

# Epidemiology of meningitis due to *Haemophilus influenzae* type b in children in Bulgaria: a prospective, population-based surveillance study

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**Objective** To assess the incidence of meningitis caused by *Haemophilus influenzae* type b (Hib) among children in Bulgaria and to provide evidence for an informed decision on the use of Hib vaccines in Bulgaria.

**Methods** From 1 July 1997 to 31 December 1999, active surveillance for meningitis was conducted in six regions. For children with suspected meningitis, a cerebrospinal fluid (CSF) specimen was sent for cytology, chemistry, latex agglutination testing, culture and sensitivity.

**Findings** During the 2.5-year study period, surveillance was conducted among 138 249 children aged <5 years — a sample representing 40% of all Bulgarian children in this age group. Overall, 285 children with suspected meningitis were identified. In eight children, clinical symptoms of meningitis resolved rapidly before a CSF specimen could be obtained. Of the remaining 277 children, 121 (44%) were classified as having probable bacterial meningitis on the basis of a CSF examination. An organism was identified for 88 (73%) of the 121 cases with probable bacterial meningitis. There were 21 cases of Hib, giving a mean annual incidence of 6.1 Hib meningitis cases per 100 000 children <5 years; the case-fatality rate was 10%. Nearly 60% of Hib isolates were resistant to one or more antibiotics, but they were not resistant to third-generation cephalosporins.

**Conclusion** On the basis of these findings, Hib conjugate vaccines have been included in the list of vaccines recommended for children by the Bulgarian Ministry of Health. The recommended initial treatment for paediatric bacterial meningitis has been changed to third-generation cephalosporins.

**Keywords** Meningitis, Haemophilus/epidemiology/etiology; Haemophilus influenzae type b/pathogenicity; Meningitis, Bacterial/microbiology; Neisseria meningitidis/pathogenicity; Streptococcus pneumoniae/pathogenicity; Child; Epidemiologic studies; Prospective studies; Bulgaria (*source: MeSH, NLM*).

**Mots clés** Méningite haemophilus/épidémiologie/étiologie; Haemophilus influenzae type b/isolement et purification; Méningite purulente/microbiologie; Neisseria meningitidis/pathogénicité; Streptococcus pneumoniae/pathogénicité; Enfant; Etude analytique (Epidémiologie); Etude prospective; Bulgarie (*source: MeSH, INSERM*).

**Palabras clave** Meningitis por haemophilus/epidemiología/etiología; Haemophilus influenzae tipo b/aislamiento y purificación; Meningitis bacteriana/microbiología; Neisseria meningitidis/patogenicidad; Streptococcus pneumoniae/patogenicidad; Niño; Estudios epidemiológicos; Estudios prospectivos; Bulgaria (*fuentes: DeCS, BIREME*).

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## Introduction

Globally, *Haemophilus influenzae* type b (Hib) is one of the leading causes of bacterial meningitis in children <5 years of age, and safe and effective vaccines are available to prevent this disease (1). Little information is available on the disease burden

due to Hib in certain regions of the world, however, and the World Health Organization (WHO) has recommended that efforts be made to evaluate the magnitude of Hib meningitis in these areas. Among the 26 countries classified by the United Nations as economies in transition<sup>a</sup> (2) — which include the

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<sup>a</sup> Economies in transition: Albania, Armenia, Azerbaijan, Belarus, Bosnia and Herzegovina, Bulgaria, Croatia, Czech Republic, Estonia, Georgia, Hungary, Kyrgyzstan, Latvia, Lithuania, Poland, Republic of Moldova, Romania, Russian Federation, Slovakia, Slovenia, Tajikistan, the former Yugoslav Republic of Macedonia, Turkmenistan, Ukraine, Uzbekistan, Yugoslavia.

Baltic States, Central and Eastern Europe (Bulgaria is within this group) and the Commonwealth of Independent States — only one country (Slovenia) has published results from a population-based study of the incidence of Hib (3).

In Bulgaria, a retrospective review of bacterial meningitis in the six largest regions in the country during 1992–96 showed a relatively low annual incidence of Hib meningitis: 1.3–11.0 per 100 000 children <5 years of age (Kojouharova, unpublished data, 2000). This study was unable to assess fully the meningitis case-fatality rates. The retrospective study found an incidence of Hib meningitis lower than that found in similar studies before Hib vaccine was introduced in Scandinavia (4) and the United Kingdom (5), but it was unclear whether this difference was due to limitations in surveillance, problems with diagnostic methods, more extensive use of antibiotics in Bulgaria or a true paucity of Hib infection in the Bulgarian population. During 1997–99 we conducted a prospective, population-based surveillance study in the same regions of the country as the 1992–96 retrospective study, to better assess the burden of Hib meningitis, including the case-fatality rate, and to provide evidence for an informed decision about the use of Hib vaccines in Bulgaria.

## Methods

Bulgaria is a central Balkan country with a population of 8.2 million, a birth rate of 7.9 per 1000 population, and an infant mortality rate of 14.3 per 1000 live births (6). The country has 28 regions. The study was carried out between 1 July 1997 and 31 December 1999 in the six largest regions: Pleven Region, Plovdiv Region, Sofia City, Sofia Region, Stara Zagora Region and Varna Region. The study population consisted of 138 249 children aged <5 years — a sample that represented 40% of the nationwide total of 348 000 children in this age group. The study received ethical approval from the Scientific Council of the National Center of Infectious and Parasitic Diseases in Bulgaria and from the WHO Secretariat Committee on Research Involving Human Subjects. Informed consent was not required, because lumbar puncture for children with suspected meningitis is the routine standard of care in Bulgaria.

This prospective study was based on two documents produced by WHO: a generic protocol for population-based surveillance of Hib meningitis (7) and a manual of microbiological methods (8). Bulgarian versions of these documents were distributed to physicians, public health officials and microbiologists in the six study regions to ensure standardization of surveillance and laboratory procedures. One physician-epidemiologist and one microbiologist from each study region participated in a pre-study workshop on meningitis surveillance and laboratory methods held in Sofia on 12–15 May 1997. The workshop was organized by the National Center of Infectious and Parasitic Diseases, Sofia, and it received technical support from WHO and the United States Centers for Disease Control and Prevention.

In Bulgaria, meningitis is an officially reportable disease, with notification of each suspected case to the regional epidemiology office required within 24 hours. Routine surveillance for infectious diseases includes daily case reports from hospitals and clinics, telephone feedback to referring physicians and case investigations by teams of physician-epidemiologists at the regional epidemiology office. The

infectious disease surveillance system was further activated at the start of the study when all physicians in the study regions were officially notified about the study and provided definitions of meningitis cases and case-reporting guidelines. In addition, regional study coordinators (epidemiologists or microbiologists) conducted weekly reviews of hospital admission and discharge records, laboratory logbooks and autopsy reports to ensure that every patient <5 years with suspected meningitis was included in the study. A study report form was completed for each case of probable or confirmed meningitis; forms were reviewed regularly for completeness and accuracy.

The existing standard of care for patients with suspected meningitis calls for routine diagnostic lumbar puncture in hospital. In Bulgaria, meningitis is not treated in outpatient facilities, and ambulance transport to hospital is provided free of charge. Deaths in children are almost always investigated by autopsy.

## Case definitions

A **suspected case** of meningitis was defined as a child <5 years of age presenting with clinical symptoms of meningitis, e.g. fever, headache, stiff neck, bulging fontanelle or change in mental status. A **probable case** of bacterial meningitis was defined as a suspected case in whom the CSF had a turbid appearance, or elevated protein (>100 mg/dl), or decreased glucose (<40 mg/dl), or leukocytosis (>100 white blood cells per mm<sup>3</sup>) with >80% neutrophils. A **confirmed case** of bacterial meningitis was defined as a probable case in whom an organism in the CSF was identified by culture or latex agglutination test.

## Laboratory procedures

### Regional laboratories

Study microbiologists participated in the pre-study workshop in May 1997. This included intensive laboratory-based training on the study methods. Specimens of CSF were tested for turbidity, number and type of cells, protein, glucose, Gram stain, latex agglutination and culture, according to WHO recommendations (6, 7). Commercial latex agglutination kits, supplemental X and V factors, chocolate agar and antibiotic discs were supplied to each regional laboratory. In addition, regional laboratories received reference strains of *H. influenzae*, *Streptococcus pneumoniae* and *Neisseria meningitidis* to be used in systematic checks to ensure that the culture media would support growth of these organisms. The head microbiologist for the study visited each study laboratory twice to review quality control procedures.

### Reference laboratory

*H. influenzae* isolates from CSF were sent for serotyping and antibiotic susceptibility testing at the study reference laboratory at the Infectious Disease Hospital in Sofia. The chief of this laboratory served as the head microbiologist for the study and was responsible for training regional laboratory personnel, supervising quality control of regional laboratories and managing laboratory resources. During the study, the reference laboratory successfully completed a proficiency test organized by the *Haemophilus* Reference Unit, Public Health Laboratory Service, United Kingdom (M. Slack, personal communication, 1999).

The reference laboratory used API NH strips (Bio Merieux, France) to identify Hib isolates, which were stored at  $-70^{\circ}\text{C}$  in serum glycerol-based medium. The antibiotic susceptibility of Hib strains was assessed by disc diffusion method on *Haemophilus* test medium agar. The antibiotics tested were ampicillin, ceftriaxone, cefuroxime, chloramphenicol, ciprofloxacin, rifampin, tetracycline and trimethoprim plus sulfamethoxazole. Production of  $\beta$ -lactamase was determined by the nitrocephin assay.

### Cohort study of antibiotic prescribing practices

At the time of the study, the government health system assigned each child in Bulgaria to a single paediatric practice. To assess the frequency of antibiotic prescribing in the first two years of life, a cohort of 277 children born in 1997 was enrolled from six paediatric practices in two towns of the Sofia Region. For each child, outpatient records made while they were 0–23 months of age were reviewed to determine the number of courses and types of antibiotics prescribed.

### Statistical methods

For incidence calculations, the population for each study year — by region and age group — was obtained from the Bulgarian National Statistical Service (6). EpiInfo software (version 6.02) was used to calculate 95% confidence intervals and Student's *t*-tests.

### Results

From 1 July 1997 to 31 December 1999, active surveillance of meningitis was conducted for 138 249 children <5 years of age. In total, 285 children <5 years of age with suspected meningitis were identified. In eight children, clinical symptoms of meningitis resolved within the first hours after admission and before a CSF specimen could be obtained. For the remaining 277 children, 121 (44%) had CSF findings that met the criteria for probable bacterial meningitis. Of the probable bacterial meningitis cases, 88 (73%) were confirmed as cases — 73 by isolation of an organism and 15 by latex agglutination (one Hib, four *S. pneumoniae* and 10 *N. meningitidis*). The

incidence of probable bacterial meningitis ranged from 21.9 cases per 100 000 children aged <5 years in Stara Zagora Region to 44.8 cases per 100 000 in Varna Region; the regional variation was not significant. For the six regions as a group, the mean annual incidence of probable bacterial meningitis was 35.1 cases per 100 000 children aged <5 years.

During the surveillance period, Hib (21 cases), *N. meningitidis* (23 cases) and *S. pneumoniae* (23 cases) were the leading organisms identified, accounting for 17%, 19% and 19%, respectively, of all cases of bacterial meningitis and 24%, 26% and 26%, respectively, of the cases of bacterial meningitis in which an organism was identified. The mean annual incidence of Hib meningitis calculated for the study period was 6.1 cases per 100 000 children aged <5 years. The highest age-specific incidence of Hib meningitis was 18.2 cases per 100 000 children aged 6–11 months (Table 1). An additional five Hib isolates were obtained from children aged <5 years with other types of invasive disease, including two cases of pneumonia and one case each of cellulitis, septicaemia and otitis media. During the study period, the mean annual incidences of meningitis caused by *N. meningitidis* and *S. pneumoniae* were both 6.7 cases per 100 000 children <5 years (Table 1).

Fig. 1 presents the age-specific cumulative proportion of meningitis caused by the three leading causative agents. For Hib meningitis, 10% of cases occurred in children aged 0–5 months and 38% in children aged 0–11 months. For *S. pneumoniae*, the proportions were 13% and 61%, respectively, and for *N. meningitidis*, 22% and 61%, respectively. For children aged 0–23 months, the difference between the cumulative percentage of Hib meningitis cases (48%) and *N. meningitidis* cases (78%) was significant (*t*-test,  $P = 0.043$ ).

Overall, 24 (20%) of 121 patients with probable bacterial meningitis died. The case-fatality rate was highest among patients with pneumococcal meningitis (44%) and only one-tenth as high among those with meningitis due to *N. meningitidis* (4%). For patients with Hib meningitis, the case-fatality rate was 10% (2 of 21 cases).

Three of the 20 *H. influenzae* isolates from CSF specimens did not survive transport to the reference

Table 1. Age-specific annual incidence (cases per 100 000 population) of probable bacterial meningitis cases and confirmed bacterial meningitis<sup>a</sup> cases, by organism, in six regions of Bulgaria between 1 July 1997 and 31 December 1999

Age (months)	Confirmed cases of bacterial meningitis <sup>a</sup>						Probable bacterial meningitis	
	<i>H. influenzae</i> type b		<i>S. pneumoniae</i>		<i>N. meningitidis</i>		Number of cases	Incidence
0–5	2	6.0	3	9.0	5	15.0	39	117.4
6–11	6	18.2	11	33.3	9	27.2	36	108.3
12–23	2	3.0	3	4.5	4	6.0	15	22.7
24–35	6	8.9	3	4.5	1	1.5	12	17.9
36–47	3	4.2	1	1.4	1	1.4	8	11.2
48–59	2	2.7	2	2.7	3	5.4	11	14.9
0–59	21	6.1	23	6.7	23	6.7	121	35.1

<sup>a</sup> An additional 21 cases of confirmed meningitis were due to the following organisms: *Escherichia coli*, *Enterococcus*, *Klebsiella pneumoniae*, *Listeria monocytogenes*, *Pseudomonas aeruginosa*, *Staphylococcus* and *Streptococcus*.

laboratory. All of the 17 surviving isolates were serotype b: three were biotype I and four biotype II. Nine Hib isolates produced  $\beta$ -lactamase. Seven (41%) strains were sensitive to all antibiotics tested; one strain was resistant to ampicillin; one to ampicillin and tetracycline; five to ampicillin, chloramphenicol and tetracycline; two to ampicillin, chloramphenicol, tetracycline and trimethoprim plus sulfamethoxazole; and one to trimethoprim plus sulfamethoxazole. None of the Hib isolates was resistant to any of the cephalosporins or to rifampin.

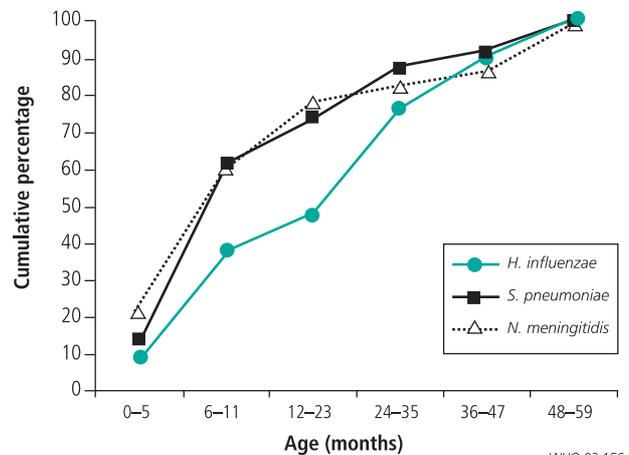
The cohort survey to assess the frequency of antibiotic prescribing at outpatient clinics found that 227 (82%  $\pm$  4.5%) of the 277 children had been prescribed antibiotics in the first 24 months of life — 159 children (70%  $\pm$  5.4%) had been prescribed ampicillin, trimethoprim plus sulfamethoxazole, or both. Sixty-three children (28%) had been prescribed one course of antibiotics, 148 children (65%) had been prescribed 2–5 courses, and 16 children (7%) had been prescribed 6–9 courses.

## Discussion

Hib is one of the leading causes of bacterial meningitis in Bulgarian children <5 years of age. The mean annual incidence of 6.1 cases of Hib meningitis per 100 000 children aged <5 years is lower than the 25–35 per 100 000 children aged <5 years reported by studies in Northern Europe before the introduction of the Hib vaccine (4, 5). However, the incidence in Bulgaria is similar to that in other population-based studies from nearby countries, including Austria (9), Germany (10, 11), Greece (12, 13), Italy (14, 15), Malta (16) and Slovenia (3) (Table 2). The availability of these data reflects a growing interest among European countries in identifying the disease burden due to Hib meningitis. This is the second population-based study of Hib disease burden reported from the 26 countries classified by the United Nations as economies in transition (2). Further studies from these countries are expected.

This study was undertaken because of concerns about potential limitations in a previous retrospective study, including strength of surveillance and problems with diagnostic methods. This prospective study used a variety of measures to reinforce and activate surveillance for paediatric

Fig. 1. Cumulative percentage of cases of bacterial meningitis caused by *H. influenzae* type b, *S. pneumoniae* and *N. meningitidis* among children aged 0–59 months, by 6-month age groups, in six regions of Bulgaria between 1 July 1997 and 31 December 1999



meningitis. It seems unlikely, therefore, that cases would have been missed, unless their clinical presentation was atypical. To deal with concerns about diagnostic methods, this prospective study included intensive laboratory training, supply of standard reagents and careful attention to quality control. Although laboratory staff successfully completed proficiency tests, this does not ensure that laboratory procedures were always performed correctly. We used bacterial culture and antigen detection — the two methods recommended by WHO (7, 8) — to identify an etiological cause for 73% of the cases of probable bacterial meningitis. Failure to identify an etiological cause in all cases may relate in part to antibiotic treatment prior to lumbar puncture. It is possible that the polymerase chain reaction (PCR) test would have identified additional cases; however, PCR testing for Hib is available in only a few reference laboratories in the world, and it remains expensive. If we assume that PCR tests would identify the same proportion of Hib among CSF specimens with unknown etiology as among those with known etiology, then an additional eight Hib

Table 2. Annual incidence of Hib meningitis per 100 000 children <5 years of age from selected population-based surveillance studies in Europe conducted before Hib vaccine was introduced (numbers in brackets indicate source in reference list)

Country	Study area	Period	Incidence of Hib meningitis
Austria (9)	National	1990–92	10.8
Bulgaria	Six regions	1997–99	6.1
Germany (10)	Former East Germany	1983–89	8.0
Germany (11)	Bochun	1972–92	9.0
Greece (12)	Greater Athens	1992–94	8.0
Greece (13)	South-west	1990–94	8.0
Italy (14)	Apulia	1994–95	4.2
Italy (15)	Naples	1987–95	2.9
Malta (16)	National	1990–94	9.2
Slovenia (3)	National	1993	10.7

cases would have been found. If these eight additional cases were included in calculations, the annual incidence would have increased to 8.4 per 100 000 children <5 years of age.

Our study shows that Hib meningitis in children in Bulgaria is a severe, life-threatening disease, which is fatal in 10% of patients. This case-fatality rate is about 2–3 times higher than rates in Canada, Scandinavia and the United States before the introduction of the Hib vaccine (17, 18). We believe this may be related, at least in part, to the high level of antibiotic resistance among the Hib strains circulating in Bulgaria. More than half of the Hib isolates in this study produced  $\beta$ -lactamase, and nearly 60% were resistant to one or more antibiotic. On the basis of these findings, the Bulgarian Ministry of Health has changed the recommended treatment protocol for initial therapy of suspected bacterial meningitis to third-generation cephalosporins.

The high prevalence of ampicillin-resistant,  $\beta$ -lactamase-producing Hib strains isolated in this study is consistent with the frequent prescribing of  $\beta$ -lactam penicillins for infants and young children <2 years of age, a practice documented in our cohort survey. Pretreatment with antibiotics before hospital admission may interfere with recovery of causative agents in bacterial meningitis (19). As prescribing of antibiotics for children aged 0–23 months was shown to be common, it seems likely that this has contributed to the relatively low incidence of Hib meningitis found in Bulgarian children.

The fact that the overall incidence of Hib meningitis among children <5 years is not very high in Bulgaria and that there is a relatively high proportion of cases in older children (52% of cases occurred in children aged 24–59 months) may be influenced by social factors. Previous studies have identified day care outside the home and the presence of siblings of elementary school age or younger as important risk factors for

Hib disease (20–22). In Bulgaria, women are routinely granted 24 months of paid maternity leave; this means that children aged 0–23 months are not likely to attend day care facilities. The lower incidence rate of Hib meningitis probably also reflects a low rate of exposure to young siblings, as the total fertility rate in Bulgaria during the 1990s was only 1.2 births per woman (23). These social factors — limited participation of very young children in day care outside the home and few siblings — may play a role in reducing the exposure of many young Bulgarian children to Hib.

The age distribution of patients showed that the proportion of cases in the youngest children was relatively low — only 10% of cases were in children <6 months old. This age distribution suggests that more than 80% of invasive infections caused by Hib among Bulgarian children would be successfully prevented by immunizing with Hib vaccine in early infancy. To address the public health problems caused by this vaccine-preventable disease — and as a first step towards the adoption of a routine Hib immunization programme — the Bulgarian Ministry of Health has included Hib conjugate vaccines on the list of officially recommended vaccines. ■

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**Conflicts of interest:** none declared.

## Résumé

### Epidémiologie de la méningite à *Haemophilus influenzae* type b chez l'enfant en Bulgarie : étude de surveillance prospective en population

**Objectif** Evaluer l'incidence de la méningite à *Haemophilus influenzae* type b (Hib) chez l'enfant en Bulgarie et fournir des données en vue d'une décision informée sur l'utilisation des vaccins anti-Hib dans ce pays.

**Méthodes** Du 1<sup>er</sup> juillet 1997 au 31 décembre 1999, une surveillance active de la méningite a été réalisée dans six régions. Chez les enfants suspects de méningite, un échantillon de liquide céphalo-rachidien (LCR) a été expédié au laboratoire pour examen cytologique, chimique, test d'agglutination au latex, culture et antibiogramme.

**Résultats** Pendant la période d'étude de 2,5 ans, une surveillance a été réalisée sur 138 249 enfants de moins de 5 ans, ce qui représente 40 % des enfants de cette tranche d'âge en Bulgarie. Au total, 285 cas suspects de méningite ont été identifiés. Chez 8 enfants, les symptômes de méningite ont

rapidement disparu avant que le prélèvement de LCR ait pu être réalisé. Chez les 277 autres, 121 (44 %) ont été classés comme cas probables de méningite bactérienne d'après l'examen du LCR. Un micro-organisme a été identifié chez 88 (73 %) des 121 cas présentant une méningite bactérienne probable. Il s'agissait de Hib dans 21 cas, ce qui donne une incidence annuelle moyenne de 6,1 cas de méningite à Hib pour 100 000 enfants de moins de 5 ans ; le taux de létalité était de 10 %. Près de 60 % des isollements de Hib étaient résistants à un ou plusieurs antibiotiques, mais non aux céphalosporines de troisième génération.

**Conclusion** Sur la base de ces résultats, les vaccins conjugués anti-Hib ont été inscrits sur la liste des vaccins recommandés chez l'enfant par le Ministère bulgare de la Santé. Le traitement initial recommandé en cas de méningite bactérienne pédiatrique a été modifié et repose désormais sur les céphalosporines de troisième génération.

## Resumen

### Epidemiología de la meningitis infantil por *Haemophilus influenzae* tipo b en Bulgaria: estudio de vigilancia prospectivo basado en la población

**Objetivo** Evaluar la incidencia de meningitis por *Haemophilus influenzae* tipo b (Hib) entre los niños en Bulgaria y aportar evidencia para tomar una decisión fundamentada sobre la utilización de las vacunas contra el Hib en Bulgaria.

**Métodos** Entre el 1 de julio de 1997 y el 31 de diciembre de 1999 se llevó a cabo una vigilancia activa de la meningitis en seis regiones. En los niños con presunta meningitis se obtuvo una muestra de líquido cefalorraquídeo (LCR) para hacer análisis de citología, química, aglutinación en látex, cultivo y sensibilidad.

**Resultados** Durante el periodo de estudio de 2,5 años, se sometió a vigilancia a 138 249 niños menores de 5 años, muestra que representaba el 40% de todos los niños búlgaros de ese grupo de edad. En conjunto se identificó a 285 niños con presunta meningitis. En ocho niños los síntomas clínicos desaparecieron rápidamente antes de que pudiera obtenerse una muestra de

LCR. De los 277 niños restantes, 121 (44%) se clasificaron como víctimas probables de meningitis bacteriana sobre la base de los resultados del análisis del LCR. Se detectó algún tipo de microorganismo en 88 (73%) de los 121 casos con probable meningitis bacteriana. Los 21 casos de Hib detectados arrojan una incidencia anual media de 6,1 casos de meningitis por Hib por 100 000 niños menores de 5 años; la tasa de letalidad fue del 10%. Casi un 60% de los aislados de Hib eran resistentes a uno o más antibióticos, pero no así a las cefalosporinas de tercera generación.

**Conclusión** Teniendo en cuenta estos resultados, en la lista de las vacunas recomendadas para los niños por el Ministerio de Salud de Bulgaria se han incluido las vacunas conjugadas contra el Hib. El tratamiento inicial recomendado para la meningitis bacteriana pediátrica ha sido sustituido por las cefalosporinas de tercera generación.

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