

EFFICACY OF HAEMOPHILUS INFLUENZAE TYPE B VACCINE AND ITS IMPACT ON THE REPRESENTATION OF CAUSATIVE AGENTS OF BACTERIAL MENINGITIS IN CHILDREN

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Objective - Research was undertaken with the aim of analyzing the frequency of causes of bacterial meningitis (BM) in children before and after introduction of the conjugate vaccine against Haemophilus influenzae type b (Hib vaccine), and to analyze the age of patients and disease outcome.

Materials and methods - Data from the medical records of patients, age 1 month to 14 years, who were treated for BM at the Infectious Diseases Clinic Tuzla, in the period from 01.05.1999 to 30.06.2009 were analyzed as a retrospective cohort study. In relation to the introduction of the Hib vaccine the patients were divided into prevaccinal and postvaccinal periods.

Results - 140 children were treated for BM. The most common pathogens were Haemophilus influenzae (13.6%), Neisseria meningitidis (8.6%) and Streptococcus pneumoniae (5.7%). In the prevaccinal period there were 94 and in the postvaccinal 46 children (13 of them had been vaccinated). The number of BM cases decreased from 17.1 (prevaccinal period) to 10.2 (postvaccinal period) per year. The number of children hospitalized with BM caused by Neisseria meningitidis significantly decreased in the postvaccinal period (Fisher's exact test, $p=0.009$), and Streptococcus pneumoniae was the most common cause of BM in the postvaccinal period (Fisher's exact test, $p=0.015$). The frequency of Haemophilus influenzae as a cause of BM also significantly decreased in the postvaccinal period (Fisher's exact test, $p=0.034$). Eleven children were under one year, and eight children were from one to five years of age. Three children died.

Conclusion - The most common causes of BM in children aged 1 month to 14 years were Haemophilus influenzae, Neisseria meningitidis and Streptococcus pneumoniae. After the introduction of Hib vaccine the number of BM cases caused by Haemophilus influenzae and the total number of BM cases was reduced.

Introduction

Bacterial meningitis (BM) is an acute purulent inflammation of the soft membranes of the brain and spinal cord caused by bacteria. It is the most serious pediatric infectious disease, which even today is an important cause of morbidity and mortality. Sequelae such as hearing loss, blindness, seizures, hydrocephalus, intrauterine growth and motor deficits are not rare after recovering from the disease (1).

The three main causes of BM are *Haemophilus influenzae* type b, *Streptococcus pneumoniae* and *Neisseria meningitidis*. These bacteria cause meningitis in children older than 4 weeks in more than 90% of cases (2). At the age of one month to five years in the United States (U.S.), *Haemophilus influenzae* type b was the most common cause of BM (3). However, the use of the conjugate vaccine against *Haemophilus influenzae* type b (Hib vaccine) has reduced the incidence of invasive diseases caused by the bacterium almost up to their complete elimination (2). In countries where the use of the Hib vaccine was introduced, *Streptococcus pneumoniae* is the most common cause of BM in children (4). Children younger than 2 years run the greatest risk of BM caused by *Streptococcus pneumoniae* (5). The incidence of meningitis caused by *Neisseria meningitidis* is highest in children younger than 1 year and a second peak of incidence of meningitis caused by this bacteria is between 15-17 years of age (6).

Since the 1990-ies, many countries have introduced the Hib vaccine into the regular immunization calendar for children (7). In the Tuzla Canton the conjugated Hib vaccine was introduced into the regular immunization calendar in January 2005.

In the U.S., before the use of the Hib vaccine, more than 70% of BM in children younger than 5 years was caused by *Haemophilus influenzae* type b (4). Published data from the U.S. show that the incidence of BM in children youn-

ger than 5 years decreased from 25/100,000, in 1984, to less than 2.5/100,000 after the introduction of the Hib vaccine in 1988 (8). In European countries there was also a reduction in the incidence of meningitis and other invasive diseases caused by *Haemophilus influenzae* type b after the introduction of the Hib vaccine. Thus, in Iceland after the introduction of the Hib vaccine in 1989, the disease caused by the bacteria disappeared within 3 years, in the Netherlands the incidence decreased to 0.3/100,000, while in Switzerland, where the earlier incidence of meningitis was the highest in Europe, after the introduction of the Hib vaccine it fell to 5.7/100,000 in 1993. In the UK, the Hib vaccine was introduced in 1992, and the incidence of disease caused by *Haemophilus influenzae* type b in children aged 0-4 years decreased to 2/100,000, or the total reduction was greater than 97% (2).

Instead of *Haemophilus influenzae* type b, which was the leading cause of bacterial meningitis in the U.S., after the introduction of the Hib vaccine, the order of causative agents of meningitis was as follows: *Streptococcus pneumoniae*, *Neisseria meningitidis*, *Streptococcus agalactiae*, *Listeria monocytogenes*, and *Haemophilus influenzae* type b (4), while in children in England and Wales, the most common causes of meningitis were *Neisseria meningitidis*, *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Streptococcus agalactiae*, *Escherichia coli*, *Listeria monocytogenes* and *Staphylococcus* (9).

The aim of this study was to examine the prevalence of BM pathogens in patients treated at the Infectious Diseases Clinic in the period from 1999 until 2009, and determine the prevalence of pathogens of BM before and after the introduction of the Hib vaccine into the regular immunization calendar for children in the Tuzla Canton. The second aim was to determine the distribution of patients in relation to age and disease outcome.

Materials and methods

By a retrospective cohort study we analyzed data gathered from the medical records of the Infectious Diseases Clinic in Tuzla, of patients 1 month to 14 years of age with the diagnosis of BM, in the period from 01.05.1999. to 30.06.2009. Data from the medical records were analyzed about the age and sex of patients, the bacterial etiology of meningitis, data about the vaccination against *Haemophilus influenzae* type b, and the outcome of the disease.

Diagnosis of BM was based on medical history and clinical features (fever, vomiting, headache, photophobia, food refusal, irritability, crying cries, different degrees of consciousness, seizures, a characteristic skin rash, prominent and tense fontanelle and positive meningeal signs) and laboratory findings (elevated sedimentation rate, leukocytosis in blood count with neutrophilia, positive C-reactive protein, blood glucose, and biochemical, cytological and microbiological findings of CSF).

We considered that the patient had BM if in addition to positive history and clinical findings, he also had findings in CSF as: $\geq 1000/\text{mm}^3$ polymorphonuclear cells /neutrophils, if the concentration of protein was ≥ 1 g/l, and glucose concentrations were lower (usually less than 70% of blood glucose) (10). To confirm the diagnosis of BM, findings of CSF culture were used, although negative findings did not exclude BM. Serotyping of causative agents of meningitis was not done, because that kind of analysis is not performed at our laboratory.

Patients were divided into two groups in relation to the timing of introduction of the Hib vaccine, ie two periods: the prevaccinal period (subjects treated for BM at the Infectious Diseases Clinic in Tuzla before the introduction of the Hib vaccine, ie from 01.05.1999 until 31.01.2005) and the period after introduction of the vaccine (patients

treated for BM at the Infectious Disease Clinic in Tuzla after the introduction of the Hib vaccine, ie from 01.02.2005 until 30.06.2009).

Statistical analysis

Results are given in absolute and relative numbers. Categorical variables were analyzed by Fisher's exact test. The difference between samples was considered significant if $P < 0.05$. Data were analyzed using the statistical software SPSS 17.0 (Chicago, IL, USA).

Results

In the ten-year period (from 01.05.1999 until 30.06.2009) 140 children with BM were treated at the Infectious Diseases Clinic, University Clinical Centre, Tuzla. In 49 children (35%) the causes of BM from CSF were isolated. *Haemophilus influenzae*, *Neisseria meningitidis* and *Streptococcus pneumoniae* were notably the most common causes (Figure 1).

In the prevaccinal period 94 patients suffered from BM and in the period after the introduction of the Hib vaccine, 46. None of the patients in the prevaccinal period had been vaccinated, whereas in the period after the introduction of the Hib vaccine of the 46 patients, 13 (28.3%) had been vaccinated.

The number of patients with BM in the postvaccinal period decreased from 17.1 to 10.2 cases per year compared to the prevaccinal period. Also, in the two observed groups the distribution of pathogens changed (Figure 2). The number of hospitalized patients who suffered from meningitis caused by *Neisseria meningitidis* was found to be statistically significantly reduced (Fisher 'exact test, 2 sided $p = 0.009$) in the period after the introduction of the Hib vaccine, compared to prevaccinal period, while *Streptococcus pneumoniae* was a significantly more common cause of BM in the period after the introduction of the Hib vaccine compared to the

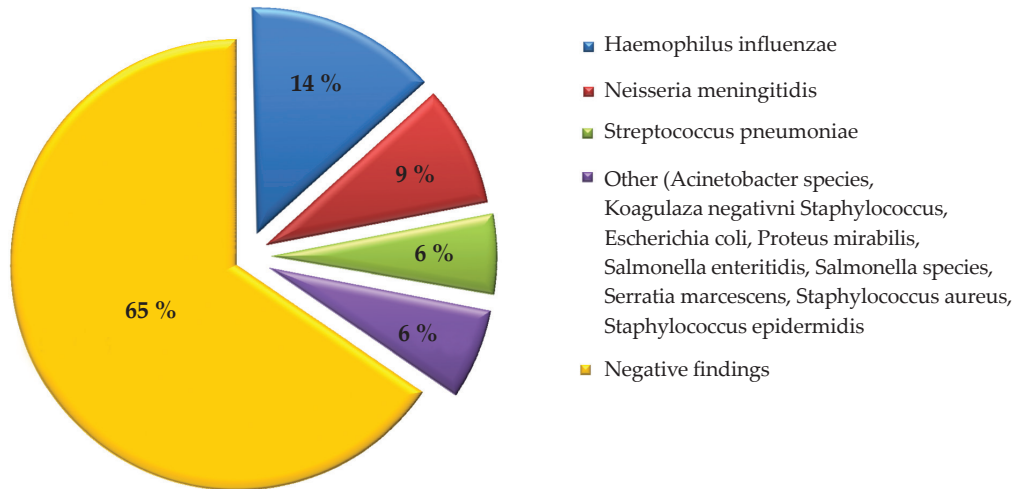


Figure 1 Frequency of pathogens isolated from cerebrospinal fluid

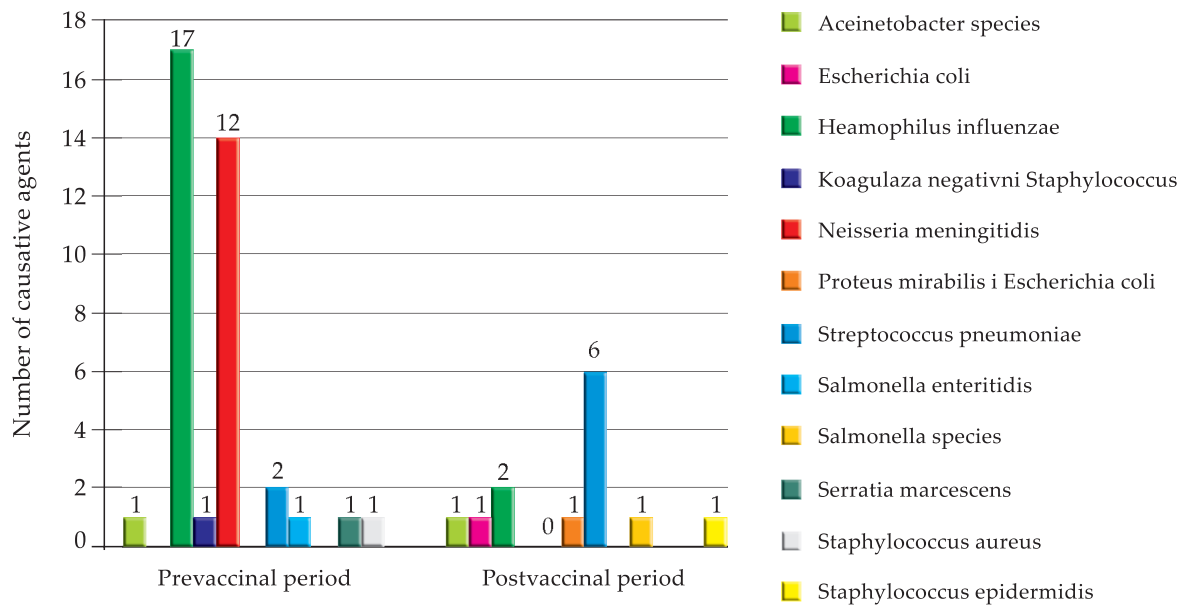


Figure 2 Distribution of pathogens of bacterial meningitis in prevaccinal and postvaccinal period

prevaccinal period (Fisher 'exact test, 2 sided $p = 0.015$).

The frequency of *Haemophilus influenzae* as a cause of BM decreased in the period after the introduction of the Hib vaccine compared to the prevaccinal period, from 17 (18.1%) to 2 (1.4%) cases, and this difference was statistically significant (Fisher 'exact test, 2 sided, $p = 0.034$). None of these 19 patients who had *Haemophilus influenzae* isolated from CSF had been vaccinated with the Hib vaccine. Eleven children were aged one year, and eight from one to five years.

There were 3/140 or 2.1% deaths during the period studied. The two patients who died were females of 8 months and 13 years of age, and the causative agent was not isolated from their CSF, and the third who died was a male, 5 years of age and *Haemophilus influenzae* was isolated from his CSF. This patient was not vaccinated with the Hib vaccine.

Discussion

In our study, in the ten-year period observed, the most common causes of BM isolated from CSF were *Haemophilus influenzae*, *Neisseria meningitidis* and *Streptococcus pneumoniae*. In most countries, these three are the most common pathogens of BM in children (11, 12, 13), but their order of appearance is different. Dash and research associates (11) found that the *Haemophilus influenzae* was the most common cause, while *Streptococcus pneumoniae* and *Neisseria meningitidis* were located in second or third place. The order of appearance of BM pathogens may vary depending on the geographic location, climate, race, and the economic development of the country (14, 15, 16, 17). For example, meningitis caused by *Neisseria meningitidis* occurs in the form of epidemics in sub-Saharan Africa and has been a leading cause of meningitis there (18, 19, 20).

In this study, besides *Haemophilus influenzae*, *Streptococcus pneumoniae* and *Neisseria meningitidis*, there were other pathogens isolated from CSF, including *Acinetobacter* spp., and *Serratia marcescens*, which in most cases were hospital strains. These pathogens were isolated from the CSF of patients who suffer from chronic diseases and who often stay in hospital.

The low percentage of isolates of BM pathogens from CSF, which in our study was 35%, can be attributed primarily to antibiotic usage before hospitalization. In addition, we may assume that other causes are mostly technical factors, such as the transport of CSF to the laboratory and deficiencies in the laboratory in isolation of agents, which thus prevented determination of the etiology of BM pathogens.

The frequency of *Haemophilus influenzae* as a cause of BM in our study differs significantly when compared to the period before and after the introduction of the Hib vaccine. Specifically, the incidence of *Haemophilus influenzae* has decreased significantly in the period after the introduction of the Hib vaccine (patients treated for BM following the introduction of the Hib vaccine) compared to the prevaccinal period (patients treated for BM before the introduction of the Hib vaccine), ie, it decreased from 17 to 2 cases. It should be noted that these 2 patients were older and had not been vaccinated against *Haemophilus influenzae* type b. These data indicate the efficiency of the Hib vaccine and provide additional justification of its introduction. In the U.S., the annual incidence of meningitis caused by *Haemophilus influenzae* before the introduction of conjugate vaccine was on average 54/100,000 (2). After the introduction of the Hib vaccine, the incidence was reduced to only 0.7/100,000 cases (21). According to the CDC (Centers for Disease Control and Prevention), the possibility for the ineffectiveness of the Hib vaccine is minimal (11).

By comparing the distribution of other causes of BM among patients who belonged to the prevaccinal period and the period after the introduction of the Hib vaccine, our study showed that the number of meningitis cases caused by *Neisseria meningitidis* in the prevaccinal period was higher than in the period after the introduction of the Hib vaccine, while *Streptococcus pneumoniae* was a more common cause of BM in the period after the introduction of Hib vaccine, compared to the prevaccinal period. After the introduction of the Hib vaccine in our patients, there was an increase in the number of patients with meningitis caused by *Streptococcus pneumoniae*. The explanation may be found in the assumption that other serotypes of *Haemophilus influenzae* and *Streptococcus pneumoniae* were occupying an ecological niche which remained empty following the introduction of the Hib vaccine, and which was earlier occupied by *Haemophilus influenzae* type b (22). A similar incidence of BM caused by *Streptococcus pneumoniae* as the leading cause after the introduction of the Hib vaccine is present worldwide, in developed and in developing countries (23-25).

In this study, we had 19 isolates of *Haemophilus influenzae*, of which 11 were in children younger than 1 year, and 8 in children aged between 1 and 5 years of age. These data are consistent with the already established fact that most cases of BM caused by the *Haemophilus influenzae* affect children younger than 5 years (2, 26, 27).

Mortality from BM in our study was 2.1%, of which *Haemophilus influenzae* was isolated in one case, and that child had not been vaccinated. The mortality rate in children with BM in developed countries like the U.S. is around 2.6% (28), and is slightly higher compared with the mortality rate in our study. This indicates that the mortality rate of BM in our study is similar to rates of mortality in developed countries.

Study limitations

Although we had a sufficient total number of respondents to this survey, the main drawback of this study is the small number of isolates of BM pathogens from CSF (only 35%), and the small number of respondents who had been vaccinated with the Hib vaccine. Therefore, there is a possibility that the results of this study underestimated the effectiveness of the Hib vaccine, as well as its impact on the representation of the causes of BM in children. The decreasing trend of BM caused by *Haemophilus influenzae* type b in children of preschool age is still visible. In addition to the introduction of the Hib vaccine, it is possible that factors such as improvement of living standards and the improving health care of patients contributed to the reduction of *Haemophilus influenzae* type b as a cause of BM.

Conclusion

The most common causes of BM in children aged 1 month to 14 years who were treated at the Infectious Diseases Clinic in Tuzla in the period from 01.05.1999 until 30.06.2009 were *Haemophilus influenzae*, *Neisseria meningitidis* and *Streptococcus pneumoniae*. The number of cases of meningitis caused by *Haemophilus influenzae* following the introduction of the Hib vaccine was reduced, and simultaneously the total number of cases of BM was also reduced. In children who were treated for BM, and who were vaccinated with the Hib vaccine, there were no isolates of *Haemophilus influenzae* from the CSF. All this points to the effectiveness and justifies the introduction of the vaccine against *Haemophilus influenzae* type b into the regular immunization calendar for children. However, the observed increase in the number of BM cases caused by *Streptococcus pneumoniae* after the introduction of the Hib vaccine, indicates the consideration of

introducing a vaccine against *Streptococcus pneumoniae* into the regular immunization calendar for children.

Conflict of Interest: The authors declare that they have no conflict of interest. This study was not sponsored by any external organization.

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