

Epidemiology of Pneumococcal Disease/ Rationale for and Efficacy of PnC7

Summary

A *Streptococcus pneumoniae* Conjugate Vaccine Managed Care Advisory Panel was presented with information on *S. pneumoniae*, the rationale for the new conjugate pneumococcal vaccine, PnC7, and clinical data on the vaccine and its cost effectiveness. The epidemiology and rationale data from the meeting are pub-

lished here. The clinical and cost-effectiveness data that were presented were original data and will be published in the near future. The clinical efficacy data published in this supplement are based on a presentation at the Interscience Conference on Antimicrobial Agents and Chemotherapy in San Francisco, California, September 1999.

At the *Streptococcus pneumoniae* Conjugate Vaccine Managed Care Advisory Panel meeting that took place from June 10 to 12, 1999, in Scottsdale, Arizona, William Hausdorff, PhD, Director of Scientific Affairs and Research Strategy for Wyeth Lederle Vaccines, discussed the rationale for the vaccine and presented an analysis of the potential public health effect.

Rationale for Vaccine Development

The pathogen *Streptococcus pneumoniae*, or pneumococcus, is a leading cause of morbidity and mortality in the United States (Table 1).¹⁻⁸ It is the most common cause of community-acquired bacterial pneumonia, a substantial cause of otitis media (OM), and a common cause of meningitis in children.^{1,4} While most

clinicians may be concerned with pneumococcal meningitis due to its high mortality rate and high level of morbidity, many parents worry about recurrent OM infections because of the direct and frequent impact that these infections have on their quality of life (ie, their children's access to daycare and their own missed days from work). As well, the potential for hearing loss and possible associated learning disorders appears to be a more proximate concern for the majority of parents.

Age distributions for pneumococcal diseases indicate that they are most prevalent in children younger than 2 years of age and in the elderly, however, the incidence of OM declines more gradually after 24 months compared to that of invasive disease (eg, meningitis and bacteremic pneumococcal disease).^{5,9}

Invasive disease remains a risk for children up to 59 months of age.

High-risk groups for OM and/or invasive pneumococcal disease have been defined—Native Americans, African Americans, daycare attendees, recurrent OM patients, and patients with chronic illness, sickle-cell disease, and who are immunocompromised—but using this stratification to define potential targets for vaccination programs is questionable. For example, it is not possible to predict who will go into daycare. Furthermore, the definition of daycare (ie, greater than or equal to 4 hours per week outside the home with 2 or more unrelated children under adult supervision) is so broad that almost all children would qualify. In addition, targeting high-risk individuals for immunization has been a difficult strategy to implement for other vaccines.

There are approximately 45 serogroups of pneumococcus; some serogroups contain related serotypes for a total of more than 90 serotypes. Infection with a member of one serogroup does not provide clinical protection against infection by another, but there does seem to be some cross-protection among certain related serotypes. Serogroups and serotypes have shown geographical and temporal (ie, year to year) variation.

The increasing prevalence of pneumococcal disease and emergence of penicillin-resistant *S. pneumoniae* (PRSP) strains prompted the development of a pneumococcal vaccine. A 23-valent pneumococcal vaccine is available and approved for use in adults and children over 2 years of age. It contains polysaccharides from 23 pneumococcal serotypes. The polysaccharides are taken from the encapsulating sugars of the bacteria, which define the serotype. The 23-valent vaccine is effective in preventing bacteremic disease in adults, but it has not been shown to be effective in controlling OM.¹⁰ Also, it does not

activate T cells nor prime for an anamnestic response. As Dr. Hausdorff explained, T cells are “happily blind” to polysaccharide. Because invasive disease and OM episodes are more prevalent in infants, a vaccine that is effective in the youngest children was needed.

PnC7 (Prevenar™), a heptavalent conjugated vaccine modeled on the *Haemophilus influenzae* type b (Hib) vaccine, contains polysaccharides from the 7 main disease-causing pneumococcal serotypes, conjugated to a mutant diphtheria toxin, CRM₁₉₇. The carrier protein recruits T cells to the immune process. According to Dr. Hausdorff, the outstanding results with the Hib vaccine (which uses the same carrier protein) provided proof-of-concept that CRM₁₉₇ was an effective conjugating agent for recruiting T cells in the immune response in infants. The public health effect seen with Hib was dramatic.^{11,12}

The 7 serotypes comprising the 7-valent pneumococcal conjugate vac-

Table 1. Disease in the United States Associated With *Streptococcus pneumoniae*

Clinical Presentation	Cases Per Year		Clinical Features in Children
	All Ages	Children <5	
Pneumonia	500,000	~71,000	~6% are bacteremic
Bacteremia	50,000	17,000	~70% are occult
Meningitis	3000	1400	Neurological sequelae and hearing loss in 25% to 50% of cases
Otitis Media	7,000,000	5,100,000	Hearing Loss, Antibiotic Use, ~65,000 PE tubes

Treatment of these diseases is complicated by increasing antibiotic resistance. *S. pneumoniae* is the leading cause of sepsis, meningitis, pneumonia, sinusitis, and otitis media.

Source: References 1-8.

cine—4, 6B, 9V, 14, 18C, 19F, and 23F—are the most significant in causing pneumococcal disease in young children in the United States and are responsible for approximately 80% to 85% of all pneumococcal invasive disease cases, and 65% to 75% of pneumococcal OM cases.¹³⁻¹⁶

Although pneumococci have historically been very sensitive to penicillin, the incidence of PRSP has increased from 4% to as high as 43% during the past decade.¹⁷ The current national average incidence of PRSP is 25%, but wide variations are found geographically and among hospitals within a geographic region.¹⁸

The PRSP strains are almost all confined to 5 serogroups (6, 9, 14, 19, and 23), which are also part of the 7 serogroups represented in PnC7.¹⁹⁻²¹ Of these most common PRSP strains, the PnC7 serotypes account for nearly 80% of strains resistant to penicillin or at least one drug class (including penicillin).^{19,20} PnC7 covers approximately 85% to 100% of all intermediate/highly resistant PRSP isolates in several countries.²²⁻²⁵

Potential Public Health Effect With PnC7

Dr. Hausdorff presented an analysis to assess the potential public

health effect on children 5 years of age or younger using 3 vaccination scenarios with PnC7: 1) routine infant immunization in children ages 0 to 59 months, using a 4-shot immunization procedure, as described in Table 2; 2) a one-time “catch-up” program in children ages 7 to 35 months; and 3) a one-time catch-up program in children ages 35 to 59 months. For those receiving routine infant immunization, children up to 6 months of age at the time of their first dose would receive 4 shots. The number of shots decreases with each age category so that children ages 24 to 59 months would receive only 1 shot.

The results of the analysis indicate a significant number of estimated invasive disease, pneumonia, and pneumococcal meningitis cases, OM visits, and tube placements that were avoided during the first 5 years of life (Table 3).¹⁻⁹ The impact of a one-time catch-up program in children 7 to 35 months of age showed an increased public health effect; in children 35 to 59 months of age, the benefits were significantly reduced although still providing a positive public health effect, particularly in children in a high-risk group.

Clinical Studies on PnC7

The mathematical analysis has been supported by clinical results indicating that the vaccine is safe and immunogenic in young children.²⁶ Beginning in October 1995, PnC7 was offered to infants at 2, 4, and 6 months of age with a fourth dose at 12 to 15 months in a double-blind trial to evaluate the safety and efficacy of the vaccine. The primary outcomes were invasive disease due to vaccine serotypes, pneumonia, and clinical OM. Approximately 38,000 children were randomly assigned 1:1 to receive either PnC7 or meningococcus type C CRM₁₉₇ conjugate. The trial protocol included an interim analysis when the first 17 cases of disease due to vaccine serotype were documented.

Table 2. Immunization Schedule Used for Public Health Effect Analysis

Age at 1st Dose	Total Doses
0-6 months	4*
7-11 months	3
12-24 months	2
24-59 months	1

*Three-dose primary series at 2, 4, and 6 months plus booster at 12 to 15 months.

At the 17-case analysis (July 1998), the trial was terminated because of the high level of efficacy demonstrated. All 17 cases in fully-vaccinated children and all 5 cases in partially vaccinated children occurred in the control group for a vaccine efficacy of 100% (95% CI; 75.7% to 100%). In the intent-to-treat (ITT) analysis (children who were partially vaccinated), effectiveness was 100% (95% CI; 81.4% to 100%). A subsequent analysis has revealed 40 cases due to vaccine serotype in the fully vaccinated study population, 39 of which are in the control group for an efficacy of 97.4% (95% CI; 82.7% to 99.9%). Likewise, in the subsequent ITT analysis, 52 cases have been identified, 49 of which are in the control group, so effectiveness is 93.9% (95% CI; 79.6% to 98.5%).

There has been no evidence of an increase of disease due to nonvaccine serotypes in this study. This is an important finding because future

serotype replacement remains a possibility.

For OM, efficacy against the number of visits, episodes, frequent OM, and PE tube placement was 8.9%, 6.4%, 9.3%, and 20.1% ($P < 0.04$ for all). Frequent OM was defined as 3 or more visits within 6 months, or 4 or more visits within a year.

In measuring pneumonia, outcomes included a clinical diagnosis of pneumonia, X ray-confirmed pneumonia, and consolidation of greater than or equal to 2.5 cm, as agreed to by both a pediatrician's and radiologist's review of the films. In the fully vaccinated population, efficacy (95% CI) for any pneumonia visits, initial abnormal X-ray reading, and consolidation was 10.7% (-0.7 to 20.8), 35.0% (5.5 to 55.8), and 62.7% (11.3 to 84.3), respectively. For the ITT analysis, efficacy was 11.4% (1.3 to 20.5), 33.0% (7.3 to 51.5), and 73.1% (38.0 to 88.3), respectively.

Table 3. Estimated Public Health Effect of PnC7 in Children up to 59 Months of Age—Number of Cases Avoided

Immunization Schedule	Invasive Disease Cases	Pneumococcal Meningitis Cases	OM Visits	PE Tube Placements	Pneumonia Cases
Routine	13,488	1152	1,375,381	63,325	53,000-89,000*
Catch-up 7-35 mo.	19,827	1670	2,268,111	127,742	N/A
Catch-up 35-59 mo.	1478	119	494,124	27,548	N/A

*A range is given because there are multiple estimates for the number of pneumonia cases in this age group.

NA = not available

Number of cases listed is the number of cases that could be avoided as a result of the respective immunization program for either a single annual US birth cohort ("Routine": approximately 3.8 million children) or for the cohorts comprised by the catch-up age groupings ("7-35 mo.": approximately 9.5 million children; or "35-59 mo.": approximately 7.6 million children), based on the cases that would otherwise occur in those cohorts until those children reach the age of 59 months. Other factors involved in estimating the public health effect include age-adjusted incidence of each relevant disease syndrome; the fraction attributable to pneumococcus, when available; the fraction attributable to specific serotypes contained within PnC7; the vaccine efficacy or effectiveness.

Source: References 1-9, 26.

These data show that PnC7, when used in this regimen, appears to be highly effective in preventing invasive disease—and has a significant impact on OM and pneumonia—in young children.

...REFERENCES ...

1. Centers for Disease Control. Prevention of Pneumococcal Disease: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *Morb Mort Wkly Rep* 1997;46(RR-8):1-24.
2. 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.
3. Kaplan SL, Mason EO Jr, Barson WJ, et al. Three-year multicenter surveillance of systemic pneumococcal infections in children. *Pediatrics* 1998;102:538-545.
4. Schuchat A, Robinson K, Wenger JD, et al. Bacterial meningitis in the United States in 1995. Active Surveillance Team. *N Engl J Med* 1997;337:970-976.
5. Thompson D, Oster G, McGarry LJ, Klein JO. Management of otitis media among children in a large health insurance plan. *Pediatr Infect Dis J* 1999;18:239-244.
6. Hausdorff WP and Paradiso PR. Unpublished data, 1999.
7. Heiskanen-Kosma T, Korppi M, Jokinen C, et al. Etiology of childhood pneumonia: Serologic results of a prospective, population-based study. *Pediatr Infect Dis J* 1998;17:986-991.
8. Hall MJ, Lawrence L. Ambulatory surgery in the United States, 1996. Advance data from vital and health statistics; Report 300. Hyattsville, MD: National Center for Health Statistics; 1998.
9. Centers for Disease Control, Active Bacterial Core Surveillance (ABCS) Report. Emerging Infections Program Network, *Streptococcus pneumoniae*, 1998. Available at <http://www.cdc.gov/ncidod/dbmd/abcs>. Accessed September 17, 1999.
10. Klein JO, Teele DW, Sloyer JL, et al. Use of pneumococcal vaccine for prevention of recurrent episodes of otitis media. In: Weinstein L, Fields BN, eds. *Seminars in Infectious Disease*. New York: Thieme-Stratton Inc; 1982:305-310.
11. Adams WG, Deaver KA, Cochi SL, et al. Decline of childhood *Haemophilus influenzae* type b (Hib) disease in the Hib vaccine era. *JAMA* 1993;269:221-226.
12. Centers for Disease Control and Prevention. Progress toward elimination of *Haemophilus influenzae* type b disease among infants and children. *Morb Mortal Wkly Rep* 1995;44:545-550.
13. Hausdorff WP, Bryant J, Kloek C, Paradiso PR, Siber GR. The contribution of specific pneumococcal serogroups to different disease manifestations: Implications for conjugate vaccine formulation and use (II). *Clin Infect Dis*. In press.
14. Hausdorff WP, Bryant J, Paradiso PR, Siber GR. Which pneumococcal serogroups cause the most invasive disease: Implications for conjugate vaccine formulation and use (I). *Clin Infect Dis*. In press.
15. Shapiro ED, Austrian R. Serotypes responsible for invasive *Streptococcus pneumoniae* infections among children in Connecticut. *J Infect Dis* 1994;169:212-214.
16. Butler JC, Breiman RF, Lipman HB, Hofman J, Facklam RR. Serotype distribution of *Streptococcus pneumoniae* infections among preschool children in the United States, 1978-1994: Implications for development of a conjugate vaccine. *J Infect Dis* 1995;171:885-889.
17. Doern GV, Pfaller MA, Kugler K, Freeman J, Jones RN. Prevalence of antimicrobial resistance among respiratory tract isolates of *Streptococcus pneumoniae* in North America: 1997 results from the SEN-TRY antimicrobial surveillance program. *Clin Infect Dis* 1998;27:764-770.
18. Centers for Disease Control and Prevention. Geographic variation in penicillin resistance in *Streptococcus pneumoniae* — Selected sites, United States, 1997. *Morb Mortal Wkly Rep* 1999;48:656-661.
19. Breiman RF, Butler JC, Tenover FC, Elliott JA, Facklam RR. Emergence of drug-resistant pneumococcal infections in the United States. *JAMA* 1994;271:1831-1835.
20. Doern GV, Brueggemann AB, Blocker M, et al. Clonal relationships among high-level penicillin-resistant *Streptococcus pneumoniae* in the United States. *Clin Infect Dis* 1998;27:757-761.
21. Butler J, Hofmann J, Martin S, et al. The continued emergence of drug-resistant *Streptococcus pneumoniae* in the US: An update from the CDC's pneumococcal sentinel surveillance system. *J Infect Dis* 1996;174:986-993.

22. Inostroza J, Trucco O, Prado V, et al. Capsular serotype and antibiotic resistance of *Streptococcus pneumoniae* isolates in two Chilean cities. *Clin Diagn Lab Immunol* 1998;5:176-180.

23. Koh TH, Lin RV. Increasing antimicrobial resistance in clinical isolates of *Streptococcus pneumoniae*. *Ann Acad Med Sing* 1997;26:604-608.

24. Nava JM, Bella F, Garau J, et al. Predictive factors for invasive disease due to penicillin-resistant *Streptococcus pneumoniae*: A population-based study. *Clin Infect Dis* 1994;19:884-890.

25. Friedland IR, Klugman KP. Antibiotic-resistant pneumococcal disease in South African children. *Am J Dis Child* 1992;146:920-923.

26. Black S. Efficacy of heptavalent conjugate pneumococcal vaccine (Wyeth Lederle) in 37,000 infants and children: Results of The Northern California Kaiser Permanente Efficacy Trial. Presented at: Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC); September 1999; San Francisco, CA.