Pneumococcal Vaccination of Children

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Streptococcus pneumoniae is the most frequent cause of invasive bacterial infection in children younger than 2 years of age, reaching a peak incidence at 6 to 12 months of age. Pneumococci also cause many cases of pneumonia, sinusitis, and otitis media. Incidence rates of invasive infection in children with sickle cell disease, acquired or congenital splenectomy, or human immunodeficiency virus infection are 20- to 100-fold higher than in healthy children. Other healthy children, such as those of American Indian, Native Alaskan, or African American descent, also have higher rates of invasive infection, and those children enrolled in out-of-home care may have modestly increased risks. Pneumococcal polysaccharide polyvalent vaccines have been available for more than 2 decades but are limited in their usefulness for children because of their inability to induce protective antibody responses in children younger than 2 years of age and lack of immunologic memory. In contrast, pneumococcal protein conjugate vaccines induce presumptive protective responses in infants younger than 6 months, and immunologic memory further enhances responses after booster doses are given. Currently, a single heptavalent pneumococcal protein conjugate vaccine is licensed for use in the United States and is recommended for routine administration to all children, beginning at 2 months of age. It is also recommended for children between 24 and 59 months of age who are at high risk of acquiring invasive disease. Copyright 2002, Elsevier Science (USA). All rights reserved.

Since the successful elimination of Haemophilus influenzae type b (Hib) infections with the advent of Hib conjugate vaccines, infection caused by Streptococcus pneumoniae has become the most common invasive bacterial infection of children. Pneumococci are the most frequent cause of bacteremia in children between the ages of 2 and 36 months with fever without an identifiable source, counting for greater than 84 percent of the pathogens recovered.1 Pneumococci cause approximately 17,000 cases of bacteremia annually among children younger than 5 years of age.2 Healthy children younger than 12 months have the highest rates of pneumococcal meningitis, with an estimated case rate of 10 per 100,000. Overall, pneumococci cause 1,400 cases of meningitis, 71,000 cases of pneumonia, and 5 to 7 million cases of otitis media annually in children younger than 5 years of age.2 Rates of pneumococcal infection in this population are at least 2-fold higher than those observed in the next highest risk group, adults older than 65 years. Rates of infection among all groups of children range from 184 to more than 1,820 infections per 100,000 for various groups of healthy children younger than 24 months (Table 1).3 These rates fall rapidly in those older than 24 months, but pneumococci continue to be associated with significant morbidity and play prominent roles in otitis media, sinusitis, pneumonia, and other infections of childhood.

Children at Increased Risk for Acquiring Invasive Pneumococcal Infection

Children with certain underlying diseases are at markedly increased risk of acquiring invasive pneumococcal disease, with rates of infection that equal or exceed 150 per 100,000 population (Table 2). They include children with a variety of underlying immune defects or acquired conditions of host compromise, but particularly those children with aplasia or splenic dysfunction, metabolic disorders, loss or failure of immunoglobulin production, other severe B-lymphocyte dysfunction, as well as multiple chronic diseases involving the kidney, lung, and heart. A high incidence of invasive pneumococcal infection in children with sickle cell disease (SCD), splenic dysfunction, asplenia, and, more recently, human immunodeficiency virus (HIV) infection has been observed for decades.4,5 Many
of these children, particularly those younger than 5 years of age with SCD, have rates of invasive pneumococcal disease that exceed those of the highest rates in healthy children by 10- to 100-fold. Rates of invasive pneumococcal infection for large populations of children with SCD prior to 1986 were calculated to be 5,200 to 6,500 per 100,000 in children younger than 5 years of age, declining to 600 to 1,100 per 100,000 in those older than 5 years. Other sickle cell hemoglobinopathies, such as sickle cell disease and certain thalassemias, may have lower risks, but even in children with these diseases, fulminant invasive disease resulting in deaths has been reported. Although the risk of acquiring invasive pneumococcal infection has not been determined with accuracy in children with congenital or surgical asplenia, high rates of invasive infection and fulminant disease, similar to those in young children, particularly those younger than 2 years of age, are reasonable to assume. For example, children with congenital heart disease and congenital asplenia have high rates of invasive pneumococcal disease that are similar to those of sickle cell disease. However, asplenic patients accounted for fewer than 1 percent of children with pneumococcal sepsis among 234 children observed in 8 medical centers, and the risk of acquiring pneumococcal sepsis persisted despite administration of polyvalent polysaccharide vaccines in more than 75 percent of children and prescriptions for antibiotic prophylaxis in 82 percent. Although antibiotic prophylaxis has resulted in reductions of greater than 85 percent in pneumococcal infections of these children, particularly those younger than 5 years of age with SCD, have rates of invasive pneumococcal disease that exceed those of the highest rates in healthy children by 10- to 100-fold. Rates of invasive pneumococcal infection for large populations of children with SCD prior to 1986 were calculated to be 5,200 to 6,500 per 100,000 in children younger than 5 years of age, declining to 600 to 1,100 per 100,000 in those older than 5 years. Other sickle cell hemoglobinopathies, such as sickle cell disease and certain thalassemias, may have lower risks, but even in children with these diseases, fulminant invasive disease resulting in deaths has been reported. Although the risk of acquiring invasive pneumococcal infection has not been determined with accuracy in children with congenital or surgical asplenia, high rates of invasive infection and fulminant disease, similar to those in young children, particularly those younger than 2 years of age, are reasonable to assume. For example, children with congenital heart disease and congenital asplenia have high rates of invasive pneumococcal disease that are similar to those of sickle cell disease. However, asplenic patients accounted for fewer than 1 percent of children with pneumococcal sepsis among 234 children observed in 8 medical centers, and the risk of acquiring pneumococcal sepsis persisted despite administration of polyvalent polysaccharide vaccines in more than 75 percent of children and prescriptions for antibiotic prophylaxis in 82 percent. Although antibiotic prophylaxis has resulted in reductions of greater than 85 percent in pneumococcal infections of these children, particularly those younger than 5 years of age with SCD, have rates of invasive pneumococcal disease that exceed those of the highest rates in healthy children by 10- to 100-fold. Rates of invasive pneumococcal infection for large populations of children with SCD prior to 1986 were calculated to be 5,200 to 6,500 per 100,000 in children younger than 5 years of age, declining to 600 to 1,100 per 100,000 in those older than 5 years. Other sickle cell hemoglobinopathies, such as sickle cell disease and certain thalassemias, may have lower risks, but even in children with these diseases, fulminant invasive disease resulting in deaths has been reported. Although the risk of acquiring invasive pneumococcal infection has not been determined with accuracy in children with congenital or surgical asplenia, high rates of invasive infection and fulminant disease, similar to those in young children, particularly those younger than 2 years of age, are reasonable to assume. For example, children with congenital heart disease and congenital asplenia have high rates of invasive pneumococcal disease that are similar to those of sickle cell disease. However, asplenic patients accounted for fewer than 1 percent of children with pneumococcal sepsis among 234 children observed in 8 medical centers, and the risk of acquiring pneumococcal sepsis persisted despite administration of polyvalent polysaccharide vaccines in more than 75 percent of children and prescriptions for antibiotic prophylaxis in 82 percent. Although antibiotic prophylaxis has resulted in reductions of greater than 85 percent in pneumococcal
disease in children with sickle cell disease, rates of greater than 3,000 per 100,000 continue to be noted in some children because of frequent failures to comply fully with prophylaxis regimens.1,11

HIV disease also is associated with very high risks of invasive pneumococcal disease. S pneumoniae is the most common cause of invasive bacterial infection in children with HIV disease and accounts for 35 to 50 percent of episodes.12,13 Relative risks of infection in these children have been 3- to 22-fold higher than those in children without HIV infection, with rates of 6,100 per 100,000 for the first 7 years of life and as high as 11,300 per 100,000 for the first 3 years of life.14,15

Children at Moderate Risk of Acquiring Invasive Pneumococcal Infection

Several groups of older children experience rates of invasive pneumococcal disease similar to those of healthy children younger than 2 years of age. These rates may exceed 150 per 100,000 and may be several-fold higher for certain groups of children. Some populations of American Indian16 and Native Alaskan17 children have rates of infection that are much higher for children younger than 2 years of age and exceed those of other children by 2- to 6-fold, with an increased risk persisting for these children well beyond the first 3 years of life.14,15

In addition, all healthy children 24 to 35 months of age (ie, in the third year of life) have moderately increased risks of acquiring pneumococcal disease, but this risk falls precipitously thereafter. In children 36 to 60 months of age, the focus of invasive infections becomes the lower respiratory tract, resulting in pneumonia, and involves the central nervous system or the blood stream less frequently than in younger children.

Enrollment in out-of-home care also greatly increases the risk of acquiring invasive disease. In Finnish studies, the odds ratio of infection in children in out-of-home care compared with that of control children was 36,18 whereas in a similar study in the United States, invasive infections occurred at a 2.63-fold ratio for children 2 to 11 months and 2.29 for children 12 to 23 months old.19 Surprisingly, even for children 24 to 59 months old, the odds ratio for acquiring invasive disease was 3.28. In addition, children in out-of-home care have increased rates of carriage of the invasive pneumococcal strains 14, 23F, 12F, and 6, which also are the serotypes most likely to be associated with resistance to penicillins, cephalosporins, and other antibiotics.20,21 Nasopharyngeal carriage of drug-resistant pneumococci have been documented in 21 to 59 percent of children in out-of-home care.

Serotypes and Serogroups Causing Pneumococcal Disease in Children

Serotypes causing invasive disease in children are not constant from country to country or from season to season (Table 3). The serotypes causing invasive infections in children in the United States and other developed countries in decreasing order of frequency are 14, 6B, 19F, 18C, 9V, 23F, 7F, 4, and 1.22 The 7 serotypes in the pneumococcal conjugate vaccine currently licensed (Prevnar® (Wyeth-Lederle Vaccines, Philadelphia, PA)—4, 6B, 9V, 14, 19F, 23F, and 18C—provide potential protection of 88 percent against bacteremia, 82 percent against meningitis, and 71 percent against pneumococcal otitis media in United States children younger than 6 years.23 For children in developing countries, however, the range of protective efficacy would be expected to be no greater than 70 percent and might be as low as 30 to 40 percent because the most frequent serotypes in developing countries in decreasing order of frequency are 6B, 14, 8, 5, 1, 19V, 23F, 18C, 15B, and 7F.24,25

Pneumococcal Vaccines

Purified Capsular Polysaccharide Vaccines

Two purified capsular polysaccharide pneumococcal vaccines, Pnu-Immune® 23 (Wyeth-Lederle Vaccines, Philadelphia, PA) and Pneumovax® 23 (Merck and Co, Inc, West Point, PA), are available. Each vaccine contains 23 purified pneumococcal capsular serotype polysaccharides of S pneumoniae (Danish serotypes 1, 2, 3, 4, 5, 6B, 8, 9N, 10A, 11A, 12F, 14, 15B, 17F [substituted with 17A in Pnu-Immune], 18C, 19A, 19F, 20, 22F, 23F, and 33F) and is denoted as 23PS. Contained within a recommended volume of 0.5 mL, each vaccine contains 25 µg of each antigen (total of 575 µg polysaccharide) in normal saline solution
with either phenol (0.25%, Pneumovax) or thimerosal (0.01%, Pnu-Immune) as preservative. These 23 serotypes theoretically provide potential serospecific protection against approximately 75 percent of pneumococcal respiratory and invasive infections in the United States and an additional 14 percent would be potentially prevented by serogroup cross-protection. Thus, the vaccines could provide protection against 85 percent to greater than 90 percent of all infections in children in the United States, provided that children mount a protective response after receiving injections of these vaccines.24

However, many of the polysaccharides in these vaccines, particularly those serotypes that cause high numbers of infections in children younger than 2 years, are not immunogenic for children.25 Even with at least minimal antibody responses in children 2 years of age or older, a reduction of the nasopharyngeal carriage of pneumococci has not been demonstrated, and antibody responses may provide only minimal protection from infection. The poor immunogenicity of polysaccharide vaccines in young children is caused by the T lymphocyte-independent characteristic of polysaccharide antigens, which not only causes a failure of primary responses in infants and young children but also is responsible for the failure to elicit immunologic memory, and, thus, lack of booster responses after repeated antigen administration.26 In addition to poor quantitative responses, functional or qualitative responses as measured by opsonization also may be poor. Adult-type responses characterized by adequate protective antibody responses with enhanced opsonization are observed after the child reaches 2 years of age. Progressively better antibody responses occur with advancing age and are roughly equivalent to those of adults.27

Prospective controlled evaluations of the efficacy of pneumococcal polysaccharide vaccines in preventing invasive disease in children have been limited, poorly controlled if at all, and generally contradictory.28 For instance, in a retrospective serogroup analysis of invasive disease in the United States, efficacy could not be demonstrated in children 2 to 10 years of age, including children at high risk.29 In addition, 2 controlled studies of polysaccharide vaccines did not demonstrate reduction in either the incidence or severity of otitis media in children older than 2 years of age.30 In contrast, a Danish retrospective analysis of the results of polysaccharide vaccines given in 1977 suggested significant efficacy against invasive disease was achieved in splenectomized children older than 2 years of age,31 and in yet another retrospective study in United States children, an efficacy of 63 percent (95% confidence interval [CI], 8%-85%) was noted in children 2 to 5 years of age.32 Adverse events associated with injection of pneumococcal polysaccharide vaccines have been minimal, occurring in fewer than 10 percent of immunized children and confined almost entirely to local reactions of redness, swelling, and local pain. Reactions of greater than 1 to 2 cm diameter are uncommon and occur in fewer than 2 to 3 percent of children. Systemic reactions other than mild fever have been rare occurrences in children.

**Poly saccharide-Protein Conjugate Pneumococcal Vaccines**

Preliminary trials of numerous conjugate vaccines are being conducted or recently have been completed (Table 4).33 Several protein conjugate oligosaccharide and polysaccharide pneumococcal vaccines linked with proteins, such as meningococcal outer-membrane protein, tetanus toxoid, CRM197 (a mutant nontoxic diphtheria toxin), and diphtheria toxoids, have been evaluated for safety and/or immunogenicity in children. These conjugates have been tested as monovalent, pentavalent, heptavalent, nanovalent, and 11-valent formulations. All have been found to induce good immune responses in infants younger than 2 years of age, and amnestic responses have been observed after administration of booster doses.34 A single pneumococcal protein conjugate vaccine, a heptavalent preparation (Prevnar®), currently is licensed in the United States. This vaccine comprises 7 pneumococcal polysaccharide antigens (serotypes 6B, 9V, 14, 19F, 23F, and an oligosaccharide, 18C) conjugated to 20 µg of CRM197 by reductive amination and denoted as PCV7. The recommended 0.5 mL dosage contains 2 µg of each antigen, except 6B, for which 4 µg is recommended. Aluminum phosphate (0.5 mg) is added as an adjuvant, but the vaccine contains no preservatives or thimerosal. A primary series is

### Table 4. Pneumococcal Conjugate Vaccines in Development

<table>
<thead>
<tr>
<th>Vaccine Conjugate</th>
<th>Serotypes Contained in Vaccine</th>
<th>Manufacturer</th>
<th>Clinical Trial Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Purified polysaccharides conjugated to CRM197</td>
<td>6B, 9V, 14, 18C, 19F, 23F</td>
<td>Wyeth Lederle Vaccines, Philadelphia, PA</td>
<td>Phase III</td>
</tr>
<tr>
<td>Purified polysaccharides conjugated to CRM197</td>
<td>11-valent vaccine: 1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 23F</td>
<td>Wyeth Lederle Vaccines, Philadelphia, PA</td>
<td>Preclinical</td>
</tr>
<tr>
<td>Purified polysaccharides conjugated to outer membrane protein of N. meningitidis</td>
<td>Heptavalent vaccine: 4, 6B, 9V, 14, 18C, 19F, 23F</td>
<td>Merck &amp; Co, Inc, West Point, PA</td>
<td>Preclinical</td>
</tr>
</tbody>
</table>

NOTE. Other vaccine combinations or conjugates that have been tested in phase II and III studies include conjugates in addition to tetanus and diphtheria toxoids and combinations of pneumococcal antigens ranging from monovalent preparations (6B) to pentavalent (6B, 14, 18C, 19F, and 23F), heptavalent (PCV7), nanovalent (PCV7 plus serotypes 1 and 3), and 11-valent (nanovalent plus 3 and 7V) combinations.

Abbreviation: CRM, cross-reacting material.
Table 5. Adverse Effects Following Pneumococcal Conjugate Vaccines

<table>
<thead>
<tr>
<th>Type of reaction</th>
<th>Dose 1</th>
<th>Dose 2</th>
<th>Dose 3</th>
<th>Dose 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any reaction at injection site (%)</td>
<td>36 vs 56</td>
<td>43 vs 58</td>
<td>35 vs 46</td>
<td>33 vs 24</td>
</tr>
<tr>
<td>Moderate local reactions (%)</td>
<td>4.9 vs 12</td>
<td>6.1 vs 11</td>
<td>5.3 vs 5.2</td>
<td>3.4 vs 3.4</td>
</tr>
</tbody>
</table>

Incidence of fever with administration of PCV7 when given with DTP and Haemophilus conjugate (CRM197; HbOC) vaccine or DTaP vaccines

<table>
<thead>
<tr>
<th>Subjects with temperature ≥38°C (%)</th>
<th>PCV+DTP/HbOC</th>
<th>PCV+DTaP</th>
<th>DTaP</th>
<th>PCV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>32.6</td>
<td>34.5</td>
<td>40.0</td>
<td>41.9</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Subjects with temperature ≥39°C (%)</th>
<th>PCV+DTP/HbOC</th>
<th>PCV+DTaP</th>
<th>DTaP</th>
<th>PCV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.3</td>
<td>3.1</td>
<td>5.2</td>
<td>4.5</td>
</tr>
</tbody>
</table>

Abbreviations: DTaP, diphtheria and tetanus toxoids and acellular pertussis vaccine; DTP, diphtheria and tetanus toxoids and whole cell pertussis vaccine; PCV, pneumococcal polysaccharide antigens conjugated to CRM197; HbOC, haemophilus polysaccharide conjugated to CRM197.

*Redness or swelling at the injection site.
†Defined by erythema ≥2.4 cm in diameter or tenderness causing limb immobility.

Recommended at 2, 4, 6, and 12 to 15 months of age, whereas schedules of fewer doses are recommended for children in whom immunization is initiated between 6 and 24 months of age.41 Children at higher risk should be given additional doses of both the conjugate vaccine and the polysaccharide vaccine to provide possible enhanced antibody responses, as well as possible expansion of protection against serotypes only in the polysaccharide vaccine.

Adverse Effects of PCV7. The licensed pneumococcal conjugate vaccine has been associated with modest adverse effects when given as a primary series in the first 6 months of life and as a booster in the second year with otherwise age-appropriate vaccines, including diphtheria and tetanus toxoids and acellular pertussis (DTaP), Hib conjugate, hepatitis B, oral and inactivated polio, measles-mumps-rubella (MMR), and varicella vaccines (Table 5).41,43 Data on hepatitis A vaccines given concurrently with PCV7 are not available.

Despite these modest adverse effects, of those vaccines currently recommended for infants and children, PCV7 may prove to be the vaccine most prone to produce local reactions and fever. In a large study by Shinefield et al.,49 moderate local reactions, which were defined by erythema of 2.4 cm or greater in diameter or tenderness causing limb immobility, occurred at injection sites in 4.9 to 6.1 percent of children after all doses, without a significant increase in the number or severity of these reactions with repeated doses in the series. The fourth dose, which often is given with the fourth dose of DTaP, MMR, or varicella vaccine, has been associated with the fewest local reactions. The incidence of fever higher than 38°C within 48 hours of vaccination occurred in a greater proportion of children receiving conjugate vaccines than those who received a control meningococcal C conjugate vaccine when administered with DTaP. The incidence of fever was nearly 2-fold higher in children receiving PCV7, compared with those who received the meningococcal vaccine, despite a high rate of antipyretic use in both groups. Fever occurs most commonly after the second or third PCV7 dose, particularly when given in conjunction with pertussis-containing vaccines. Temperatures of at least 38°C and higher than 39°C were reported in 13 percent and 1.2 percent, respectively, of 727 children who received PCV7 vaccine alone without any concurrent vaccines; this small group of children also experienced irritability (46%), drowsiness (16%), restless sleep (21%), decreased appetite (18%), vomiting (6.3%), diarrhea (12.8%), and rash or hives (1.2%).40 Drowsiness also was observed in more than 27 percent to 49 percent of children and "fussiness" in more than one-third of children receiving pneumococcal conjugate vaccines in conjunction with other vaccines.

Immunogenicity of PCV7. Protective concentrations of pneumococcal antibody have not been defined. Based on the concentrations of antipneumococcal antibody considered to be protective against Hib infection, a surrogate minimum serum concentration of 0.15 μg/mL has been proposed to be protective. Similar concentrations of specific pneumococcal antibody of 0.10 to 1.15 µg/mL have been associated with lowered mortality rates in rat models of pneumococcal infection.41 Pneumococcal conjugate vaccines induce good antibody responses in infants when administered in the current
schedules during the first 15 months of life. After receiving 3 doses, 92 to 100 percent of children had at least 0.15 µg/mL of antibody ("protective") against the 7 vaccine serotypes contained in the current vaccine, and 51 to 90 percent had at least 1.0 µg/mL, depending upon which serotype antibody was measured. Administration of a fourth dose at 12 to 15 months of age is followed by a prompt amnestic response to all 7 serotype antigens. In trials of the vaccine performed in the United States, geometric mean titers after 3 priming infant doses varied from 1.0 µg/mL for serotype 9V to 7.7 µg/mL for serotype 14, with more than 90 percent of recipients achieving concentrations exceeding 0.15 µg/mL for all serotypes. The proportion of children with concentrations exceeding 1.0 µg/mL ranged from 51 percent for serotype 9V to 89 percent for serotype 14. Immunologic priming, including induction of antibody memory, occurred after only 2 doses for some antigens, whereas 3 doses were necessary to induce priming against all serotypes. Significant booster responses were observed with additional doses given at intervals of a few months to a year or more after the completion of the primary series.

Concurrent administration of pneumococcal conjugate vaccines with diphtheria and tetanus toxoids and pertussis (DTP), DTaP, or Hib conjugate vaccines produced no meaningful increase or reduction in the concentration of pneumococcal or other vaccine antibodies, including those to pertussis antigens (eg, pertussis toxin, fimbriae, 6d protein, fimbrial hemagglutinin), diphtheria or tetanus antitoxins, or the Hib polysaccharide. Limited data on concurrent administration of MMR and varicella vaccines with PCV7 also demonstrate a primary response to measles, mumps, rubella, and varicella that varied from 80 to 95 percent and did not differ from historical data for these antigens.

**Effect on Carriage of Nasopharyngeal Pneumococci.** In limited observations, decreases in carriage of vaccine pneumococcal serotypes from prevaccination baselines rates of approximately 25 percent to rates of 7 to 9 percent during short periods of follow-up have been documented with a similar conjugate vaccine (6B, 9V, 14, 18C, 19F, and 23F capsular polysaccharides conjugated to the meningococcal outer membrane protein). Decreases in carriage have been observed with similar conjugate pneumococcal vaccines but have not been demonstrated in prospective trials with the vaccines currently licensed in the United States. In a study of a novelvalent CRM197 conjugate pneumococcal vaccine, a decrease in vaccine serotype carriage occurred but was followed by an increase in the carriage of nonvaccine types.

**Efficacy Against Pneumococcal Infection of Conjugate Vaccines.** A single efficacy trial has been completed in the United States to assess efficacy of the pneumococcal conjugate vaccine in healthy children without underlying disease. This trial enrolled more than 37,000 children in a prospective double-blinded study that compared the heptavalent pneumococcal conjugate vaccine with a CRM197 conjugated meningococcal C vaccine. Both vaccines were given concurrently at 2, 4, 6, and 12 to 15 months of age. After initiation of vaccination, children were followed until they reached 24 months of age. Surveillance for pneumococcal invasive disease—the primary end point—was conducted using an automated laboratory database, and all pneumococcal isolates were serotyped. The occurrence of otitis media and pneumonia was assessed retrospectively with defined physician-confirmed and radiologically confirmed criteria. Of enrolled children, 18,927 were randomized to receive PCV7, and 18,941 received meningococcal conjugate vaccine. The mean age at immunization for each dose was 2.1 months (dose 1), 4.3 months (dose 2), 6.5 months (dose 3), and 13.7 months (dose 4).

Three cases of vaccine serotype invasive disease occurred in children randomized to receive PCV7, compared with 49 cases in infants who received the meningococcal vaccine (93.9% efficacy; 95% CI, 79.5%-98.5%; P < .001). Against bacteremic pneumonia, the estimated efficacy was at least 85 percent against serotype-specific disease.

The efficacy of PCV7 on the incidence of pneumonia was evaluated in a tertiary, post hoc analysis. Hospital outpatient and emergency records were reviewed to measure outcomes of clinical pneumonias. Administration of PCV7 reduced all clinical episodes of pneumonia by 11.4 percent (95% CI, 1.3%-20.5%), radiographically confirmed pneumonias by 33.7 percent (95% CI, 7.3%-51.5%), and lobar pneumonias by 73.1 percent (95% CI, 3.9%-88.3%). The efficacy against otitis media was evaluated as a secondary end point in a total of more than 47,000 visits for otitis media in children who had been fully immunized according to the protocol. Of these visits, 3,456 children had frequent episodes of otitis media, defined as ≥3 or more episodes in a year, and 355 had undergone tympanostomy tube placement. In vaccine recipients, all visits for otitis media decreased by 8.9 percent (95% CI, 5.8%-11.8%) and the use of tympanostomy tubes decreased by 20.1 percent (95% CI, 3.6%-34.1%). The effect of PCV7 was higher in those children with progressively more severe disease.

In a study of otitis media in Finland, administration of PCV7 reduced the incidence of all episodes of otitis media by 6 percent (95% CI, 4%-16%). However, culture-confirmed pneumococcal episodes were reduced by 34 percent and those due to 1 of the 7 vaccine serotypes by 57 percent. The number of episodes attributed to cross-reactive serotypes with those in PCV7 was reduced by 51 percent, but the number of episodes due to all other serotypes increased by 33 percent.

**Immunogenicity in Children at High Risk of Developing Invasive Pneumococcal Infection.** Limited safety and immunogenicity trials of pneumococcal conjugate vaccines have been completed in 2 groups of children at very high risk of developing invasive pneumococcal infections—specifically children with sickle cell disease (SCD) and those with HIV infection. In a trial enrolling 24 children with SCD older than 2 years, 2 doses of PCV7 were given at an 8-week interval, followed in another 8 weeks by a single dose of 23PS with or without a third dose of PCV7. Antibody concentrations to all 7 antigens were higher after the combined dosing regimen of PCV7 plus 23PS as the third dose, compared with the regimen of the 23PS vaccine given
alone as the third dose. Fever was reported in 3 of 11 subjects after administration of the first dose of PCV7, in 1 of 11 after the second dose, and in 4 of 11 after the third dose of those who had received combined regimens of PCV7 and 23PS. Local reactions of swelling and erythema were similar in children who received 23PS alone, compared with those who received the combined regimen. The median reaction sizes were 4.0 and 3.5 cm, respectively, and ranged from 1 to 14 cm in diameter. However, these reactions occurred more frequently than they did in those children receiving the priming dose of PCV7; the median diameter was 1.0 cm (range, 0-16 cm) in these children.

Small numbers of children with HIV infection and given PCV7 vaccine have been studied. Results of 2 studies suggest that conjugate pneumococcal vaccines induce higher antibody responses than do polysaccharide vaccines. The responses were determined to 5 serotypes—6B, 14, 18C, 19F, and 23F—conjugated to CRM197 and given in 3 doses at 2-month intervals to 18 children younger than 2 years of age. Of the HIV-infected children, 78 percent achieved antibody concentrations of at least 1.0 µg/mL, in contrast to 88 percent of the children not infected with HIV. Children with more advanced HIV disease were less likely to respond after receiving 2 doses, but these differences were not observed after the third dose. Only minor reactions were noticed in these small studies and were similar to those observed for healthy children.

Recommendations for Use of Pneumococcal Vaccines

Lieu et al have evaluated the potential cost benefit of pneumococcal vaccines for children. The annual birth cohort of the United States is approximately 3.8 million infants. Assuming that the routine administration of PCV7 could prevent a minimum of 78 percent of meningitis cases (2219 cases), 69 percent of bacteremia cases (52,319 cases), and 7 percent of otitis media cases (1,009,505 cases), a net savings in health care and associated costs to the United States society occurs at a vaccine cost of less than $46/dose. Net savings to healthcare insurers would occur if the vaccine cost were less than $18/dose. However, current costs for the vaccine are at the break-even point; costs for the 4-dose infant and booster series range from $194 to more than $230.

The American Academy of Pediatrics and the Advisory Committee on Immunization Practices currently recommend the PCV7 vaccine for routine immunization of all children 23 months of age and younger. The dosing schedule for the 3 priming doses and the booster dose are listed in Table 6. Each 0.5 mL dose is recommended for intramuscular administration. The initial "2 month" dose should be given no earlier than 6 weeks of age, and infants of low birth weight (≤51,500 g) should be immunized at the time they are 6 weeks of age or older. All doses of PCV7 and 23PS vaccines may be given with other childhood vaccines, including all DTaP vaccines, Hib conjugate vaccines, hepa-
titis B vaccines, inactivated polio vaccines, and MMR and varicella live-virus vaccines. Separate syringes and separate intramuscular sites should be used for each individual vaccine. Children who begin PCV7 immunization after 6 months of age require a reduced number of injections until 2 years of age, when only a single injection is necessary for healthy children (Table 6).

PCV7 also is strongly recommended for children 24 to 59 months of age with high-risk conditions for acquiring invasive pneumococcal disease (Table 2). Because these children remain at high risk, particularly until 5 years of age, and because the number of causative serotypes increases after 2 years of age beyond those contained in the conjugate pneumococcal vaccine, 23PS vaccine should be given as well.

Children at moderate risk of developing invasive pneumococcal disease, such as those of American Indian, Native Alaskan, or African American descent, should be considered strongly for PCV7 vaccine administration if they are older than 2 years of age and have not received doses of vaccine previously. This group of children also may benefit from supplemental doses of 23PS vaccine. For other healthy children at moderate risk of acquiring invasive pneumococcal infection, such as those children 24 to 35 months of age, children with recurrent or complex otitis media, or those children enrolled in out-of-home care, a single dose of PCV7 should be considered if they have reached 2 years of age and have not received pneumococcal vaccines previously.

Antibiotic prophylaxis for children with sickle cell disease or splenectomy has been associated with a marked reduction in the incidence of invasive pneumococcal infection. These studies were conducted during a time when only polysaccharide vaccines were available. The efficacy of newer protein conjugate vaccines in reducing incidence of pneumococcal disease without antibiotic concomitant prophylaxis in these groups of children is not known. Therefore, antibiotic prophylaxis continues to be recommended for children with SCD and splenectomy. Antibiotic prophylaxis is given as 125 mg penicillin VK orally twice daily for children younger than 3 years of age and as 250 mg twice daily for children older than 3 years.

**Future of Pneumococcal Vaccines**

The conjugate vaccines hold the promise of markedly altering the future epidemiology of invasive pneumococcal infections in children in the United States and in European countries. However, the vaccine currently available has been developed largely for use in developed countries and incorporates polysaccharides of the vaccine serotypes that predominantly cause invasive disease in these countries. More than 1 million children worldwide have been estimated to die each year of invasive pneumococcal infections, mostly in developing countries where rates of both death and neurologic sequelae are higher than those observed in the United States. Serotypes 8, 15B, and particularly 5 and 1 are frequent causes of invasive infections in developing countries. For example, serotypes 1 and 5 account for only approximately 5 percent of invasive infections in most developed countries, whereas these 2 isolates may account for 15 to 35 percent of infections in many countries in Africa and Latin America.

Development of optimal pneumococcal vaccines for global use will require antigenic formulations that include the serotypes causing invasive disease in developing countries. In these vaccines, however, the addition of a larger number of serotypes could be associated with either increased rates of reactions or interference with immune responses to individual antigens.

The use of pneumococcal conjugate vaccines, similar to that of Hib conjugate vaccines, has been associated with a reduction of nasopharyngeal carriage of vaccine serotypes. Of concern is the reduction in carriage that has been followed by a 25 to 40 percent increase in carriage of nonvaccine serotypes, so-called “replacement” serotypes. Because protection is serospecific, the use of conjugate pneumococcal vaccines could be followed by the emergence of new pathogenic strains among the 83 known serotypes not contained within the current heptavalent conjugate vaccine. Pneumococci can transform and recombine new capsular biosynthetic loci, and new pathogenic serotypes might emerge via “vaccine antibody selection” or genetic exchange of new capsular polysaccharides.

Careful post-vaccine surveillance and enhanced rapid identification of serotype-specific pneumococcal infections could facilitate our understanding of the postepidemiology of pneumococcal carriage and disease after widespread use of conjugate vaccine. In addition, the use of pneumococcal vaccines also may reduce the frequency of antibiotic-resistant serotypes in disease because PCV7 includes most of the penicillin nonsusceptible strains.

Protein vaccines eventually may replace polysaccharide vaccines, and many other potentially protective proteins of pneumococci have been studied. Antibody against pneumococcal protein surface protein A (PspA) is protective in animal models against otitis media. Similarly, recombinant vaccines of PspA administered to adult humans provide passive antibody that is protective against fatal infections in an experimental mouse model. Other proteins such as surface adhesins (PsaA) and pneumolysin proteins are protective against carriage and invasive disease in animal models. Antibodies against PspA, adhesin A, and pneumolysin are produced either by infection or carriage by nearly all children younger than 24 months. Antibody concentrations against pneumolysin correlate with a decreased risk of developing bacteremia in adults with pneumococcal pneumonia.

The serological antipolysaccharide antibody correlate of protection against pneumococcal infection is poorly defined. More precisely defined correlates would facilitate the development and licensure of future polysaccharide vaccines composed of additional polysaccharide serotypes, new conjugate proteins, or those that may be used in vaccine combinations, such as combinations with currently recommended childhood vaccines or with other polysaccharide conjugates of Hib or Neisseria meningitidis.
References


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