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Epidemiological study of bacterial meningitis cases in Brazil between 2009 and 2018

Estudo epidemiológico sobre meningite bacteriana no Brasil no período entre 2009 e 2018

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ABSTRACT: *Introduction*: Meningitis can be defined as the occurrence of an inflammatory process in the meninges, which can be triggered by several infectious or non-infectious agents. Bacterial etiology has a high potential for producing mortality and sequelae, facts that contribute to its epidemiological importance and to the validity of tests seeking to describe and quantify it. *Objectives*: To carry out an epidemiological study on the reported cases of bacterial meningitis in Brazil, years 2009 to 2018. *Methodology:* Quantitative and retrospective study based upon data found on the Information and Recordings System (SINAN), reporting to the period between 2009 and 2018, and available on the Department of Informatics of the Unified Health System (DATASUS); Included data were: gender, race, age, outcome and state of origin. *Results*: 52,926 confirmed cases were reported to SINAN, in Brazil, between 2009 and 2018, with a tendency to decreasing numbers over the years; the most frequent etiologies were pneumococcal (19.9%), meningococcal (14.8%) and tuberculous (7.0%). Bacterial meningitis predominated in males (59.6%), with a greater involvement of children under 10 years old (35.2%), followed by individuals aged 20 to 39 years (21.1%), mostly white (44.5%), having a hospital discharge as the outcome (70.7%), and originated from Southern and Southeastern Brazil. *Conclusion*: Bacterial meningitis tend to decrease in number of cases, which are presented alongside a slight oscillation in the incidence of pneumococcal etiology, and a predominance in children under 10 years, male, white, originated in Southern and Southeastern Brazil, evolving to discharge.

Keywords: Meningitis; Meningitis, Bacterial; Epidemiology.

RESUMO: *Introdução:* A meningite é a ocorrência de processo inflamatório das meninges, podendo ser desencadeado por diversos agentes infecciosos ou não infecciosos; a etiologia bacteriana possui elevado potencial de morbimortalidade, o que contribui para a significância epidemiológica e a validade de esforços que busquem descrevê-la e quantificá-la. *Objetivos:* realizar estudo epidemiológico acerca dos casos notificados de meningite bacteriana no Brasil durante os anos de 2009 a 2018. *Metodologia:* estudo quantitativo e retrospectivo a partir de dados coletados no Sistema de Informações e Agravos de Notificação (SINAN) referentes ao período de 2009 a 2018, disponível nos Departamento de Informática do Sistema Único de Saúde (DATASUS); informações obtidas: sexo, idade raça, evolução e estado de origem. *Resultados:* Foram notificados 52.926 casos confirmados por meio do SINAN no Brasil, entre 2009 e 2018, havendo tendência à redução no número de casos com o decorrer dos anos; as etiologias mais frequentes foram a pneumocócica (19,9%), a meningocócica (14,8%) e a tuberculosa (7,0%). Predominou o sexo masculino (59,6%), com maior acometimento em indivíduos menores de 10 anos de idade (35,2%), seguido de indivíduos entre 20 a 39 anos (21,1%), majoritariamente em brancos (44,5%), com evolução para alta (70,7%) e originários dos Estados do Sul e Sudeste brasileiro. *Conclusão:* Observou-se tendência à redução dos casos de meningite bacteriana, com discreto padrão oscilatório na incidência de meningite por pneumococo, e predominância em crianças menores de 10 anos, do sexo masculino, raça/cor branca, advindas do Sul e Sudeste brasileiro, que evoluíram para alta.

Palavras-chave: Meningite; Meningites bacterianas; Epidemiologia.

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INTRODUCTION

Meningitis is defined as the occurrence of an inflammatory process of the meninges, which can be triggered by a number of different infectious (bacteria, virus, fungi and others) or non-infectious (e.g. medication and neoplasms) agents[1,2]. Bacterial meningitis is the most relevant to public health, given the magnitude of its occurrence and the high potential for producing outbreaks[2,3]. Furthermore, elevated morbidity and mortality rates contribute to the increased epidemiological relevance of such etiology and to the validity of efforts that seek to describe and quantify it[3,4].

In that regard, the clinical presentation varies with age and disease duration, being subject to non-specific symptoms (fever and intense headache) and meningeal irritation signs (neck stiffness and lumbar pain**).** As for sequelae, these are associated with focal neurological deficits, hearing loss, cognitive disability and epilepsy[2,3,5]. In addition, bacterial meningitis encounters its largest expression within the meningococcal etiology, caused by any of the identified serogroups of *Neisseria meningitidis*: A, B, C, W, X and Y[3,4]. In Brazil, the disease was under healthcare public agencies' maximum attention between the '70s and the '80s, when epidemics in many towns over the country were attributed to serogroups A, B and C. Serogroup C is currently responsible for most of the cases, which were made progressively less incident by the implantation of immunization policies for meningococcal C conjugated vaccine, whose full coverage became mandatory in 2010[7].

Other etiologies include *Streptococcus pneumoniae*, *Haemophilus influenzae* B and *Mycobacterium tuberculosis* infections, considered most frequent among the elderly, the preschoolers and the immunosuppressed patients, respectively[8]. These agents are also covered by the National Vaccination Calendar and, along with *N. meningitidis*, answer for the known-etiology records notified to the Ministry of Health[7,8].

Nevertheless, active vigilance is necessary, since bacterial meningitis is still an unsolved public health issue that has accumulated a national total number of at least 2,208 deaths in 2016, against 1,532 in high-income North America and 1,630 in Western Europe, as for the same year[10]. The endemic occurrence of meningitis in the country could explain this fact[1].

Moreover, it is worth highlighting that some limitations related to public healthcare assistance concur to notification failure, among which the most relevant are: failure of the process of suspicion and diagnosis of the cases brought into the public system; insufficient routines and protocols; limited technical capacity of healthcare teams with the consequent dismissal of Epidemiological Surveillance[11]; inequality in accessing healthcare and diagnosis, especially in locations where services are highly concentrated in the capital, such as North and Northeast Regions[10,11].

In that regard, studies that approach bacterial meningitis macroregional distribution in a continental country as Brazil, full of intra and interregional disparities, are needed. Thus, the objective of this research is to perform an epidemiological study on the bacterial meningitis cases notified in Brazil between years 2009 and 2018, in order to subsidize information for the creation and implementation of measures aimed at the reduction of the disease.

METHODOLOGY

This is a quantitative and retrospective study, based on bacterial meningitis cases, notified and registered on the Notifiable Diseases Information System (SINAN), as referred to the period of 2009 to 2018, in Brazil, and available on the Department of Informatics of the Unified Health System (DATASUS). SINAN consists in a digital platform that gathers data on compulsory notification diseases in Brazil, and that is liable to utilization to evaluate the healthcare assistance provided to these diseases by the Unified Health System (SUS). Since it relies on a public domain database, this study was not subject to a Research Ethics Committee.

The data was collected prior to grouping according to the variables: age, gender, race/color, State of residence and health macroregion and etiology, as operationalized in the notification form: meningococcal meningitis (MM); tuberculous meningitis (MTBC); bacterial meningitis (MB); haemophilus meningitis (MH); and pneumococcal meningitis (MP).

Shapiro-Wilk and D'Agostinho Pearson tests were used for normality analysis. Non-parametric variables were evaluated through chi-squared test, whilst one-way ANOVA test was applied to parametric variables, both of which were performed on Prism 8 (GraphPad®) and BioStat 5.4 (Mamirauá Institute).

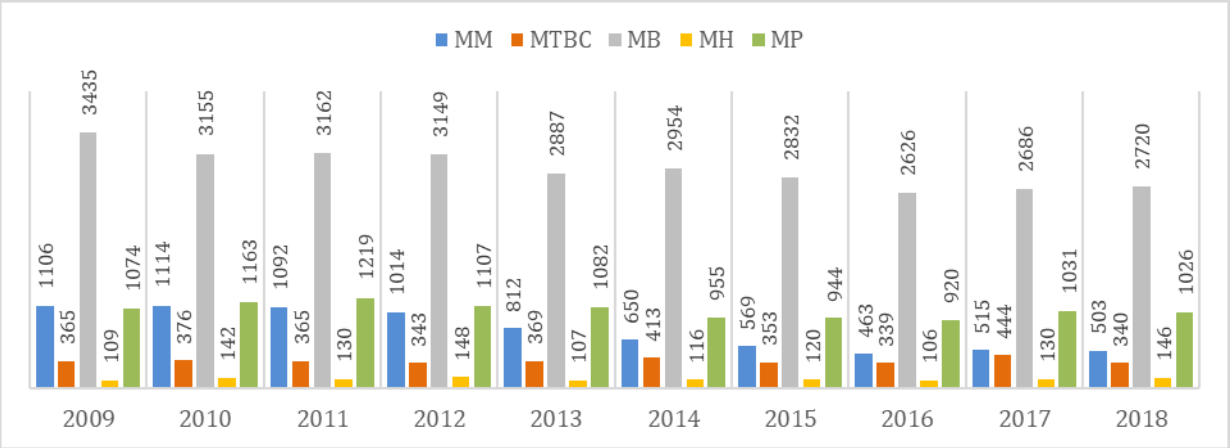
The analysis was performed through nonparametric chi-squared test, used to investigate an association between variables. *BioStat 5.4* was used while observing a p-value of less than 0.05.

Lastly, a 95% confidence interval was constructed based on case proportion. *TabWin 4.15* georeferencing software, available on DATASUS, was used to create spatial distribution maps. The coefficient's calculation was performed by dividing the absolute number of cases (numerator) by the resident population in a same region (denominator) and multiplying the result by 100,000[3,9]. The distribution was made for equal frequencies, as suggested by the software.

RESULTS

A total number of 52,926 confirmed cases were notified in Brazil through SINAN between 2009 and 2018, with an estimated mean of 5,292.6 cases per year. The cases of meningitis caused by other bacteria (MB) – among which are *Mycobacterium tuberculosis; Streptococcus sp.*, particularly B group; *Streptococcus agalactiae*; Listeria *monocytogenes*; *Staphylococcus aureus*; *Pseudomonas aeruginosa*; *Klebsiella pneumoniae*; *Enterobacter sp.*; *Salmonella sp.*; *Proteus sp.*[13]- were responsible for 55.9% of all cases, thus ranking first. Additionally, pneumococcal, meningococcal and tuberculous meningitis were responsible for 19.9% (n=10,521), 14.8% (n= 7,838) e 7.0% (n=3,707), respectively. A decrease in the number of meningococcal meningitis cases, from 1,106 cases in 2009 to 503 cases in 2018, was observed. Also, the number of cases caused by the other etiologic agents was maintained over the evaluated period (Graph 1 e Table 1; p<0,0001; R^2=0,98).

Graph 1 – Distribution of notified meningitis cases in Brazil, by year and etiologic agent



MM: meningococcal meningitis, MTBC: tuberculous meningitis, MB: bacterial meningitis, MH: haemophilus meningitis, MP: pneumococcal meningitis.
Source: Ministry of Health/SVS – Notifiable Diseases Information System - Sinan Net

Table 1 - Distribution of notified meningitis cases in Brazil, by year and etiologic agent

Etiology	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	Total	%
MM	1,106	1,114	1,092	1,014	812	650	569	463	515	503	7,838	14.8
MTBC	365	376	365	343	369	413	353	339	444	340	3,707	7.0
MB	3,435	3,155	3,162	3,149	2,887	2,954	2,832	2,626	2,686	2,720	29,606	55.9
MH	109	142	130	148	107	116	120	106	130	146	1,254	2.4
MP	1,074	1,163	1,219	1,107	1,082	955	944	920	1,031	1,026	10,521	19.9
Total	**6,089**	**5,950**	**5,968**	**5,761**	**5,257**	**5,088**	**4,818**	**4,454**	**4,806**	**4,735**	**52,926**	**100.0**

MM: meningococcal meningitis, MTBC: tuberculous meningitis, MB: bacterial meningitis, MH: haemophilus meningitis, MP: pneumococcal meningitis.
Source: Ministry of Health/SVS – Notifiable Diseases Information System - SINAN Net

After distributing cases by gender, it was observed that males (59.6%; 31,655) predominated over females (n=21,466). Only 11 cases had been registered as ignored gender (<0.5%). The predominance of males was a constant in all the studied etiologies, as can be observed in Graph 2 (p=0,24; R^2=0,31).

In concerning the age for the total number of cases, a higher involvement of individuals younger than 10 years old (35.2%, n=18,726), followed by those aged 20-39 (21.1%, n=11,206) and 40-59 (20.0%, n=10,635), was demonstrated. A predominance of up to 10-years-olds was perceived for the MM, MB and MH etiologies. Tuberculous and pneumococcal meningitis, on the contrary, found a higher concentration among the patients aged 20-39 and 40-59, respectively (Gráfico 3; p=0,24; R^2=0,31).

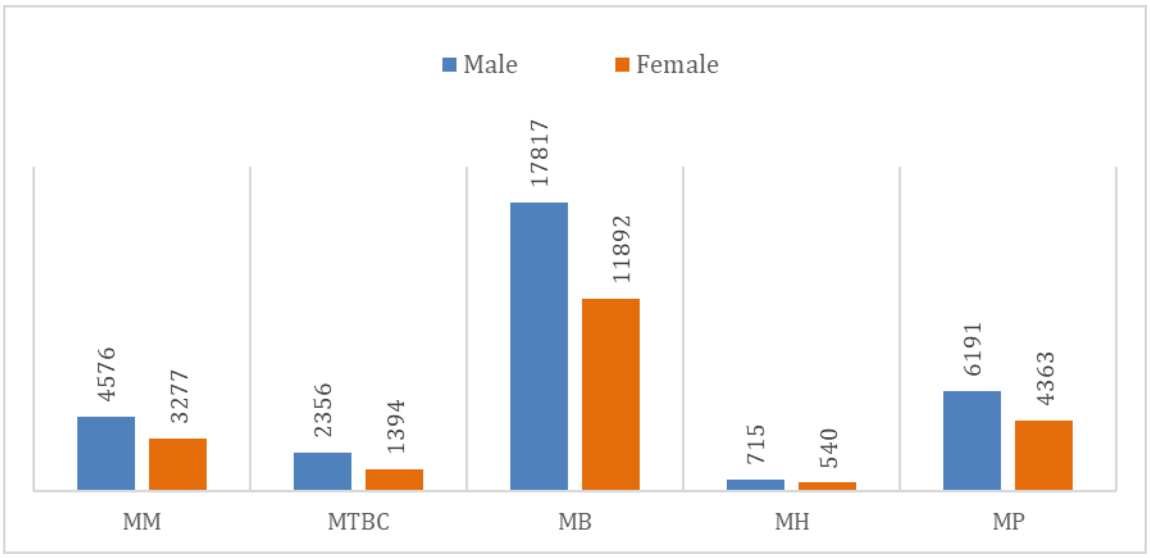
As observed in Graph 4 (p=0,24; R^2=0,31), the distribution of cases according to race/color determined a predominance of white people (44.5%, n=23,616), followed by brown people (31.9%, n=16,950). It is worth highlighting a large number of cases for which this variable is ignored (17.4%, n=9,227). As for etiologies, MTBC was the only one to have color brown as higher in incidence

than other races/colors.

Of all registered cases, 70.7% (n=37,590) were discharged from the hospital, 16.6% (n=8,814) individuals died from meningitis and other 2,906 (5.5%) encountered an unfavorable outcome from a different cause. Of the studied etiologies, pneumococcal meningitis was the one with a higher mortality rate as compared to its absolute number (29.27% of deaths, n=3,090), followed by tuberculous meningitis (18.21% of deaths, n=683), according to Table 2 ($p<0,0001$; $R^2=0,15$).

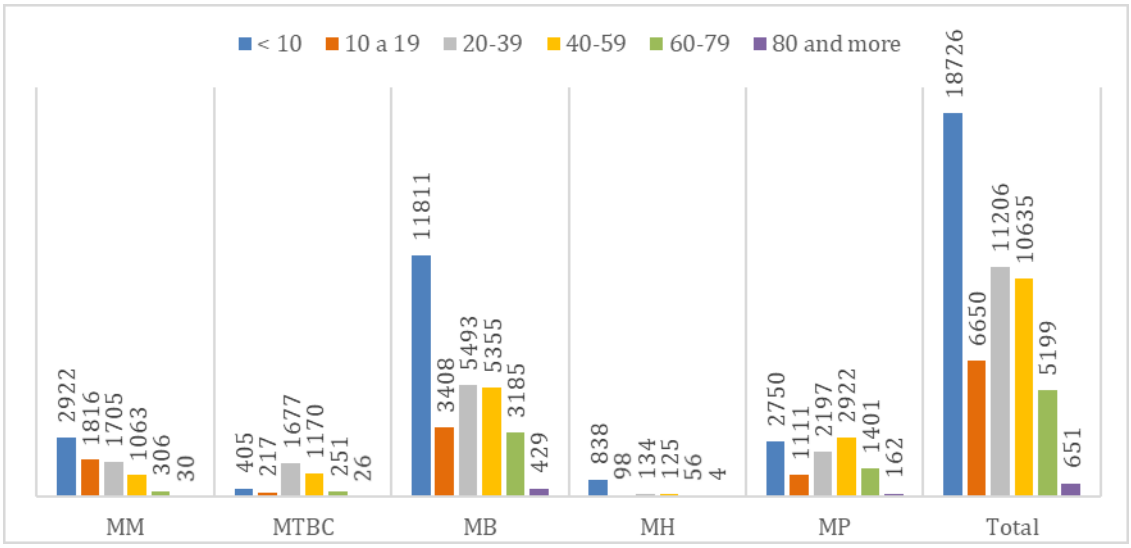
When observing the distribution of cases per State, a higher concentration was noticed in South, Southeast and Northeast regions for all studied etiologies, according to the maps (Figures 1 to 5) and Table 3 ($p=0,003$; $R^2=0,85$).

Graph 2 - Distribution of notified meningitis cases in Brazil, by etiology and gender



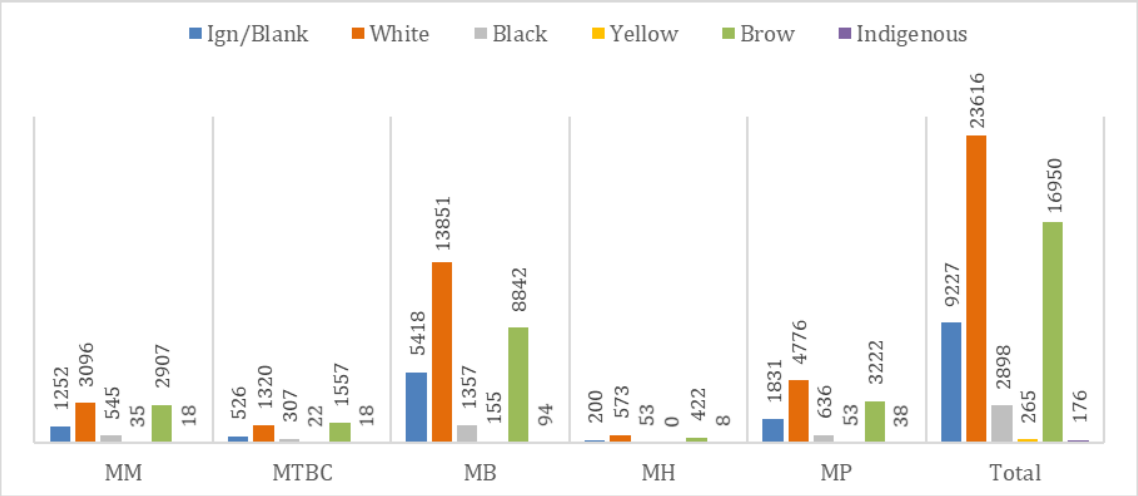
MM: meningococcal meningitis, MTBC: tuberculous meningitis, MB: bacterial meningitis, MH: haemophilus meningitis, MP: pneumococcal meningitis.
Source: Ministry of Health/SVS – Notifiable Diseases Information System - SINAN Net

Graph 3 - Distribution of notified meningitis cases in Brazil, by etiology and age



MM: meningococcal meningitis, MTBC: tuberculous meningitis, MB: bacterial meningitis, MH: haemophilus meningitis, MP: pneumococcal meningitis.
Source: Ministry of Health/SVS – Notifiable Diseases Information System - SINAN Net

Graph 4 - Distribution of notified meningitis cases in Brazil, by etiology and race/color



MM: meningococcal meningitis, MTBC: tuberculous meningitis, MB: bacterial meningitis, MH:haemophilus meningitis, MP: pneumococcal meningitis.
Source: Ministry of Health/SVS – Notifiable Diseases Information System - SINAN Net

Table 2 - Distribution of notified meningitis cases in Brazil, by clinical outcome

Clinical Outcome	MM	MTBC	MB	MH	MP	Total	%
Ignored/Blank	690	253	2.023	106	750	3,822	7.2
Discharge	6,182	2,346	21,723	919	6,420	37,590	70.7
Death from meningitis	923	683	3,913	205	3,090	8,814	16.6
Death from other cause	58	468	2,058	26	296	2,906	5.5
Total	**7,853**	**3,750**	**29,717**	**1,256**	**10,556**	**53,132**	**100.0**

MM: meningococcal meningitis, MTBC: tuberculous meningitis, MB: bacterial meningitis, MH:haemophilus meningitis, MP: pneumococcal meningitis.
Source: Ministry of Health/SVS – Notifiable Diseases Information System - SINAN Net

Table 3 - Distribution of notified meningitis cases in Brazil, by etiology and State, between years 2009 and 2018

State	MM	MTBC	MB	MH	MP	Total
São Paulo	3,327	640	10,350	517	4,319	19,153
Rio de Janeiro	684	417	2,434	95	1,066	4,696
Minas Gerais	605	272	2,154	130	964	4,125
Espírito Santo	93	37	193	12	199	534
Southeast Region	**4,709**	**1,366**	**15,131**	**754**	**6,548**	**28,508**
Paraná	297	235	2,927	61	645	4,165
Rio Grande do Sul	408	488	1,913	43	639	3,491
Santa Catarina	201	261	1,426	41	385	2,314
South Region	**906**	**984**	**6,266**	**145**	**1,669**	**9,970**
Bahia	477	125	1,659	67	396	2,724
Pernambuco	256	293	1,330	49	217	2,145
Ceará	216	166	150	34	223	784
Piauí	89	37	459	10	118	713
Rio Grande do Norte	62	59	397	11	60	589
Alagoas	60	99	322	13	95	589
Paraíba	35	11	282	5	26	359
Maranhão	76	9	184	12	53	334
Sergipe	32	9	119	7	50	217

Table 3 - Distribution of notified meningitis cases in Brazil, by etiology and State, between years 2009 and 2018 *continuation*

State	MM	MTBC	MB	MH	MP	Total
Northeast Region	**1,303**	**808**	**4,902**	**208**	**1,238**	**8,459**
Goiás	203	50	770	35	225	1.,283
Distrito Federal	135	13	314	30	118	610
Mato Grosso	143	17	318	7	118	603
Mato Grosso do Sul	75	36	253	9	124	497
Midwest Region	**556**	**116**	**1,655**	**81**	**585**	**2,993**
Pará	168	310	1,086	21	212	1,797
Amazonas	94	139	212	20	142	607
Rondônia	48	19	152	1	67	287
Tocantins	31	1	189	8	51	280
Acre	11	3	53	12	17	96
Roraima	7	3	55	1	10	76
Amapá	20	1	16	5	17	59
North Region	**379**	**476**	**1,763**	**68**	**516**	**3,202**
Total	**7,853**	**3,750**	**29,717**	**1,256**	**10,556**	**53,132**

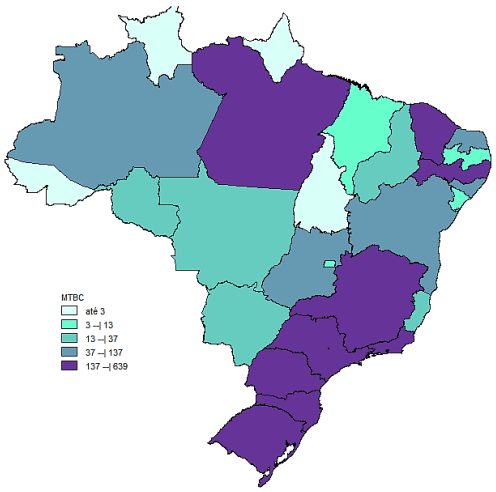
MM: meningococcal meningitis, MTBC: tuberculous meningitis, MB: bacterial meningitis, MH: haemophilus meningitis, MP: pneumococcal meningitis.
Source: Ministry of Health/SVS – Notifiable Diseases Information System - SINAN Net

When distributing the occurrences of meningitis for the population of each Brazilian Region, it was found that the quantity of cases per 100,000 inhabitants is greater in South (34.49) and Southeast (33.62), and minimum in Northeast (15.11). The tuberculous etiology was the only one to present a higher density of cases in South Region (3.40), the others being more frequent in Southeast (MM=5.55; MB=17.85; MH=0.89; MP=7.72), as described in Table 4 (p=0,11).

Table 4 – Distribution of notified meningitis in Brazil, by Region, between years 2009 and 2018 (cases per 100,000 inhabitants)

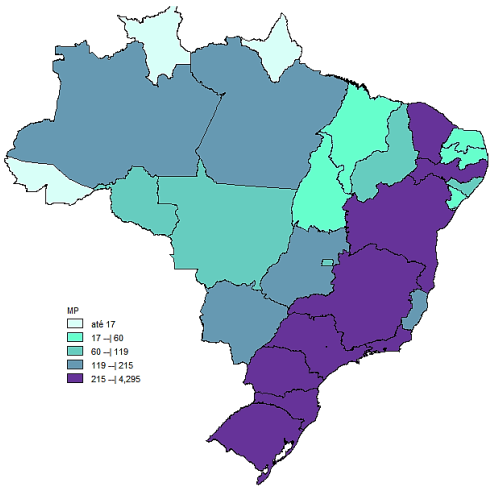
Region	MM	MTBC	MB	MH	MP	Total	Population†
North	2.21	2.77	10.29	0.40	3.01	18.68	17,137,771
Northeast	2.33	1.44	8.76	0.37	2.21	15.11	55,990,448.5
Southeast	5.55	1.61	17.85	0.89	7.72	33.62	84,790,596.5
South	3.13	3.40	21.68	0.50	5.77	34.49	28,905,938
Midwest	3.68	0.77	10.96	0.54	3.87	19.81	15,106,399.5
Total	3.89	1.86	14.72	0.62	5.23	26.31	201,931,153.5

MM: meningococcal meningitis, MTBC: tuberculous meningitis, MB: bacterial meningitis, MH: haemophilus meningitis, MP: pneumococcal meningitis.
†: population equivalent to half of the evaluated period
Source: Ministry of Health/SVS – Notifiable Diseases Information System - Sinan Net



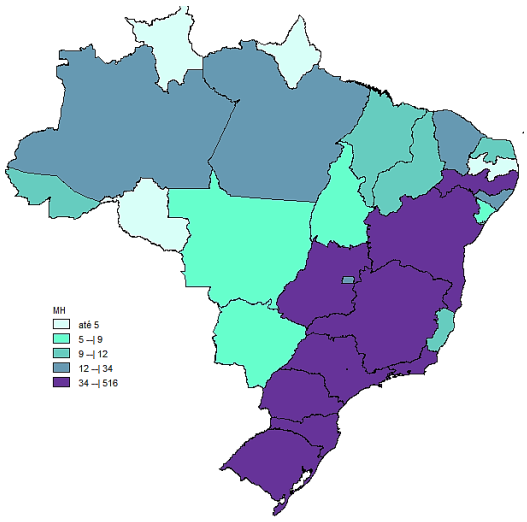
Fonte: Ministry of Health/SVS - Notifiable Diseases Information System – SINAN Net

Figure 1 – Number of Tuberculous Meningitis cases in Brazil, by State, from 2009 to 2018 (p<0,0001)



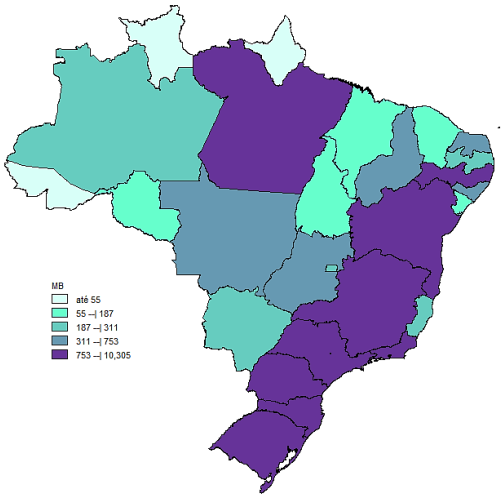
Fonte: Ministry of Health/SVS - Notifiable Diseases Information System – SINAN Net

Figure 2 - Number of Pneumococcal Meningitis cases in Brazil, by State, from 2009 to 2018 (p=0,08)



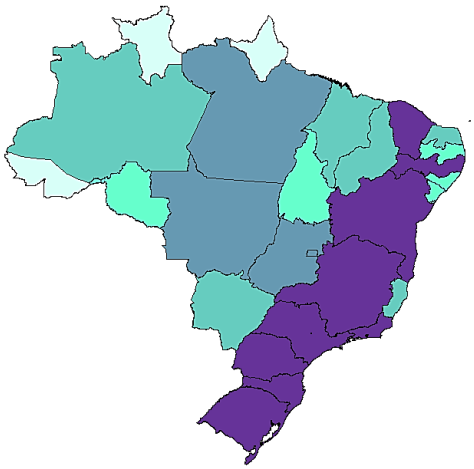
Fonte: Ministry of Health/SVS - Notifiable Diseases Information System – SINAN Net

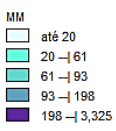
Figure 3 - Number of Haemophilus Meningitis cases in Brazil, by State, from 2009 to 2018 (p=0,029)



Fonte: Ministry of Health/SVS - Notifiable Diseases Information System – SINAN Net

Figure 4 - Number of (Unspecific) Bacterial Meningitis cases in Brazil, by State, from 2009 to 2018 (p=0,11)





Fonte: Ministry of Health/SVS - Notifiable Diseases Information System – SINAN Net

Figure 5 - Number of Meningococcal Meningitis cases in Brazil, by State, from 2009 to 2018 (p<0,0001)

DISCUSSION

In this study, an epidemiological analysis of bacterial meningitis was performed that identified a variation in the incidence rate of the disease[14], with a notorious reduction in MM throughout the years. Foreign studies suggest that this reduction results from the positive impact of prevention strategies, although Magalhães e Santos disagree when they state that Brazilian coverage is inadequate[15,16].

In this sense, these authors[15] defend that homogeneously achieving and sustaining vaccination coverage goals, for each vaccine and in all States, is a challenge for public health. It has also been suggested that mean per capita income and level of economic inequality hold influence over vaccination coverage: in North and Northeast States, for instance, the coverage of meningococcal C conjugate vaccine for children aged 4 years or less is inferior to the recommended by the Ministry of Health, due to lower per capita income and greater socioeconomical inequality[16].

Nevertheless, the present study observed that Southeast, South and some Northeast States that, in theory, present favorable socioeconomical scenarios for proper vaccination coverage, are the ones showing higher numbers of meningococcal meningitis cases.

In concerning MM, the distribution of notified cases by the number of inhabitants in each Region did not reach statistical significance, making the high values encountered in the aforementioned Regions unjustifiable as a function of population volume. Thus, it is important to note that the number of cases might have suffered influence from other aspects, such as South and Southeast's colder climate and lower humidity[23], as well as better notification routines in these Regions.

This study also focused on other pertinent variables, such as age of disease onset, a higher prevalence in children younger than 10 (35.2%), followed by adults aged 20 to 39 (21.1%) having been observed. The obtained data is in accordance with the literature[14,17,18] as to the first incidence peak being between ages 1 and 9 (27%), but disagrees as to the second peak, previously set after 60 years[15].

The affection of children aged 1 to 4, young adults and people older than 60 occurs due to the immunological frailties of each age group (immaturity, immunosuppression and reduction in immune capacity, respectively), as well as to the concentration of people in small spaces, such as schools, rest homes and hospitals[14,19].

As for the race/color proportion, a higher prevalence of white people (44.5%), followed by brown people (31.9%) was identified. Being that this is a study of a nationwide nature, it is worth highlighting that Southeast Region is the most populous in Brazil (42.2%), with a total of 44.48 million (50.7%) people self-declared white. The second most populous is Northeast Region (27.2%), with a total of 40.60 million (71.8%) self-declared brown. Thus, our results were compatible with the national statistical findings[20,21].

Like other works[14,19,22], this study found a higher prevalence of the male gender among those affected by meningitis (59.6%). Nevertheless, it was not possible to stablish a correlation between variables, and literature data was not found that justified this association. Moreover, bacterial meningitis is worrisome due to its elevated morbimortality rates: around 3 to 19% of affected people die from it[14], a value close to the encountered in our study (16.6%). In addition, 70.7% were discharged from hospital, a value inferior to the findings of Paim et al.[19], who considered that 80% of patients had this outcome. It is suggested that such disparity of results occurs due to the evaluated group, since the mentioned study enables for the sole analysis of Santa Catarina State, i.e., of a sample much more restrict than that of the present study.

Among the main etiological agents of bacterial meningitis are *Neisseria meningitidis* (meningococcus), *Haemophilus influenzae* B and *Streptococcus pneumoniae* (pneumococcus)[3,5,6,8]. Although pneumococcal (MP-30.78%) and meningococcal (MM-21.32%) etiologies occupy prominent positions in this study, undetermined bacterial meningitis (MB-39.01%) leads the group. This data might identify frailties in lab techniques for etiological and serotype diagnosis, since failing to recognize the pathological agent leads to listing data as not registered ("blank") or not notified on SINAN[15].

Conversely, underreporting is alleged due to the lack of identification of etiologic agents, as well as flaws in the epidemiological vigilance programs of, primarily, São Paulo, Paraná, Rio de Janeiro, Minas Gerais, Santa Catarina, Bahia, Paraiba and Pará States[15], where MB incidence is greater.

Even if the implantation of real-time PCR (*Polymerase Chain Reaction*) has been considered a valuable tool for the rapid elucidation of undetermined cases of bacterial meningitis, only some States have access to this analysis technique. This corroborates to underreporting and unreliable incidence rates, not corresponding to the reality of the States, i.e., resulting in inconclusive national epidemiological diagnosis[15,19].

CONCLUSION

Bacterial meningitis in Brazil is inferred to have presented a reduction in the number of notified cases between years 2009 and 2018. Furthermore, it was noted that the prevalence of non-specified bacterial meningitis suggests an underreporting pattern for the disease, as well as failed etiological analysis techniques. In addition, as for patients' etiological agent profile, it was observed that in meningococcal, haemophilus and non-specified meningitis, there was a higher prevalence of children under 10 years of age. As for pneumococcal and tuberculous meningitis, the predominant age groups were 40-59 and 20-39, respectively.

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survey, data analysis and interpretation, discussion of results, abstract and title translation, manuscript elaboration. *Valente FS* – responsible for bibliographic survey, data collection, data tabulation, construction of results, data analysis and interpretation and reference update. *Sousa LD* – responsible for data collection, data tabulation, construction of results, data analysis and interpretation, reference update. *Cardoso PNM* – responsible for data analysis, discussion of results and data update. *Silva MA* – data analysis, discussion of results and data update. *Santos DR* – research advisor, elaborated theme and participated in all research stages, performed critical review of the paper's technical content.

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