



## Invasive Meningococcal Disease in Brazil: a literature review

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### ABSTRACT

*Neisseria meningitidis* is one of the major etiologic agents of bacterial meningitis and one of the most important causes of invasive bacterial disease worldwide. In Brazil, Invasive meningococcal disease is endemic, predominantly caused by serogroups C and B currently. Periods of hyper-endemic have been regularly recorded since the 1920s. In late 2010, meningococcal C conjugate vaccine was introduced into the National Immunization Program schedule, with two doses in the first year, at ages 3 and 5 months, and a booster dose at 12 months. This work summarizes available epidemiological data on meningococcal infection in Brazil obtained in the last 10 years from literature review in the PubMed, LILACS and SciELO databases. The incidence of meningococcal C disease has declined as a result of effective vaccination among the age groups targeted for the vaccine. However, no impact was observed in unvaccinated age groups suggesting that there has been little effect on population transmission. Furthermore, we discuss future challenges. It is very important to monitor meningococcal disease in Brazil, identify new strains and to consider the inclusion of a new vaccination strategy.

### Doença Meningocócica Invasiva no Brasil: uma revisão de literatura

### RESUMO

*Neisseria meningitidis* é um dos principais agentes etiológicos da meningite bacteriana, uma das causas mais importantes de doença bacteriana invasiva em todo o mundo. No Brasil, a doença meningocócica invasiva é endêmica, atualmente é causada predominantemente pelos sorogrupos C e B. Períodos hiperendêmicos são registrados regularmente desde a década de 1920. No final de 2010, a vacina conjugada contra meningite C foi introduzida no Programa Nacional de Imunização. As crianças recebem duas doses da vacina no primeiro ano de idade, com 3 e 5 meses, e uma dose de reforço aos 12 meses. Este trabalho resume os dados epidemiológicos disponíveis sobre a infecção meningocócica no Brasil, obtidos nos últimos 10 anos através de uma revisão de literatura nos bancos de dados PubMed, LILACS e SciELO. Com a vacinação a incidência da doença meningocócica C diminuiu entre as faixas etárias alvo da vacina. No entanto, nenhum impacto foi observado nas faixas etárias não vacinadas, sugerindo que houve pouco efeito na transmissão da doença na população. Além disso, discutimos desafios futuros. É muito importante monitorar a meningite no Brasil, identificar novas cepas circulantes e considerar a inclusão de novas estratégias vacinais.

### Palavras-chave:

Meningite; vigilância;

estratégia de

vacinação; Brasil

## 1. Introduction

Invasive meningococcal disease (IMD), caused by *Neisseria meningitidis* (*N. meningitidis*), is an important public health problem. In 2016, the Institute for Health Metrics and Evaluation (IHME) Global Burden of Disease estimated that there were 127 000 deaths and 1.6 million cases of meningococcal disease globally. However, due to inadequate surveillance programs in many parts of the world, IMD is likely to be underreported (1).

In higher income countries, the incidence of IMD tends to be greatest among infants, with a second peak in adolescents and young adults. *N. meningitidis* is the main etiological agent

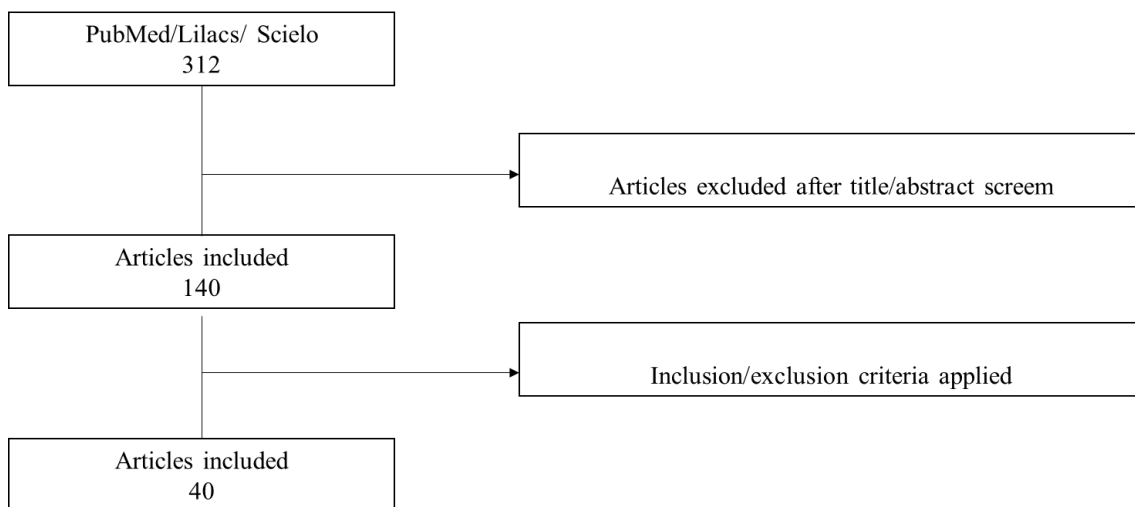
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of meningitis in children above the age of 3 months and in young adults in Brazil (2). The most common clinical manifestations of meningococcal infection are meningitis, septicaemia and less commonly, pneumonia. IMD is associated with high case fatality, of around 10%. Further, IMD can result in significant sequelae, including deafness, skin scarring, chronic pain, neurologic deficiency and amputation (3).

*N. meningitidis* is a Gram-negative, encapsulated, diplococcus and the polysaccharide capsule is used to define 12 serogroups. However, the majority of invasive meningococcal infections are caused by serogroups A, B, C, W, Y, and X are transmitted person-to-person through close contact with infected or colonized individuals (4). In 2010, Brazil introduced the meningococcal C conjugate vaccine (MCC), which provided protection against serogroup C, into its routine immunization program, with doses scheduled at three and five months of age, plus a booster at 12–15 months of age (5).

## 2. Methods

In this study we searched the literature using Medline (via PubMed), LILACS and SciELO for “Meningococcal disease”, or “Invasive Meningococcal disease”, or “*Neisseria meningitidis*”, or “carriage” and “Brazil”. Studies published in the last 10 years and containing information on IMD in Brazil were included. Abstracts, case reports, letters to the editor, studies with only immunological outcomes, and those reporting results associated with other etiologies of meningitis were excluded (Figure 1). As the final step, key findings from the included publications were synthesized.



**Figure 1** – Selection of studies on invasive meningococcal disease for systematic review

## 3. Results and discussion

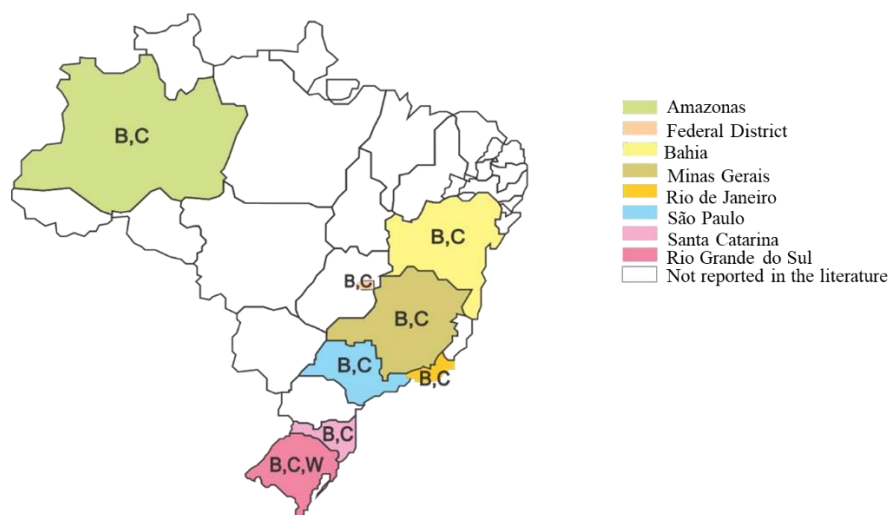
### 3.1 Epidemiology of IMD in Brazil

Generally, meningococcal disease is endemic in Brazil, with hyper-endemic periods of increased incidence. In Brazil during the 1920s and 1940s *N. meningitidis* serogroup A (NmA) caused several epidemics, with an annual incidence of 12–25 per 100000 population (6). Since the 1970s, Brazil experienced three clonal outbreaks of serogroup C disease, caused by C:2a:P1.5,2:ST-11 (cc11), C:2b:P1.3:ST-8 (cc8) and, most recently, since 1989 by C:23:P1.14-6: ST-103 (cc103) (5, 7). However, during the 1980s and 1990s, *N. meningitidis* serogroup B (NmB) spread throughout Brazil until it became more

common than serogroup C, with a peak in 1996 of 7.8 cases per 100 000 population. Between 1990 and 2001, the annual incidence rate was approximately 1–3 cases per 100 000 population (7). From 1996 to 2002, almost 80% of reported IMD cases in northern and north-eastern Brazil were caused by serogroup B, and strain B:4:P1.15,19:ST-32 (cc32) predominated throughout the country (8,9).

Another significant shift from NmB to NmC was observed from 2002 onwards; a substantial increase in the proportion of cases attributed to serogroup C, associated with appearance of a serogroup C strain belonging to a hypervirulent lineage (ST-103) was recorded and NmC became the most frequent cause of IMD in Brazil. Serogroup C became predominant in the following regions: Southeast, since 2002-2003; Midwest, since 2005-2006; Northeast, since 2007-2008; Northern, since 2008-2009; and more recently, Southern since 2012 (please see figure 2) (10). In Brazil, the increasing number of cases caused by NmC prompted the introduction of routine MCC vaccination in November 2010 (11).

Moreover, there are an increasing number of cases caused by serogroup W (ST-11 complex) (12). According to Abad and colleagues, Brazil was the first country in Latin America to report outbreaks caused by ST-11 serogroup W (13). In recent years there have been virtually no case reports of IMD caused by serogroup A in Brazil (5).



**Figure 2** – Map of Brazil, showing the current distribution of major meningococcal serogroups. See text for details.

### 3.2 Clinical characteristics

*N. meningitidis* causes severe and life-threatening invasive disease, such as meningitis and meningococcal sepsis (meningococemia). In addition, meningococcal infection has a rapid and severe clinical progression over 8 hours, and in some cases results in death within 12–24 hours of onset of symptoms (1, 14).

The colonization of the nasopharynx is typically asymptomatic, however, *N. meningitidis* can translocate from nasopharynx to the blood stream, resulting in disease. In previous studies in Brazil, it has been found that in the first 4-6 hours of disease onset, non-specific manifestations mimic the symptoms of common viral infections (15). The median time from symptom onset to hospitalization was one day (ranging from less than 24h to five days) and median time from symptom onset to the outcome (discharge/death)

was 10 days, ranging from less than 24h to 123 days (16). Additionally, the overall case fatality rate was 33%, with 50% of these deaths occurring within 48 hours of hospitalization (17). Similarly, non-specific symptoms in the first 4-6 h has also been reported in England, Wales, and Northern Ireland and mean hospital length of stay was 11 days in Spain (18).

Different studies have detected that clinical symptoms more frequently observed in confirmed cases of IMD in Brazil were fever, vomiting, headache, petechiae, haemorrhagic rash, irritability somnolence and mental confusion, while the least frequent were Kernig's sign, seizures, coma, diarrhoea, abdominal pain, convulsions, sore throat, and myalgia (19, 20). Furthermore, among patients <1 year of age an important and frequent symptom was a bulging fontanelle (20). Nascimento and colleagues found that stiff neck was observed in 64.9% of cases in Minas Gerais, whereas, ISER and colleagues reported that only 5% of cases presented nuchal rigidity in a study performed in Goias State (19, 20).

### 3.3 *Diagnosis*

The criteria for clinical diagnosis are: fever, stiff neck, severe headache, vomiting, signs of meningeal irritation, seizures, purpuric rash and/or petechiae. In children aged less than 1 year old, IMD should be suspected when fever is accompanied by bulging fontanel (21). Cases are confirmed by the isolation of *N. meningitidis* or by the detection of bacterial DNA by multiplex real-time PCR (RT-PCR) from blood, cerebrospinal fluid (CSF) or skin lesions (21).

In many developing countries, surveillance for bacterial meningitis is limited to the use of bacterial isolation. However, the administration of antibiotics before collection of the CSF, prolonged transport times that compromised sample integrity and the lack of microbiology resources resulted in failure to isolate meningococci (22-24).

PCR techniques have improved the diagnosis of IMD and even when the meningococci were nonviable due to antibiotic treatment, PCR could still detect *N. meningitidis* DNA (25). In Brazil, access to molecular diagnostics is available in sentinel sites in the state of São Paulo and the introduction of RT-PCR for *N. meningitidis* improved the yield for detection in 85% compared to culture-based methods. Moreover, the sensitivity of RT-PCR in cerebrospinal fluid (CSF) was 100% and specificity ranged from 98.9% to 100% was reported (24). The incorporation of molecular diagnostic techniques, like PCR/RT-PCR, into routine surveillance and the expanded use of Gram staining, rapid diagnostic tests and culture isolation in Latin America was proposed by Global Meningococcal Initiative (GMI), with the aim to obtain more insight into IMD.

### 3.4 *Meningococcal carriage*

Acquisition of meningococci in the upper respiratory tract can be transient, can result in meningococcal carriage, or can result in IMD. Carriage plays an important role in the transmission and spread of meningococcal infection (26). For most people, carriage is an immunizing process that results in the production of protective antibodies (27). Nasopharyngeal carriers can transmit meningococci through direct contact with upper respiratory tract secretions and aerosolized droplet nuclei (28).

While the incidence of IMD is highest in infants, the asymptomatic carriage of meningococci in high-income countries is highest among adolescents (29). The relation between disease incidence and carriage prevalence in a population is unclear, but age is one of the most important factors related to carriage rates. The high carriage prevalence

observed in teenagers in the United Kingdom has been linked to social behaviour such as cigarette smoking, passive exposure to smoke, kissing, overcrowding and socialising in bars and clubs (30, 31).

Published data on meningococci carriage in Brazil are limited (Table 1) although studies conducted in the post-MCC vaccination period reported that serogroup C was predominant, followed by serogroup B. Moreover, the highest carriage prevalence was observed in adolescents aged 10–19 years old (32, 33). The carriage prevalence of *N. meningitidis* was 4.9% among adolescents from Salvador, Bahia, after the mass MCC vaccination campaign. This low rate was potentially influenced by the low prevalence of NmC during the post-vaccination period in Salvador, as the vaccination campaigns targeted adolescents and young adults. In addition, the campaign may have prevented transmission and colonization of the organism in non-vaccinated individuals through the effect of herd immunity (34). An analysis of risk factors for *N. meningitidis* carriage found that a low level of education (i.e., not completing secondary education) of the parents was associated with increased risk of carriage, probably reflecting socioeconomic conditions (32). Further, factors associated with carriage included having only one, shared bedroom in the household, a mother as the only smoker in the home and going to pubs/parties (34-36).

**Table 1** – Summarized of *N. meningitidis* from carriers in Brazil.

State	Age group targeted for vaccination campaign	Age of participants	Prevalence of carriage	References
São Paulo	≤ 1 Y	18–39	104/483 (21.5%)	(32)
São Paulo	≤ 1 Y	1-24	87/967 (9%)	(33)
São Paulo	≤ 1 Y	11-19	120/1,208 (9.9%)	(35)
Bahia	<5 Y and 10–24 Y	11-19	59/1,200 (4.9%)	(34, 37)

Y: years old.

### 3.5 Vaccines

Since 2005, health technology assessments and economic evaluation studies have been requested for evaluating the introduction of new vaccines into the National Immunization Programme (NIP) (38). Brazil was the first country in Latin America to introduce MCC vaccine in NIP. Routine infant immunization with the MCC vaccine began in Brazil in November 2010, with doses scheduled at three and five months of age, plus a booster at 12-15 months of age. The 3- and 5-month visit schedule was chosen because many vaccines are already given at 2 and 4 months. Toddlers aged between 12-23 months of age received a single dose of the vaccine, without a ‘catch-up’ campaign in older age groups (1,39). The introduction of the MCC vaccine into the NIP provided an immediate reduction in the incidence of IMD in children aged <2 years, the age group targeted for vaccination (40).

The implementation of the MCC vaccine in NIP was done through a partnership between a pharmaceutical company (Novartis vaccines) and a Brazilian public-run vaccine manufacturer (Fundação Ezequiel Dias). All vaccines that are part of the NIP in Brazil are fully funded by the government. Technology transfer from pharmaceutical companies to local vaccine manufacturers in Brazil has resulted in lower prices and increased vaccine supply (39).

The Bexsero vaccine was licensed in Brazil in 2015. Although serogroup B is the second more prevalent in Brazil we showed recently that a vaccination program with Bexsero

against MenB disease is unlikely to be cost-effective in part, due to high program cost driven by the cost of the Bexsero vaccine (41).

### 3.6 Future Challenges

There was a hyper-endemic period between 1995 and 2000 associated with serogroup W, and this group became endemic again after 2000 in Southern Brazil (42). An unexpected increase in the incidence of NmW was noticed in different countries in Latin America (13). In Chile, was reported a large increase in the number of cases and in the mortality rate associated with ST11/ET37 CC strains. However, a continuous diversification of the W ST11/ET37 CC with new variants has been associated with clinical cases (13, 43). In addition, a meningococcal vaccination program was implemented in Chile with tetravalent (A, C, Y and W) conjugate vaccine (21). It is very important to monitor in Brazil the evolution of NmW, identify new strains and to consider the inclusion of this serogroup in any vaccination strategy, particularly in the Southern region.

In relation to serogroup C, the MCC vaccine can prevent IMD by direct effects in vaccinated individuals and by indirect effects that benefit unvaccinated individuals, by herd protection. Herd protection arises from meningococcal vaccines, when they prevent acquisition of carriage, which interrupts transmission in the population (34). The success of the MCC vaccination program in reducing disease in the United Kingdom and other European countries was attributed to the combined efficacy of the vaccine by direct and indirect effects (32, 44).

In Brazil vaccination programs have successfully reduced, its incidence in those children targeted for vaccination. However, no early impact was observed in other age groups, probably reflecting the lack of a catch-up program including adolescents (40). Additionally, the results of a study performed in Campinas, Brazil, that evaluated the carriage prevalence of *N. meningitidis* among adolescent students between 11–19 years old found that the carriage rate was 9.9%, with an unusually high carriage prevalence for serogroup C (35). The results of these studies reinforce the importance of considering the catch-up campaign for young people up to the age of 18 years in the NIP to achieve indirect protection. Optimizing strategies for MenC vaccination to achieve maximum protection in Brazil is strongly recommended.

*N. meningitidis* is still susceptible to most antibiotics that are used for treatment and prophylaxis of IMD, however, the incidence of strains with resistance to antibiotics (as indicated by increased minimum inhibitory concentrations [MIC]) is increasing worldwide (45). Mutations in *penA* gene are involved with reduced susceptibility to penicillin. Non-susceptibility (or resistance) to penicillin arises from modifications in bacterial penicillin-binding proteins (PBPs), enzymes that are involved in peptidoglycan biosynthesis, that bind to penicillin and other beta-lactam antibiotics.

Alterations in the PBP2 protein encoded by the *penA* gene led to modifications of the bacteria's peptidoglycan structure, as well as a 10-fold reduction in its affinity for penicillin (45,46). It is also important to consider that strains with reduced susceptibility to penicillin, first-line drug for treating meningococcal infection, have been reported in Brazil and can be represents an additional public health threat (46).

## 4. Conflict of interest

C.T. reports receiving consulting payments from GSK (2013) and an honorarium from Sanofi-Pasteur (2015).

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