Population-based surveillance for bacterial meningitis in the Dominican Republic: implications for control by vaccination

E. GOMEZ[1], M. PEGUERO[1], J. SANCHEZ[2], P. L. CASTELLANOS[3], J. FERIS[2], C. PEÑA[2], L. BRUDZINSKI-LaCLAIRE[4] AND O. S. LEVINE[4]*

[1] *Epidemiología, Secretaría de Estado de Salud Pública y Asistencia Social, Santo Domingo, Republica Dominicana*
[2] *Departmento de Infectología, Clínica Infantil Dr Robert Reid Cabral, Santo Domingo, Republica Dominicana*
[3] *Pan American Health Organization, Santo Domingo, Republica Dominicana*
[4] *Respiratory Diseases Branch, Division of Bacterial and Mycotic Diseases, National Center for Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, GA, USA*

SUMMARY

Quantifying the local burden of disease is an important step towards the introduction of new vaccines, such as *Haemophilus influenzae* type b (Hib) conjugate vaccine. We adapted a generic protocol developed by the World Health Organization for population-based surveillance of bacterial meningitis. All hospitals that admit paediatric patients with meningitis in the National District, Dominican Republic were included in the system and standard laboratory methods were used. The system identified 111 cases of confirmed bacterial meningitis. Hib was the leading cause of bacterial meningitis, followed by group B streptococcus, *S. pneumoniae*, and *N. meningitidis*. Unlike hospital-based case series, this population-based system was able to calculate incidence rates. The incidence of Hib meningitis was 13 cases per 100 000 children < 5 years old. The data from this study were used by the Ministry of Health to support the introduction of routine Hib vaccination and will be used to monitor its effectiveness.

INTRODUCTION

Bacterial meningitis is a leading cause of severe illness and death in developing countries [1–3]. Among children, the leading cause, *Haemophilus influenzae* type b, is preventable by vaccination, and new vaccines against other leading causes, *Streptococcus pneumoniae* and *Neisseria meningitidis*, are under development and should be available soon. These new vaccines are more expensive than the existing ones and consequently, the decision to introduce them as routine vaccines depends, in part, on demonstrating

that the local burden of disease warrants the cost of vaccination, [4, 5].

Hospital-based studies that report the leading causes of bacterial meningitis are common. However, reports of population-based surveillance for bacterial meningitis are relatively uncommon. One distinguishing feature of population-based surveillance is the ability to calculate incidence rates. Incidence rates can be used to estimate the total number of cases expected in an area and they provide a standard measure that can be used to compare various regions. Other important functions of population-based surveillance include providing important information to develop preventive strategies and baseline data to evaluate their effectiveness.

* Author for correspondence: NIAID/DMID/RDB, 6700-B Rockledge Drive, Room 3255, MSC 7630, Bethesda, MD 20892-7630, USA.

As part of a national strategy to assess the potential impact of Hib vaccination in the Dominican Republic, our team established a population-based surveillance system for bacterial meningitis in children < 5 years old. Herein we report on the incidence of bacterial meningitis by agent, age group, and hospital and discuss the implications of these results for the prevention of bacterial meningitis in the Dominican Republic.

METHODS

Population under surveillance

The Dominican Republic is the second largest country in the Caribbean region with a total population of ∼ 7·9 million. In 1996, the per capita gross national product was US$ 1460, and the infant mortality rate was estimated at 45 per 1000 live births [6]. The National District includes the capital, Santo Domingo, and the periurban areas surrounding it. According to national census projections, an estimated 329 000 children < 5 years old reside in the National District.

Case definition

In 1998, population-based surveillance for laboratory-confirmed bacterial meningitis in children < 5 years old was conducted in the National District of the Dominican Republic. The approach to population-based surveillance was developed in order to field test a generic surveillance protocol developed by the World Health Organization [7]. Surveillance personnel visited weekly the 8 hospitals (4 public and 4 private) that regularly admit paediatric patients with serious illnesses. Laboratory records and admission log books were reviewed to identify patients with suspected meningitis. Suspected meningitis was defined by clinical criteria of fever and at least one of the following signs or symptoms: stiff neck, bulging fontanell, irritability, insomnia, convulsions, or headache. In each of these hospitals, lumbar punctures are routinely performed on patients with suspected meningitis. A standardized case-report form was completed for each patient identified. Information collected included demographic data, dates of onset and admission, clinical signs and symptoms, and the results of laboratory (microbiologic and biochemical) testing of cerebrospinal fluid (CSF) samples. Confirmed bacterial meningitis was defined as micro-

biologic isolation or identification by latex agglutination of a bacterium from CSF in a patient < 5 years old who resided in the National District. Probable bacterial meningitis was defined as a patient with suspected meningitis with at least one of the following findings in the CSF: turbid appearance, 100 cells/mm³, > 80 % polymorphonuclear cells, protein > 45 mg/dl, or glucose < 40 mg/dl. For this report, only patients who had onset between 1 Jaunary and 31 December 1998 are included.

Laboratory methods

Several steps were taken to standardize laboratory methods for isolation and identification of bacteria from CSF specimens in each of the hospitals in surveillance. First, all laboratory personnel were trained by surveillance personnel in the proper methods of isolation and identification of *H. influenzae*, *S. pneumoniae*, and *N. meningitidis* from CSF samples. The laboratory at Clinica Infantil Robert Reid Cabral (CIRRC) was identified as the reference laboratory for the surveillance project. The personnel in this laboratory have extensive experience in the isolation and identification of bacteria from CSF and other specimens, including studies of the epidemiology of Hib infections in children [8]. Second, these personnel trained the laboratory personnel in each laboratory to isolate these bacteria from CSF and to use latex agglutination tests. Third, the preparation of all blood and chocolate agar plates was centralized at the CIRRC laboratory. All chocolate agar plates were prepared with supplemental X and V factors. Plates were checked systematically for their ability to support the growth of *H. influenzae*, *S. pneumoniae*, and *N. meningitidis*. In addition to testing in each hospital laboratory, a sample of each CSF specimen was sent to the CIRRC laboratory where results were confirmed. Finally, all positive cultures were sent to the Streptococcal Reference Laboratory, Centers for Disease Control and Prevention, Atlanta, GA for confirmation, serotyping/serogrouping, and antimicrobial susceptibility testing (for *S. pneumoniae* only).

S. pneumoniae cultures were identified and confirmed by alpha haemolysis, optochin sensitivity, and bile solubility. Serotype was determined by the Quellung reaction with type-specific antisera prepared at the CDC. Confirmatory streptococcal serogrouping was done by the Lancefield capillary precipitin method using grouping rabbit antisera [9]. *Streptococcus*

agalactiae serotyping followed a capillary precipitin method [10] with CDC group B streptococcal typing rabbit antisera Ia, Ib, Ic, II, III, V, and VI and Statens Serum Institut typing antisera IV and VII (Copenhagen). Confirmatory testing of *H. influenzae* included X- and V-factor dependency (Remel, Lenexa) and serotyping using Difco (Detroit) *H. influenzae* typing antisera A, B, C, D, E, and F. Discrimination of the Hib isolates was achieved through biotyping [11].

Calculation of rates

Rates were calculated by dividing the number of cases by the denominator of children at risk. For age-specific rates, the population 329 000 children < 5 years old was divided evenly into smaller units of 6 or 12 month age groups, as appropriate. Analysis and calculation of 95 % confidence intervals was conducted using EpiInfo version 6.02 software.

RESULTS

In 1998, 767 cases of suspected meningitis were identified among residents of the National District aged < 5 years and 754 (98 %) had a CSF specimen collected (Table 1). There was a substantial variation in the number of CSF specimens collected by each hospital. While each of the hospitals identified suspected cases of meningitis, 662 of the 754 (88 %) CSF specimens were collected from three hospitals, and 72 % of the total came from the largest children's hospital, CIRRC, alone. Of the 754 with a CSF specimen, 672 (89 %) had biochemical analysis of the specimen performed, and 391 (58 %) of these met the definition of a probable case. One hundred and eleven confirmed cases of bacterial meningitis were identified.

The definition of probable meningitis was based on the presence of one of five CSF indicators. The predictive value positive of each indicator for predicting confirmed bacterial meningitis was 24–51 %. The best predictor of confirmed bacterial meningitis was a cloudy or turbid CSF appearance, and the least sensitive was having ≥ 80 % polymorphonuclear cells. Of the 25 patients who had all 5 indicators present, 16 (64 %) were confirmed as bacterial meningitis (Table 2).

Overall, Hib was the leading bacterial cause of meningitis in children < 5 years old, causing 40 % of all confirmed meningitis (Table 3). The incidence of meningitis and the leading bacterial agents, however,

Table 1. *Distribution of suspected, probable, and confirmed cases by hospital*

	Suspected	Probable	Confirmed
CIRRC	620	309	94
HSLLM	103	62	9
HC FF AA	23	8	2
Other hospitals	21	12	6
Total	767	391	111

Table 2. *Relationship between CSF indicators of bacterial meningitis and the proportion that were confirmed by isolation or latex agglutination*

CSF findings	Cases (*n*)	Confirmed cases (% of probables)
Cloudy/turbid	160	83 (51)
Leucocytosis (> 100 cells/mm³)	191	74 (39)
Protein ≥ 45 mg/dl	265	71 (27)
Glucose ≤ 40 mg/dl	308	80 (26)
≥ 80 % polymorphonuclear cells	45	11 (24)
All five indicators	25	16 (64)

varied substantially by age. Infants < 6 months old had the highest risk of meningitis and most of the infections occurred during the first month of life. Group B streptococcus was the leading cause, with common causes of hospital-acquired infections such as *Serratia marcsesens*, *Pseudomonas* spp., *Klebsiella* spp., and *E. coli* also prominent. The risk of Hib disease peaked in infants 6–11 months old. The incidence of meningitis declined rapidly after the first year of life, with 82 % of cases occurring in the first year of life and 93 % by the age of 2 years. The incidence of bacterial meningitis varied from 13·4 per 100 000 per year for Hib to 2·7 per 100 000 per year for *N. meningitidis*. Overall, 23 patients died during hospitalization. The risk of death varied by organism but less by age. The case-fatality rate was greatest among patients with pneumococcal meningitis (6 of 15 patients, 40 %, died) and lowest among group B streptococcus (13 %) and Hib cases (14 %). Overall 21 % of patients with bacterial meningitis died, but age-specific case-fatality rates did not vary substantially from the overall rate, ranging from 21 % in the age groups 0–5 months, 6–11 months up to 27 % in the 12–23 month old age group.

Serogrouping and serotyping information relevant to the use of polysaccharide-protein conjugate

Table 3. *Cases of confirmed bacterial meningitis in children < 5 years old, by bacteria and age group, National District, Dominican Republic, 1998*

Age group	Microorganism					Total	Incidence (cases per 100 000/year)
	Hib	*S. pneumoniae*	*N. meningitidis*	Group B streptococcus	Other*		
0–5 months	11	6	4	13	19	53 (48)	161·1
6–11 months	24	6	2	2	4	38 (34)	115·5
1 year	6	4	1	0	1	12 (11)	18·2
2–4 years	3	1	2	0	2	8 (7)	4·1
Total	44	17	9	15	26	111	33·7
Incidence (cases per 100 000/yr)	13·4	5·2	2·7	4·6	7·9	33·7	

* Other organisms include 4 *Pseudomonas* spp., 4 *Klebsiella* spp., 14 *Serratia marcsesens*, 1 *Enterobacter* spp., 1 *E. coli*, and 2 unidentified organisms.

vaccines. Isolates from 41 patients were sent to CDC for confirmation and additional testing. Of the 7 pneumococcal isolates available for testing, 4 were serotype 14 and 3 were serotype 6B. Both of these serotypes are included in the current 7-valent, 9-valent, and 11-valent pneumococcal conjugate vaccine formulations under evaluation. Of the 3 group B streptococci tested, two serotypes were identified, serotypes III and VII. The 5 meningococcal isolates were divided between serogroups B and C (1 and 4 isolates, respectively). The 25 *H. influenzae* isolates tested were all serotype B. The *H. influenzae* biotypes identified were 1, 2, and 5 accounting for 72, 24, and 4%, respectively, of isolates. The results of *H. influenzae* serotyping, pneumococcal serotyping, and meningococcal serogrouping from Santo Domingo and CDC were identical.

DISCUSSION

The study shows the value of population-based surveillance for bacterial meningitis in the process of evaluating new vaccines for control of meningitis [12]. By documenting the incidence of bacterial meningitis by bacterial agent (including serogroup/serotype), the potential impact of vaccination, in terms of meningitis cases prevented, can be determined. By assessing the incidence by age, vaccination strategies can be determined to assure the highest risk children are protected and vaccine resources are used efficiently. Furthermore, the development of a population-based surveillance system provides the opportunity to monitor changes in the incidence of meningitis subsequent to vaccine introduction.

Table 4. *Reported annual incidence of Hib meningitis from population-based surveillance systems in Latin America, before the introduction of routine Hib vaccination*

Country	Surveillance period	Meningitis cases per 100 000 children < 5 years
Argentina	1985–92	17
Brazil	1991	24
Chile	1985–7	25
Dominican Republic	1998	13

References [13, 15, 16].

The finding of Hib as the most common cause of bacterial meningitis in children < 5 years old is consistent with many other studies, including hospital-based studies [13, 14]. The incidence of Hib meningitis observed was somewhat lower, however, than other population-based studies from South America (Table 4). For example, in the only other population-based data from the region, rates of 17, 24, and 25 cases of Hib meningitis per 100 000 < 5 year olds per year were reported from Argentina, Brazil, and Chile [13, 15, 16]. The somewhat lower rate observed in this study may reflect, in part, the fact that some Hib vaccination is already being used in the Dominican Republic. For example, nearly all private paediatricians administer Hib vaccine routinely to their clients who can afford to pay for it. Furthermore, in May 1997 the Ministry of Health used a large donation of Hib vaccine to administer a single dose of vaccine to all 1-year-olds nationwide.

The importance of group B streptococcus as a cause of meningitis in young infants in the Dominican Republic was not well appreciated before this surveillance system was started. The role of latex agglutination in describing this pattern was essential. Of the 15 cases of group B streptococcal meningitis identified, 8 (53%) were culture-negative specimens identified by latex agglutination only. Nearly 25 000 infants per year are born in the two major maternal–infant hospitals in Santo Domingo annually. Consequently, it may be worthwhile to investigate the feasibility of implementing intrapartum prophylaxis guidelines in these hospitals to prevent group B streptococcal meningitis in newborns [17, 18]. The prominence of several Gram-negative infections in the newborn period and its associated mortality highlights the importance of improving infection control in hospitals in developing countries.

The rates of culture-confirmed bacterial meningitis reported here probably represent a minimal estimate of the burden of meningitis in the Dominican Republic. First, there is a high rate of probable bacterial meningitis that was not confirmed by culture or latex. In some instances, the patient may have been partially treated with antibiotics, and consequently, the negative results may represent a 'false-negative'. Also, 106 patients with probable bacterial meningitis did not have culture or latex testing performed on their CSF specimens. Of the 228 probable cases that had culture and latex testing done, 44 (15·4%) were positive for Hib. Assuming that 15·4% of the 106 untested probable cases were due to Hib, an additional 16 patients with Hib meningitis may have been missed. The inclusion of these 16 additional cases would have increased the annual incidence of Hib meningitis to 18 cases per 100 000 children < 5 years old. Second, the National District is not representative of the entire country. A largely urban area, residents of the National District may have generally better access to care than many of the more rural areas of the country. Efforts are underway to build upon the success of this system in the National District by expanding surveillance to other areas of the country.

The results of serotyping and serogrouping of the pneumococcal, meningococcal, and group B streptococcal isolates provide useful data for evaluating new vaccines. New generation pneumococcal and meningococcal conjugate vaccines, based on the same principle as the highly successful Hib conjugate vaccines, are near licensure. The first generation of vaccine will protect against seven pneumococcal serotypes and the first meningococcal conjugate vaccine licensed may only protect against serogroup C. However, these vaccines are going to be much more expensive than existing vaccines and the proportion of all infections covered by these formulations may vary by region [19], and thus, local data on the important pneumococcal serotypes and meningococcal serogroups causing disease in children will be important for determining whether to introduce these vaccines as a routine immunization [20]. Group B streptococcal conjugate vaccines are under development but will eventually be subject to the same issues of serotype-specific immunity as the pneumococcal and meningococcal vaccines.

The data from this surveillance system also provided valuable feedback to practising physicians in the community. The evaluation of the predictive value positive of various indicators of bacterial meningitis is useful reinforcement of these commonly used tests. Although not presented here, the isolates obtained during surveillance can be tested for their susceptibility to commonly used antibiotics and thereby assist physicians with the rational selection of agents for empiric therapy of bacterial meningitis.

The surveillance system described in this paper was based on the WHO generic protocol for assessing the burden of Hib meningitis [7]. Its success represents the concerted and coordinated efforts of clinicians, laboratorians, and epidemiologists to address an important issue in the process of evaluating a new vaccine. In the process, this activity has strengthened links between these groups in all areas. Importantly, the data from this surveillance system were recently used by the Ministry of Health to take a decision on routine Hib immunization in the Dominican Republic. The Ministry plans to institute routine vaccination in the autumn of 2001, and to use this surveillance system as a way to monitor the impact of vaccination on meningitis incidence, and as a source of cases for a case-control study of vaccine efficacy.

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