MAJOR ARTICLE

Bordetella Pertussis Infections in Vaccinated and Unvaccinated Adolescents and Adults, as Assessed in a National Prospective Randomized Acellular Pertussis Vaccine Trial (APERT)

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Background. Acellular pertussis (aP) booster immunizations have been recommended for adolescents and older persons to enhance long-term protection and to possibly reduce community transmission of infections.

Methods. This was a multicenter, randomized, double-blind vaccine trial in which one-half of the subjects received aP vaccine and one-half received hepatitis A vaccine (control subjects). All subjects were observed for almost 2 years for cough illnesses, and all underwent microbiologic and serologic studies for detection of pertussis infection. Immunoglobulin G (IgG) and immunoglobulin A (IgA) antibodies to pertussis toxin, filamentous hemagglutinin, pertactin, and fimbriae 2/3 were measured by enzyme-linked immunosorbent assay in serum samples obtained 1 and 12 months after immunization. Infection rates were determined with a variety of serologic criteria for control and vaccinated subjects. The incidence of prolonged cough illness was ascertained for subjects with and subjects without serologic evidence of infection.

Results. Infection rates among control subjects are particularly representative of those in nonimmunized adults. Among control subjects, 0.4%–2.7% had increases in pertussis antibody of various types and degrees over 1 year, and 20%–46% had prolonged cough illnesses during this interval. Pertussis toxin antibody had the greatest specificity for detecting increases in antibody levels. Asymptomatic infections were ~5 times more common than clinical illnesses that met a strict clinical and microbiologic case definition. Relative to control subjects, aP-immunized subjects may have fewer increases in the antibody level (i.e., infections), especially for antibodies to fimbriae 2/3 (an antigen not in the vaccine).

Conclusions. Pertussis infections in older persons are largely asymptomatic. aP boosters confer protection for adolescents and adults against symptomatic pertussis and likely confer protection against mild and asymptomatic infections, and use of boosters may reduce transmission to others, especially infants.

Pertussis vaccines have been in routine pediatric use for half a century and have brought about a dramatic decrease in the incidence of childhood whooping cough [1]. Nonetheless, the control of pertussis infection is not optimal, because neither vaccination nor natural infection induces long-lived immunity [1–8]. Most cases of pertussis occur in incompletely immunized infants and older persons with waning immunity; the later group often serves as the source of transmission to children [1, 3, 8–17]. Infections in adolescents or adults can be classic in presentation, mildly symptomatic, or asymptomatic. Increasing proportions of reports of pertussis cases in the United States involve adolescents and adults [1, 3, 5, 8–19]. On the basis of prospective

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studies with active surveillance, the estimated annual incidence of clinical pertussis in persons >15 years of age is ~370–500 cases per 100,000 person-years, representing at least 1 million cases of pertussis in the United States each year in this older age group [18, 19].

The diagnosis of pertussis in older individuals is problematic because of the lack of specific clinical criteria, insensitivity of culture and PCR, and the limited availability of standardized serologic tests and criteria for diagnosis [1, 5, 10, 13, 17]. Consequently, most pertussis infections in adolescents and adults are incompletely detected or reported and are often only suspected in families when they occur in association with whooping cough in children.

This study is part of a National Institutes of Health–sponsored multicenter, prospective, randomized acellular pertussis vaccine (aP) efficacy trial in adolescents and adults (APERT) reported elsewhere [19]. The article about efficacy focused on the prevention of disease with prolonged cough illness, whereas this article looks primarily at serologic evidence of infection (symptomatic and asymptomatic) during the first year after receiving aP or control immunization and associates the occurrence of prolonged cough during this interval with infected and uninfected status. Our intent is to define, among unimmunized control subjects, a yearly infection rate and to characterize the proportion of those infections that include prolonged coughs. A similar analysis is attempted for aP-vaccinated subjects, but this analysis is more difficult to perform because of vaccine exposure.

METHODS

Subject population and vaccines. During the period of July 1997 through December 1999, the National Institutes of Health (National Institute of Allergy and Infectious Disease/Division of Microbiology and Infectious Disease) sponsored a prospective, randomized, double-blind clinical trial involving adolescents and adults conducted at 8 sites in the United States. A total of 2781 healthy 15–65-year-old subjects were enrolled and randomized equally to receive a single intramuscular dose of either aP or hepatitis A vaccine (control subjects). Additional details are provided elsewhere [19].

Subjects received a single 0.5-mL intramuscular dose of either HAV (Havrix, 720 ELISA European Units) or a tri-component aP vaccine; both vaccines were provided by GSK. The aP was formulated to contain 8 μg of pertussis toxin (PT), 8 μg of filamentous hemagglutinin (FHA), and 2.5 μg of pertactin (PRN; without diphtheria or tetanus toxoid components)—approximately one-third of the content of the licensed pediatric aP vaccine. The vaccines were visually indistinguishable, and study groups were blinded.

Serum specimens and cough illness. Blood specimens were obtained from all subjects just before immunization and at 1 and 12 months after immunization. Additional specimens were obtained for serologic testing with each purported illness [19], but data are not included in this report, except to estimate expected antibody decay rates [19, 20]. Phone calls were made to all study subjects every 2 weeks for the duration of the study to ascertain cough illnesses. Subjects with cough illness lasting ⩾5 days were evaluated, as described elsewhere [19].

Serologic studies. IgA and IgG antibodies to PT, FHA, PRN, and fimbriae 2/3 (FIM) were quantitated by ELISA using a method modified slightly from that described elsewhere [3, 7, 13, 19–25]. Details of the assay methods and other serologic evaluations have been reported elsewhere [3, 7, 13, 19–25]. Assays were validated using US Food and Drug Administration reference serum panels. One panel of 18 serum specimens was used to establish minimum level of detection and assay reproducibility. Blood samples were obtained from another panel of 40 healthy subjects daily over 4 sequential days to establish reproducibility and the limit of quantitation. These assays evaluated intra-assay variability (i.e., same assay and same day) and interassay variability (i.e., between assays on sequential days). On the basis of these standardizations, the minimum level of detection for each IgG or IgA pertussis antibody was established at 2 ELISA Units (EU)/mL. The limit of quantitation for IgG and IgA PT was 6 EU/mL, and for IgG and IgA FHA, PRN, and FIM antibody assays, it was 8 EU/mL. Sequential (paired) serum samples evaluated for each subject were run simultaneously in the same assay. IgG and IgA pertussis antibody results were reported in subjects in both study groups as a rate of seropositivity, which was defined as the number of seropositive subjects who met a specified antibody criteria divided by the number with antibody assessments.

Statistical analyses. Independent analyses were performed for each study group. Because nonimmunized subjects did not have vaccine-induced immunity, the observed changes in *Bordetella pertussis* antibody levels during the study period were assumed to be due to interval natural *B. pertussis* exposure, exposure to other organisms with cross-reacting antigens, or polyclonal responses. The ratio of the 12-month to 1-month antibody levels was evaluated.

The sensitivity analysis of different serologic criteria for *B. pertussis* infection involved ascertainment of the following increases in *B. pertussis* antibodies: (1) a 12-month titer greater than that at the 1-month level (i.e., ratio >1), (2) a ratio of 2, 3, or 4 times greater, (3) a value greater than the 95th percentile of the standard normal distribution (i.e., log ratio of the 12-month to 1-month value), and (4) a value greater than the 99th percentile of the standard normal distribution of the log ratio. Either IgG or IgA antibody levels to any antigen or combinations thereof were used to further categorize antibody increases over the 11-month period. Categories 3 and 4 are single titer–based ascertainments and have been used in previous

Table 1. Number and rate of pertussis antibody increases among nonvaccinated subjects, by various serologic criteria observed during the first year of the APERT Study.

IgG or IgA pertussis antibody	No. of paired subject assays performed at 1 and 12 months	No. (%) of subjects with interval antibody increases over an 11-month period[a]		No. (%) of subjects with high titers 1 year after enrollment[b]	
		2-fold	4-fold	>95th percentile	>99th percentile
PT	1228	16 (1.3)	13 (1.1)	15 (1.2)	13 (1.1)
PRN	686	14 (2.0)	9 (1.3)	13 (1.9)	7 (1.0)
FHA	686	12 (1.8)	10 (1.5)	16 (2.3)	8 (1.2)
FIM	699	11 (1.6)	9 (1.3)	10 (1.4)	7 (1.0)
PT plus any other antibody	700	5 (0.7)	4 (0.6)	5 (0.7)	4 (0.6)
PRN plus FHA[c]	686	4 (0.6)	3 (0.4)	5 (0.7)	3 (0.4)
PRN plus FIM	685	5 (0.7)	4 (0.6)	5 (0.7)	3 (0.4)
FHA plus FIM	685	6 (0.9)	6 (0.9)	6 (0.9)	5 (0.7)
Increases in any of the antibodies above	1228	33 (2.7)	24 (2.0)	33 (2.7)	22 (1.8)

NOTE. FHA, filamentous hemagglutinin; FIM, fimbriae 2/3; PRN, pertactin; PT, pertussis toxin.

[a] To avoid false-positive results, the 12-month value needed to be twice the limit of quantitation to be considered a true increase.

[b] Determined on the basis of the Gaussian distribution of all of the 12-month pertussis serologic test results.

[c] Marker for *Bordetella parapertussis* infection; excludes PT.

studies with independent controls; thus, they are included here for comparison [3, 22, 26–29, 31].

It is more difficult to distinguish infection-related pertussis antibody changes in the aP-vaccinated group (the vaccine includes PT, FHA, and PRN antigens); thus, it is not possible to use the same serologic criteria as that used for the unimmunized control subjects, who have not received such antigenic exposures by vaccination. The subjects in the aP group had high vaccine-induced antibody levels that decay over time [20]. Serologic evidence of infection among aP-immunized subjects was assessed by differences between observed and expected titers at 1 year. In vaccinated subjects, the criteria for an interval infection takes into account differences between observed and expected titers based on an expected decay of vaccine-induced antibody, as estimated from observed peak antibody levels 1 month after immunization, the observed antibody decay rate, and the time after immunization. The determination of expected antibody decay was based on the results for the initial 101 vaccinated subjects, as described elsewhere [20]. For the vaccinated subjects, we evaluated a ratio of the observed 12-month antibody levels to that predicted for a 12-month value on the basis of expected antibody decay from the 1-month value. These categories were categorized as follows: (1) >2 times, on the basis of a minimal decay rate; (2) >2 times, on the basis of an average decay rate; (3) >3 times, on the basis of an average decay rate; or (4) >4 times, on the basis of an average decay rate. Finally, individuals were also considered to have had an interval pertussis exposure if their 12-month antibody level was greater than the 1-month antibody level by an amount greater than the coefficient of variation for the limit of quantitation (120%). These categorizations were evaluated for both IgG and IgA PT antibodies, which had the most specific antibody changes and also the greatest rate of decay.

Finally, for each of the serologic response criteria described above, a count of the number of individuals who developed a cough illness of ⩾5, ⩾14, and ⩾21 days' duration during the 11-month period of surveillance was prospectively determined.

RESULTS

Table 1 shows the rates of antibody increases over an 11-month period in the unimmunized control group, a surrogate for the general population. Several criteria for IgG or IgA antibody increases were categorized in 4 ways, as shown in the 4 columns. Two- and 4-fold antibody increases are shown in the first 2 columns, and serum antibody levels observed at 1 year that were greater than the 95% and 99% upper bound for the distribution of antibody levels before immunization (self controls) are shown in the last 2 columns. Seroconversion rates for each antigen (PT most specific for *B. pertussis*) or groups of antigens ranged from 0.4% to 2.7%. Regardless of the criteria used, there was surprisingly little variation in the rate of subjects with antibody increases suggestive of recent infection. We conclude that the infection rate among adult subjects who had not been recently immunized is ~1% over an 11-month period (range, 0.4%–2.7%).

Because of the presence of vaccine-induced antibodies, one must take care not to underestimate natural infection rates among immunized subjects, because antibody changes might be obscured by antibodies induced by vaccine. Therefore, the

Table 2. Pertussis toxin (PT) antibody changes among 1283 vaccinated subjects, by various serologic criteria.

Serologic criterion	No. (%) of infected patients, by antibodies to PT		
	IgG	IgA	IgG or IgA
One-year postvaccination levels greater than 1-month postvaccination level	5 (0.41)	6 (0.47)	10 (0.78)
One-year postvaccination level 2-fold greater than expected titer using average decay rate from peak postvaccination titer[a]	33 (2.57)	6 (0.47)	37 (2.88)
One-year postvaccination level 3-fold greater than expected titer using average decay rate from peak postvaccination titer[a]	3 (0.23)	0 (0)	3 (0.23)
One-year postvaccination level 4 fold greater than expected titer using average decay rate from peak postvaccination titer[a]	0 (0)	0 (0)	0 (0)

[a] Predicted value based on average decay rate in a cohort of subjects from whom 5 serum samples had been collected [20].

PT antibody criteria in table 2 for vaccinated subjects are analyzed differently and with more complexity than the analysis shown in table 1 for unimmunized subjects. As described in the Methods, 4 different serologic criteria were employed to evaluate differences between observed and expected titers for each vaccinated subject. Only 6 vaccinated subjects (0.47%) had IgG or IgA PT titers at 1 year that were equal to or higher than the titers 1 month after immunization. Another criterion for an unexpectedly high PT titer at 1 year after immunization was based on there being an observed titer at 12 months higher than would have been predicted from decay of the peak antibody level at 1 month after immunization. Although 33 aP-vaccinated subjects (2.57%) had observed titers that were ⩾2-fold higher than that predicted from the peak (determined on the basis of an average decay rate), most of these were barely at the 2-fold cutoff. Only 3 (0.23%) of 1283 vaccinated individuals had evidence of a high PT antibody level with a 3-fold cutoff. None of the vaccinated subjects had increases that were 4-fold higher than predicted, and none had persistently high titers (without decay). If the minimum rate of antibody decay had been used to estimate the predicted titers, as opposed to the mean rate, none of the immunized subjects had evidence of infection.

Shown in table 3 are the proportions of subjects, by study group, with increases in antibody levels during the first year of the study. For all aP vaccine antigens (PT, FHA, and PRN), antibody increases over time were seen significantly less often among vaccinated subjects than among control subjects ($P <$ .001), suggesting that interval natural infections were less common among vaccine recipients. However, the vaccine group that received a dose of vaccine with PT, FHA, and PRN had significantly higher antibody increases at 1 month and for the following 11 months, relative to nonimmunized controls. The antibody increases were greatest for IgG, compared with IgA, for each antigen. Of particular interest between the study groups are the relative differences in FIM antibody (a pertussis antigen not contained in the vaccine) shown in the last 3 rows of table 3. FIM antibody increases were significantly less common in the aP group ($P = .046$). This trend (which was marginally significant) suggests that infections may have been less common among vaccinated subjects.

Table 4 shows the incidence and duration of cough illnesses (lasting ⩾5, ⩾14, or ⩾21 days) during the 11-month period of observation for vaccinated and unvaccinated subjects. These subjects were further categorized by those meeting and not meeting the various pertussis serologic criteria detailed above.

Table 3. Comparison of increases pertussis antibody levels among vaccinated and unvaccinated subjects in specimens obtained at months 1 and 12.

Antibody, criterion	No. of subjects with finding/no. tested (%)		P[a]
	Vaccinated subjects	Unvaccinated control subjects	
IgG or IgA PT			
Any increase	10/1222 (0.82)	49/1228 (3.99)	<.0001
2-fold increase	0/1222 (0)	16/1228 (1.30)	<.0001
4-fold increase	0/1222 (0)	13/1228 (1.06)	.0002
IgG or IgA FHA			
Any increase	1/276 (0.36)	93/686 (13.56)	<.0001
2-fold increase	0/276 (0)	12/686 (1.75)	.02
4-fold increase	0/276 (0)	10/686 (1.46)	.07
IgG or IgA PRN			
Any increase	10/276 (3.62)	118/686 (17.20)	<.0001
2-fold increase	0/276 (0)	14/686 (2.04)	.014
4-fold increase	0/276 (0)	9/686 (1.31)	.067
IgG or IgA FIM			
Any increase	39/290 (12.41)	123/699 (17.60)	.046
2-fold increase	1/290 (0.34)	11/699 (1.57)	.20
4-fold increase	0/290 (0)	9/699 (1.29)	.065

NOTE. As detailed elsewhere [20], the pertussis toxin (PT), filamentous hemagglutinin (FHA), and pertactin (PRN) antibody levels were significantly higher among pertussis vaccinees than among unvaccinated control subjects, because these antigens were vaccine components. However, there is a trend shown in the last 3 rows for fimbriae 2/3 (FIM; an antigen not in the vaccine) to suggest that infections may be more common among control subjects than among vaccinated subjects.

[a] Determined by Fisher's exact test.

Table 4. Frequency of cough illness lasting ⩾5, ⩾14 or ⩾21 days among subjects with and without evidence of pertussis infection among vaccinated and unvaccinated subjects, according to various serologic criteria, at 1–12 months of follow-up.

Study group, specific serologic criterion at follow-up[a]	No. (%) of subjects							
	Met specified pertussis serologic criteria				Did not meet specified pertussis serologic criteria			
	Infected subjects	Duration of cough illness			Uninfected patients	Duration of cough illness		
		⩾5 days	⩾14 days	⩾21 days		⩾5 days	⩾14 days	⩾21 days
No pertussis vaccination								
PT level increase								
2-fold	16 (1.3)	7 (44)	6 (38)	6 (38)[b]	1212 (98.7)	399 (33)	298 (25)	201 (17)[b]
4-fold	13 (1.1)	6 (46)	6 (46)	6 (46)[b]	1215 (98.9)	400 (33)	298 (25)	201 (17)[b]
PT level >99th percentile at 12-month follow-up	13 (1.1)	6 (40)	6 (40)	6 (40)[b]	1215 (98.9)	400 (33)	298 (25)	201 (17)[b]
Increase in PT plus any other antibody								
2-fold	5 (0.7)	1 (20)	1 (20)	1 (20)	695 (99.3)	222 (32)	159 (23)	113 (16)
4-fold	4 (0.6)	1 (25)	1 (25)	1 (25)	696 (99.4)	222 (32)	159 (23)	113 (16)
Level of PT plus any other antibody >99th percentile at 12-month follow-up	4 (0.3)	1 (25)	1 (25)	1 (25)	1224 (99.7)	405 (33)	303 (25)	206 (17)
Any increase in level of PRN plus FHA, but not in PT level	3 (0.4)	1 (33)	1 (33)	1 (33)	683 (99.6)	220 (32)	158 (23)	113 (17)
Any increase in level of PT, FHA, PRN, or FIM	22 (1.8)	8 (36.4)	7 (31.8)	7 (31.8)	1206 (98.2)	398 (33)	297 (25)	200 (17)
Pertussis vaccination								
PT level greater than antibody value predicted using average decay rate								
2-fold greater	37 (2.9)	18 (49)	15 (41)	13 (35)[b]	1246 (97.1)	450 (36)	348 (28)	236 (19)[b]
3-fold greater	3 (0.2)	0 (0)	0 (0)	0 (0)	1280 (99.8)	468 (37)	363 (28)	249 (19)
4-fold greater	0 (0)	0 (0)	0 (0)	0 (0)	1283 (100)	468 (36)	363 (28)	249 (19)
PT level 1 year after vaccination greater than level 1 month after vaccine	10 (0.78)	5 (50)	5 (50)	5 (50)	1273 (99.2)	463 (36)	358 (28)	244 (19)

NOTE. FHA, filamentous hemagglutinin; FIM, fimbriae 2/3; PRN, pertactin; PT, pertussis toxin.

[a] Serologic categories for each study group are explained in the Methods section.

[b] A statistical comparison of the frequency and duration of cough between those with or without pertussis serologic criteria is shown for the 3 time intervals (⩾5 days, ⩾14 days, and ⩾21 days) ($P < .05$, by χ^2 test for homogeneity).

Among nonimmunized control subjects, there was a significantly higher proportion of subjects with cough illnesses lasting ⩾21 days among subjects who had pertussis serologic evidence of infections relative to those who did not meet any diagnostic pertussis serologic criteria. This was clearest for those with PT antibody responses (38% and 46% had prolonged cough that met PT serologic criteria, compared with 17% who did not meet the criteria). A similar observation was made in the vaccine group for those with a 2-fold PT antibody response (35% of those with prolonged cough vs. 19% of those without serologic evidence). There was no significant difference for subjects with a duration of cough illness of <21 days.

DISCUSSION

Epidemiologic studies of pertussis infections in adolescents and adults are fraught with difficulties. Relative to primary infections in children, older individuals seem to have fewer severe infections and a greater number of asymptomatic infections, and their infections are more difficult to prove. Diagnostic clinical criteria are nonspecific, and cultures and PCR are rarely available or performed early in illness [3, 5, 8, 13, 17, 22, 26–31]. Therefore, findings regarding most infections in older persons must be ascertained serologically. For this study of infection rates, we assessed IgG and IgA antibodies to PT, FHA, PRN, and FIM by ELISA over the first year of the APERT trial. IgG or IgA antibodies to PT were most helpful and specific for *B. pertussis*, because it is a toxin unique to *B. pertussis*. It also decays at the greatest rate [20]. Because older individuals are partially immune as a result of prior immunization or natural infection, it is difficult to distinguish new infections from prior immunity unless serum samples are obtained before or early in the course of illness, so that changes in antibody levels can be demonstrated. There are also nonspecific patterns of increases in antibody levels that are presumably associated with other organisms with similar antigens (especially with antibodies to PRN and FHA) or polyclonal responses. There are differences in decay of *B. pertussis* antibodies to different antigens, and there are accentuated responses associated with prior immunologic priming (not observed in infants).

There have been several types of earlier studies of pertussis

in older individuals: cough illness etiology studies [3, 8, 18, 22, 26–31], surveillance studies of reported cases [9–12, 16, 17], secondary attack rate and outbreak studies [13, 14, 16], and serologic studies of various cohorts of subjects [23, 24, 32, 33]. These studies have attempted to estimate the incidence of infection and disease, but they have intrinsic methodologic limitations, including small unrepresentative samples, lack of representative control subjects, incomplete case ascertainment or subject follow-up, lack of well-controlled validated serologic methods, and lack of sequential prospective serologic evaluations for prolonged periods of time.

Our study is unique in several respects, because it afforded us the opportunity to prospectively evaluate infection and disease rates in a national cohort of adolescent and adult subjects (randomized immunized and nonimmunized groups) [19–21]. To ascertain whether infection and disease were present, we employed microbiologic, serologic, and clinical end points (i.e., duration of cough illness) and used a variety of serologic case definitions. Because there are no defined serologic diagnostic criteria, we performed a sensitivity analysis to observe trends with different infection serologic criteria for PT, FHA, PRN, and FIM antibodies. All assays were carefully standardized to minimize ascertainment of false-positive results. Each subject serves as his or her own control subject, and differences between randomized, nonimmunized subjects and immunized subjects could also be evaluated. In some past serologic studies, the seropositivity of presumed cases has been arbitrarily ascribed to those with high antibody titers and not on the basis of observed changes in their antibody titers. For example, such cutpoints have been selected as those greater than the 95% or 99% upper bound of the confidence interval for some distribution of titers in an unrelated healthy control group [22, 29, 33, 34]. Because PT is specific for *B. pertussis,* antibodies to this antigen (particularly IgG) provide the greatest diagnostic specificity and sensitivity.

As shown in table 1, for unimmunized subjects, the annual infection rate (symptomatic and asymptomatic) is ~1% (range, 0.4%–2.7%). As previously reported for this study, the incidence of symptomatic disease in persons aged 15–65 years is 370–450 cases per 100,000 persons per year [19]. Therefore, there are ~5 asymptomatic or clinically insignificant infected subjects for every classic case of clinical pertussis.

One must be more cautious in interpreting the data on immunized subjects (tables 2–4), which are not directly comparable to the data from nonimmunized control subjects. We used several different serologic criteria to identify unexpected high levels of antibody to PT, FHA, PRN, or FIM among immunized subjects in the year after immunization. An unexpected high titer was identified by the difference between an observed and predicted titer extrapolated from the peak postimmunization titer, the observed antibody decay rate [20], and the time since immunization. With conservative criteria, we could distinguish very few immunized subjects that had antibody titers at 1 year that were greater than or near the peak 1-month postimmunization titer. There were also few that had titers that, at 1 year, remained higher than one would have predicted by decay alone. Thus, one might conclude that there were fewer interval infections among aP-vaccinated subjects relative to unimmunized control subjects, but this conclusion cannot be made with complete assurance. Additionally, the only *B. pertussis* antigen that is not included in the vaccine (FIM) had antibody levels that were marginally less frequent among aP-vaccinated subjects than among control subjects ($P = .046$), further suggesting fewer natural infections in vaccinees. Given the differences in serologic criteria of infection used between the 2 study groups, we did not attempt to calculate a vaccine efficacy for the prevention of infection.

An additional observation of interest was that the incidence and duration of cough illness was greater in individuals with serologic evidence of *B. pertussis* infection (table 4). It also appeared that prolonged cough illnesses were more common among control subjects than among immunized subjects, at least for most of the case definitions.

We observed no relationship between antibody levels or antibody decay rates and subject occupation, season, region, or smoking status [19–21], suggesting that infection rates are not influenced by these factors.

The incidence of *B. pertussis* infection in adolescents and adults appears to be ~1% per year, and this infection risk is greatest among those with cough illnesses with a duration of ⩾21 days. There seemed to have been ~5 cases of asymptomatic or clinically insignificant infections for every case that met the primary symptomatic case definition. Some of these infections might be an important source of transmission in the community, particularly for young infants who have less immunity and who experience more serious illness. It is hoped that the immunization of adolescents and adults will provide herd immunity and thereby reduce infections and transmission of *B. pertussis* in the community. Ultimately, this may be the best way to further reduce disease burden in all age groups.

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