, \(~50\%\) of the reported pertussis cases were in persons >10 years old. Since 1984 there has been a modest but steady increase in reported cases in the United States.\(^8\) In 2002 there were 9771 reported cases, for a yearly rate of 3.4 per 100,000 population.\(^9\) As noted in the introduction, in the vaccine era reported pertussis still has a cyclic pattern, and the peaks still occur at 2- to 5-year intervals.

In recent years there has been much concern in the lay and scientific literature about the “resurgence of pertussis.” This resurgence was discussed recently in a *Pediatrics* commentary.\(^8\) To summarize, there are 5 possible causes for the increased reporting of pertussis: (1) genetic changes in \(B\) pertussis making vaccines less effective; (2) lessened potency of pertussis vaccines; (3) waning of vaccine-induced immunity; (4) greater awareness of pertussis; and (5) the general availability of better laboratory tests in some areas of the country. Of these possible causes, it was felt that that the most significant factor was a general greater awareness of pertussis that has occurred in recent years. However, the observation of multiple outbreaks of pertussis in preadolescent and adolescent school populations suggest that, in my opinion, waning vaccine-induced immunity caused by vaccines that were less efficacious than in the past has also been a contributor.

Specifically, before the introduction of and universal use of DTaP vaccines in the United States there were 2 whole-cell pertussis component diphtheria and tetanus toxoids and pertussis (DTP) vaccines available. Both of these vaccines in the mid 1980s were immunogenic, but 1 of the 2 subsequently was found to be poorly immunogenic and had poor efficacy.\(^10\)\(^12\) In contrast, the other DTP vaccine remained highly immunogenic and efficacious.\(^13\)\(^14\) In conjunction with the DTaP-vaccine efficacy trials in the early 1990s, it was found that all DTP vaccines except the Connaught USA vaccine were more efficacious than the comparative DTaP vaccines. Of the 3 DTaP vaccines in use in the United States today, 2 had less efficacy than a comparative DTP vaccine.\(^15\)\(^16\) The use of lesser potency vaccines from the late 1980s until the present may well be a contributing factor in the rise in preadolescent and adolescent pertussis.

### The Epidemiology of \(B\) pertussis Infections

During the last 2 decades a number of studies have provided data that are useful in the delineation of \(B\) pertussis infection from reported pertussis. These studies include the study of prolonged cough illnesses in adolescents and adults, serologic studies over time used to determine infection rates in populations, and studies in defined populations to determine rates of symptomatic infections in adolescents and adults.
Percentage of Prolonged Cough Illnesses in Adolescents and Adults Caused by B pertussis Infection

Since 1987 there have been 13 published studies of adolescents and adults with prolonged cough illnesses in which the rates of B pertussis infections could be evaluated.3,17–28 The breakthrough that allowed these investigations was the development of quantitative ELISA to determine antibodies to B pertussis and selected B pertussis antigens.29 The ELISA, as developed by Manclark et al,29 allows a high level of precision so that twofold changes in ELISA antibodies between acute-phase and convalescent-phase sera are diagnostic. Furthermore, B pertussis infection in adolescents and adults can be reliably diagnosed by high single-serum ELISA antibody titers.3,30 This is an important breakthrough, because adolescents and adults often do not come to medical attention until the 3rd or 4th week of illness, a time at which the peak antibody titer has already occurred.3,19 Because of this, titer changes between acute-phase and convalescent-phase sera frequently do not occur.

Presented in Table 1 are the details and results of the 13 studies in which the percentage of prolonged cough illnesses resulting from B pertussis infection are presented. As noted, the rates vary from 12% to 52%. The extreme variation in rates can be explained by multiple factors such as the number of B pertussis antigens for which antibody was determined, the biases of the study physicians, and the precision of the ELISA studies.

The studies done in Germany, Chicago, Illinois, Denmark, and Paris, France, were all done during known regional outbreaks of pertussis so that physician bias (selecting patients who they think have pertussis) led to the selection of more typical cases rather than all persons with prolonged coughs. This approach will reveal a greater percentage of positives than if a protocol that dictates the study of all persons with prolonged cough is followed.

The other studies in Table 1 (Seattle, WA; New South Wales, Australia; Los Angeles, CA; Nashville, TN; San Diego, CA; San Francisco, CA; Minneapolis/St Paul, MN; and Korea) were investigations of cough illnesses in populations during times at which pertussis was not recognized as an outbreak. As seen in Table 1, the determined rate in these 8 studies still varies from 12% to 50%. These differences can be explained largely by the number of antigens for which antibody was determined. In general, the studies in which antibodies to FHA, FHA and PRN, or FHA, PRN, and FIM were analyzed in addition to antibody to PT found a greater percentage of positives.

It is now recognized that infection with Bordetella parapertussis commonly elicits an antibody response to B pertussis FHA and PRN and also occasionally to

### Table 1. Percentage of Prolonged Cough Illnesses in Adolescents and Adults Caused by Infections With Serologic, PCR, or Culture Evidence of Bordetella Infections

<table>
<thead>
<tr>
<th>Source</th>
<th>Location</th>
<th>Study Performed During Pertussis Outbreak?</th>
<th>Year</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jackson et al</td>
<td>Seattle, WA</td>
<td>No</td>
<td>1983–1987</td>
<td>15</td>
</tr>
<tr>
<td>Robertson et al</td>
<td>New South Wales, Australia</td>
<td>No</td>
<td>1985–1986</td>
<td>26</td>
</tr>
<tr>
<td>Mink et al</td>
<td>Los Angeles, CA</td>
<td>No</td>
<td>1986–1989</td>
<td>26</td>
</tr>
<tr>
<td>Jansen et al</td>
<td>San Diego, CA</td>
<td>No</td>
<td>1993–1994</td>
<td>17</td>
</tr>
<tr>
<td>Birkebaek et al</td>
<td>Denmark</td>
<td>No</td>
<td>1995–1997</td>
<td>17</td>
</tr>
<tr>
<td>Vincent et al</td>
<td>Korea</td>
<td>No</td>
<td>1997–1998</td>
<td>50</td>
</tr>
<tr>
<td>Gilberg et al</td>
<td>Paris, France</td>
<td>Yes</td>
<td>1999</td>
<td>52</td>
</tr>
</tbody>
</table>

Significant ELISA titer rise or high titer to PT, FHA, PRN, or FIM or significant agglutinin titer or titer rise.
TABLE 2. Percentage of Prolonged Cough Illnesses in Adolescents and Adults Caused by Infections With Serologic, PCR, or Culture Evidence of *B. pertussis* Infections

<table>
<thead>
<tr>
<th>Source</th>
<th>Location</th>
<th>Years</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mink et al&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Los Angeles, CA</td>
<td>1986–1989</td>
<td>13</td>
</tr>
<tr>
<td>Wright et al&lt;sup&gt;20&lt;/sup&gt;</td>
<td>Nashville, TN</td>
<td>1992–1994</td>
<td>16</td>
</tr>
<tr>
<td>Jansen et al&lt;sup&gt;23&lt;/sup&gt;</td>
<td>San Diego, CA</td>
<td>1993–1994</td>
<td>1</td>
</tr>
<tr>
<td>Nennig et al&lt;sup&gt;24&lt;/sup&gt;</td>
<td>San Francisco, CA</td>
<td>1994–1995</td>
<td>12</td>
</tr>
<tr>
<td>Strebel et al&lt;sup&gt;25&lt;/sup&gt;</td>
<td>Minneapolis/St Paul, MN</td>
<td>1995–1996</td>
<td>13</td>
</tr>
<tr>
<td>Birkebaek et al&lt;sup&gt;26&lt;/sup&gt;</td>
<td>Denmark</td>
<td>1995–1997</td>
<td>17</td>
</tr>
<tr>
<td>Vincent et al&lt;sup&gt;27&lt;/sup&gt;</td>
<td>Korea</td>
<td>1997–1998</td>
<td>7</td>
</tr>
</tbody>
</table>

Significant immunoglobulin A or G antibody-titer rise or high titer to PT or culture or PCR positive.

*B pertussis* FIM.<sup>1,13</sup> It is likely that human infection with *Bordetella bronchiseptica* and perhaps *Bordetella holmesii* also elicit similar antibody responses. In addition, it is clear that other infectious agents have proteins that, with infection, result in antibodies to FHA.<sup>27</sup> Therefore, the studies shown in Table 1 in which FHA, PRN, and FIM antibodies contributed to the percentage of positives overestimate *B pertussis* infections.

In contrast with the above, antibody to PT is *B pertussis* specific.<sup>1</sup> Therefore, the use of PT alone in ELISA-antibody studies gives a better indication of the rate of prolonged cough illnesses that are caused by *B pertussis* infection.

In Table 2 the data from the 7 studies done at nonoutbreak periods in which antibody to only PT was determined are presented. The rate in these 7 analyses varied from 1% to 17% (median: 13%). The 1% value in the San Diego study is difficult to explain, because there was a high rate of positives noted by FIM analysis.<sup>23</sup> It seems most likely to me that the low percentage of PT antibody was an artifact caused by the care of the sera before assay.<sup>17,31</sup>

The data in Table 2 suggest that ~13% of prolonged cough illnesses in adolescents and adults are a result of *B pertussis* infection. However, because all persons infected with *B pertussis* do not have an antibody response to PT, this percentage is an underestimate. In children, as many as 24% of those with culture-proven pertussis do not have a PT-antibody response.<sup>13</sup> In adults, the percentage is ~10% (ref 26; unpublished data).

It is important to note that all 13 studies of adolescents and adults with prolonged cough illnesses have found evidence of *B pertussis* infection. These studies have been conducted in 6 countries and 7 geographic areas of the United States over a 16-year period. These data suggest that *B pertussis* infection in adolescents and adults is endemic and independent of the cyclic pattern observed with reported pertussis.

Rate of *B pertussis* Infections in Adolescents and Adults

There have been 5 studies performed in the United States in which data on rates of *B pertussis* infection have been presented<sup>32–36</sup> (Table 3). In all of these studies the rates have been determined by the demonstration of significant ELISA antibody-titer rises in sera collected from the same individuals over an extended time period. In 4 of the studies the sera were collected for other purposes, but in 1 study the sera were collected from controls in an adolescent and adult acellular pertussis vaccine efficacy trial (APERT). As can be seen in Table 3, the rates vary from ~1% to 8% (median: 2.2%).

Rate of Cough Illnesses (Pertussis) Caused by *B. pertussis* Infection

Attempts to determine the annual rate of pertussis resulting from *B pertussis* infection were made in 4 of the cough-illness studies presented in Table 1 and 2 of the studies presented in Table 3.<sup>3,19,24,25,34,36</sup> These data are presented in Table 4. As noted, the estimates vary by almost 10-fold. The relatively low rates noted in the Los Angeles, San Francisco, and Germany studies may be due to an overestimate of the whole population.<sup>3,19,24</sup> In contrast, the study by Strebel et al<sup>25</sup> was specifically designed to obtain rate data, and the APERT data<sup>36</sup> were obtained from controls in the vaccine efficacy trial. They were a defined population that had been monitored closely.

The Cleveland, OH, study with the highest rate involved 100 adults who were monitored for respiratory illness and had serum assayed for PT antibody every 4 months for 3 years.<sup>34</sup> The rate of 1500 per 100 000 assumes that all the respiratory illnesses in the specific time periods were a result of *B pertussis* infection.

The data from the APERT, Minneapolis/St Paul, and Cleveland studies indicate a total yearly adolescent and adult pertussis burden of between ~800 000 and 3.3 million in the United States.<sup>25,34,36</sup>

**DISCUSSION**

Today there is a preoccupation with the resurgence of pertussis without a clear understanding of the epidemiology of *B. pertussis* infection.<sup>1,37</sup> One problem in this regard has been the opinion that...
immunity after \textit{B pertussis} infection is lifelong, whereas that after immunization is relatively short-lived.\textsuperscript{1,2} This has led to the prevalent idea today that the increase in the observation of pertussis in adolescents and adults is because of waning vaccine-induced immunity. Although this is technically true, it is also apparent that waning immunity after infection was a problem in the prevaccine era in the United States and more recently in countries such as Germany, where immunization was infrequent until the very recent present.\textsuperscript{1,2,19,21,38}

Data presently exist that suggest that vaccine-induced immunity is actually better than that induced by \textit{B pertussis} infection.\textsuperscript{1,2,38} It is clear that pertussis in adults is not new, and in Germany in the early 1990s when pertussis was still epidemic, symptomatic adults were a common source for infections in young children.\textsuperscript{19,21}

The data presented here suggest that \textit{B pertussis} infection is common and endemic in adolescents and adults. All 9 studies done in the United States, New South Wales, Denmark, and Korea conducted at non-outbreak times found cases in adolescents and adults.\textsuperscript{3,17,18,20,23–27} Recent serologic data in adults in 8 geographic regions of the United States note the prevalence of antibodies to 4 \textit{B pertussis} proteins (PT, FHA, PRN, and FIM).\textsuperscript{39} There are few differences by either geographic area or age. These data suggest that adults in Los Angeles have the same susceptibility possibilities as those in the 7 other regions studied. Similarly, 30-year-olds have the same potential risk of infection as all other adult age groups.

Household-contact studies have indicated that infection without illness is common.\textsuperscript{40,41} These data suggest that frequent exposures maintain antibody levels in many persons at protective levels. Illness only occurs when antibody values have fallen below critical values, and then exposure occurs.

The results of this study as well as a careful literature review lead me to suggest the following conclusions:

1. The epidemiology of reported pertussis is different from the epidemiology of \textit{B pertussis} infection.
2. The modest increase in reported pertussis in the United States since 1984 is mainly a result of an increased awareness of \textit{B pertussis} illness and also the use of many vaccines that were less efficacious than DTP vaccines of the past.
3. \textit{B pertussis} infections in adolescents and adults are common and endemic.
4. Immunity after infection or vaccination is not long-lasting.
5. The outcome of an exposure depends on the time since vaccination or a previous infection.
6. Endemic adolescent and adult disease is responsible for the cyclic pattern in unvaccinated children.
7. \textit{B pertussis} circulation cannot be controlled by present immunization programs.
8. Acellular vaccines make adolescent and adult booster immunizations possible.
9. A program with adolescent and adult boosters will decrease the circulation of \textit{B pertussis} in these age groups and could lead to the elimination of the organism from the population.

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