This article by Hudeckova et al. provides a very interesting look at causation and disease patterns of bacterial meningitis in Slovakia, a small country of about five million people with one of the fastest-growing economies in Eastern Europe. The authors were able to analyze and compare retrospectively the mortality and morbidity rates of bacterial meningitis during two periods of time: 1997–2001 and 2002–2007. This analysis was facilitated by the requirement for obligatory vaccination of infants against invasive infections caused by \textit{Haemophilus influenzae} type b (Hib) in 2000. This “natural experiment” provided evidence of the value of comprehensive and obligatory vaccination programs.

As the authors note, the improvement of the epidemiologic situation of bacterial meningitis caused by Hib was seen most dramatically in children younger than 4 years of age—in other words, those who are most susceptible to this pathogen. Their results follow findings in other developed countries. In 2003, Sáez-Llorens and McCracken found that the beginning of this millennium has witnessed the virtual disappearance of \textit{Haemophilus} invasive disease in some countries, emergence of pneumococcal strains that are resistant to multiple antibiotics, isolation of pneumococci with tolerance to vancomycin, outbreaks and clusters of meningococcal meningitis in several geographic areas, and intense research in the development of effective conjugate pneumococcal and meningococcal vaccines.\textsuperscript{1} In April 2009, British Department of Health Director of Immunization David Salisbury commented that since the Hib vaccine was introduced in 1992, cases of bacterial meningitis have dropped by 99%—from about 800 cases a year to a record low of 12 cases in 2008 in children younger than 5 years of age.\textsuperscript{2}

The work reported from Slovakia and other locations reinforces the importance of basic public health measures in improving the overall quality of life for a particular country’s citizens. In Slovakia and many other locations, Hib is the leading cause of bacterial meningitis and other invasive bacterial disease among children younger than 5 years of age.

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REFERENCES

NATIONAL ANALYSIS OF BACTERIAL MENINGITIS IN SLOVAKIA, 1997–2007

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Acute bacterial meningitis is one of the most severe and feared infectious diseases of childhood, with a high risk of neurological consequences (e.g., epilepsy, mental retardation, and sensorineural deafness) if treatment is delayed. Epidemic meningitis can have a devastating impact on entire populations. The three most common etiological agents are \textit{Haemophilus influenzae} type b (Hib), \textit{Streptococcus pneumoniae}, and \textit{Neisseria meningitidis}, which are responsible for 90% of reported cases of acute bacterial meningitis in infants and children older than four months of age.\textsuperscript{3} Hib meningitis is a disease affecting primarily young children, and most cases occur in children aged one month to 3 years. \textit{Streptococcus pneumoniae} is a major cause of childhood bacterial meningitis in countries where Hib disease has been eliminated by vaccination, and it is the second most frequently reported cause of septic meningitis in some European and sub-Saharan African countries. \textit{Neisseria meningitidis} is now considered to be the most important pathogen in several regions of the world.\textsuperscript{2} Determination of the mortality in relationship to particular bacteria requires laboratory identification of the pathogen from various biological specimens.\textsuperscript{5} An accurate laboratory confirmation of the etiology in acute bacterial meningitis is essential for providing optimal patient therapy, appropriate case contact management, and reasoned public health actions.
Attention is aimed especially toward children, because bacterial meningitis reaches the highest prevalence before the age of 5 years. Current strategies for prevention and therapy of bacterial meningitis require multifactorial concepts and approaches, which include advances in vaccinology, epidemiology of meningitis, emergence of antimicrobial-resistant pathogens, knowledge of pharmacokinetics and pharmacodynamics of antimicrobial agents, as well as the pathogenesis of meningitis. The introduction of the protein conjugate vaccines against Hib, Neisseria meningitidis, and Streptococcus pneumoniae has positively changed the epidemiology of bacterial meningitis caused by these pathogens.

We analyzed the prevalence of bacterial meningitis in the Slovak Republic from 1997 to 2007, using the etiological agents and their relationship to the newly introduced vaccination against Hib.

METHODS

For our analysis, we used all the relevant data about the patients with bacterial meningitis reported in the Epidemiological Informative System of Transmitted Diseases in Slovakia (EPIS) during the period 1997–2007: identification data (name, age, gender); geographical settings; personal family and epidemiologic history; social background; initiation, duration, type, and severity of the symptoms; provided therapy; complications; outcome; epidemiologic data (e.g., transfer mechanism, source of infection, risk factors, and vaccination); and laboratory and microbiological tests. We based diagnoses of all reported cases on the clinical, biochemical, cultivation, and serological findings.

For nonspecific meningitis (so-called “probable meningitis” or “bacterial meningitis of unknown origin”), we marked those cases with culture-negative results but with the typical finding in cerebrospinal fluid: leukocytosis (polymorphonuclear leucocytes) >100 cells/millimeter$^3$ (mm$^3$) or leucocytosis (polymorphonuclear leucocytes) >10–100 cells/mm$^3$ and either elevated protein (>100 milligrams/deciliter [mg/dL]) or decreased glucose (<40 mg/dL). We confirmed etiological diagnosis by the microbiological examination of cerebrospinal fluid from patients with clinical signs of meningitis and/or by antigen detection (latex agglutination).

We analyzed and compared retrospectively the morality and morbidity rates of bacterial meningitis during two periods of time: 1997–2001 and 2002–2007. We based this division of the decade on the introduction of obligatory vaccination of infants against invasive infections caused by Hib in 2000, with expected impact after the end of the complete vaccination scheme.

RESULTS

During the period 1997–2007, 2,067 patients were registered with the diagnosis of bacterial meningitis in Slovakia. From the total number of all reported cases, 134 were caused by Hib (6.5%), 269 by Streptococcus pneumoniae (13.0%), 545 by Neisseria meningitidis (26.4%), and 262 (12.7%) by other less prevalent pathogens (e.g., Acinetobacter species, Escherichia coli, Pseudomonas species, Staphylococcus aureus, Streptococci Groups A and D, and Klebsiella species). In 857 (41.5%) patients, no etiological agent was detected and the microbiological cultivation tests gave negative results. Figure 1 shows in detail the distribution of bacterial meningitis according to the causal etiological agents during the period 1997–2007 (Figure 1a) and during two separate periods of time, 1997–2001 and 2002–2007 (Figure 1b).

Figure 2 shows the incidence of acute bacterial meningitis caused by Hib, which varied from 0.6/100,000 in 1997 to 0.0/100,000 in 2006. The incidence of pneumococcal meningitis ranged from 0.6/100,000 in 2004 to 0.2/100,000 in 2006, and the incidence of meningococcal meningitis changed from 1.9/100,000 in 1997 to 0.4/100,000 in 2004. We observed quite high incidence of culture-negative meningitis or those caused by other, less prevalent bacterial pathogens. Since 2002, we have noticed a significant decrease of meningitis caused by Hib.

Regarding patients’ age, we observed 318 cases of bacterial meningitis (15.4%) in infants within the first year of life, 369 cases (17.8%) in 1- to 4-year-olds, 192 cases (9.3%) in children aged 5 to 9 years, and 1,188 cases (57.5%) among patients 10 years of age or older. Children 4 years of age or younger represented 687 cases (33.2%) of the total number of reported cases with bacterial meningitis in EPIS, and the rest (1,380 cases, 66.8%) were patients aged 5 years or older (Table). Among children 4 years of age or younger, the most frequent pathogen was Neisseria meningitidis (292 cases, 42.5%), followed by Hib (109 cases, 15.9%), and Streptococcus pneumoniae (51 cases, 7.4%). Some other, less prevalent bacterial pathogens caused meningitis in 43 patients (6.3%). In 192 patients 4 years of age or younger (27.9%), we were not able to detect any bacteria from cerebrospinal fluid (so-called nonspecific meningitis).

The total reported mortality on bacterial meningitis varied from 4.9/100,000 in 1997 to 2.6/100,000 in 2004. The mean age-specific morbidity in the analyzed period was several times higher in the group of children 4 years of age or younger (22.1/100,000; range: 13.8/100,000 in 2004 to 30.9/100,000 in 1997) compared with patients 5 years of age or older.
(2.3/100,000 in 2004, \( p<0.05 \); 3.3/100,000 in 1997, \( p<0.05 \)). Morbidity on particular meningitis regarding the etiological pathogen declined in 2002–2007 compared with the period 1997–2001. We found the most dramatic decline of age-specific morbidity in the group of infants younger than 1 year of age and in children aged 1–4 years, especially due to an evident reduction of the cases caused by Hib (\( p<0.001 \)) (Figure 3).

During the analyzed period, the mortality rate of bacterial meningitis reported in EPIS was 8.7% (179 cases). In detail, during the period 1997–2001, 116 patients died due to bacterial meningitis (mortality rate = 64.8%); in the later period, 2002–2007, 63 patients died due to bacterial meningitis (mortality rate = 35.2%). Distribution of mortality in relationship to causal pathogen evoking meningitis is shown in Figure 4, and the differences among various age groups can be seen in Figure 5. We observed the highest mortality rate in connection with meningococcal meningitis and in children younger than 1 year of age. The cases of bacterial meningitis were noticed during the whole year, and there were no seasonal differences between incidences of new cases of bacterial meningitis.

**DISCUSSION**

Through our retrospective epidemiologic study, we analyzed the contribution of particular bacterial pathogens to the incidence of bacterial meningitis reported in EPIS during the period 1997–2007. We were also interested in the impact of introduced vaccination against Hib on the incidence of meningitis cases. The most frequent causal bacterial pathogens were Hib, *Streptococcus pneumoniae*, and *Neisseria meningitidis*.
especially in children younger than 5 years of age. In our population, previously named pathogens were responsible for 45.9% of all reported cases. In 12.7% of cases, the disease was caused by other, less prevalent bacterial species. In 41.5% of cases, we were not able to detect any responsible bacterial pathogen through our microbiological or other tests, and we based the diagnosis of bacterial meningitis in these cases on the analysis of cerebrospinal fluid and clinical status (bacterial meningitis of unknown origin).

Table. Reported cases of bacterial meningitis according to patients’ age, Slovakia, 1997–2007

<table>
<thead>
<tr>
<th>Age (in years)</th>
<th>1997</th>
<th>1998</th>
<th>1999</th>
<th>2000</th>
<th>2001</th>
<th>2002</th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>N</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–4</td>
<td>108</td>
<td>91</td>
<td>78</td>
<td>86</td>
<td>63</td>
<td>43</td>
<td>51</td>
<td>37</td>
<td>43</td>
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<td>687</td>
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<tr>
<td>0</td>
<td>36</td>
<td>30</td>
<td>36</td>
<td>30</td>
<td>27</td>
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<td>30</td>
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<td>72</td>
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<td>13</td>
<td>16</td>
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<td>15</td>
<td>369</td>
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<tr>
<td>≥5</td>
<td>153</td>
<td>152</td>
<td>142</td>
<td>168</td>
<td>130</td>
<td>101</td>
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<td>9</td>
<td>16</td>
<td>11</td>
<td>10</td>
<td>192</td>
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<td>&gt;10</td>
<td>126</td>
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<td>119</td>
<td>136</td>
<td>115</td>
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<td>98</td>
<td>89</td>
<td>98</td>
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<td>261</td>
<td>243</td>
<td>220</td>
<td>254</td>
<td>193</td>
<td>144</td>
<td>159</td>
<td>141</td>
<td>157</td>
<td>147</td>
<td>148</td>
<td>2,067</td>
<td>100.0</td>
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</table>
Before the introduction of an effective vaccine, Hib was the leading cause of bacterial meningitis and other invasive bacterial disease among children younger than 5 years of age. Hib vaccine introduction in many countries has substantially reduced morbidity and mortality due to invasive Hib infections by more than 80%. The effectiveness of the Hib vaccine in preventing Hib meningitis has also been confirmed by many other researchers. Incomplete vaccination provides weaker protection in these children. Our data showed that after the introduction of anti-Hib vaccination, Hib meningitis was reported only in two non-vaccinated children and in one child without complete vaccination schema. We also found reduced occurrence of Hib disease in countries with irregular vaccine supplies; therefore, it is recommended that this vaccination be incorporated into routine immunization programs, not only in developing countries. According to our data, we observed a greater impact of Hib vaccination on Hib meningitis than on unspecified bacterial meningitis. After the vaccine was introduced, a significant decrease in incidence and mortality rates indicated the vaccine’s positive impact one year after its introduction.

Hib vaccination has also had an effect on unspecified bacterial meningitis rates, but not as evident as for Hib meningitis. Case fatality rate was influenced by vaccination only to a small extent. The possible influence of Hib vaccination on the incidence of bacterial meningitis of unknown origin has also been shown in the study by Nascimento-Carvalho et al. In the Dominican Republic, introduction of the Hib vaccine substantially reduced the incidence of confirmed and probable bacterial meningitis. The estimated impact of Hib vaccination was twice as great when non-culture-confirmed disease was included, a finding that is in agreement with the trend in our national results. In Cuba, the incidence of Hib meningitis dropped by 47% after initial vaccination, especially in young children. Subsequent declines in the incidence of Hib

**Figure 3. Comparison of incidences of cases with bacterial meningitis using age and causal pathogen, Slovakia, 1997–2001 and 2002–2007**

<table>
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<td>≥10 years</td>
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<td>5–9 years</td>
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<td>&lt;1 year</td>
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NM = *Neisseria meningitidis*
Hib = *Haemophilus influenzae* type b
SP = *Streptococcus pneumoniae*
Other = other pathogens
Nonspecific = nonspecific meningitis with negative microbiological exams
meningitis were also observed after the introduction of Hib vaccination in Australia.\textsuperscript{18,19} Another beneficial effect of conjugated Hib vaccine is the elimination of carriage among vaccinated populations.\textsuperscript{20} Despite the evident decrease in the incidence of bacterial meningitis caused by Hib, this severe infection still occurs in a small number of cases, as was reported by another Slovak group.\textsuperscript{21} In several countries, \textit{Streptococcus pneumoniae} is now replacing Hib as the leading potentially vaccine-preventable cause.\textsuperscript{22} Subsequent to the decreased prevalence of invasive Hib infections, we did not observe a concomitant increase in the incidence of invasive pneumococcal infections as reported in the literature.\textsuperscript{23} The effect of vaccination has also been confirmed by our observations and by the observations of others that in the higher age group, there is no significant change in the incidence of invasive Hib disease.\textsuperscript{24} Therefore, a future challenge is possible vaccination of older children.\textsuperscript{8}

\textbf{CONCLUSION}

Prevention and control of infectious diseases, especially among children and adolescents, is a major task for the public health service. Vaccines are the most promising and effective tools for preventing community-acquired bacterial meningitis. The development of Hib vaccine is one of the most important events in the history of the prevention and control of infectious diseases in children. The situation of Hib bacterial meningitis in the pre-vaccine era was previously analyzed by Novakova et al.\textsuperscript{4} They hypothesized that the true incidence of Hib meningitis could be considerably higher with the possible contribution of some bacterial meningitis

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure4.png}
\caption{Distribution of mortality on bacterial meningitis in relationship to causal pathogen, 1997–2007 (Panel A) and 1997–2001 and 2002–2007 (Panel B)}
\end{figure}

\textsuperscript{NM} = \textit{Neisseria meningitidis}  \\
\textsuperscript{Hib} = \textit{Haemophilus influenzae} type b  \\
\textsuperscript{SP} = \textit{Streptococcus pneumoniae}  \\
\text{Other} = \text{other pathogens}  \\
\text{Non-specific} = \text{non-specific meningitis with negative microbiological exams}
with negative culture tests. The expected effect on Hib disease morbidity and mortality, especially among children, was confirmed by our data on the national level. Other improvements in the epidemiologic situation regarding the incidence of bacterial meningitis of children could be expected as a consequence of spreading vaccination against *Streptococcus pneumoniae* and *Neisseria meningitidis*.24–26

Figure 5. Comparison of mortality rates of bacterial meningitis in Slovakia using age and causal pathogen, 1997–2001 and 2002–2007

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<tbody>
<tr>
<td>Hib</td>
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<td>NM</td>
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<tr>
<td>SP</td>
<td></td>
<td></td>
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<tr>
<td>Other</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonspecific</td>
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