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Efficacy of an Acellular Pertussis Vaccine among Adolescents and Adults

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ABSTRACT

BACKGROUND

Pertussis immunization of adults may be necessary to improve the control of a rising burden of disease and infection. This trial of an acellular pertussis vaccine among adolescents and adults evaluated the incidence of pertussis, vaccine safety, immunogenicity, and protective efficacy.

METHODS

Bordetella pertussis infections and illnesses were prospectively assessed in 2781 healthy subjects between the ages of 15 and 65 years who were enrolled in a national multicenter, randomized, double-blind trial of an acellular pertussis vaccine. Subjects received either a dose of a tricomponent acellular pertussis vaccine or a hepatitis A vaccine (control) and were monitored for 2.5 years for illnesses with cough that lasted for more than 5 days. Each illness was evaluated with use of a nasopharyngeal aspirate for culture and polymerase-chain-reaction assay, and serum samples from patients in both acute and convalescent stages of illness were analyzed for changes in antibodies to nine *B. pertussis* antigens.

RESULTS

Of the 2781 subjects, 1391 received the acellular pertussis vaccine and 1390 received the control vaccine. The groups had similar ages and demographic characteristics, and the median duration of follow-up was 22 months. The acellular pertussis vaccine was safe and immunogenic. There were 2672 prolonged illnesses with cough, but the incidence of this nonspecific outcome did not vary between the groups, even when stratified according to age, season, and duration of cough. On the basis of the primary pertussis case definition, vaccine protection was 92 percent (95 percent confidence interval, 32 to 99 percent). Among unimmunized controls with illness, 0.7 percent to 5.7 percent had *B. pertussis* infection, and the percentage increased with the duration of cough. On the basis of other case definitions, the incidence of pertussis in the controls ranged from 370 to 450 cases per 100,000 person-years.

CONCLUSIONS

The acellular pertussis vaccine was protective among adolescents and adults, and its routine use might reduce the overall disease burden and transmission to children.

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BORDETELLA PERTUSSIS INFECTS THE human respiratory tract and in nonimmune persons causes whooping cough, a severe illness associated with prolonged cough.^{1,2} The severity of illness varies with age, immune status (prior immunization or infection), and probably such factors as the extent of exposure and the virulence of the organism. Disease risk and severity are greatest in unimmunized infants.³⁻⁵ During the past 50 years, routine pediatric pertussis immunization has dramatically decreased the pediatric disease burden.^{1,2} In the United States, the annual incidence of pertussis fell from 157 per 100,000 persons in the prevaccine era to less than 1 per 100,000 persons; mortality was even more dramatically reduced.⁶ Nonetheless, pediatric immunization has not decreased the incidence of disease in older persons or the occurrence of outbreaks, nor has it eliminated the transmission of infections to unimmunized children.

Infections among adolescents and adults result from waning immunity, since immunization or infection does not induce long-lived immunity. Infections can be asymptomatic, mildly symptomatic, or classic in presentation.¹ Pertussis vaccines have not been recommended for persons older than six years of age; consequently, pertussis continues to circulate among older persons, which creates a source of contagion for young children.⁷⁻¹³ During the 1990s, both the number and the proportion of reported pertussis cases among adolescents and adults more than doubled in the United States and Canada.^{5,14} Most adult cases are not suspected, detected, or reported, and the possibility of a case of pertussis is usually considered only when it occurs in association with classic whooping cough in children.^{1,7-10,13} Many factors contribute to the failure to detect pertussis, including the lack of clinical awareness, the lack of availability and insensitivity of culture and polymerase-chain-reaction (PCR) assay, a lack of standardized serologic testing for pertussis, the difficulty of obtaining appropriate specimens, and the absence of clear serologic diagnostic criteria.

Component vaccines that combine diphtheria and tetanus toxoids with acellular pertussis are safe and effective in children and are routinely used worldwide.^{1,2} The safety and immunogenicity of several acellular pertussis vaccines have been evaluated in formulations with diphtheria and tetanus toxoids and have been shown to be safe and immunogenic.¹⁴⁻¹⁷ The adult vaccines have lower concen-

trations of acellular pertussis and diphtheria toxoids than do the pediatric vaccines, and two of these preparations have recently been licensed in the United States (www.fda.gov/cber).

The objectives of the Adult Pertussis Trial (APERT), which was sponsored by the National Institutes of Health (NIH), were to ascertain among adolescents and adults the clinical spectrum, incidence, and epidemiology of infection and disease, assess the safety of the acellular pertussis vaccine, characterize both natural and vaccine-induced immune responses, and (with the use of multiple outcome measures) assess the protective efficacy of an acellular pertussis vaccine. In this article, we focus on protective efficacy.

METHODS

STUDY POPULATION

Between July 1997 and December 1999, 2781 healthy subjects between the ages of 15 and 65 years were recruited at eight participating U.S. sites: Baylor College of Medicine, Houston; Cincinnati Children's Hospital, Cincinnati; Saint Louis University, St. Louis; the University of Maryland, Baltimore and College Park; the University of Rochester, Rochester, New York; Vanderbilt University, Nashville; the University of Pittsburgh, Pittsburgh; and the UCLA Center for Vaccine Research at Harbor-UCLA Medical Center, Torrance, California.

Subjects were ineligible if they had participated in other clinical trials, were immunocompromised, had chronic disease, had received pertussis vaccine within the previous five years, had received immune globulin therapy or blood products within the previous three months, had vaccine hypersensitivity, had received erythromycin or a related antibiotic recently, or had been diagnosed with pertussis within the previous five years. Women of childbearing age were tested for pregnancy and were required to use birth control for the month after vaccination.

STUDY DESIGN

This randomized, multicenter, double-blind, parallel-group, controlled trial was designed to evaluate subjects who had received a single intramuscular dose of either an acellular pertussis vaccine or a hepatitis A vaccine (control). Written informed consent was obtained from all participants. After recruitment and immunization, subjects were followed for up to 2.5 years with twice-monthly phone calls to ascertain all illnesses with cough. There were five

scheduled visits for blood sampling in addition to paired visits during acute illness and convalescence to obtain microbiologic and serologic evaluations for each illness lasting more than five days. All subject-months of observation were included; 94 percent of the subjects completed 12 to 17 months of follow-up, and 80 percent completed 18 to 24 months.

VACCINES AND BLINDING

Vaccines were manufactured by GlaxoSmithKline Biologicals. Each 0.5-ml dose of the three-component acellular pertussis vaccine (without diphtheria or tetanus toxoid) contained 8 µg of toxoided pertussis toxin, 8 µg of filamentous hemagglutinin, and 2.5 µg of pertactin — a dose whose pertussis-antigen content was approximately one third that of the acellular pertussis vaccine for children (Infanrix, GlaxoSmithKline). The hepatitis A vaccine (Havrix) contained hepatitis A virus (strain HM 175, 720 enzyme-linked immunosorbent assay [ELISA] units). The vaccines were visually indistinguishable and identically packaged and were administered intramuscularly with the use of standard techniques.

SAFETY ASSESSMENTS

Each subject was observed for 30 minutes after vaccination. Diary cards were used to record temperature and local or systemic adverse events for 14 days after vaccination. Telephone calls were also made, and purported reactions were referred for evaluation. Late reactions were assessed at the one-month and one-year follow-up visits. Serious adverse events and pregnancies were monitored for the entire study period. A safety monitor and a data monitoring and safety committee provided ongoing study oversight.

DETECTION OF ILLNESS AND MICROBIOLOGIC ASSESSMENT

All illnesses with cough of a duration of five days or more were ascertained by telephone surveillance every other week during the trial and by self-reporting by subjects. Each episode was evaluated clinically, serologically, and microbiologically (nasopharyngeal aspirate for culture and PCR assay by a method modified from Hallander et al.¹⁸). Cultures were processed as previously described,¹⁹ and throughout the trial, blinded evaluations of proficiency culture testing were conducted at each study site to validate results. PCR analysis was carried out at a centralized laboratory (UCLA Clinical Laboratory) with the use of primers PTP1 and PTP2 with methods previously described.²⁰⁻²² The sensitivity

of the assay was from 10 to 100 organisms per milliliter, and specificity and sensitivity were evaluated with the use of blinded controls, as well as with primers for β globin.²³

SEROLOGIC ASSESSMENTS

In all study subjects, blood specimens for antibody assays were obtained before immunization and one month and one year after vaccination. To assess decay of antibody to acellular pertussis antigens after vaccination, additional blood samples were obtained from the first 10 percent of subjects who were enrolled at each study site 6 and 18 months after vaccination.²⁴ In addition, for each episode of prolonged illness with cough, an acute-phase specimen was collected 5 to 14 days after the onset of cough, and a convalescent-phase specimen was obtained 21 to 45 days after the onset. Serum samples were stored at -70°C until the assays could be performed in a blinded manner in a central laboratory with the use of standardized procedures validated by the Food and Drug Administration (FDA). ELISA serologic assays were performed for IgG and IgA antibodies to pertussis toxin, filamentous hemagglutinin, pertactin, and fimbriae (types 2 and 3), as well as by microagglutination assay with the use of *B. pertussis* strain B 460.^{12,24-28} The sensitivity, reproducibility, and specificity were carefully assessed for each assay, and the lower limit of quantitation was used as the lower limit for assessment of the increases in titer in paired serum samples that were run in the same microtiter plates.²⁴

PERTUSSIS CASE DEFINITIONS

The primary pertussis case definition was established before the trial began and required the presence of illness with cough lasting 5 days or more that was clinically, microbiologically, and serologically evaluated within 14 days after onset and that occurred more than 28 days after vaccination. Confirmation required a positive culture, PCR analysis, or stringent serologic evidence of *B. pertussis* infection (an increase in the titer of antibody to pertussis toxin by a factor of two or more or a similar response to two other pertussis antigens). The primary and secondary case definitions are specified in Table 1.

STATISTICAL ANALYSIS

All patient-months of observation and prolonged (>5 day) episodes of illness with cough are included in rate analyses. Approximately 25 percent of

Table 1. Summary of Pertussis Case Definitions.*

| Case Definition | Illness with Cough Lasting >5 Days | Culture or PCR Assay | Timing of Serum Specimens | | Serologic Criteria for Pertussis Antibody Change | |
|-----------------|------------------------------------|----------------------|---|-----------------------------|--|------------------------------|
| | | | Acute-Phase Specimen | Convalescent-Phase Specimen | Primary Serologic Criteria† | Any Pertussis Antibody Rise‡ |
| Primary | Positive | Positive or negative | 5–14 days after the onset of illness | 21–42 days | Positive | Positive |
| Secondary | Positive | Negative | Within 6 mo before the onset of illness | 21–42 days | Positive | Positive |
| Tertiary | Positive | Negative | 5–14 days after the onset of illness | 21–42 days | Negative | Positive |
| Quaternary | Positive | Negative | Within 6 mo before the onset of illness | 21–42 days | Negative | Positive |

* The primary case definition was intended to be the most specific for pertussis and was specified in the protocol for the primary analysis of efficacy. Other less specific categories (which are listed as secondary, tertiary, and quaternary) have various intervals between paired blood specimens and various pertussis-antibody requirements. With the diagnostic stringency reduced, more potential cases (although with potentially more false positives) are seen in these other categories. Few studies to date have used factor changes in pertussis titers that are observed in paired serum samples for diagnostic criteria, since most studies have used antibody levels in convalescent-phase specimens for diagnosis.

† Serologic criteria for the primary case definition included an antibody increase by a factor of 2 or more between acute-phase and convalescent-phase specimens for pertussis toxin alone (IgG or IgA); or fimbriae (IgG or IgA) plus filamentous hemagglutinin (IgG or IgA); or fimbriae (IgG or IgA) plus pertactin (IgG or IgA); or filamentous hemagglutinin (IgG or IgA) plus agglutinins; or pertactin (IgG or IgA) plus agglutinins.

‡ Data show the increase by a factor of 2 or more in IgG or IgA antibodies to any single pertussis antigen (pertussis toxin, filamentous hemagglutinin, pertactin, or fimbriae) in serum specimens obtained before the onset of illness and those obtained after onset.

subjects had more than a single prolonged illness with cough (50 percent had none), but none had evidence of *B. pertussis* infection more than once during the trial. The comparisons of baseline characteristics between vaccine groups were performed with use of the chi-square test for categorical variables and t-test for numeric variables. The comparisons of outcomes of illness with cough between the two groups were performed with use of a two-tailed Fisher's exact test. Vaccine efficacy was calculated (as a percentage) as follows: $(1 - IR) \times 100$, where IR is the case incidence-rate ratio between the group that received acellular pertussis vaccine and the group that received hepatitis A vaccine. The estimate of vaccine efficacy was further adjusted for the duration of illness by means of multivariable Poisson regression analysis. This estimate was calculated with the use of a time-homogeneous Poisson model, and the 95 percent confidence interval was constructed with the use of the method for exact Poisson distribution available in LogXact 5 software.

RESULTS

A total of 1391 subjects were randomly assigned to receive the acellular pertussis vaccine, and 1390 subjects to receive the hepatitis A vaccine (controls). Subjects ranged in age from 15 to 65 years (average,

34.8) and included health care workers (32 percent), students (21 percent), and community volunteers (47 percent). Sixty-seven percent of the subjects were female; 71 percent were white. Demographic characteristics of the subjects in the two study groups were similar, and there was no meaningful difference in follow-up (Table 2, and Table 1 of the Supplementary Appendix, available with the full text of this article at www.nejm.org). The groups were similar in the types of preexisting medical conditions, history of smoking, and the age of household contacts; there were no recognized outbreaks or clusters of pertussis during the two-year study period. A total of 547 subjects withdrew during the trial, but most of these withdrawals occurred during the final six months of a trial extension period. All patient-months of follow-up were included in the analyses. The median duration of follow-up for all subjects was 22 months, with no difference between the groups.

VACCINE SAFETY

A total of 165 serious adverse events, as defined by established FDA criteria, occurred in 140 subjects, including 5 deaths, 14 cases of cancer, 1 emergency room visit, and 145 hospitalizations. A total of 86 serious adverse events occurred among 69 subjects in the acellular pertussis group and 79 among the

Table 2. Characteristics of Subjects in the Acellular Pertussis and Control Groups.*

| Characteristic | Acellular Pertussis Vaccine (N=1391) | Hepatitis A Vaccine (N=1390) |
|---|---|---------------------------------|
| Person-yrs of surveillance for illness with cough | 2421 | 2444 |
| Left study before 18 mo of follow-up — no. (%) | 288 (20.7) | 272 (19.6) |
| Male sex — no. (%) | 459 (33.0) | 466 (33.5) |
| White race — no. (%) | 978 (70.3) | 1002 (72.1) |
| Age — yr | 34.8±11.8 | 34.7±11.6 |
| Health care providers — no. (%) | 444 (31.9) | 453 (32.6) |
| Students — no. (%) | 291 (20.9) | 297 (21.4) |
| Previously received pertussis vaccine — no. (%) | 1008 (72.5) | 1017 (73.2) |
| Current smokers — no. (%) | 236 (17.0) | 238 (17.1) |

* Plus-minus values are means ±SD. There was no significant difference between the study groups in any characteristic.

71 control subjects. Four hospitalizations (two in each group) occurred within 14 days after immunization. None of the serious adverse events were deemed by the data monitoring and safety committee to be vaccine-related. Sixty pregnancies were reported during the trial (10 within two months after vaccination); none were associated with neonatal abnormalities.

ALL ILLNESSES WITH COUGH

A total of 2672 illnesses with cough that lasted five days or more were evaluated, yielding an average incidence of prolonged illness with cough of 0.63 episode per subject-year. Approximately half the subjects had no prolonged episodes of illness with cough, but 24 percent had two or more episodes. The mean duration of illness was 24 days (median, 18); 66 percent of the illnesses lasted more than 15 days, and 46 percent lasted more than 20 days. The peak seasonal incidence occurred between December and March, and there was little difference according to age. There was no significant difference in the incidence of prolonged illness between patients who received the acellular pertussis vaccine and controls, even after stratification according to season, age, study site, and duration of cough.

PRIMARY PERTUSSIS CASES

As shown in Table 3, there were 10 cases of pertussis that met the primary case definition; 4 of the cases were culture-positive, and 5 were PCR-positive. All the cases met the primary serologic case criteria. The five *B. pertussis* isolates were analyzed by pulsed-field gel electrophoresis at the Centers for Disease Control and Prevention, and all isolates were clonally

different. Two potential cases were ruled out by the data monitoring and safety committee after blinded consideration. One subject, whose illness was not included as a case, had a positive culture for *B. bronchiseptica* and a negative test for *B. pertussis* on PCR assay and serologic analysis. The other excluded case involved 16 days of illness with cough and a positive *B. pertussis* culture but a negative PCR assay (which was repeated blindly three times), and all serologic analyses were negative. The subject also had a consistent decline in all *B. pertussis* antibodies as assessed in 10 sequential serologic specimens over a period of two years. Although the isolate from this subject was confirmed to be *B. pertussis*, it was probably a laboratory contaminant, since other *B. pertussis* cultures were in the incubator at the same time. There was one vaccine failure (in Subject 10), with clinical illness indistinguishable from that in the controls, and this episode was confirmed by serologic analysis alone.

There were few distinguishing epidemiologic or clinical characteristics among the 10 primary cases and the other prolonged illnesses with cough of undefined cause. The pertussis cases tended to be in younger subjects ($P=0.027$), and the duration of cough was significantly greater than in subjects who had an illness with cough from other causes ($P<0.001$). Fever was significantly less common among those with pertussis than among others with a prolonged illness with cough ($P=0.047$). There were no significant differences in the rate of coryza, malaise, sore throat, chest congestion, chest pain, productive cough, or difficulty in breathing between the subjects with primary pertussis and those with prolonged illness with cough of undefined cause.

Table 3. Summary of Pertussis Cases Meeting the Primary Case Definition.*

| Subject No. | Study Group | Culture | PCR Assay | Ratio of Increase in Antibody Titer | | | | | | | |
|-------------|---------------------|----------|-----------|-------------------------------------|-----|---------------------------|-----|-----------|-----|----------|-----|
| | | | | Pertussis Toxin | | Filamentous Hemagglutinin | | Pertactin | | Fimbriae | |
| | | | | IgG | IgA | IgG | IgA | IgG | IgA | IgG | IgA |
| 1 | Control | Positive | Positive | 488 | 6 | 14 | 11 | 42 | 20 | 11 | 7 |
| 2 | Control | Positive | Positive | 323 | 38 | 80 | 196 | 157 | 109 | 76 | 147 |
| 3 | Control | Positive | Positive | 208 | 16 | 7 | 6 | 46 | 33 | 1 | 1 |
| 4 | Control | Positive | Positive | 4 | 5 | 5 | 16 | 60 | 20 | 5 | 2 |
| 5 | Control | Negative | Positive | 123 | 8 | 43 | 8 | 39 | 4 | 10 | 13 |
| 6 | Control | Negative | Negative | 2 | 1 | 3 | 1 | 3 | 2 | 2 | 2 |
| 7 | Control | Negative | Negative | 1 | 1 | 1 | 2 | 13 | 35 | 10 | 42 |
| 8 | Control | Negative | Negative | 24 | 7 | 7 | 6 | 25 | 4 | 1 | 7 |
| 9 | Control | Negative | Negative | 1 | 1 | 2 | 2 | 3 | 4 | 2 | 3 |
| 10 | Acellular pertussis | Negative | Negative | 3 | 3 | 1 | 1 | 1 | 1 | 1 | 1 |

* Data show the factor increase in antibody titers between the acute-phase specimen obtained approximately 5 days after the onset of illness and the 30-day convalescent-phase specimen. A factor of one represents no change in antibody titer.

VACCINE EFFICACY

As shown in Table 4, nine cases of pertussis in the control group and one in the acellular pertussis vaccine group met the primary case definition, yielding an overall vaccine efficacy of 92 percent (95 percent confidence interval, 32 to 99 percent) when adjusted for the duration of illness and 89 percent (95 percent confidence interval, 19 to 99 percent) when unadjusted for the duration of illness. Among cases that were confirmed by culture or PCR assay, five were in the control group and none were in the acellular pertussis vaccine group. When less stringent and less specific serologic secondary case definitions were employed, there was a trend toward lower vaccine efficacy. No additional cases were identified when a serum sample obtained before illness was evaluated (with serologic analysis performed within six months after the onset of illness) relative to the convalescent-phase sample. This was a secondary case definition for 681 subjects with such serum samples available, and it was thought to be more sensitive for the detection of early antibody increases (before the acute-illness specimen was obtained).

ESTIMATE OF DISEASE INCIDENCE

The incidence of pertussis is best assessed in the unimmunized control group. For the primary case definition, there were nine cases per 2444 persons during two years of observation, which yielded 370

cases per 100,000 person-years. When various pertussis case definitions were used (Table 1), the incidence among controls was estimated to be 370 to 450 cases per 100,000 persons per year.

PROPORTION OF PROLONGED ILLNESSES DUE TO *B. PERTUSSIS* INFECTION

In Table 5, the proportion of subjects meeting the primary case definition of pertussis in each study group is stratified according to duration of illness. Among the controls who had illnesses with cough of a duration of five days or more, 0.7 percent had evidence of *B. pertussis* infection. If illnesses of longer duration are considered, the proportion of subjects with *B. pertussis* infection increases sequentially to 5.7 percent for illnesses lasting more than 56 days. This finding is also shown in the adjusted values for efficacy in Table 4, since there is a higher vaccine efficacy in the prevention of pertussis when the analysis accounts for the duration of illness with cough.

DISCUSSION

Illness with cough that is prolonged (five days or more) is common and is associated with substantial morbidity and health care costs. During this trial, 63 percent of subjects had a prolonged illness with cough each year, with an average duration of 24.4 days. Such illnesses can have many causes, but

we found that *B. pertussis* accounted for 0.7 to 5.7 percent of the episodes, depending on the duration of cough. Risk factors for pertussis included adolescent age, an absence of fever, and a prolonged duration of cough. Immunization with the acellular pertussis vaccine prevented pertussis but did not decrease the overall burden of prolonged illnesses with cough, because pertussis constituted only a small proportion of these illnesses.

In adolescents and adults, it is difficult to establish the diagnosis of pertussis. Consequently, pertussis in older persons is rarely suspected, detected, reported, or well studied, and the disease burden is underappreciated. Furthermore, since older persons are partially immune from previous immunizations and natural infections, it is difficult to distinguish infections by serologic analysis without carefully assessing changes in antibody levels (changes in titer between the acute and convalescent phases). Some antibody levels wane quickly (especially pertussis toxin), and other antibodies lack specificity for pertussis (especially pertactin and filamentous hemagglutinin).^{13,24,25,29}

In this study, prospective data obtained from unimmunized controls over a period of 2.5 years are particularly useful to assess the incidence of pertussis in older age groups. On the basis of the primary case definition, the overall annual incidence was 370 cases of pertussis per 100,000 persons between the ages of 15 and 65 years. This rate is similar to that measured in another active surveillance study.³⁰ If these rates are extrapolated to the total U.S. population, almost a million pertussis cases per year occur in the United States in persons 15 years of age and older. This does not include asymptomatic or mildly symptomatic infections or infections that are identified with less specific diagnostic criteria.³¹ Data from this study that are not presented here showed that the number of asymptomatic patients (those with seroconversion) exceeded the number of symptomatic patients by a factor of 5 to 10. A high proportion of the disease burden is potentially preventable by vaccination, which might reduce community transmission.

Since immunity to pertussis wanes, the disease continues to occur in adolescents and adults in spite of high levels of administration of acellular pertussis vaccine in children.^{24,31,32} Therefore, the control of pertussis will probably require immunization of all adolescents and adults in addition to children. Two acellular pertussis vaccines formulated for adolescents and adults have recently been licensed.³³

Table 4. Vaccine Efficacy with Use of Various Case Definitions.*

| Pertussis Case Definition† | Acellular Pertussis Vaccine Group (2421 person-yr) | | Hepatitis A Vaccine Group (2444 person-yr) | | Vaccine Efficacy (95% CI) | |
|---|---|---|---|---|------------------------------|----------------|
| | No. of Cases by Category | Cumulative No. of Cases for Successive Categories‡ | No. of Cases by Category | Cumulative No. of Cases for Successive Categories‡ | Unadjusted | Adjusted§ |
| Primary | | | | | | |
| With positive culture or PCR assay only | 0 | 0 | 5 | 5 | 100 (NA)¶ | 100 (NA)¶ |
| With positive culture, PCR assay, and serologic analysis | 1 | 1 | 4 | 9 | 89 (19 to 99) | 92 (32 to 99) |
| Secondary | 0 | 1 | 0 | 9 | 89 (19 to 99) | 92 (32 to 99) |
| Tertiary | 3 | 4 | 1 | 10 | 60 (-40 to 91) | 67 (-9 to 90) |
| Quaternary | 1 | 5 | 1 | 11 | 54 (-42 to 88) | 63 (-11 to 87) |

* CI denotes confidence interval, PCR polymerase chain reaction, and NA not applicable.

† The primary case definition was intended to be the most specific for pertussis and was specified in the protocol for the primary analysis of efficacy. Other less-specific categories (which are listed as secondary, tertiary, and quaternary) have various intervals between paired blood specimens and various pertussis antibody requirements. With the diagnostic stringency reduced, more potential cases (although with potentially more false positive results) are seen in these other categories. Few studies to date have used factor changes in pertussis titers that are observed in paired serum samples for diagnostic criteria, since most studies have used antibody levels in convalescent-phase specimens for diagnosis.

‡ The numbers shown are those used to obtain the unadjusted and adjusted efficacy estimates.

§ Estimates are adjusted for the duration of cough.

¶ The 95 percent confidence interval could not be calculated because there were no observed cases among subjects receiving acellular pertussis vaccine.

Table 5. Incidence of Cases of Confirmed Pertussis According to the Duration of Illness with Cough.*

| Duration of Cough | Acellular Pertussis Vaccine | Hepatitis A Vaccine (Control) |
|-------------------|---|-------------------------------|
| | no. of cases/total no. of subjects with cough >5 days (%) | |
| >5 Days | 1/1388 (0.1) | 9/1284 (0.7) |
| >7 Days | 1/1301 (0.1) | 9/1197 (0.8) |
| >14 Days | 1/903 (0.1) | 8/794 (1.0) |
| >21 Days | 0/574 | 8/473 (1.7) |
| >28 Days | 0/363 | 6/308 (1.9) |
| >35 Days | 0/247 | 5/217 (2.3) |
| >42 Days | 0/172 | 5/138 (3.6) |
| >49 Days | 0/116 | 4/93 (4.3) |
| >56 Days | 0/83 | 4/70 (5.7) |

* Pertussis was diagnosed on the basis of the primary case definition.

Although the vaccines differ slightly in formulation, they are thought to have equivalent safety, immunogenicity, and protective efficacy. Both of these vaccines have one third the concentration of pertussis toxin that is found in the pediatric formulation; with a single dose, both vaccines induce an antibody response to *B. pertussis* antigens that is significantly greater in adults than that observed in infants at seven months of age after three doses of the two manufacturers' pediatric vaccines. Such data suggest that both of the newly licensed acellular pertussis vaccines will be efficacious among adolescents and adults. In this trial, the efficacy of a single dose of acellular pertussis vaccine among adolescents and adults (92 percent) supports this conclusion, because pertussis antigen components

of the monovalent vaccine that was used in this trial are identical to the acellular pertussis components in one recently licensed vaccine (Boostrix, Glaxo-SmithKline) and are similar to those in the other acellular pertussis vaccine (Adacel, Sanofi Pasteur). The duration of protection and prevention of secondary disease were not assessed.

Pertussis is one of the least well controlled illnesses that are preventable by vaccine, and optimal control will probably require routine immunization of adolescents and adults to reduce disease burden and transmission.³¹ Older persons serve as a reservoir of infection for young children, who have greater morbidity than adults.⁷⁻¹⁰ Several strategies for the delivery of acellular pertussis vaccines to adolescents and adults have been evaluated,^{34,35} including the routine immunization of all adolescents and adults, targeted immunizations of special groups, and the use of vaccine during outbreaks. The immunization of adolescents between the ages of 10 and 19 years may be the most cost-beneficial initial strategy in view of the ease and cost of implementation. Our data provide additional support for the use of acellular pertussis vaccines among adolescents and adults for the enhanced control of pertussis.

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APPENDIX

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