

# AMERICAN ACADEMY OF PEDIATRICS

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## Technical Report: Prevention of Pneumococcal Infections, Including the Use of Pneumococcal Conjugate and Polysaccharide Vaccines and Antibiotic Prophylaxis

**ABSTRACT.** Pneumococcal infections are the most common invasive bacterial infections in children in the United States. The incidence of invasive pneumococcal infections peaks in children younger than 2 years, reaching rates of 228/100 000 in children 6 to 12 months old. Children with functional or anatomic asplenia (including sickle cell disease [SCD]) and children with human immunodeficiency virus infection have pneumococcal infection rates 20- to 100-fold higher than those of healthy children during the first 5 years of life. Others at high risk of pneumococcal infections include children with congenital immunodeficiency; chronic cardiopulmonary disease; children receiving immunosuppressive chemotherapy; children with immunosuppressive neoplastic diseases; children with chronic renal insufficiency, including nephrotic syndrome; children with diabetes; and children with cerebrospinal fluid leaks. Children of Native American (American Indian and Alaska Native) or African American descent also have higher rates of invasive pneumococcal disease. Outbreaks of pneumococcal infection have occurred with increased frequency in children attending out-of-home care. Among these children, nasopharyngeal colonization rates of 60% have been observed, along with pneumococci resistant to multiple antibiotics. The administration of antibiotics to children involved in outbreaks of pneumococcal disease has had an inconsistent effect on nasopharyngeal carriage. In contrast, continuous penicillin prophylaxis in children younger than 5 years with SCD has been successful in reducing rates of pneumococcal disease by 84%.

Pneumococcal polysaccharide vaccines have been recommended since 1985 for children older than 2 years who are at high risk of invasive disease, but these vaccines were not recommended for younger children and infants because of poor antibody response before 2 years of age. In contrast, pneumococcal conjugate vaccines (Prevnar) induce proposed protective antibody responses ( $>0.15 \mu\text{g}/\text{mL}$ ) in  $>90\%$  of infants after 3 doses given at 2, 4, and 6 months of age. After priming doses, significant booster responses (ie, immunologic memory) are apparent when additional doses are given at 12 to 15 months of age. In efficacy trials, infant immunization with Prevnar decreased invasive infections by  $>93\%$  and consolidative pneumonia by 73%, and it was associated with a 7% decrease in otitis media and a 20% decrease in tympanostomy tube placement. Adverse events after the administration of Prevnar have been limited to areas of local swelling or erythema of 1 to 2 cm and some increase in the incidence of postimmunization fever when it is given

with other childhood vaccines. Based on data in phase 3 efficacy and safety trials, the US Food and Drug Administration has provided an indication for the use of Prevnar in children younger than 24 months.

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ABBREVIATIONS. AOM, acute otitis media; SCD, sickle cell disease; HIV, human immunodeficiency virus; OR, odds ratio; CI, confidence interval; NP, nasopharyngeal; PCV7, heptavalent pneumococcal CRM<sub>197</sub> conjugate vaccine; DTaP, diphtheria and tetanus toxoids and acellular pertussis; HbOC, *Haemophilus influenzae* type b conjugate; DTP, diphtheria and tetanus toxoids and pertussis; OPV, oral poliovirus; IPV, inactivated poliovirus; MMR, measles-mumps-rubella; MenCRM, meningococcal C conjugated to CRM<sub>197</sub>; 23PS, 23-valent pneumococcal polysaccharide; 14PS, 14-valent pneumococcal polysaccharide vaccine.

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**S***treptococcus pneumoniae* is the most common cause of bacteremia, sepsis, meningitis, pneumonia, sinusitis, and acute otitis media (AOM) in children. Children at increased risk of pneumococcal infections include those with anatomic or functional asplenia (including sickle cell disease [SCD]); recipients of immunosuppressive chemotherapy (particularly children with hematopoietic and lymphoreticular malignancies); those with congenital and acquired immunodeficiency (including human immunodeficiency virus [HIV] infections); those with chronic renal disease (including nephrotic syndrome); and healthy Native American (American Indian and Alaska Native) and African American children. Since 1988, outbreaks of pneumococcal infection have been reported with increasing frequency in children attending out-of-home care. Children younger than 60 months in out-of-home care have a twofold to threefold higher risk of experiencing invasive pneumococcal infections than do children in home care. Many outbreaks of pneumococcal infections in out-of-home-care settings have been caused by penicillin-nonsusceptible strains of *S pneumoniae*.

In 1985, the American Academy of Pediatrics Committee on Infectious Diseases provided recommendations for the use of pneumococcal polysaccharide vaccines in children and indications for antibiotic prophylaxis in targeted populations.<sup>1</sup> In 1997, updated recommendations for the prevention of pneumococcal infections were provided,<sup>2</sup> and recommendations for the management of infections caused by penicillin-nonsusceptible pneumococci were published.<sup>3</sup> The purposes of this technical report are to provide an update on the epidemiology of

The recommendations in this statement do not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.

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pneumococcal infections in children, including the infections in high-risk populations, and to present new information on the pneumococcal conjugate vaccine, Prevnar (Lederle Laboratories, Pearl River, NY/Wyeth-Ayerst Laboratories, Marietta, PA), and capsular polysaccharide vaccines. In addition, the rationale for the use of prophylactic antibiotics in asplenic children will be reviewed. The use of antibiotics to control pneumococcal outbreaks among children in out-of-home care also will be discussed.

## Epidemiology of Pneumococcal Infections

### Invasive Pneumococcal Infection in Children

Following the widespread use of *Haemophilus influenzae* type b vaccines, *S pneumoniae* has become the most common cause of invasive bacterial infection in children in the United States.<sup>4,5</sup> Pneumococci are the most common cause of bacteremia in young children between 2 and 36 months old who have fever without an identifiable source, accounting for >84% of recovered bacterial pathogens.<sup>6</sup> Children younger than 12 months have the highest rates of pneumococcal meningitis (estimated to be 10/100 000).<sup>5,7</sup> Among children younger than 5 years, pneumococcal infections cause an estimated minimum of 1400 cases of meningitis, 17 000 cases of bacteremia, 71 000 cases of pneumonia, and 5 to 7 million cases of otitis media annually. Rates of pneumococcal infection among children younger than 5 years are at least twofold higher than those observed in the next highest risk group (adults older than 65 years). The highest rates of invasive pneumococcal infection are observed in children 6 to 23 months old, with rates among all racial and ethnic groups varying from 184

to 1820/100 000 (Table 1). Rates of infection decrease steadily with increasing age beyond 24 months.

Pneumococcal disease, other than sepsis and meningitis, also is associated with considerable morbidity in children. Pneumococcal infection is a common cause of community-acquired pneumonia in children, accounting for 13% to 28% of bacterial pneumonia in industrialized nations<sup>8-10</sup> and up to 28% in developing countries.<sup>11</sup> Pneumococci are isolated from pleural fluid in 18% of children with empyema.<sup>12</sup> *S pneumoniae* also is the most common bacterial cause of AOM and sinusitis.<sup>13-15</sup> AOM is responsible for >20 million visits to pediatricians annually,<sup>14</sup> and ~30% to 50% of AOM infections are caused by pneumococci.<sup>15</sup> In US studies, nearly two thirds of children have at least 1 episode of AOM by their first birthday, and nearly one half have 3 or more episodes before their third birthday.<sup>16</sup>

### SCD and Splenectomy

A high incidence of invasive pneumococcal infection in children with SCD has been demonstrated in several epidemiologic studies throughout the past 3 decades (Table 1). Before the use of penicillin prophylaxis, pneumococcal polysaccharide vaccines, and neonatal screening for hemoglobinopathies, rates of invasive pneumococcal disease in children with SCD exceeded those in healthy children by 20- to 100-fold, with the greatest risk in children younger than 5 years.<sup>17</sup> Rates of invasive pneumococcal infections calculated for large populations of children with SCD from 1977 through 1986 were ~5200 to 6450/100 000 in children younger than 5 years, declining to 62 to 1100/100 000 in persons older than 5 years.<sup>17</sup> Children with sickle cell hemoglobinopathy

**TABLE 1.** Comparative Rates of Invasive Pneumococcal Infections in Healthy and High-Risk Children, Expressed as the Number Per 100 000 Population

Population	Age	Subgroups or Conditions	Rate/100 000†		Reference(s)
			Total	African American	
US children and adults	0-5 mo	US and African American	73.4	163.5	4, 5
	6-11 mo	US and African American	227.8	542.2	
	12-23 mo	US and African American	184.2	440.7	
	24-35 mo	US and African American	64.7	116.4	
	36-47 mo	US and African American	26.7‡	46.1	
	48-59 mo	US and African American	14.3	20.6	
	>5 y	US and African American	5.7	9.3	
	≥64 y	Total US	61.0		
	All ages	Total US	24.0‡		
	SCD	<5 y	*	5500-6500	
SCD	≥5 y	*	600-1100		17, 19
SCD	>2 y	†	3100-3600		20, 69
HIV infection	<7 y		6100		27
HIV infection	<3 y		11 300		25
White Mountain Apache	<2 y	Healthy	1820		28
	2-4 y		227		
	5-9 y		54		
	<2 y		624	29	
2-4 y	98				
5-9 y	23				
Navajo	0-11 mo	Healthy	664		O'Brien K, personal communication, 1999
	12-23 mo		453		

\* Children with SCD without vaccine or penicillin prophylaxis.

† Children on penicillin prophylaxis and/or given polyvalent pneumococcal polysaccharide vaccine.

‡ Estimates of invasive disease in the total US populations include high-risk and moderate-risk persons; rates in children without other risk factors have been estimated to be <20 000 cases/100 000 annually after 36 months of age.

and certain other sickle cell hemoglobinopathies (including thalassemias) have lower rates of infection than do children with SS hemoglobinopathy, but their rates are much greater than those of other children, and deaths attributable to fulminant pneumococcal infection have been reported in these children as well.<sup>18</sup> Despite the use of pneumococcal polysaccharide vaccines and penicillin prophylaxis, high rates of invasive pneumococcal infection have continued to be observed (3000/100 000) in some groups of children with SCD.<sup>19,20</sup>

The risk of invasive pneumococcal disease in children with congenital or surgical asplenia has not been defined precisely.<sup>21,22</sup> Asplenic children younger than 2 years are assumed to have high risks similar to young patients with SS hemoglobinopathy who are functionally asplenic (autosplenectomized) by 18 months of age. For example, children with congenital heart disease and associated congenital asplenia have high rates of invasive pneumococcal disease that parallel those of children with SCD.<sup>23</sup>

#### *HIV Infection*

Children with HIV infection have high rates of morbidity and mortality attributable in part to high rates of infection caused by encapsulated bacteria (Table 1). *S pneumoniae* is the most common cause of invasive bacterial infection in these children, accounting for 35% to 50% of such episodes, with relative risks of pneumococcal disease 3- to 22-fold higher than those of children without HIV infection.<sup>24,25</sup> Rates of invasive pneumococcal infection for children with HIV infection through 7 years of age have been calculated to be 6100/100 000, with rates as high as 11 300/100 000 during the first 3 years of life.<sup>26</sup> Children infected with HIV and with acquired immunodeficiency syndrome or those with increased levels of immunoglobulin G or immunoglobulin M are at greatest risk for invasive pneumococcal disease.<sup>27</sup>

#### *Specific Populations of Children With High Risk of Pneumococcal Infection*

Certain groups of children of Native American descent have moderate risks ( $\geq 20/100\ 000$ ) of pneumococcal infection, compared with other healthy children. Most groups of Native American children who are at high risk of invasive pneumococcal infection ( $>150/100\ 000$ ) are younger than 2 years (Table 1). The degree of risk may vary by factors other than age, including tribal affiliation and residence on or off reservation sites. For many groups, the precise risk of pneumococcal infection remains to be defined. Annual incidence rates for pneumococcal infection among White Mountain Apache children are 1820, 227, and 54/100 000 for children younger than 2, 2 to 4, and 5 to 9 years old, respectively.<sup>28</sup> Rates of pneumococcal infection in Navajo children in Arizona and New Mexico have been estimated to be 664, 453, and 163/100 000 per year in children 12 months or younger, 12 to 23 months old, and 24 to 35 months old, respectively, with rates declining to  $\sim 50\%$  of this level by 3 to 5 years of age (O'Brien K, personal communication, 1999). Alaska Natives have an inci-

dence of invasive pneumococcal disease of 624/100 000 in children younger than 2 years.<sup>29</sup> Children of African American descent have rates of invasive pneumococcal infection that are twofold to threefold higher at all ages from birth to 59 months of age, compared with all US children (Table 1).

#### *Infants and Children in Out-of-Home Care*

Pneumococcal disease among children in out-of-home care has been reported more often throughout the last decade in the United States and other developed countries. In Finland, an increased risk for invasive pneumococcal disease among children younger than 2 years has been associated with attendance at out-of-home care (odds ratio [OR]: 36; 95% confidence interval [CI]: 5.7–233) or family home care (OR: 4.4; 95% CI: 1.7–12).<sup>30</sup> A history of frequent episodes of otitis media was a risk factor independent of out-of-home care. Attendance in out-of-home care also has been shown to increase the risk of respiratory tract infections and otitis media in US children.<sup>31,32</sup> In the United States, out-of-home care (defined as  $\geq 4$  hours/week outside the home) increases the risk for invasive pneumococcal infection (2.63-fold risk in children 2–11 months old, 2.29-fold risk in children 12–23 months old, and 3.28-fold risk in children 24–59 months old).<sup>33</sup>

Among children in out-of-home care, outbreaks of invasive pneumococcal disease and respiratory tract infections, along with high rates of pneumococcal colonization, have been reported for several pneumococcal serotypes, particularly 14, 23F, and 12F.<sup>34–37</sup> Pneumococcal infections in such outbreaks have included sepsis, meningitis, purulent conjunctivitis, recurrent otitis media, and sinusitis. In one center, 3 cases of meningitis attributable to multiply resistant serotype 14 *S pneumoniae* occurred during a 5-day period, and nasopharyngeal (NP) carrier rates with the same pulsed-field genotype of multiply resistant pneumococcus varied from 44% to 65% at 2 other out-of-home care centers and 1 pediatric practice in the same community.<sup>37</sup> In another center, presumptive serogroup 19 pneumococcal disease, identified by serologic and polymerase chain reaction, caused hemorrhagic shock and resulted in the deaths of 2 children who were 4 and 7 months old.<sup>38</sup>

NP carriage of *S pneumoniae* is common among young children attending out-of-home care. Rates of NP carriage range from 21% to 59% in point prevalence studies and up to 65% in longitudinal studies.<sup>39–42</sup> The most common serogroups associated with respiratory tract carriage in children attending out-of-home care have been 6, 14, 19, and 23. Several studies have documented carriage of outbreak strains in child and adult contacts as well as in staff personnel. Transmission of antibiotic-resistant pneumococci has been documented in 8 studies. In these studies, high concentration penicillin resistance (penicillin concentration  $> 2\ \mu\text{g}/\text{mL}$ ) has occurred in 7% to 56% of isolates of serogroups 23, 14, 6, 19, and 11, and resistance to intermediate penicillin concentrations ( $.1\text{--}1.0\ \mu\text{g}/\text{mL}$ ) has been documented in many outbreaks as well. Some investigators also have documented resistance to multiple antibiotics, including

penicillin, extended-spectrum cephalosporins, trimethoprim-sulfamethoxazole, clindamycin, and erythromycin. Factors associated with carriage of antibiotic-resistant pneumococci have included age younger than 2 years, frequent upper respiratory infections, use of prophylactic antibiotics, frequent use of antibiotics for febrile illnesses, and a history of recurrent AOM or AOM unresponsive to antibiotic treatment.<sup>39–42</sup>

The use of antibiotics to eliminate NP carriage or to prevent transmission of invasive pneumococci has been evaluated in 4 outbreaks of pneumococcal infection among children in out-of-home care. In an outbreak causing cases of sepsis and meningitis attributable to a multiply resistant *S pneumoniae*, the administration of rifampin (10 mg/kg, twice daily for 2 days) resulted in a 70% reduction in the NP carriage of pneumococci at 1 week after completion of antibiotics, and no additional disease caused by this strain of pneumococcus was identified in the subsequent 9 months.<sup>34</sup> In another study, rifampin (20 mg/kg, once daily for 4 days) was not effective in eliminating serotype 12F pneumococci from the nasopharynges of the 6 children attending the child care home or from their 16 family contacts.<sup>35</sup> In a child care center where 2 deaths were caused by serogroup 19 pneumococcal disease, 6 children and 2 staff members had NP colonization. Children older than 2 years were given a single dose of pneumococcal polysaccharide vaccine, and those younger than 2 years were given 2 doses of benzathine penicillin administered 1 month apart. No further cases of invasive type 19 pneumococcal infection occurred, but data regarding NP colonization were not collected.<sup>38</sup> In an outbreak of multiply resistant type 14 pneumococcal invasive infections, the administration of rifampin (20 mg/kg/day) and clindamycin (25–30 mg/kg/day) for 7 days was associated with a marked but transient decrease in NP carriage of the epidemic strain.<sup>37</sup>

## Pneumococcal Vaccines

### *Purified Capsular Polysaccharide Pneumococcal Vaccines*

Currently, 2 licensed formulations of pneumococcal polysaccharide vaccine are available in the United States: Pnu-Immune 23 (Lederle Laboratories) and Pneumovax (Merck and Co, Inc, West Point, PA). Each vaccine contains 23 purified pneumococcal capsular polysaccharides of *S pneumoniae* serotypes (Danish serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F [17A, Lederle], 18C, 19A, 19F, 20, 22F, 23F, and 33F), and each .5-mL dose contains 25 µg of each antigen (575 µg total polysaccharide) in normal saline solution with either phenol (.25%, Merck and Co, Inc) or thimerosal (.01%, Lederle Laboratories) as a preservative. Based on US surveillance of respiratory tract and invasive pneumococcal isolates, these 23 capsular polysaccharide antigens provide potential serospecific protection against at least 75% of pneumococcal infections and potential serogroup cross-protection against an additional 14% of isolates. Thus, these vaccines provide potential protection against 85% to 90% of invasive

and respiratory infections caused by pneumococci in US children.<sup>43</sup> The serotypes that most frequently cause invasive infections in children in developed countries, in decreasing order of frequency, are 14, 6B, 19F, 18C, 9V, 23F, 7F, 4, and 1, while in developing countries the most frequent serotypes, in decreasing order of frequency, are 6B, 14, 8, 5, 1, 19F, 9V, 23F, 18C, 15B, and 7F.<sup>44</sup>

The 23-valent pneumococcal polysaccharide vaccine has been recommended for children 2 years and older who are at increased risk for invasive pneumococcal infection.<sup>45</sup> However, many of the polysaccharides contained in the vaccine are not immunogenic in children younger than 2 years, and may not be immunogenic for all serotypes until children are 5 years or older. In addition, despite at least minimal antibody responses in children 2 years or older, a reduction of NP carriage of pneumococci has not been demonstrated. The poor immunogenicity of polysaccharide vaccines in young children is related to the T-cell-independent nature of polysaccharide antigens. T-cell independence is also responsible for a failure to elicit memory after repeated administration of polysaccharide antigens.<sup>46</sup> In addition to poor quantitative responses, qualitative or functional (eg, opsonization) responses are also poor. The incidence of adverse reactions and the serospecific antibody responses in children older than 2 years after administration of polysaccharide pneumococcal vaccines have been reviewed previously.<sup>1,2,45</sup>

Prospective controlled evaluations of the efficacy of pneumococcal polysaccharide vaccines in preventing invasive disease in children have not been performed. However, in a retrospective serogroup analysis of US invasive disease, efficacy could not be demonstrated in children 2 to 10 years old, including those children at high risk of pneumococcal infection.<sup>47</sup> In addition, 2 controlled studies found that polysaccharide vaccines do not reduce the incidence or severity of otitis media in children older than 2 years.<sup>48,49</sup> In contrast, a recent Danish retrospective analysis of pneumococcal polysaccharide vaccines licensed since 1977 suggested significant efficacy against invasive diseases in splenectomized children older than 2 years.<sup>50</sup> Another recent retrospective study of the efficacy of pneumococcal polysaccharide vaccines in US children also suggested an efficacy of 63% (95% CI: 8–85) in children 2 to 5 years old.<sup>51</sup>

### *Protein Conjugate Pneumococcal Vaccines*

Several protein conjugate oligosaccharide and polysaccharide pneumococcal vaccines linked with proteins, such as meningococcal outer membrane protein,<sup>52</sup> tetanus toxoid,<sup>53</sup> a mutant nontoxic diphtheria toxin, CRM<sub>197</sub>,<sup>54</sup> and diphtheria toxoids<sup>55</sup> have been evaluated for safety and immunogenicity in infants and children. These conjugate polysaccharide vaccines have been studied as monovalent (6B), pentavalent (6B, 14, 18C, 19F, and 23F), heptavalent (6B, 14, 19F, 23F, 18C, 4, and 9V), novavalent (heptavalent serotypes plus 1 and 5), and 11-valent (novavalent serotypes plus 3 and 7V) formulations with doses of each polysaccharide or oligosaccharide ranging from 1 to 20 µg. Each of these polysaccharide conjugate

pneumococcal vaccines has been found to induce good immune responses in infants younger than 1 year, and amnestic (ie, memory) responses have been observed after booster doses.

#### Heptavalent Pneumococcal CRM<sub>197</sub> Conjugate Vaccine (PCV7)

The heptavalent pneumococcal conjugate vaccine (PCV7), Prevnar (Lederle Laboratories/Wyeth-Ayerst Pharmaceuticals), licensed on February 17, 2000 by the US Food and Drug Administration, is composed of 7 pneumococcal antigens (polysaccharide serotypes 4, 6B, 9V, 14, 19F, and 23F and an oligosaccharide serotype 18C) conjugated to 20  $\mu\text{g}$  of CRM<sub>197</sub> by reductive amination.<sup>54</sup> Each .5-mL dose contains 2  $\mu\text{g}$  of each antigen except for 6B, which is a 4- $\mu\text{g}$  dose. Aluminum phosphate (.5 mg) is added as an adjuvant. The vaccine contains no thimerosal or other preservatives. The recommended primary series is 3 doses given at 2, 4, and 6 months of age with a minimum of 6 weeks between doses. A fourth (booster) dose is recommended at 12 to 15 months of age or at least 60 days after completion of the primary series. The PCV7 provides potential serotype and serogroup cross-protection (eg, 6A) for 88% of the cases of bacteremia, 82% of the cases of meningitis, and 71% of the cases of pneumococcal otitis media episodes in US children under 6 years of age.<sup>44</sup>

#### Adverse Effects and Safety

The PCV7 vaccine has been associated with an acceptable incidence of adverse effects when given at 2, 4, 6, and 12 to 15 months of age with concurrent administration of recommended, age-appropriate vaccines (diphtheria and tetanus toxoids and acellular pertussis [DTaP], *H influenzae* type b conjugate [HbOC], diphtheria and tetanus toxoids and pertussis [DTP]/HbOC, hepatitis B, oral poliovirus [OPV], inactivated poliovirus [IPV], and measles-mumps-rubella [MMR] and varicella vaccine), compared with the administration to children of a control investigational vaccine of meningococcal C polysaccharide conjugated to CRM<sub>197</sub>.<sup>54</sup> No hepatitis A vaccine has been given concurrently with PCV7.

Available data suggest that PCV7 may prove to be among the most reactogenic (eg, local reactions and incidence of fever) vaccine of those currently used, including the DTaP and *Haemophilus* conjugate vaccines. Moderate local reactions (any erythema  $\geq 2.4$  cm and/or tenderness) occurred at the injection site in 4.9% to 6.1% of children after all doses, without a statistically significant increase in the number or severity of these reactions with any subsequent dose in the series (Table 2). The fourth dose (given with DTaP and MMR) was associated with the fewest local reactions. Young infants experienced local re-

actions at the PCV7 site less often than at the DTP/HbOC site.

The incidence of fever (body temperature  $\geq 38^\circ\text{C}$  within 48 hours of vaccination) occurred in a greater proportion of children in the PCV7 group than in those who received the meningococcal C conjugate vaccine when administered with DTP/HbOC or DTaP (Table 3). The incidence of fever was nearly twofold higher in children receiving PCV7, compared with children who received the meningococcal vaccine, despite a high rate of antipyretic use in both groups. Fever is most common after the second or third dose of PCV7 when given concurrently with DTP/HbOC.<sup>56</sup> Drowsiness occurred in 27.4% to 48.9%, fussiness occurred in 37.6% to 39.9%, and decreased appetite occurred in 12.7% to 17.8% of children given DTaP, *H influenzae* type b vaccine, and OPV or IPV with PCV7. In addition to higher rates of fever in children receiving PCV7, there was more frequent use of antipyretics than in children who received meningococcal conjugate vaccines. Body temperatures of at least  $38^\circ\text{C}$  and higher than  $39^\circ\text{C}$  were reported in 13% and 1.2%, respectively, of 727 children who received PCV7 without any concurrent vaccines. This small group of children also experienced irritability (45.8%), drowsiness (15.9%), restless sleep (21.2%), decreased appetite (18.3%), vomiting (6.3%), diarrhea (12.8%), and rash or hives (1.2%; Food and Drug Administration package insert).

#### Immunogenicity

The protective concentrations of pneumococcal antibody against invasive infections have not been defined. Based on the levels of anticapsular antibody that are protective against *H influenzae* type b infection, a surrogate minimum concentration of protective anticapsular antibody has been proposed to be at least .15  $\mu\text{g}/\text{mL}$ . Similar levels of specific pneumococcal antibody (.1–1.15  $\mu\text{g}/\text{mL}$ ) have been associated with lower mortality in rat models of pneumococcal infection.<sup>57</sup>

The PCV7 vaccine induces good antibody responses in infants when administered at 2, 4, 6, and 12 to 15 months of age. After 3 doses, 92% to 100% of children had at least .15  $\mu\text{g}/\text{mL}$  of antibody against all 7 of the vaccine serotypes, and 51% to 90% achieved a level of at least 1.0  $\mu\text{g}/\text{mL}$  against the 7 vaccine serotypes. Administration of the fourth-dose results in a prompt increase in antibody levels to all 7 serotypes.<sup>54</sup> These antibody responses have been confirmed in the Northern California efficacy trials.<sup>56</sup> Geometric mean titers after 3 priming doses of the PCV7 vaccine varied from 1.0  $\mu\text{g}/\text{mL}$  for serotype 9V to 3.7  $\mu\text{g}/\text{mL}$  for serotype 14, with  $>90\%$  of titers for all serotypes being  $\geq .15$   $\mu\text{g}/\text{mL}$ . The proportion

**TABLE 2.** Incidence of Local Reactions in Children Receiving PCV7 Versus MenCRM With the Concomitant Recommended Vaccines of Infancy at 2, 4, 6, and 12 to 15 Months of Age

Reaction	Dose 1	Dose 2	Dose 3	Dose 4
Injection site, any	36% vs 56%	43% vs 58%	35% vs 46%	33% vs 24%
Injection site, moderate	4.9% vs 12%	6.1% vs 11%	5.3% vs 5.2%	3.4% vs 3.4%

**TABLE 3.** Incidence of Fever With Administration of PCV7 by Dose When Given With DTP/HbOC Versus Acellular DTP

Vaccines	Percentage of Subjects With Temperature $\geq 38^{\circ}\text{C}$			
	Dose 1	Dose 2	Dose 3	Dose 4
PCV7 + DTP/HbOC	32.6	34.5	40.0	41.9
PCV7 + DTaP	15.7	26.6	22.1	19.6
DTaP	9.5	15.3	18.3	—
PCV7	—	—	—	13.4
Vaccines	Percentage of Subjects With Temperature $\geq 39^{\circ}\text{C}$			
	Dose 1	Dose 2	Dose 3	Dose 4
PCV7 + DTP/HbOC	1.3	3.1	5.2	4.5
PCV7 + DTaP	.8	2.8	1.8	1.5
DTaP	.5	.6	.0	—
PCV7	—	—	—	1.2

of children with titers  $\geq 1.0 \mu\text{g/mL}$  ranged from 51% for serotype 9V to 89% for serotype 14.<sup>56</sup> Immunologic priming (eg, induction of antibody memory) seems to occur after only 2 doses for some serotypes, whereas 3 doses are necessary to induce priming for all serotypes. Significant booster responses are observed with additional doses given at intervals of a few months to a year or more after the completion of the primary series.<sup>58</sup>

After concurrent administration of PCV7 with DTP, DTP/HbOC, or DTaP, no meaningful differences were noted in geometric mean concentrations of antibodies to pertussis antigens (pertussis toxin, fimbriae, 69 kDa protein, fimbrial hemagglutinin), diphtheria, and tetanus, compared with concurrent administration of the investigational meningococcal CRM<sub>197</sub> conjugate vaccine. After concurrent administration of PCV7 with MMR or varicella vaccines, the percentage of children achieving protective antibody titers against measles, mumps, rubella, and varicella was 80% to 95% and did not differ from historical controls.<sup>56</sup>

In limited observations, a decrease in NP carriage of vaccine pneumococcal serotypes from prevaccine baseline rates of 25% to postvaccine rates of 7% to 9% during short periods of follow-up has been observed after administration of a similar investigational heptavalent pneumococcal vaccine (4, 6B, 9V, 14, 18C, 19F, and 23F capsular polysaccharides conjugated to the outer membrane protein of *Neisseria meningitidis*).<sup>59</sup> Decreases in carriage have been observed during similar trials of other conjugate pneumococcal vaccines, but decreases in rates of colonization have not been demonstrated by active surveillance of NP carriage during efficacy trials with PCV7. However, in a study of a nanovalent CRM<sub>197</sub> conjugate pneumococcal vaccine, the conjugate vaccine resulted in a decrease in the NP carriage of vaccine-type pneumococci but also was associated with an increase in the carriage of nonvaccine pneumococcal serotypes.<sup>60</sup>

#### Efficacy

A single efficacy trial has been completed by the Northern Kaiser Permanente Vaccine Study Center. In this trial, 37 868 children were randomized to receive the heptavalent pneumococcal vaccine (PCV7) or an experimental vaccine of meningococcal

C conjugated to CRM<sub>197</sub> (MenCRM) at 2, 4, 6, and 12 to 15 months of age.<sup>61,62</sup> Children were followed for up to 24 months after vaccination. Study vaccines were given with age-appropriate injections of hepatitis B, Tetramune (Lederle Laboratories/Wyeth-Ayerst Pharmaceuticals; HbOC/DTP), OPV or IPV, and MMR and varicella vaccines; later in the trial, the use of HbOC/DTP vaccine was changed to DTaP and HbOC (HibTITER, Lederle Laboratories/Wyeth-Ayerst Pharmaceuticals) vaccines, administered separately. Surveillance for invasive pneumococcal disease was conducted as the primary end point, using an automated laboratory database. All invasive isolates were serotyped. Otitis media and pneumonia were identified from automated clinic encounter sheets using predefined physician-confirmed and radiologically confirmed criteria. Of enrolled children, 18 927 were randomized to receive PCV7 and 18 941 to receive MenCRM vaccines. The mean age at each immunization procedure was 2.1 months (dose 1), 4.3 months (dose 2), 6.5 months (dose 3), and 13.7 months (dose 4).

An analysis to determine the primary end point of invasive disease identified 3 cases of vaccine serotype-specific invasive disease in the children randomized to receive PCV7 versus 49 cases in the infants randomized to receive MenCRM vaccine (93.9% efficacy; 95% CI: 79.5–98.5;  $P < .0001$ ; Table 4). Against bacteremic pneumonia, the estimated efficacy was at least 85% against serotype-specific disease.

The effect of PCV7 on the incidence and severity of otitis media was evaluated as a secondary end point in the Northern California Kaiser efficacy trial. A total of 47 392 visits and 33 529 episodes for otitis media in children immunized according to protocol were recorded. Of these, 3456 children had frequent episodes of otitis media, defined as at least 3 episodes within 6 months or 4 episodes in 1 year, and 355 children had undergone placement of polyethylene tympanostomy tubes. All visits for otitis media were decreased by 8.9% (95% CI: 5.8–11.8) in vaccine recipients, and the use of tympanostomy tubes was decreased by 20.1% (95% CI: 3.6–34.1). Further reductions in otitis media were observed among those children with frequent episodes, from a 9.3% (95% CI: 3.0–15.1) decrease in those children with 3 epi-

**TABLE 4.** Efficacy of PCV7 Versus MenCRM Against Invasive Disease and Pneumonia in the Northern California Kaiser Vaccine Trial

Outcome Measured	Efficacy Against Invasive Infection		
	Number of Cases: PCV7-Vaccinated	Number of Cases: MenCRM-Vaccinated	% Efficacy (95% CI)
Fully vaccinated* (vaccine serotypes)	1	39	97.4 (82.4–99.9)
Intent to treat† (vaccine serotypes)	3	49	93.9 (79.5–98.5)
All serotypes (including nonvaccine types)	6	55	89.1 (73.7–95.8)

  

Outcome Measured	Efficacy Against Pneumonia			
	Total Number of Cases	Cases in PCV7 Vaccinated	Cases in MenCRM Vaccinated	% Efficacy (95% CI)
Any clinically diagnosed pneumonia	1309	615	694	11.4 (1.3–20.5)
Pneumonia by any abnormal radiograph	152	61	91	33.7 (7.3–51.5)
Radiographically confirmed pneumonia with consolidation‡	33	7	26	73.1 (38.0–88.3)

\* Fully vaccinated received at least a 3-dose primary series.

† Intent-to-treat analysis includes partially and fully vaccinated children.

‡ Radiographic consolidation of  $\geq 2.5$  cm.

sodes in 6 months or 4 in 1 year to a 22.8% decrease (95% CI: 6.7–36.2) in those children with 5 episodes in 6 months or 6 episodes in 1 year. The efficacy against vaccine-specific serotypes in otitis media was 57%.

The effect of PCV7 on the incidence of pneumonia was evaluated in a tertiary, posthoc analysis. Hospital outpatient and emergency records were reviewed to measure the outcomes of clinically diagnosed pneumonia, radiographically confirmed pneumonia, and consolidative pneumonias ( $\geq 2.5$  cm; Table 4). Use of PCV7 resulted in an 11.4% (95% CI: 1.3–20.5) decrease in clinical episodes of pneumonia and a 33.7% (95% CI: 7.3–51.5) decrease in radiographically confirmed pneumonias. Pneumonias with radiographic consolidation were decreased 73.1% (95% CI: 3.0–88.3) among children vaccinated with PCV7.

Additional clinical trials with PCV7, including trials of its safety and efficacy against invasive disease and pneumonia among Native American and South African children, are currently in progress. Efficacy in AOM has been evaluated in Finnish children, and preliminary results have demonstrated efficacy in the prevention of otitis media similar to that found in the Northern California Kaiser Permanente trials.

#### SCD

Limited safety and immunogenicity trials of PCV7 have been completed in children with SCD. In 1 trial, 24 children 2 years or older with SCD were given 2 doses of PVC7 at an 8-week interval, followed 8 weeks later by a single dose of 23-valent pneumococcal polysaccharide (23PS) vaccine with or without a third dose of PCV7.<sup>62</sup> Antibody levels to all 7 antigens were higher after the combined dosing regimen (eg, PCV7 plus 23PS vaccine as the third dose), compared with the regimen of the 23PS vaccine given alone as the third dose, although the difference was statistically significant only for serotypes 14 and 19. Fever was reported by 3 of 11 subjects after the first dose of PCV7, by 1 of 11 after the second dose, and by 4 of 11 after the third dose of those who received the combined regimen (PCV7 plus 23PS vaccine) and by 2 of 11 of those who received 23PS

vaccine alone. Local reactions of swelling and erythema were similar in those children who received 23PS vaccine alone, compared with those who received a combined regimen of PVC7 and 23PS vaccine (median: 4.0 and 3.5 cm, respectively; range: 0–14 cm), but they were more frequent than in those children receiving priming doses of PCV7 (median: 1.0 cm; range: 0–16 cm).

#### HIV Infection

Studies of conjugate pneumococcal vaccines in children with HIV infection have been limited to small numbers of children evaluated for safety and immunogenicity. Two studies have suggested that conjugate pneumococcal vaccines induce higher antibody responses than do polysaccharide vaccines.<sup>63,64</sup> One study specifically examined responses to a vaccine with 5 pneumococcal oligosaccharides (6B, 14, 18C, 19F, and 23F) conjugated to the CRM<sub>197</sub> protein.<sup>64</sup> Eighteen children younger than 2 years (mean: 12.9 months) with HIV infection were given 3 doses at 2-month intervals. The immune responses were compared with those of 33 children without HIV infection. Of the HIV-infected children, 78% achieved antibody titers of at least 1.0  $\mu\text{g/mL}$  in contrast to 88% of the children not infected with HIV. Children with more advanced HIV disease were less likely to respond than were children in Centers for Disease Control and Prevention classes N1-2, A1-2, and B1, but these differences were not observed after the third dose. Only minor reactions were noted and were similar to those reported for healthy children.

#### Cost-Effectiveness Analysis

The potential cost-effectiveness of a routine pneumococcal conjugate vaccine program in healthy children has been evaluated.<sup>65</sup> Based on an annual birth cohort of 3.8 million infants, it was assumed that routine PCV7 immunization would prevent 78% of annual pneumococcal meningitis cases ( $n = 2219$ ), 69% of annual bacteremia cases ( $n = 52\,319$ ), and 7% of annual otitis media cases ( $n = 1\,009\,505$ ). This would result in net savings to society, if the cost of each dose of vaccine was  $\leq \$46$ . Net savings to health

care insurers would accrue at vaccine costs of  $\leq$ \$18 per dose. Additionally, a 1-dose catch-up program for all healthy children from 24 to 40 months old and those children in child care from 24 to 50 months old would result in reduced societal expenditures at a vaccine cost of  $\leq$ \$40/dose. The private sector cost per dose of PCV7 is  $\sim$ \$58/dose, or \$232 for the 4 infant doses, not including administration costs.

### Antibiotic Prophylaxis

Antibiotic prophylaxis is recommended for all children with SCD beginning at 2 months of age or earlier. This recommendation is commonly extended in clinical practice to include all children with congenital asplenia or surgical splenectomy. Recommendations for prophylaxis are made based on efficacy against invasive pneumococcal infection demonstrated in children with SCD enrolled in a prospective multicenter, randomized, double-blind trial of prophylactic penicillin administration (125 mg of penicillin V potassium, administered orally twice daily to 3 years of age, and 250 mg twice daily thereafter).<sup>66</sup> An 84% decrease was observed in the incidence of pneumococcal infection in the antibiotic prophylaxis group. In another prospective randomized trial, infants receiving benzathine penicillin in monthly home injections were compared with infants receiving 14-valent pneumococcal polysaccharide vaccine (14PS).<sup>67</sup> No episodes of pneumococcal infection occurred among infants with SCD receiving benzathine penicillin versus 10 cases in concurrently followed infants who were not given monthly injections of penicillin (but who were given 14PS).

It is not clear whether prophylactic doses of penicillin reduce NP carriage of pneumococci. One trial conducted during a single winter season demonstrated a decrease of 50% to 75%.<sup>68</sup> Problems with the use of orally administered prophylactic penicillin in children with SCD have included reports of breakthrough invasive infections and compliance rates of only 66%.<sup>69</sup> In addition, several investigators have demonstrated an increase in the number of children with SCD who have NP colonization with penicillin-nonsusceptible strains of pneumococci. Although the NP colonization rates of 10% to 12% in these studies have been similar to those observed in previous studies, 33% to 62% of colonizing strains have been resistant to penicillin, with as many as 29% of strains resistant to high concentrations of penicillin ( $\geq$ 2.0  $\mu$ g/mL).<sup>70,71</sup> Penicillin-nonsusceptible pneumococci also have been implicated in invasive infections and deaths in children with SCD.<sup>72</sup> Reduction of infection risk, compliance with prophylaxis, and effects on NP colonization with pneumococci have not been studied in other groups of children at high risk for invasive pneumococcal disease infection, such as those with congenital or surgical splenectomy, nephrotic syndrome, or lymphoreticular malignancy.

A multicenter study of children with SCD examined the safety of discontinuing penicillin prophylaxis after 5 years of age.<sup>73</sup> Children with SCD or thalassemia who had received at least 2 years of penicillin prophylaxis before their fifth birthday and 1 dose of pneumococcal polysaccharide vaccine were

randomized to receive continued prophylaxis or placebo. There was no difference in the rate of invasive pneumococcal infection among the children receiving penicillin prophylaxis and those receiving placebo—4 cases (2%) and 2 cases (1%), respectively. All invasive isolates were serotypes 6A, 6B, or 23F, and of these 6 isolates, 2 were multiply antibiotic-resistant. The small numbers of enrolled children and the low incidence of pneumococcal disease limit the interpretation of these data.

### CONCLUSIONS AND RECOMMENDATIONS FOR FUTURE RESEARCH

Pneumococcal conjugate vaccines are a significant new contribution to the potential control of pneumococcal disease in young children. Antibiotic prophylaxis continues to play a role in the protection of children with SCD or splenectomy. It is not certain whether the use of pneumococcal conjugate vaccines will decrease the need for antibiotic prophylaxis in the future. However, the emergence of antibiotic-resistant strains of pneumococci threatens to jeopardize the efficacy of current antibiotic prophylactic regimens.

Further studies of pneumococcal conjugate vaccines are needed, including studies of the optimal dosage schedules for safety and efficacy for the administration of PCV7 and 23PS vaccine for healthy and high-risk children older than 24 months. Safety, immunogenicity, and efficacy data are needed for PCV7 used in children older than 5 years and for children with late-acquired immune deficiencies and splenectomy. Serologic correlates of protection have been proposed based on experimental models and extrapolated from similar (eg, *H influenzae* type b) encapsulated organisms. Better-defined correlates of immunity could facilitate the licensure and approval of future pneumococcal conjugate vaccines. In addition, there is a need for continuous surveillance of the causative serotypes of pneumococci involved in pneumococcal disease, particularly as the number of children who receive pneumococcal vaccines increases. Disease with replacement serotypes could be a significant problem. Safety and immunogenicity studies of combinations of pneumococcal conjugate vaccines with other polysaccharide conjugates (eg, *H influenzae* type b and *N meningitidis*) or other childhood live and inactivated vaccines are needed as well to facilitate the administration of fewer doses of vaccines at immunization visits.

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## Technical Report: Prevention of Pneumococcal Infections, Including the Use of Pneumococcal Conjugate and Polysaccharide Vaccines and Antibiotic Prophylaxis

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