

Conjugate Vaccine Update

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INTRODUCTION

Disease due to encapsulated bacteria accounts for a significant proportion of serious morbidity in hospitalized patients as well in children and the elderly. The immune response to polysaccharide is often poor and is not associated with boosting. Capsular vaccines such the PRP *Haemophilus influenzae* type b vaccine and the 23 valent pneumococcal vaccine elicit only a moderate response in young children and a very poor response in children under two years of age. Since the populations at highest risk for disease due to Hib and the pneumococcus are the same young children who do not respond to capsular vaccination, a new immunization strategy was required to protect these groups. Conjugate vaccines were initially discussed in the 1970s and testing in humans began shortly thereafter. These vaccines combine a bacterial saccharide with a protein carrier. The protein carrier allows the immune system of young children to respond to these vaccine with a significant and boostable response. It is the purpose of this presentation to describe the impact of immunization with Hib conjugate vaccines and to describe results of the recent efficacy trial in the United States of a seven valent pneumococcal conjugate vaccine.

HIB DISEASE AND HIB CONJUGATE VACCINATION

Prior to the introduction of Hib conjugate vaccines in the USA, approximately 10,000 cases of meningitis occurred due to this organism annually with an additional 10,000 cases of other serious disease such as epiglottitis or pneumonia. About 800 children died per year and an additional 3,000 or more were left neurologically damaged. The total cost in 1990 US dollars was 2.5 billion. Most cases of illness, about 80%, occurred in children less than two years of age with the peak incidence between 6-11 months of age. Within our own population, 59% of members are white with 15.2% Hispanic, 12.8% Asian and 9.4% Black. Of the Asians in our population, 34.9% are Chinese, 30.3% Filipino, and 12.2% Japanese. Although some have suggested that Asians are at low risk for invasive Hib disease, in a case-control study conducted in our population, we found no statistically significant difference in the disease rates in Asians as compared with whites or other groups.

We began the pivotal efficacy trial of the HbOC conjugate PRP-CRM₁₉₇ vaccine used in a three dose regimen in infancy in 1988. This trial showed the vaccine to be highly effective with no cases in children who have received two or more doses of the vaccine. In addition, although 80-100 cases of invasive disease occurred within Kaiser Permanente annually prior to the vaccine study, we have observed no cases of disease in our population since 1991. This vaccine was then introduced for routine use in the US with a similar dramatic reduction in Hib disease nationally. It has been estimated that 99% of the total disease burden due to Hib has been eliminated following vaccine introduction.

It is important to point out that although there are several conjugate Hib vaccines, they differ regarding the nature of the polysaccharide used and the type of carrier protein. These differences are reflected in the immune response seen. For example, the PRP-D conjugate vaccine combined PRP with diphtheria toxoid as a carrier protein. This vaccine has been associated with a diminished immune response and with substantially lower efficacy in field trials. Because of this, the PRP-D vaccine has never been licensed for infant use in the US. Also, unlike HbOC, many of these vaccines have been associated with immune interference when used in combination or mixed with DPT. Interference has been noted with PRP-T for the Hib response as well as response to other antigens for example, whereas synergy or a heightened immune response has been seen with the HbOC-DPT fixed combination. Therefore, careful consideration must be given to the agent chosen for immunization and to assure that combinations or mixtures with DPT are effective.

PNEUMOCOCCAL DISEASE AND CONJUGATE VACCINATION

With the success of the conjugate vaccination program for Hib, attention was turned toward the development of conjugate vaccines for the pneumococcus. Although the emergence of antibiotic resistance and the substantial disease burden in children and adults made this a logical choice for vaccine development, several factors made this more complicated than vaccine development for Hib. The primary difference in the necessary logistic approach was that with *Haemophilus influenzae*, only one type, type b, accounted for almost all invasive disease. For the pneumococcus, there are more than 80 serotypes and many of these cause invasive disease in children and adults. Furthermore, different groups of serotypes cause disease in different areas of the world. These factors make the design of an effective vaccine much more complicated than the Hib case.

The epidemiology of the pneumococcus is similar to Hib in that there is a substantial disease burden in children under two years of age and these children do not respond well to the existing 23 valent capsular vaccine. The peak disease incidence is slightly older being between 12-17 months of age. Also, unlike Hib, most of the cases are non-CNS disease.

In evaluating risk factors for invasive pneumococcal disease in a case-control study in our population, the key risk factors were day care attendance (RR=2.3, $p<0.01$), frequent otitis media (RR=1.45, $p<0.01$), and Asian race (RR=2.46, $p=0.039$). In addition, it was noted that 83% of disease occurring in our population was due to seven serotypes and that these serotypes included the strains accounting for most antibiotic resistance.

In October 1995, we began a prospective double blind evaluation of the Wyeth Lederle pneumococcal conjugate vaccine in our population. In this study, 38,000 children were randomized to receive either the pneumococcal conjugate vaccine or the meningococcal type C conjugate vaccine at 2,4, 6 and 12-15 months of age. When an initial look at the data for invasive disease was taken following seventeen cases of vaccine serotype disease, it was observed that all of the cases of invasive disease were in the control group – that is that the point estimate for the efficacy of the vaccine was 100% (95% confidence interval 75.7-100%). Studies of otitis media and pneumonia are ongoing. To date, we have concluded that this seven valent pneumococcal conjugate vaccine including serotypes responsible for more than 80% of invasive disease in children in our population was safe and highly effective.

CONCLUSION

Capsular-protein conjugate vaccines have been shown to be safe and effective means of preventing invasive bacterial disease due to two of the primary pathogens in childhood. Prevention of such infections should lead to decreased antibiotic use and hopefully decreased pressure forcing the emergence of resistant strains of bacteria.