

## Using the Pneumococcal Conjugate Vaccine in the Pediatric Population: Clinical and Economic Issues

Since the introduction and widespread adoption of the *Haemophilus influenzae* type b (Hib) vaccine, the pneumococcus has become the primary bacterial cause of community-acquired pneumonia (CAP), sepsis, meningitis, and otitis media (OM) among children in the United States.

The standard pneumococcal 23-valent polysaccharide vaccine is ineffective in children under 2 years of age, the group most vulnerable (80% of all cases) to invasive pneumococcal disease.

Thus, the approval from the Food and Drug Administration of the first 7-valent pneumococcal conjugate vaccine (PNCRM7) in February 2000 as safe, effective, and immunogenic in the prevention of invasive pneumococcal disease in infants and children has come as welcome news to clinicians. Indications for use against OM and CAP are expected to follow shortly.

This Special Report supplement to *The American Journal of Managed Care* contains 2 articles concerned with the new vaccine. One, by Derek Weyker, PhD, et al, of Policy Analysis Inc, Brookline, Massachusetts, reports the expected economic costs and benefits of vaccination with PNCRM7 against pneumococcal otitis media and CAP, the most frequent manifestations of pneumococcal disease in children less than 5 years of age. Dr. Weyker's study was funded by Wyeth-Ayerst.

The second article, by Steven Black, MD, codirector of the Northern California Kaiser Permanente Vaccine Study Center, presents the results of the first study to determine the efficacy, safety, and immunogenicity of PNCRM7 in children. Dr. Black led a team of researchers to conduct this randomized, double-blind trial [originally published in *Pediatr Infect Dis J* 2000;19:187-195.].

### Epidemiology

The rise and spread of drug-resistant pneumococci and the infections they cause have spurred the development of pneumococcal conjugate vaccines (PCVs). Compared to Hib, in which 1 serotype causes almost all *H. influenzae* disease, many of the more than 90 serotypes of the pneumococcus are responsible for disease. The standard 23-valent polysaccharide vaccine is antigenic against serotypes that cause invasive pneumococcal disease in elderly, immunocompromised, and chronically ill people, but not in immunocompetent children younger than 2 years of age, who have the highest rates of the disease.

Because the polysaccharide vaccine is T-cell independent, vaccinated infants fail to develop an immunologic memory, so that their immunologic response is weak and short-lived. This shortcoming led pneumococcal conjugate vaccine researchers to add a protein carrier for the bacterial poly-

saccharide. The increased immunogenicity in infants that resulted may, as with Hib, have positive consequences that extend far beyond immediate clinical benefits. For example, PCV-vaccinated children, whose pneumococcal carriage serotypes are reduced, might transmit less to unvaccinated people.

**Principle Efficacy and Safety Results**

The unmasking of 38,000 fully vaccinated, immunocompetent infants and toddlers in the Kaiser study revealed that 40 children had developed invasive disease caused by vaccine serotypes. All but 1 was in the control group, for an efficacy rate of 97.4%.

In infants 15 months of age and younger, a 4-dose regimen of PNCRM7 at ages 2, 4, and 6 months with a booster dose during the child's second year provided immunogenicity and safety. Systemic and local reactions to vaccination were mild.

Although the 7 serotypes in PNCRM7 cause only approximately 85% of pneumococcal disease in young children, the reduction in all invasive disease caused by both vaccine and nonvaccine serotypes was 89.1% in children administered 1 or more doses of the vaccine. Cross protection among related serotypes may be the causative factor in this increased result.

Pneumococci are the most common bacterial cause of OM cases in the United States. The reduction of clinical visits for simple OM was lower than Black et al had anticipated (8.9%). However, efficacy in children with severe disease, frequent episodes, ventilatory tube placement, and antimicrobial-resistant disease was higher.

**Costs Versus Benefits**

Weycker et al used a model of the risks and economic costs of AOM, TRP, and CAP to age 10 years to estimate the economic consequences of PNCRM7 vaccination in children less than 5 years of age. Vaccine safety and efficacy were estimated based on the results of the Kaiser study. Risks and costs of AOM, TRP, and CAP were estimated using the healthcare claims database of a sizable New England-based health plan.

The authors report that vaccination against pneumococcal disease would result in substantial reductions in the numbers of cases of AOM, TRP, and CAP and related costs of medical treatment and work loss. On balance, net economic benefits of vaccination would range from -\$88 to \$31 per vaccinee, depending on age. Thus, the authors concluded that vaccination with PNCRM7 against pneumococcal

**ACRONYM LIST**

The following acronyms appear within this Special Report:

<b>AOM</b>	Acute otitis media
<b>CAP</b>	Community-acquired pneumonia
<b>CPT-4</b>	<i>Current Procedural Terminology, Fourth Edition</i>
<b>DTaP</b>	Diphtheria-tetanus toxoid-acellular pertussis vaccine
<b>DTwP</b>	Diphtheria-tetanus toxoid-whole cellular pertussis vaccine
<b>Hib</b>	<i>Haemophilus influenzae</i> type b
<b>ICD-9-CM</b>	<i>International Code of Diseases, Ninth Edition, Clinical Modification</i>
<b>IgG</b>	Serum antibody responses
<b>NCKP</b>	Northern California Kaiser Permanente
<b>NIP</b>	National Immunization Program
<b>OM</b>	Otitis media
<b>PCV</b>	Pneumococcal conjugate vaccine
<b>PNCRM7</b>	7-valent pneumococcal conjugate vaccine
<b>SIDS</b>	Sudden infant death syndrome
<b>TRP</b>	Tympanostomy and related procedures
<b>VTP</b>	Ventilatory tube placement

otitis media and pneumonia would generally be cost increasing for children less than 2 years of age who require multiple doses, but would be cost saving for children aged 2 to 5 years who require only a single PNCRM7 dose.

There is little information at present, however, on the duration of protection afforded by pediatric bacterial vaccines. It is known that pneumococcal disease decreases after age 5 years. Weycker et al assumed that immunity would extend to age 10 years for children less than 2 years of age at initial vaccination, but at half the initial rate after 5 years of age. Long-term studies and clinical use are needed to accurately estimate the persistence of PCV protection.

The Kaiser study results for pneumonia will be published separately, and results of a study of the herd effect of widespread PNCRM7 vaccination will soon be forthcoming. However, the efficacy as well as the costs versus benefits of PCVs in invasive disease, severe AOM and CAP, and against drug-resistant bacterial strains must still be addressed. For example, recurrent episodes of OM cost far more than first infections because of the expense of additional office visits and alternative antibiotics prescribed to prevent antimicrobial resistance. Health organizations will require a broader basis of data from which to make decisions about appropriate ages and schedules for dosing, reimbursement, and other vaccination-related concerns.