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## Hospital-based surveillance of meningococcal meningitis in Salvador, Brazil

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### Summary

This study aimed to describe the clinical, epidemiological and microbiological features of meningococcal meningitis in Salvador, Brazil. Between February 1996 and January 2001, a hospital-based surveillance prospectively identified cases of culture-positive meningococcal meningitis. Demographic and clinical data were collected through interview and medical chart review. Antisera and monoclonal antibodies were used to determine the serogroup and serotype:serosubtype of the isolates, respectively. Surveillance identified a total of 408 cases of meningococcal meningitis, with a case fatality rate of 8% (32/397). The mean annual incidence for the 304 culture-positive cases residing in metropolitan Salvador was 1.71 cases per 100 000 population. Infants <1 year old presented the highest incidence (14.7 cases per 100 000 population). Of the 377 serogrouped isolates, 82%, 16%, 2% and 0.3% were serogroups B, C, W135 and Y, respectively. A single serotype:serosubtype (4,7:P1.19,15) accounted for 64% of all cases. Continued surveillance is necessary to characterise strains and to define future prevention and control strategies.

### Keywords

Meningococcal disease; Meningitis; *Neisseria meningitidis*; Serogroup; Epidemiology; Brazil

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**Authors' contributions:** MGR and AIK conceived the idea for the project; SMC, ELG, JNR and AIK designed the study protocol; ABN, CTR, TSL, ELG and GSR performed the clinical evaluations and patient interviews; JNR, KMS and SMC performed the laboratory analyses; SMC, CTR, ABN, MLP and ELG performed the data analysis; SMC, ABN and MLP drafted the manuscript and JNR, MGR and AIK made the final revision. All authors read and approved the final manuscript. AIK is guarantor of the paper.

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## 1. Introduction

*Neisseria meningitidis* is a common cause of disease worldwide, responsible for significant morbidity and mortality in infants and young children (Bilukha and Rosenstein, 2005). Without appropriate antimicrobial treatment, most cases of meningococcal meningitis are fatal (Flexner, 1913), and even with prompt intervention the case fatality rate (CFR) reaches 10% (Caugant, 1998). Among those who survive, permanent sequelae, including deafness, cognitive impairment and paralysis, are common (Edwards and Baker, 1981;Kirsch et al., 1996).

In 1999, the UK introduced a highly efficacious protein-conjugate vaccine against *N. meningitidis* serogroup C (Trotter et al., 2004). Six years later, a tetravalent conjugate meningococcal vaccine, including the capsular polysaccharides of serogroups A, C, Y and W-135, was licensed for use among persons aged 11–55 years (Bilukha and Rosenstein, 2005). Despite these advances, an effective vaccine against serogroup B, a major cause of invasive meningococcal disease in many European countries and the Americas, is not currently available (Bjune et al., 1991;De Moraes et al., 1992;Sierra et al., 1991;Tappero et al., 1999;Tsolia et al., 2006). Future prevention of serogroup B disease will rely both on outer membrane vesicle (OMV) vaccines being used for specific serosubtypes and new vaccines containing multiple other antigens.

In Brazil, serogroup B meningococcal disease has been endemic since the 1980s and is associated with the majority of meningococcal disease. Furthermore, specific serotype:serosubtype combinations of the ET-5 complex, including B:4,7:P1.19,15, have been identified as the predominant serogroup B strain both in epidemic and endemic situations (Sacchi et al., 1992,2001).

Data on the epidemiology of meningococcal meningitis from population-based surveillance is necessary to characterise better circulating strains and to guide decisions regarding future prevention and control strategies for meningococcal meningitis. However, prior studies in Brazil were based on notification reports and on isolate collections. In the present study, we report the clinical, epidemiological and microbiological findings of a 5-year active hospital-based surveillance for meningococcal meningitis in Salvador, Brazil.

## 2. Materials and methods

### 2.1. Surveillance

From 1 February 1996 to 31 January 2001, active hospital-based surveillance for meningococcal meningitis was performed in Couto Maia Hospital, the state reference hospital for infectious diseases in Salvador, Brazil. Currently, metropolitan Salvador is the third largest urban area in Brazil, with a population of 2.6 million inhabitants (Brazilian Institute for Geography and Statistics, 2002). As part of the State Health Department protocol, all suspected cases of meningitis should be referred to this hospital, where diagnostic evaluation, including lumbar puncture and cerebrospinal fluid (CSF) analysis, is performed at the emergency room. Notification of meningitis cases to state health officials is mandatory and the study hospital reports 98% of the cases among residents of metropolitan Salvador. After the initial evaluation, patients with evidence of meningitis are admitted. Rarely, they are transferred to another facility.

During the surveillance period, project personnel reviewed the clinical laboratory results 5 days a week to identify culture-confirmed cases of meningococcal meningitis. All patients with clinical signs and symptoms of meningitis and CSF culture positive for *N. meningitidis* were entered into the study according to the study protocol.

A standardised data entry form was administered for each case, which collected information on demographics, clinical history and laboratory findings during patient interviews and medical chart review. Physicians routinely performed neurological examinations and assessment of sequelae during hospitalisation. Information on sequelae present at the time of hospital discharge were analysed.

## 2.2. Laboratory methods

*Neisseria meningitidis* isolates from CSF cultures were incubated overnight at 37°C on chocolate agar in a CO<sub>2</sub> atmosphere. Coagglutination with specific antisera was used to identify the isolate serogroup (Difco Laboratories, Detroit, MI, USA). Monoclonal antibodies were used to identify isolate serotype and serosubtype, using the dot-blot method as described previously (Wedge et al., 1990).

## 2.3. Statistical analysis

Patients residing in the city of Salvador or in one of the 29 municipalities located within 75 km of Salvador (aggregate population of 3.5 million) were included for incidence calculations. The surveillance hospital is the only infectious disease reference centre within this metropolitan area. Incidence calculations were based on the 2000 Brazilian census, provided by the Brazilian Institute for Geography and Statistics without adjusting for population growth (Brazilian Institute for Geography and Statistics, 2002).

Data were entered and managed by Epi Info version 6.04 (CDC, Atlanta, GA, USA) and analysed with SAS for Windows version 8.02 (SAS Institute, Cary, NC, USA) and Epi Info version 6.04. Ratios and 95% CI were calculated by the Mid-P algorithm (Berry and Armitage, 1995). Statistical significance for comparison of proportions was assessed by  $\chi^2$  test or, when the expected cell value was <5, by Fisher's exact test. Median values were compared by the Kruskal–Wallis method. Differences were considered statistically significant when the two-tailed *P*-value was <0.05.

## 3. Results

During the 5-year study period of active hospital-based surveillance, 408 cases of meningococcal meningitis were identified. The monthly number of cases of meningococcal meningitis varied by season, with the highest proportion of cases observed during the months of increased rainfall in the fall and winter and the lowest proportion of cases occurring during the summer (Figure 1).

Epidemiological data were available for 397 (97%) of the cases. The CFR was 8% (32/397) and neurological sequelae occurred in 3% (11/365) of survivors at the time of hospital discharge (Table 1). The CFR was significantly higher in cases presenting with petechiae (11% vs. 3%; *P* = 0.003) and in cases with a hospital course including seizures (15% vs. 6%; *P* = 0.04). Blood cultures were performed for 28% of the patients (112/397), of whom 31% (35/112) had positive cultures for *N. meningitidis*. Patients with positive blood culture results had a higher CFR (17% vs. 5%; *P* = 0.06).

The mean annual incidence of meningococcal meningitis, based on the 304 culture-positive cases who were residents of metropolitan Salvador, was 1.71 cases per 100 000 population between February 1996 and January 2001 (Table 2). During the same period, the incidence of culture-positive *Streptococcus pneumoniae* and *Haemophilus influenzae* meningitis was 1.38 and 2.05 cases per 100 000 population, respectively. Overall annual incidences of meningococcal meningitis were 2.00, 1.55, 2.23, 1.55 and 1.24 per 100 000 population in Years 1 through 5, respectively ( $\chi^2$  test for trend, *P* = 0.029). The age-specific incidence was highest

in children <1 year of age (14.7/100 000), peaking at age 4–5 months (29.4/100 000) and declining with increasing age thereafter (Table 2).

Laboratory data were available for 377 (92%) of the cases. Serogroup B was the most frequent serogroup (309/377; 82%), followed by serogroup C (60/377; 16%), W135 (7/377; 2%) and Y (1/377; 0.3%) (Table 1). The most frequent serotype:serosubtype was 4,7:P1.19,15, followed by 4,7:P1.7,1, then 4,7:P1.3 and 2a:P1.2, which were identified in 63.7%, 3.7%, 2.7% and 2.4% of cases, respectively (Table 3).

The median age of patients with serogroups B, C and W135 disease was 7, 10, and 9 years, respectively. Patients with serogroup C disease were more likely to be >2 years of age compared with other serogroup infection (87% vs. 73%;  $P = 0.03$ ), whilst patients with serogroup B isolates were more likely to be <2 years old (27% vs. 15%;  $P = 0.05$ ).

#### 4. Discussion

This study describes the clinical, epidemiological and microbiological features of meningococcal meningitis in Salvador, Brazil. Active hospital-based surveillance was performed in metropolitan Salvador and detected a mean annual incidence of 1.71 cases of meningococcal meningitis per 100 000 population, with a CFR of 8.1%. These rates are comparable with those seen in the USA and Europe (Bilukha and Rosenstein, 2005; Rosenstein et al., 1999, 2001). As a caveat, rates of culture-positive meningococcal meningitis are likely to underestimate the true disease burden, which is expected to be higher than that encountered in developed countries, since case ascertainment may not have been complete and use of antibiotics prior to hospitalisation may have interfered with the efficiency of culture isolation.

Our data support previous observations where the incidence of meningococcal meningitis was higher in young children, peaking in infants 4–5 months of age (Peltola, 1983; Rosenstein et al., 1999). However, in the USA and Europe, an elevated rate of meningococcal disease has been reported among teenagers and young adults (Cartwright et al., 2001; Rosenstein et al., 1999). In this situation, increased risk was associated with exposure to diverse strains of *N. meningitidis* during college attendance, especially for students residing in dormitories (Cartwright et al., 2001; Rosenstein et al., 2001). In contrast, meningococcal meningitis cases in Salvador were predominantly members of poor slum (*favela*) communities. A large proportion of the population is presumably exposed early in life owing to high endemic transmission of meningococcal strains in these densely populated communities. The lower attack rates observed among adolescents and adults in comparison with infants may relate to early acquisition of naturally acquired immunity in this high transmission setting.

Increased numbers of meningococcal cases tended to occur during the fall and winter months in Salvador, which is situated in the Southern Hemisphere tropics and has a mean daily relative humidity of 75–90%. The fall and winter seasons occur between April and September and correspond to the seasonal period of increased rainfall and cooler temperatures. However, variation in temperature is small throughout the year with mean temperatures ranging between 25 °C and 34 °C. In temperate zones in the Northern Hemisphere, seasonal increases in meningococcal cases occurs during the winter and spring (Jackson and Wenger, 1993). Seasonality may vary from place to place depending on other risk factors such as age and meningococcal phenotype (Jensen et al., 2003). The observed seasonal increase in cases in Salvador may relate to rainfall and, in turn, to increased household crowding during these periods, which facilitates transmission. However, evaluation of seasonal patterns and the influence of climatic factors will require the use of appropriate analytical approaches such as time-series modelling.

Serogroup B meningococcus emerged in the 1990s to become the major cause of meningococcal meningitis in Salvador. Eighty-two percent of cases were caused by serogroup B strains and 64% of all cases were caused by a single serosubtype, P1.19,15. These findings confirm results from passive surveillance performed throughout Brazil in 2001, in which 67% of cases were caused by serogroup B and 54% were caused by serosubtype B:4,7:P1.19,15 (Lemos et al., 2006). The high predominance of a single serogroup and serosubtype and the moderately high incidence sustained throughout the study period are characteristic of extended outbreaks, as described in Latin America and other parts of the world following introduction and establishment of strains from the ET-5 complex (Caugant, 1998;Caugant et al., 1987;Diermayer et al., 1999;Poolman et al., 1986;Sacchi et al., 2001).

The overwhelming dominance of serogroup B disease shows that there is no indication for administration of a capsular vaccine against serogroups A and C in Salvador at this time. Continued follow-up in the same hospital revealed that to date serogroup B has remained the prominent serogroup in Salvador, Brazil (data not shown). However, the incidence of serogroup C has increased in most regions of Brazil since 2002, mainly in the southeastern area (SVS/MS, 2005). Thus, continued surveillance is necessary to detect possible changes in the meningococcal meningitis pattern.

Owing to the poor immunogenicity of the serogroup B capsular polysaccharide, attempts to develop a vaccine protecting against serogroup B disease have involved many bacterial components, including the proteins determining type and subtype specificity. An effective OMV-based vaccine against the dominant serosubtypes present in Brazil could prevent significant morbidity and mortality. The OMV vaccines can be 'tailor-made' and current approaches to vaccine development have been based on preparations derived from strains such as B:4,7:P1.19,15, which are the most predominant invasive strains in high endemicity settings. To address the potential usefulness of such vaccines, it is important to monitor the circulating serogroup B phenotypes as defined by serotype:serosubtype patterns (Lind and Berthelsen, 2005).

A hexavalent OMV-based vaccine developed in The Netherlands against six common serosubtypes (P1.19,15, P1.7,1, P1.7,4, P1.5,2, P1.5,10 and P1.12,13) appears to be safe and immunogenic in adults and older children (Pollard and Levin, 2000). This vaccine, which includes strains with serosubtypes that account for 70.6% of cases of meningococcal meningitis in Salvador, would be a candidate for use in Salvador if it proves efficacious. However, existing limitations of OMV-based meningococcal vaccines, including lower efficacy in young children (Costa et al., 1996;De Moraes et al., 1992;Sierra et al., 1991;Tappero et al., 1999), inability to induce immunological memory (Wedge et al., 1998) and failure to provide cross-protection against non-vaccine strains, may delay their use (Pollard and Levin, 2000). Alternatively, reverse vaccinology approaches have identified antigens that induce antibactericidal antibody responses against the spectrum of meningococcal serogroup B strains associated with invasive disease (Giuliani et al., 2006;Masignani et al., 2003). These target antigens are being evaluated as candidates for a universal serogroup B subunit vaccine and, if effective, will be an important intervention against this disease in epidemiological situations such as encountered in Brazil.

In conclusion, this is the first active hospital-based surveillance study of meningococcal meningitis in Brazil since the 1970s. It confirms that the epidemiological features of meningococcal meningitis have changed dramatically over the past three decades in Brazil, with the disappearance of large-scale epidemics caused by serogroups A and C and the introduction and establishment of serogroup B strains of the ET-5 complex (Sacchi et al., 2001). This study demonstrates that potentially important differences exist between the epidemiological features of meningococcal disease in Brazil and the developed world. Improved understanding of these differences and of the changing trends in the epidemiological



features of this disease is essential to plan and implement strategies in order to prevent and reduce the high morbidity and mortality caused by *N. meningitidis*. It is noteworthy that the active hospital-based surveillance became continuous and has provided valuable information regarding meningococcal meningitis today.

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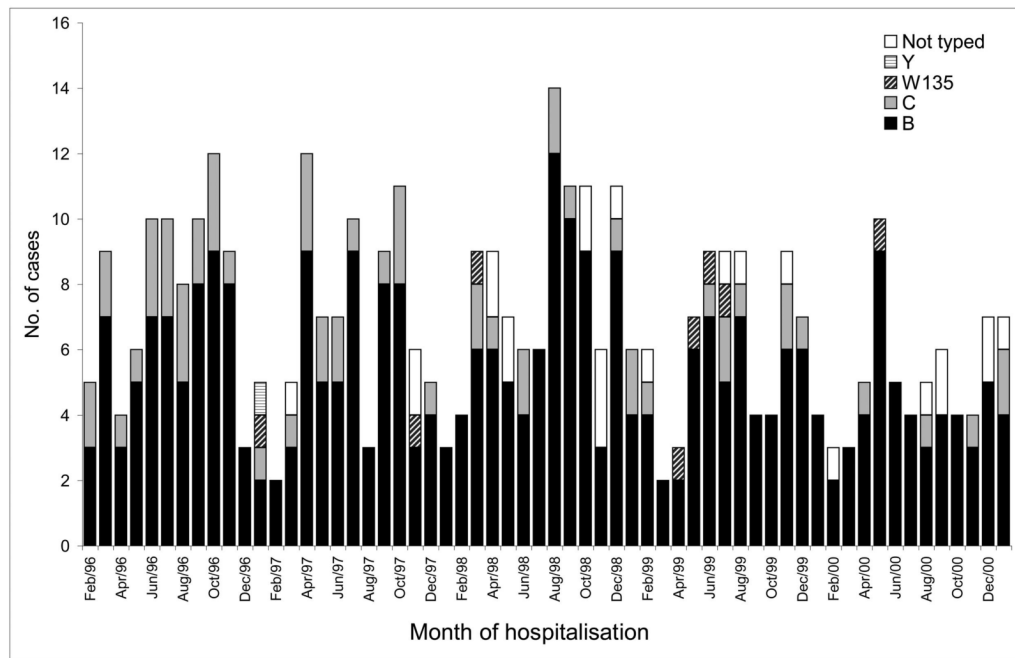
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**Figure 1.** Distribution of meningococcal meningitis cases according to serogroup and month of identification during active hospital-based surveillance in Salvador, Brazil.

**Table 1**

Characteristics of the *Neisseria meningitidis* cases identified during active hospital-based surveillance in Salvador, Brazil, between February 1996 and January 2001

Characteristic	Total no. of responses	No. (%) of patients <sup>a</sup>
Demographic data		
Male sex	397	223 (56)
Age 0–2 years	397	98 (25)
Median (range) age (years)		8 (0–66)
Clinical presentation		
Fever	325	319 (98)
Nausea or vomiting	325	268 (82)
Purpura or petechiae	342	141 (41)
Nuchal rigidity	326	134 (41)
Seizures	326	51 (16)
Neurological focal signs	281	13 (5)
Hospital course		
Seizures	373	41 (11)
ICU admission	377	53 (14)
Laboratory data		
CSF examination		
Median (range) leukocyte count ( $\times 10^3 \mu/l$ )	393	10.0 (7.0–21.2)
Median (range) glucose level (mg/dl)	394	20 (0–220)
Median (range) protein level (mg/dl)	392	300 (0–800)
Positive blood culture	112	35 (31)
Serogroup		
B	377	309 (82)
C	377	60 (16)
W135	377	7 (2)
Y	377	1 (0.3)
Clinical outcome		
Median (range) days of hospitalisation	383	11 (0–43)
Neurological sequelae on hospital discharge <sup>b</sup>	323	11 (3)
No. of deaths (case fatality rate (%))	397	32 (8)

ICU: Intensive Care Unit; CSF: cerebrospinal fluid.

<sup>a</sup>Data are No. (%) of patients, unless otherwise indicated.

<sup>b</sup>Sequelae among 323 survivors with available information included ataxia (5), auditory deficit (3), motor deficit (2) and cognitive deficit (1).

Annual incidence of meningococcal meningitis and case fatality rates (CFR) by age group and year during active surveillance in Salvador, Brazil, between February 1996 and January 2001 <sup>a</sup>

Table 2

Age group (years)	No. of cases	No. (%) of deaths (CFR)	Annual incidence <sup>b</sup>				Average incidence
			1996	1997	1998	1999	
<1	47	5 (10.6)	20.3	15.6	9.4	14.1	14.7
1-2	35	2 (5.7)	3.9	5.4	10.1	2.3	5.4
3-4	30	1 (3.3)	8.7	0.8	6.3	5.5	2.4
5-9	55	5 (9.1)	2.8	3.5	5.0	2.5	3.5
10-14	52	4 (7.7)	3.5	4.1	3.5	2.0	3.0
15-19	40	2 (5.0)	2.4	1.4	2.9	1.9	1.9
20-29	23	3 (13.0)	0.6	0.6	1.3	0.6	0.7
30-39	12	1 (8.3)	0.7	0.2	0.4	0.7	0.4
40-49	4	2 (50.0)	0.5	0.2	0.0	0.2	0.2
50-59	1	0 (0)	0.4	0.0	0.0	0.0	0.1
>60	1	0 (0)	0.0	0.0	0.4	0.0	0.1
All ages	300	25 (8.3)	2.00	1.55	2.23	1.55	1.71

<sup>a</sup>The table encompasses cases from the metropolitan region of Salvador ( $n = 304$ ) less 4 cases whose ultimate outcome was unknown.

<sup>b</sup>Cases per 100 000 inhabitants. In 1996, all incidence data were corrected to represent a 12-month period.

**Table 3**

Serotype:serosubtype distribution of *Neisseria meningitidis* isolates identified during active surveillance in Salvador, Brazil, between February 1996 and January 2001

Serotype:serosubtype	No. (%) of isolates (n = 377)
4,7:P1.19,15	240 (63.7)
4,7:P1.7,1	14 (3.7)
4,7:P1.3	10 (2.7)
2a:P1.2	9 (2.4)
2a:P1.5,2	6 (1.6)
2b:P1.5	5 (1.3)
4,10:P1.9	5 (1.3)
4,7:nt	5 (1.3)
7:P1.19,15	5 (1.3)
Other <sup>a</sup>	64 (17.0)
Non-typeable	14 (3.7)

<sup>a</sup>Other includes serotype:serosubtype strains isolated at a frequency of <1%.