A CONTROLLED TRIAL OF A TWO-COMPONENT ACELLMAR, A FIVE-COMPONENT ACELLMAR, AND A WHOLE-CELL PERTUSSIS VACCINE

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Abstract. Background. Because of concern about safety and efficacy, no pertussis vaccine has been included in the vaccination program in Sweden since 1979. To provide data that might permit the reintroduction of a pertussis vaccine, we conducted a placebo-controlled trial of two acellular and one whole-cell pertussis vaccines.

Methods. After informed consent was obtained, 9829 children born in 1992 were randomly assigned to receive one of four vaccines: a two-component acellular diphtheria–tetanus–pertussis (DTP) vaccine (2566 children), a five-component acellular DTP vaccine (2587 children), a whole-cell DTP vaccine licensed in the United States (2102 children), or (as a control) a vaccine containing diphtheria and tetanus toxoids (DT) alone (2574 children). The vaccines were given at 2, 4, and 6 months of age, and the children were then followed for signs of pertussis for an additional 2 years (to a mean age of 2 1/2 years).

Results. The whole-cell vaccine was associated with significantly higher rates of protracted crying, cyanosis, fever, and local reactions than the other three vaccines. The rates of adverse events were similar for the acellular vaccines and the conventional whole-cell vaccine. After three doses, the efficacy of the vaccines with respect to pertussis linked to a laboratory-confirmed case of pertussis or contact with an infected household member with paroxysmal cough for > or = 21 days was 58.9 percent for the two-component vaccine (95 percent confidence interval, 50.9 to 65.9 percent), 85.2 percent for the five-component vaccine (95 percent confidence interval, 80.6 to 88.8 percent), and 48.3 percent for the whole-cell vaccine (95 percent confidence interval, 37.0 to 57.6 percent).

Conclusions. The five-component acellular pertussis vaccine we evaluated can be recommended for general use, since it has a favorable safety profile and confers sustained protection against pertussis. The two-component acellular vaccine and the whole-cell vaccine were less efficacious. (N Engl J Med 1996;334:349-55.) ©1996, Massachusetts Medical Society.

The most widely used vaccine against pertussis is whole-cell pertussis vaccine, which is given in three primary injections in infancy, usually followed by booster injections at preschool age. Acellular vaccines, which are likely to cause fewer reactions than whole-cell vaccines, have been in routine use in Japan since 1981, but there was initially little information on their efficacy. In the absence of animal models for the disease, the development of acellular vaccines relied on data from a single randomized, placebo-controlled trial of two acellular vaccines conducted in Sweden in the mid-1980s. The trial did not include a whole-cell vaccine because of poor public acceptance of such vaccines in Sweden at that time. The efficacy of two doses of a one-component vaccine, containing chemically inactivated pertussis toxin, given to infants ranging from 6 to 12 months of age, was 54 percent against culture-confirmed pertussis with cough lasting at least one day. The efficacy of a two-component vaccine, in which the second component was filamentous hemagglutinin, was 69 percent. Both vaccines were about 80 percent effective against culture-confirmed pertussis with cough lasting at least 30 days. After three years of further unblinded follow-up, the relative efficacy was greater for the two-component vaccine than the one-component vaccine whether these efficacy estimates were in the range of those for licensed whole-cell vaccines could not be established at that time. A number of acellular pertussis vaccines have since become available for study. The present trial compared a two-component vaccine with a five-component vaccine and with a conventional whole-cell vaccine used in the United States, all of which were formulated with diphtheria and tetanus toxoids. Since a diphtheria–tetanus–pertussis (DTP) vaccine was not routinely administered in Sweden, the inclusion of a control vaccine consisting of diphtheria and tetanus toxoids (DT) alone was ethical.

Methods

Subjects

Parents of infants born in 1992 and living in the catchment area of defined child health centers were informed about the trial by letter. Study nurses contacted parents who expressed interest in the study, explained the study again orally and in writing, and asked whether the families would like to participate. Infants were excluded from the study if neither parent spoke Swedish, if other difficulties with communication or follow-up were anticipated, or if the family planned to move from a study area before the trial was completed. Infants were also excluded if any of the following were present: serious chronic illness with signs of cardiac or renal failure, failure to thrive, progressive neurologic disease, uncontrolled epilepsy, infantile spasm, immunosuppression, and previous culture-confirmed pertussis. Informed consent was obtained from the parents of all participants. The trial was approved by the ethics committee at the Karolinska Institute in Stockholm.

Vaccines

Two experimental vaccines were used. The two-component acellular DTP vaccine (SmithKline Beecham, Rixensart, Belgium) contained 25 μg of pertussis toxin inactivated by glutaraldehyde and formalin, 25 μg of formalin-treated hemagglutinin, 25 flocculation units of diphtheria toxoid, and 10 flocculation units of tetanus toxoid in each 0.5-ml dose. The five-component acellular DTP vaccine (Connaught Laboratories, Toronto) contained 10 μg of glutaraldehyde-inactivated pertussis toxin, 5 μg of filamentous hemagglutinin, 5 μg of fimbriae 2 and 3 combined, 3 μg of pertactin (a 69-kd outer-membrane protein of *Bordetella pertussis* that has been shown to confer protection in animal models), 15 flocculation units of diphtheria toxoid, and 5 flocculation units of tetanus toxoid per 0.5-ml dose.

The whole-cell DTP vaccine licensed in the United States (Con...
There was no major overlap.

Blinding and Randomization

The vaccines were supplied in identical vials, each of which was labeled with a unique computer-generated randomization number. Twelve-unit blocks were used to ensure balanced assignment of infants to the three groups randomized during the first two months of the trial, and thereafter, 16-unit blocks were used for randomization to the four groups. The block sizes were not revealed to the investigators. Blinding was maintained until data analysis began in June 1995. The adequacy of blinding was checked by means of a questionnaire administered to parents and study nurses 14 days after the third study dose. The possibility of partial unblinding of the whole-cell–vaccine group was raised early in the trial, since the DT and acellular vaccines were easily resuspended to homogeneous opaque suspensions, whereas the whole-cell vaccine required vigorous shaking to resuspend. Also, the rates of general symptoms and local reactions were notably higher after the introduction of the whole-cell vaccine.

Administration of Vaccines

The trial vaccines were given in a series of three intramuscular injections on the side of the thigh. The first injection was given at 2 months of age (56 to 92 days of age), with the two subsequent doses scheduled to be given at 8-week intervals (range between doses, 28 to 90 days). Vaccination was deferred if the child was febrile (temperature, $\geq 38.0 ^{\circ} C$) or had received another vaccine within six days. Contraindications for subsequent doses were cyanois, persistent crying for 3 or more hours, fever (temperature, $\geq 40.0 ^{\circ} C$) within 24 hours after a dose, shock-like reaction within 48 hours, seizures, and encephalopathy. Inactivated poliovirus vaccine and a vaccine against Haemophilus influenzae type b were given two weeks or more after a dose of study vaccine or were given simultaneously in the other leg.

Follow-up

Nurses were specially trained for the study. Each nurse enrolled approximately 250 infants and was responsible for vaccination and standardized follow-up.

Adverse Events

The study nurses telephoned the parents and asked structured questions about common adverse events 1 and 14 days after each dose of vaccine. Serious adverse events were defined as collapse (hypotonic, hyporesponsive episodes$^{13}$) or generalized allergic reaction within 48 hours after a dose and sudden death, acute or subacute encephalitis or encephalomyelitis, encephalopathy, convulsions, invasive bacterial infections, other life-threatening events, and onset of a serious chronic disease within two months after a dose. Serious adverse events and contraindicating events were reported to the clinical coordinators. For all study participants who were hospitalized, hospital records were collected from the beginning of the study until two months after the last dose of vaccine or until the child was at least eight months of age. This period was selected to cover invasive bacterial infections$^{14}$ and other unexpected late events.

Ascertainment of Cases and Clinical Follow-up

The study nurse contacted each household every six to eight weeks. The parents were instructed to call if their child coughed for more than seven days or if they suspected that whooping cough was present in the household. In such instances the nurse visited the household, collected standardized clinical information, and obtained nasopharyngeal aspirates from all persons suspected of having whooping cough. For study children suspected of having whooping cough, paired serum samples were collected for diagnosis, with the second sample obtained six to eight weeks after the first. A second aspirate was obtained after one week if the first culture was negative and symptoms of pertussis persisted.

Serologic Samples

For a study of immunogenicity at one site, venous samples were collected before vaccination, one month after the third dose, and at 12 months and 2 1/2 years of age. Capillary serum samples were collected from all study children at 12 months of age, from children with even randomization numbers at 2 years of age, and from children with odd randomization numbers at 2 1/2 to 3 years of age.

Culture

Nasopharyngeal aspirates were collected as previously reported.$^{15}$ The nasopharyngeal aspirate and the tip of the catheter used to collect the aspirate were inserted into transport–enrichment medium and sent to the local bacteriologic laboratory, usually on the day of collection. The aspirate was inoculated onto charcoal medium with 40 mg of cephalexin per liter according to the method of Regan and Lowe$^{16}$ for primary isolation, and the plates were read after seven days. The enrichment medium was subcultured after 72 hours and ex-

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Table 1. Base-Line Characteristics of the 9829 Infants in the Four Vaccine Groups.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Two-Component Infant (N = 2566)</th>
<th>Five-Component Infant (N = 2587)</th>
<th>Whole-Cell Infant (N = 2102)</th>
<th>DT Vaccine (Control) (N = 2574)</th>
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<tr>
<td>Study site†</td>
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<td>5.1</td>
<td>5.2</td>
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<tr>
<td></td>
<td>Örebro</td>
<td>7.9</td>
<td>7.8</td>
<td>7.7</td>
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<td></td>
<td>Norrköping</td>
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<td>6.5</td>
<td>6.6</td>
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<tr>
<td></td>
<td>Linköping</td>
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<td>7.9</td>
<td>7.9</td>
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<td></td>
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<td>8.8</td>
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<td></td>
<td>Kalmar</td>
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<td>5.1</td>
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<td>3</td>
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<td>No. of unprotected elder siblings‡</td>
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<td>60</td>
<td>57</td>
</tr>
<tr>
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<td>11</td>
<td>10</td>
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</tbody>
</table>

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*Because of rounding, not all categories total 100 percent.
†There were two study sites in Lund and six in Stockholm.
‡An unprotected sibling was one who had not been vaccinated, had no history of pertussis, or both. The percentages are approximate since the categories were not mutually exclusive. There was no major overlap.
amined four days later. Slide agglutination with commercial antisera specific for *B. pertussis* and *B. parapertussis* was used for the primary identification of isolates. All strains were sent to the Swedish Institute for Infectious Disease Control for biochemical verification and serotyping. Analysis with the polymerase chain reaction (PCR)\(^\text{17}\) (and unpublished data) was used to identify suspected colonies of *B. pertussis* or *B. parapertussis* that could not be subcultured or identified by slide agglutination.

**Serologic Analysis**

Serum samples were analyzed by a standardized enzyme-linked immunosorbent assay,\(^\text{11}\) with two types of U.S. reference human antisera (identified by the Food and Drug Administration as lot 3 for pertussis toxin, filamentous hemagglutinin, and fimbriae and lot 4 for pertactin) used as controls.\(^\text{20}\) A reference-line method was used to calculate arbitrary units of measure for the assays.\(^\text{19}\) Levels of IgA and IgG antibodies against pertussis toxin and filamentous hemagglutinin were measured for diagnosis. A substantial serologic response was defined as an increase in the level of IgG or IgA antibodies of at least 100 percent. The results were accepted if the coefficient of variation of controls within tests was less than 15 percent. For analysis of the IgG antibody response to vaccination, levels of IgG antibody against pertussis toxin, filamentous hemagglutinin, pertactin, and fimbriae were determined before and after vaccination. The minimal level of detection was set at 1 arbitrary unit.\(^\text{11}\) Serum samples without measurable antibodies were assigned a value of 50 percent of the minimal level of detection.

**Case Definitions**

In the primary case definition, the disease was defined according to criteria established by the World Health Organization\(^\text{26}\) in order to permit comparisons with other trials and to overcome the differences in the diagnostic sensitivity of culture and of pertussis-toxin serologic analyses in vaccine and placebo recipients.\(^\text{27}\) A primary case was defined as the presence of at least 21 consecutive days of paroxysmal cough plus one of the following: culture-confirmed *B. pertussis*, an increase of 100 percent or more in IgG or IgA antibodies against pertussis toxin, an increase of 100 percent or more in IgG or IgA antibodies against filamentous hemagglutinin (in the absence of positive results for *B. parapertussis* on culture or PCR), or documented contact with an infected household member with culture-confirmed *B. pertussis* who began cough within 28 days before or after the onset of cough in the study child. In the secondary case definitions, the diagnosis was established by the presence of laboratory-confirmed pertussis (by culture, serologic analysis, or PCR) with cough for \(\geq 1, \geq 7, \geq 21, \) or \(\geq 30\) consecutive days and paroxysmal cough for \(\geq 14\) or \(\geq 21\) consecutive days.

**Statistical Analysis**

The true efficacy of all the pertussis vaccines studied was assumed to be 80 percent. The null hypothesis to be tested was that the efficacy of any of the vaccines was 70 percent or less, corresponding to a relative risk of pertussis of 1.5 or greater for the comparison of the acellular vaccines with the whole-cell vaccine.\(^\text{28}\) Hazard ratios obtained by Cox proportional-hazards regression were used to estimate absolute and relative vaccine efficacy\(^\text{23}\) with SPSS software for personal computers (SPSS, Chicago). The Kolmogorov–Smirnov two-sample test was used to compare the distributions between groups of IgG antibody levels after vaccination. Calculations of chi-square, relative risk, and differences of paired proportions with 95 percent confidence intervals were done as appropriate. All analyses were performed according to plans outlined before blinding was suspended.\(^\text{11}\)

**RESULTS**

A total of 24,336 infants were eligible for the study. A total of 14,507 infants did not participate for the fol-
lowing reasons: parents declined to participate (34.4 percent), parents did not respond to the letter of invitation and were not reached by telephone (16.9 percent), parents did not speak Swedish (3.6 percent), other known reasons (2.9 percent), medical contraindications (1.1 percent), and the family planned to move from the study area (0.7 percent). The remaining 9829 infants (40.4 percent) were randomly assigned to a group at the first injection. The four groups did not differ significantly with respect to several prognostic characteristics (Table 1). A total of 199 children did not complete the primary vaccination series because of culture-confirmed pertussis before the third dose (n = 47), withdrawal from the study (n = 40), or contraindicating events (11 in the group given two-component acellular vaccine, 18 in the group given five-component acellular vaccine, 67 in the group given whole-cell vaccine, and 16 in the group given DT vaccine [control]; overall P < 0.001). Later losses to follow-up (as of January 8, 1995) included 205 children (2.1 percent) who moved out of the study area and 116 children (1.2 percent) who did not complete follow-up for other reasons. One child died of sudden infant death syndrome 1 day after the first dose of the whole-cell vaccine, and another child died of this syndrome 27 days after the first dose of the two-component vaccine. Two deaths — one due to progressive convulsions with renal and liver failure and the other to bronchiolitis — occurred 7 and 14 months, respectively, after the third dose of the DT vaccine. All four deaths were judged to be unrelated to vaccination.

Adverse Events

Serious adverse events developed within 60 days after vaccination in 48 children, including 2 of the 4 who died. The number of events was similar between groups (P = 0.66). Five hypotonic, hyporesponsive episodes occurred among recipients of the whole-cell vaccine: four after the first dose and one after the second dose. One episode was reported after the third dose in a recipient of the five-component vaccine. There were 24 convulsions (5 in the group given two-component vaccine, 7 in the group given five-component vaccine, 3 in the group given whole-cell vaccine, and 9 in the group given DT vaccine). Five of the convulsions occurred within 48 hours after a dose of vaccine (two in the two-component–vaccine group, one in the whole-cell–vaccine group, and two in the DT-vaccine group). There were 16 other serious events, which occurred 4 to 61 days after vaccination: 3 invasive bacterial infections (2 in the group given whole-cell vaccine and 1 in the group given two-component vaccine), 2 apparently life-threatening events, and 11 serious chronic illnesses (3 malignant tumors, 2 cases of hydrocephalus, 2 cases of cardiac failure, 1 neurologic malformation, and 1 case each of Kawasaki’s syndrome, suspected Leigh’s disease, and psychomotor retardation with amaurosis).
There were 163 events that contraindicated the administration of further doses of vaccine, including the episodes of hypotonic hypo responsiveness and convulsions. Protracted crying for three hours or more was noted in 25 recipients of the whole-cell vaccine as compared with 0 to 4 recipients of the other three vaccines (1.1 percent vs. 0 to 0.2 percent, P < 0.001). A rectal temperature of at least 40.0°C was noted within one day of vaccination in 28 recipients of whole-cell vaccine (1.3 percent) and in 2 to 7 recipients of the other three vaccines (0.1 to 0.4 percent). Four recipients of whole-cell vaccine had generalized cyanosis on the day of the first dose (P = 0.040 by Fisher’s exact two-tailed test for the comparison with either of the groups given acellular vaccine). Pronounced local reactions with general symptoms contraindicated the administration of further trial doses in 13 recipients of whole-cell vaccine and 1 recipient of five-component vaccine (P < 0.001). The rates of minor general symptoms and local reactions were high in the group given whole-cell vaccine and low in the other three groups, with no clinically relevant differences in the low rates between the acellular-vaccine and DT-vaccine groups (Table 2).

Fourteen days after the third dose, the study nurses could identify 53.5 percent of the recipients of whole-cell vaccine but could not distinguish between recipients of the acellular vaccines and the DT vaccine.

**Postvaccination Antibody Levels**

Paired serum samples obtained before the first dose and one month after the third dose were available for 689 study children. Some prevaccination samples contained high levels of maternal antibodies against pertussis. Therefore, as specified in the protocol, before breaking the code, we evaluated only the postvaccination levels. The frequencies of IgG antibody levels against four pertussis antigens are shown in Figure 1. Both acellular-vaccine groups had high levels of antibodies against pertussis toxin (Fig. 1A), but the levels in the groups given the five-component vaccine were significantly lower than those in the group given the two-component vaccine (P < 0.001). Levels of antibodies against pertussis toxin in the whole-cell–vaccine group were very low. The levels of IgG antibodies against filamentous hemagglutinin (Fig. 1B) were significantly lower in the group given the five-component vaccine than in the group given the two-component vaccine (P < 0.001), and the levels in the group given whole-cell vaccine were much lower than the levels in either of the acellular-vaccine groups. Levels of antibodies against fimbriae (Fig. 1C) and pertactin (Fig. 1D) were significantly higher in the group given the five-component vaccine than in the group given whole-cell vaccine (P < 0.001); the flatness of the distribution curves for these two antibodies suggests a nonuniform response to whole-cell vaccine.

**Efficacy**

During the main follow-up period, which lasted an average of 21 to 23.5 months after the third dose, 737 cases of pertussis were diagnosed that met the primary case definition (Table 3). The proportions of culture-confirmed cases were as follows: 56 percent in the two-component–vaccine group, 42 percent in the five-component–vaccine group, 59 percent in the whole-cell–vaccine group, and 73 percent in the DT-vaccine group. The proportions of cases confirmed on the basis of an increase of 100 percent or more in IgG or IgA antibodies against pertussis toxin were as follows: 29 percent in the two-component–vaccine group, 37 percent in the five-component–vaccine group, 36 percent in the whole-cell–vaccine group, and 24 percent in the DT-vaccine group. The proportions of cases confirmed on the basis of an increase of 100 percent or more in IgG or IgA antibodies against filamentous hemagglutinin were as follows: 13 percent in the two-component–vaccine group, 12 percent in the five-component–vaccine group, 5 percent in the whole-cell–vaccine group, and 2 percent in the DT-vaccine group. The proportions of cases documented only on the basis of contact with an infected household member were as follows: 2 percent in the two-component–vaccine group, 9 percent in the five-component–vaccine group, 0 percent in the whole-cell–vaccine group, and 1 percent in the DT-vaccine group.

The two-component vaccine and the whole-cell vaccine conferred some protection against laboratory-con-
firmed typical pertussis but did not meet the preset standard of at least 70 percent efficacy. The five-component vaccine conferred good protection against typical pertussis. Figure 2 shows that the efficacy of whole-cell vaccine declined during the two years of follow-up, whereas the efficacy of the five-component vaccine was sustained. This vaccine also conferred substantial protection against mild and atypical pertussis, with an estimated efficacy of 77.9 percent (95 percent confidence interval, 72.6 to 82.2 percent) against laboratory-confirmed pertussis with at least one day of cough. With the use of the same case definition, the efficacy of the two-component vaccine was 42.3 percent (95 percent confidence interval, 32.6 to 50.6 percent) and of the whole-cell vaccine, 41.2 percent (95 percent confidence interval, 29.7 to 50.9 percent).

**DISCUSSION**

In this controlled trial the rates of adverse events among children who received an acellular pertussis vaccine and those who received the control DT vaccine with no pertussis component were similar. The acellular vaccines were much less likely to cause reactions than the whole-cell vaccine, as shown previously. The same pattern was observed in an Italian trial, reported in this issue of the *Journal*, which used the same whole-cell vaccine, two three-component vaccines, and a different DT-vaccine control. A temperature of 40.5°C or higher and convulsions are contraindications for additional doses of whole-cell vaccine, and the 1994 *Red Book* advises physicians to consider carefully an individual patient’s history before vaccination. Our data suggest that the medical contraindications for acellular pertussis vaccines, like those for DT vaccine, are few. We found that the five-component acellular vaccine was both safe and efficacious.

The whole-cell vaccine produced low antibody responses to all pertussis antigens studied, reflecting the varying serologic responses reported for licensed whole-cell vaccines. Both acellular vaccines were immunogenic with regard to each antigen studied. Because of its higher content of filamentous hemagglutinin and pertussis toxin, the two-component vaccine produced higher postvaccination antibody levels than the five-component vaccine. The anti–pertussis-toxin response to the two-component vaccine seemed lower than previously reported and may reflect a variation in immunogenicity from lot to lot or methodologic differences.

Efficacy was determined with unusual accuracy, since a pertussis epidemic occurred during the trial. Furthermore, the laboratory confirmation of cases was improved by the use of one or two bedside nasopharyngeal aspirates and by the use of serum collected before the episode (i.e., at one or two years of age), before a significant increase in the serum antibody titer had occurred. Failure to demonstrate a serologic response was expected mainly in vaccine recipients, for whom exposure to the bacteria could lead to a rapid increase in antibodies. Because we included serum obtained before exposure to pertussis, as much as 49 percent of the cases meeting the primary case definition were serologically confirmed among the recipients of the five-component vaccine, as compared with 26 percent among recipients of the DT vaccine. Hence, the issue of the differences in the sensitivity of culture and serologic methods between groups was avoided. Cases confirmed on the basis of an anti–filamentous-hemagglutinin response alone were evenly distributed between the groups. The exclusion of these potentially false positive cases only marginally changed the efficacy estimates. In this trial, vaccines with low and high rates of efficacy were identified, supporting the impression that the case ascertainment was sensitive and essentially not biased.

The efficacy of the whole-cell vaccine was lower than expected, as was found in the Italian trial. The efficacy may even have been overestimated because of partial unblinding. The declining efficacy of the whole-cell vaccine might have been avoided if a fourth dose had been given at 18 months of age, as is done in the United States. The efficacy of the Japanese two-component vaccine was lower than that of a two-component vaccine that was given in two doses to children 6 to 12 months of age in our previous placebo-controlled trial. The pertussis-toxoid vaccine used in that trial was as efficacious (with the use of similar case definitions) as a U.S. pertussis-toxoid vaccine given at 3, 5, and 12 months of age. Such historical comparisons may indicate that the practice of primary vaccination with three doses before six months of age without a booster is not optimal. Hence, it is remarkable that the efficacy of the five-component vaccine was sustained during the entire two-year follow-up period. An optimal vaccination schedule for highly efficacious acellular vaccines may involve two primary doses at 2 to 6 months of age, followed by a booster at 12 to 18 months of age. The five-component vaccine was also highly efficacious against mild disease. The data from this and three other randomized, placebo-controlled trials suggest that multicomponent vaccines are more protective against both typical pertussis and mild disease than one-component and two-component vaccines. The rela-
The contribution of each antigen remains to be shown. Improved protection against infection may diminish the spread of the disease, which in turn should improve the control of pertussis. Furthermore, a reduction in the number of doses needed may have economic and public health advantages that would lead many countries to switch from whole-cell to acellular vaccines.

We are indebted to the participating parents and study nurses, whose intimate collaboration formed the backbone of the trial; to the scientific community, public health authorities, and vaccine manufacturers for collaborating in a most constructive way, which depended on an unusual degree of openness among the persons assigned to the project by each organization; to William Blackwelder, David Klein, and Mark van Raden, National Institute of Allergy and Infectious Diseases; and to Francis André, SmithKline Beecham Biologicals, and Luis Barreto, Connaught Laboratories, for constructive criticism of the manuscript.

REFERENCES