ABSTRACT

After an initial decline in the incidence of pertussis that was a result of the introduction of the diphtheria, tetanus, and whole-cell pertussis vaccine, the Centers for Disease Control and Prevention has reported a marked increase in the prevalence of this disease since the 1970s. Most of the cases of pertussis occur in infants too young to receive vaccine. Research has shown that these infections are secondary to primary infections in older family members. However, the incidence of pertussis is increasing among adolescents and adults. The reason for this may be a combination of previous underrecognition of pertussis in noninfant age groups and that immunity conferred by pertussis vaccination and disease wanes over time. Because of this realization, new methods of disease prevention in persons over the age of 7 years are needed. (Adv Stud Med. 2005;5(5A):S440-S443)

Introduction of the diphtheria, tetanus, and whole-cell pertussis vaccine in the late 1940s led to a precipitous decline in pertussis cases (Figure).1-4 Incidence continued to decline for more than 2 decades with the all-time low of just over 1000 cases reported in 1976. Since then, pertussis incidence has been on the rise with over 11,000 cases reported to the Centers for Disease Control and Prevention (CDC) in 2003. The increased incidence has spanned most age groups. Incidence remains highest in neonates, who are too young to have received any of their scheduled pertussis-containing vaccines. Rates in infants have been increasing, particularly in ages 2 to 3 months; rates in infants ages 4 to 11 months have also been increasing, but at a slower rate. Reported cases in children ages 10 to 19 years have increased almost 10-fold in the last decade and an increase has also been reported in adults. The only age group in which rates have remained steady is children aged 1 to 9 years, an age span characterized by optimal protection from pertussis-containing vaccines.

Although a few pertussis-related deaths have been reported in persons older than 6 months, including adults, the vast majority of reported deaths from pertussis continue to occur in infants younger than 6 months (Table 1).5 Moreover, pertussis-related deaths in this age group have been increasing substantially over the last several years.

One might expect passively acquired maternal antibodies to protect neonates against pertussis. To investigate this more fully, Healy and colleagues evaluated pertussis antibody levels in sera from maternal, cord, and infant samples and determined titer levels to pertussis toxin (PT), filamentous hemagglutinin (FHA), and fimbrial proteins (fim).6 Efficient placental transfer of passive immunity was shown by evidence of higher titer levels in umbilical cord sera than in mothers. However, because maternal titers were extremely low, neonates derived very little passive immunity. Further, by 2 months of age, these low titers declined to undetectable levels, leaving the infants with little or no protection against pertussis.

Even as the CDC reports substantial increases in the reported numbers of pertussis cases, evidence shows actual incidence is likely much higher due to substantial underreporting. Researchers assessed the
Figure. Reported Cases of Pertussis in the United States, 1922-2003

completeness of reports to the Supplemental Pertussis Surveillance System (SPSS), a CDC-coordinated system that captures pertussis cases and outcomes, by comparing its data with death certificates listing pertussis as an underlying cause, as reported to the National Center for Health Statistics (NCHS). From 1989 to 1993, 45 pertussis-related deaths were reported to SPSS and 46 were reported to NCHS, but just 13 were reported to both. When these data were evaluated by capture-recapture methodology, it was determined that 71% of deaths went unreported to either CDC surveillance system. This suggests that 3 times as many deaths occurred (153) than were reported during the 5-year period from 1989 to 1993.

A second report confirms that approximately two thirds of pertussis cases resulting in hospitalization or death are not reported. This study compared data reports with the CDC (NCHS) and the Commission on Professional Hospital Activities (CPHA), which tracks illnesses at participating US hospitals by International Classification of Diseases code. Data comparisons showed only 32% of hospitalizations were reported to NCHS and 23% to CPHA. Further examination of cases revealed that severe complications of pertussis are reported preferentially to the NCHS. While more recent data are not available, these studies provide evidence that substantial underreporting occurs.

**Source of Infection**

Widespread silent transmission of pertussis within families was reported by Long et al when they evaluated 4 hospitalized infants diagnosed with classic culture-confirmed pertussis and 18 of their family members with both culture and serology. Although pertussis cultures were positive in only 20% of family members, serologic rises were seen in 83%, with at least 1 symptomatic infected contact in each household. Investigators concluded that infant cases were secondary to primary infections in older family members. Data also led them to conclude that immunity against symptomatic pertussis is greater than immunity against infection.

A similar but larger study in the mid-1990s enrolled 39 children, 90% younger than 4 years, who were hospitalized with classic pertussis symptoms, and 255 of their household contacts. More than half (53%) of the primary cases were in individuals ages 13 years and older, again highlighting the importance of adolescents and adults as a source of *Bordetella pertussis* infection in young children and infants.

**Table 1. Pertussis-Related Deaths in the United States, 1997-2000**

<table>
<thead>
<tr>
<th>Age</th>
<th>Number of Cases</th>
<th>Deaths</th>
</tr>
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<tbody>
<tr>
<td>Under 6 months</td>
<td>7203</td>
<td>56</td>
</tr>
<tr>
<td>6-11 months</td>
<td>1073</td>
<td>1</td>
</tr>
<tr>
<td>1-4 years</td>
<td>3137</td>
<td>1</td>
</tr>
<tr>
<td>5-9 years</td>
<td>2756</td>
<td>2</td>
</tr>
<tr>
<td>10-19 years</td>
<td>8273</td>
<td>0</td>
</tr>
<tr>
<td>20 years or over</td>
<td>5745</td>
<td>2</td>
</tr>
</tbody>
</table>

Data from the Centers for Disease Control and Prevention.

*2003 data provisional.
DTaP = diphtheria, tetanus and whole-cell pertussis vaccine.
Data from Davis et al; Cherry; Guris et al; and the Centers for Disease Control and Prevention.*
During an outbreak of pertussis in Chicago in 1993, risk factors for acquisition of infection in infants were assessed. Infants of adolescent mothers (aged 15-19 years) were significantly more likely to have pertussis than those with mothers aged 20 to 29 years. In addition, maternal cough lasting at least 7 days was also associated with a marked increase in the risk of pertussis in their infants. Infants residing in households with other children younger than 5 years were not found to be at increased risk of infection. This suggests mothers in the adolescent age group pose a risk of transmitting pertussis to their infants.

Halperin et al reported 1082 pertussis-related hospitalizations in Canada from 1991 to 1997 and found that approximately half of them were culture-confirmed. The median age of the infected subjects was 12.4 weeks; nearly 80% were younger than 6 months of age. All 10 reported deaths were in children younger than 6 months; 60% were in neonates. The primary source of infection was identified in approximately 40% of the cases. Siblings were the most common source (53%), followed by parents (20%), other relatives (12%), neighbors (8%) and day-care contacts (3%).

EXAMINING INCREASED RATES IN ADOLESCENTS AND ADULTS

While data show infant cases are increasing and that the primary sources are often adolescents and young adults, the question remains, why is incidence increasing in adolescents and adults? The answer may be a simple combination of previous underrecognition of pertussis in noninfant age groups and that immunity conferred by pertussis vaccination and disease wanes over time.

Evidence of waning immunity was reported nearly 40 years ago in an epidemiological study of a pertussis outbreak in Michigan (Table 2). The longer the time since vaccination, the higher the associated attack rate. Those vaccinated 12 or more years prior had an attack rate of 95% compared with 21% for those vaccinated less than 3 years earlier.

More recently, a seroprevalence study measured PT and FHA titers in sera taken from 585 healthy individuals aged 1 to 65 years. A peak in antibody titers was noted at 4 to 6 years of age, coinciding with diphtheria, tetanus, and acellular pertussis booster dosing. A remarkable decline in antibody titers was noted just a few years later but this was followed by a second peak in adolescents ages 13 to 17 years. Since no pertussis-containing vaccine is administered after age 6 years, this spike in antibody titers must be due to natural exposure to disease.

Recently, Baughman and colleagues determined population-based antibody titers in sera from many individuals of various ages living throughout the country. In these studies, the investigators measured immunoglobulin G levels against PT, FHA, and fim in sera collected in the National Health and Nutrition Examination Survey (NHANES) from over 6000 US residents aged 6 to 59 years. Young children who had been vaccinated had the highest titers against PT. As in earlier studies, titers declined precipitously in the years following vaccination and then peaked again in adolescent years. After another protracted decline, a peak in PT positivity was noted in persons aged 40 to 45 years. This final peak in the older age group is likely explained by a number of parents whose adolescent children have exposed them to pertussis infection.

A prospective study was conducted to determine the prevalence of pertussis infection in an urban population of adults (≥18 years) presenting to a clinic with prolonged cough. Pertussis was defined as a single PT titer greater than 2 standard deviations above age-matched persons. The study enrolled 153 persons with cough illness present for 2 or more weeks. The study reported a pertussis prevalence rate of 12.4% and incidence of 176 cases per 100,000 adults, a rate comparable with that of peptic ulcer disease.

A CDC-funded prospective study estimated pertussis incidence in adolescents and adults. Culture, polymerase chain reaction, and serology were used to determine the disease rate in adolescents and adults.

Table 2. Relationship Between Time Since Vaccination and Attack Rate

<table>
<thead>
<tr>
<th>Interval Since Vaccination (years)</th>
<th>Percentage Infected</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-3</td>
<td>21</td>
</tr>
<tr>
<td>4-7</td>
<td>47</td>
</tr>
<tr>
<td>8-11</td>
<td>65</td>
</tr>
<tr>
<td>Over 12</td>
<td>95</td>
</tr>
<tr>
<td>Total</td>
<td>45</td>
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</table>

Data from Lambert.
(aged 10-49 years) who presented with cough illness of 2 weeks’ duration at 10 clinics in the St. Paul/Minneapolis metropolitan area. The study estimated a cumulative incidence of 170 to 630 pertussis cases per 100 000. The rates in the adolescent population (aged 10-19 years) were almost 2-fold higher, at 1140 cases per 100 000.

Finally, a prospective acellular pertussis vaccine efficacy trial (APERT) funded by the National Institutes of Health examined vaccine efficacy in nearly 3000 subjects followed with active surveillance for 2 years.18 Pertussis cases in the control group were used to extrapolate the burden of pertussis disease. The data suggest annual confirmed cases of pertussis number 674 000, probable cases number 820 000, all possible cases are just over 1.5 million, and all cough illness is nearly 10 million per year. These data confirm the substantial burden of pertussis.

CONCLUSION

The overall number of cases reported to the CDC is increasing, but still likely underestimate incidence by as much as 70%. The greatest incidence and highest burden of disease is in infants, most specifically neonates who are too young to have received any pertussis-containing vaccine and who receive inadequate amounts of passive maternal antibody protection. Data confirm that adolescents and adults are a very important route by which B pertussis is transmitted to these infants. Increased reports of cases in adolescents and adults may be a result of better recognition and diagnosis, but are likely due to waning immunity. New prevention strategies are needed to reverse the troubling trend in pertussis incidence and burden noted over the last 2 decades.

REFERENCES