Conjugate vaccines for *Streptococcus pneumoniae*

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The success of glycoconjugate vaccines for *Haemophilus influenzae* type b (Hib) has paved the way for applying a similar strategy to other encapsulated bacterial pathogens (1). *Streptococcus pneumoniae* (pneumococcus) is an important target for this technology for many reasons. The first is the significant disease burden associated with pneumococcus in infants and young children. With the dramatic reduction in Hib disease in infants, pneumococcus has become the major cause of bacterial invasive disease and meningitis in infants (2). Around the world, pneumococcal pneumonia is a significant cause of morbidity and mortality in young children, and is probably the number one cause of this disease. Similarly, pneumococcus has been identified as the major pathogen in bacterial otitis media.

Second, the need for pneumococcal conjugate vaccines for infants is driven by the inability of infants to respond to the currently available 23-valent polysaccharide vaccine (4). Because the age of greatest susceptibility to invasive disease and otitis media in children is under two years of age, glycoconjugates are the logical way to overcome the immunological barrier in infants and confer protection early in life.

Last, the impetus to protect young children from pneumococcal disease is augmented by the increasing evidence of antibiotic resistance associated with *S pneumoniae* (5). In general, this resistance has been associated with the most prevalent disease-causing serotypes that would, therefore, be included in conjugate vaccine formulations.

The challenges with pneumococcal conjugate development are much greater than with Hib vaccine because of the number of serotypes that cause disease. Over 80 serotypes of *S pneumoniae* are known, and the available polysaccharide vaccines cover 23 serotypes. Unfortunately, it is not practical, either economically or technically, to make conjugates to all of these 23 serotypes. Fortunately, in most populations, it is possible

to use fewer components and still achieve significant coverage of invasive disease serotypes.

Another important challenge for pneumococcal vaccine development is assessing the ability of infants to produce a protective antibody response to many conjugates given simultaneously and the ability of these responses to protect against a broad range of diseases including invasive disease, otitis media and pneumonia. The data discussed below show that infants can respond well to multivalent conjugate vaccines and that efficacy trials are ongoing to assess efficacy against the various disease etiologies.

PNEUMOCOCCAL SEROTYPE EPIDEMIOLOGY

The greatest set of data for the prevalence of pneumococcal serotypes is for invasive disease in infants and adults. Hausdorff and Eby (6) have recently completed an analysis of currently available data on serotype prevalence. There are several striking features of these data. The first is that the vast majority of disease worldwide is caused by 11 or fewer serotypes. The second is that the prevalence of serotypes varies by geographical location, but the most prevalent types tend to be quite consistent.

In North America, seven serotypes account for greater than 80% of invasive pneumococcal disease. The serotypes are 4, 6B, 9V, 14, 18C, 19F and 23F. Addition of further serotypes to this group has little impact. It is striking, however, that in Europe the coverage from these serotypes is considerably lower (70% to 75%). This is due largely to the higher prevalence of serotypes 1 and 5, which are currently under-represented in the North American population. Inclusion of these serotypes to the seven mentioned above increases the coverage in Europe to around 80%, but has little impact on coverage in North America.

If invasive disease by serotype in Latin America and Asia is considered, the coverage of the nine serotypes is around 80%

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TABLE 1
Ongoing efficacy trials for *Streptococcus pneumoniae* vaccine

Conjugate vaccine	Site	Principal investigator	Primary end-point
7-valent	Northern California Kaiser Permanente	Steve Black Henry Shinefield	Invasive disease
7-valent	Navajo and Apache population, Arizona	Mathu Santasham	Invasive disease
7-valent	Tempere, Finland	Juhana Eskoli	Otitis media
9-valent	Soweto, South Africa	Keith Klugman	Pneumonia

and 60%, respectively. If the number of serotypes is increased to 11 by the addition of types 3 and 7, the coverage increases to around 85% and 70% in Latin American and Asia, respectively. Similarly, Africa and Oceania are well covered by the 9-11 valent formulation. Addition of further serotypes has no significant impact on total disease coverage.

VACCINE DEVELOPMENT

Over the past 10 years, pneumococcal conjugate vaccines have evolved considerably. While the use of the glycoconjugate technology was clear, the number of serotypes tested has evolved from 4-6 (7,8) to 7-8 (9,10) to 9-11. Early studies focused on formulation looking at such variables as polysaccharide size and glycoconjugate dose.

After initial phase one studies, Wyeth Lederle Vaccines's (New York) first generation vaccine contained the seven most prevalent serotypes in North America and most of the world as described above. The 7-valent vaccine is prepared by linking the CRM₁₉₇ carrier protein (a nontoxic variant of diphtheria toxin that is also used in the HibTITER vaccine [Wyeth Lederle Vaccine, New York] [11]) to the specific serotype polysaccharides in doses of 2 to 4 µg/serotype.

Rennels et al (9) have recently published immunogenicity data in infants who have received the 7-valent vaccine at two, four and six months of age. The data show that after three doses, infants are able to respond to all seven serotypes with geometric mean antibody titres ranging from 0.98 µg/mL for

type 9V to 3.48 µg/mL for type 14. Data indicate that the children were also primed for a booster dose in the second year of life. Importantly, the antibody response based on antibody titres measured by ELISA also has functional activity based on an opsonophagocytic assay.

Second generation pneumococcal conjugate vaccine contains nine components, adding types 1 and 5 to the 7-valent vaccine. This vaccine is also distinguished from the 7-valent vaccine by being a lyophilized product to facilitate the potential for combining it with other components. Recent studies show that the addition of two new conjugates does not negatively effect the response to the previous seven components and induces a brisk response to the two new serotypes.

EFFICACY TRIALS

Efficacy trials are currently ongoing in a variety of populations and with a variety of primary end-points (Table 1). The need for multiple trials is driven by both the diversity of disease entities caused by pneumococcus and the population differences in disease susceptibility and rate. Through these trials, it will be possible to assess the efficacy of the pneumococcal conjugate vaccine to three important diseases caused by these bacteria.

CONCLUSIONS

The prospects for an effective vaccine against invasive disease caused by *S pneumoniae* are quite good. This conclusion is derived from the current understanding of previous studies with the polysaccharide vaccine showing that functional anti-capsular antibodies are protective, coupled with the ability of the conjugate vaccines to induce such functional antibodies in young children. Infants immunized three times responded to all of the glycoconjugate antigens in the vaccines.

The control vaccine for many of the studies with the pneumococcal conjugates is a glycoconjugate for *Neisseria meningitidis* group C. Vaccines for these important bacterial pathogens, coupled with the currently available vaccine for Hib, will control all of the important causes of invasive bacterial disease in infants and young children.

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