Childhood Bacterial Meningitis in Ulaanbaatar, Mongolia, 2002–2004

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Background. Childhood bacterial meningitis is severe and largely preventable by vaccination. Few data on childhood bacterial meningitis in Northeast and Central Asia exist. Our aim was to determine the incidence and etiology of childhood bacterial meningitis in Ulaanbaatar, Mongolia.

Methods. We conducted prospective, population-based, active hospital surveillance for clinical meningitis in children 2 months to 5 years of age. Clinical data, blood, and cerebrospinal fluid were collected according to a standard protocol. Laboratory testing was performed at 2 reference laboratories in Ulaanbaatar.

Results. From February 2002 to January 2005, 201 suspected meningitis cases were identified in residents of Ulaanbaatar. The average annual incidence rate for confirmed and probable bacterial meningitis (cases with culture-negative, purulent cerebrospinal fluid) was 68 cases per 100,000 children aged 2 months to 5 years. The average annual incidence rate of confirmed cases was 28 cases per 100,000 children for *Haemophilus influenzae* type b meningitis, 11 cases per 100,000 children for pneumococcal meningitis, and 13 cases per 100,000 children for meningococcal meningitis. Adjusting for cases without complete cerebrospinal fluid information and culture-negative, probable bacterial cases, the estimated incidence rate was 40 cases per 100,000 children for *H. influenzae* type b meningitis, 15 cases per 100,000 children for pneumococcal meningitis, and 17 cases per 100,000 children for meningococcal meningitis.

Conclusion. *H. influenzae* type b is the leading cause of childhood bacterial meningitis in Ulaanbaatar, and the incidence rate is higher than that reported from other Asian countries. These data supported the recent introduction of *H. influenzae* type b conjugate vaccine in Mongolia. Ongoing surveillance will monitor the impact of the vaccine.

Childhood bacterial meningitis is a severe disease, and many affected children die or experience long-term neurologic complications. In the absence of vaccination, the most common causes of bacterial meningitis in children 2 months to 5 years of age are *Haemophilus influenzae* type b (Hib), *Streptococcus pneumoniae* (pneumococcus), and *Neisseria meningitidis* (meningococcus) [1–3]. In children in the first 2 months of life, different pathogens predominate, particularly group B streptococci and *Escherichia coli* [3]. Childhood bacterial meningitis is largely preventable by the use of safe and effective Hib, pneumococcal, and meningococcal conjugate vaccines.

Data on the incidence and origin of childhood bacterial meningitis in different Asian countries are conflicting [4]. Recent meningitis surveillance studies in China, Vietnam, Thailand, and South Korea have found a low incidence of confirmed bacterial meningitis, compared with studies from other regions [5–9]. However, recent studies using Hib vaccine as a probe have found higher than expected rates of Hib disease and have suggested that surveillance studies may underestimate the incidence of Hib meningitis [4, 8, 10].

Before this project, data on childhood bacterial meningitis in Mongolia were limited. Hib and pneumococcus were rarely identified by clinical laboratories, and there was no known use of Hib vaccine from 2002 to 2004 by private physicians or pharmacies. To assist the government of Mongolia in making decisions about

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the introduction of new conjugate vaccines, we implemented surveillance for childhood bacterial meningitis in Ulaanbaatar, the capital city of Mongolia. The objective of this surveillance was to estimate the incidence and determine the etiology of childhood bacterial meningitis in Ulaanbaatar.

METHODS

Design. Prospective, active, hospital-based surveillance for bacterial meningitis was initiated in February 2002. We analyzed surveillance data for the period February 1, 2002, through January 31, 2005.

Population and setting. Children 2 months to 5 years of age who were hospitalized in Ulaanbaatar for suspected meningitis were identified according to World Health Organization (WHO) guidelines [11]. The population of children in this age group in Ulaanbaatar was 60,047, according to national census data from 2000 (Bureau of Population Census, State Statistical Office, Ulaanbaatar, Mongolia). All identified cases were included in the analysis of meningitis characteristics, but only cases that occurred in residents of Ulaanbaatar were included in the analysis of incidence rates. Residency was determined by review of identification cards and interview of family members. Surveillance was performed at the 6 hospitals in Ulaanbaatar that admit children: The National Centre for Communicable Diseases, the Maternal and Child Health Research Centre, KhanUul District Hospital, Songinokhairkhan District Hospital, Sukhbaatar District Hospital, and Bayanzurkh District Hospital. Clinical data were collected by surveillance personnel using a structured form.

Case identification. Before the start of surveillance, clinicians in all 6 participating hospitals were trained in the inclusion criteria and case definitions. Clinicians were encouraged to perform lumbar puncture on all patients suspected of having meningitis. Monthly reviews of hospital admission records for diagnoses consistent with bacterial meningitis (e.g., sepsis, encephalitis, meningitis) were performed to identify any missed cases. Routine feedback on laboratory results, missed cases, and surveillance data was given to clinicians and hospital epidemiologists to encourage participation. A comprehensive project review was performed in January 2003, and additional training of hospital personnel was performed to reinforce surveillance procedures.

Case definitions. For surveillance purposes, suspected meningitis was defined as clinically suspected meningitis with at least 1 of the following: fever, headache, stiff neck, bulging fontanelle, or mental status change. Possible bacterial meningitis was defined as the presence of a WBC count of 10–99 cells/mL in CSF with either ⩾80% neutrophils or abnormal CSF protein and glucose levels. Probable bacterial meningitis was defined as the presence of a WBC count of ⩾100 cells/mL in CSF or turbid appearance of CSF (if the WBC count was not measured). Confirmed bacterial meningitis was defined as the isolation of a bacterial pathogen from CSF culture, detection of bacterial antigen in CSF by latex agglutination, detection of bacterial nucleic acid by PCR (if criteria for probable bacterial meningitis were met), or isolation of a bacterial pathogen from blood culture (if CSF was not obtained or if criteria for probable bacterial meningitis were met). Detection of bacterial DNA in clinical samples using real-time PCR is a sensitive technique, and false-positive PCR results can be generated by cross-contamination of samples [12]. Therefore, our a priori case definition required that a PCR result would only be taken as the sole method of confirming an infection if the case also satisfied the criteria for probable bacterial meningitis. If there were any discrepancies between laboratory tests, an expert in pediatric infectious diseases who was not involved in the surveillance project was asked to determine the final diagnosis. Common skin flora, such as coagulase-negative staphylococci or diphtheroids, were considered contaminants. Aseptic meningitis was defined as suspected meningitis with a WBC count ⩾10 cells/mL of CSF that did not meet the criteria for possible, probable, or confirmed bacterial meningitis. Patients who had WBC counts of less than 10 cells/mL were categorized as not having meningitis.

Laboratory methods. The CSF and blood specimens were collected at each treating hospital. At least 1 mL of blood per patient was inoculated into a Hemoline blood culture bottle (bioMérieux). Specimens from the Maternal and Child Health Research Center were tested in a laboratory in that hospital. For other hospitals, neat CSF and blood culture bottles were transported to the National Center for Communicable Disease with warm packs and thermometers to ensure that the specimens were transported at 20°C–25°C. Specimens were transported on the day of collection or in the morning of the following day if collected at night. On arrival at the laboratory, the blood culture bottles were placed in an incubator at 35°C–37°C. They were then subcultured onto locally manufactured sheep blood and chocolate agar plates along with growth factors and incubated with a candle jar. In the laboratory, CSF specimens were immediately plated onto supplemented sheep blood and chocolate agar plates and incubated for 48 h at 35°C–37°C with a candle jar. All plates were checked for growth after 18–24 h of incubation, and any organisms isolated were identified according to standard laboratory procedures. Detection of bacterial antigen in CSF was performed using the Meningite 5 latex agglutination test kit (bioMérieux) according to the manufacturer's instructions. External quality assurance for both surveillance laboratories was provided by the Health Protection Agency of the United Kingdom.

PCR analysis. A sample of stored CSF specimens was delivered to the Health Protection Agency of the United Kingdom on dry ice and stored at −80°C. DNA was extracted from 200

Table 1. Characteristics of children hospitalized with suspected meningitis, Ulaanbaatar, Mongolia, February 2002 to January 2005.

Type of case	No. of patients	Male sex, no. (%) of patients	Age, mean ± SD, y	Died, no. (%) of patients
Suspected	247	140 (57)	1.1 ± 1.1	23 (9)
Incomplete data[a]	23	14 (61)	1.1 ± 1.1	3 (13)
Aseptic meningitis or not meningitis	73	45 (62)	1.1 ± 1.2	4 (5)
Possible bacterial, not confirmed	4	2 (50)	1.7 ± 1.6	0 (0)
Probable bacterial, not confirmed	36	20 (56)	1.5 ± 1.3	4 (11)
Confirmed bacterial, by pathogen				
Haemophilus influenzae type b	61	35 (57)	0.7 ± 0.4	8 (13)
Streptococcus pneumoniae	23	12 (52)	0.7 ± 0.7	1 (4)
Neisseria meningitidis	25	10 (40)	1.5 ± 1.3	3 (12)
Other	2	2 (100)	0.8 ± 0.5	0 (0)

[a] Includes patients without lumbar puncture and those with insufficient CSF or blood culture data to permit categorization

μL of each CSF specimen using the MagNA Pure LC Total Nucleic Acid Isolation Kit (Roche) and a MagNA Pure LC robotic workstation (Roche), eluting the DNA in a final volume of 100 μL of buffer. Each DNA sample (volume of 5 μL) was assayed for the presence of bacterial DNA encoding the *H. influenzae* gene *bexA* (specific to serotypes b and c only), the *N. meningitidis* gene *ctrA*, and the *S. pneumoniae* gene *ply* using the multiplex real-time PCR method of Corless et al. [14]. Results with a cycle threshold value of >38 were considered negative. Because contaminants that interfere with PCR are sometimes purified along with DNA from CSF, each DNA sample was tested both neat and after 1/10 dilution in water. Successful amplification of target DNA at either of these 2 concentrations was considered a positive result.

Data analysis. Annual incidence rates were calculated by dividing the number of cases in eligible children by the Ulaanbaatar population aged 2 months to 5 years. Because surveillance started on February 1, 2002, the annual periods for analysis ran from February 1 to January 31 of the following year. The WHO Hib Rapid Assessment method was used to adjust Hib meningitis incidence rates for clinical meningitis cases that did not have CSF test results available and for culture-negative, probable bacterial meningitis cases [13].

Ethical considerations. This project was approved by the Ministry of Health in Mongolia. Deidentified data were provided to collaborators outside the Mongolian Ministry of Health.

RESULTS

From February 1, 2002, through January 31, 2005, there were 247 patients with suspected meningitis identified by the surveillance system. The characteristics of the case patients and the etiologic agents identified are given in table 1. CSF was obtained from 234 individuals (94.7%), and sufficient labo-

Table 2. Number of cases of meningitis identified in hospitalized Ulaanbaatar residents 2 months to 5 years of age, February 2002 to January 2005.

Type of case	Feb 2002 to Jan 2003	Feb 2003 to Jan 2004	Feb 2004 to Jan 2005
Suspected	70	77	54
Incomplete data[a]	11	5	6
Aseptic meningitis or not meningitis	22	24	6
Possible bacterial, not confirmed	2	0	0
Probable bacterial, not confirmed	7	12	11
Confirmed bacterial, by pathogen			
Haemophilus influenzae type b	12	19	19
Streptococcus pneumoniae	7	8	4
Neisseria meningitidis	8	9	7
Other	1	0	1

[a] Includes patients without lumbar puncture and those with insufficient CSF or blood culture data to permit categorization.

Table 3. Annual incidence rates (number of cases per 100,000 population) of meningitis among hospitalized children, Ulaanbaatar, Mongolia, February 2002 to January 2005.

Type of case	Feb 2002 to Jan 2003	Feb 2003 to Jan 2004	Feb 2004 to Jan 2005	Mean
Suspected	117	128	90	112
Probable or confirmed bacterial	57	80	68	68
Confirmed bacterial, by pathogen				
Haemophilus influenzae type b	20	32	32	28
Streptococcus pneumoniae	12	13	7	11
Neisseria meningitidis	13	15	12	13

ratory information to permit assignment of one of the case definitions was available for 224 (91%). Of these 224, 106 (45%) satisfied the criteria for confirmed bacterial meningitis, 35 (15%) satisfied the criteria for unconfirmed probable bacterial meningitis, and 4 (2%) satisfied the criteria for unconfirmed possible bacterial meningitis. Overall, 111 individuals had confirmed bacterial meningitis, including 5 who did not have lumbar puncture performed but had positive blood culture results. Hib was responsible for 61 (55%) of the confirmed cases, *S. pneumoniae* for 23 (21%), and *N. meningitidis* for 25 (23%). One case of meningitis due to Enterobacteriaceae species and 1 case due to *Staphylococcus aureus* were also identified.

Of the 61 cases of Hib meningitis identified by the surveillance system, 54 (89%) were confirmed by the results of multiple diagnostic tests (blood culture, CSF culture, CSF antigen detection, and/or PCR). Of the 7 cases identified by a single test, 2 were identified by blood culture (CSF was not obtained in 1 case), 1 by CSF culture, 2 by CSF antigen detection, and 2 by CSF PCR. Of the 7 cases confirmed by a single test, CSF was collected from the patient in 6. Five of those 6 patients had a CSF WBC count $\geqslant$100 cells/mL, and 1 had a CSF WBC count of 71 cells/mL (>80% neutrophils), an elevated protein level, and a low glucose level.

PCR for Hib, *S. pneumoniae,* and *N. meningitidis* was performed on 117 CSF specimens. Results of PCR confirmed the results of other laboratory tests in 93 cases (79%). In 14 cases (12%), the origin was determined by PCR only (Hib in 2 cases, *S. pneumoniae* in 4, and *N. meningitidis* in 8). All of these 14 cases met the definition of probable bacterial meningitis. In 7 cases (6%), positive PCR results were discounted because the cases did not meet the definition of probable bacterial meningitis. In 3 cases (3%), the PCR result was negative and the CSF culture and/or antigen detection test result was positive.

Of the 247 patients with suspected meningitis, 201 were confirmed as residents of Ulaanbaatar (table 2). Using this subset of patients, incidence rates for different categories of meningitis among residents of Ulaanbaatar were calculated (table 3). The results reveal an average incidence rate of probable or confirmed bacterial meningitis of 68 cases per 100,000 in this population. The annual incidence rate of confirmed cases was 28 cases per 100,000 children for Hib meningitis, 11 cases per 100,000 children for pneumococcal meningitis, and 13 cases per 100,000 children for meningococcal meningitis.

We identified 2 ways in which cases of Hib meningitis may have been missed by the surveillance system and calculated an adjusted incidence rate. First, among Ulaanbaatar residents with suspected meningitis, lumbar puncture was not performed or CSF was not tested for 22 (11%), of whom 5 had a pathogen isolated from blood culture (Hib, 1 patient; *N. meningitidis,* 3; and Enterobacteriaceae species, 1). Assuming that the proportion of cases due to Hib among case patients who did not undergo CSF testing was the same as the proportion due to Hib among case patients who had lumbar puncture performed, an additional 5 cases of Hib meningitis would be expected during the 3-year study period, after subtracting the 1 case without CSF testing performed that was identified by blood culture. Second, there were 30 cases of probable bacterial meningitis with no organism identified, among Ulaanbaatar residents. Assuming that the pro-

Table 4. Estimated case counts and incidence of bacterial meningitis, adjusting for surveillance limitations, Ulaanbaatar, Mongolia, February 2002 to January 2005.

Pathogen	No. of confirmed cases	Estimated no. of cases: Cases with incomplete CSF data	Estimated no. of cases: Probable bacterial cases without confirmed cause	Estimated no. of cases: Total	Estimated incidence, no. of cases per 100,000 children
Haemophilus influenzae type b	50	5	17	72	40
Streptococcus pneumoniae	19	2	6	27	15
Neisseria meningitidis	24	0	7	31	17

portion of culture-negative, probable bacterial cases has the same distribution of etiologic agents as do the culture-positive cases, an additional 17 cases of Hib meningitis would be expected during the 3-year study period. The mean annual incidence of Hib meningitis during the 3-year study period adjusted for these 2 factors would be 40 cases per 100,000 children younger than 5 years (table 4). By use of a corresponding approach, the mean adjusted annual incidence was 15 cases per 100,000 children for *S. pneumoniae* meningitis and 17 cases per 100,000 children for *N. meningitidis* meningitis.

The number of children identified with suspected meningitis decreased substantially in the third year of the study. This decrease was primarily the result of a smaller number of children identified with aseptic meningitis and disease that was not meningitis.

DISCUSSION

We found that Hib was the leading cause of childhood bacterial meningitis in Ulaanbaatar. After adjusting for limitations in the surveillance system, we estimated that the incidence of Hib meningitis in children younger than 5 years was 40 cases per 100,000. This incidence rate was higher than reported in recent studies from Thailand [6], South Korea [5], Indonesia [8], and Vietnam [7]. Although we found a lower rate of suspected meningitis than that found in these other 4 studies, the rate of probable or confirmed bacterial meningitis in Ulaanbataar was similar to the rates found in Indonesia, South Korea, and Vietnam and higher than the rate found in Thailand. Hib was the leading cause of bacterial meningitis in all 5 studies, and the proportion of cases due to Hib among those with a confirmed etiologic agent was also similar across all 5 studies. However, the rate of laboratory-confirmed Hib meningitis found in Ulaanbataar was 2–7 times higher than that found in the other 4 studies. The main reason for this difference was that the proportion of probable bacterial meningitis with a confirmed cause was substantially higher in Ulaanbaatar than in the other 4 studies.

There are several possible explanations for the differences between our results and those of other studies. The lower incidence of suspected meningitis could be the result of physicians in Ulaanbaatar using more selective criteria for diagnosing suspected meningitis in children than in the other 4 study areas. If this were the case, then we may have missed some additional cases of bacterial meningitis, and the difference between the Hib meningitis incidence rate that we measured and the rates found in other studies could be even higher. Alternatively, some illnesses (e.g., viral encephalitis) that have clinical findings similar to those of bacterial meningitis may be less common in Mongolia than in the other 4 countries. This would explain the finding of a relatively low proportion of CSF specimens with low WBC counts but similar rates of suspected bacterial meningitis in our study. The higher proportion of suspected bacterial meningitis cases with a confirmed cause could be explained by a lower frequency of antibiotic use before presentation in Mongolia than in the other 4 countries. However, ~50% of parents of children included in the Ulaanbaatar surveillance reported administering antibiotics before hospital admission. Of note, the study from Indonesia [8] found that use of Hib conjugate vaccine had a much greater impact on outcomes of probable bacterial meningitis or clinical meningitis than on outcomes of confirmed Hib meningitis. This finding suggests that the culture, antigen detection, and PCR tests used in the study from Indonesia [8] were only able to identify a small percentage of the incident Hib meningitis cases and that the actual incidence of Hib meningitis in Indonesia is similar to, or greater than, that found in the present study in Mongolia. Finally, it is possible that the laboratory testing used in our study had poor specificity. This is unlikely because almost 90% of bacterial origins were confirmed by multiple tests.

The number of cases of suspected meningitis identified by the Ulaanbaatar meningitis surveillance system decreased in the third year of the study primarily because of a large decrease in the number of cases identified as aseptic meningitis or not meningitis. There were no intentional changes in the surveillance system during the study period to explain this difference. One possible explanation for this finding is that there was an unidentified outbreak of viral meningitis or encephalitis that ended in late 2004.

The most common bias in surveillance for bacterial meningitis is underestimation of disease incidence due to limited sensitivity. Because the case definitions for bacterial meningitis require specific laboratory confirmation, false-positive cases are uncommon. However, cases may be missed for a variety of reasons. First, some children with bacterial meningitis may not reach the hospital. Health care is provided free to all children in Ulaanbaatar, and the network of district hospitals is easily accessible. Therefore, we do not believe that this was a major source of underestimation in this project. Second, some children who present to the hospital with meningitis may be given an alternative diagnosis and be missed by the surveillance system. We attempted to reduce this source of bias by reviewing all hospital admissions on a regular basis. There did not appear to be any missed cases based on these reviews. Third, some children with suspected meningitis did not undergo lumbar puncture or did not have sufficient testing of CSF to permit categorization. We attempted to adjust our results to account for cases that were possibly missed for this reason. Fourth, some cases of suspected bacterial meningitis had no cause identified. In many countries, this finding is probably attributable to frequent outpatient use of antibiotics [4, 6, 15]. In Ulaanbaatar, antibiotic use before hospital admission is also common. Again, we attempted to adjust our results accordingly. The finding in

Indonesia [8] and in Bangladesh [10] that Hib vaccine has a substantially higher impact on all cases of probable bacterial meningitis than on cases of laboratory-confirmed Hib meningitis supports the decision to adjust surveillance results to account for culture-negative cases of probable meningitis.

We also estimated the incidence of childhood meningitis due to *S. pneumoniae* and *N. meningitidis*. Limited data are available on the incidence of pneumococcal meningitis in Asia. We found a higher incidence than has been reported from South Korea [5]. Pneumococcal isolates from this study were not systematically serotyped, and additional research is needed to characterize the serotype distribution of invasive pneumococcal disease in Mongolia to determine the potential benefit of pneumococcal conjugate vaccine. The incidence of *N. meningitidis* meningitis was also substantial in our study; of 16 cases in which the serotype was known, 8 (50%) were due to serogroup A, and 8 (50%) were due to serotype B.

CONCLUSION

Hib was the leading cause of bacterial meningitis in Ulaanbaatar, and the incidence was higher than has been reported from other Asian countries, primarily because a larger proportion of suspected bacterial meningitis cases had a cause identified. These data support the recent decision to introduce Hib vaccination into the routine immunization program in Mongolia. This surveillance system is continuing and will be used to monitor the impact of Hib vaccine on meningitis in Ulaanbaatar.

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