

Efficacy, Safety, and Immunogenicity of Heptavalent Pneumococcal Conjugate Vaccine in Children

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Abstract

Objective: To determine the efficacy, safety, and immunogenicity of the heptavalent CRM₁₉₇ pneumococcal conjugate vaccine (PCV) against invasive disease caused by vaccine serotypes and to determine the effectiveness of this vaccine against clinical episodes of otitis media.

Methods: The Wyeth Lederle heptavalent CRM₁₉₇ PCV was given to infants at 2, 4, 6 and 12 to 15 months of age in a double-blind trial; 37,868 children were randomly assigned 1:1 to receive either the

pneumococcal conjugate vaccine, or meningococcus type C CRM₁₉₇ conjugate. The primary study outcome was invasive disease caused by vaccine serotype. Other outcomes included overall impact on invasive disease regardless of serotype, effectiveness against clinical otitis media visits and episodes, and impact against frequent and severe otitis media and ventilatory tube placement. In addition the serotype-specific efficacy against otitis media was estimated in an analysis of spontaneously draining ears.

Results: In the interim analysis in August 1998, 17 of the 17 cases of invasive disease caused by vaccine serotype in fully vaccinated children and 5 of 5 of partially vaccinated cases occurred in the control group for a vaccine efficacy of 100%. Blinded case ascertainment was continued until April 1999. As of that time 40 fully vaccinated cases of invasive disease caused by vaccine serotype had been identified, all but 1 in controls for an efficacy of 97.4% (95% confidence interval, 82.7% to 99.9%), and 52 cases, all but 3 in controls in the intent-to-treat analysis for an efficacy of 98.9% (95% confidence interval, 79.6% to 98.5%). There was no evidence of any increase of disease caused by nonvaccine serotypes. Efficacy for otitis media against visits, episodes, frequent otitis, and ventilatory tube placement was 8.9%, 7.0%, 9.3% and 20.1% with $P < 0.04$ for all.

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In the analysis of spontaneously draining ears, serotype-specific effectiveness was 66.7%.

Conclusion: This heptavalent pneumococcal conjugate appears to be highly effective in preventing invasive disease in young children and to have a significant impact on otitis media.

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Although the pneumococcus was first isolated more than 100 years ago and the first pneumococcal vaccine trials began in 1911, there is still no routinely recommended pneumococcal vaccine for use in childhood. The currently available 23-valent pneumococcal polysaccharide vaccine is not effective in children younger than 2 years of age in whom 80% of invasive pneumococcal disease in childhood occurs. This vaccine has also not been effective in the control of otitis media in children.

During recent years there has been considerable effort devoted toward developing a pneumococcal vaccine that is effective in infants and children. After the licensure of conjugate *Haemophilus influenzae* type b (Hib) vaccines in late 1990, there has been a more than 98% elimination of Hib disease in this country.¹ This leaves the pneumococcus as the most common cause of bacterial meningitis in young children. In addition there has been a rapid emergence of drug-resistant pneumococci that have caused invasive infection worldwide and in the United States.² The increasing prominence of pneumococcal infections and of antimicrobial resistance has emphasized the need for the development of an effective vaccination program to reduce the risk of pneumococcal disease in childhood.

The pneumococcus is responsible for a wide spectrum of infection ranging from asymptomatic carriage to

overwhelming sepsis. Unlike Hib, where only one serotype accounted for virtually all *H. influenzae* disease, there are more than 90 described serotypes of the pneumococcus, many of which cause disease in adults and children. However, within the United States 7 serotypes are responsible for 83% of invasive disease in children younger than 4 years of age.

We report the results of the Kaiser Permanente trial evaluating the efficacy, safety, and immunogenicity of the heptavalent pneumococcal conjugate vaccine (Wyeth; PNCRM7) conducted in Northern California between October 1995 and August 1998 and the posttrial blinded efficacy follow-up through April 20, 1999.

...METHODS...

This study was a randomized, double-blind trial conducted at 23 medical centers within Northern California Kaiser Permanente (NCKP). The study was approved by the Institutional Review Board of the Kaiser Foundation Research Institute. Written informed consent was obtained from parents or guardians. A Study Advisory Committee (Drs. Donna Ambrosino, William Blackwelder, and Jerome Klein) monitored the conduct of the study and functioned as a Safety Monitoring Committee.

Healthy infants were randomized 1:1 to receive either the heptavalent pneumococcal conjugate or the meningococcus type C conjugate vaccine at 2, 4, 6, and 12 to 15 months of age. Children with sickle-cell disease, known immunodeficiency, any serious chronic or progressive disease, a history of seizures, or a history of either pneumococcal or meningococcal disease were excluded.

The pneumococcal conjugate vaccine contained 2µg each of saccharides of serotypes 4, 9V, 14, 18C, 19F, and 23F and 4µg of 6B coupled to the protein carrier CRM₁₉₇ (a nontoxic

mutant of diphtheria toxin). The control meningococcal conjugate vaccine contained 10µg of group C oligosaccharide conjugated to the same carrier protein. The 2 vaccines were identical in appearance. Multiple lots of both the pneumococcal and meningococcal conjugate vaccines were used in this study. The following routine childhood vaccines were administered at the recommended ages: diphtheria-tetanus toxoid-whole cell pertussis vaccine (DTwP) or diphtheria-tetanus toxoid-acellular pertussis vaccine (DTaP); oral poliovirus vaccine or inactivated poliovirus vaccine; Hib; hepatitis B; measles-mumps-rubella vaccine; varicella. Initially all subjects received TETRAMUNE (a vaccine combining *Haemophilus b* conjugate and DTwP) into the opposite leg and oral poliovirus vaccine concurrently. When recommendations changed the protocol was amended to allow administration of DTaP and inactivated poliovirus vaccine. Vaccines not given concomitantly were given at least 2 weeks apart from study vaccine.

Efficacy

The primary endpoint for the evaluation of efficacy of the pneumococcal conjugate vaccine was the protective efficacy of the heptavalent pneumococcal conjugate vaccine against invasive pneumococcal disease caused by vaccine serotypes. Secondary endpoints included the efficacy of the vaccine against clinical episodes of otitis media as defined below. An additional outcome, pneumonia, will be reported separately.

Active surveillance for cases of invasive pneumococcal disease in the study population was conducted using automated clinical and laboratory databases. Invasive pneumococcal disease was defined as a positive culture of *Streptococcus pneumoniae* from a normally sterile body fluid obtained from a child presenting with an acute illness compatible with

pneumococcal disease. To be included in the main efficacy analysis, cases must have been caused by a pneumococcal serotype included in the vaccine, must have occurred longer than 14 days after the third dose of study vaccine, and must have occurred in subjects vaccinated according to protocol. In addition potential cases were tested for immunocompetence evaluated by obtaining quantitative immunoglobulins, a complete blood count with differential, and CD4/CD8 cell counts.

This trial incorporated a sequential design with an interim evaluation by the Study Advisory Committee at 17 cases in fully vaccinated per protocol cases of invasive disease caused by vaccine serotype in fully vaccinated immunocompetent children. For each child follow-up ended for the main efficacy analysis at the earliest of the following dates: the onset of invasive pneumococcal disease of any serotype; the child died; or at the end of the trial. A child younger than 16 months of age was considered fully vaccinated if the child had received 3 or more doses of vaccine, and a child 16 months of age or older was considered fully vaccinated after receipt of a fourth dose of vaccine. Protective efficacy was estimated by calculating the ratio of the number of cases of invasive disease in the pneumococcal conjugate group to the number of cases in the meningococcal group and subtracting this ratio from 1.

Vaccine efficacy against invasive disease was evaluated with the binomial test of the null hypothesis that the vaccine has no efficacy for the 7 serotypes. In the interim analysis this was to be rejected if the case split was 15:2 or more favorable, $P = 0.0023$ at this interim assessment with a final evaluation at 26 cases, and an overall 2-tailed P value of < 0.05 . Exact binomial confidence intervals were calculated by the conservative Kupper-Pearson method.³

In addition an intent-to-treat

analysis included all invasive disease caused by any pneumococcal serotype occurring after randomization regardless of whether the child completed the 3-dose primary series or received the booster dose. For this analysis the null hypothesis was 0 efficacy and the statistical test used was the exact binomial test.

Clinical diagnoses of acute otitis media for the study population were obtained from computerized data sources using diagnoses registered by emergency physicians and pediatricians in the NCKP population. There was no cross-training of the estimated 500 observers, and cultures were not routinely obtained. Several outcomes were evaluated for otitis media. The primary otitis media outcome was the number of episodes of otitis media in fully vaccinated per protocol follow-up time in the 2 vaccine groups. For this analysis each clinic visit constituted a new episode unless it was classified as a follow-up visit. A visit less than 21 days after another otitis visit was always considered a follow-up visit. A visit 42 days or more after the most recent otitis visit was considered a new episode. Visits occurring between 21 and 42 days, if the appointment was made less than 3 days in advance, were considered new episodes.

Additional otitis outcomes included differences between treatment groups in the time to diagnosis of frequent otitis, in placement of ventilatory tympanostomy tubes in each group, and in the number of cases of spontaneously draining ruptured tympanic membranes with culture of a vaccine serotype pneumococcus. Frequent otitis was defined as at least 3 episodes in 6 months, or 4 or more episodes within 1 year. To evaluate the effectiveness of the pneumococcal vaccine in reducing the total number of otitis media episodes, the Anderson-Gill formulation of the proportional hazards model was used (with robust variance estimation).^{4,5}

The difference in the number of spontaneously draining and cultured otitis media episodes was determined with the binomial test.

Assessment of Vaccine Safety

Multiple methods were used to assess the safety of the study vaccine. Local and systemic reactions were collected at 48 to 72 hours and 14 days after each dose by telephone inter-

The frequency of uncommon events requiring medical attention after vaccination was evaluated for all study participants through the use of comprehensive hospitalization and emergency room utilization databases within Northern California Kaiser Permanente.

views conducted on 2 subsets of the study population: 1 subset receiving DTwP, and 1 set receiving DTaP concurrently.

The frequency of uncommon events requiring medical attention after vaccination was evaluated for all study participants through the use of comprehensive hospitalization and emergency room utilization databases within NCKP. Rates of utilization for specific diagnoses were compared for 30-day and 60-day exposure windows for emergency room and hospitalization, respectively. Mortality was evaluated by deaths reported within utilization databases and supplemented by California State mortality tapes to identify all mortality within the population. In addition surveillance of utilization databases maintained at NCKP was used to generate line listings for review by the investigators. All events were classified as to severity, recovery, and relation to vaccine. Events that were severe, were unexpected, or had a possible causal relationship to study vaccination were further investigated through chart

review, parent contact, or both.

Telephone interview data evaluating local and systemic reactions were analyzed by chi square or Fisher's exact test as appropriate for the expected cell counts in each 2 by 2 table. For a paired analysis of local reactions, the sign test was used to assess differences between injection sites. Analyses of hospitalizations and emergency room visits were performed with person-time-based relative risk estimates, and the associated 95% confidence limits were calculated by the exact test of incidence density function with a mid-P correction.

Immunogenicity

Immunogenicity of the conjugate vaccine was evaluated in a subset of children who received DTwP concurrently and in a subset given DTaP in the first year of life. Serum antibody responses (IgG) to the 7 pneumococcal vaccine serotypes were determined by enzyme-linked immunosorbent assay as previously described.⁶ Serum samples were obtained before the first vaccination and 1 month after the third dose. Additional samples were obtained in a subset before and after the fourth dose. Specimens were sent to Wyeth Lederle Laboratories for blinded analysis.

Geometric mean titers of antibody against each pneumococcal vaccine serotype and the percentage of subjects achieving titers of 0.15, 0.5, and 1.0 µg/mL were determined for both treatment groups. Means were evaluated for statistically significant differences using the 2 sample *t* test on a log scale. Comparison of proportions of children achieving at least a given concentration were made using Fisher's exact test.

... RESULTS ...

Study Population

Between October 1995 and August 1998, 37,868 children were enrolled into the trial; 18,927 received 1 or

more doses of pneumococcal conjugate and 18,941 received 1 dose or more of the control meningococcal conjugate vaccine. Of the children who received at least 1 dose of pneumococcal conjugate vaccine, 17,174 received at least 2 doses, 15,565 received at least 3 doses, and 10,940 received at least 4 doses. Of the children who received at least 1 dose of meningococcal conjugate vaccine, 17,196 received at least 2 doses, 15,536 received at least 3 doses, and 10,995 received at least 4 doses.

Efficacy Against Invasive Disease: Interim Analysis

At the time of the interim evaluation there were by design 17 cases of invasive disease caused by vaccine serotype in fully vaccinated children. All of these cases were in the control group with a point estimate of 100% for vaccine efficacy (95% confidence interval, 75.7% to 100%; *P* < 0.0001). Of the 17 fully vaccinated cases of vaccine serotype, 13 had a diagnosis of bacteremia, 2 of sepsis, 1 of bacteremic cellulitis, and 1 of bacteremic pneumonia. The 17 cases included cases of serotypes 6B, 9V, 14, 18C, 19F, and 23F.

In the intent-to-treat analysis of effectiveness against vaccine serotype disease after 1 dose or more of vaccine, all 22 cases of disease occurred in the control group, for a point estimate for effectiveness after 1 dose or more of vaccine of 100% (95% confidence interval, 81.4% to 100%; *P* < 0.0001). The point estimate of the effectiveness of partial vaccination was 100%, but this was not statistically significant, *P* = 0.06. Of the 5 partially vaccinated controls, 2 had a diagnosis of bacteremia, 2 of meningitis, and 1 of sepsis. There were also 8 cases of invasive disease caused by nonvaccine serotype including cases caused by serotypes 3, 10F, 11A, 18B, 19A, 23A, and 38.

Because of the high level of efficacy demonstrated at this interim evalua-

tion, termination of the trial was recommended by the Study Advisory Group. Enrollment therefore was discontinued at the end of August 1998, but blinded follow-up and per-protocol vaccination of the 2 groups was continued until April 20, 1999. Subsequently pneumococcal conjugate vaccine was offered to children who had received control vaccine.

Final Efficacy Analysis

At the time of the unblinding of the study there were 40 fully vaccinated cases of invasive disease caused by vaccine serotypes, of which 39 had occurred in controls, for an efficacy of 97.4% (95% confidence interval, 82.7% to 99.9%; $P < 0.001$) (Table 1). The 1 vaccine failure was a child with bacteremic pneumonia caused by serotype 19F who had received 4 doses of vaccine. There were 52 cases of invasive disease in the intent-to-treat analysis in the pneumococcal group for an effectiveness of 93.9% (95% confidence interval, 79.6% to 98.5%; $P < 0.001$). The 3 vaccine failures in the intent-to-treat analysis included the fully vaccinated child mentioned above, 1 child who developed acute myelogenous leukemia after vaccination and became bacteremic from serotype 19F while receiving immunosuppressive chemotherapy, and a partially vaccinated child who developed infection caused by type 6B, 317 days after a single dose.

There were 9 cases of invasive disease caused by nonvaccine serotype pneumococci. Six cases occurred in the control group (3, 6A, 11A, 18B, 19A, and 38) and 3 in children who received pneumococcal conjugate vaccine (types 10F and 38 in 2 fully vaccinated children and 1 case of an infected thyroglossal duct cyst caused by serotype 23A in a child who had received 2 doses of vaccine). Only 1 case of nonvaccine serotype disease in pneumococcal vaccine recipients was caused by a potentially cross-

reacting serotype, and that child did not have a bloodstream infection. There was no evidence in this trial of an increased risk of disease among pneumococcal vaccine recipients caused by serotypes not contained in the vaccine.

To evaluate the overall potential impact of vaccination against pneumococcal disease, an analysis was performed that compared the risk of invasive disease regardless of pneumococcal serotype. This analysis included all the cases in the intent-to-treat analysis as well as the cases that were caused by nonvaccine serotypes. There was a 89.1% (95% confidence interval, 73.7% to 95.85%; $P < 0.001$) reduction in the total invasive pneumococcal disease burden in children who had received 1 or more doses of the pneumococcal conjugate.

There were sufficient cases to evaluate the serotype-specific efficacy of vaccination against 4 of the 7 serotypes in an intent-to-treat analysis (Table 2). Point estimates for serotype-specific efficacy ranged between 84.6% and 100%. No cases were seen during the study caused by serotype 4.

Table 1. Invasive Disease Efficacy Results as of April 20, 1999

Analysis for Serotypes Contained in the Vaccine	Case Split Control: Pneumococcal Vaccine Groups	Efficacy (%)	P
Per protocol fully vaccinated	39:1	97.4 (82.7-99.9)*	< 0.001
Intent to treat	49:3	93.9 (79.6-98.5)	< 0.001
Partially vaccinated only	7:1	85.7 (0-100)	0.05
All cases regardless of serotype	55:6	89.1 (73.7-95.8)	< 0.001

*Numbers in parentheses, 95% confidence interval.

Efficacy Against Otitis Media

Data on otitis media have been analyzed through April 30, 1998. A total of 73,041 visits for otitis media and 52,789 episodes of otitis had occurred in the study population as of that time. A total of 5451 children had frequent otitis as defined by 3 episodes or more within 6 months or 4 episodes or more within 1 year. The vaccine was 7.0%

effective in preventing otitis media episodes (Table 3). The effectiveness of the vaccine against frequent otitis media increased from 9.3% to 22.8% as the frequency of episodes increased. Four hundred thirty-two children had ventilatory tube placement (VTP) during the study. Children who had received the pneumococcal conjugate vaccine were 20.1% less likely to require tube placement than controls.

Twenty-three children in the study population had positive cultures for pneumococci of vaccine serotype obtained from cultures of spontaneously ruptured tympanic membranes. In the intent-to-treat analysis there were 17 control cases and 6 cases in the pneumococcal vaccine group for a point estimate of efficacy of 64.7%, $P = 0.035$. In the analysis of fully vaccinated children there were 12 cases in controls and 4 in the pneumococcal group with a point estimate of 66.7% efficacy, $P = 0.077$. All of the vaccine failures in both analyses were serotype 19F.

The impact of vaccination on severity of otitis media episodes was also evaluated. The number of children with a given number of medical visits for 1 episode was compared in the 2 vaccine groups. In children 6 to 12 months of age, the reduction in the number of children experiencing 1, 2, 3, or 5 or more visits per episode was 2%, 6%, 15%, and 18%, respectively. Similarly for children older than 12 months of age, the reduction in the number of children experiencing 1, 2, 3, or 5 or more visits per episode was 7%, 8%, 15%, and 43%, respectively.

Safety

Reactogenicity as assessed through telephone interviews was analyzed separately for children who had received DTaP and DTwP vaccine concurrently. Rates of these local and systemic reactions for children who received whole-cell pertussis vaccine concurrently were very similar to those we have reported in a prior publication.⁷ For the children who received acellular pertus-

Table 2. Serotype Distribution of Invasive Disease as of April 20, 1999

Serotype	Case Split Control: Pneumococcal Vaccine Groups	Effectiveness (%)
19F	13:2	84.6 (32.0-98.4)*
14	11:0	100 (60.2-100)
18C	9:0	100 (49.3-100)
23F	6:0	100 (15.1-100)
6B	7:1	85.7 (-11.2-99.7)
9V	3:0	100 (-142-100)
4	0:0	

*Numbers in parentheses, 95% confidence interval.

Table 3. Efficacy Results for Otitis Media

Analysis	Per Protocol (%)	Intent to Treat (%)
Otitis media visits	8.9 (5.8-11.8)*	7.8 (5.2-10.5)
Otitis media episodes	7.0 (4.1-9.7)	6.4 (3.9-8.7)
Frequent otitis 3/4 [†]	9.3 (3.0-15.1)	9.1 (4.1-13.8)
Frequent otitis 4/5 [†]	11.9 (1.6-21.1)	10.0 (2.4-17.0)
Frequent otitis 5/6 [†]	22.8 (6.7-36.2)	12.3 (0-23.2)
Ventilatory tube placement	20.1 (1.5-35.2)	20.3 (3.6-34.1)

*Numbers in parentheses, 95% confidence interval.

[†]Number of episodes in 6 months/number of episodes in 1 year.

Table 4. Local Reactions Comparing Pneumococcal Conjugate and Meningococcal Conjugate as Well as Each of These with DTaP

Reaction	PNCRM7 (%)	DTaP (%)	P	MnCC (%)	DTaP (%)	P	PNCRM7 vs. MnCC P
Redness							
Dose 1	10.0	6.7	< 0.001	6.5	5.6	0.345	0.124
Dose 2	11.6	10.5	0.512	7.6	10.8	0.011	0.003
Dose 3	13.8	11.4	0.143	9.3	8.2	0.557	0.011
Dose 4	10.9	3.6	0.004	4.5	4.0	> 0.999	0.226
Redness > 3 cm							
Dose 1	0.3	0	0.500	0.1	0.3	> 0.999	> 0.999
Dose 2	0.0	0.2	> 0.999	0.2	0.4	> 0.999	0.481
Dose 3	0.2	0.2		1.3	0.8	0.625	0.105
Dose 4	0.6	0.6	> 0.999	0.0	0.0		0.225
Swelling							
Dose 1	9.8	6.6	0.002	4.2	4.3	> 0.999	0.013
Dose 2	12.0	10.5	0.312	5.1	7.4	0.080	0.001
Dose 3	10.4	10.4	> 0.999	6.9	8.3	0.473	0.001
Dose 4	12.1	5.5	0.013	4.5	3.4	0.688	0.247
Swelling > 3 cm							
Dose 1	0.1	0.1		0.0	0.0		> 0.999
Dose 2	0.4	0.6	> 0.999	0.2	0.0	> 0.999	> 0.999
Dose 3	0.5	1.0	0.500	0.3	0.5	> 0.999	> 0.999
Dose 4	0.6	0.6	> 0.999	0.0	0.0		0.224
Tenderness							
Dose 1	17.9	16.0	0.053	17.9	18.9	0.265	0.970
Dose 2	19.4	17.3	0.080	15.0	15.6	0.677	0.069
Dose 3	14.7	13.1	0.265	12.3	12.0	> 0.999	0.280
Dose 4	23.3	18.4	0.096	15.4	14.9	> 0.999	0.052

MnCC = meningococcal conjugate.

Table 5. Fever Within 48 Hours of Vaccination Among Infants Receiving PNCRM7 or MnCC Vaccine*

	PNCRM7		MnCC		P
	%	N	%	N	
Fever ≥ 38°C					
Dose 1	15.1	709	9.4	710	0.001
Dose 2	23.9	556	10.9	507	0.001
Dose 3	19.1	461	11.8	414	0.003
Dose 4	21.0	224	17.0	230	0.274
Fever > 39°C					
Dose 1	0.9	709	0.3	710	0.178
Dose 2	2.5	556	0.8	507	0.029
Dose 3	1.7	461	0.7	414	0.180
dose 4	1.3	224	1.7	230	> 0.999

*Concomitantly with DTaP and other recommended vaccines.

MnCC = meningococcal conjugate.

sis vaccine concurrently, rates of local and systemic reactions for doses 1 through 4 of the study are shown in Tables 4 and 5.

Swelling, redness, and fever were more common in the pneumococcal conjugate vaccine group than in the control DTaP limb. For the local reactions these differences were observed for mild reactions only, and there was no statistical difference in the rate of more severe reactions. In the primary series but not after the booster dose, fever of 38°C or higher was observed more commonly in the pneumococcal vaccine recipients than in the meningococcal vaccine controls. For a fever of 39°C or higher, this was true only after dose 2. Reactions were self-limited and resolved by the 14-day telephone interview.

Overall 513 pneumococcal vaccine recipients and 579 controls were hospitalized within 60 days of receipt of a dose of vaccine ($P = 0.047$). Rate comparisons were made for the 92 separate diagnostic categories observed, but significant differences were seen for only 2. Febrile seizures in children who had also received DTwP were more common in the pneumococcal vaccine group than in controls (7:1,

$P = 0.039$). In those who had received DTaP concomitantly, there was no such difference (4:5, respectively; $P = 0.76$). There was no clustering of febrile seizures within the 3-day period after receipt of vaccine in either group of children. Elective admissions (including ventilatory tube placement) occurred more commonly in the control group (116 controls vs. 87 pneumococcal recipients, $P = 0.048$).

Review of emergency room visits within 30 days of vaccination revealed 1188 visits in pneumococcal vaccine recipients and 1169 visits in controls ($P = 0.679$). Comparisons of 80 different diagnoses were made, revealing significant differences only for breath holding (0 controls vs. 5 pneumococcal vaccine recipients, $P = 0.031$) and cellulitis (7 controls vs. 1 pneumococcal vaccine recipient, $P = 0.039$). Cellulitis was not observed at the injection site, and no episodes were culture-positive. Of the 5 children with breath holding, 3 had a prior history of similar episodes. None of these statistical analyses takes into account the large number of multiple comparisons.

In an analysis of selected outpatient clinic visit categories, there were no significant differences between pneumococcal vaccine recipients and controls for allergic reactions/hives (10 controls vs. 12 pneumococcal recipients, $P = 0.677$), asthma, wheezing, shortness of breath, or breath holding (46 controls vs. 40 pneumococcal recipients, $P = 0.522$) within 3 days of any dose. There were significant differences in outpatient clinic visits for seizures overall (11 pneumococcal vaccine recipients vs. 28 controls, $P = 0.041$), but none of the subcategories of seizure (epilepsy, febrile seizures, afebrile seizures or seizures, type unknown) was significantly different. In addition there was no time clustering of these events in association with vaccination.

There were a total of 12 cases of sudden infant death syndrome (SIDS) observed in the study population: 4 in

Table 6. Geometric Mean Concentration to Each Pneumococcal Serotype in Subjects Receiving Primary and Booster Doses of PNCrM7 When Given With DTaP Vaccine

Pneumo Serotype	Geometric Mean Concentration (µg/mL)			
	Predose 1 (N = 61)	Postdose 3 (N = 75)	Preboost (N = 52)	Postboost (N = 41)
4	0.086	1.365	0.418	2.826
6B	0.394	2.143	1.099	8.268
9V	0.192	1.234	0.539	2.695
14	0.328	5.041	1.481	5.053
18C	0.203	1.880	0.389	3.005
19F	0.629	1.524	0.598	2.543
23F	0.223	1.207	0.310	2.783

the pneumococcal vaccine group (0.2 case per 1000 children) and 8 in controls (0.4 case per 1000 children). This compares favorably with 0.5 case per 1000 children observed in the state of California during 1996 and 1997, the most recent data available (Carole Traylor, RNC, MSN, Program Coordinator, California SIDS Program, personal communication). Of the SIDS cases 1 was observed within 1 week of pneumococcal vaccine, and 2 were observed within 1 week of meningococcal vaccine. In an age- and seasonality-adjusted analysis based on the California State SIDS data, we would have expected 1.06 cases within 1 week of either vaccine.

Immunogenicity

The antibody responses to pneumococcal serotypes in children receiving pneumococcal conjugate vaccine in controls can be seen in Table 6. A substantial immunologic response to pneumococcal polysaccharide was elicited to all 7 pneumococcal serotypes by the heptavalent pneumococcal conjugate as shown in Figure 1. There was variability in the magnitude of this response and the kinetics of decay of antibody titers before the booster dose was dependent on serotype. Before the booster dose geometric mean antibody titers fell below 1 µg/mL for all serotypes except types 6B and 14. A booster response was seen for all serotypes. Reverse cumulative distribution curves for the 7 vaccine serotypes after the primary series are shown in Figure 2. More than 95% of pneumococcal conjugate recipients developed antibody concentrations of 0.15 µg/mL or higher after dose 3 whereas more than 95% of controls were below 0.5 µg/mL.

safety and immunogenicity of this vaccine.^{6,9} It is clear from this study that PNCRM7 is efficacious in preventing pneumococcal invasive disease as well as clinical otitis media.

Figure 1. Serotype-Specific Pneumococcal Antibody Response in Children Receiving DTaP

Figure 2. Reverse Cumulative Distribution Curves of Postdose 3 Antibody Concentrations: PNCRM7 Concurrent with DTwP or DTaP

... DISCUSSION ...

This is the first report of the efficacy of pneumococcal conjugate vaccine in healthy infants and toddlers. Previous reports have detailed the

The 89.1% reduction in all cases of invasive disease is striking considering the fact that PNCRM7 contains serotypes that are responsible for only an estimated 85% of pneumococcal disease in infants and children.¹⁰ This may be a result of cross-protection among related serotypes. It is reasonable to expect a marked diminution in the total pneumococcal disease burden with licensure and widespread use of this vaccine.

Knowledge of the protection afforded by this vaccine may have a profound effect on the management of infants who present to physicians with fever and no localized signs of infection. It is likely that clinical laboratory diagnostic procedures, hospitalizations, and presumptive antibiotic use in the vaccinated children will be significantly reduced. Because the pneumococcal vaccine strains are the same strains that exhibit resistance to penicillin and other antibiotics,^{11,12} there should also be less pressure to utilize broad-spectrum antibiotics, which cause further antibiotic resistance.

Previous studies have hypothesized immunologic correlates of protection against invasive disease ranging between 0.06 and 2 µg/mL.¹³⁻¹⁶ By comparing the antibody concentrations of pneumococcal antibodies obtained in the immunized population in this trial with those in controls, it is possible to infer the antibody concentrations that are likely to be associated with protection against invasive disease in infants and children.¹⁶ As seen in Figure 2 we observed that more than 97% of pneumococcal vaccine recipients achieved 0.15 µg/mL or greater of anticapsular antibody for all serotypes after the primary series. This correlates with the observed protective efficacy of 97.3%. Conversely the majority of controls for each serotype did not have 0.5 µg/mL or more antibody. The percent of controls achieving concentrations of 0.15 µg/mL or more ranged from 5% for type 4 to 35% for type 19F.

However, the reverse cumulative distribution curves were different for each serotype in both vaccines and controls. A more conservative protective estimate could be inferred to be as high as 0.5 µg/mL. Between 82% (for type 23F) and 97% (for type 14) of vaccines achieved this titer compared with less than 6% of all controls. In fact the proportion of vaccine with titers of 0.5 µg/mL or more was less than 90% for 4 of 7 serotypes (types 4, 6B, 19F, and 23F). Because the proportion of immunized individuals achieving titers of 0.5 µg/mL is lower than the proportion protected by the vaccine, this estimate is likely to be higher than the minimum protective level. We therefore propose that the minimum antibody titer after the primary series associated with long-term protection against invasive disease is in the range of 0.15 to 0.5 µg/mL. Establishing a more precise correlate would require assessment of the specific serotype involved, the avidity of the antibody in question, and the role of priming for a response to polysaccharide antigen in protection. It is likely that titers associated with protection against mucosal pneumococcal disease and pneumonia will be different and that they might vary by serotype.

The success of PNCRM7 in causing a reduction in otitis media must be evaluated with an awareness of the role of the pneumococcus in the etiology of otitis media and the trial design. Visits and diagnosis for otitis media were based on the clinical diagnosis of otitis media. It has been estimated that 50% to 60% of otitis media cases are bacterial.¹⁷ Of these an estimated 20% to 40% are caused by pneumococci.¹⁸ The vaccine contains approximately 85% of the serotypes responsible for pneumococcal disease in infants and children.⁷ Multiplying these fractions together the maximum impact on vaccination of clinical otitis media would be expected to be 8.5% to 20%. The observed 8.9% reduction

in otitis media visits is at the lower end of expected percentages. More impressive is the protection against frequent episodes or severe otitis media, bacteriologically confirmed middle-ear pneumococcal disease, and ventilatory tube placement. PNCRM7 reduced clinical otitis media episodes by 22.8% in subjects who experienced 5 episodes in 6 months. Ventilatory tube placements were reduced by 20.1%, and bacteriologically confirmed middle-ear disease was diminished by 66.7%. The efficacy of PNCRM7 in a subset who returned for multiple otitis media visits within an episode increased from 2% to 18% in infants younger than 12 months of age and from 7% to 43% in infants older than 1 year of age as the number of visits per episode increased. Individuals who failed to respond to antibiotics or had more severe disease and thus returned more frequently to the physician had a greater benefit from vaccination. This greater degree of benefit was also experienced by children with frequent otitis media. These data suggest that both of these groups are more likely to have a pneumococcal infection and have a greater benefit from vaccination.

Among the children with spontaneously draining ears, all 6 vaccine failures were caused by serotype 19F. This is the same serotype observed in the 1 fully vaccinated invasive disease vaccine failure. Review of the immunologic response to 19F in children in our study does not suggest that these failures are a result of a suboptimal immunologic response to this serotype. However, S. Bloch (personal communication) noted that the mean antibody titer in children who developed otitis caused by types 6A or 6B was 0.23 µg/mL, whereas children who developed otitis caused by type 19F had a mean circulating antibody titer of 1.35 µg/mL. These data suggest that a higher titer of circulating antibody may be necessary to protect

against middle-ear disease caused by serotype 19F. Our study did not evaluate antibody avidity or immunologic priming, both of which may also be important factors in protection against disease.¹⁹ Follow-up with larger numbers of children in a postmarketing study is necessary to further evaluate protection induced by the heptavalent pneumococcal conjugate vaccine to serotype 19F. More data on the serotype-specific bacteriologic efficacy of PNCRM7 in otitis media will be forthcoming from a study in Finland by Eskola²⁰ that includes tympanocentesis of all otitis media.

It is worth emphasizing that in the United States there are approximately 24.5 million visits for otitis media and more than 500,000 ventilatory tube placements per year.^{21,22} Therefore, we would expect the widespread use of PNCRM7 could eliminate more than 2,000,000 visits for otitis media, with a concomitant reduction in the number of antibiotic prescriptions and a reduction of 100,000 VTPs.

After the introduction of Hib conjugate vaccination, a large herd immunity effect was seen as a result of reduction in carriage of that organism in vaccinees. It was not possible in this trial to evaluate any potential herd immunity induced by pneumococcal conjugate vaccination. Whether pneumococcal conjugate vaccination will result in a similar herd immunity effect awaits the results of an ongoing trial by Santosham and colleagues among Southwest Native Americans and widespread use of the vaccine after licensure.

Studies of carriage have suggested reduction in colonization by vaccine serotypes after pneumococcal conjugate vaccination.^{23,24} These studies have also suggested that colonization with nonvaccine serotypes may occur in vaccinated individuals. It is not known, however, whether these results are caused by true replacement by nonvaccine serotypes or unmasking of serotypes already pre-

sent in the same individuals. No evidence for an increased risk of disease caused by nonvaccine serotypes was observed in our trial.

This trial included an extensive evaluation of the safety of both the pneumococcal and meningococcal conjugate vaccines. Safety monitoring in this cohort of more than 37,000 children did not reveal any severe adverse events related to vaccination that resulted in hospitalization, emergency visits, or clinic visits. Local and systemic reactions observed were generally relatively mild with either vaccine, and more severe local and systemic reactions were uncommon and self-limited.

We conclude that when used in a 4-dose regimen at 2, 4, and 6 months of age with a booster dose in the second year of life, this heptavalent pneumococcal conjugate vaccine appeared safe and immunogenic. This vaccine was highly effective in preventing invasive disease caused by the 7 serotypes contained in the vaccine. In addition, a significant reduction in otitis media and otitis media-related events was seen and was most marked for children with frequent otitis media and for tympanostomy tube placement.

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