Clinical experience with pneumococcal conjugate vaccines in infants and children

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Streptococcus pneumoniae is a leading cause of morbidity and mortality in pediatric patients, particularly in infants and children younger than 2 years. Each year, S pneumoniae is responsible for significant morbidity and mortality in the United States. During the past several decades, the emergence of penicillin-nonsusceptible and multidrug-resistant pneumococcal isolates has become a major cause for concern, with the overuse or inappropriate use of antibiotics playing a significant role in the increase of resistance. Because the resistance of S pneumoniae to antibiotics has complicated the treatment of pneumococcal infections, attention has focused on the need to prevent disease through vaccination. The objective of this article is to describe the rationale for the development of pneumococcal conjugate vaccines and to summarize the clinical experience to date with these vaccines in infants and children.

(Key words: antibiotic resistance, pediatrics, PnC-OMP, PNCRM7, pneumococcal disease prevention, pneumococcal vaccine, Prevenar/Prevnar, Streptococcus pneumoniae)

S pneumoniae is one of the leading causes of morbidity and mortality in children. This ubiquitous organism, which often colonizes the human nasopharynx, causes a variety of localized, noninvasive (eg, sinusitis, otitis media) and invasive (eg, meningitis, bacteremia) infections. The burden of pneumococcal disease cannot be understated, as S pneumoniae is responsible for approximately 17,000 cases of invasive disease annually, including 700 cases of meningitis and 200 deaths, in children younger than 5 years.1 Furthermore, worldwide estimates from the World Health Organization suggest that pneumococcal pneumonia causes more than 1 million deaths in children each year.2

Although most clinicians are concerned with the morbidity and mortality associated with pneumococcal meningitis, other forms of pneumococcal disease have a significant impact on the healthcare system as well. The foremost cause of upper respiratory tract disease is S pneumoniae, the most common bacterial pathogen isolated from cases of otitis media and acute sinusitis.3 In addition, S pneumoniae is responsible for more than 90% of all cases of bacteremia in febrile children younger than 2 years.1,4

Those at greatest risk for infections caused by S pneumoniae are the elderly (those aged 65 years and older), infants, and children younger than 2 years (Table 1).1,5 Although the incidence of invasive pneumococcal disease (eg, pneumonia, bacteremia, and meningitis) peaks for children aged 6 to 18 months, children aged up to 5 years remain at risk.1,6,7 This age group is particularly vulnerable to infection for several reasons, including an incompletely developed anatomy, an immature immune system response, and frequent exposure and colonization by S pneumoniae.

During the past several decades, the emergence of penicillin-nonsusceptible and multidrug-resistant pneumococcal isolates has become a major cause for concern, with the overuse or inappropriate use of antibiotics playing a significant role in this increase.6-10 In addition, the spread of drug-resistant organisms has been linked with child care attendance, as evidenced by the particularly high antibiotic resistance rates noted in children who attend out-of-home child care.8,11,12 Because the increased resistance of S pneumoniae to antibiotics has complicated the treatment of pneumococcal infections, attention has focused on the need to prevent pneumococcal disease through vaccination. This review describes the rationale for the development of pneumococcal conjugate vaccines and summarizes the clinical experience to date with these vaccines in infants and children.

Effects on nasopharyngeal colonization

Bacterial pathogens such as S pneumoniae are frequently found as part of the normal flora in the upper respiratory tract of healthy individuals, as well as in those with disease.12,13 Because S pneumoniae pathogens are spread from person to person in droplets of respiratory tract secretions, nasopharyngeal colonization plays a major role in the pathogenesis and transmission of pneumococcal diseases.11,12 Children also play an important role in the transmission of pneumococcal disease, as nasopharyngeal carriage rates are highest in preschool-aged children, especially among those who attend daycare centers and live-in institutions.14-17 In addition, children influence carriage rates in adults. In households with children, 18% to 29%...
of adults are carriers, compared with 6% of adults who live in households without children. Thus, vaccines that effectively reduce the nasopharyngeal carriage of \textit{S} \textit{pneumoniae} would be expected to reduce the overall incidence of pneumococcal disease. Indeed, several studies have shown that pneumococcal conjugate vaccines reduce the nasopharyngeal carriage of vaccine-type \textit{S} \textit{pneumoniae}.\cite{19,24}

**Prevention: Rationale for developing pneumococcal conjugate vaccines**

As the prevalence of drug-resistant \textit{S} \textit{pneumoniae} has increased, immunization has emerged as the best strategy for controlling pneumococcal disease in infants and children. However, the development of a vaccine for this age group—specifically, one that effectively induces the formation of antibodies to the pneumococcal polysaccharide capsule—has posed a significant challenge.

Differences in the polysaccharide capsule of \textit{S} \textit{pneumoniae} account for the differing virulence among strains. Based on these differences, more than 90 structurally and antigenically distinct types of \textit{S} \textit{pneumoniae} have been identified, classified into serogroups (designated by numbers such as 1, 2, 3), and further subdivided into serotypes (designated by letters such as A and B). The serotypes associated with invasive disease and penicillin resistance vary geographically. In the United States, the seven pneumococcal serotypes most frequently associated with invasive disease are 4, 6B, 9V, 14, 18C, 19F, and 23F.\cite{4,25,26}

These seven serotypes also account for 80% to 90% of antibiotic-resistant pneumococcal strains in most US reports.\cite{27,28} The serogroups most frequently associated with otitis media somewhat overlap those of invasive disease, and include 3, 6, 9, 14, 18, 19, and 23.\cite{25,29}

The currently licensed polysaccharide pneumococcal polyvalent vaccines (ie, Pneumovax 23 and Pnu-Imune 23) contain antigens for 23 different capsular polysaccharides, providing protection against the pneumococcal strains that cause 85% to 90% of invasive infections in developed countries.\cite{14}

Although these vaccines are immunogenic in children 2 years and older, they fail to induce an adequate immune response in children younger than 2 years, presumably because of the T-cell–independent nature of the immune response to polysaccharide antigens.\cite{30} Furthermore, the 23-valent pneumococcal polysaccharide vaccines have limited efficacy for reducing the incidence of otitis media, have no effect on nasopharyngeal carriage of \textit{S} \textit{pneumoniae}, and do not elicit a booster response with repeated exposure to the bacteria.\cite{1,14,31,32} All these factors limit the use of the pneumococcal polysaccharide vaccine in the population at greatest risk for invasive pneumococcal disease, infants and children younger than 2 years.

Protein conjugate vaccines have recently been developed to address the limitations of the polysaccharide vaccines in eliciting an adequate immunologic response in these young children. This approach of vaccine development involves the covalent linking of the polysaccharide to a protein to enhance immunogenicity and increase serum antibody levels by stimulating a T-helper cell response that primes for a booster response. This approach is identical to that used to develop the protein conjugate vaccine for \textit{Haemophilus influenzae} type b, and has been shown to stimulate T-cell–dependent responses in infants and children, thus providing successful protection against pneumococcal infection.\cite{33,34}

Unlike the experience with the \textit{Haemophilus influenzae} type b vaccine, however, the pneumococcal conjugate vaccine will need to provide protection against a broad range of serotypes that not only vary by geographic location, but also by age group. Based on epidemiologic data, several different combination pneumococcal conjugate vaccines have been developed, each containing the capsular antigen for several (from 4 to 11) of the predominant serotypes. The pneumococcal conjugate vaccines currently in clinical development are listed in Table 1. Of these, only the heptavalent pneumococcal vaccines conjugated to a nontoxic diphtheria variant have been approved by the Food and Drug Administration for use in infants and children younger than 2 years against invasive disease due to \textit{S} \textit{pneumoniae}. \textit{Pneumococcal 7-valent Conjugate Vaccine (Diphtheria CRM197 Protein) (PNCRM7 [Prevnar/Prevenar])} is directed against serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F, and protects against 85% or more of the invasive pneumococcal disease in the United States. Worldwide, this vaccine can protect against 50% to 70% of pediatric pneumococcal invasive disease.\cite{25,26} By comparison, the 9-valent and 11-valent vaccines

<table>
<thead>
<tr>
<th>Age, y</th>
<th>Cases</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (Rate)</td>
<td>No. (Rate)</td>
</tr>
<tr>
<td>&lt;1</td>
<td>394 (147.8)</td>
<td>9 (3.4)</td>
</tr>
<tr>
<td>1</td>
<td>433 (161.6)</td>
<td>8 (3.0)</td>
</tr>
<tr>
<td>2-4</td>
<td>242 (30.1)</td>
<td>4 (0.5)</td>
</tr>
<tr>
<td>5-17</td>
<td>137 (3.8)</td>
<td>5 (0.1)</td>
</tr>
<tr>
<td>18-34</td>
<td>291 (6.0)</td>
<td>11 (0.2)</td>
</tr>
<tr>
<td>35-49</td>
<td>831 (17.1)</td>
<td>97 (2.0)</td>
</tr>
<tr>
<td>50-64</td>
<td>678 (23.2)</td>
<td>92 (3.1)</td>
</tr>
<tr>
<td>&gt;65</td>
<td>1270 (58.1)</td>
<td>234 (10.7)</td>
</tr>
<tr>
<td>Total</td>
<td>4276 (21.6)</td>
<td>460 (2.3)</td>
</tr>
</tbody>
</table>

The safety and immunogenicity of two tetravalent pneumococcal conjugate vaccines have been evaluated in infants. These vaccines consist of serotypes 6B, 14, 19F, and 23F, and are conjugated to either tetanus toxoid (ie, PnC-T) or diphtheria toxoid (ie, PnC-D). Both vaccines were well tolerated, immunogenic, and induced immunologic memory when administered as a series at ages 2, 4, and 6 months and followed by a booster dose of the 23-valent polysaccharide vaccine at 12 months.

The safety and immunogenicity of PNCRM7 has been established in two clinical trials. In both studies, healthy infants were given the pneumococcal conjugate vaccine or the control, an investigational meningococcal group C conjugate (MnCC) vaccine, at ages 2, 4, and 6 months, followed by a booster dose at 12 to 15 months. Routine immunizations were administered concomitantly. Following the third dose of vaccine, postvaccination antibody concentrations of 0.15 μg/mL being investigated for use in developing countries are expected to increase global coverage to 75% and greater than 80%, respectively.

**Pneumococcal conjugate vaccines Safety and immunogenicity**

The safety and immunogenicity of any vaccine is foremost in the minds of clinicians. All the pneumococcal conjugate vaccines that have been tested to date in infants as young as 2 months appear to be well tolerated, with local reactions occurring less frequently than with concomitantly administered diphtheria, pertussis, and tetanus vaccines. Of note, the pneumococcal conjugate vaccines induce immunologic memory through a T-cell–dependent response, thereby inducing a booster antibody response with subsequent doses of either conjugate or pure polysaccharide vaccine.

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### Table 2

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Serotypes</th>
<th>Protein component</th>
<th>Approved use</th>
<th>Investigational use</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tetravalent</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PnC-D</td>
<td>6B, 14, 19F, 23F</td>
<td>Diphtheria toxoid</td>
<td></td>
<td>Vaccination of infants and children against invasive and noninvasive disease.</td>
</tr>
<tr>
<td>PnC-T</td>
<td>6B, 14, 19F, 23F</td>
<td>Tetanus toxoid</td>
<td></td>
<td>Vaccination of infants and children against invasive and noninvasive disease.</td>
</tr>
<tr>
<td><strong>Heptavalent</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PNCRM7*</td>
<td>4, 6B, 9V, 14, 18C, 19F, 23F</td>
<td>Nontoxic diphtheria variant (CRM197)</td>
<td>Vaccination of infants and children against invasive disease caused by Streptococcus pneumoniae due to capsular serotypes included in the vaccine and administered at ages 2, 4, 6, and 12 to 15 months.</td>
<td>Vaccination of infants and children against acute otitis media.</td>
</tr>
<tr>
<td>PNC-OMP</td>
<td>4, 6B, 9V, 14, 18C, 19F, 23F</td>
<td>Meningococcal outer membrane protein of group B</td>
<td></td>
<td>Vaccination of infants and children against invasive and noninvasive disease.</td>
</tr>
<tr>
<td><strong>9-valent</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PNCRM9</td>
<td>1, 4, 5, 6B, 9V, 14, 18C, 19F, 23F</td>
<td>Nontoxic diphtheria variant (CRM197)</td>
<td></td>
<td>Vaccination of infants and children against invasive and noninvasive disease.</td>
</tr>
</tbody>
</table>

*PNCRM7 was approved by the US Food and Drug Administration in February 2000 for immunization of infants and children at ages 2, 4, and 6 months with a booster dose at ages 12 to 15 months.
or more were present in 92% to 100% of children who received PNCRM7. A sharp booster response to each of the seven vaccine serotypes was demonstrated after the fourth dose, indicating that the vaccine induces immunologic memory. Of note, antibody levels against every serotype were significantly higher after the booster dose compared with the third dose of vaccine.35,39

Infants were also monitored for local reactions (eg, erythema, induration, and/or tenderness) at the injection site. Fewer children experienced reactions at the PNCRM7 site of injection than at the site of concurrently administered routine immunizations; these reactions were generally mild and typically resolved within 72 hours.35,39,40 Interestingly, the incidence of local reactions did not increase with subsequent doses of PNCRM7, a phenomenon that has frequently been noted with the pneumococcal polysaccharide vaccines.40 Fever of 39°C (102.2°F) or higher was observed more frequently in the PNCRM7 group than in the control group after the second dose of vaccine; however, reactions were self-limited and resolved within 14 days of onset.39

Also currently under development—and containing the same pneumococcal serotypes included in PNCRM7—is a pneumococcal heptavalent vaccine conjugated to the outer membrane protein complex of Neisseria meningitidis (PnC-OMP). The difference between the two vaccines is that PnC-OMP is conjugated to a meningococcal outer membrane protein, whereas PNCRM7 is conjugated to a nontoxic diphtheria variant. The safety and immunogenicity of PnC-OMP has been investigated in a small-scale trial consisting of 25 infants who received the vaccine at ages 2, 4, and 6 months.36 In 20 of these infants, the 23-valent polysaccharide vaccine was administered as a booster dose at 12 to 15 months. The PnC-OMP vaccine was well tolerated and produced significant increases in the levels of antibodies to all vaccine serotypes after two or three doses. In addition, the 23-valent polysaccharide vaccine booster induced antibody responses for all serotypes.

Conjugating the serotypes 1, 4, 5, 6B, 9V, 14, 18C, 19F, and 23F to the diphtheria CRM197 protein has created a 9-valent vaccine. Results from a double-blind, placebo-controlled trial in Soweto, South Africa, involving 500 infants given the vaccine at ages 6, 10, and 14 weeks indicated that the vaccine was well tolerated, induced high levels of antibodies to the target serotypes and significantly reduced the carriage of penicillin- and cotrimoxazole-resistant pneumococci 9 months after vaccination.41

**Pneumococcal nasopharyngeal carriage**

A subset of patients in a large, randomized efficacy trial were evaluated for PNCRM7 efficacy compared with MnCC on nasopharyngeal carriage rates among Native American children and their household members.42 Of the 563 vaccinated children and 288 unvaccinated household members, pneumococcal carriage rates of vaccine serotypes were 39% and 46%, respectively, in the first year. By the second year, carriage rates dropped to 22% in the vaccinated children and 11% in the household members. Thus, vaccination not only resulted in decreased nasopharyngeal carriage rates among children, but it also reduced the carriage rate among other household members. The precise efficacy of PNCRM7 compared with MnCC will be determined after unblinding and study completion.42

**Efficacy**

Data on the ability of pneumococcal conjugate vaccines to prevent disease are only available for PNCRM7, and are primarily the result of a large, prospective, randomized clinical trial conducted by the Northern California Kaiser Permanente Vaccine Study Center (KPVSC) in Oakland, Calif.39 This trial was designed to determine the efficacy of PNCRM7 against invasive pneumococcal disease. The reduction in the incidence of acute otitis media was an important secondary endpoint.

Infants within the Northern California Kaiser Permanente Health System were randomly assigned at 2 months to immunization with either PNCRM7 (n = 18,927) or an experimental MnCC vaccine (control, n = 18,941) at ages 2, 4, and 6 months, followed by a booster dose of the vaccine at 15 months.39 The first data analysis was conducted after 17 confirmed cases of invasive pneumococcal disease had been recorded. By this time, the majority of the children had received all four doses of the vaccine. These preliminary results demonstrated the remarkable efficacy of PNCRM7: all 17 cases of invasive vaccine-serotype pneumococcal disease had occurred in the control group, giving a calculated efficacy of 100% (95% confidence interval; 75.7%–100%; P < .001 by the Clopper-Pearson Exact Binomial Method). These unequivocal results led to the early cessation of the trial in August 1998. However, blinded follow-up and protocol vaccination continued until April 1999 (final efficacy analysis), at which time 40 documented cases of invasive disease caused by vaccine serotypes had occurred; 39 of which were in the control group, for an efficacy rate of 97.4% (95% confidence interval; 82.7%–99.9%; P < .001).39 As of August 2000, there were an additional six vaccine-specific serotype cases of invasive disease reported, all of which were in the MnCC control group.43 Furthermore, in a post-licensure evaluation of PNCRM7 in the KPVSC trial population, the incidence of invasive pneumococcal disease caused by vaccine serotypes was substantially reduced.44 For children younger than 1 year, the incidence of invasive disease caused by the vaccine serotypes dropped from a range of 51.52 to 98.15 cases per 100,000 person-years before licensure and routine use of pneumococcal conjugate vaccine to 9.35 cases per 100,000 person-years after the vaccine’s introduction.44 For children younger than 2 years, incidence of invasive disease dropped from a range of 81.7 to 113.80 cases per 100,000 person-years to 38.22 cases per 100,000 person-years.44 No increases in cases with crossreacting or nonvaccine serotypes occurred.

The efficacy of PNCRM7 against otitis media has also been analyzed in two studies: the KPVSC trial and the Finnish Otitis Media (FinOM) study.39,44 Although the KPVSC trial
was not designed to determine the rate of pneumococcal otitis media, the overall impact of vaccination on the total rates of otitis media due to any cause was measured. The FinOM study used direct assessment (routine tympanocentesis) of the impact of the vaccine in pneumococcal otitis media. Overall, the results from these studies demonstrated that vaccination with PNCRM7 resulted in a 6% to 7% reduction in physician-diagnosed episodes of acute otitis media.39,44,45 Acute otitis media caused by culture-confirmed, vaccine-specific serotypes decreased by 57% in the KPVS trial and by 67% in the FinOM study,39,44 and the need for tympanotomy was reduced by 20.1% in the KPVS trial and by 39% in follow-up evaluation of children aged 2 to 5 years in the FinOM study.39,46

The greatest impact of the vaccine on the prevention of otitis media seems to be found in children with frequent episodes of acute otitis media. In the KPVS trial, otitis media was reduced by 7% overall; however, when the effectiveness of the vaccine was examined in children with frequent episodes of otitis media, the efficacy increased from 9.3% to 22.8% as the frequency of episodes increased.39 While the overall impact on otitis media may appear modest, it should be noted that not all cases of otitis media are bacterial in origin, nor is S pneumoniae the only bacterial cause of otitis media. In addition, PNCRM7 does not contain antigens for all the most common S pneumoniae serotypes that cause otitis media.

Comment

Invasive pneumococcal infections are a leading cause of morbidity and mortality in the United States and throughout the world. The resistance of this organism to antibiotics continues to rise at an alarming rate. Children younger than 2 years are at high risk for pneumococcal infection, a problem compounded by daycare attendance, which further increases the risk of transmission of pneumococcal disease. The increase in antibiotic-resistant S pneumoniae has focused attention on the prevention of disease through vaccination.

The 23-valent pneumococcal polysaccharide vaccines, though efficacious in older children, fail to produce an adequate immune response in children younger than 2 years. Consequently, a number of pneumococcal conjugate vaccines have been developed and have demonstrated excellent safety, immunogenicity, and efficacy. The recently approved PNCRM7 is safe, immunogenic, and decreases nasopharyngeal carriage of S pneumoniae. Clinical efficacy data of PNCRM7 demonstrated that the vaccine virtually eliminates invasive pneumococcal disease caused by the targeted serotypes, and reduces the incidence of acute otitis media. Pneumococcal 7-valent Conjugate Vaccine (Diphtheria CRM197 Protein) should have a significant positive impact on the costs of healthcare and may slow the emergence of antibiotic resistance among pneumococci by decreasing the prophylactic and therapeutic use of antibiotics.

Several unanswered questions remain surrounding the use of pneumococcal conjugate vaccines:

- Is there a role for immunization of pregnant women, to provide passive immunity to infants younger than 6 months (until active immunity is induced by vaccination of the infant)?
- Will vaccination exert ecologic pressure on the S pneumoniae population? Would that ecologic pressure induce alterations in the serotype epidemiology?
- Will nontargeted serotypes fill the vacuum left by targeted serotypes? Would this ecologic pressure induce alterations in the genes controlling the polysaccharide capsules of targeted serotypes (via transfer of genetic information from nontargeted serotypes)?

Although there is no evidence of an increase of disease due to nontargeted serotypes among infants and children vaccinated with PNCRM7, continued surveillance will be required to determine if additional serotypes should be added in the future.

References


