Progress Towards Meningitis Prevention in the Conjugate Vaccines Era

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Acute bacterial meningitis is an important cause of morbidity and mortality among children less than five years old. *Haemophilus influenzae*, *Streptococcus pneumoniae* and *Neisseria meningitidis* are the most important agents of bacterial meningitis in developing countries. The development of the conjugate vaccines in the beginning of the 90’s, especially type b *H. influenzae* (Hib), and more recently the heptavalent pneumococcal and the serogroup C meningococcal vaccines, have contributed directly to changes in the epidemiological profile of these invasive diseases (direct effect) and of their carriage status (indirect effect). We review the impact of the Hib conjugate vaccine in Latin American countries, where this vaccine has been implemented, and the potential of pneumococcal and meningococcal conjugate vaccines for the reduction of meningitis worldwide. We also address constraints for the development and delivery of these vaccines and review new candidate state-of-the-art vaccines. The greatest challenge, undoubtedly, is to implement these vaccines worldwide, especially in the developing regions.

Key Words: Conjugate vaccines, Hib conjugate vaccine, pneumococcal conjugate vaccine, meningococcal conjugate vaccine, impact of Hib conjugate vaccine.
**H. influenzae Type b Vaccine**

Finland, Canada, Iceland, United States, United Kingdom, Israel and Australia were the first countries to use the Hib vaccine on a large scale at the end of the 1980's and the beginning of the 90's. Heath, in a review about the efficacy of Hib vaccine in these countries, indicated a spectacular reduction of invasive disease incidence due to *H. influenzae b* [14]. In the USA, Adams et al. observed a decrease of 82% in *H. influenzae* meningitis between 1985 and 1991 based on national surveillance data [7]. Dawson et al. [15], in a retrospective study, detected a fall in the number of meningitis cases by *H. influenzae b*, from 73% to 69%, with the polysaccharide vaccine, and to 16%, within a 5-year period after the introduction of the conjugate vaccine.

In Latin America (LA), the conjugate vaccine was first introduced into Uruguay in 1994, followed by Costa Rica and Chile, and it is currently incorporated into the immunization programs of almost all LA countries [16]. In Uruguay, the incidence rate of Hib meningitis fell from 15.6 to 0.03 per 100,000, 2 years after the introduction of this vaccine [17]. In Brazil, this vaccine was first used in Curitiba (southern Brazil) in 1996, and after a year of routine use, a 72% reduction was observed in the incidence of meningitis [18]. Nationwide immunization in Brazil began in mid 1999, and after 2 years, Simões et al. [19], in a prospective population surveillance carried out in Goiás State (Central Brazil), demonstrated a 78% decline in the risk of meningitis by *H. influenzae b* among children under 5 years of age. Furthermore, studies conducted in Brasília and Salvador detected a reduction of meningitis cases of 80% and 69.9%, respectively, after the first year of the initiation of Hib vaccination [20,21]. The impact of Hib vaccine on the reduction of meningitis in Latin America countries after the introduction of the Hib vaccine in this region ranged from 40.0% to 95.6%, depending on the time-period of assessment (Table 1) [18-26].

The significant decline of bacterial meningitis caused by Hib was due not only to the direct effect of this vaccine on individual protection, but also to the reduction of colonization of the nasopharynx [27-31], decreasing the transmission of Hib and therefore the incidence of meningitis by *H. influenzae b* in vaccine recipients as well as in non-vaccinated children (indirect effect of the vaccine – herd immunity) [32].

Despite the availability of the Hib conjugate vaccine and its impressive impact on invasive diseases in countries where it has been implemented, about 132 million children have not been treated with this vaccine, most of them in poor countries in Africa and Asia. A map (Figure 1) shows the current geography of Hib vaccine implementation in the world [33].

Important obstacles have hampered the introduction of this vaccine into the African and Asian continents. Information about the production, the estimated costs, the use of the vaccine on a large scale, as well as the safety and efficacy of this vaccine are essential in these regions. Various investigations have shown cost to be the most critical issue to introduce the vaccination in these countries, whereas safety and efficacy, although significant, are less relevant. The unfavorable economic and financial situation in many countries in Africa have impeded increases in per capita spending on health, making it unfeasible to introduce the Hib vaccine [34]. Most countries in Africa have limited medical and laboratory support, making the proper identification of etiological agents involved in invasive diseases difficult. Moreover, other complex health problems, including tuberculosis, malaria, HIV and meningococcal disease, compete against *H. influenzae b* for priority. The public health policy makers need to be aware of the magnitude and the social costs of the Hib diseases, and they should maximize efforts to incorporate this vaccine into routine health services [35,36].

**Pneumococcal Conjugate Vaccine**

In comparison with Hib, *Streptococcus pneumoniae* is involved in a broader range of disorders, including invasive (pneumonia and meningitis), and non-invasive (acute otitis media and sinusitis) diseases. It also contributes to the highest levels of mortality and morbidity in the world, especially in children under 5 years old [37-39]; at least 1.2 million deaths occur annually due to pneumonia, 39% are children less than 5 years, with 100,000 to 500,000 deaths by pneumococcal meningitis [37].
Table 1. Impact of *Haemophilus influenzae* b conjugate vaccine on meningitis in Latin American countries

<table>
<thead>
<tr>
<th>Country</th>
<th>Author, year</th>
<th>Vaccine introduction</th>
<th>Age group</th>
<th>Timing after Hib vaccine introduction</th>
<th>Coefficients x10^5</th>
<th>% Decrease post vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cuba</td>
<td>Dickinson et al. 2001 [23]</td>
<td>1999</td>
<td>&lt; 5 years</td>
<td>1 year</td>
<td>13.6 / 7.6</td>
<td>52.8</td>
</tr>
<tr>
<td>Colombia</td>
<td>Agudelo et al. 2000 [24]</td>
<td>1998</td>
<td>&lt; 1 year</td>
<td>1 year</td>
<td>-</td>
<td>40.0</td>
</tr>
<tr>
<td>Uruguay</td>
<td>Ruocco et al. 1999 [17]</td>
<td>1994</td>
<td>&lt; 5 years</td>
<td>2 years</td>
<td>15.6 / 2.7</td>
<td>82.7</td>
</tr>
<tr>
<td></td>
<td>Landaverde et al. 1999 [25]</td>
<td>1994</td>
<td>All ages</td>
<td>6 months</td>
<td>-</td>
<td>95.6</td>
</tr>
<tr>
<td>Chile</td>
<td>Diaz et al. 2001 [26]</td>
<td>1996</td>
<td>&lt; 5 years</td>
<td>2 years</td>
<td>36.4 / 9.9</td>
<td>72.7</td>
</tr>
<tr>
<td>Brazil</td>
<td>Takemura &amp; Andrade 2001 [18]</td>
<td>1996</td>
<td>&lt; 5 years</td>
<td>1 year</td>
<td>35.4 / 9.7</td>
<td>72.6</td>
</tr>
<tr>
<td></td>
<td>Freitas 2000 [20]</td>
<td>1999</td>
<td>&lt; 5 years</td>
<td>1 year</td>
<td>-</td>
<td>80.0</td>
</tr>
<tr>
<td></td>
<td>Simões et al. 2002 [19]</td>
<td>1999</td>
<td>&lt; 5 years</td>
<td>1 year</td>
<td>10.8 / 2.3</td>
<td>78.7</td>
</tr>
<tr>
<td></td>
<td>Ribeiro et al. 2003 [21]</td>
<td>1999</td>
<td>&lt; 5 years</td>
<td>1 year</td>
<td>2.6 / 0.8</td>
<td>69.0</td>
</tr>
</tbody>
</table>

Source: Adapted from Simões 2002 [22].

a not reported.
b metropolitan area of Santiago.
c incidence in non-exposed to vaccine.
d incidence in exposed to vaccine.
The success achieved by Hib immunization has stimulated the development of a pneumococcal conjugate vaccine. In February 2000 the Food and Drug Administration approved the use of a seven-valent conjugate vaccine for American children under 2 years old. Among the 90 *S. pneumoniae* serotypes identified so far [40], the formulation of this vaccine contains only 7 serotypes – 4, 6B, 9V, 14, 18C, 19F and 23F, but these are responsible for 70% to 90% of the invasive disease cases in children in the USA, Canada, Africa and Europe and are 70% of the pneumococci that cause acute otitis media in USA, Canada and Europe [41,42]. Clinical trials carried out with the 7-valent vaccine in USA have revealed high levels of protection against invasive pneumococcal disease, and another review found a 50% to 60% protection range against serotype specific pneumococcal otitis in Finland [43,44]. In Brazil, the heptavalent vaccine was licensed in February 2001 [45], but it has still not been added to the PNI (national program of immunizations) schedule. The 9-valent conjugate vaccine contains the 7-valent serotypes, as well as serotypes 1 and 5, and it has been evaluated by large-scale field trials in South Africa and Gambia [46]. The 11-valent vaccine includes the 9-valent serotypes, as well as serotypes 3 and 7V, and it is currently under test in clinical trials in the Philippines, Israel, Argentina and Chile [13,38,47].

While the expected impact of the Hib conjugate vaccine is a reduction in meningitis cases, the pneumococcal vaccines are also expected to reduce pneumonia and acute otitis media cases, as well as carriage prevalence, which will significantly modify pneumococcal disease epidemiology [48-50]. Eskola and Anttila [19] have shown that in clinical trials with the 7-11 valent pneumococcal conjugate vaccines, the coverage against invasive disease, including meningitis, can reach 92%. DiFabio et al. [51] estimated a 64.4% serotype coverage (95% confidence interval (CI: 60.7%-67.8%) for meningitis with the use of the heptavalent pneumococcal vaccine in Brazil. Similar results were reported by Brandileone et al. [52], who found that the 7-valent vaccine would cover 61% (95% CI: 57.0%-64.9%) of the most prevalent meningitis serotypes in Brazil in children under 2 years old (1, 14, 19A, 19F, 5, 6A and 6B). It is worthwhile emphasizing the high prevalence of serotypes 1 and 5 in Latin American countries, which are not included in the heptavalent vaccine.
The efficacy of pneumococcal vaccine against meningitis needs to be better evaluated. So far, clinical trials conducted in California by the Kaiser group, and in Navajo children, did not find any case of meningitis in the vaccinated group; however, as the number of cases in the control group has not yet been reported [48,53,54], it is probable that the efficacy of the heptavalent vaccine against pneumococcal meningitis would be better evaluated through meta-analyses, which have the advantage of pooling to attain a higher sample size, increasing the power to detect significant differences between vaccinated and unvaccinated groups. Observational studies may also be conducted to assess the effectiveness of the pneumococcal vaccine during the vaccine post-licensure period.

Although there has been optimism concerning the impact of the *S. pneumoniae* conjugate vaccine, there are some restrictions against its incorporation into health services routine, including: (i) the high cost for implementation at a public health level, especially in the developing world, (ii) controversy about cross-protection against serotypes not contained in the vaccine, and (iii) the technical difficulties of having all pneumococcal serotypes in the same formulation. Consequently, alternative candidates to the pneumococcal vaccine have been tested for immunogenicity and safety, including protein vaccines. A large number of investigators have searched for proteins capable of inducing immunity to invasive and non-invasive pneumococcal infection. Pneumococcal surface proteins, including protein A (PspA), protein C (PspC), adhesin (PsaA) and pneumolysin, have been considered as alternatives to promote protective immunity in children [55,56]. These proteins can induce protection regardless of pneumococcal serotype; for example, PspA has been found in all isolates of *S. pneumoniae* [57]. According to the amino acids sequences, PspA can be classified into three families. Families 1 and 2 are the main ones, and are found in more than 98% of the PspA molecules [58,59]. Studies conducted in animal models have showed that PspA was the most efficacious protein for immunization against carriage, otitis media, pneumonia and sepsis. A synergistic effect has been detected when two proteins are associated. A combination of PspA and pneumolysin can induce a higher immunity to lung infections and probably against septicemia, when compared to PspA alone [55,60]. The relative protective capacities of several different pneumococcal proteins against sepsis, bacteremia, pneumonia, otitis media and carriage suggest that the association of different proteins optimizes protection against a broad variety of strains and diseases. Therefore, it is plausible that vaccines against *S. pneumoniae* composed of mixtures of polysaccharides and several protein antigens might be a better approach than a vaccine based on a single type.

**Meningococcal Conjugate Vaccine**

Meningococcal meningitis is an important public health problem worldwide, especially in sub-Saharan Africa, where it occurs as an endemic disease, with outbreaks every 2 years [61,62]. *Neisseria meningitidis* isolates can be classified into 12 groups, based on chemically and antigenically distinct polysaccharide capsules, but only 5 groups are responsible for almost all meningococcal disease: A, B, C, Y and W135. Serogroup A is responsible for epidemic disease in sub-Saharan Africa and in developing countries in other regions. Serogroups B and C are responsible for most of the infections in developed countries, as well as in developing regions. The pattern of disease caused by serogroup B is typically hyperendemic or sporadic, in contrast to the endemic nature of serogroup A. In the United Kingdom, 32% of the reports of invasive disease caused by *N. meningitidis* in 1996 were associated with serogroup C [6]. Meningococcal disease caused by serogroups Y and W135 is mainly found in the USA [62].

The polysaccharide vaccines against serogroups A and C, widely used for many years with relative success in mass immunizations during outbreaks, are efficacious in older children and in adults, but are much less immunogenic in children under 5 years old [63]. The development and use of meningococcal conjugate vaccine is an alternative to polysaccharide vaccines. The conjugate vaccines for *N. meningitidis* are at
several stages of development and clinical trials. Besides being more immunogenic than the polysaccharides, the meningococcal conjugate vaccines induce “herd immunity” [64]. Most of the efforts toward the development of meningitis conjugate vaccines first concentrated on serogroups A and C, at the end of the 1980’s. Studies conducted on children in Gambia and the United Kingdom showed good immunogenicity and tolerability for the bivalent conjugate vaccine A-C [65,66]. Recently, several clinical trials made with children and teenagers have confirmed the safety, immunogenicity and capacity to induce immunological memory of serogroup C meningococcal vaccine [67-70].

In Africa, an extensive project to wipe out epidemic meningitis has begun, based upon the utilization of two vaccines. One of them, a heptavalent product (DTPw, hepatitis b, Hib, meningococcal conjugate A–C), is to be used in the expanded program of immunization, and another product, a monovalent vaccine against meningococcus A, will be used in the population from 1 to 29 years old [71]. Field trials with both vaccines are scheduled to begin soon.

The United Kingdom was the first country to include the conjugate vaccine against serogroup C in a routine immunization program, in November 1999. After the use of this vaccine in children and teenagers less than 19 years old, a strong reduction in serogroup C meningococcal disease was observed [11,72,73]. Recently, Trotter et al. [74] reported that, with a coverage of 89% vaccination, a reduction of 80% in the incidence of meningitis by serogroup C was detected and the number of deaths fell from 78 to 8 during the same time period.

Serogroup B meningococcus is an important problem in the Americas and Europe due to its high incidence in these regions, and no effective vaccine is available to date [75,76]. The development of a vaccine against serogroup B is a more difficult task. The similarity between the polysaccharide structure of the bacterial capsule and carbohydrates naturally found in humans make this antigen auto-limited or poorly immunogenic. Furthermore, the use of this polysaccharide in a vaccine can stimulate the production of auto-antibodies [77,78]. An alternative approach to vaccine development is based on outer-membrane vesicles. Although such vaccines induce an antibody response and protect against meningococcal disease, especially among children more than four years of age [79-82], they do not protect against several known heterologous strains [83]. On the other hand, many previously unrecognized proteins were identified and characterized during the genome sequencing of a virulent strain, MC58, of meningococcus B [84,85]. Some of these proteins induce bactericidal antibodies in serum against serogroup B meningococcus. Thus, there is a new potential vaccine candidate, which should be safe and capable of promoting strong homologous and heterologous protection against *N. meningitidis* B strains, although it is also likely to promote cross-protection against other serogroups.

**Final Remarks**

In this epidemiological scenario post-introduction of conjugate Hib vaccine into routine immunization programs, the greatest challenge is to improve the current surveillance systems. Considering the sharp decrease of invasive disease as well as the carriage status of Hib, more sensitive and specific diagnostic tools are essential to the early detection of the emergence of other *H. influenzae* serotypes, especially the non-typeable *H. influenzae* and also the *S. pneumoniae*, which could occupy the ecological niche left by Hib [86-89]. The monitoring of possible vaccine failure [90,91], the reemergence of cases of invasive disease by Hib, despite adequate levels of vaccine coverage, and the antimicrobial susceptibility of *H. influenzae*, including the “non-b” strains and *S. pneumoniae*, are also imperative in this post-vaccine era [92-98].

While waiting for a more effective vaccine against all meningococcus groups, the best strategy for meningococcal meningitis prevention is prompt large-scale mass vaccination during the epidemic period. Studies carried out in African countries have suggested that an efficient surveillance system, especially for the detection of meningococcal meningitis outbreaks, might guide appropriate control measures, such as a mass
catch-up vaccination campaign, to timely decrease the number of cases of the disease [99].

Incorporation of new epidemiological information might be attained with the use of molecular typing techniques for the characterization of the invasive and colonizing serotypes, allowing systematic evaluations of the Hib vaccine and of the forthcoming conjugate vaccines of *S. pneumoniae* and *N. meningitidis*, when they become widely available and implemented.

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