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Bacterial Meningitis

The Impact of Vaccination

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Abstract

Acute bacterial meningitis remains an important cause of morbidity and mortality in children. Children <2 years of age are particularly susceptible to infection with encapsulated bacteria due to their immature response to polysaccharide antigens. Conjugate vaccines, which induce T cell memory, can provide immunological protection for these children.

The *Haemophilus influenzae* type b (Hib) conjugate vaccine was the first such vaccine to become available. The efficacy of the vaccine has been quoted as being 98%. Its introduction was followed by a dramatic decrease in the incidence of all invasive Hib disease, including meningitis. This reduction was in part due to the ability of these vaccines to reduce nasopharyngeal carriage of the organism and thereby induce herd immunity.

Different Hib vaccines use a variety of protein carriers and differ in their immunogenicity and efficacy. The most suitable vaccine needs to be determined according to the local epidemiology of Hib disease. Commercial combination vaccines may lead to lower antibody levels. A recent increase in the incidence of Hib disease in the UK highlights the importance of continued surveillance and the need for booster vaccinations to ensure continued protection.

Conjugate vaccines to *Streptococcus pneumoniae* and *Neisseria meningitidis* have been developed. The introduction of a pneumococcal conjugate vaccine in the US has led to a decrease in the rate of infection by nearly 60% in children <5 years of age. A reduction in pneumococcal carriage may also modify disease epidemiology.

The UK introduced the conjugate meningococcal C vaccine into its infant schedule with a corresponding reduction in *N. meningitidis* group C disease. A recent decrease in the effectiveness of the vaccine, however, suggests a booster may be necessary in the future. Our present understanding of the immunology of conjugate vaccines is far from complete.

Developed countries have introduced conjugate vaccines into their immunisation schedules to prevent bacterial meningitis; however, their high cost precludes

their use in many developing countries. Progress needs to be made in order to get these highly effective vaccines to those areas that need them.

Acute bacterial meningitis is an important cause of morbidity and mortality among children in both developed and developing countries.[1,2] Despite potent antimicrobial agents and optimal intensive care, mortality rates and neurological sequelae remain high.[3,4]

Children <2 years of age are at high risk of bacterial meningitis caused by *Haemophilus influenzae* type b (Hib), *Streptococcus pneumoniae* and *Neisseria meningitidis*.[2] The advent of conjugate vaccines has launched a new era in vaccinology. In contrast to polysaccharide vaccines, conjugate vaccines produce a T-cell-dependent response. This leads to the development of immunological memory and protection in children <2 years of age.[5,6]

In the early 1990s, the introduction of the Hib conjugate vaccine led to changes in the epidemiological profile of invasive diseases, particularly meningitis, caused by Hib in developed countries.[7,8] More recently, pneumococcal and meningococcal serogroup C conjugate vaccines have been included in vaccine schedules.[9-11]

The aim of this article is to review the impact of Hib conjugate vaccines on the incidence of invasive Hib disease, especially meningitis. It will also discuss the potential of the newer conjugate pneumococcal and meningococcal vaccines in relieving the burden of disease caused by these organisms around the world.

1. *Haemophilus influenzae* Type b (Hib) Disease

Hib is an important cause of invasive infection in children <5 years of age, with 60% of such infection being meningitis. Overall fatality for Hib meningitis is 5%, with up to 11% of survivors having neurological sequelae.[12]

In the UK, the majority of invasive disease due to Hib occurs during the first 2 years of life,[13] whilst in the developing world the majority of such disease occurs even earlier.[14] It is difficult to know the true burden of Hib disease, especially in developing countries. Annually, it is estimated to cause at least three million cases of serious disease and many hundreds of thousands of deaths worldwide.[15]

1.1 Hib Conjugate Vaccine

The first generation capsular polysaccharide Hib vaccines were found to be ineffective in children <18 months of age, in whom most Hib disease occurred. The reason for this poor response was that bacterial polysaccharides do not generate memory B cells in young infants. To improve the immunogenicity of these vaccines, the capsular polysaccharide polyribosylribitol phosphate (PRP) was conjugated to an immunogenic carrier protein. Four such vaccines, conjugated to different carrier proteins, have been licensed for use in children:

- diphtheria toxoid as the carrier protein (PRP-D), with moderate antibody response after second dose;
- CRM197 mutant *Corynebacterium diphtheria* toxin protein as the carrier (HbOC), with good antibody response after second dose;
- *N. meningitidis* protein outer membrane protein as the carrier (PRP-OMP), with moderate antibody response after first dose;
- tetanus toxoid as the carrier protein (PRP-T), with good antibody response after second dose.

The PRP conjugated to tetanus toxoid (PRP-T) is the most widely used.[16]

1.2 Vaccine Efficacy

The efficacy of the Hib vaccine is approximately 98%;[17,18] however, the various Hib vaccines, despite being immunogenic and efficacious, are not identical in performance.[19-22] Infant vaccination with Hib conjugates usually occurs whilst there is persistence of maternal antibodies and this can modestly suppress the response to Hib conjugate vaccines.[23] This is particularly important in a population with high infection rates in the first few weeks of life. A reduced antibody response to the first dose of vaccine could affect efficacy, even if the peak response following a full course remained unaltered.

The carrier protein also influences priming. In a comparison study of three different Hib conjugate vaccines given at 2, 3 and 4 months, the priming response for a 'booster' at 1 year of age was lower in magnitude for PRP-T compared with other carrier proteins.[24] The relevance of this measure of priming to long-term vaccine efficacy remains unclear.

Hib vaccines can be administered on their own or in combination with other vaccines. Coadministration creates the potential for interaction with other vaccine antigens. This interaction may be physical, between individual components, or the immune response to one antigen may be altered by the immune response to another. This complex interaction is illustrated by the combination of Hib vaccine with diphtheria, tetanus and acellular pertussis (DTaP) vaccine that led to reduced antibody levels to Hib after primary immunisation.[25] This effect was not seen with simultaneous administration at separate sites.

The choice of conjugate, number of vaccine doses and their timing, and the local epidemiology of invasive Hib disease are all important in determining vaccine efficacy. PRP-T and PRP conjugated to diphtheria toxoid (PRP-D) have been shown to be highly efficacious in several clinical trials;[26-28] however, a PRP-D conjugate vaccine that had shown efficacy in Finland did not confer protection in an Alaskan population with high levels of disease in early life.[29] The introduction of a Hib vaccine featuring PRP conjugated to an *N. meningitidis* outer membrane protein complex (PRP-OMP) in 1991 did lead to a substantial decline in Hib disease, reflecting the earlier onset of immunity with this conjugate.[29] When the regimen was changed to a combination preparation of an Hib conjugate vaccine with a CRM197 mutant *C. diphtheria* toxin protein (commonly referred to as HbOC) combined with diptheria, tetanus and pertussis (DTP) vaccine to reduce the number of injections at each visit, there was an increase in invasive Hib disease related to the later onset of immunity following the two doses of HbOC.[29]

A recent systematic review examining the effects of conjugate Hib vaccine in preventing Hib disease or death in children <5 years, when compared with placebo/control, included four trials in a meta-analysis.[30] The relative risk for invasive Hib disease following vaccination was 0.2 (95% CI 0.07, 0.54) compared with no vaccination, but there was statistically significant unexplained variation between the effects in the four trials ($p = 0.002$). The meta-analysis found no difference in the size of effect with different vaccine types, number of doses, age at first vaccination or use in developed/developing countries, but the confidence intervals for estimates were wide. Hib-related mortality data, available from two of the trials, showed a nonsignificant trend towards benefit from vaccination, with a relative risk of 0.29 (95% CI 0.07, 1.20) with no adverse effects in the 257 000 infants included. The relative risk for all-cause mortality in the single trial from which such data were available was 1.01 (95% CI 0.38, 2.67). The authors concluded that the size of the effect could be anywhere in a 46–93% reduction in invasive Hib disease, before the effect of herd immunity was taken into account.

Table I. The impact of *Haemophilus influenzae* type b (Hib) conjugate vaccination on the incidence of Hib meningitis[33,34]

Country of study	Year data published	Effectiveness of vaccine in reducing Hib meningitis
Finland[45]	2005	Only three cases of Hib meningitis in the Greater Helsinki area after 1991 (12-year data) compared with between 19 and 30 cases per year between 1979 and 1986
Denmark[40]	2004	99% effective after three doses in reducing Hib meningitis
Australia[46]	2004	35 cases from 1989–93. Only one case after the introduction of the vaccine
Cuba[35]	2001	Hib meningitis cases reduced from 1.3/100 000 (1998) to 0.6/100 000 (1999). Vaccine efficacy 99%
Uruguay[47]	1999	Hib meningitis cases reduced from 15.6/100 000 (1979–1994) to 0.03/100 000 (1996)
USA[48]	1999	Hib meningitis cases reduced from 73% of childhood cases (1981–1985) to 16% (1991–1995)
Sweden[49]	1996	92% reduction in cases of Hib meningitis 1 year after vaccine introduction
England/Wales[50]	1994	Hib meningitis cases reduced from 10/100 000 (August 1991–July 1992) to 0.6/100 000 (August 1993–July 1994)
Netherlands[51]	1994	Hib meningitis cases reduced from 40/100 000 (April 1992–April 1993) to 0.3/100 000 (April 1993–April 1994)
Germany[52]	1994	Hib meningitis cases reduced from 33/100 000 before vaccination to 6/100 000 over 4 years after introduction of Hib vaccine in 1990. Vaccine efficacy 94%
USA[7]	1993	82% decrease in Hib meningitis between 1985 and 1991

1.3 Implementation

After the introduction of the Hib vaccine in the UK in 1992, rates of invasive Hib disease, including meningitis, declined markedly in children aged 0–4 years.[18,31] The vaccine was used for routine vaccination in infants at 2, 3 and 4 months of age and was offered to those aged <4 years as part of a 'catch-up' programme; those aged >12 months received a single dose. Similar reductions in invasive Hib disease following Hib vaccine introduction were seen for Finland, Canada, Iceland, the US, Israel and Australia.[32] Peltola[33] reviewed the reduction in rates of Hib meningitis in Europe, whilst Laval et al.[34] examined the worldwide impact (table I). Reductions in rates of Hib meningitis have been reported from all countries using Hib conjugate vaccines in their immunisation schedules.[34-38] The dramatic decline in Hib-related bacterial meningitis was also due to an unexpected bonus of the vaccine programme: carriage was decreased in recipients, leading to herd immunity whereby unvaccinated children were protected because they were less likely to be exposed to the infection.[39,40] This led to a more rapid decline in disease following introduction of the vaccines than if there was no herd immunity effect.[41] Economic analysis from the US has shown that the national Hib vaccination campaign starting at 2 months of age was highly cost beneficial and resulted in substantial cost savings compared with no vaccination against Hib.[42] Similar conclusions were reached in Sweden[43] and France.[44]

1.4 The Need for a Booster Dose

Implementation of the Hib conjugate vaccines in those countries able to afford them has shown remarkable success.[53] Most countries adopted regimens involving three doses in infancy followed by a fourth, booster dose in the second year of life. In contrast, the UK regimen used an accelerated schedule in which the Hib vaccine is given at 2, 3 and 4 months, but no booster. Studies had suggested that Hib disease was close to elimination in the UK and there was persistence of satisfactory antibody levels to 4.5 years of age using this schedule.[54] Within a

few years, administration of a combined Hib-DTP vaccine became routine as studies suggested similar immunogenicity to the separately administered components.[55] There was considerable concern when infants immunised with an Hib-DTaP combination vaccine had Hib antibody titres below protective levels following three doses.[56] These children showed good immunological memory with substantial booster responses to further conjugate doses. Those immunised with separate Hib conjugate vaccines had Hib antibody levels below the 'protective thresholds' by the end of the first year of life, without developing Hib disease.[25]

An increase in Hib disease in the UK from 0.66/100 000 children <5 years of age in 1998 to 2.96/100 000 in 2002,[57] led to the demonstration of lowered efficacy rates in children vaccinated during infancy compared with those vaccinated after their first year of life.[58] Effectiveness was higher in children vaccinated after 1 year of age, which was consistent with the lowered immunogenicity of Hib vaccines conjugated to either tetanus toxoid or modified diphtheria toxin administered according to the UK schedule compared with the response to a single dose in toddlers in the US.[59,60] Estimated effectiveness declined beginning 2 years after vaccination, and this decline was most marked in those immunised during infancy.[58] This decline correlated with the low antibody levels observed in pre-school children,[59] and suggested that the immunological memory demonstrated in UK infants aged 1 year[61] may not be sufficient to provide long-term protection to all children. The use of the combination Hib and DTaP vaccine[62] between January 2000 and August 2002, together with the lack of a booster dose, exacerbated the increase in invasive disease. The increase could not be attributed to colonisation, because there was a marked reduction in the prevalence of Hib colonisation over the period.[63] A comparison of vaccinated and unvaccinated children presenting with Hib meningitis demonstrated immunological memory in the vaccinated children, suggesting that immunological priming was not necessarily protective.[64] A booster programme to provide pre-school children with a fourth Hib dose was rapidly instituted[65] and aimed to boost the anti-PRP antibodies in those immunised, to increase herd immunity. A recent study from Finland found no increase in Hib meningitis with a schedule using vaccine at 4, 6 and 14–18 months.[45] Our present understanding of the relative importance of circulating antibody and of immunological memory in the prediction of protection provided by conjugate vaccines is therefore far from complete, but a booster dose in the second year of life seems to give longer protection.

1.5 The Resource-Poor Setting

The majority of Hib disease occurs in the countries that are the least able to purchase and implement routine immunisation. Despite the availability of Hib conjugate vaccines, approximately 132 million children worldwide have still not been immunised with this vaccine, most of them in resource-poor countries where Hib is the leading cause of bacterial meningitis.[1,66]

The introduction of these vaccines has been hampered by several factors. The most critical issue is cost. In South Africa, Hib vaccine costs six times more per dose than the total costs of a routine immunisation schedule with the DTP, polio, measles and Bacille Calmette-Guérin (BCG) vaccines.[30] Impeded increases in *per capita* spending on health due to unfavourable economic and financial situations make it unfeasible to introduce the Hib vaccine.[67] A possible way of combating the price issue is reducing the number of doses given; two primary doses could be given instead of three,[33] and although a booster dose is recommended in most countries, it may not be necessary in developing countries where most of the Hib disease occurs before 12–18 months of age;[14,68] however,

the importance of control of carriage in controlling disease should not be underestimated.

The Global Alliance for Vaccines and Immunisation (GAVI) has been developed to provide opportunities to build consensus around policies, strategies and priorities in developing countries and assign responsibility to those that have a comparative advantage. Through the Vaccine Fund, GAVI aims to provide financial resources to purchase vaccines and to support the operational costs of immunisation. By the end of 2003, support from GAVI and the Vaccine Fund had ensured that almost 5 million children had been immunised against Hib.[69]

The conclusion of a recent Cochrane review suggested that there was insufficient evidence about the effects of Hib conjugate vaccine on either Hib-specific or on all-cause mortality from present randomised controlled trials[30] and, therefore, further data are needed on these outcome measures to help determine the cost effectiveness of vaccine introduction. This is important in the setting of developing countries, because they have complex health problems, including malaria, tuberculosis and HIV, all competing for priority against Hib. Despite these problems, public health policy-makers need to define the burden of Hib disease, be aware of the potential magnitude of social costs, and maximise efforts to incorporate this vaccine into routine health services.[68,70]

2. Pneumococcal Disease

Pneumococcus presents a more complex problem than Hib regarding the future control by immunisation. With over 90 serotypes,[71] there is some limit to the number that can be practically included in a conjugate vaccine. Nasopharyngeal carriage rates of those serotypes included in a conjugate vaccine are reduced for up to 2 years following immunisation in infancy,[72] although the difference between vaccinated and unvaccinated children is less apparent by 3–4 years of age due to natural aquisition of mucosal immune responses.[73] However, there is a compensatory rise in colonisation with serotypes not in the vaccine,[74] with a modest increase in otitis media caused by these serotypes.[75] Another feature of pneumococcus is that it is capable of capsular switching, which could be selected for by immunisation.[76] It is therefore clear that monitoring of epidemiological trends will be especially important with vaccines against pneumococcal disease, although data from the US are encouraging and indicate significant herd immunity and consistent effectiveness in vaccine recipients.[77]

S. pneumoniae is involved in a broader range of disorders than Hib. Annually, between 100 000 and 500 000 deaths are attributable to pneumococcal meningitis in children <5 years of age.[78] In recent years, resistance to one or more antimicrobials has developed in certain serotypes of *S. pneumoniae*, adding to the difficulty of treating patients with pneumococcal disease.[79]

2.1 Pneumococcal Conjugate Vaccine

For the US and Finland, the epidemiology of bacterial meningitis in children made *S. pneumoniae* the logical second target for conjugate vaccines after Hib.

In February 2000, a conjugate pneumococcal vaccine was approved in the US for use in children <2 years of age. Of the 90 serotypes identified so far, this vaccine contained only seven of them: 4, 6B, 9V, 14, 18C, 19F and 23F. These are responsible for up to 90% of invasive disease in the US, Canada, Africa and Europe.[80,81] Clinical trials in the US suggest vaccine efficacy levels of 97% against invasive pneumococcal disease, including meningitis, resulting from infection with the serotypes contained in the vaccine.[82]

The nine-valent vaccine currently under trial contains the seven-valent serotypes plus serotypes 1 and 5. It has been evaluated in large scale trials in South Africa and the Gambia,[83] whilst trials of an

11-valent vaccine (including serotypes 3 and 7V) are underway in Israel, Argentina and Chile.[84,85]

It is hoped that a reduction in the nasopharyngeal carriage of pneumococci will modify the disease epidemiology of *S. pneumoniae*.[86-88] The introduction of the seven-valent vaccine in the US led to a decrease in the rate of infection by nearly 60% in children aged <5 years, but also a decrease in adults aged ≥20 years who had not received the vaccine.[77] This study also demonstrated that vaccination could reduce the number of antibiotic-resistant pneumococcal infections.

3. Meningococcal Disease

Meningococcal disease remains an important public health concern worldwide, especially in sub-Saharan Africa, where it occurs as regular epidemics.[89] Five of the 13 *N. meningitidis* groups cause most meningococcal disease: A, B, C, Y and W135. Serogroup A is responsible for epidemic disease in sub-Saharan Africa and in other developing countries. Serogroups B and C cause most of the infection in developed countries. The pattern of disease caused by serogroup B is typically sporadic. In the UK, 32% of the reports of invasive disease caused by *N. meningitidis* in 1996 were associated with serogroup C.[6]

3.1 *Neisseria meningitidis* Conjugate Vaccines

For the UK, the epidemiology of bacterial meningitis in children made *N. meningitidis* the second target after Hib. This was all the more important because of the steady rise in the incidence of invasive disease specifically due to *N. meningitidis* during the latter part of the 1990s.[90]

The polysaccharide vaccines against serogroups A and C were efficacious in older children and adults but much less immunogenic in children aged <5 years of age.[91] The conjugate vaccines, besides being more immunogenic, also offer herd immunity.

3.2 Group C

A dramatic reduction in the incidence of group C disease was observed after the introduction of the conjugate meningococcal group C vaccine into the UK immunisation programme.[92] Figures from 2002 showed that with a coverage of 89%, the incidence of serogroup C meningitis was reduced by 80% compared with historical data from before the introduction of the vaccine, whilst the number of deaths fell from 78 to 8 in the same period.[93] Cost-effectiveness analysis estimated a cost per life-year gained of £6259 (€10 726) for the meningococcal group C immunisation campaign in the UK, from its introduction in 1999 to 2001.[94] There has been a significant reduction in carriage rates of *N. meningitidis* group C in teenagers and young adults, coincident with introduction of immunisation.[95] Following the introduction of the meningococcal group C vaccine in the UK, it has been introduced in several other European countries, as well as in Canada. However, as with the Hib vaccine, protection has been age dependent, with the older age groups being found to have greater and longer lasting protection than those vaccinated in infancy.[96] Despite the rapid waning of vaccine effectiveness in infants, the number of cases of disease due to *N. meningitidis* group C in this age group remains low, probably due to herd immunity.[97] The implications of these findings would suggest that accelerated schedules may not be optimal for conjugate vaccines, and alternative vaccine schedules may need to be considered. This may require the administration of a booster dose in late infancy or a change in the age at which the final dose is given.

3.3 Group B

Despite the effectiveness of the meningococcal C conjugate vaccine campaign, only a portion of the worldwide meningococcal disease burden can be addressed by its use. Serogroup B meningococcus

remains an important problem in Europe.[98,99] The serogroup B capsular polysaccharide is poorly immunogenic in humans because it resembles self antigen,[100] and an effective vaccine for widespread use is therefore still not available. Vaccines made from vesicles of meningococcal OMPs have been used successfully in Group B outbreaks. Their success, however, has been limited to outbreaks caused by a single circulating sero-subtype. Such a vaccine is being used in New Zealand at present, where a group B epidemic has been ongoing since 1991.[101] Several other OMPs have been identified and investigated but few offer promise for vaccine development.

3.4 Groups A, Y, W135

A vaccine focusing on the protection against serogroups A, C, Y and W135 meningococci offers the potential for addressing epidemic meningococcal disease in sub-Saharan Africa,[102] controlling the W135 strains associated with the Hajj,[103] and serogroup Y, which is particularly prevalent in the US.[104] Trials of the conjugate ACYW vaccine in infants have been disappointing,[105] despite promising results in adults and toddlers.[106,107]

In January 2005, a quadrivalent meningococcal conjugate vaccine was licensed for 11- to 55-year-olds (Menactra®, manufactured by Sanofi Pasteur)[1]. A single dose contains A, C, Y and W135 polysaccharides conjugated to diphtheria toxoid. Although not licensed for use 2- to 3-year-olds, Menactra was shown to be more immunogenic for all four serogroups than the polysaccharide vaccine Menomune®, also manufactured by Sanofi Pasteur.[108] In addition, antibodies were found to persist for at least 2–3 years, although a large proportion of immunised children had suboptimal serum bactericidal antibody titres suggesting a lack of protection and the need for a booster dose.[109] Presently, routine immunisation of adolescents is recommended either at 11–12 years of age or before high school entry,[110] although an application has been filed with the US FDA to obtain approval for use in 2- to 10-year-olds.[111]

In Africa, the utilisation of two vaccines in an attempt to reduce the incidence of epidemic meningitis has begun. A heptavalent product (diphtheria-tetanus-whole pertussis [DTwP], hepatitis B, Hib, meningococcal conjugate A-C) is to be used in an expanded programme of immunisation, and a monovalent conjugate vaccine against meningococcus A will be used in the population aged 1–29 years.[112] The efficacy of this vaccine regimen against meningitis will need to be evaluated.

4. Future Use of Conjugate Vaccines

With an increasing number of conjugate vaccines becoming available, the potential for interaction with other vaccines increases. For example, a combination pneumococcal and meningococcal C vaccine showed reduced immunogenicity of the group C component and of concomitantly administered Hib and DTwP vaccines.[113] Studies confirming the safety and efficacy of combination conjugate vaccines are needed.

5. Conclusion

Polysaccharide conjugate vaccines have proven highly successful in preventing Hib meningitis, and show similar promise for *S. pneumoniae* and *N. meningitidis*. It will be important to continue to monitor and investigate possible vaccine failures. Surveillance of colonisation and disease isolates must remain an essential component of immunisation strategy. Combination vaccines that include conjugate vaccines will need to be studied carefully to ensure efficacy.

1 The use of trade names is for product identification purposes only and does not imply endorsement.

Advances in the primary prevention of bacterial meningitis have been made through the untargeted use of the conjugate vaccines in the immunisation schedules of wealthy countries. However, their high cost still precludes their use in many developing countries and progress needs to be made in order to get these highly effective vaccines to those areas that need them most.

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