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REVIEW ARTICLE

Haemophilus influenzae type b vaccination: long-term protection

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Abstract

Objective: To identify evidence of the impact of *Haemophilus influenzae* type b (Hib) conjugate vaccine on the epidemiology of invasive Hib disease.

Sources of data: This review was based on a search of MEDLINE, LILACS, technical reports, national and international guidelines (publications from 1991 to 2005). The keywords *Haemophilus influenzae* type b, immunization, impact and effectiveness, alone or in combination, were used to retrieve the articles. Studies published before 1991 and cited in the references of the studies reviewed were analyzed for useful information.

Summary of the findings: Introduction of the Hib conjugate vaccine produced great decline in the incidence of invasive Hib disease in childhood in countries where this vaccine was introduced into the routine immunization schedule. Nevertheless, the resurgence of invasive Hib disease in some regions has challenged several researchers to identify the reasons for this epidemiological pattern, as well as the measures to be implemented in order to avoid such a phenomenon.

Conclusions: The use of Hib conjugate vaccine on a population scale has been greatly effective; nonetheless, changes in the vaccination scheme seem to be necessary to keep invasive Hib disease under control.

J Pediatr (Rio J). 2006;82(3 Suppl):S109-14: Haemophilus influenzae type b, immunization, vaccine, meningitis, pneumonia.

Introduction

Haemophilus influenzae is a gram-negative bacterium that may, depending on the chemical structure of the external polysaccharide layer, be capsulated or non-encapsulated. In the latter case, it is also called non-typable. Of the six capsulated types of *H. influenzae* (a, b, c, d, e, f), type b (Hib) is the main cause of invasive disease in childhood, especially in non-industrialized regions, including meningitis, epiglottitis, septicemias, osteomyelitis, arthritis and non-invasive diseases such as pneumonia and otitis. Although there is a highly effective vaccine available, at the beginning of the 21st century Hib still represents an important cause of morbidity and mortality in childhood in developing countries, especially where the Hib vaccine has not yet been introduced.[1] Technology capable of conjugating a protein derivative to capsular polysaccharide has culminated in the production of a vaccine able to stimulate the immunologic system with a T-dependent response, for use in children under the age of 2 years. The efficacy and safety of conjugate Hib vaccines has been proved by several investigations, even when associated or combined with other vaccines.[2,3] However, knowledge of the efficacy and safety of these vaccines is not enough for their large-scale implementation. In developing regions, the cost-effectiveness of vaccination becomes the main aspect in the decision to introduce the vaccine in public health.[4-7] In addition, the scarcity of local data on the incidence of Hib, the high cost of the vaccine and the lack of knowledge about the effectiveness of vaccination in populations with different epidemiologic and genetic characteristics than those of developed countries, has limited the incorporation of the vaccine in immunization programs in developing countries. From this standpoint, studies on the burden of disease to be prevented are paramount for supporting control programs.[8-10]

The worldwide burden of *H. influenzae* b

The majority of countries in Africa and Asia have not yet incorporated the Hib conjugate vaccine in their immunization program (Figure 1).[11] Consequently, it is estimated that Hib still causes around 3 million serious infections and 400,000 to 700,000 childhood deaths

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annually all over the world.[1] In several world regions, the relevance of Hib as a cause of invasive infections in childhood are well documented, thus justifying the cost-effectiveness of vaccination in these countries.[7] In Gambia, Hib incidence rates of 60 x 10^5 were detected at the end of the 1980s.[12] More recently, countries like Ghana (72 x 10^5) and Uganda (59 x 10^5) presented the highest rate of meningitis due to Hib in a World Health Organization (WHO) assessment in 11 African countries.[13] In subpopulations of industrialized countries, such as the Apache nation in the United States, the incidence of Hib in the period 1973-1980 reached extreme values of 254 x 10^5. In European countries, the risk for infection by Hib in the early 1990s was 14 x 10^5 in Spain and 11 x 10^5 in Austria.[1,12,14] On the other hand, in Asia, conflicting and sometimes inconclusive results about the incidence of meningitis[15-17] have made it difficult to obtain reliable evidence to support control programs, thus retarding the introduction of Hib vaccine on that continent. However, in countries like Bangladesh, surveillance data have proven that Hib is the main cause of meningitis in childhood.[18] The recently published results of the field trial in Lombok, Indonesia, generated astounding information, showing not only the high incidence of meningitis due to Hib in the region (134 x 100,000), but also a high incidence of meningitis prevented by Hib vaccine under routine immunization conditions.[19]

In Latin America, Chile was the first country to show the cost-effectiveness of the Hib vaccine in preventing Hib invasive disease.[20] In Brazil, Hib vaccination was introduced in mid-1999. The scarce publications that measured the role of Hib as etiologic agent of meningitis in children before the introduction of conjugate vaccines showed coefficients close to those found in European countries in the 1990s. The risk for meningitis due to Hib in the pre-vaccination period in Brazil ranged from 10.8 to 17 per 100,000 children.[21,22]

Effectiveness of vaccination against Hib

Randomized clinical trials (phase III) are the gold standard to evaluate the efficacy and safety of new vaccines under "ideal" conditions. Efficacy studies – clinical trials – supported the release of Hib vaccine for commercial use. In spite of the credibility of results provided by phase III trials, after the introduction of the Hib vaccine in the routine of the health services, the impact of vaccination on the reduction of disease at the population level will be lower than that observed in trials conducted under ideal conditions. Therefore, such an impact must be monitored along the years to assess the possible influence of other variables, such as compliance by the population, vaccination coverage, conservation, dose and way of administration of the vaccine, and adverse reactions. When evaluating the vaccination impact (phase IV), observational studies such as case-control and case series are the ideal designs to provide information about vaccination effectiveness under programmatic conditions. In recent years, population-based randomized trials using Hib vaccine as probe have been used as a methodological tool to estimate the burden of Hib disease and the incidence of the disease which would be preventable by vaccination.[19,23-25] This type of design, known as probe trial, adds on the gold standard in vaccinology, in this current evidence-based medicine era.

Invasive Hib disease has practically disappeared in the industrialized countries in which the conjugate vaccine has been used for over 15 years in routine immunization programs.[26-30] Similarly, the vaccination produced great impact in developing countries, with significant decline

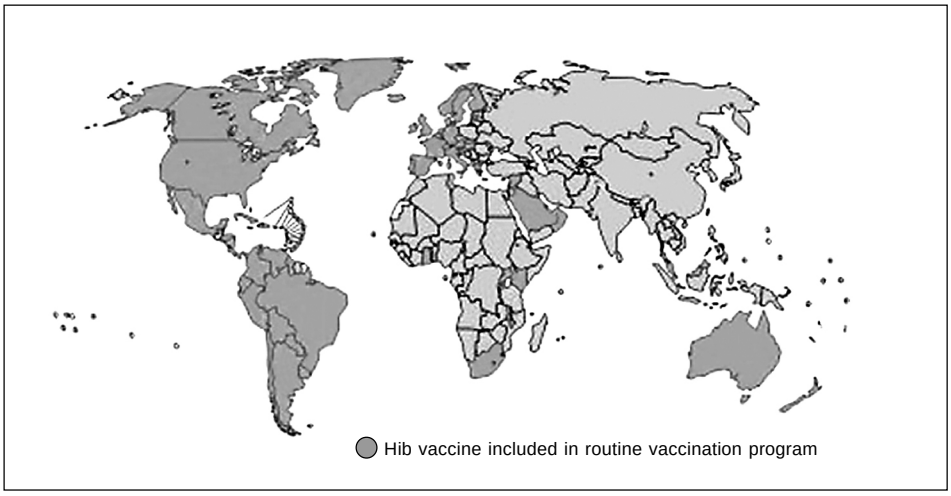

Figure 1 - Countries including Hib vaccine in the immunization program
Source: WHO (http://www.who.int/vaccines-surveillance/graphics/html/hibmap.htm).

especially of meningitis due to Hib.[7,31,32] In several industrialized regions, the availability of efficient surveillance systems with reliable epidemiological baseline made it feasible to monitor Hib meningitis under programmatic conditions. Thus, the majority of studies about the effectiveness of vaccination come from the USA and Europe. Surveillance data in these countries have detected a decline higher than 80% in Hib meningitis soon after the vaccine was introduced.[14,26,29,33]

In Latin America, the vaccination impact on meningitis was assessed in Cuba, Colombia, Uruguay, Chile and Brazil,[31] showing a 40 to 95% decline in the incidence rates of Hib meningitis in the post-vaccination period, compared with the pre-vaccination period, as shown in Table 1.[22,34-42]

Few African and Asian countries have incorporated the Hib vaccine in the health services routine, partly due to lack of local data on Hib epidemiology which could justify the high cost of large-scale use of the vaccine. In 1997, Gambia was the first African country to introduce the vaccination against Hib. This was possible only as a result of support from abroad for conducting population-based efficacy studies.[23] After 8 years of vaccination in Gambia, Hib has now been completely eliminated. No case of meningitis has been detected, compared with the rates of 200 x 10^5 (< 1 year) and 60 x 10^5 (< 5 years) in the pre-vaccination period (1990-1993).[32] In Asia, in the probe trial conducted in Lombok, vaccination was introduced in the health services in a randomized fashion, with DPT vaccination as a comparison group, and the results showed a considerable decline in the incidence of meningitis preventable by vaccination against Hib, which ranged from 67 to 158 per 100,000 children-year.[19]

In pneumonia, vaccination effectiveness was initially shown in the field trial conducted in Gambia in Africa, where the vaccine reduced pneumonia cases with alveolar consolidation by 22.4% in the vaccinated group compared with the control group.[23] A similar result was observed in Chile after the vaccine was introduced in the health services, where a 22% reduction in pneumonia was observed, assessed by a retrospective study of hospital charts.[24] More recently, three case-control studies were conducted, two in South America and one in Asia. In Brazil, the investigation was designed to be part of the structure of a population-based prospective surveillance system to detect radiologically diagnosed cases of pneumonia. Under programmatic conditions, vaccination against Hib reduced the incidence of pneumonia by 31% in Brazil, by 55% in Colombia and by 45% in Bangladesh.[43-45]

In the current state of the art there is well established evidence of the causal relationship between vaccination against Hib and reduction in mortality by pneumonia in children under 5 years of age in developing countries.[46,47] However, there is still scarce information on the effect of Hib vaccination on mortality due to invasive diseases worldwide. Recent surveillance data from central Brazil

Table 1 - Impact of vaccination against *H. influenzae* b on meningitis and pneumonia in children under the age of 5 years in Latin American countries

Disease	Study	Time elapsed since introduction of the vaccine	Incidence x 10^5 Pre / Post-vaccination (reduction)
Meningitis			
Cuba	Dickinson et al., 2001[39]	1 year	13.6 / 7.6 (52.8%)
Colombia	Agudelo et al., 2000[36]	1 year	– (40.0%) *
Uruguay	Ruocco et al., 1999[34]	2 years	15.6 / 2.7 (82.7%)
	Landaverde et al., 1999[35]	6 months	– (95.0%) †
Chile	Diaz et al., 2001[40]	2 years	36.4 / 9.9 (72.7%)
Brazil	Takemura & Andrade, 2001[38]	1 year	35.4 / 9.7 (72.6%)
	Freitas, 2000[37]	1 year	– (80.0%)
	Ribeiro et al., 2003[41]	1 year	2.6 / 0.8 (69.0%)
	Kmetzsch et al., 2003[42]	2 years	36.5 / 3.4 * (90.7%)
	Simões et al., 2004[22]	2 years	10.8 / 2.2 (78.7%)
Pneumonia		**Type of design**	**Effectiveness (95%CI)**
Chile	Levine et al., 1999[24]	Retrospective cohort	22% (-7.0; 43.0)
Brazil	Andrade et al., 2004[43]	Case-control	31% (-9.0; 57.0)
Colombia	de la Hoz et al., 2004[44]	Case-control	55% (7.0; 78.0)

– = data not available.
* < 1 year of age.
† all ages.

showed that the mortality rate due to bacterial invasive disease in children from 2 to 23 months old fell from 72.8% to 49.0% per 100,000 children-year of observation, in the second year after Hib vaccine was introduced.[48] The greatest reduction was observed in mortality by bacterial meningitis (12.8 to 3.5/100,000), followed by reduction in radiologically confirmed pneumonia (36.5 to 24.5/ 100,000).

Reappearance of invasive Hib disease cases

The United Kingdom (UK) is among the countries in which a marked reduction was documented in the number of cases of invasive infections caused by Hib after the conjugate Hib vaccine was included in the routine vaccination program for infants in 1992.[29] However, in that country, a growing number of cases of severe infection due to Hib began to be observed from 1998 onwards, in children born as of 1996.[49] The number of cases among children under the age of 5 years was over 800 per year before the vaccine had been implemented, whereas in 2002 there were 134 cases registered in the same age group, and 266 in all age groups.[50] In addition to the use of a basic vaccination scheme in the first year of life (1 dose at 2, 3 and 4 months of life) in the routine National Immunization Program, the UK implemented a vaccination campaign with a single dose of conjugate Hib vaccine for all children aged between 1 and 4 years in 1992/1993.[50] The mass campaign strategy for children aged from 1 to 4 years probably accelerated the drop in the frequency of invasive Hib disease cases in the UK, as it caused a rapid reduction in the number of susceptible individuals (< 5 years). Nonetheless, in The Netherlands, where the above strategy was not used, the speed of reduction of the frequency of invasive Hib disease was much lower.[51] But the increased incidence of meningitis and epiglottitis due to Hib in 2002 was described in The Netherlands in a similar manner as it occurred in the UK.[52] Therefore, it is unlikely that the increased incidence of cases in the UK had been due to chance.

The number of invasive Hib disease cases in the UK has doubled every year, as of 1998, and the great majority of cases occurred in inadequately vaccinated children.[50] Several factors have been identified as being responsible for this fact: a lower direct protection in vaccinated infants in comparison with what had been previously reported,[53] loss of initial impact of the mass campaign conducted between 1992/1993,[54] use of combined vaccines with less immunogenic acellular pertussis component[55] and non-application of the booster dose after 1 year of age.

In addition to the reduction in cases among immunized children, a reduction has been documented in invasive Hib disease in non-immunized individuals of an age equal to or older than 15 years.[56] The indirect protection established in this age group may be attributed to the so called herd immunity, in which the effect is extended to groups of a community, in addition to the groups in which the preventive action was implemented. This herd immunity may be attributed to the reduced circulation of Hib in the community. However, a rise in the number of infections by Hib among adults has also been documented in the UK as of 1998, reaching pre-vaccination levels in 2003.[57] In a study in which the antibody levels for Hib among English adults were measured, significant reduction was described in 1994, in comparison with the antibody levels measured in 1991 in the same age group ($p = 0.006$).[57] In another study, the antibody level for Hib was measured in the serum of English individuals between the ages of 1 and 15 years who had been vaccinated in childhood: the antibody titers for Hib in the samples obtained in 1997 and 2000 of children between the ages of 3 and 4 years were substantially lower than the titers of the same age group whose samples were collected in 1994.[54]

Therefore, in the absence of a booster stimulus, the antibodies for Hib induced by vaccination during the first year of life tend to progressively diminish during the period from 2 to 3 years.[54] The titer levels of Hib antibodies with protective effect in the short and long-term were previously determined (0.15-1.0 mg/L).[58] It is possible that the increase in the number of invasive Hib disease cases is secondary to a lesser protection than it was expected.[59] The reduction in Hib circulation in the community led to the loss of the natural booster stimulus that existed when the immunized child was colonized by Hib. Thus, the reduction in this circulation, which resulted from the initial use of the vaccine in the 1990s,[60] may be blamed as one of the causes for the increased number of cases, as previously discussed.[57]

Several limitations of the vaccine have been recognized as partially responsible for the vaccinal protection documented, which is below the protection provisionally expected[61]: Hib vaccine results from the capsular polysaccharide (PRP) conjugation to protein (diphtheria or tetanic toxoid and external meningococcus membrane protein B-PRP-OMP); this conjugation was necessary to recruit T cells for the primary immunologic response, because isolated PRP is not able to do it during the first two years of life. Since it is the protein that stimulates the immunologic response and the protein is strange to the bacteria, it is possible that the conjugate compounds do not induce the T cells to recognize the specific Hib peptides, leading to less lasting protection. In the natural model, protection is acquired as of 2 years of age, as the individual is colonized by Hib, by recognition of the specific Hib proteins and establishment of lasting immunity. Introduction of the vaccine combined with an acellular pertussis component (DTaP-Hib) in the years

1999/2000 coincided with the increase in the number of cases. Actually, this combination reduced the Hib component immunogencity.[62] In a case-control study in previously immunized children who presented with infection by Hib, a larger number of cases had received the three doses of the vaccine combined with the acellular component (OR 6.35; 95%CI 3.06-13.18).[55] In turn, in The Netherlands, the triple vaccine (DPT) used had the pertussis component with a whole cell, and it was not used in combination with the vaccine for Hib. Furthermore, in The Netherlands there was an increase in the number of cases, similar to what happened in the UK.[52] Therefore, if the introduction of the combined vaccine has some influence on this increased number of cases, it is small and insufficient to justify the epidemiological development of this disease in these two countries. This hypothesis also does not explain why an increase in the disease was also observed in children born before 1999. One could question whether the vaccine for Hib is being administered too early in the UK (2,3 and 4 months of age) with repercussion on the duration of protection.[57] In Ireland, where the three-dose scheme (2, 4 and 6 months), without the booster dose was used, an increase was also observed in the number of cases of invasive Hib disease, which encouraged the adoption of an additional dose of the conjugate Hib vaccine in all children under the age of 4 years, as of November 2005.[63] In the UK, in response to the reappearance of invasive Hib disease, the Ministry of Health launched a catch-up program in 2003, offering an additional dose of the conjugate Hib vaccine to all children between the ages of 6 months and 4 years.[50] In countries where a third dose in the first year of life was administered after the sixth month of life, as in the USA, no increase has been documented in the number of cases of invasive Hib disease. However, in that country the routine vaccination schedule also includes a booster dose.[63,64]

Final considerations

The Hib conjugate vaccine represented a landmark in modern vaccinology and a model for the development of other conjugate vaccines, such as for pneumococci and meningococci. Few vaccines have produced such a high impact in so short a period of time. In spite of the uncertainty about the actual incidence of diseases caused by Hib in many world regions and the low incidence in many South East Asian countries, universal vaccination seems to be the only strategy available for control and potential eradication of Hib infection in a globalized world with high migration rates. Furthermore, the epidemiologic scenario observed in recent years in some European countries signals the need to review the vaccination schedules to include a booster dose of Hib vaccine after the first year of life. Thus, new guidelines should be supported by solid evidence driven by continued surveillance of Hib infection in every region.

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