EFFICACY OF A PNEUMOCOCCAL CONJUGATE VACCINE AGAINST ACUTE OTITIS MEDIA

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ABSTRACT

Background Ear infections are a common cause of illness during the first two years of life. New conjugate vaccines may be able to prevent a substantial portion of cases of acute otitis media caused by *Streptococcus pneumoniae.*

Methods We enrolled 1662 infants in a randomized, double-blind efficacy trial of a heptavalent pneumococcal polysaccharide conjugate vaccine in which the carrier protein is the nontoxic diphtheria-toxin analogue CRM197. The children received either the study vaccine or a hepatitis B vaccine as a control at 2, 4, 6, and 12 months of age. The clinical diagnosis of acute otitis media was based on predefined criteria, and the bacteriologic diagnosis was based on a culture of middle-ear fluid obtained by myringotomy.

Results Of the children who were enrolled, 95.1 percent completed the trial. With the pneumococcal vaccine, there were more local reactions than with the hepatitis B vaccine but fewer than with the combined whole-cell diphtheria–tetanus–pertussis and *Haemophilus influenzae* type b vaccine that was administered simultaneously. There were 2596 episodes of acute otitis media during the follow-up period between 6.5 and 24 months of age. The vaccine reduced the number of episodes of acute otitis media from any cause by 6 percent (95 percent confidence interval, −4 to 16 percent [the negative number indicates a possible increase in the number of episodes]), culture-confirmed pneumococcal episodes by 34 percent (95 percent confidence interval, 21 to 45 percent), and the number of episodes due to the serotypes contained in the vaccine by 57 percent (95 percent confidence interval, 44 to 67 percent). The number of episodes attributed to serotypes that are cross-reactive with those in the vaccine was reduced by 51 percent, whereas the number of episodes due to all other serotypes increased by 33 percent.

Conclusions The heptavalent pneumococcal polysaccharide–CRM197 conjugate vaccine is safe and efficacious in the prevention of acute otitis media caused by the serotypes included in the vaccine. (N Engl J Med 2001;344:403-9.)

P I C O

ACUTE otitis media in children accounts for 20 million office visits per year in the United States, and 18 percent of ambulatory care visits among preschool children.[1,2] Impaired hearing and delayed speech development are the most frequent long-term effects of recurrent episodes of otitis.[3,4] The economic effect of acute otitis media also indicates that prevention is needed. The estimated annual cost associated with otitis is $138 million in Finland (population, 5 million)[5] and $2 billion to $5.3 billion in the United States.[6-8]

Streptococcus pneumoniae is the most commonly reported bacterial cause of acute otitis media, accounting for 28 to 55 percent of cases.[9-12] Of the 90 pneumococcal serotypes that have been identified so far, the most common ones that cause acute otitis media are 3, 6B, 9V, 14, 19F, and 23F.[13-15] In the first attempts to prevent pneumococcal otitis in young children, a polysaccharide vaccine was used, but its immunogenicity and efficacy were low.[15-19]

Multivalent conjugate vaccines are pneumococcal capsular polysaccharides covalently coupled to molecules of carrier protein. They have proved immunogenic in infants,[20-26] inducing immunologic memory[21,25,27] and the formation of antibodies detectable in mucosal secretions[28] and reducing nasopharyngeal carriage of pneumococci.[29-32] In the first efficacy trial, conducted in northern California, such a vaccine had almost 100 percent efficacy against invasive pneumococcal infections in children.[33] The efficacy of the vaccine in reducing the number of episodes of otitis media from any cause was 7 percent and its efficacy in reducing the number of visits to physicians because of otitis media was 9 percent.[33] We studied the protective efficacy of the same heptavalent pneumococcal conjugate vaccine against culture-confirmed, serotype-specific pneumococcal acute otitis media in children.

METHODS

Durchführung

The Finnish Otitis Media Vaccine Trial was a prospective, randomized, double-blind cohort study conducted between December 1995 and March 1999 and originally designed to evaluate the efficacy of two heptavalent conjugate vaccines in the prevention of pneumococcal acute otitis media. The vaccines contained pneumococcal serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F, conjugated either to the nontoxic diphtheria-toxin analogue CRM197 or to meningococcal outer membrane protein complex. The two vaccines were studied in parallel and compared with the same control vaccine (hepatitis B vaccine). We present here the results related to the efficacy and safety of the pneumococcal–CRM197 conjugate vaccine.

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*Other members of the study group are listed in the Appendix.

Rekrutierung

Study Clinics and Subjects

Eight study clinics, each with a specially trained study nurse and a study physician, were established in the communities of Tampere (population, 191,000), Kangasala (22,000), and Nokia (27,000), Finland. Families living in these communities were informed about the study at prenatal health clinics, as well as by public health nurses in child health centers during the first visit after the birth of a child. Parents interested in participating made an appointment at the study clinic in their own area. Study personnel then provided detailed information about the study design and procedures, and parents who were willing to participate signed a consent form to enroll their child in the study.

The study was conducted according to the provisions of the Declaration of Helsinki (as amended in Hong Kong, 1989). The study protocol was evaluated before the start of the trial by the ethics committee of the National Public Health Institute of Finland, by the National Agency for Medicines, and by the relevant local health authorities (the ethics committee and the health board of Tampere, and the health boards of Kangasala and Nokia). An external advisory committee was appointed to advise the investigators and to review the progress of the study and the safety of the subjects.

Vaccines and Vaccinations

The pneumococcal vaccine prepared by Wyeth Lederle Vaccines (Pearl River, N.Y.) consisted of 2 μg each of capsular polysaccharides of pneumococcal serotypes 4, 9V, 14, 19F, and 23F, 4 μg of serotype 6B polysaccharide, and 2 μg of serotype 18C oligosaccharide, each conjugated individually to the CRM197 protein. The hepatitis B vaccine, prepared by Merck Sharp & Dohme (West Point, Pa.), contained 5 μg of recombinant hepatitis B surface protein.

The study vaccine was administered to children intramuscularly at the age of approximately 2 months (6 to 13 weeks), 4 months (14 to 21 weeks), 6 months (22 to 29 weeks), and 12 months (11 to 14 months). An interval of 6 to 11 weeks was required between the first and second vaccinations and between the second and third vaccinations.

A combination vaccine containing whole-cell diphtheria–tetanus–pertussis (DTP) and *Haemophilus influenzae* type b was given in the child's opposite thigh at the same visit as the pneumococcal vaccine at two, four, and six months of age. In half of the study clinics, the carrier protein in the DTP and *H. influenzae* vaccine was CRM197 (Tetramune, Wyeth Lederle Vaccines), and in the other half it was tetanus toxoid (TetrAct-HIB, Pasteur Mérieux Sérums et Vaccins, Lyons, France). Inactivated poliovirus vaccine (Imovax, Pasteur Mérieux Sérums et Vaccins) was given at 7 months of age and again at the same time as the fourth dose of the study vaccine at 12 months of age. Measles–mumps–rubella vaccine was administered at 18 months.

Definitions

Messung

Acute otitis media was defined by the presence of tympanic membrane that was visibly abnormal in terms of color, position, or mobility, suggesting middle-ear effusion; plus at least one of the following symptoms or signs of acute infection: fever, earache, irritability, diarrhea, vomiting, acute otorrhea not caused by otitis externa, and other symptoms of respiratory infection.[34]

Episodes of acute otitis media were classified in several overlapping ways: all episodes; culture-confirmed, pathogen-specific episodes; episodes due to the serotypes included in the vaccine, to serotypes that cross-react with those serotypes, and to other pneumococcal serotypes and groups; episodes due to *H. influenzae*; and episodes due to *Moraxella catarrhalis*. For the overall and pathogen-specific categories, a new episode was considered to have started if at least 30 days had elapsed since the beginning of the previous episode. For the categories defined according to serotype, a new episode was considered to have started if 30 days had elapsed since the beginning of an episode due to the same serotype, or if any interval had elapsed since the beginning of an episode due to a different serotype. If more than one serotype was recovered from the middle-ear fluid at the same time, only one episode was considered to have started (there were five such cases in the control-vaccine group). Recurrent acute otitis media was defined as at least three episodes within six months or four or more episodes within one year.

Durchführung

The follow-up period for the analysis according to the treatment received (per-protocol analysis) started 14 days after the third injection of the pneumococcal vaccine (at approximately 6.5 months of age), and the follow-up period for the intention-to-treat analysis began on the day the first dose of the pneumococcal vaccine was administered. Both follow-up periods ended on the day of the final visit at the age of 24 months or, if the follow-up was discontinued, on the day of discontinuation.

Follow-up

All children attended one of the study clinics for enrollment at 2 months of age and thereafter at 4, 6, 7, 12, 13, 18, and 24 months. The follow-up for acute otitis media was carried out in these clinics. Among the children enrolled in Kangasala, blood samples were taken at 2, 4, 6, 7, 12, 13, and 24 months of age.

All children were observed at the study clinics for at least 15 minutes after each vaccination. Parents then recorded any adverse reactions within 24, 48, and 72 hours after the vaccination and were encouraged to notify the study personnel whenever they suspected a vaccine-related adverse event in their child. An adverse event was assessed as serious if it was fatal, life-threatening, or permanently disabling or if it necessitated hospitalization. Adverse events were recorded throughout the entire follow-up period.

Parents were encouraged to bring their child to the study clinic for evaluation of symptoms suggesting respiratory infection or acute otitis media. Myringotomy and aspiration of middle-ear fluid were performed if acute otitis media was diagnosed.

Laboratory Methods

Samples of middle-ear fluid were plated immediately on selective sheep's-blood agar containing gentamicin (5 μg per milliliter) and on enriched chocolate agar. *S. pneumoniae* was identified on the basis of susceptibility to ethylhydrocupreine (optochin); *H. influenzae* and *M. catarrhalis* were identified by standard procedures. Serotyping was performed by means of counterimmunoelectrophoresis and latex agglutination[35] and was confirmed by the quellung reaction when necessary, with antiserum obtained from the Statens Serum Institut, Copenhagen, Denmark. Concentrations of IgG antibodies against the seven serotypes in the pneumococcal vaccine were measured by means of an enzyme immunoassay.[20,21]

Statistical Analysis

Durchführung

The primary efficacy analysis was based on the follow-up period defined for the per-protocol analysis. The relative risk of acute otitis media was estimated by means of a generalized Cox regression model with a robust method for estimating variance.[36] The effects of the vaccine in preventing first and subsequent episodes of otitis media were evaluated by means of a generalized Cox-type model that allowed these two effects to be separated in the same risk model.[37] The numbers of children with recurrent acute otitis media in the two vaccine groups were compared to derive the relative risk and an exact 95 percent confidence interval.[38] Vaccine efficacy was estimated as 1 minus the relative risk.

The chi-square test was used to compare the rate of reactogenicity in the pneumococcal-vaccine group with that in the control-vaccine group, and McNemar's test for matched pairs was used for the comparison of the presence or absence of reaction at the injection site after each dose of the pneumococcal vaccine with that of the other vaccine given simultaneously. The overall rates of serious adverse events per person-year of follow-up in the two vaccine groups were compared to derive estimates of relative risk, with associated 95 percent confidence intervals.

Rekrutierung

Allokation

Durchführung

Effektivität

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Allokation

RESULTS

Demographic Characteristics of the Children

A total of 2497 children, representing 55 percent of the eligible children in the study communities, were enrolled between December 1, 1995, and April 30, 1997. Of the total enrolled, 831 children were assigned to receive the pneumococcal–CRM197 conjugate vaccine and 831 the control (hepatitis B) vaccine; the remaining 835, who were not included in the analysis reported here, received the other pneumococcal conjugate vaccine. Of the enrolled children, 786 in the group assigned to the pneumococcal–CRM197 conjugate vaccine (94.6 percent) and 794 in the control-vaccine group (95.5 percent) completed the follow-up as specified in the protocol. There were no major differences in the demographic characteristics or distribution of risk factors between the pneumococcal-vaccine and control-vaccine groups (Table 1).

TABLE 1. CHARACTERISTICS AND RISK FACTORS OF THE PATIENTS.

VARIABLE	PNEUMOCOCCAL-VACCINE GROUP (N=831)	CONTROL-VACCINE GROUP (N=831)
Male sex (%)	52	52
Gestational age <37 wk at birth (%)	5	6
Mean no. of siblings	0.7	0.7
Maternal education at least secondary school or college (%)	71	69
Day care outside home (%)		
At 12 mo	16	12
At 18 mo	32	27
Breast-feeding for ≥6 mo (%)	53	53

Efficacy of the Vaccine

A total of 2596 episodes of clinical acute otitis media were diagnosed among the 1662 children in the pneumococcal-vaccine and control-vaccine groups during the protocol-specified follow-up from 6.5 to 24 months of age (Table 2). The overall incidence of acute otitis media was 1.16 episodes per person-year in the pneumococcal-vaccine group and 1.24 episodes per person-year in the control-vaccine group. The efficacy of the vaccine against acute otitis media from any cause was thus 6 percent (95 percent confidence interval, −4 to 16 percent; the negative value indicates a possible increase in episodes of otitis media).

A sample of middle-ear fluid was obtained for bacterial culture during 93 percent of visits due to acute otitis media. In the per-protocol analysis, there were 271 episodes of culture-confirmed pneumococcal acute otitis media during follow-up in the pneumococcal-vaccine group and 414 in the control-vaccine group. The reduction in the rate of episodes was 34 percent (95 percent confidence interval, 21 to 45 percent).

The primary end point of the trial was the number of episodes of acute otitis media due to the pneumococcal serotypes included in the vaccine. In the per-protocol analysis, there were a total of 107 such episodes in the pneumococcal-vaccine group and 250 in the control-vaccine group during follow-up, corresponding to a point estimate for vaccine efficacy of 57 percent (95 percent confidence interval, 44 to 67 percent). The difference between the two vaccine groups persisted throughout follow-up (Fig. 1). The corresponding estimate in the intention-to-treat analysis was 54 percent (95 percent confidence interval, 41 to 64 percent). The vaccine also reduced by 51 percent (95 percent confidence interval, 27 to 67 percent) the frequency of episodes due to serotypes that cross-react with those in the vaccine (serotypes 6A, 9N, 18B, 19A, and 23A). At the same time, there were 33 percent more episodes due to all other serotypes (95 percent confidence interval, −1 to 80 percent) in the pneumococcal-vaccine group than in the control-vaccine group (125 vs. 95 episodes). The estimates of vaccine efficacy for the individual serotypes included in the vaccine ranged from 25 percent (for serotype 19F) to 84 percent (for serotype 6B) (Table 2).

The efficacy of vaccination for the prevention of a first episode of otitis caused by any one of the serotypes included in the vaccine was 52 percent (95 percent confidence interval, 39 to 63 percent), and for the prevention of subsequent episodes the efficacy was 45 percent (95 percent confidence interval, 5 to 69 percent). The efficacy calculated for the period between the first and second doses was 21 percent (95 percent confidence interval, −75 to 65 percent); between the second and third doses, 43 percent (95 percent confidence interval, −10 to 71 percent); between the third and fourth doses, 57 percent (95 percent confidence interval, 36 to 72 percent); and between the fourth dose and the end of follow-up, 56 percent (95 percent confidence interval, 41 to 68 percent). According to the intention-to-treat analysis, the risk of recurrent disease (at least three episodes within six months or at least four episodes within one year) during the follow-up period was reduced by 9 percent (95 percent confidence interval, −12 to 27 percent); recurrent disease occurred in 158 of 831 children in the pneumococcal-vaccine group, as compared with 174 of 831 children in the control-vaccine group. According to the per-protocol analysis, the risk of recurrent acute otitis media was reduced by 16 percent (95 percent confidence interval, −6 to 35 percent), the relative proportions being 123 in 811 children and 149 in 821 children, respectively.

Immunogenicity

Geometric mean antibody concentrations measured at seven months in the serum of the 115 children in

TABLE 2. EPISODES OF ACUTE OTITIS MEDIA FROM VARIOUS CAUSES AND ESTIMATES OF THE PROTECTIVE EFFICACY OF THE PNEUMOCOCCAL–CRM197 CONJUGATE VACCINE DURING FOLLOW-UP, PER PROTOCOL.*

TYPE OR CAUSE OF ACUTE OTITIS MEDIA	NO. OF EPISODES		VACCINE EFFICACY (%)	
	PNEUMOCOCCAL VACCINE	CONTROL VACCINE	POINT ESTIMATE†	95% CI
Any	1251	1345	6	−4 to 16
Any confirmed by presence of middle-ear fluid	1177	1267	7	−5 to 17
Culture-confirmed pneumococcus	271	414	34	21 to 45
Caused by pneumococcal serotypes included in the vaccine				
All seven combined	107	250	57	44 to 67
4	2	4	49	−176 to 91
6B	9	56	84	62 to 93
9V	5	11	54	−48 to 86
14	8	26	69	20 to 88
18C	7	17	58	−4 to 83
19F	43	58	25	−14 to 51
23F	33	82	59	35 to 75
Caused by cross-reactive pneumococcal serotypes				
All combined	41	84	51	27 to 67
6A	19	45	57	24 to 76
9N	2	8	75	−24 to 95
18B	2	1	−103	−213 to 82
19A	17	26	34	−26 to 65
23A	1	4	75	−151 to 97
Caused by other pneumococcal serotypes‡				
All combined	125	95	−33	−80 to 1
3	13	13		
11	32	24		
15	24	23		
16	5	3		
22	7	7		
33	6	0		
35	14	10		
38	7	3		
Rough	6	2		
Other (7, 10, 12, 28, 34, Pool G§)	11	11		
Caused by *H. influenzae*	315	287	−11	−34 to 8
Caused by *M. catarrhalis*	379	381	−1	−19 to 15

*Because the definition of episodes varied with the cause, the numbers of episodes due to individual serotypes do not add up to the number of episodes due to all serotypes combined, and the combined numbers of episodes due to vaccine, cross-reactive, and other serotypes do not add up to the total number of pneumococcal episodes. CI denotes confidence interval.

†The estimates were derived from the generalized Cox model.

‡Serotyping was performed only to the serogroup level.

§Pool G consists of the following serogroups or types: 29, 34, 35, 42, and 47.

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the cohort in which serologic follow-up was conducted were consistently higher in the pneumococcal-vaccine group than in the control-vaccine group (data not shown). In the pneumococcal-vaccine group, geometric mean concentrations were between 1.7 and 6.3 μg per milliliter, depending on the serotype. In at least 85 percent of children, concentrations reached 0.3 μg per milliliter; in at least 83 percent they reached 0.5 μg per milliliter; and in at least 67 percent they reached 1.0 μg per milliliter. Geometric mean concentrations after the fourth dose ranged from 2.6 to 10.8 μg per milliliter (Table 3), representing an increase of 50 to 350 percent from the levels measured after the primary immunization series.

Safety

The pneumococcal–CRM197 conjugate vaccine caused local reactions during the three days after each dose more often than did the hepatitis B vaccine (data available at http://www.nejm.org) but less often than the simultaneously administered combination DTP–*H. influenzae* vaccine ($P<0.01$ for all comparisons) (data not shown). After each of the first three doses, a temperature higher than 39°C was more common in the pneumococcal-vaccine group than in the control-vaccine group, but the difference was statistically significant only after the third dose (2.0 percent vs. 0.5 percent, $P=0.01$).

Ten serious or unexpected adverse events that oc-

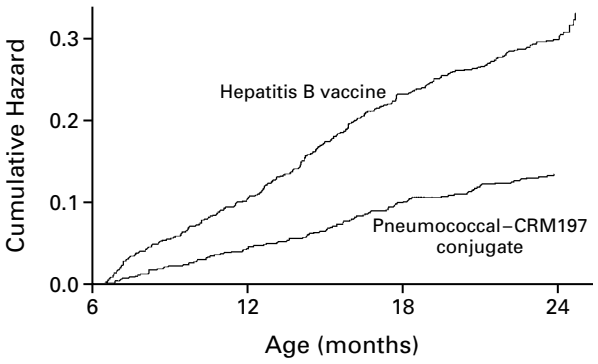

Figure 1. Cumulative Hazard in the Pneumococcal-Vaccine Group and in the Control-Vaccine Group of Episodes of Acute Otitis Media Due to the Serotypes Included in the Pneumococcal–CRM197 Conjugate Vaccine.

The cumulative hazard is the cumulative number of episodes of acute otitis media divided by the number of children at risk at the time. The follow-up period used is that specified in the protocol (from approximately 6.5 to 24 months of age).

curred within seven days after vaccination were judged by a study physician to be possibly related to the study vaccines. Six of these occurred in the pneumococcal-vaccine group; they were urticaria (three cases), rash (one), excessive crying (one), and transient granulocytopenia (one).

One child died during the study period from bowel obstruction, necrosis, and shock at the age of eight months, 85 days after administration of the third dose of the pneumococcal–CRM197 conjugate vaccine. An autopsy revealed mesenteric defects with volvulus and other congenital anomalies. Death was assessed as unrelated to the study vaccine.

The only statistically significant difference in the rate of occurrence of serious adverse events was the lower number of suspected infections requiring hospitalization in the pneumococcal-vaccine group (4 cases) than in the control-vaccine group (13 cases), resulting in a relative risk of 0.31 (95 percent confidence interval, 0.10 to 0.95). There was only one invasive pneumococcal infection in the pneumococcal-vaccine group (bacteremia with *S. pneumoniae* serogroup 7), as compared with three such infections in the control-vaccine group (two cases of meningitis, one serotype 23F and one serogroup 15, and one case of bacteremia, serotype 19F).

DISCUSSION

Messung

We conducted this prospective, randomized, double-blind study of pneumococcal conjugate vaccine in an unselected population of children in Finland. All children were followed in study clinics, and standardized criteria were used in their clinical evaluation. When middle-ear effusion was suspected and collection of middle-ear fluid attempted by myringotomy, the success rate of obtaining a sample was high (97.2 percent), which indicates that the diagnosis was reliable.

Effektivität

The pneumococcal vaccine was associated with a 6 percent reduction in the number of episodes of acute otitis media, as compared with the number among children who did not receive this vaccine. The reduction was not statistically significant but was essentially the same as the reduction in the number of episodes of clinical otitis in a California trial in which the same pneumococcal vaccine was used in a considerably larger population (38,000) but without standardization of the diagnosis of otitis media.[33] The overall reduction of 6 percent seems small, but as in the California trial, the vaccine was associated with a 9 per-

TABLE 3. GEOMETRIC MEAN SERUM CONCENTRATIONS AND PERCENTAGES OF THE 57 CHILDREN TESTED IN WHOM THE PREDEFINED LEVELS OF PNEUMOCOCCAL ANTICAPSULAR ANTIBODIES WERE REACHED AT 7 AND 13 MONTHS OF AGE.*

SEROTYPE	7 MONTHS OF AGE				13 MONTHS OF AGE			
	GMC (95% CI)	CHILDREN WITH ≥0.3 μg/ml	CHILDREN WITH ≥0.5 μg/ml	CHILDREN WITH ≥1.0 μg/ml	GMC (95% CI)	CHILDREN WITH ≥0.3 μg/ml	CHILDREN WITH ≥0.5 μg/ml	CHILDREN WITH ≥1.0 μg/ml
	μg/ml		percent		μg/ml		percent	
4	1.7 (1.32–2.20)	94.4	92.6	75.9	2.6 (2.00–3.28)	98.2	94.5	90.9
6B	2.0 (1.35–2.96)	85.2	83.3	66.7	9.0 (6.50–12.59)	98.2	96.4	92.7
9V	2.5 (1.97–3.11)	98.1	94.4	88.9	4.0 (3.20–4.91)	100.0	100.0	96.4
14	6.3 (4.78–8.23)	100.0	96.3	94.4	10.8 (8.30–14.09)	100.0	100.0	100.0
18C	3.6 (2.80–4.49)	100.0	100.0	94.4	6.5 (5.04–8.41)	100.0	100.0	96.4
19F	3.3 (2.57–4.18)	100.0	100.0	90.7	5.0 (3.86–6.37)	100.0	100.0	94.5
23F	2.5 (1.84–3.43)	94.4	92.6	77.8	6.3 (4.54–8.61)	100.0	100.0	94.5

*Data are from the 57 children in the subgroup of the pneumococcal-vaccine group in which serologic follow-up was performed. GMC denotes geometric mean concentration, and CI confidence interval.

cent reduction in the frequency of recurrent acute otitis media during follow-up.

The vaccine reduced by 57 percent the incidence of acute otitis media due to serotypes included in the vaccine, but the efficacy varied with the serotype. Statistically significant efficacy was demonstrated against otitis due to serotypes 6B, 14, and 23F, whereas the efficacy against serotype 19F was clearly poorer. Surprisingly, the vaccine had almost the same effect on acute otitis media attributed to serotypes that cross-react with those in the vaccine (a reduction of 51 percent) as on disease attributed to the serotypes in the vaccine themselves; efficacy against otitis caused by the cross-reactive serotype 6A was even statistically significant. Although there was a reduction in the rate of otitis due to the serotypes in the vaccine and those that cross-react with them, the use of the vaccine was associated with an increase (of 33 percent) in the rate of acute otitis media attributed to other pneumococcal serotypes. This was not totally unexpected, since recent studies have reported similar changes in nasopharyngeal carriage, with a shift after vaccination with a pneumococcal conjugate to serotypes not included in the vaccine.[29-32] Our findings indicate that serotypes not included in the vaccine have important pathogenic potential.

There was a substantial immune response to each of the seven pneumococcal serotypes in the heptavalent pneumococcal–CRM197 conjugate vaccine, with antibody concentrations after the primary immunization series slightly higher than those reported for the same vaccine among children in the United States.[22,23] The antibody concentrations were not directly correlated with protective efficacy. For example, there was good protection but a relatively low geometric mean concentration for serotype 6B, in contrast to a much lower degree of protection but a higher concentration for serotype 19F.

As expected,[23] the vaccine was well tolerated. The vast majority of the reactions were mild. The fact that there were fewer suspected infections in the pneumococcal-vaccine group (4) than in the control-vaccine group (13) could be due to the inclusion in this category of febrile illnesses in which the specific cause was undiagnosed and blood cultures were negative. Some of these infections may have been pneumococcal bacteremia, which would probably have been prevented in the recipients of the pneumococcal–CRM197 conjugate vaccine.[33] This finding suggests that the true incidence of invasive pneumococcal disease could be several times higher than that indicated by the number of cases with positive blood cultures (three in the control-vaccine group).

Although the estimates of the vaccine's efficacy against otitis — 57 percent efficacy against serotype-specific pneumococcal otitis media and 6 percent efficacy against acute otitis media from any cause — were lower than the estimated efficacy of other childhood vaccines, the effect of the pneumococcal conjugate vaccine can be substantial. On the basis of our data, we calculate that up to 1.2 million of the 20 million yearly episodes of acute otitis media in the United States could theoretically be prevented if the vaccine were widely used. Moreover, the vaccine also helps to prevent invasive infections and pneumonia due to *S. pneumoniae*.[33,39]

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APPENDIX

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