Research, Society and Development, v. 11, n. 11, e463111133824, 2022
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Are we able to prevent invasive meningococcal disease in Brazil?

Somos capazes de prevenir a doença meningocócica invasiva no Brasil?

Podemos prevenir la enfermedad meningocócica invasiva en Brasil?

Received: 08/07/2022 | Reviewed: 08/19/2022 | Accept: 08/20/2022 | Published: 08/28/2022

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Abstract
Background: Invasive meningococcal disease (IMD) remains a major public health problem associated with death and severe consequences, especially in children. However, IMD is preventable through vaccination, with vaccines available to cover five of the six most common disease-causing strains (A, B, C, X, Y, and W). Surveillance systems are necessary for monitoring IMD incidence, together with the severity and serogroup prevalence of the disease. knowledge of the prevalence of *Neisseria meningitidis* (Nm) serogroups in IMD is critical for adopting the best strategies for meningococcal immunization. Method: In Brazil, all IMD cases are reported to the National Disease Notification System (SINAN). The goal of this study is to evaluate the epidemiological and microbiological data retrieved from SINAN from 2007–19. Results: During this period, 251,773 cases were reported with around 9% of them progressing to death. Furthermore, in approximately 95% of cases, the serogroup was not identified. Conclusions: Hence, improving the SINAN information is crucial for guiding future IMD prevention, such as vaccination and control strategies.
Keywords: National immunization program; Health; Infectious disease.

Resumo
Introdução: A doença meningocócica invasiva (DMI) continua a ser um importante problema de saúde pública associado à morte e consequências graves, especialmente em crianças. No entanto, a DMI é evitável através da vacinação, com vacinas disponíveis para cobrir cinco das seis cepas causadoras de doenças mais comuns (A, B, C, X, Y e W). Sistemas de vigilância são necessários para monitorar a incidência de DMI, juntamente com a gravidade e a prevalência do sorogrupo da doença. o conhecimento da prevalência dos sorogrupos de *Neisseria meningitidis* (Nm) na DMI é fundamental para a adoção das melhores estratégias de imunização meningocócica. Método: No Brasil, todos os casos de DMI são notificados ao Sistema Nacional de Notificação de Agravos (SINAN). O objetivo deste estudo é avaliar os dados epidemiológicos e microbiológicos recuperados do SINAN de 2007 a 2019. Resultados: Nesse período, foram notificados 251.773 casos com cerca de 9% deles evoluindo para óbito. Além disso, em aproximadamente 95% dos casos, o sorogrupo não foi identificado. Conclusões: Assim, melhorar as informações do SINAN é crucial para orientar futuras ações de prevenção de DMI, como estratégias de vacinação e controle.
Palavras-chave: Programa Nacional de Imunização; Saúde; Doenças Infecciosas.

Resumen
Antecedentes: La enfermedad meningocócica invasiva (EMI) sigue siendo un importante problema de salud pública asociado con muerte y graves consecuencias, especialmente en niños. Sin embargo, la EMI se puede prevenir mediante la vacunación, con vacunas disponibles para cubrir cinco de las seis cepas causantes de enfermedades más comunes (A, B, C, X, Y y W). Los sistemas de vigilancia son necesarios para monitorear la incidencia de la EMI, junto con la severidad y la prevalencia del serogrupo de la enfermedad. el conocimiento de la prevalencia de los serogrupos de *Neisseria meningitidis* (Nm) en la EMI es fundamental para adoptar las mejores estrategias para la inmunización meningocócica. Método: En Brasil, todos los casos de EMI son notificados al Sistema Nacional de Notificación de Enfermedades (SINAN). El objetivo de este estudio es evaluar los datos epidemiológicos y microbiológicos recuperados del SINAN entre 2007 y 2019. Resultados: Durante este período, se

notificaron 251.773 casos, de los cuales alrededor del 9% progresaron a muerte. Además, en aproximadamente el 95% de los casos no se identificó el serogrupo. Conclusiones: Por lo tanto, mejorar la información del SINAN es crucial para orientar futuras estrategias de prevención de EMI, como la vacunación y el control.
Palabras clave: Programa nacional de inmunización; Salud; Enfermedad infecciosa.

1. Introduction

Neisseria meningitidis (Nm) is a gram-negative bacterium that colonizes the epithelia of the nasopharynx in the upper respiratory tract in a high proportion of healthy children and adults (Nunes et al., 2016; J. Presa, Serra, Weil-Olivier, & York, 2022; Serra, Presa, Christensen, & Trotter, 2020). Although the majority of individuals colonized by the bacteria remain asymptomatic, devastating consequences are associated with invasive meningococcal disease (IMD) that can lead to serious manifestations, including meningitis and septic shock. Furthermore, up to 20% of survivors suffer permanent damage, including deafness, brain injuries, and amputated limbs. Currently, six serogroups (A, B, C, W, X, and Y) are responsible for most IMD cases (Chicuto, de Moraes, Cassio de Moraes, & Safadi, 2020; Morello, Milazzo, Marshall, & Giles, 2021; M. A. P. Safadi et al., 2017; Xu et al., 2022).

Effective surveillance, the identification of serogroups, and assessments of all diagnosed IMD cases are important strategies that may support the elimination of or at least significantly reduce the mortality caused by Nm. In this regard, the World Health Organization/Pan American Health Organization (WHO / PAHO) implemented a Latin American laboratory-based passive surveillance program in 1993, known as the Regional Vaccine System (SIREVA) and, later, the Surveillance Network System for Agents Responsible for Pneumonia and Bacterial Meningitis (SIREVA II) for the collection of relevant laboratory and epidemiological data (Ibarz-Pavon et al., 2012; M. A. P. Safadi et al., 2017). In Brazil, data also can be found from the Notifiable Diseases Information System (SINAN) (Moura Silveira, McBride, & Trotter, 2019; Tauil Mde, Carvalho, Vieira, & Waldman, 2014).

The SINAN is a system that contains standardized instruments for collecting information on infectious diseases and deaths that represent major public health problems in Brazil (Moura Silveira et al., 2019). After different vaccines for IMD are in production, surveillance is essential for monitoring their impact (J. V. Presa, de Almeida, Spinardi, & Cane, 2019). Furthermore, knowledge of the identification of the serogroup is essential for determining the better IMD control strategy and how to prevent the deaths caused by Nm. Given this context, the present study aims to analyze the epidemiological, microbiological, and clinical data provided by SINAN during the period of 2007–19.

2. Methodology

This study is a descriptive study that uses publicly-available data from SINAN gathered from 2007–19. The SINAN database is managed by the Brazilian Ministry of Health and is available from the Department of the Unified Health System (DATASUS). Epidemiological, demographics, laboratory diagnostics, and clinical data are routinely collected as part of this surveillance system.

IMD notification is mandatory in Brazil. Furthermore, SINAN registers data from both public and private health services (Moura Silveira et al., 2019). All IMD cases diagnosed by laboratory and/or clinical/epidemiologic criteria have been included in this study. Moreover, the cases reported to SINAN are classified as meningococcal meningitis, meningococcemia, or meningococcemia combined with meningococcal meningitis (Moraes, Moraes, Silva, & Duarte, 2017).

Considering the diagnostic criteria for IMD confirmation cases includes: culture, the detection of bacterial DNA by polymerase chain reaction (PCR), antigen detection, clinical-epidemiological criteria (cases resulting from close contact then confirmed by laboratory tests), Gram-staining, and clinical criteria (with petechial or purpuric rash). The serogroup was determined only for IMD cases confirmed by culture, PCR, antigen detection, and clinical-epidemiological criteria (Moraes et al., 2017).

The variables collected from SINAN include: case outcome (cure, death from the IMD, or death from other causes) and serogroup (A, B, C, Y, W-135, X, 29-E, D, Z, and non-identification). Additionally, data on age groups (<1, 1–4, 5–9, 10–14, 15–19, 20–39, 40–59, 60–64, 65–69, 70–79, and ≥80) was also used.

3. Results

Between January 1st, 2007, and December 31st, 2019, 251,773 cases of IMD were notified to SINAN and, of these, 239,506 (95%) were not identified as belonging to a serogroup. A total of 8,616 cases were caused by Nm serogroup C (MenC); approximately 3.4%. Furthermore, 2,545 and 781 cases were attributed to serogroup B and W, respectively. Sporadic cases have been attributed to the other serogroups of X, A, and Z (Table 1). Overall, during the evaluated period, there were 22,969 deaths from Nm infection.

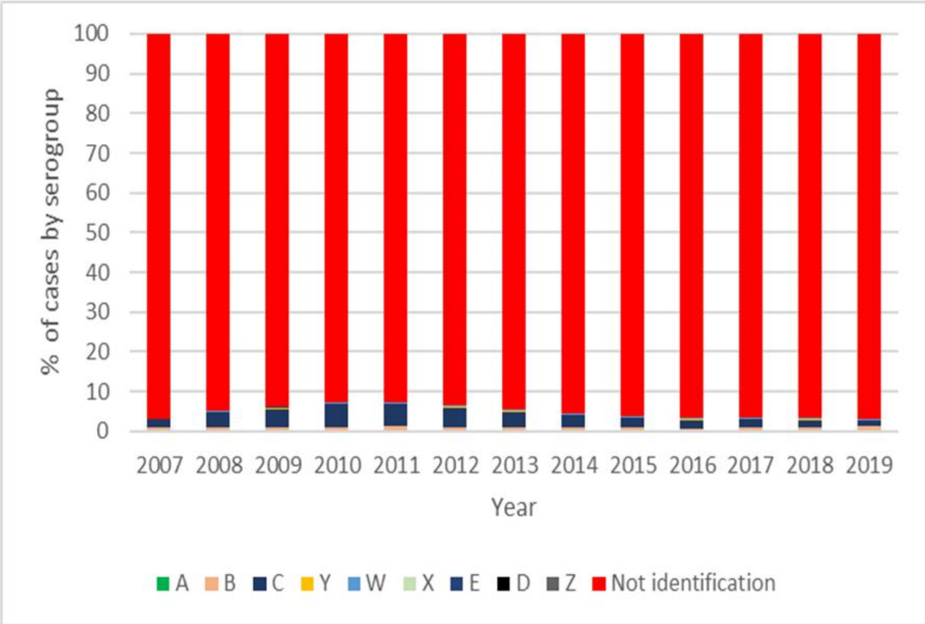
Table 1: Number total of invasive meningococcal diseases cases caused by each serogroup in Brazil between 2007–19 period. Data provided from SINAN

Year	Total cases	Cases by serogroup									
		A	B	C	Y	W	X	E	D	Z	Not identification
2007	29,007	2	267	590	10	40		6			28,162
2008	23,216	5	257	850	11	79	1	5	1	3	22,004
2009	21,271	8	221	972	17	64	…	3	1	…	19,985
2010	20,167	6	197	1201	13	74	…	3	…	…	18,673
2011	20,376	1	240	1132	30	85	…	1	…	…	18,887
2012	21,349	7	236	1026	36	63	…	3	…	…	19,978
2013	18,721	4	201	725	25	77	…	…	…	…	17,689
2014	17,358	3	145	546	22	58	…	…	…	…	16,584
2015	15,711	3	155	358	13	53	…	…	…	1	15,128
2016	15,228	1	118	316	17	48	3	1	…	…	14,724
2017	16,615	1	141	365	17	52	2	1	…	…	16,036
2018	17,130	1	179	307	18	52	…	…	…	…	16,573
2019	15,554	2	188	228	17	36	…	…	…	…	15,083

… cases were not reported. Source: Authors.

Over the 13-year period, the proportion of non-identified serogroup was as high as 95%, with the highest number of cases with serogroup determinate occurring in 2010 (7.4%). This proportion progressively decreased in recent years when only 3.4% and 3.0% of cases were identified in 2015 and 2019, respectively – the results are presented in Figure 1.

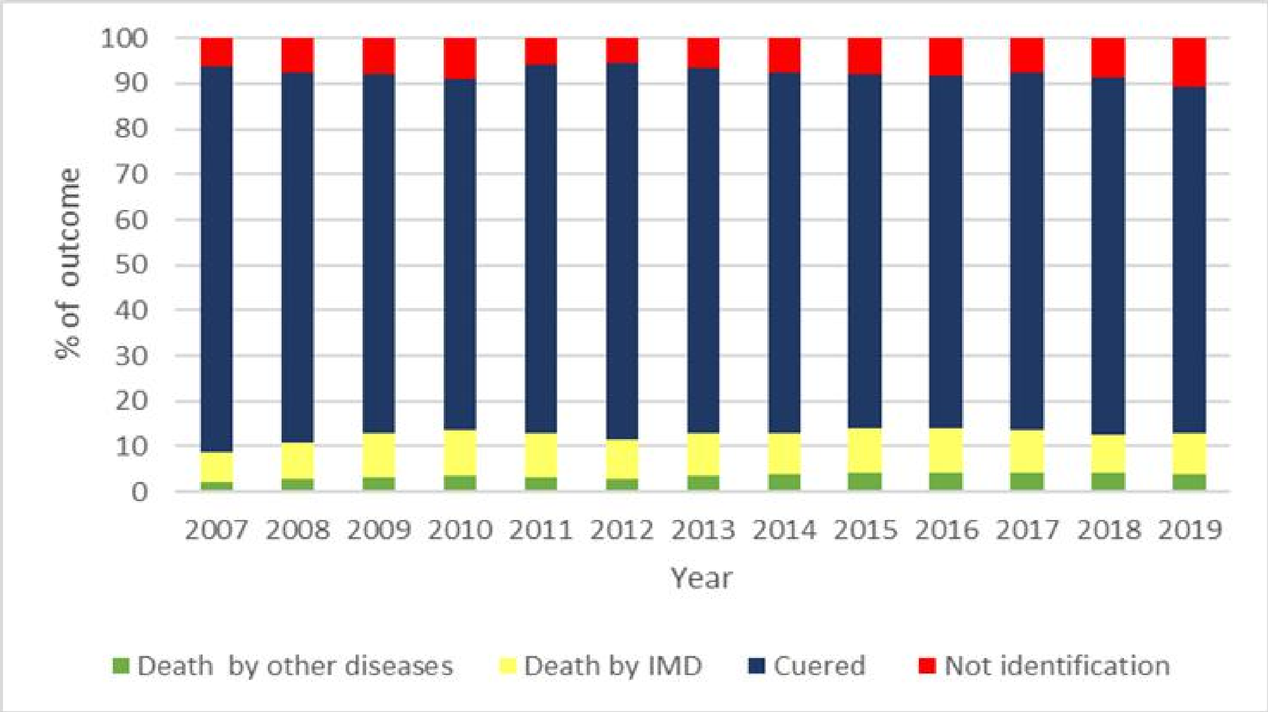
Figure 1: The percent of each serogroup associated with IMD in Brazil from 2007–19. Data provided by SINAN.



Source: Authors.

Based on SINAN, the study period saw a decrease in the number of deaths (Figure 2). The higher number of deaths was reported in 2009 when 2,131 patients died from Nm infection. These numbers progressively decreased and, in 2019, 1,418 deaths were caused by IMD. However, there was an increase in the proportion of non-identified outcomes. During the 2011–12 period, almost 95% of cases were identified in relation to outcomes and, in 2019, 89% were identified. Furthermore, approximately 85% of patients were cured in 2007, with this percentage decreasing to 76% in 2019.

Figure 2: The percent of IMD outcomes in Brazil according to SINAN from 2007–19.



Source: Authors.

4. Discussion

In our study, we examine the data provided from SINAN, the system surveillance used to monitor IMD and other infectious diseases in Brazil, including epidemiological, microbiological, and clinical data. A total of 251,773 IMD cases and 22,969 deaths were notified by SINAN from 2007–19. Furthermore, in approximately 95% of cases, the serogroup was not identified during this period.

Vaccination is a principal and highly cost-effective means of controlling infectious diseases (Sheerin, Openshaw, & Pollard, 2017; Silveira, Conrad, & Leivas Leite, 2021). In 2010, Brazil introduced the routine meningococcal C conjugate (MCC) vaccine into the National Immunization Program (NIP) schedule, requiring two doses at ages 3 and 5 months, and a booster dose at 12 months. Furthermore, children between 12 and 23 months received 1 dose of the vaccine, with no catch-up campaign for older age groups. An early study, in 2014, showed that the incidence of meningococcal serogroup C disease decreased in those age-groups targeted for vaccination. However, no early impact was observed in other age groups, which probably reflects the lack of a catch-up program (Andrade et al., 2017; M. A. Safadi, Berezin, & Arlant, 2014).

Although the majority of people colonized by Nm remain asymptomatic, they can transmit the bacteria through respiratory droplets and cause epidemics, deaths, or severe consequences for those who are infected. Thus, vaccines used to control IMD can prevent the infection not only by direct effect in vaccinated people but also by herd protection, preventing the acquisition of carriage, interrupting transmission, and leading to protection for unvaccinated individuals (Nunes et al., 2016). In the United Kingdom and other European countries, the success of the MCC program has been attributed to the combined vaccine efficacy against both disease and carriage (M. A. Safadi et al., 2014; Trotter & Maiden, 2009).

In Brazil, the importance of a catch-up vaccination was demonstrated by Salvador, where a low prevalence rate of MenC carriage (0.17%) was found in adolescents after the state government initiated mass MCC vaccination campaigns for children <5 and for the 10–24 years age group, in 2010 (Nunes et al., 2016). On the other hand, in a similar study conducted in Campinas, after introducing the MCC vaccine only among children <2 years old, levels were reported as almost eight times higher than the prevalence rate of MenC carriage. These results reinforce the importance of including the vaccination of the 10–25-year-old population group (Nunes et al., 2016). In 2017, the Brazilian Ministry of Health included a dose of MCC for adolescents aged between 12 and 13 years and, in 2018, extended this to 11–14-year-olds (J. V. Presa et al., 2019).

Considering the data provided by SINAN on age and the associated serogroup, we found that 97.9% of serogroups were not identified in cases of children <1-year-old. Moreover, approximately 96.5% of cases were not identified in any age group during the 2019 period (data not shown). In this context, strengthening IMD surveillance systems of SINAN will provide insights into the epidemiology of the disease and help to understand the age group that is more important for receiving a catch-up vaccination.

A study carried out by Chicuto and colleagues reported that the mean case fatality rates (CFR) associated with MenW (26.8%) are higher in Brazil – followed by MenC and MenB, found at 18.1% and 15.7% respectively, between 2001 and 2015 (Chicuto et al., 2020). In addition, an increase in serogroup W prevalence has been shown mainly in young adults (J. V. Presa et al., 2019). Brazil was the first country in Latin America to show an increase in the percentage of cases associated with MenW (J. V. Presa et al., 2019).

Data on the epidemiology from population-based surveillance is important to characterize the circulating serogroup and to guide decisions on IMD prevention and control strategies (Cordeiro et al., 2007). However, as demonstrated by our results, the serogroup was not identified in approximately 95% of cases from 2007–19. Meningococcal vaccines to protect against serogroups A, B, C, W, and Y are currently in use around the world (M. A. P. Safadi et al., 2017). The quadrivalent MenACWY and MCC vaccines are available in Brazil. Furthermore, a new protein-based vaccine (Bexsero) offering protection against MenB has also been licensed (Moura Silveira et al., 2019).

Regarding MenB, our study has performed the first analysis on the cost-effectiveness of Bexsero vaccination in a lower or middle-income country. However, due to some issues, such as lower MenB incidence and the high cost of the vaccine, the Bexsero is unlikely to be cost-effective in Brazil (Moura Silveira et al., 2019). Nonetheless, during outbreak situations, this vaccination program can be important. Enhancing the number of reported cases in order to understand the burden presented by each serogroup is critical for economic evaluation as well for achieving a cost-effectiveness analysis that is vital for the introduction of a new vaccine into the NIP.

The SIVERA II performs a systematic analysis of Nm isolates recovered by the epidemiologic survey network from countries in Latin America and the Caribbean, while efforts to improve surveillance systems have been reported in Latin America. However, only a limited number of countries have implemented IMD surveillance programs and the data provided is usually neither uniform nor easily accessible (M. A. Safadi et al., 2015; M. A. P. Safadi et al., 2017).

In this context, PAHO recommends continuing the surveillance. Moreover, in order to reduce the global burden of IMD in Latin America, the Global Meningococcal Initiative – comprising of an international team of scientists, clinicians, and public health officials with expertise in meningococcal disease – highlights the implementation of active population- and laboratory-based surveillance for invasive IMD, together with the estimation of age-specific incidence rates and serogroup distribution (M. A. Safadi et al., 2015).

With regard to SINAN, it has been reported that there are serious weaknesses at all levels of the health system, such as a lack of human resources (limited number of staff) and also a lack of infrastructure (office space, computers, supplies, etc.) (Galvao et al., 2008). Probably, these limitations have contributed at least in part to the high numbers of cases in which the serogroups were not identified. However, it is important to highlight that there have been improvements in IMD surveillance systems over the last few years (M. A. Safadi et al., 2015).

5. Conclusion

During IMD outbreaks, people often ask, "How many individuals will die before action is taken?" (M. A. P. Safadi et al., 2017). Improving surveillance systems to capture the mortality rates, the distribution of each serogroup, and the age of patients infected is crucial for determining the better vaccine and also the more effective catch-up campaigns for older age groups. Understanding this data now ensures that we will save lives.

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