PNEUMOCOCCAL VACCINES

Most pneumococcal strains causing severe disease are surrounded by a characteristic polysaccharide capsule, a major virulence factor that allows the bacteria to evade phagocytosis. Pneumococcal vaccines containing purified polysaccharides from a subset of serotypes have been available for over 60 years. The 23-valent pneumococcal polysaccharide vaccine (Pneumovax® 23, Merck and Company, Inc., Whitehouse Station, New Jersey, U.S.), generally used in older children and adults with high-risk medical conditions and adults ≥65 years, has been available since 1983. Vaccines comprising polysaccharide antigens alone, however, produce weak or short-lived immune responses in infants and toddlers (15). Covalently linking pneumococcal polysaccharide to a carrier protein induces a T-cell-dependent immune response that can occur even in early infancy.

A PCV was licensed for use in infants and young children in the United States in 2000. The vaccine [known as Prevnar® (Wyeth, Madison, New Jersey, U.S.) in the United States and Prevenar® elsewhere] includes capsular saccharides of seven serotypes (4, 6B, 9V, 14, 18C, 19F, 23F), each coupled to a nontoxic variant of diphtheria toxin, CRM197. As of 2008, the PCV7 remains the only formulation that is currently licensed, although two other formulations with 10 and 13 serotypes, respectively, are in phase III clinical trials and may be available between 2008 and 2010 (Table 1). Other pneumococcal conjugate formulations have also undergone phase III testing; for example, two clinical trials of a PCV9 manufactured by Wyeth showed significant protective efficacy in African infants (16,17), but the formulation was not ultimately licensed. The pneumococcal vaccine pipeline contains at least 20 different vaccine candidates in various stages of testing, including projects by emerging market manufacturers and projects to develop alternatives to PCVs (e.g., common protein vaccines). These vaccines are in early stages of development and will likely become available between 2015 and 2020.

CLINICAL TRIALS OF PNEUMOCOCCAL CONJUGATE VACCINES

Carriage

Studies evaluating PCV effects on carriage suggest that vaccination reduces acquisition of vaccine-type strains (13). In most but not all studies, carriage of nonvaccine-type strains increased among children receiving conjugate vaccine so that the overall prevalence of pneumococcal carriage was not different in vaccinated and unvaccinated children. Among toddlers in Israel, vaccination reduced carriage of antibiotic-resistant strains in vaccinated children and in their unvaccinated siblings through reduced transmission (18).

Otitis Media

Clinical trials also have evaluated the effects of conjugate vaccines on otitis media. In a large randomized, double-blinded clinical trial in Northern California, infants receiving PCV7 had 7% fewer episodes of otitis media, 9% fewer infants with frequent otitis media, and 20% fewer children requiring ventilatory tube placement compared with controls (19). In Finland, infants receiving PCV7 had 6% fewer episodes of otitis media overall and 57% fewer episodes of otitis media caused by pneumococci of vaccine serotypes (20). Notably, children in the pneumococcal vaccine group had 33% more episodes of otitis media caused by serotypes not in the vaccine or related to vaccine types.

In Israel, a trial of a PCV9 evaluated otitis media and other upper respiratory tract infections among children of 12 to 35 months attending day care centers (21). Vaccination reduced episodes of otitis media but the change was not statistically significant (17% fewer episodes, 95% CI −2% to 22%). Significant reductions were seen for upper and lower respiratory tract infections and days of antibiotic use. Conversely, in the Netherlands, in children aged 1 to 7 years with a history of recurrent otitis media, PCV7 in combination with 23-valent pneumococcal polysaccharide vaccine showed no significant benefit for reducing ear infections (22).

More recently, a randomized, controlled-trial of an 11-valent pneumococcal vaccine formulation from GlaxoSmithKline (precursor to the 10-valent formulation currently in development [Streptorix, Brentford, London, U.K.]) showed significant efficacy against culture-proven acute otitis media because of *S. pneumoniae* (23). This vaccine uses an outer membrane protein from *Haemophilus influenzae* as a carrier protein for the pneumococcal saccharides. Trial results indicated that the vaccine appeared to confer protection against otitis media because of nontypeable *H. influenzae*, in addition to otitis caused by vaccine-type pneumococci.

Invasive Disease and Pneumonia

The efficacy of pneumococcal vaccines for prevention of invasive disease and pneumonia has been evaluated in five clinical trials. These trials include three different formulations from two different manufacturers (7- and 9-valent from Wyeth; 11-valent from Sanofi Pasteur, Lyon, France). In the Northern California Kaiser trial, vaccination reduced episodes of pneumonia confirmed by radiograph by 20% (Table 2) (24). A reanalysis of the trial using WHO criteria for pneumonia with consolidation on X ray found an efficacy of 30% (25). Efficacy against invasive disease caused by vaccine serotypes was 97% (19). In a second U.S. trial that employed community randomization, the 7-valent conjugate vaccine was found to be effective against invasive disease among Navajo and Apache children younger than two years, reducing episodes caused by vaccine serotypes by 83% (26).

Two trials of PCV9 have been completed in developing countries. In South Africa, vaccination prevented invasive disease in both HIV-positive and HIV-negative infants, although point estimates of efficacy were higher in HIV-negative children

Table 1 Pneumococcal Conjugate Vaccines in Use or in Late-Stage Trials as of 2008

	Manufacturer	Serotypes	Carrier protein	Stage
7-Valent conjugate (Prevnar, Prevenar)	Wyeth	4, 6B, 9V, 14, 18C, 19F, 23F	Diphtheria CRM197	Licensed, in use
10-valent conjugate (Streptorix)	GSK	1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 23F	Protein D	Submitted for licensure and in phase III trials
13-valent conjugate (Prevnar 13)	Wyeth	1, 3, 5, 4, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F	Diphtheria CRM197	Phase III trials