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ORIGINAL PAPER

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Safety and efficacy of the seven-valent pneumococcal conjugate vaccine: evidence from Northern California

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Abstract Pneumococcal disease remains a significant cause of morbidity among young children. A large-scale efficacy trial in the Northern California Kaiser Permanente system (the KP trial) demonstrated that a seven-valent conjugate vaccine (PCV) is safe and immunogenic in young children and effective in preventing both invasive pneumococcal disease caused by vaccine serotypes (97.4% efficacy) and episodes of otitis media (7.0% efficacy). Since the publication of the results of the KP trial in 2000, we have performed an additional analysis on the safety, immunogenicity, and efficacy of the vaccine in low birth weight (LBW) and preterm (PT) infants, and have examined the efficacy of the vaccine during 1 year of wide-scale post-licensure use. The vaccine was at least as immunogenic in LBW and PT infants as in normal-weight, full-term infants and was 100% effective, although the LBW and PT infants had higher rates of adverse events such as redness and swelling. LBW and PT infants receiving pneumococcal vaccine also had higher rates of adverse events, such as hives, than those receiving control meningococcal vaccine, but these reactions were not severe. When the PCV was used in the general population, the efficacy remained high and there was no corresponding increase in disease caused by nonvaccine serotypes. There was also evidence that vaccine administration led to herd immunity. Febrile illness was the only adverse event seen more frequently after vaccine administration than during a control period. *Conclusion:* the seven-valent conjugate vaccine is safe and effective for use in the general population.

Keywords seven-valent conjugate vaccine · efficacy · trial · immunogenecity

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Abbreviations *DTaP* diphtheria-tetanus-toxoid acellular pertussis · *DTwP* diphtheria-tetanus-toxoid whole cell pertussis · *FT* full-term · *IPD* invasive pneumococcal disease · *ITT* intent-to-treat · *KP* Kaiser Permanente · *LBW* low birth weight · *NBW* normal birth weight · *PCV* seven-valent conjugate vaccine · *PT* preterm

Introduction

The highest rates of invasive pneumococcal disease (IPD) and otitis media occur in children less than 2 years of age [1]. In the United States, the peak incidence of IPD, 235 per 100,000 person-years, occurs between 6 and 11 months of age [1], and the majority of children have at least one episode of acute otitis media by their first birthday [5]. In addition, otitis media is the leading reason for prescribing antibiotics during childhood [1] and therefore contributes substantially to the growing problem of antibiotic-resistant bacteria.

Despite the high rates of pneumococcal disease early in life, until early 2000 there was no pneumococcal vaccine that was routinely recommended for use in young children. The polysaccharide vaccines that have been available for decades are ineffective in infants. As a result, considerable effort has been put into developing a pneumococcal vaccine conjugated to protein that would be immunogenic in infants.

Between October 1995 and April 1999, we and our colleagues conducted a large clinical trial to evaluate a seven-valent vaccine containing the saccharides of serotypes 4, 6B, 9V, 14, 18C 19F, and 23 conjugated to CRM_{197}, a nontoxic mutant of diphtheria toxin [2]. This vaccine, produced by Wyeth Lederle, was licensed for use in the United States in February 2000.

In this paper we summarize the safety, immunogenicity, and efficacy of the seven-valent conjugate vaccine in the clinical trial, both in the whole study population and in the subset of infants who were preterm (PT) or of low birth weight (LBW). We also review the effectiveness

of the vaccine in the general population in the year after it was licensed. These data have been published previously [2, 3,10].

Subjects and methods

Clinical trial

A double-blind study was conducted at 23 Northern California Kaiser Permanente (KP) medical centers [2], in which 37,868 infants were randomized to receive either the Wyeth Lederle sevenvalent pneumococcal conjugate vaccine (PCV) or a meningococcus type C conjugate vaccine as a control. Study vaccine was given at 2, 4, 6, and 12 to 15 months of age, concomitantly with other routine childhood vaccines. Children with sickle-cell disease, known immunodeficiency, any serious chronic or progressive disease, a history of seizures, or a history of pneumococcal or meningococcal disease were excluded from the study.

Safety

Information about local and systemic reactions was obtained by telephone interview 48 to 72 h and 14 days after each dose. The frequency of uncommon events requiring medical attention after vaccination was evaluated through the use of comprehensive hospitalization and emergency room utilization databases. The incidence of these events was followed for 30 days following vaccination for events in hospitalized children and for 60 days for events seen in the emergency department. Adverse events that were severe, unexpected, or had possibly been caused by the study vaccine were followed up through chart review, parent contact, or both.

Invasive disease

The primary outcome measure was the incidence of IPD caused by vaccine serotypes. To be included in the main efficacy analysis, the disease must have been caused by a vaccine serotype, occurred more than 14 days after the third dose of the vaccine, and occurred in a subject vaccinated according to protocol. Children less than 16 months of age were considered to be fully vaccinated if they had received three or more doses of vaccine; children at least 16 months of age were considered to be fully vaccinated after receipt of a fourth dose. In addition to the per-protocol analysis, an intent-to-treat (ITT) analysis was performed that included all invasive disease caused by any pneumococcal serotype occurring after randomization, regardless of whether the child had completed the three-dose primary series or received the booster dose.

Otitis media

The primary otitis media outcome measure was the number of episodes of otitis media in fully vaccinated infants. Each clinic visit was considered a new episode unless it met the criteria for a follow-up visit, which included any visit that was the second within 21 days, or which occurred 21 to 42 days after a previous visit and for which an appointment had been made at least 3 days in advance. Additional otitis outcomes included differences between the groups in effectiveness against frequent otitis media, in the number of placements of ventilatory tympanostomy tubes, and in the number of cases of spontaneously draining tympanic membranes with a culture positive for a vaccine-serotype pneumococcus.

Post-licensure evaluation

A post-licensure follow-up study was conducted after the vaccine was approved for use in infants in February 2000. In April 2000, the vaccine was introduced into the general KP population, and it began to be used routinely by June 2000. Using the KP databases, we compared age-specific disease incidence in both vaccinated and unvaccinated children during the year following vaccine introduction with age-specific disease within the KP population during the 5 years before vaccine licensure.

Results

Safety

In all subjects, local reactions were mild, self-limited, and did not escalate with dose. Mild swelling and redness were more common at the site of pneumococcal vaccine injection than at the site of the diphtheria-tetanus-toxid acellular pertussis (DTaP) vaccine injection in the other limb and were also more common following PCV than following the control meningococcal vaccine. No differences were seen for more severe reactions. Fever higher than 38°C was observed more often in the pneumococcal vaccine group than in the control meningococcal vaccine group ($P \leq 0.003$ for Doses 1–3). For fever greater than 39°C, this was true only after Dose 2 ($P = 0.029$).

Within 60 days of receipt of a vaccine, 1092 subjects were hospitalized (513 PCV recipients, 579 controls, $P = 0.047$), and 92 diagnostic categories were observed in these subjects. However, significant differences were seen for only two diagnostic categories, febrile seizures and elective admissions. Febrile seizures requiring hospitalization were more common in PCV recipients than in controls, but only in those patients who had received diphtheria-tetanus toxoid-whole cell pertussis vaccine (DTwP) at the same time (seven PCV, one control; $P = 0.039$); there was no difference in rate of seizure between recipients of PCV and control vaccine who had received a concomitant DTaP vaccine (four PCV, five controls; $P = 0.76$). There was no clustering of febrile seizures within the 3-day period following vaccine administration, and furthermore, the rates of seizure in this study were below the historic rates of seizure seen following DTwP vaccination. Rates of sudden infant death syndrome were also similar to or lower than those expected from historical data. Elective admissions, including ventilatory ear tube placement, occurred more frequently in the control group (116 controls versus 87 recipients of PCV, $P = 0.043$). In an analysis of selected categories of outpatient clinic visits, there were no significant differences between PCV recipients and controls in any category except overall seizures, which occurred more frequently in controls; no seizure subcategory was different between the two groups, and there was no time clustering of the seizures relative to vaccination.

An analysis of vaccine effects in LBW and PT infants found that LBW infants had higher rates of serious redness and swelling (> 3 cm) than normal birth weight (NBW) infants following the third dose in the primary series, and LBW infants receiving PCV had higher rates of hives compared with those receiving control vaccine,

but not compared with NBW infants. PT infants had swelling >2.4 cm more often than full-term (FT) infants. PT infants receiving PCV had stronger reactions than those receiving control meningococcal vaccine: fever >38°C, swelling, tenderness at injection site, irritability, loss of appetite, vomiting, diarrhea, and hives all occurred more frequently than in PT infants receiving control vaccine. However, these reactions were not severe enough to preclude the use of PCV in PT infants.

Immunogenicity

All seven vaccine serotypes elicited a substantial immunologic response in all subjects, although the absolute magnitude varied (Fig. 1). More than 95% of those who received the PCV developed a geometric mean concentration of antibody of at least 0.15 μg/ml after the third dose, but only antibodies against 6B and 14 remained at concentrations above 1 μg/ml before the booster dose was given. A booster response was seen for all serotypes.

Most infants, regardless of birth weight or gestational age, achieved serum antibody concentrations of at least 0.15 μg/ml following vaccination, and there was no significant difference between the groups on this measure. There was also no significant difference in geometric mean titer between LBW and NBW infants, but PT infants had significantly higher serum concentrations of antibodies against serotypes 19F, 9V, and 4 than did FT infants.

Efficacy

Of the 37,868 children enrolled in the trial, 18,927 received one or more doses of PCV and 18,941 received one or more doses of meningococcal conjugate vaccine. In the per-protocol analysis, 40 cases of IPD were seen in fully vaccinated children. Of these, 39 were in the control group, representing a vaccine efficacy of 97.4% (95% confidence interval 82.7% to 99.9%, $P < 0.0001$). The one vaccine failure was a child who had received four doses of vaccine, yet developed bacteremic pneumonia caused by serotype 19F.

In the ITT analysis, there were 52 cases of vaccine-serotype IPD, three of which were in recipients of the PCV, representing a vaccine efficacy of 93.9%. The three failures included the one described above, a child who developed leukemia after vaccination and was receiving immunosuppressive chemotherapy, and a partially vaccinated child who developed a 6B infection 317 days after a single dose of vaccine. We were able to determine point estimates of serotype-specific efficacy for four vaccine serotypes, which ranged from 84.6% for serotype 19F to 100% for serotypes 14, 18C, and 23F.

There was no evidence of an increased risk of disease caused by nonvaccine serotypes. Nine cases of IPD caused by pneumococci of nonvaccine serotype occurred during the study, six in the control group and three in vaccinated children. Only one case was caused by a potentially cross-reactive serotype in a vaccinated child. The ITT analysis revealed an 89.1% reduction in the total IPD burden in children who had received at least one dose of conjugate vaccine. This is particularly striking considering that the vaccine serotypes are responsible only for an estimated 85% of pneumococcal disease in infants and children.

Otitis media

On the primary otitis media measure, the vaccine was 7.0% effective (95% CI 4.1%–9.7%) in the per-protocol analysis. The efficacy of the vaccine increased as the frequency of the episodes increased, reaching 22.8% in children who had five episodes of otitis within 6 months. Children who received the PCV were also 20.1% less likely to require ventilatory tube placement than controls.

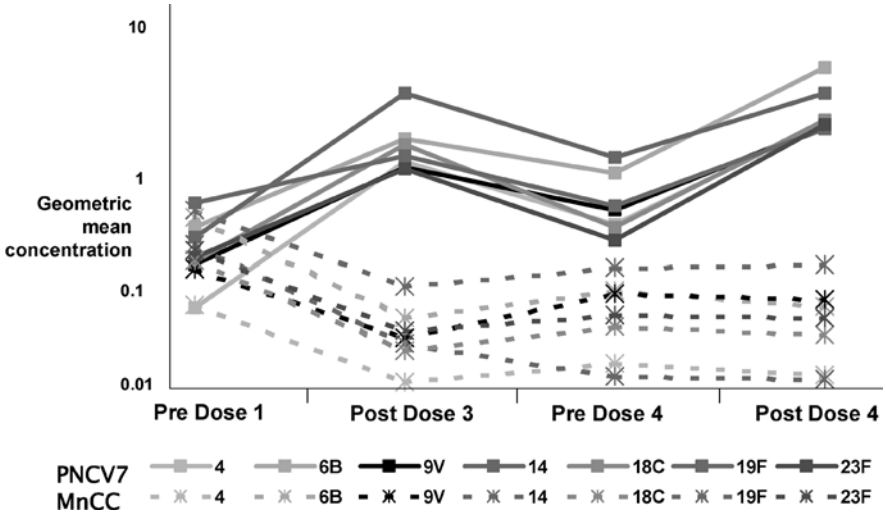

Fig. 1 Serotype specific pneumococcal antibody response in children receiving DTaP

Of the children in the study, 23 had spontaneously ruptured tympanic membranes which yielded cultures positive for vaccine-serotype pneumococci. In the per-protocol analysis, there were four cases among children who had received PCV and 12 among the controls (point estimate of efficacy 66.7%, $P = 0.077$). In the ITT analysis, there were six cases among children who had received PCV and 17 among the controls (point estimate of efficacy 64.7%, $P = 0.035$). All of the vaccine failures in both analyses were of serotype 19F. The PCV also reduced the severity of otitis episodes, as estimated by the number of medical visits for each episode. The number of children making five or more visits per otitis episode was reduced by 18% for children aged 6 to 12 months, and by 43% for children older than 12 months of age. The total number of visits per child was also reduced by 11.0% for five or more visits ($P = 0.001$) up to 15.4% for 15 or more visits ($P = 0.0114$) (Fig. 2).

	% Reduction (95% CI)	P-Value
All Otitis Visits	8.2% (5.6, 10.6)	0.0001
All Otitis Episodes	5.8% (3.7, 7.8)	0.0001
Total Otitis Visits/Child		
≥ 5	11.0% (7.4, 14.5)	0.0001
≥ 10	14.7% (8.1, 20.8)	0.0001
≥ 15	15.4% (3.7, 25.6)	0.0114
Ear Tube Placement	24.9% (13.1, 35.1)	0.0001

Fig. 2 Otitis media efficacy (per protocol as of April 20, 1999)

	Disease in Controls	Disease in PNCV7 Vaccine Recipients	Efficacy	P-Value*
Birthweight < 2500 g (N=1762)	6	0	100%	0.031
Gestational Age < 38 wks (N=4314)	9	0	100%	0.004
< 37 wks (N=2374)	6	0	100%	0.031

* Fisher Exact Test

Fig. 3 Vaccine efficacy against invasive disease of vaccine serotypes by gestational age and birth weight

Efficacy of the PCV was also analyzed separately for the LBW and PT infants who had been included in the KP study. Although the study protocol required that patients be vaccinated at outpatient clinics, LBW and PT infants were eligible once they were discharged from the hospital. No difference in mean age of administration of vaccine resulted for LBW and PT infants compared to NBW and FT infants. For LBW infants who received the control vaccine, the relative risk of IPD was 2.6 compared with NBW infants, and for PT infants the relative risk was 1.6 compared with FT infants. However, no LBW or PT recipient of pneumococcal vaccine contracted an IPD, compared with six LBW infants who received the control meningococcal vaccine and nine PT controls; the vaccine was therefore 100% efficacious for both groups (Fig. 3).

Post-licensure use

Between April 2000 and March 2001, 44,946 of the more than 200,000 children in the KP system less than 5 years of age received 152,041 doses of PCV. In this time period, an average of 57.8% of children less than 1 year of age received at least one dose of vaccine; the averages were 52.6% and 34.3% for children less than 2 and 5 years of age, respectively. The percentages of children who were fully vaccinated were considerably lower (13.6% to 16.2%). However, the impact on disease was greater than expected based on vaccination rates: in children less than 1 year of age, an 87.3% reduction was seen in IPD caused by vaccine serotypes, in children less than 2 years of age the reduction was 58.1%, and in children less than 5 years of age the reduction was 62.4%. There was no corresponding increase in disease caused by nonvaccine serotypes (Fig. 4).

Discussion

Supporting the results of previous studies [4, 7, 8, 9], we have shown the PCV to be safe and immunogenic in

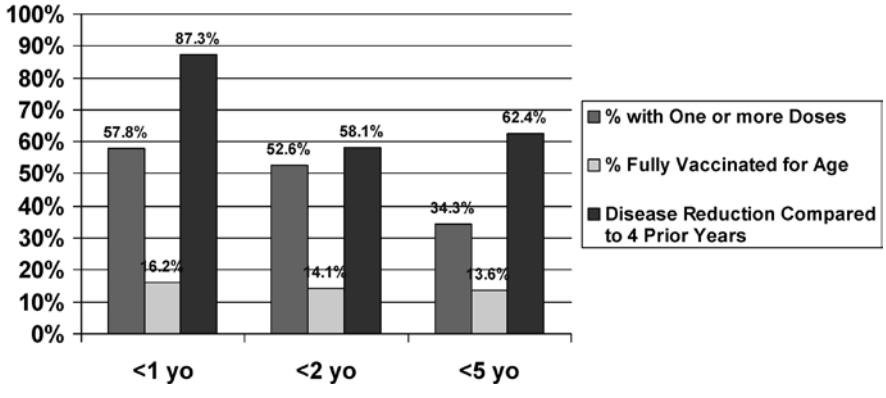

Fig. 4 Vaccine coverage and disease reduction observed since licensure (February 2000–March 2001)

infants, and have extended this finding to specifically include LBW and PT infants, who do not always respond to vaccination as robustly as FT, NBW infants [6]. We have also shown that the PCV is highly effective in preventing invasive disease caused by the seven vaccine serotypes when administered in a three-dose primary series supplemented with a booster dose at 12 to 15 months of age. Even when this vaccination schedule is not strictly followed, the protection afforded by the vaccine is considerable: in the clinical study, the vaccine was 89.1% effective against IPD in an ITT analysis that considered disease caused by all serotypes and in all subjects who had received at least one dose of vaccine. Most importantly, however, the vaccine resulted in a substantial reduction in the incidence of invasive disease when used in the general population: an 87.3% reduction in children less than 1 year of age, a 58.1% reduction in children less 2 years of age, and a 62.4% reduction in children less than 5 years of age. Because these reductions are higher than the percentage of children who had been even partially vaccinated, and much higher than the percentage that had been fully vaccinated, it appears that the vaccine protects unvaccinated as well as vaccinated children; that is, its use results in a herd immunity effect.

The vaccine also protected infants and toddlers against otitis media. It has been estimated that only 50% to 60% of clinical episodes of otitis media are bacterial in origin. Of these, 20%–40% are caused by pneumococcal bacteria, and the vaccine contains 60% to 85% of the pneumococcal serotypes that cause disease. By multiplying these percentages together, the theoretical impact of the vaccine can be calculated to be a reduction in episodes of otitis media between 6% and 20%. The reduction seen in the per-protocol analysis, 7.0%, is at the lower end of this range; however, the impact of the vaccine was much more pronounced when severe or frequent episodes and ventilatory tube placements were considered, and the number of medical visits per episode was also reduced. This suggests that severe, frequent, or antibiotic-resistant cases of otitis, which are more likely to result in increased numbers of medical visits and ventilatory tube placements, are also more likely to be caused by pneumococci.

Six children who had received vaccine experienced a ruptured tympanic membrane; all had cultures positive for serotype 19F. This is the same serotype that caused the only case of IPD in a fully vaccinated child. Although there appeared to be an adequate immunogenic response to serotype 19F, it is possible that a higher titer of circulating antibody is required to protect against disease caused by 19F than that caused by other serotypes. This may be due to differences in antibody avidity or immunogenic priming.

We have shown that the PCV licensed for use in the United States is safe, immunogenic, and extremely effective in reducing the incidence of pneumococcal disease, even resulting in a herd immunity effect when used in the general population. Although we observed no increase in IPD caused by nonvaccine serotypes during the clinical trial or during the 1st year of general use, continued surveillance is necessary to determine whether ongoing use will lead to serotype replacement in the future.

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