Reducing Fatal Childhood Infections

The importance of Haemophilus influenzae type b (Hib) as a cause of severe infections in young children is not generally appreciated by health care workers outside children's hospitals or the general public. This is probably because severe Hib disease is largely restricted to young children (at least 80 per cent of cases occur by five years of age), although there have been a number of case series reporting disease in adults, particularly epiglottitis.

Despite the restricted age group affected, the annual mortality caused by Hib in the US has been calculated as comparable to that of epidemic poliomyelitis in the early 1950s. Universal immunisation against Hib disease has been recommended in a number of countries, including the US (since 1985) and Canada.

To assess the value to the Australian community of immunisation, data on the costs of Hib disease (which depends on disease incidence and sequelae) and the efficacy, costs and side-effects of the vaccine (which depends on population characteristics and vaccine type) are needed. Decisions about vaccine delivery (universal vs targeted and timing and number of doses) are also important.

Epidemiology of Hib Disease

Pattern of Hib disease

The epidemiology of invasive Haemophilus influenzae disease differs markedly in different geographic areas. The most important differences are the total disease incidence, the age distribution and the proportion of epiglottitis, which are inter-related and have important implications.

The highest reported annual incidence of invasive Haemophilus influenzae disease in the world is that in Central Australian Aboriginal children (900 per 100,000 children under five years). Epiglottitis rarely occurs in these groups, in whom most cases occur in the first six months of life, affecting up to 2 per cent of children by their first birthday.

Population-based data on childhood Hib disease show a pattern of Hib disease in urban Australia which resembles that in Seattle with an annual incidence of 30-60 per 100,000 for all Hib disease with a relatively high incidence of epiglottitis (13-23 per 100,000). Using a mid-range estimate of incidence (40), a minimum of 500 cases occur each year in children under five years in Australia.

In a recent study of childhood Hib disease in the greater Sydney metropolitan area, 292 cases in children 0-14 years were identified between 1985 and 1987, an average of about 100 a year. Meningitis accounted for the majority of cases (51 per cent), and epiglottitis (32 per cent), with the remainder predominantly cellulitis (6 per cent), arthritis (5 per cent) and pneumonia (4 per cent).

Most studies from the US report a higher incidence for all Hib disease (60-100 per 100,000) but much less epiglottitis (2-11 per 100,000). This difference in the incidence of epiglottitis largely explains the differences in age distribution, with 50 per cent of cases being over 24 months in Australia and Finland compared to 20 per cent or fewer in the US. In general, as a higher disease incidence occurs, a lower median age of onset is noted and epiglottitis is found to be relatively less.

Risk factors for Hib disease

Case control studies in the US and Finland have identified day-care outside the home and the presence of young siblings as independent risk factors, whereas breast feeding was protective. The interaction of day-care attendance and age differed in two US studies, increasing indirectly with age in Atlanta but directly with age in Colorado. The attributable risk for Hib disease from day-care was protective. The interaction of day-care attendance and age differed in two US studies, increasing indirectly with age in Atlanta but directly with age in Colorado.

Hib Vaccine Efficacy

Four vaccines produced by four different manufacturers, with the Hib capsular polysaccharide (PRP) conjugated to a different protein, are at or near marketing stage in the US. The protein carriers are diphtheria toxoid (PRP-D), a mutant diptheria toxin (PRP-CRM), an outer membrane protein from Corynebacterium diphtheriae, and tetanus toxoid (PRP-T). The clinical trials were conducted in children aged 2 to 12 months, with long-term follow-up studies in children aged 6 to 15 months. The vaccines were highly effective in preventing invasive Hib disease, with Protection rates ranging from 85 to 98 percent. The vaccines were generally well tolerated, with minor side effects such as local injection site reactions and fever reported.

The use of Hib vaccines has led to a significant decrease in the incidence of Hib disease in children worldwide, with reductions ranging from 80 to 90 percent in some areas. The vaccines have been shown to be effective in preventing both meningitis and epiglottitis, and have been adopted into routine immunization schedules in many countries.

Overall, the use of Hib vaccines has been associated with a marked reduction in the burden of Hib disease and its associated morbidity and mortality in children. Continued on page 55.
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protein of Neisseria meningitidis (PRP-OMP) and tetanus toxoid (PRP-T). The former two vaccines are licensed in the US for use at six months of age; the latter two, which may be more immunogenic in the first six months of life, are likely to be licensed soon. An additional advantage of the conjugate vaccines is that children who have developed Hib disease despite receiving PRP vaccine appear to respond to them.18

The efficacy of vaccines has been controversial because of widely varying observations, first with PRP vaccine and more recently with the conjugate vaccines.19 The only large trials have been conducted in Finland, where the most recent results from a trial using PRP-D give an efficacy of 94 per cent (CI 85-98 per cent) among children 7-24 months after vaccine at 3, 4, 6 and 18 months.20 This vaccine has been used routinely in Finland since 1988, with a decrease in cases of Hib disease among children under five years from 172 in 1986 to 27 in 1989.21

PRP-D vaccine in Alaska had an efficacy of only 37 per cent,22 although the calculated number of children required to vaccine with PRP-D to prevent one case of invasive Hib disease in Alaska (270) was much fewer than Finland (2410) because of the high incidence of disease there (1000 per 100,000 vs 50 per 100,000).19

VACCINE SIDE-EFFECTS

There are extensive data documenting the safety of PRP vaccine in the US. A Finnish study has shown that PRP-D conjugate vaccine in Alaska (270) was much fewer than Finland (2410) because of the high incidence of disease there (1000 per 100,000 vs 50 per 100,000).19

VACCINE COSTS

Vaccine administration differs markedly between States, which can have a substantial impact on costs. However these costs are largely fixed, and as any Hib vaccine could be given within the current schedule, additional administration costs should be minimal. Two cost analyses of PRP vaccine at two years24,25 and one of PRP-D vaccine at 18 months26 in the US concluded that immunisation was cost-effective. In Australia, the pattern of an older disease peak and greater public funding of vaccination would be expected to make the equation more favourable. The cost of prevention of Hib disease should be put in the context of other potentially vaccine-preventable diseases, such as hepatitis B and varicella, when decisions about funding priorities are made.

CONCLUSIONS

- Invasive Hib disease is a common cause of serious morbidity and mortality in Australian children, with an estimated minimum of 500 cases and 18 deaths annually.
- Protein conjugate vaccines are among the safest. They appear to be highly immunogenic, however, good-quality data on effectiveness are available only from Finland and substantial differences may exist between populations in their response to polysaccharide vaccines. One of these conjugate vaccines has recently been licensed for use at two, four and six months in the US; licensing of two such vaccines in Australia is being reviewed.

For vaccination against Hib to be effective as a public health measure, it should be introduced in a co-ordinated fashion after consideration of the various competing alternatives. There is the most prominent of which is vaccination against hepatitis B. Detailed consideration of the costs and benefits of universal as opposed to directed immunisation and specific vaccination schedules, both timing and number of doses, in the context of Australian data is needed.

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