

## Prevention of Pneumococcal Disease in High-Risk Pediatric Groups

Based on a presentation by Stephen I. Pelton, MD

### Presentation Summary

Three of the pediatric groups at highest risk for pneumococcal disease are patients infected with human immunodeficiency virus, children with sickle cell disease (SCD), and children with recurrent otitis media. All 3 groups remain at risk for pneumococcal disease well beyond the traditional clustering of disease during the first 3 years of life as seen in the general population. Despite the different epidemiology, the spectrum of *Streptococcus*

*pneumoniae* serotypes recovered from these children is essentially identical to that found in otherwise healthy children. Patients with SCD respond better—as indicated by immunoglobulin G levels and by functional antibody assays—to the new pneumococcal conjugate vaccine than they do to the polysaccharide vaccine. The conjugate vaccine may play a significant role in reducing the incidence of pneumococcal disease in children with well-defined risk factors.

**B**ecause the pediatric population is extremely vulnerable to pneumococcal disease, this group is likely to benefit the most from an effective pneumococcal conjugate vaccine. Examining the epidemiology, serotypes, and immune response within the pediatric groups at highest risk may help clinicians develop and implement a targeted pneumococcal immunoprophylaxis strategy for children older than 3 years of age.

### © Medical World Communications, Inc. Defining Risk Factors

The peak incidence of pneumococcal meningitis and invasive disease usually occurs before 4 years of age. Although pneumococcal disease occurs after age 4, the incidence is extremely low in otherwise healthy

children and in adults until they are age 55 years of age or older when invasive disease and pneumococcal pneumonia become prevalent again (Figure 1).<sup>1</sup> This typical age distribution pattern varies in patients with specific risk factors.

Over the past decade, infection with human immunodeficiency virus (HIV) has become the main risk factor for invasive pneumococcal disease in both children and adults. In one recent study, 25% of adults and 20% of children with invasive disease were HIV positive.<sup>2</sup> Other risk factors reported in association with pneumococcal disease included immunosuppressive therapy, malignancy, splenectomy, and diseases such as diabetes and liver disease. In another recent pediatric study, the predomi-

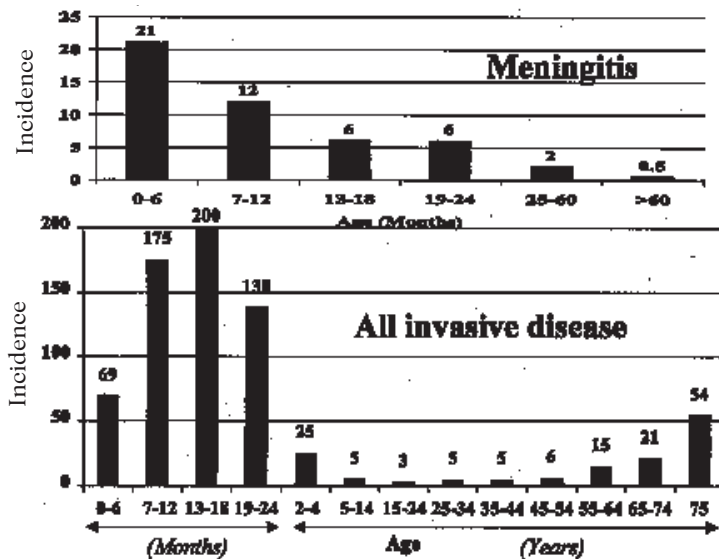
nant risk factors for pneumococcal disease were hemoglobinopathy, HIV infection, and leukemia. Other underlying chronic illnesses such as central nervous systems disorders, heart disease, and renal disease may also be risk factors. Overall, an underlying illness was seen in 27% of children with systemic pneumococcal infections.<sup>3</sup>

In children with HIV infection or sickle cell disease (SCD), invasive pneumococcal disease continues to occur well beyond the usual 24 to 36 months of age. Thus, while the number of pneumococcal cases per year peaks before 24 months of age in the general pediatric population, a substantial rate of infection continues in HIV-infected children through at least 7 years of age.<sup>4</sup> A similar epidemiology for pneumococcal disease has also been noted in children with SCD.<sup>5</sup> The overall risk in children with SCD is 10- to 50-fold greater than normal and has been shown to persist through at least 8 years of age. At Boston Medical Center, a case review of all children with pneumococcal bacteremia identified over the past 18 years confirmed the absence of age-related clustering in children with HIV infection or SCD (Figure 2). Studies of pneumococcal disease in children with SCD indicate that invasive pneumococcal infection is not only more prevalent in children with sickle cell anemia—including those in the older age group—but it also results in a higher mortality rate.<sup>6</sup> The mortality rate in HIV-infected children with pneumococcal disease does not appear to differ from that of children in the general population.

*Streptococcus pneumoniae* continues to be an important pathogen in otitis media even

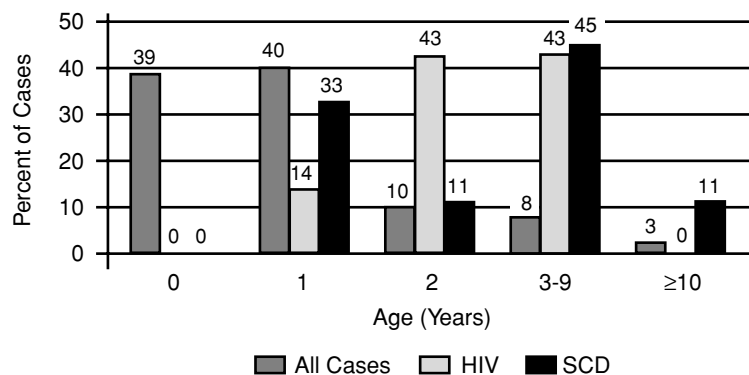
in infants and toddlers with recurrent disease. In a study of children with acute otorrhea and tympanostomy tubes, pneumococci were the predominant pathogen, followed by *Haemophilus influenzae* and *Moraxella catarrhalis*.<sup>7</sup> This observation supports the use of immunoprophyl-

**Figure 1.** Incidence of Pneumococcal Meningitis and Invasive Pneumococcal Disease, By Age (Per 100,000 Population/Year)



Source: Zangwill KM, Vadheim CM, Vannier AM, Hemenway LS, Greenberg DP, Ward JI. Epidemiology of invasive pneumococcal disease in southern California: Implications for the design and conduct of a pneumococcal conjugate vaccine efficacy trial. *J Infect Dis* 1996;174:752-759. Reprinted with permission from The University of Chicago Press.

**Figure 2.** Age Distribution of Pediatric Pneumococcal Bacteremia in High-Risk Groups at Boston Medical Center (1981-1998)



laxis against *S. pneumoniae* in this population. Research has also recently demonstrated that otitis-prone children have an enhanced immune response to pneumococcal conjugate vaccines compared to polysaccharide vaccines (Table).<sup>8</sup>

### Evaluating Serotypes

Analysis of the serotype distribution in high-risk pediatric groups may provide valuable information about the potential efficacy of vaccines. Thus far, most published reports show similar distribution patterns of the major serotypes in populations of HIV-positive and HIV-negative patients with invasive pneumococcal disease. This parallel distribution pattern, which has been noted in both children and adults, indicates that the vaccine would provide at least 65% coverage in either population. Specific data comparing pneumococcal serotypes in children with SCD is limited, although the distribution of pneumococcal serotypes also appears to match that seen in children without SCD.<sup>9</sup>

Children with acute otorrhea and tympanostomy tubes might be expected to be infected with less common serotypes as they get older because they probably had infection with the common serotypes at younger ages. To evaluate the hypothesis that older children with tubes and recurrent acute otitis media display a different pattern of pneumococcal serotypes, the distribution of *S. pneumoniae* in this population was determined and analyzed by age (Pelton, unpublished). Overall, the proportion of disease caused by the 7 most common serotypes decreased with increasing age. Heptavalent vaccine coverage dropped from about 80% in the youngest group to 70% in the 2- to 5-year-old group and to 50% in the oldest children. However, the number of children in the oldest age group was small.

**Table.** Immune Response to 2 Pneumococcal Vaccines

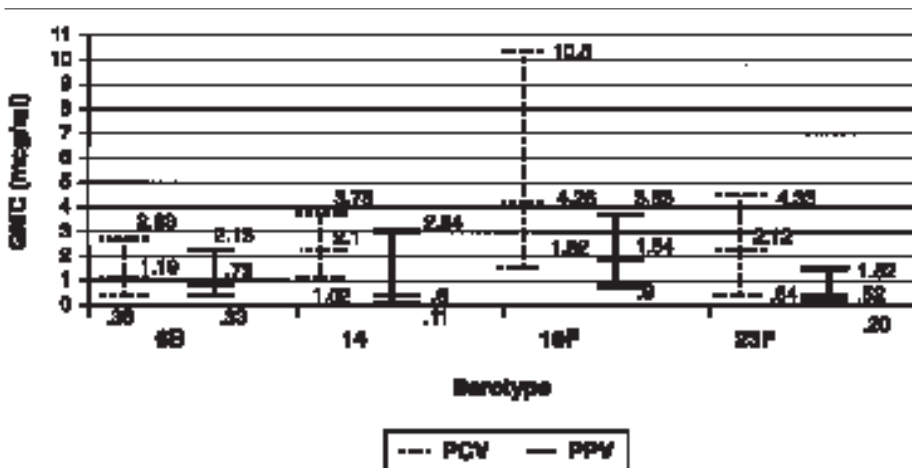
Assay* Serotype	ELISA (µg/mL)*		Opsonophagocyt	
	PPV	PCV	PPV	PCV
4	2.39	2.94	304	1920
6B	2.45	4.12	43	962
9V	3.96	7.63	767	1920
14	5.16	21.8	215	1810
19F	4.10	16.7	30	290 <sup>†</sup>
23F	2.08	5.99	6	659 <sup>†</sup>

PPV = Pneumococcal polysaccharide vaccine; PCV = pneumococcal conjugate vaccine.

\*Geometric mean concentration (for ELISA) and titer (for opsonophagocytic assay).

<sup>†</sup>P < 0.01.

**Figure 3.** Immune Response to PCV and PPV in Otitis-Prone Children



GMC = Geometric mean concentration; PPV = pneumococcal polysaccharide vaccine; PCV = pneumococcal conjugate vaccine.

Children with recurrent otitis media appear to be appropriate candidates for receipt of the heptavalent vaccine.

### Immunogenicity of Pneumococcal Vaccines in High-Risk Populations

A study of the pneumococcal polysaccharide vaccine (PPV) plus penicillin for prevention of pneumococcal disease in children with SCD found 6 (7%) cases among 88 children over a 2-year period,<sup>10</sup> with 4 of these children older than 3 years of age. Three (37%) of the 8 episodes of invasive disease in the 6 affected children resulted in death. The serotypes identified in these patients were 6A, 6B, 9A, and 23F.

The limited success of the PPV in these young high-risk patients raises concern about the functional capacity of the immune response in children with SCD. As shown in the Table, the antibody response as measured by enzyme-linked immunosorbent assay (ELISA) in a recent study suggests that the polysaccharide vaccine elicits antibody concentrations equivalent to the pneumococcal conjugate vaccine.<sup>11</sup> However, when an assay of functional antibody activity is employed, clear differences between the polysaccharide and conjugate vaccines emerge. Specifically, the opsonophagocytic assay indicates that for each serotype, the conjugate vaccine provoked a more vigorous level of immune response. For serotypes 19F and 23F, the differences between the 2 vaccines were highly statistically significant ( $P < 0.01$ ). In HIV-infected patients immunized with the pneumococcal polysaccharide vaccine, a similar paucity of functional antibody response has been noted.<sup>12</sup> Compared with responses seen in HIV-negative patients, the titers of opsonophagocytic activity were reduced for 3 of the 4 serotypes studied. (The difference was statistically significant for serotypes 6B, 19F, and 23F). The ELISA measurements of immunoglobulin G (IgG) concentra-

tions, on the other hand, were not different between the 2 groups.

Children with recurrent otitis media have been reported to respond less well to polysaccharide vaccines than healthy controls. Evaluation of

*“Evaluation of the mean concentration of IgG antibody by ELISA showed that for each serotype evaluated (6B, 14, 19F, 23F), the conjugate vaccine produced a significantly greater response than the polysaccharide vaccine ( $P < 0.05$ )...”*

the mean concentration of IgG antibody by ELISA showed that for each serotype evaluated (6B, 14, 19F, 23F), the conjugate vaccine produced a significantly greater response than the polysaccharide vaccine ( $P < 0.05$ ) and should be more effective in preventing recurrent episodes of pneumococcal otitis media in otitis-prone children (Figure 3).

### Summary

Universal immunization for all children who are younger than 3 years of age is likely to be recommended by the American Academy of Pediatrics and the Centers for Disease Control and Prevention. Attempts to prevent further cases of pneumococcal disease will likely focus on targeting the highest risk groups for immunization first. Studies to date indicate that invasive pneumococcal disease occurs with a much greater frequency in children and adults with HIV infection and children with SCD. Pneumococcal disease in these high-risk children persists throughout the first decade of life, showing no clustering at younger ages. Pneumococci are also the major pathogen in recurrent episodes of acute otitis media in otitis-prone children.

In these high-risk pediatric groups, the pneumococcal serotypes causing disease are identical to those found in healthy children. The heptavalent conjugate vaccine would provide protection against more than 70% of episodes. This vaccine has demonstrated immunogenicity in high-risk pediatric populations and, therefore, has the potential to be an effective tool in limiting the burden of pneumococcal disease in those children most at risk.

... DISCUSSION HIGHLIGHTS ...

**Dr. Santosham:** Are the published data on vaccination in high-risk pediatric groups sufficient for use in creating guidelines?

**Dr. Van Beneden:** The ACIP [Advisory Committee on Immunization Practices] guidelines for pneumococcal vaccination are not complete. Eventually, they will include criteria such as age, daycare attendance, and recurrent otitis. Of course, HIV-infected children may benefit most from the conjugate vaccine, possibly the sickle cell patients as well. But many issues remain unresolved. We still need to determine the best dosage and the proper schedule of conjugate and polysaccharide vaccination. These issues require more data.

**Dr. Pelton:** Yes, especially data on timing of vaccination in HIV-infected children. The 1997 *MMWR* [Morbidity and Mortality Weekly Report] recommendation to give a vaccine early in the course of HIV infection may not be ideal. Immunization after antiretroviral therapy and immune system reconstitution may work better, but we don't know.

**Dr. Black:** How effective are the other preventive approaches at this point?

**Dr. Pelton:** Many attempts at antibiotic prophylaxis fail in these patients.

Often, patients don't take the antibiotic; they run out of their prescription or fail to refill it.

**Dr. Block:** Is antibiotic resistance to pneumococci an issue in these high-risk children?

**Dr. Pelton:** About 3 years ago, we looked at penicillin prophylaxis in children with sickle cell disease. We cultured their nasopharynx and found the colonization was reduced from about 30% to 10%, but the proportion of resistant isolates of pneumococci increased somewhat.

**Dr. Black:** So isn't prophylaxis a detriment if you're selecting strains that are more difficult to treat?

**Dr. Santosham:** This is hard to say without large multicenter trials.

**Dr. Pelton:** Even in a very large study like Dr. Kaplan's with 300 to 400 cases of invasive disease, this would be hard to answer. Without development of nonantibiotic mechanisms of interrupting colonization, such as xylitol, abandoning penicillin prophylaxis would be difficult. It's inexpensive, very safe, and it does have some efficacy.

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