Impact of *Haemophilus influenzae* b (Hib) vaccination on meningitis in Central Brazil

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Abstract

Objective
To assess the impact of the *Haemophilus influenzae* b (Hib) conjugate vaccine in reducing the incidence of meningitis among children under five years old.

Methods
A 'before-after' design was used to compare Hib meningitis incidence rates in the pre-vaccine (July 1995 - June 1999) and post-vaccine (July 1999 - June 2001) periods in the state of Goiás, central Brazil . Bacterial meningitis case definition was based on World Health Organization criteria. Incidence rates of *S. pneumoniae* and *N. meningitidis* were used for comparison purposes. Chi-squared and Student's t tests were used for statistical analysis. P-values below 0.05 were considered as statistically significant.

Results
979 children with acute bacterial meningitis were detected throughout the entire period. The incidence rate of Hib meningitis decreased from 10.8 ($x10^5$) in the pre-vaccine period to 2.3 ($x10^5$) in the 2nd year post vaccination, leading to a risk reduction of 78%, targeted to the 7-23 months age group ($p<0.05$). A total of 65 cases of Hib meningitis were prevented. An increase in *S. pneumoniae* meningitis was observed. Vaccine failure was detected in one child.

Conclusions
This study showed that mass immunization with Hib conjugate vaccine brought about an expressive decline in childhood Hib meningitis in Goiás soon after the first year. Notwithstanding, an enhancement of surveillance using high-accuracy tools is essential to: (i) detect a possible reemergence of Hib; (ii) identify vaccine failure, and (iii) monitor changes in the *H. influenzae* serotype profile over time.

INTRODUCTION

Acute bacterial meningitides are an important cause of morbidity and mortality during childhood. *Haemophilus influenzae* b (Hib) is an etiological agent of acute meningitis in a large proportion of countries in which the conjugate vaccine has not yet been introduced. In these areas, Hib is among the three primary causes of death in children under five years old.[18] In Latin America, the relevance of Hib to meningitis has recently been highlighted in a systematic review of laboratory surveillance data on *H. influenzae*.[1] The expressive impact of Hib vaccination on invasive diseases is well documented in industrialized areas such as the United States and several European countries, and, more recently, in certain regions of Latin America.[9] Despite its availability, the conjugate vaccine has not yet been introduced in most developing countries, especially Africa and Asia, and thus millions of children continue to lack protection against Hib invasive dis-

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eases.[5,17] The uncertainty regarding local incidence data, the high cost of the vaccine, and the lack of knowledge concerning vaccine effectiveness in populations with different epidemiological and genetic characteristics from those of developed countries have limited the incorporation of the Hib vaccine in the immunization programs of most developing countries.

In several industrialized countries, efficient surveillance systems have allowed for the definition of an epidemiological baseline, thus facilitating the monitoring of Hib meningitis, in programmatic conditions, in order to guide future public health actions and measures. In Latin America, Hib vaccination was first introduced in Uruguay in 1994, which was followed by Costa Rica and Chile. Currently, the Hib vaccine is part of the national immunization programs of almost all countries in this region.[17] In Brazil, the role of Hib in invasive disease underfives has been evaluated by independent retrospective studies, based on data from hospitals and/or referral laboratories.[6] The Hib vaccine was incorporated into the national immunization program (PNI) in mid 1999, and publications addressing the impact of vaccination are still scarce.[12,13]

The present study is aimed at identifying the impact of Hib vaccination on the incidence of meningitides among underfives in the State of Goiás, in Central Brazil, two years after the introduction of the conjugate vaccine.

METHODS

This investigation included children between ages 24 and 59 months diagnosed with acute bacterial meningitis between 1 July 1995 and 30 June 2001. In order to evaluate the effect of Hib vaccination on the risk of acquiring meningitis, a 'before-after' design was adopted. The period preceding vaccine implementation (July 1995-June 1999) was considered as the pre-vaccine period and the subsequent period (July 1999-June 2001), as the post-vaccine period. The Hib conjugate vaccine with diphtheria protein (CRM_{197}; HibTITER®; Wyeth® Lederle) was administered between July and November 1999. After this period, the vaccine containing the Hib polysaccharide conjugate with tetanus toxoid (PRP-T), produced by the Brazilian laboratory Biomanguinhos (*Fundação Oswaldo Cruz* - Brazilian Ministry of Health) was used. Children under age 12 months were given three doses of the vaccine (at ages two, four, and six months) and those between 12 and 24 were given a single dose.

Acute bacterial meningitis was diagnosed based on the criteria established by the World Health Organization (WHO)[15,16] and by the Brazilian Ministry of Health (MoH). Confirmed cases were defined by microbiological isolation or antigen detection (latex agglutination or counterimmunoelectrophoresis) in cerebrospinal fluid (CSF). For surveillance purposes, WHO recommends the inclusion of probable cases of acute bacterial meningitis (pABM).[15] The definition of such cases is based on clinical suspicion of meningitis associated with a turbid ("cloudy") CSF and at least one of the following findings in the CSF: elevated protein (>100 mg/dl), decreased glucose (<40 mg/dl), or leukocytosis (>100 mg/dl) with >80% neutrophils.

From July 1995 to April 2000 the completeness .hospital admission data on bacterial meningitis was maximized by reconciling reports,[11] thus ensuring greater accuracy of data. A single database was built by incorporating the data obtained from different sources: the National Notifiable Disease Surveillance System, logbooks of the state central reference laboratory and of pediatric hospitals, and death certificate records. Entries were subsequently confirmed or excluded based on additional information from patient records, according to the case definition criteria described above.

In May 2000 an active prospective populational surveillance system was implemented for the detection of cases of acute bacterial meningitis among underfives in Goiás state capital Goiânia, to which roughly 70% of all cases statewide are referred. All pediatric hospitals in the city were included in the enhanced surveillance. Demographical and clinical data were collected. The immunization status of children, including dates and number of doses of Hib vaccine was obtained from children's immunization cards.

Laboratory diagnosis followed WHO recommendations.[16] CSF was streaked on chocolate agar plates supplemented with factors X and V. Difco® antisera were used for serotyping *Haemophilus influenzae* isolates.

Incidence rates were calculated based on populational estimates obtained from the Brazilian Institute for Geography and Statistics (IBGE). Cases of meningitis due to *Streptococcus pneumoniae* and *Neisseria meningitidis* were used for comparison purposes. The number of prevented cases per etiological agent in the first and second years post-vaccine was estimated based on the cumulative incidence in the pre-vaccine period. A modified version of the analytical graphic method used at the Centers for Disease Control and Prevention (Atlanta, USA) for notifiable diseases was used to compare the number of cases of meningitis in the periods before and after the implementation of Hib vaccination.[3] According to this

Table 1 – Characteristics of acute bacterial meningitis cases in the pre-and post-vaccine periods.

Characteristics	Pre-vaccine (N=752) N (%)	95%CI	Post-vaccine (N=227) N (%)	95%CI
Age				
2-6 months	156 (20.7)	17.9-23.8	59 (26.0)	20.4-32.2
7-23 months	319 (42.4)	38.8-46.0	85 (37.4)	31.1-44.1
24-59 months	277 (36.8)	33.4-40.4	83 (36.6)	30.3-43.2
Mean (standard-deviation)	20.7 (15.5)		21.1 (17.9)	
Median	16		12	
Sex*				
Male	427(56.8)	53.1-60.3	134(59.0)	52.3-65.5
Female	325 (43.2)	39.7-46.9	92 (40.5)	34.1-47.2
Deaths	103 (13.7)	11.4-16.4	33 (14.5)	10.2-19.8
Hi 25 (24.3)	16.4-33.7	4 (12.1)	3.4-28.2	
SP 4 (3.9)	1.1-9.6	7 (21.2)	9.0-38.9	
NM	13 (12.6)	6.9-20.6	1 (3.0)	0.1-15.8
Other	3 (2.9)	0.6-8.3	3 (9.2)	1.9-24.3
pABM	58 (56.3)	46.2-66.1	18 (54.5)	36.4-71.9
Etiological agent**				
Hi	194 (25.8)	22.7-29.1	36 (15.9)	11.4-21.3
SP	20 (2.7)	1.7- 4.2	29 (12.8)	8.7-17.8
NM	79 (10.5)	8.5-13.0	22 (9.7)	6.2-14.3
Other	15 (2.0)	1.1-3.3	9 (3.9)	1.8-7.4
pABM	444 (59.0)	55.4-62.6	131 (57.7)	51.0-64.2

*Information missing for one case
**Hi: *Haemophilus influenzae*; SP: *Streptococcus pneumoniae*; NM: *Neisseria meningitidis*; pABM: probable Acute Bacterial Meningitis

method, the number of cases of meningitis during the pre-vaccine period was considered as the historic value (expected value), and was compared with the number of cases in the first and second years after the introduction of the vaccine (observed values). A bar chart was constructed using a vertical axis which crosses a horizontal logarithmic axis at the unit (point 1). Results were presented in terms of a ratio *r*, calculating the number of cases observed per etiological agent over the arithmetic mean of the number of cases expected. Over the horizontal axis, a horizontal bar was constructed for each etiological agent according to the value of *r*. Hatched bars extend either to the right or to the left of the vertical axis, depending on if the ratio was higher or lower than the unit, respectively. Confidence intervals, based on the normal distribution theory, were constructed for *r*, and the portion of the bar extending beyond these confidence intervals is represented by a blank bar. The number of cases exceeding the upper limit of the 95%CI was considered as the number of 'excess' cases, whereas values below the lower limit were considered as 'decreases'.

Comparisons between proportions were evaluated by χ^2 tests and differences between means by Student's t test. P-values below 0.05 were considered as statistically significant. Data analysis was carried out using SPSS (v. 10.0.1) and Epi Info 6.04d software.

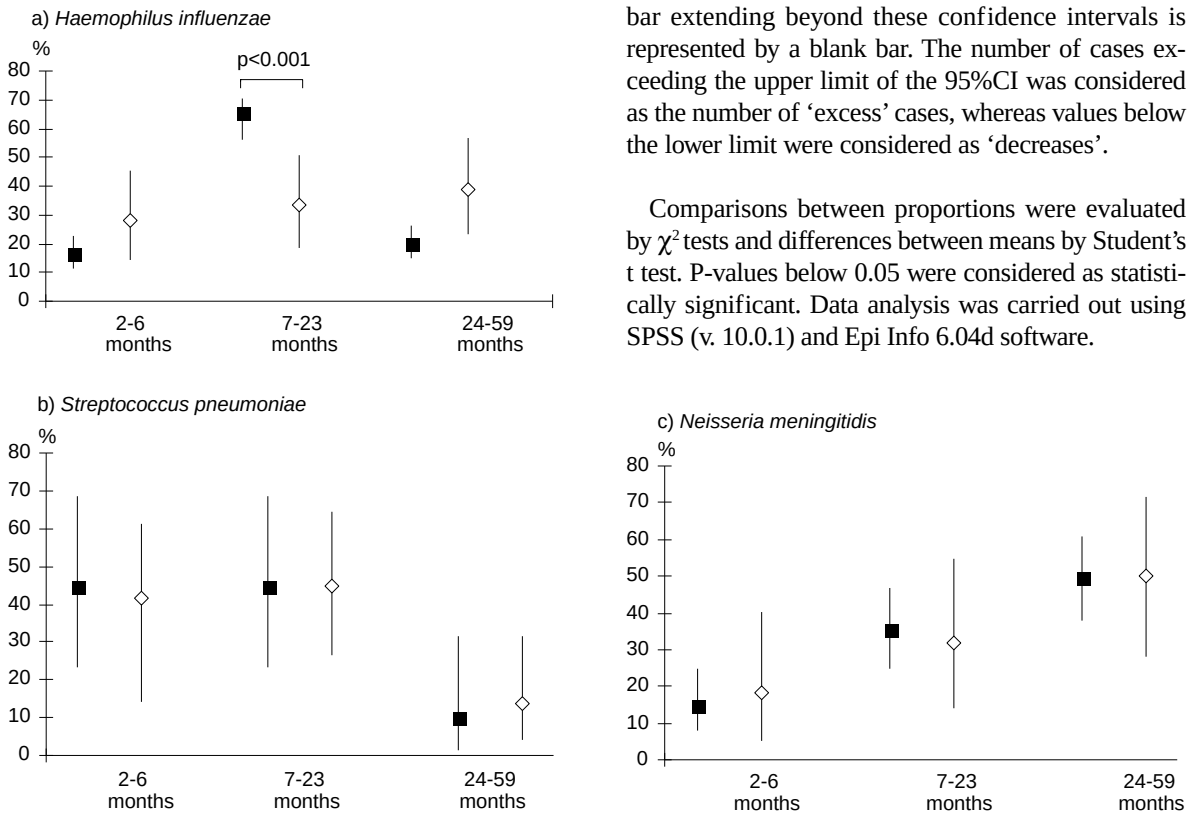

Figure 1 - Proportion of cases of bacterial meningitis according to age group, vaccine period, and etiological agent. Vertical lines represent the amplitude of the 95%CI. ■ = pre-vaccine period; ◊ = post-vaccine period.

Table 2 – Incidence rates and cases of meningitis prevented by vaccination.

	Haemophilus influenzae			*Streptococcus pneumoniae*			*Neisseria meningitidis*			Probable Meningitis		
	pre-vaccine*	post-vaccine 1st yr**	post-vaccine 2nd yr***	pre-vaccine	post- vaccine 1st yr	post- vaccine 2nd yr	pre-vaccine	post- vaccine 1st yr	post- vaccine 2nd yr	pre-vaccine	post- vaccine 1st yr	post- vaccine 2nd yr
Detected cases	48****	25	11	5	12	17	20	9	13	111	73	58
Incidence rate (x10^5)	10.8	5.3	2.3	1.1	2.6	3.6	4.4	1.9	2.7	24.8	15.7	12.2
Expected cases*****	-	50	51	-	5	5	-	20	21	-	115	118
Prevented/excess cases******	-	-25	-40	-	+7	+12	-	-11	-8	-	-42	-60

*July 1995 - June 1999: population in the 2-59 m age group =447,623
** July 1999 - June 2000: population in the 2-59 m age group =465,663
***July 2000 - June 2001: population in the 2-59 m age group =474,743
****Mean number of cases detected in the pre-vaccine period (July 1995 - June 1999)
*****(Incidence in the pre-vaccine period x denominator of the post-vaccine period / 100.000)
******(N of detected cases – N of expected cases). (-) = prevented; (+) = excess

RESULTS

Between July 1995 and June 2001, 979 cases of bacterial meningitis were detected in children aged two to 59 months in the State of Goiás, of which 752 were in the pre-vaccine period and 227 in the post-vaccine period (Table 1). There were no statistically significant differences between age groups in the pre- and post-vaccine periods. There was a greater proportion of male cases in both periods ($p<0.05$). The overall case fatality rate did not vary between the two periods. However, *H. influenzae* was the main cause of death in the pre-vaccine period, whereas no statistically significant differences were detected in the post-vaccine period. There was a decrease in the proportion of cases of meningitis caused by *H. influenzae*, from 25.8% in the pre-vaccine period to 15.9% in the post-vaccine period ($p<0,05$), especially in the seven to 23 months age group ($p<0,01$) (Figure 1). On the other hand, there was a significant increase in *S. pneumoniae* cases, from 2.7% to 12.8%.

The log scale bar chart in Figure 2 shows that the number of cases of Hib meningitis decreased 41% (expected 0.92 - observed 0.51) in the first 12 months after the introduction of the vaccine and 69% (expected 0.92 - observed 0.23) in the subsequent year. By contrast, the number of cases of meningitis caused by *S. pneumoniae* increased 98% (expected 1.42 - observed 2.40) in the first 12 months and 198% (expected 1.42 - observed 3.40) in the following year. The number of cases of meningitis caused by *N. meningitidis* fell 53% in the first post-vaccine period, and 33% in the second. The number of probable cases of meningitis fell 39% in the first post-vaccine period and 53% in the second.

A comparison of incidence rates in the pre-vaccine ($10.8x10^5$) and post-vaccine ($2.3x10^5$) periods shows a 78% reduction in the risk of Hib meningitis. There was a progressive increase in the risk of *S. pneumoniae* meningitis, from $1.1x10^5$ in the pre-vaccine period to $2.6x10^5$ in the first year and $3.6x10^5$ in the second year post-vaccine, a 227% increase. Furthermore, there was a reduction of 50.8% in the risk of probable meningitides between the pre-vaccine period and the second year post-vaccine. (from $24.8x10^5$ to $12.2x10^5$) (Table 2). In the post vaccine period, 65 cases of Hib meningitis and 102 cases of probable bacterial meningitis were prevented. Nineteen predicted cases of *N. meningitidis* failed to occur and there were 19 excess cases of *S. pneumoniae* meningitis (Table 2).

Seven cases of meningitis caused by *H. influenzae* occurred in children who had received at least one

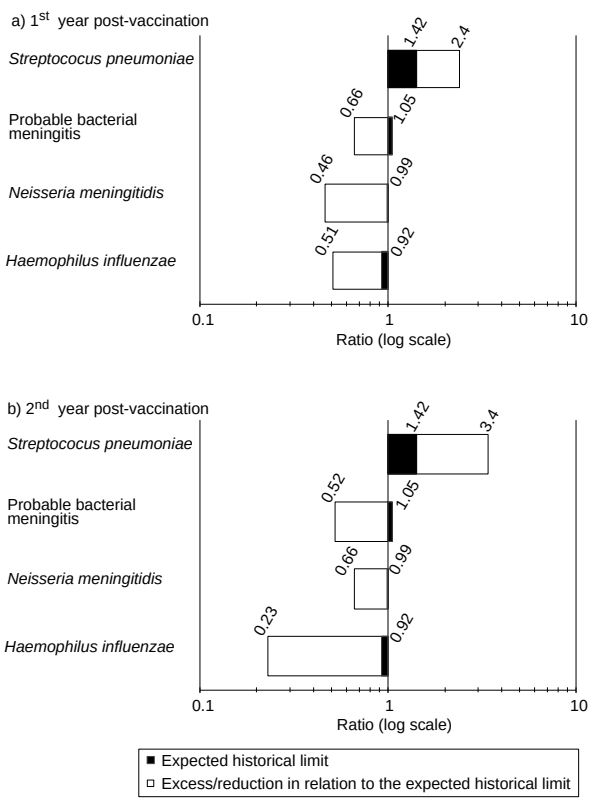

Figure 2 - Bar chart for assessing excess or reduction in number of cases in 12 months in relation to historical values (July 1995 - June 1999), by etiological agent.

dose of the Hib vaccine. *H. influenzae* type "a" was detected in three of these cases. Vaccine failure was observed in a single case. This was a child over one year old, without chronic diseases or immunodeficiencies, who had received three doses of the vaccine, and who presented with Hib meningitis 16 months after receiving the last dose of the vaccine.

DISCUSSION

The present study shows an important reduction in the number of cases of Hib meningitis after the first year of anti-Hib vaccination. The reduction in the risk of meningitis – 51% in the first year and 78% in the second year post-vaccine – was significantly higher in the seven to 23 month age group, which is consistent with the protective immune response acquired after the third dose (sixth month of life).[8] A comparison of the risk of Hib meningitis before vaccination ($10.8x10^5$) and after the second year post-vaccine ($2.3x10^5$) shows that this risk was 4.7-fold greater in the former period. In Brazil, few publications have measured the role of Hib as an etiological agent of meningitides in childhood before the introduction of the conjugate vaccine. The risk of Hib meningitis found for the pre-vaccine period was similar to that observed in Campinas, southeastern Brazil ($17x10^5$), and is comparable to those found in European countries such as Austria, Spain, and England.[9,14] The impact of the Hib vaccination has also been evaluated in other Brazilian regions. In Curitiba, southern Brazil, the incidence of meningitis dropped from 35.5 to $9.7x10^5$ (72% reduction), one year after the introduction of the vaccine.[13] In Salvador, northeastern Brazil, similar results were found (69% reduction) after the first year of vaccination.[12]

There was a significant reduction in the number of probable acute bacterial meningitis (pABM) cases in the post-vaccine period, most likely due to the implementation of the surveillance system as well as to the accuracy of diagnostic tests. We may thereby infer that, in the pre-vaccine period, many of the cases labeled as 'probable' were caused by Hib. However, high rates of probable cases still persist, which may be explained by the practice of self-medication, including the use of antimicrobials.[1] Considering that the sensitivity of the prospective surveillance component was greater than that of the retrospective component, the incidence rate in the pre-vaccine period was probably higher than that observed, and, therefore, vaccination impact may have been underestimated. It is well established that the effectiveness of vaccination also depends on vaccine coverage. In the state of Goiás vaccine coverage was 78% in the first year and 90% in the second year after implementation* which may have contributed towards the progressive reduction in the incidence of Hib meningitis.

In the present study, we observed an increase in the incidence of *S. pneumoniae* meningitis in the post vaccine period. Some investigators have raised the possibility that other serotypes of *H. influenzae*, and even *S. pneumoniae* itself may be occupying the ecologic niche left open by Hib.[7] Our results show that the increase in the incidence of *S. pneumoniae* meningitis began already two years before the introduction of the Hib vaccine. It is therefore unlikely that the increase in pneumococcal meningitis has occurred as consequence of the effect of Hib vaccination on the reduction of Hib nasopharyngeal carriage. Such increase may be due to the diagnostic methods implemented after 1998. Only the continuous and efficient surveillance of bacterial meningitides will be able to provide evidence of the current increase of *S. pneumoniae* in the etiology of bacterial meningitis.

Recent studies have documented the emergence of invasive diseases caused by non-*b H. influenzae* as well as by the unencapsulated strains, and even the reemergence of Hib, causing concern among researchers in regions where the vaccine has been introduced over a decade ago.[4] In Brazil, the appearance of serotype *a* after the introduction of Hib vaccination has recently been documented.[12] In the United Kingdom, the combination of Hib and acellular diphtheria-tetanus-pertussis vaccine and the use of a accelerated scheme, with one-month intervals between doses and without a booster dose, are among the hypotheses proposed to explain the reemergence of Hib in the UK in the last four years.[10] The vaccination schedule adopted in Brazil does not include a booster dose after 12 months, which should be taken into consideration by the surveillance system in order to monitor a possible reemergence of Hib. These findings reinforce the need for maintaining an efficient surveillance system in the post-vaccine period, since a new epidemiological scenario of invasive diseases due to *H. influenzae* has been revealed, thus requiring the definition of new laboratory strategies for the detection and serotyping of *H. influenzae*.

The potential limitations of surveillance systems have recently been underscored. In this sense, when evaluating the incidence of meningitis after routine vaccination, the sensitivity and specificity of the clinical definition of cases and of laboratory tests is crucial. If the specificity of case definition is low, when the actual incidence decreases, the predictive value of diagnostic tests also decreases, and the proportion of false-positive *H. influenzae* diagnoses increases. Fur-

*Data provided by the Goiânia Municipal Secretariat of Health and by the Brazilian Ministry of Health, 2001.

thermore, a recent study[2] of *H. influenzae* isolates obtained from different Brazilian regions showed discordant results between routine serotyping (latex agglutination) and the PCR technique, considered as the gold standard. The results of this study ratify the need for a reevaluation of the laboratory procedure protocols used in *H. influenzae* serotyping. Correct identification of *H. influenzae* is essential in order do minimize biases when monitoring alterations in the incidence of invasive Hib infections in the post-vaccine period and when estimating the long-term impact of Hib vaccination.

The present study evaluated the effectiveness of Hib vaccination in the state of Goiás, in central Brazil, detecting a significant impact on meningitis. Active continuous surveillance is now needed in order to monitor changes in the epidemiological pattern of meningitides and a possible reemergence of Hib. An increase in the mean age of cases of Hib meningitis may occur, so new strategies for control should be adopted. Surveillance will also be useful in detecting decreases in vaccine coverage and cases of vaccine failure, with implications on the need for a booster dose after the child's first year of life. Cases of meningitis caused by non-*b* or by unencapsulated strains of *H. influenzae*, along with alterations in the incidence of pneumococci and meningococci must also be monitored. Finally, an efficient surveillance system will also provide an epidemiological baseline for the evaluation of the impact of conjugate vaccines against *S. pneumoniae* and *N. meningitidis* C.

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