

Published in final edited form as:

Int J Infect Dis. 2009 July ; 13(4): 456–461. doi:10.1016/j.ijid.2008.09.006.

Burden of group A streptococcal meningitis in Salvador, Brazil: report of 11 years of population-based surveillance

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1.2 Summary

Background—Over recent decades, a resurgence of invasive group A streptococcal (GAS) infections has been observed; GAS remains a rare cause of pyogenic meningitis. We report herein population-based findings of long-term surveillance for GAS meningitis in Salvador, Brazil, and estimate the overall burden of invasive GAS infections.

Methods—From February 1996 to January 2006 we conducted active surveillance for GAS meningitis in the state reference hospital for infectious diseases in Salvador, Brazil. Data on clinical presentation, laboratory records, and outcome were collected through interviews and chart review. GAS isolates were evaluated for antimicrobial susceptibility and *emm* type.

Results—We identified 20 cases of GAS meningitis, which accounted for 0.9% of all culture-proven bacterial meningitis in the study period. The mean annual incidence of GAS meningitis was 0.03 cases per 100 000 population in metropolitan Salvador and peaked in children <1 year of age (0.67 cases per 100 000 population). Among 17 cases with clinical information available, 41% required intensive care unit support and 25% died. Tested isolates were susceptible to penicillin and exhibited large *emm* type diversity. Based on the incidence of GAS meningitis, we estimate that the annual incidence of GAS infection is 3 cases per 100 000 population in metropolitan Salvador.

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Corresponding Editor: Timothy Barkham, Tan Tock Seng, Singapore

Conflict of interest: The authors do not have any commercial or other association that might pose a conflict of interest.

Ethical approval: Ethical approval was obtained from the institutional review boards of the Oswaldo Cruz Foundation, Brazilian Ministry of Health in Salvador, Bahia, Brazil, and Weill Medical College of Cornell University in New York, NY, USA.

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Conclusions—Although rare, GAS is a life-threatening cause of bacterial meningitis. Knowledge of the incidence and *emm* type variability of the disease is necessary for planning immunization strategies.

Keywords

Streptococcus pyogenes; Group A streptococcus; Meningitis; M typing

1.2.1 Introduction

Streptococcus pyogenes, also known as group A Streptococcus (GAS), is one of the most common human pathogens and causes a wide spectrum of disease, including invasive and non-invasive infections, as well as non-suppurative complications.^{1,2} In the late 1980s, global attention to GAS increased because of reports of severe invasive GAS infections.^{3–5} Recently, Carapetis et al. reviewed population-based data to estimate the worldwide burden of GAS diseases. They found an unexpectedly high figure of over 660 000 cases of invasive GAS infections and 163 000 deaths each year.⁶ Although epidemiological studies from Europe and the USA have shown a sustained, high incidence of severe invasive streptococcal infections,^{7,8} there are scarce data on the burden of invasive GAS infections in developing countries, where the burden is expected to be higher.⁶

Meningitis is an uncommon presentation for GAS invasive disease, accounting for only 1% of all GAS systemic infections.^{7–9} Conversely, GAS is an uncommon source of meningitis; less than 1% of all bacterial meningitis is due to GAS.^{10,11} Most articles about GAS meningitis are case reports with clinical descriptions of disease. There is little population-based data on the frequency and severity of the invasive GAS disease in less developed countries.

We report herein the epidemiology and clinical characteristics of GAS meningitis cases prospectively identified during 11 years of population-based surveillance for bacterial meningitis in Salvador, Brazil. We used GAS meningitis incidence data to estimate the overall burden of invasive GAS infections in the region. In addition, we evaluated the microbiologic features of the isolates to determine their *emm* type (M-protein gene) distribution and penicillin susceptibility.

1.2.2 Materials and methods

Surveillance

In 1996, we established hospital-based surveillance for bacterial meningitis at Hospital Couto Maia, the state infectious disease reference hospital, in Salvador, Brazil. State health procedures require that all suspected cases of meningitis in the region be referred to this hospital for diagnostic procedures, including routine lumbar puncture, cerebrospinal fluid (CSF) examination, and isolation precaution as indicated. Notification of bacterial meningitis cases to health officials is mandatory in Brazil, and the study hospital reports 95% of the cases among residents of metropolitan Salvador. From February 10, 1996, to February 9, 2006, the study team actively reviewed laboratory records 5 days a week to identify new culture isolates from patients with suspected meningitis.

Case definition and data collection

A case of culture-proven bacterial meningitis was defined as a patient who had: (1) clinical presentation of meningitis, characterized by fever, neck stiffness, and altered mental status, (2) abnormal CSF examination, and (3) positive CSF or blood culture. A case of culture-proven GAS meningitis was defined as above, with the addition of culture isolation of *S. pyogenes*.

The study team of physicians and medical students conducted interviews and medical record reviews, using a standardized data entry form to collect information on demographics, clinical presentation, and outcome characteristics. Patients were enrolled in the study according to informed consent procedures approved by the institutional review boards of the Oswaldo Cruz Foundation, Brazilian Ministry of Health, and the New York-Presbyterian Hospital, New York, USA.

Laboratory analysis

GAS isolates were identified on the basis of standard methods, which included colony morphology, hemolytic activity on blood agar medium, Gram staining characteristics, catalase reaction, and susceptibility to bacitracin. We used Lancefield group A-specific antiserum (Avipath-Strep, Omega Diagnostics, UK) to confirm the isolate serogroup. Penicillin susceptibility was tested using the broth microdilution method as recommended by the Clinical and Laboratory Standards Institute (CLSI).¹² *Emm* typing was performed on the basis of sequencing of the variable M serotype-specific region of the *emm* gene amplicon as described by the Centers for Disease Control and Prevention (CDC) protocol.¹³ The type was assigned using the *emm* type database at CDC¹⁴ and GenBank (<http://www.ncbi.nlm.nih.gov/BLAST/>).

Statistical analysis

Epi Info version 3.2 software (CDC, Atlanta, GA, USA) was used for data entry and statistical analysis. Categorical and continuous variables are presented as number and proportion, and median and range, respectively. We estimated the mean annual cumulative incidence for GAS meningitis for cases with residence in metropolitan Salvador, a region comprised of Salvador and 10 surrounding municipalities (population 3 021 572). Based on the incidence of GAS meningitis for metropolitan Salvador and on recent population-based studies from Europe, the USA, and Canada showing that meningitis corresponds to 1% of all cases of invasive GAS disease,^{7–9} we estimated the overall burden of invasive GAS infections for metropolitan Salvador. Incidences were calculated using population data from the 2000 Brazilian National Census.¹⁵

1.2.3 Results

Burden of GAS infections

During the 11-year study period, the surveillance hospital consecutively identified 2255 cases of culture-positive bacterial meningitis, of which 20 (0.9%) were identified as GAS meningitis. Based on the nine (45% of 20) cases that resided in metropolitan Salvador, the mean annual incidence of GAS meningitis was 0.03 cases per 100 000 population. Children <1 year old had the highest incidence (0.67 cases per 100 000 population), which markedly decreased with age (Figure 1). The incidence for age groups <5, <19, and ≥ 20 years of age were 0.17, 0.05, and 0.01 cases per 100 000 population, respectively. Meningitis is believed to account for 1% of all invasive GAS infections.^{7–9} Based on this ratio and the observed incidence of GAS meningitis in Salvador, we estimate that the annual incidence of GAS infection is 3 cases per 100 000 population.

Case characteristics and outcome

Overall, GAS meningitis patients had a median age of 4.5 years (range 19 days–52 years). Of note, eight (40%) cases occurred in children <1 year old and two (10%) in newborns <1 month of age. Males accounted for 11 (55%) cases. Data on clinical presentation and outcome were available for 17 of the 20 cases. The median length of symptoms before hospitalization was 3 days. The majority of cases presented with fever, vomiting, headache, and seizures; the most

frequent findings on clinical exam were neck stiffness and altered mental status (Table 1). We were able to identify a presumptive source of infection for 10 cases (59% of 17), which included otitis media (four cases), rhinopharyngitis (three cases), and ventriculoperitoneal shunt, meningomyelocele, and mild cranial trauma (one case each) (Table 2).

All 17 cases received penicillin or ceftriaxone as the initial antibiotic therapy, and eight (47%) cases also received steroids on the first day of treatment. Intensive care unit (ICU) admission was indicated for seven (41%) cases. Despite ICU care, four (25% of 16) patients died. Outcome was unknown for one of the 17 patients, who was transferred to another hospital. Although age was not significantly associated with a poor outcome, all deaths occurred in patients <15 years of age (Table 2).

Laboratory analysis

All 20 cases of GAS meningitis had positive CSF cultures, while two (18%) had positive blood cultures among the 11 patients from whom cultures were obtained. Complete data on the CSF findings were available for 19 of the 20 cases. The median CSF white cell count was 2.4×10^9 cells/l (interquartile range (IQR): $0.65\text{--}9 \times 10^9$ cells/l), median glucose was 20 mg/dl (IQR: 20–22 mg/dl), and median protein was 400 mg/dl (IQR: 250–500 mg/dl).

We examined penicillin susceptibility for 17 GAS strains isolated from cases with clinical information available. All tested isolates were fully susceptible to penicillin; the minimum inhibitory concentration ranged from <0.016 $\mu\text{g/ml}$ to 0.062 $\mu\text{g/ml}$. *emm* typing of the 20 isolates found 17 different *emm* type sequences. *emm* types 25 and 73 were found in more than one isolate (three isolates (18% of 20) and two isolates (12% of 20), respectively) (Table 2). Among the 20 isolates, two had *emm* types (11 and 92) that are represented in the 26-valent GAS vaccine.

1.2.4 Discussion

This series of 20 cases of GAS meningitis in Salvador, Brazil is the largest reported from a developing country. GAS meningitis corresponded to 0.9% of all cases of culture-proven bacterial meningitis, consistent with previous reports of 0.2% to 1% of cases.^{10,11}

The overall incidence of GAS meningitis was similar to the incidence of 0.04 cases per 100 000 population found in the Netherlands between 1987 and 2000.¹¹ The Dutch incidence was 0.06 cases per 100 000 in children and 0.03 cases per 100 000 in adults, similar to ours results, although we found that children <1 year of age had a risk (0.67 cases per 100 000 population) 15 times greater than that for the rest of the population. The identification of this high-risk age group may have implications for future GAS immunization programs.

A review estimated the annual incidence of invasive GAS infections to range from 2.45 cases per 100 000 population in more developed countries to 13.00 cases per 100 000 population in less developed countries.⁶ Although Brazil is considered a middle-income country, the estimated burden of GAS invasive disease of 3 per 100 000 for Salvador is closer to that described for developed countries. This may be due to inaccuracy in our estimation. However, the basis for the estimate for less developed countries was a single population-based study in Kenya; this prediction, therefore, may not be valid for Brazil, since health statistics in Brazil differ from those of Kenya.^{16,17} Moreover, as the incidence of GAS meningitis for metropolitan Salvador was similar to that of the Netherlands, we believe that our estimate of the burden of invasive GAS in Salvador is reliable.

Although many reports have suggested that GAS meningitis usually occurs in association with a recognized infection focus, most commonly upper respiratory tract infections, the absence

of a predisposing condition has also been reported.^{18–23} In our study, 59% of the GAS meningitis cases were preceded by a predisposing factor, most commonly otitis media or rhinopharyngitis. Since GAS infections of the upper respiratory tract are among the most common non-invasive presentations of GAS diseases and GAS meningitis is a rare disease, it would be of interest to study the mechanisms that lead from GAS invasion of the upper respiratory mucosa to the pathogenesis of central nervous system infections.

Case-fatality data for GAS meningitis are somewhat controversial. Literature reviews of well-documented cases of GAS meningitis, including all age groups, have estimated a case-fatality rate ranging from 4% to 12%.^{19,22,23} However, literature reviews are limited by publication bias and combinations of cases from heterogeneous settings where management differences may influence outcome. In 2002, van de Beek et al. reported the largest case series of GAS meningitis in adults.¹¹ Using the database of the Netherlands Reference Laboratory for Bacterial Meningitis to identify GAS meningitis cases, they found a case-fatality rate of 27%, similar to our data, but at least twice that found in other review articles.^{19,22,23} This cannot be explained by antimicrobial resistance. All 17 cases with available clinical information were treated with a β -lactam antimicrobial agent or a third generation cephalosporin and as anticipated, all strains were susceptible to these agents. Since both the study by van de Beek et al. and our investigation used surveillance systems to identify cases of GAS meningitis among defined populations, we believe that the actual case-fatality rate associated with GAS meningitis may be higher than previously thought.

A comparative study of non-invasive GAS isolates from Belgium and Brazilian children conducted in 2004 found that 20 distinct *emm* types were identified among 200 Belgian isolates, whereas a significantly larger diversity of *emm* types (48 among 128 strains) were found in Brazil. Furthermore, *emm* types 1 and 3 were much more commonly isolated from Belgian children than from Brazilian children.²⁶ *emm* types 1 and 3, which have previously been associated with severe invasive infections,^{24,25} were not found in isolates from meningitis cases in this study; the *emm* types varied widely. Prior studies of invasive GAS isolates have also detected a large diversity of *emm* types in different regions.^{27–29} In this study the most prevalent *emm* type identified was *emm* type 25 (18%), which has been described associated with invasive infection in Spain, the UK, and Thailand.^{30–32} Together these findings suggest that, as proposed by Rogers et al.,³³ the isolation of a particular *emm* type among invasive isolates may simply indicate widespread transmission of these strains in the population, rather than a particular ability to cause disease.

Our study has potential limitations. First, we may have underestimated the true incidence of GAS meningitis because antibiotic use prior to hospitalization may have led to reduced isolation rates. Second, active surveillance was performed in only one hospital for an extended period, so changes in case ascertainment could have affected incidence estimation. However, state and local protocols for the referral of suspected meningitis cases to the study hospital did not change during the study period. Although clinical information and outcome were missing for three cases, we had complete information on demographics and city of residence for all 20 cases. Since the study was performed in a single region our findings may not be generalizable to other settings. However, a large proportion of the population in Brazil lives in climatic and socio-economic conditions similar to those in Salvador. The study incidence estimates may also be applicable to other countries with a demographic and socio-economic profile similar to Brazil.

The availability of a multivalent, M protein-based vaccine against GAS prompted this attempt to define population-based data on the burden of GAS invasive disease and on the distribution of *emm* types. We used the incidence of GAS meningitis to estimate the overall burden of invasive GAS infections, as population-based surveillance for bacterial meningitis is simpler

than for other GAS invasive diseases. As several developing countries have received support from the World Health Organization and the Global Alliance for Vaccines and Immunization (GAVI) to build surveillance systems to monitor trends in bacterial meningitis,^{34,35} we propose the use of population-based data on GAS meningitis to estimate the burden of GAS invasive diseases and to plan appropriate immunization strategies.

Our findings indicate that the 26-valent, M protein-based vaccine will not be useful in preventing GAS meningitis in our setting. Among GAS meningitis cases, 40% were <1 year of age, an age group that may not be targeted for immunization. Furthermore, only 10% of the meningitis isolates had *emm* types represented in the 26-valent vaccine. It is important to note that GAS meningitis is a rare disease and the primary goal of the multivalent vaccine is the prevention of more common forms of invasive disease, pharyngitis, and sequelae such as rheumatic fever. However, the low proportion of meningitis isolates with vaccine *emm* types in our study raises the question of whether the 26-valent vaccine will provide adequate coverage of the circulating GAS that cause invasive disease in Brazil. The distribution of *emm* types in meningitis may differ from those of types that cause invasive disease in general. Nevertheless, further research is required to determine the distribution of *emm* types in invasive disease, such that recommendations can be made on the benefits that multivalent GAS vaccines may afford in Brazil.

Acknowledgments

We thank the clinical and laboratory staff of Hospital Couto Maia for their cooperation, Dr Bernard Beall for providing support in *emm* typing, Dr Maria da Glória Carvalho for her assistance and contribution for broth microdilution determination (CDC), and most of all the patients and their families.

Funding: This study was supported by grants from the Brazilian National Research Council (491345/2005-4), Research Support Foundation for the State of Bahia (FAPESB – 1431040054051), and National Institute of Health, USA (D43 TW00919 and R01 TW007303).

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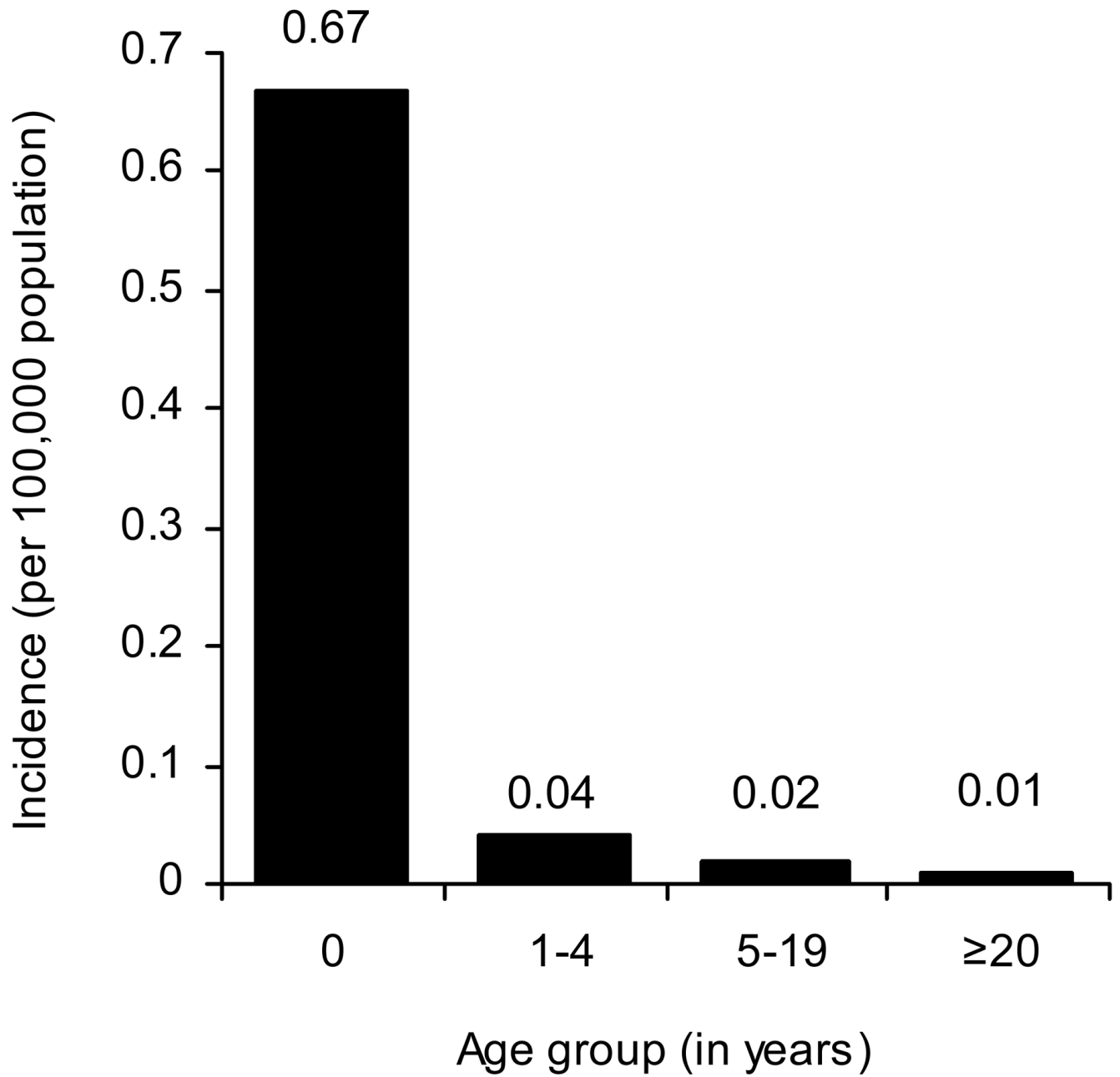


Figure 1. Mean annual cumulative incidence of group A streptococcal meningitis for metropolitan Salvador, 1996–2006.

Table 1
Clinical characteristics of group A streptococcal meningitis cases identified during surveillance; Salvador, Brazil

Characteristic	No. of cases (%) or median (IQR) (<i>N</i> = 17) ^a
Symptoms and signs	
Days of symptoms	3 (2–5)
Fever	16 (94)
Vomiting	13 (76)
Neck stiffness	12 (71)
Headache ^b	7 (64)
Seizures	10 (59)
Altered mental status ^c	10 (59)
Focal neurological deficit ^d	3 (18)
Outcome	
ICU hospitalization	7 (41)
Death ^e	4 (25)
Length of hospitalization, in days ^e	
For survivals	17 (14–22)
For deaths	7 (4–9)

IQR, interquartile range; ICU, intensive care unit.

^aData on symptoms and outcome were available for 17 of the 20 cases, except when noted.

^bData on headache were available for 11 cases.

^cAltered mental status was defined by inability to follow commands, lethargy, torpor, or coma.

^dFocal neurological deficit included nystagmus, mydriasis, and ptosis.

^eData on death and length of hospitalization were available for 16 cases because one patient was transferred and final outcome was unknown.

Table 2
 Characteristics of group A streptococcal meningitis cases and isolates identified during surveillance; Salvador, Brazil

Case	Month/year of diagnosis	Age	Sex	Presumptive infection source ^a	Isolate <i>emm</i> type	Outcome
1	05/1996	5 years	F	Otitis media	25	Discharged
2	05/1996	6 years	M	None	85	Died
3	08/1996	5 months	M	Mild cranial trauma	123	Discharged
4	09/1996	6 months	M	Ventriculoperitoneal shunt	25	Discharged
5	04/1998	4 years	M	Rhinopharyngitis	25	Discharged
6	05/1998	31 years	F	NA	98	NA
7	02/1999	17 years	F	Otitis media	112	Discharged
8	07/2000	52 years	M	Otitis media	88	Discharged
9	11/2000	8 years	M	None	55	Discharged
10	09/2001	19 days	F	Meningomyelocele	73	Discharged
11	04/2002	2 months	M	None	73	Discharged
12	07/2002	23 days	M	None	39.1	Discharged
13	10/2002	8 years	F	NA	86.1	NA
14	11/2002	4 years	M	None	95	Died
15	09/2003	40 years	F	Otitis media	53	Discharged
16	11/2003	7 months	F	Rhinopharyngitis	81	Discharged
17	05/2004	45 years	M	NA	44/61.0	NA
18	10/2004	1 month	F	None	92	Transferred
19	04/2006	4 months	M	Rhinopharyngitis	11	Died
20	12/2006	13 years	F	None	118	Died

F, female; M, male; NA, not available.