Antibody Responses to \textit{Bordetella pertussis} Antigens and Clinical Correlations in Elderly Community Residents

Sally L. Hodder,\textsuperscript{1} James D. Cherry,\textsuperscript{2} Edward A. Mortimer, Jr.,\textsuperscript{1} Amasa B. Ford,\textsuperscript{1} Jeffrey Gornbein,\textsuperscript{3} and Klara Papp\textsuperscript{1}

A serological study to determine the frequency of \textit{Bordetella pertussis} infection in 100 adults aged \(\geq 65\) years was carried out over a 3-year period. Ten serum samples (collected every 4 months) from each subject were examined for IgA and IgG antibodies to the following \textit{B. pertussis} antigens: pertussis toxin (PT), filamentous hemagglutinin (FHA), pertactin, and fimbriae-2. A \(\geq 2\)-fold titer increase in ELISA units from one time period to the next was considered serological evidence of infection. The rate of serologically defined infection (i.e., in which there was an increase in titer against any antigen) was 19.7 per 100 person-years. With the use of more specific criteria that indicate definite \textit{B. pertussis} infection (\(\geq 2\)-fold increase in titer to PT) and probable \textit{B. pertussis} infection (\(\geq 2\)-fold increase in titer to PT or \(\geq 2\)-fold increase to fimbriae-2), the rates were 3.3 and 8.0 per 100 person-years, respectively. Fifty percent of individuals with definite \textit{B. pertussis} infections had time-associated symptomatology. Antibody patterns over time suggest that antibody to FHA and perhaps to pertactin is stimulated by infections with other organisms, as well as \textit{B. pertussis} infections. Our data suggest that symptomatic pertussis occurs in elderly individuals. Consideration should be given to immunization of the elderly with acellular pertussis vaccines.

During the past 25 years there has been an increased awareness of pertussis in adolescents and adults [1–16]. Investigations of prolonged cough illnesses in adolescents and adults have suggested that a substantial number of the illnesses are due to \textit{Bordetella pertussis} infections [2–11, 14–16]. In addition, serological survey data over time for identified populations have suggested high rates of \textit{B. pertussis} infections in these populations [12, 13]. The breakthrough that made these illness and surveillance studies possible was the development of quantitative ELISA techniques using \(\geq 1\) \textit{B. pertussis} antigens [17–19].

The findings of recent pertussis vaccine efficacy trials and other epidemiological studies have led to some concern on our part as to the specificity of the serological diagnosis of \textit{B. pertussis} infections with use of some \textit{B. pertussis} antigens [20, 21]. For example, infection with \textit{Bordetella parapertussis} regularly results in an ELISA antibody response to \textit{B. pertussis} filamentous hemagglutinin (FHA) and pertactin [20]. In addition, another study performed by members of our group suggests that high values of antibody to FHA without concomitant high values to pertactin or pertussis toxin (PT) may be due to cross-reactions with antibodies to \textit{Mycoplasma pneumoniae}, \textit{Chlamydia pneumoniae}, or an as-yet-unidentified infectious agent or agents [21].

In this report, we describe the ELISA patterns of IgA and IgG antibody to 4 \textit{B. pertussis} antigens in 100 elderly community residents, aged \(\geq 65\) years, over a 3-year period. Available clinical data on our study subjects permit correlation of symptomatology to variously defined groups of \textit{Bordetella} infections.

Subjects and Methods

\textit{Subjects}. One hundred subjects were randomly chosen from members of a previously reported larger study cohort of 574 individuals, aged \(\geq 65\) years, from whom clinical information and serum samples were prospectively collected over a 3-year period for purposes of ascertaining the incidence and etiology of common respiratory infections [22]. In brief, cohort participants were recruited from a registry of older people who lived independently and were interested in participating in research studies, a foster grandparents group, and residents of several large apartment complexes for independent elder persons. Subjects were excluded if \(\geq 1\) of the following criteria were present: (1) dementia, (2) moribund state (defined as presence of illness likely to cause death in <1 year), (3) inability to cooperate, or (4) absence from the Cleveland area for >1 month per year. All study subjects were offered payment of $50 per year for participation.
After subjects gave informed consent, they were each visited at home at the time of enrollment and subsequently every 4 months by a study nurse, who recorded a standard medical history and obtained a serum sample. If acute illness occurred between routine visits, participants were asked to contact study personnel so that a study nurse could visit to record a brief history and obtain a serum sample for antibody studies and nasal washings for viral isolation. A follow-up visit and convalescent serum sampling occurred 4–6 weeks later. The sample of 100 persons in the present analysis was retrospectively and randomly selected from among subjects who participated for the entire 3 years of observation and for whom complete clinical and serological data were available.

Serological studies. Studies of antibodies to B. pertussis antigens were performed on the 10 sera that had been collected routinely every 4 months from each subject. IgA and IgG antibodies to PT, FHA, pertactin, and fimbriae-2 were detected by ELISA as described elsewhere [2, 8, 12, 17], except that ELISA unitage was calculated with the reference-line bioassay program rather than the parallel-line program [18, 19]. ELISA unitage was determined with use of US Reference Pertussis Antiserum (human) lots 3 and 4 (US Food and Drug Administration) [18]. The limit of quantitation for IgA and IgG antibody to each of the 4 antigens was estimated to be 6 EU/mL.

Validation of the assay for IgG antibody to PT, FHA, pertactin, and fimbriae-2 and IgA antibody to FHA, pertactin, and fimbriae-2 was done with use of serum specimens collected from 29 laboratory control subjects on consecutive days. With 290 comparisons for IgG and IgA antibody to each antigen, there was only 1 instance of a ≥2-fold change in determined titer, with 1 value of ≥20 EU/mL. This variation occurred with IgG antibody to fimbriae-2. Since few of the laboratory control sera had IgA antibody to PT, we carried out 9 repeats on 9 sera with known IgA antibody to PT. Among the 324 comparisons, there were 2 instances in which a ≥2-fold change in determined titer occurred (with 1 value being ≥20 EU/mL). Both of these variations represented interassay rather than intra-assay variation.

On the basis of these data, serological evidence of an infection was defined as a ≥2-fold increase in either IgA or IgG antibody to ≥1 B. pertussis antigens between 2 consecutive time periods, with the second serum having a titer ≥20 EU/mL. Serological criteria for specific causes of infection are presented in table 1. In 10 instances, presumably when an infection occurred just before a serum collection, titer increases occurred in 2 consecutive time periods, and in 3 instances, in 3 consecutive time periods. These uncommon instances were defined as single infections. All other increases occurring in different time periods in the same individual were considered evidence of separate infections.

Antibody titers to adenovirus, influenza A and B, parainfluenza viruses 1, 2, and 3, M. pneumoniæ, and respiratory syncytial virus were determined by standard CF techniques. A ≥4-fold titer increase between 2 time periods was considered evidence of infection.

Statistics. We used analysis of variance to assess demographic differences among various study samples, and χ² analysis to assess associations among various groups of seropositive and seronegative individuals.

Results

Population characteristics. In the study group, 26% were men, 15% were black, and 57% were aged >75 years. Significantly fewer of the study subjects were men and/or black in the subsample of 100 individuals than were the remainder of the individuals (n = 474) recruited for the original cohort (P < .001). Income and age were not significantly different.

Serological evidence of infection. On the basis of the overall definition of infection (a ≥2-fold increase in titer of either IgA or IgG antibody to ≥1 antigens, with the second titer ≥20 EU/mL), 48 subjects had serological evidence of 59 infections, and 52 subjects had no serological evidence of infection during the 3-year observation period. When we compared the groups with and without infection, significantly more subjects were black in the group without evidence of infection (P < .01). Age, sex, and income were not significantly different between the two groups.

Table 1 shows infection and illness rates according to the various definitions of infection in previous studies [2, 20, 21]. The 59 serologically defined episodes of infection occurred at a rate of 19.7 infections per 100 person-years. Of the 59 infections, 41 were identified by a single antibody titer increase, 12 by an antibody titer increase in 2 tests, and 2 each by an antibody titer increase in 3 tests, 4 tests, and 6 tests. Thirty of the 59 infections (51%) were associated with an increase in titer of IgA or IgG antibody to pertactin. Twenty-three of the infections (39%) were associated with an increase in titer of IgA or IgG antibody to FHA; 17 (29%), to fimbriae-2; and 10 (17%), to PT. There were 15 episodes of temporally related cough illnesses among the 59 episodes of identified infection (25%).

Table 1. Infection and cough illness rates by serologically defined etiology among 100 adults aged ≥65 years.

<table>
<thead>
<tr>
<th>Category of infection</th>
<th>Serological definition: increase in titer of antibody</th>
<th>No. of subjects with infection</th>
<th>Rate of infection per 100 person-years</th>
<th>No. (%) of subjects with cough illness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any serologically defined</td>
<td>≥2-fold of IgA or IgG to ≥1 antigen</td>
<td>59</td>
<td>19.7</td>
<td>15 (25)</td>
</tr>
<tr>
<td>Definite Bordetella pertussis</td>
<td>≥2-fold of IgA or IgG to PT</td>
<td>10</td>
<td>3.3</td>
<td>5 (50)</td>
</tr>
<tr>
<td>Probable B. pertussis</td>
<td>≥2-fold of IgA or IgG to FIM-2 (but none to PT)</td>
<td>14</td>
<td>4.7</td>
<td>4 (29)</td>
</tr>
<tr>
<td>Probable non-pertussis sp. of Bordetella</td>
<td>≥2-fold of IgA or IgG to both FHA and PRN (but none to PT or FIM-2)</td>
<td>4</td>
<td>1.3</td>
<td>2 (50)</td>
</tr>
<tr>
<td>Possible B. pertussis or other Bordetella or presence of cross-reacting antibodies</td>
<td>≥2-fold of IgA or IgG to only FHA or PRN</td>
<td>31</td>
<td>10.3</td>
<td>6 (19)</td>
</tr>
</tbody>
</table>

NOTE. FHA, filamentous hemagglutinin; FIM-2, fimbriae-2; PRN, pertactin; PT, pertussis toxin; sp., species.
Nasal discharge and hoarseness were present in 12 of these illnesses, while shortness of breath occurred in 6 of the 15 reported cough illnesses. One individual was admitted to the hospital for pneumonia.

There were 10 infections identified by increases in titer of IgA or IgG antibody to PT (definite *B. pertussis* infections) and 14 infections identified by increases in titer of IgA or IgG antibody to fimbriae-2 (probable *B. pertussis* infections). When considered together, these data suggest a *B. pertussis* infection rate of 8 infections per 100 person-years. In contrast, there were 35 infections identified by increases in antibody to FHA or pertactin, without increases to PT or fimbriae-2, which suggests infection with another (non-*B. pertussis*) *Bordetella* species or infection with another agent identified by cross-reacting antibodies. Of these cases, 4 had increases in titer of IgA or IgG to both FHA and pertactin, which suggests probable infection with a non-*pertussis* species of *Bordetella*; 2 of these 4 subjects had cough illnesses.

Cough illnesses occurred in half of study subjects with infections identified by increases in titer of antibody to PT. Three of the 5 subjects had cough lasting for >10 days, 1 had cough for 1 week, and another had cough of unknown duration. Two of the subjects with cough illnesses also had parainfluenza virus 1 infection, diagnosed by a 4-fold increase in CF antibody titer, and respiratory syncytial virus was isolated from the nasal secretions of another individual. Nine (37.5%) of the 24 infections identified by >2-fold increases in titer of IgA or IgG antibody to either PT or fimbriae-2 had cough illnesses. Study subjects who had >2-fold increases in titer of IgA or IgG antibody to only FHA or pertactin, without titer increases to PT or fimbriae-2 or to both FHA and pertactin, were significantly less likely to have cough illnesses (*P < .05*). Only 4 (13%) of 31 in this group had an identified cough illness during the period of infection.

The study observation period began in January 1989 and concluded in April 1992. During these 3 1/3 years, infections were identified in each of the 10 4-month periods. There were 9 infections in 1989, 17 in 1990, 28 in 1991, and 5 in the first 4 months of 1992. *B. pertussis* infections identified by an increase in titer of IgG or IgA to PT were also noted each year, with no remarkable peaks of infection; there were 3 infections in 1989 and 1990 and 2 infections in 1991 and 1992. When increases in titer of IgG or IgA antibody to fimbriae-2 or PT were used as indicators of definite or probable *B. pertussis* infections, there were 5 infections in 1989, 5 in 1990, 11 in 1991, and 3 in 1992.

Individual antibody patterns. Figures 1 and 2 show the patterns of IgA and IgG antibody to the *B. pertussis* antigens associated with infections in selected study subjects. In figure 1, the 4 selected infections for which data are shown were chosen because they had titer increases in >2 assays. Subject 30, who had a definite *B. pertussis* infection, had multiple antibody-titer increases, including increases in IgA and IgG to PT, which spanned 2 4-month periods. Subject 632 had 1 infection that may have been due to non-*B. pertussis* species of *Bordetella*, which was identified by antibody titer increases that spanned 3 time periods. This subject also had evidence of a second infection between month 32 and month 36, in which this subject showed significant increases in IgA and IgG antibodies to pertactin.

Subject 800 had definite *B. pertussis* infection, identified by 6 significant increases in IgA or IgG antibody titer between months 20 and 24. A second possible infection was identified by an increase in IgA antibody to FHA between the 32nd and 36th month. Subject 1080 had significant increases in titer of IgA antibody to FHA, pertactin, and fimbriae-2, as well as an increase in IgG to FHA between months 24 and 28, which suggests probable *B. pertussis* infection. Subject 800, who experienced nasal congestion, hoarseness, shortness of breath, fatigue, and a cough that lasted >30 days, was the only symptomatic individual among the 4 for whom data are given in this figure.

In contrast to the patterns in figure 1, the antibody patterns in figure 2 are less definitive. Subject 155 had evidence of 2 separate asymptomatic infections, identified by IgA antibody to pertactin, but in spite of these 2 antibody increases, antibody titers to all other antigens except IgG FHA remained below the limit of quantitation. Subject 180 had an increase in titer of IgA antibody to FHA during the first time period, and the IgA antibody to FHA had an upward trend throughout the study. The initial single titer increase in subject 303 seemed to be independent of the other antibody values. A second infection between months 32 and 36 was identified by an IgA fimbriae-2 antibody increase that was associated with increases below the >2-fold limit of antibody to PT, FHA, and pertactin.

Subject 769 had an illness characterized by nasal congestion, hoarseness, headache, shortness of breath, loss of appetite, and 11 days of cough in the first observation period. This subject had a significant increase in IgG antibody to PT between months 0 and 4 and a prolonged IgA response to FHA, which spanned 2 time periods.

Population antibody patterns. Figure 3 shows the geometric mean values of IgA and IgG antibody (EU/mL) to the 4 *B. pertussis* antigens in the 52 study subjects without serological evidence of infection. As can be seen, IgA antibodies to PT and IgG antibodies to pertactin, fimbriae-2, and PT remained constant throughout the 3-year study period. In contrast, IgA antibodies to pertactin, FHA, and fimbriae-2 and IgG antibodies to FHA showed a slight increase over the 3-year observation period.

Postinfection antibody patterns. Figure 4 shows the geometric mean values of IgA and IgG antibody (EU/mL) to the 4 *B. pertussis* antigens in study subjects with infections. After the geometric mean value peaked, IgA antibody to pertactin decreased modestly over 1 year and then rose to almost the peak value 8 months later. Twenty months after the peak value,
Figure 1. Antibody patterns associated with infection in 4 study subjects who had titer increases indicated in ≥2 assays. Subject (ID) 30 had significant IgA and IgG titer increases between months 24 and 32; increases in IgA to pertactin (PRN), filamentous hemagglutinin (FHA), fimbriae-2 (FIM-2), and pertussis toxin (PT); and IgG increases to FHA and PT. Subject 632 had significant IgA and IgG titer increases between months 8 and 20, increases in IgA to pertactin and FHA, and an increase in IgG to FHA. In addition, this subject had significant increases in IgA and IgG to pertactin between months 32 and 36. Subject 800 had significant IgA and IgG titer increases between months 20 and 24; increases in IgA to FHA and PT; and increases in IgG to pertactin, FHA, PT, and fimbriae-2. In addition, this subject had a significant increase in titer of IgA to FHA between months 32 and 36. Subject 1080 had significant IgA and IgG titer increases between months 24 and 28; increases in IgA to pertactin, FHA, and fimbriae-2; and an increase in IgG to FHA.

Discussion

During the past 2 decades, investigators have identified a number of antigenic components of *B. pertussis*, and these findings have led to the development, study, and use of less reactogenic acellular pertussis vaccines [23]. In conjunction with these events, ELISA techniques have evolved that have assisted markedly in epidemiological studies and in the evaluation of new vaccines [17–19]. During the past decade refinements in quantitative ELISA methods have resulted in high levels of precision, so that infections have been confirmed on the basis of 50% changes in antibody titers between acute-phase and convalescent-phase serum sampling [24]. In addition, population surveys of antibody prevalence have allowed the diagnosis
Figure 2. Antibody patterns in 4 study subjects in whom infection was identified by a single titer increase. Subject (ID) 155 had 2 significant increases in titer of IgA to pertactin, between months 16 and 20 and months 32 and 36. This subject had low values (<6 EU/mL) of IgA and IgG to all antigens, except for an IgG filamentous hemagglutinin (FHA) antibody value of 11 EU/mL (at 36 months), throughout the 3-year study period. Subject 180 appeared to have increases in titer of antibody to pertactin and FHA in the first time period, but only the increase in IgA antibody to FHA was significant. The IgA antibody to FHA and the IgG antibodies to FHA and pertactin had an upward trend throughout the observation period. Subject 303 had a significant increase in IgA to pertactin between months 12 and 16 and an increase in IgA to fimbriae-2 between months 32 and 36. Subject 769 had a significant increase in IgG to pertussis toxin (PT) between months 4 and 8. Between months 4 and 12, titers of IgA antibody to FHA increased and then remained high throughout the remaining observation period.

of pertussis on the basis of high values of single antibody to ≥1 B. pertussis antigens [2, 6].

Multiple studies involving adolescents and adults with prolonged cough illnesses have found that between 12% and 32% of these illnesses are associated with serological evidence of infection [2–11]. In general, the higher rates of illness attributed to B. pertussis infection have been found in studies in which multiple antigens have been used and both IgA and IgG antibodies evaluated [4, 9]. When multiple antigens per subject have been evaluated, there is concern that some positives are due to laboratory variation rather than to infection. This potential problem has led in many instances to the requirement of a titer increase in ≥2 assays or the setting of higher fold-change limits [4, 5, 8, 12].

Another potential problem with the serological diagnosis of B. pertussis infections is the possibility of false positives due to increases in titer of antibody to other infectious agents or polyclonal responses stimulated by illnesses due to other causes [20, 21, 25]. In particular, these include increases in titer of antibody to FHA and pertactin due to B. parapertussis infections and perhaps infections with other Bordetella species [20, 26].

Since the serological criteria in this study were stringent, it is unlikely that many observed titer increases were artifacts due to laboratory variation. In the laboratory validation process, only 3 ≥2-fold changes were noted among 2354 comparisons, and 2 of these represented interassay variation rather than an intra-assay difference. These variations occurred in the IgA PT and IgG fimbriae-2 assays, and only 2 of the 59 infections were identified by either of these two tests.

In 2 previous studies, members of our group looked for
changes in *B. pertussis* antibodies over defined time periods [12, 13]. In one study involving 51 adults in which yearly serum specimens were available over a 5-year period, it was noted that the annual infection rate was 33%; if increases in titer of only IgA or IgG antibody to PT were evaluated, the annual infection rate was 8%. With use of similar criteria, the annual infection rates in the present study were 19.7% and 3.3%. An important difference between the present study and the 2 previous studies is that clinical illness data were not available in the earlier studies. Other studies have indicated that asymptomatic infections are common [8, 27], and the present study suggests that between 50% and 87% of infections occur without recognized illness.

The study of *B. pertussis* infections in adults by serological methods is different is several respects from similar studies involving unvaccinated children. Previous serological data indicate that all adults have previously had *B. pertussis* infections; therefore, all adult infections are reinfections in persons with some immunologic experience [1, 8, 28]. In a previous study, 3 adults aged 33, 37, and 40 years with no history of pertussis or pertussis immunizations were studied serologically [29]. All 3 had culture-confirmed *B. pertussis* infections, and their illnesses were typical of pertussis, with a long duration of paroxysmal coughing episodes, associated with whoop in 2 cases and posttussive vomiting in the third case. All 3 patients had a significant ELISA increase in titer of IgG antibody to PT; 1 had only 1 additional increase to FHA, whereas the other 2 had multiple IgA and IgG increases to other *B. pertussis* antigens.

Since *B. pertussis* is the only organism known to liberate PT, it is reasonable to accept a significant increase in titer of antibody to this antigen as definitive evidence of *B. pertussis* infection. It is possible that a nonspecific polyclonal response could result in an increase in PT antibody, but with the stringent criteria of this study (>2-fold change and convalescent-phase value ≥20 EU/mL), this seems remote.

Accepting antibody responses to FHA, pertactin, and perhaps fimbriae-2 is problematic. In a previous study, the ELISA antibody responses to the various *B. pertussis* antigens were examined in 23 subjects (children) with culture-confirmed *B. parapertussis* infections [20]. In this group, 4 (17%) did not have an IgA or IgG antibody response to PT, FHA, pertactin, or fimbriae-2. Of the 19 responders, all had a significant increase in titer of antibody to FHA, 15 (79%) had a response to pertactin, 8 (42%) had a response to fimbriae-2, and, surprisingly, 3 (16%) had a response to PT. Since *B. pertussis*-induced disease was prevalent during the time of this study, it was assumed that the PT responses and perhaps the fimbriae-2 responses were due to mixed infections and not to cross-reacting antibodies.

In a recent study of soldiers with prolonged afebrile cough illnesses, it was found that illness was associated with high ELISA titers of antibody to FHA as well as high *C. pneumoniae* antibody titers and the presence of *M. pneumoniae* IgM antibody [21]. Since the study subjects with high titers of antibody to FHA did not have concomitantly high titers of antibody to PT or pertactin, it was concluded that these subjects did not have infections due to *B. pertussis* or other *Bordetella* species. The data were suggestive of cross-reacting antibodies to *M. pneumoniae, C. pneumoniae, or an unidentified infectious agent*.

In regard to the above discussion, the data in figures 1–4 are of interest. Subject 30 (figure 1) had strong evidence of a *B. pertussis* infection but no identified illness, whereas subject 800 had similar laboratory evidence and had a prolonged cough illness compatible with pertussis. In contrast with subjects 30 and 800, subject 632’s serological pattern suggested a *B. parapertussis* or other *Bordetella* infection. The single non–PT antibody re-
sponses seen in subjects 155, 180, and 303 (figure 2) suggest other *Bordetella* infections or responses to other unidentified agents, and subject 769 may have had a *B. pertussis* infection followed by another *Bordetella* infection or cross-reacting antibody to *M. pneumoniae*, *C. pneumoniae*, or an unidentified agent.

The antibody-prevalence patterns in study subjects with and without serological evidence of infection presented in figures 3 and 4 are revealing. Among the 52 study subjects without identified infections, antibody to FHA was high throughout the observation period, whereas *B. pertussis*-specific antibody (IgA and IgG antibody to PT) remained low. After infection, the pattern of IgG antibody to PT differed from the other responses. These observations suggest that probably multiple exposures to a number of antigens resulted in prolonged and continuous high titers of antibody to FHA and perhaps to pertactin. In contrast, antibody to PT decreases rapidly because it is stimulated only by *B. pertussis* exposure. Since recent data indicate that antibody to pertactin is most important in preventing pertussis [30, 31], it is possible that some protection against *B. pertussis* infection in adults is due to cross-reacting antibodies and not to antibodies resulting from a specific *B. pertussis* infection.

In this study there were no reported symptomatic features that distinguished study subjects with serological evidence of *Bordetella* infection on clinical grounds. Though study nurses did not seek histories for presence of the characteristic "whoop" as described in children, none was spontaneously reported. Symptomatic cough illness was more frequently observed in individuals with serological increases in titer of antibody to PT or to PT and/or fimbriae-2 (definite or probable adult *B. pertussis* infections) than it was in those with increases in antibody to only FHA or pertactin. Since other *Bordetella* infections are often symptomatic, these observations suggest that some of the titer increases to FHA and pertactin are due to other noncough-illness-causing agents.

As discussed above, there are limitations to the data generated in this extensive study. Nevertheless, the data support the results of previous studies involving adults. With more specific diagnostic criteria (increase in titer of antibody to PT or to PT and/or fimbriae-2), adults of the age group studied had frequent *B. pertussis* infections. Between 3.3% and 8% of the population had infections each year, and between 37.5% and 50% were symptomatic.

Our data suggest that elderly individuals may suffer morbidity with *B. pertussis* infection, and since as grandparents they can transmit infection to nonimmunized infants, this group as well as adolescents and younger adults should be vaccinated when adult-formulated acellular pertussis vaccines become available.

References

20. Stehr K, Cherry JD, Heiningger U, et al. A comparative efficacy trial in Germany in infants who received either the Lederle/Takeda acellular pertussis component DTP (DTaP) vaccine, the Lederle whole-cell component DTP vaccine, or DT vaccine. Pediatrics 1998; 101:1–11.
25. Jackson LA, Cherry JD, Wang SP, Grayston JT. The frequency of serologic
evidence of *Bordetella* infections and mixed infections with other respiratory pathogens in university students with cough illnesses. Clin Infect Dis 2000;31:3-6 (in this issue).


