

## *Haemophilus influenzae type B meningitis: Is there a re-emergence? 24 years of experience in a children's hospital*

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### ABSTRACT

**Introduction.** *Haemophilus influenzae* type B (Hib) used to be the main cause of bacterial meningitis in children younger than 5 years old. Following the introduction of the Hib vaccine in the immunization schedule (1998), its incidence reduced significantly but it has increased over the last years. The objectives of this study included describing the characteristics and analyzing the epidemic curve of *Haemophilus influenzae* type B (Hib) meningitis by comparing the pre- and post-immunization periods.

**Material and methods.** Time-series study. All patients hospitalized with Hib meningitis at Hospital de Niños "R. Gutiérrez" (January 1992-May 2016). Hospitalization rates were compared before (pre-immunization) and after (post-immunization) the introduction of the Hib vaccine. The post-immunization period was divided into three similar periods.

**Results.** Eighty-five patients with Hib meningitis were admitted (73.3% in the pre-immunization period). No differences were observed in relation to the clinical and sociodemographic characteristics of cases in both periods. Pre-immunization: 10.5 cases/year; post-immunization: 0.7 cases/year. As of 2014, the rate has increased. Lethality rate: 4.8% (all pre-immunization). Post-immunization data (n=15): 40% had completed their primary immunization schedule, 40% were delayed on the immunization schedule for their age. Overall reduction in the hospital rate of Hib meningitis by 89.8% (95% confidence interval: -82.79-93.96%, p < 0.001) in the post-immunization period. The analysis of the different post-immunization periods shows a decline in reduction over time.

**Conclusions.** A very significant reduction in hospitalizations due to Hib meningitis was observed after the Hib vaccine was introduced; however, over the past years, the number of cases has increased although no changes have been observed in patient characteristics.

**Key words:** *Haemophilus influenzae type B, vaccines, time-series studies.*

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### INTRODUCTION

*Haemophilus influenzae* type B (Hib) is a Gram-negative coccobacillus, and humans are its exclusive hosts. Hib pharyngeal colonization is relatively common, especially by non-typeable isolates (30-90%) and encapsulated non-b-type serotypes. In the pre-immunization era, the Hib carriage rate ranged between 3% and 5%.<sup>1,2</sup> Its main reservoir are infants and toddlers who carry the microorganism in their upper airways;<sup>1,3,4</sup> overcrowding, attendance to a day care center, and living with a person with invasive disease are the factors associated with higher Hib carriage rates and disease.<sup>5</sup>

In Argentina, before the introduction of the vaccine, Hib was the main cause of bacterial meningitis documented in children younger than 5 years old, with a mortality rate of approximately 5% (in spite of adequate treatment) and neurological sequelae in about 25-35% of patients.<sup>6</sup>

The first countries of America that introduced the Hib vaccine were Chile (1994) and Uruguay (1996).<sup>7</sup> The World Health Organization recommended it in 1997 and, by the end of 2015, it had been introduced in 191 countries.<sup>4,8</sup>

At present, the worldwide coverage with 3 doses of Hib vaccine is 64% but there are major disparities among regions. In the Americas, coverage is estimated at 90% whereas, in the Western Pacific and South-East Asia, it is only 25% and 56%, respectively.<sup>8</sup>

Since the introduction of the Hib vaccine (as a quadrivalent conjugate vaccine) in the Argentine immunization schedule in 1998, the

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number of cases reduced significantly from 400 cases per year to 16 cases in 2006 (national rate lower than 0.1 case / 100 000 inhabitants sustained from 1999 to 2011).<sup>9</sup> Such phenomenon may be explained not only by the vaccine itself but its herd effect. As of 2005, the Hib vaccine has been administered as a pentavalent vaccine. In the private health sector, the combined acellular pertussis vaccine is administered; however, the percentage of the population receiving the latest combinations is so low that it does not influence national coverage.<sup>10</sup>

In the setting of the National Epidemiological Meningitis Surveillance Program of Hospital de Niños Ricardo Gutiérrez (HNRG), suspected cases are reported daily in an individual and immediate manner. In Argentina, over the past years, the number of reported Hib meningitis cases has increased.<sup>11</sup> Consistently with the latest report by the Surveillance System for Bacterial Agents Responsible for Pneumonia and Meningitis (Sistema de Redes de Vigilancia de los Agentes Bacterianos Responsables de Neumonía y Meningitis, SIREVA II), 51 Hib meningitis cases were reported in 2014; 76.4% of patients were younger than 12 months old, and 96%, younger than 24 months old. According to the report, type B is still the most common serotype (47.7%) isolated in *Haemophilus influenzae* invasive disease.<sup>12</sup>

Faced with the hypothesis that invasive disease may be re-emerging, the objectives of this study included describing the characteristics of patients with Hib infection and analyzing the epidemic curve of Hib meningitis cases by comparing the pre- and post-immunization periods.

## MATERIAL AND METHODS

This was a quasi-experimental, epidemiological study with time-series of Hib meningitis cases.

Inclusion criteria: all patients hospitalized and diagnosed with Hib meningitis detected through the National Epidemiological Meningitis Surveillance Program of HNRG between January 1992 and May 2016 (24-year period).

The HNRG is a children's tertiary care facility that provides services mostly to patients from the Autonomous City of Buenos Aires (CABA) and the metropolitan area of the province of Buenos Aires.

Exclusion criteria: a) patients with bacterial meningitis without Hib rescue or with rescue of other microorganisms; b) patients with hospital-acquired meningitis.

## Diagnostic methods

Hib meningitis diagnosis was based on the following:

- a) Clinical assessment: presence of signs and symptoms indicative of acute meningitis, and/or
- b) Cerebrospinal fluid (CSF) analysis: CSF cytochemistry, Gram stain, rapid antigen detection test, and culture, and/or
- c) Other bacterial tests (blood culture).

Given the severity of some cases, it was not possible to perform a lumbar puncture, but patients were included based on clinical and laboratory confirmation.

## Theoretical definitions

- Comorbidities: any primary or acquired immune deficiency.
- Complications: neurological (hydrocephalus, brain abscess, subdural fluid collection, paresis, cerebral palsy, persistent seizures or seizures lasting beyond 72 h); non-neurological (suppurative and non-suppurative meningitis).
- Status on discharge: deceased, discharged with sequelae, discharged without sequelae.

After discharge, patients were not followed-up for long-term sequelae.

*Case:* clinical condition and / or CSF cytochemistry compatible with bacterial meningitis and identification of specific capsular polysaccharides or Hib isolation in CSF and / or blood.

Data were collected in an epidemiological card, including date of admission, demographic data, date of symptom onset, personal history and history of current disease, immunization status, CSF and blood culture findings, complications and course during hospitalization, and length of stay.

In this study, the 1992-1997 period was defined as the pre-immunization period, and 1999-2016 was established as the post-immunization period. The intervention was carried out in 1998, so it was excluded from the time-series analysis but not from the descriptive case analysis. The post-immunization period was divided into three similar periods for series comparison purposes (1<sup>st</sup>: 1999-2005; 2<sup>nd</sup>: 2006-2011; 3<sup>rd</sup>: 2012-2016).

## Data analysis

A descriptive analysis was done in the first place to estimate the median and interquartile range of continuous outcome measures. The Mann-Whitney statistical test was used for median differences. Ratios and their

corresponding 95% confidence intervals (CIs) and the  $\chi^2$  test with Yates' correction were used for categorical data. Analysis was done using Epi Info v. 7 (CDC, Atlanta). An alpha error below 5% was considered significant. Reductions in hospitalization rates for each post-immunization period were estimated as absolute risk reduction.

## RESULTS

Between 1992 and 2016, 85 patients with Hib meningitis were admitted (Figure 1). Of these cases, 73.3% occurred in the pre-immunization period; the highest number was observed in 1993 (19 cases) (Figure 2).

The clinical and sociodemographic characteristics of cases were compared for both periods, excluding 1998 (transition year). No patient showed immunosuppression in any period. A CSF cytochemistry sample was obtained from 70 patients (82.3%) (Table 1).

In the pre-immunization period, the average hospitalization rate due to Hib meningitis was 10.5 cases per year. Hib meningitis cases were sporadic in the post-immunization period, with an average of 0.7 cases/year; however, as of 2014, the number of hospitalized patients has increased (Figure 2).

Mortality across the entire series period was 4.8%; 4 patients died, all between 1992 and 1998.

Immunization data were obtained for the 15 cases occurred between 1999 and 2016: 6/15 had completed their primary immunization schedule with 3 doses (2 had completed it in a delayed manner). Six children were delayed on the schedule for their age, and 4 out of 6 had received less than 3 doses.

An overall reduction by 89.8% was observed in Hib meningitis cases per 10 000 hospital discharges (95% CI: -82.79-93.96%,  $p < 0.001$ ) in the period following the Hib vaccine introduction.

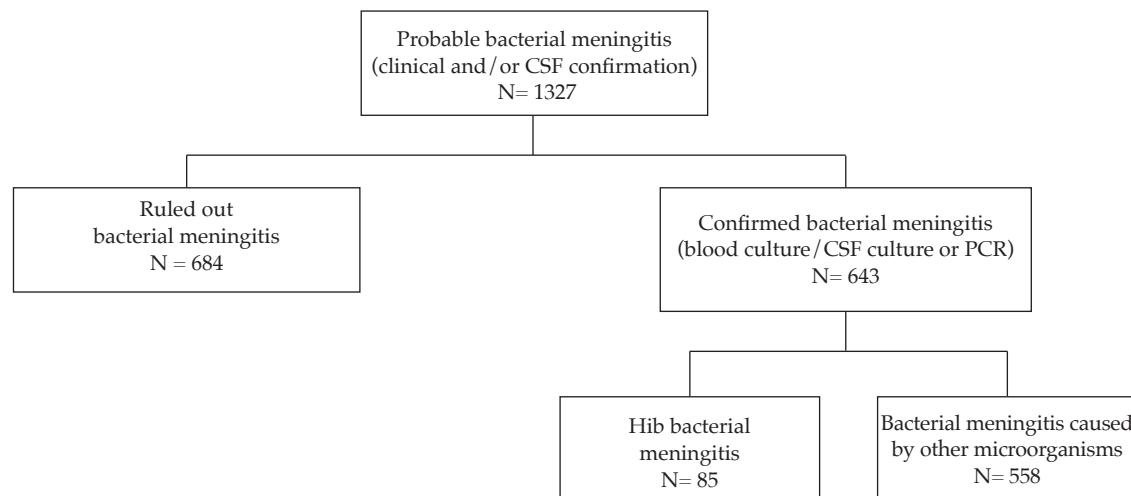
Once the different post-immunization periods were analyzed, it was observed that such reduction decreased over time (Figure 3).

Differences in case reduction were significant once the first and the third post-immunization periods were compared.

## DISCUSSION

This study shows the impact of the Hib vaccine following its introduction in our population and the increase in Hib meningitis cases in the past 3 years. This is consistent with what has been observed at a local level<sup>13</sup> and also worldwide, with a major impact over the past 20 years and sporadic invasive cases.<sup>14</sup> An active and constant epidemiological surveillance of notifiable disease reports helps us establish the patterns of different diseases and any changes in such

FIGURE 1. Flow chart of case screening and inclusion process



CSF: cerebrospinal fluid; PCR: polymerase chain reaction; Hib: *Haemophilus influenzae* type B.

patterns for the purpose of making fundamental public health decisions. In the setting of the surveillance program of HNRG, a re-emergence of Hib meningitis was observed and its characteristics and course were identified.

No statistically significant differences were observed in the study population between the pre- and post-immunization periods in terms of sociodemographic characteristics and clinical course that may have accounted for the increased rate. The median age in both periods is within the

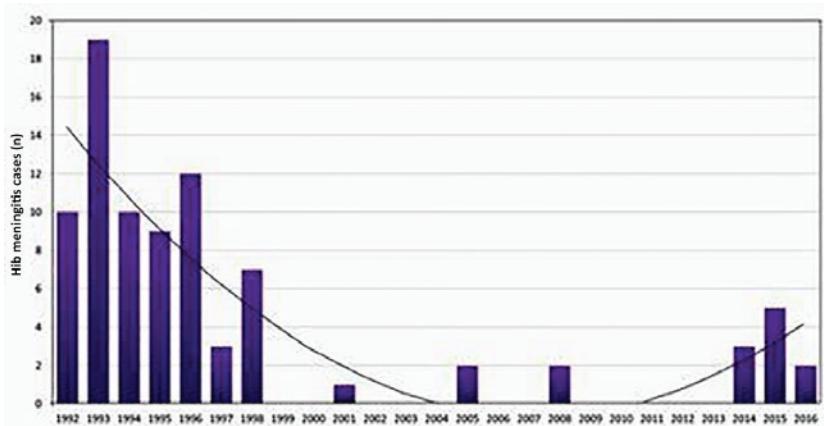
expected age range for the peak incidence of this disease, 6-18 months old<sup>4</sup> (most at < 12 months old).<sup>14,15</sup> The differences observed in relation to microorganism rescue as per culture medium (blood or CSF) may be the result of the fact that this is a tertiary care facility for the referral of patients from the Metropolitan area that have already started an intravenous antibiotic treatment. The results of this study are consistent in terms of Hib meningitis mortality (5%) and sequelae (20-60%).<sup>3</sup>

TABLE 1. Characteristics of cases by immunization period. Hospital de Niños "Ricardo Gutiérrez" (N= 78)

Characteristics of the population	Pre-immunization period, 1992-1997 (n= 63)	Post-immunization period, 1999-2016 (n= 15)	OR (CI)	P
Clinical and sociodemographic characteristics				
Age in months (median, IQR)	8 (6-12)	9 (4-18)	----	0.10
Male sex (%)	68.2 (43)	60 (9)	1.43 (0.44-4.57)	0.76
Place of origin (province of Buenos Aires) (%)	67.2 (41)	71.4 (10)	1.21 (0.34-4.37)	0.98
Referral from other hospital (%)	22.2 (14)	33.3 (5)	0.57 (0.16-1.94)	0.57
Course during hospitalization				
Length of stay in days (median, IQR)	15 (11-18)	16 (15-20)	----	1.0
Complications (%)				
Total	53.9 (34)	50 (6)	1.17 (0.34-4.03)	0.94
Neurological	76.4 (26)	66.6 (4)	1.62 (0.24-10.57)	1.0
Sepsis/septic shock	8.8 (3)	16.6 (1)	0.48 (0.04-5.62)	0.88
Septic arthritis	5.8 (2)	16.6 (1)	0.31 (0.02-4.11)	0.93
Sequelae (%)	26.6 (16)	7.1% (1)	4.72 (0.57-39.1)	0.22
CSF characteristics (n= 70)				
Cellularity (range)	20 not measurable	3 not measurable	---	---
CSF glucose level in g/dL (median, IQR)	10 (5-32)	12 (5-46)	---	0.47
CSF protein level in mg/dL (median, IQR)	115 (71-181.5)	143 (87-191)	---	0.57
Culture				
Positive CSF culture (%) (n= 68)	95.2 (60)	53.3 (8)	17.5 (3.74-81.68)	< 0.001
Positive blood culture (%) (n= 45)	58.9 (33)	85.7 (12)	0.23 (0.04-1.17)	0.11

OR: odds ratio, CI: confidence interval; IQR: interquartile range; CSF: cerebrospinal fluid.

FIGURE 2. Time-series of Haemophilus influenzae type B meningitis cases. Hospital de Niños "Ricardo Gutiérrez". 1992-2016 (N= 85)



Hib: *Haemophilus influenzae* type B.

In this series, the number of Hib meningitis cases reduced dramatically in the post-immunization period, similarly to the reduction observed in other countries that introduced the Hib vaccine in their immunization schedules.<sup>15-18</sup>

However, Hib meningitis has increased in several countries years after the vaccine introduction.<sup>14,19</sup> Such increase may be explained by several factors, including a reduction in indirect protection or herd effect, a decrease in antibody titers among children vaccinated before turning 1 year old who did not receive a booster dose, emergence of more virulent or contagious strains, or differences in vaccine types that many times result in programmatic errors.

The herd effect is achieved with the booster dose after 1 year old.<sup>20,21</sup> As per the research conducted by Ramsay<sup>22</sup> and Landhani,<sup>23</sup> this booster dose contributes to at least one third of the reduction observed in the post-immunization period. It is worth noting that almost 20% of children living in the geographic area where most patients in this study come from do not receive the booster dose.

It is also worth considering that antibody titers decrease in children vaccinated before 1 year old (primary schedule) compared to those who receive the booster dose between 1 and 4 years old.<sup>23</sup> In the absence of a booster dose, vaccine-induced antibody titers reduce in the following 2-3 years.<sup>24</sup>

Booy<sup>25</sup> has studied all invasive Hib disease cases occurred in the 3 years following the administration of at least 1 dose of the conjugate

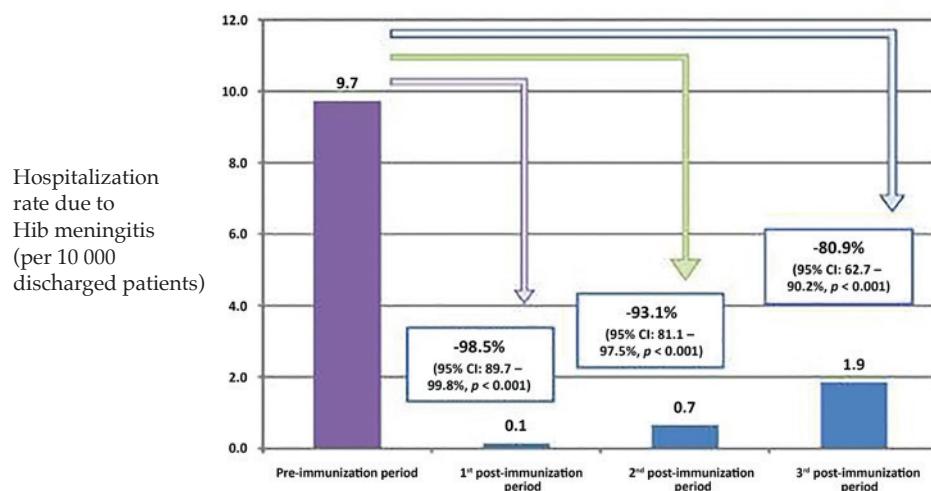
Hib vaccine among children from the United Kingdom and identified two types of vaccine failure: apparent (early) and true (late).

Considering the severity of this disease, it is worth studying the host's specific predisposing factors, genetics, natural immunity pattern, and nasopharyngeal carriage prevalence. In our study, no clinical immunosuppression was detected.

There is no conclusive evidence regarding differences in the immune response against combined or monovalent conjugate Hib vaccines.<sup>26</sup> Notwithstanding this, data indicate that combined acellular vaccines (diphtheria, tetanus and acellular pertussis [DTaP]/Hib) lead to a smaller humoral response than cellular vaccines (diphtheria, tetanus and whole-cell pertussis [DTwP]/Hib) or than the co-administration of the monovalent conjugate Hib vaccine and the acellular vaccine (DTaP).<sup>16,21</sup>

Given the increased number of cases among British children in relation to the generalized use of the combined acellular vaccine (DTaP/Hib), antibody titers against polyribosylribitol phosphate (PRP) and avidity were studied before and after the Hib booster dose in 176 children aged 2-4 who had received 3 doses of DTP/Hib (either cellular or acellular) during infancy. Patients who received the primary immunization schedule of DTaP/Hib had a 50% lower antibody titer than those who received the first 3 doses of DTwP/Hib. Hib carriage was 2.1% among studied participants, which means it was circulating in this susceptible age group.<sup>27</sup>

FIGURE 3. Case reduction by period



Hib: *Haemophilus influenzae* type B; CI: confidence interval.

Hib re-emergence has also been observed in countries using the cellular vaccine, e.g., Chile, which introduced a booster dose at 18 months old in 2006, after Hib invasive disease cases increased.<sup>28</sup>

In Germany, the effectiveness of hexavalent vaccines (DTaP / hepatitis B virus [VBV] / inactivated polio vaccine [IPV] / Hib) was 90.4% for the primary series and 100% for a complete primary series plus a booster dose.<sup>29</sup> The effectiveness of a combined DTaP / Hib schedule at 3, 5, and 11 months old has also been adequate in Sweden, where the incidence among children younger than 4 years old was 0.4/100 000 between 2005 and 2008.<sup>30</sup>

These results compel to conduct studies with both vaccines to measure their effectiveness and provide public health tools.

Virulence is another factor to be taken into consideration. Luscher described a series of Alaskan cases related to a Hib strain that was more virulent and contagious.<sup>31</sup>

This study poses certain limitations. Patients were not followed-up in the long-term so they might have developed late sequelae that were not reported. In addition, given that this is a hospital-based study, it is not possible to infer results in the actual population. Other sociodemographic outcome measures that may have influenced results were not analyzed, e.g., socioeconomic level, housing conditions, overcrowding, attendance to a day care center or kindergarten, number of people sharing the household and their age.

## CONCLUSION

A very significant reduction in hospitalizations due to Hib meningitis was observed after the Hib vaccine was introduced; however, over the past years, the number of cases has increased but there have been no changes in patient characteristics. ■

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