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Meningococcal disease epidemiology in Brazil (2005–2018) and impact of MenC vaccination

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ABSTRACT

Background: Meningococcal disease (MD) presents a substantial public health problem in Brazil. Meningococcal C conjugate (MenC) vaccination was introduced into the routine infant immunization program in 2010, followed by adolescent vaccination in 2017. We evaluated changes in national and regional MD incidence and mortality between 2005 and 2018, serogroup distribution and vaccine coverage.

Methods: Data were obtained from national surveillance systems from 2005 to 2018. Age-stratified incidence and mortality rates were calculated and a descriptive time-series analysis was performed comparing rates in the pre-(2005–2009) and post-vaccination (2011–2018) periods; MD due to specific meningococcal serogroups were analyzed in the pre-(2007–2009) and post-vaccination (2011–2018) periods.

Results: From 2005 to 2018, 31,108 MD cases were reported with 6496 deaths; 35% of cases and deaths occurred in children < 5 years. Incidence and mortality rates declined steadily since 2012 in all age-strata, with significantly lower incidence and mortality in the post-vaccine introduction period in children aged < 1-year, 1–4 years, 5–9 years and 10–14 years. A significant decline in MenC disease in children < 5 years was observed following MenC vaccine introduction; infants < 1 year, from 3.30/100,000 (2007–2009) to 1.08/100,000 (2011–2018) and from 1.44/100,000 to 0.42/100,000 in 1–4-year-olds for these periods. Reductions in MenB disease was also observed. MenW remains an important cause of MD with 748 cases reported across 2005–2018. While initial infant vaccination coverage was high (>95% nationwide), this has since declined (to 83% in 2018); adolescent uptake was < 20% in 2017/18). Regional variations in outcomes and vaccine coverage were observed.

Conclusion: A substantial decline in incidence and mortality rates due to MD was seen following MenC vaccine introduction in Brazil, especially among children < 5 years chiefly driven by reductions in MenC serogroup. While these benefits are considerable, the prevalence of MD due to other serogroups such as MenW and MenB remains a concern. A video summary linked to this article can be found on Figshare: https://doi.org/10.6084/m9.figshare.13379612.v1

1. Introduction

Meningococcal disease (MD) caused by *Neisseria meningitidis* represents a substantial public health burden, both globally and in Latin America [1–5]. In many countries, including Brazil, surveillance data indicates that *N. meningitidis* is the most frequent cause of bacterial meningitis [6]. Serogroups (Men) A, B, C, W, X and Y are responsible for most invasive MD, and while disease due to MenC and MenB dominates in Latin America the dynamic nature of MD epidemiology is such that the relative contribution of these and other serogroups is in constant flux [2,7]. If untreated, MD has a 50–80% case fatality rate (CFR) with an estimated CFR of 15% in those receiving treatment, while 12–20% of survivors suffer substantial clinical sequelae, including neurological sequelae (e.g., hearing loss, mental impairment, paralysis, seizures) and limb or digital amputations [8].

Vaccination against those at greatest risk is an effective health strategy to reduce the burden of endemic disease and epidemic outbreaks, with a range of vaccines against specific serogroups available for use [9,10]. Although patterns vary in different countries and regions, the highest incidence is seen in children < 5 years of age, and especially in children < 1 year [11]. In their appraisal of MD cases reported in Brazil between 2000

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and 2010, Azevedo et al reported that 40% of cases occurred in children < 5 years [6].

Furthermore, the highest rates of *N. meningitidis* nasopharyngeal carriage, which may act as a reservoir for transmission to more vulnerable age-groups, are seen in adolescents (in particular serogroup C) [5,12,13]. Data indicates that vaccination of adolescents is also an important preventive strategy [5,12,14,15].

During the period from 2002 to 2010, a notable shift in the epidemiology of MD was observed in Brazil, with a shift from a predominance of disease due to serogroup B to an increasing prevalence of cases due to serogroup C, which was the most frequent causative serogroup for the latter years of this period. This shift was associated with the emergence of specific hypervirulent serogroup C clones comprising a range of clonal complexes (CC), in particular CC103 (which includes the ST-3780 genotype), and also CC11 and CC32. These CCs represent an important cause of endemic disease and were also associated with specific disease outbreaks [16–19]. In response, the meningococcal C conjugate vaccine (MenC vaccine) was introduced into the National Immunization Program (NIP) in November 2010, for children < 2 years of age. For infants < 1 year of age, MenC vaccine was given in a 2-dose primary schedule, at three and five months, with a booster dose given at 12–15 months [20]. At the time of introduction, while children aged between 12 and 23 months received a single vaccine dose, no catch-up campaign was implemented for older children. Subsequently the NIP for MenC vaccination was expanded to target adolescents, with immunization of those aged 12–13 years introduced in January 2017 [21], and then of those aged 11–14 years in March 2018 [22].

Studies reporting on the early benefits of this strategy, focusing on its effect in specific regions and on disease due to specific serogroups (e.g., Men C disease) indicate that MenC vaccination has led to reductions in MD in younger children [5,14,23,24]. We aim to describe the nationwide burden of MD from 2005 to 2018 and evaluate epidemiological trends of serogroup-specific disease in the overall population before and after the implementation of the MenC vaccination program in 2010. We also evaluated vaccine uptake in infants and older children and adolescents since introduction into the NIP.

2. Methods

2.1. Study design and study population

This was an observational population-based ecological database study (GSK study identifier: HO-16-18041) examining trends in the number and incidence rates of MD cases, associated serogroups, and deaths in Brazil from 2005 to 2018 using national passive surveillance data. Brazil is the largest country in South America, with an estimated population of 185,150,806 inhabitants in 2005, rising to 208,494,900 in 2018, of which approximately 14.8 million were <5 years of age [25] (Supplementary Figure 1).

We performed a descriptive time-series analysis comparing MD incidence and mortality rates before (2005–2009) and after (2011–2018) introduction of the MenC vaccine in the NIP, with the year of introduction (2010) considered a transition period (**Supplementary Figure 2**). Data on population demographics, circulating causative serogroups across the study period was also obtained (and vaccine coverage in eligible subjects since 2010). As the study used non-nominative secondary data no ethical board approval or informed consent was required.

2.2. Data sources

In Brazil, MD is a notifiable disease with mandatory reporting of suspected MD cases (based on relevant ICD-10 codes) to the National Information System for Notifiable Diseases (*Sistema de Informação de Agravos de Notificação* [SINAN]). For laboratory confirmed cases, SINAN reports on identification and capsular typing of invasive MD isolates on the basis of microbial culture, PCR and antigen detection techniques [26,27]. We obtained data retrospectively from SINAN for each year and by relevant age-group from 2005 to 2018 with confirmed cases identified using the following ICD-10 codes: A39.0, A39.2 and A39.4 [28]. MD-related deaths were identified by searching SINAN and the national Mortality Information System (SIM) database using the same ICD-10 codes. For all MD cases we captured data on causative serogroups when available in SINAN for the years 2007–2018.

Overall and age-stratified population data at the national level and overall population estimates for the five Brazilian regions (North, Northeast, Southeast, South, Midwest) were obtained from the Brazilian Institute of Geography and Statistics [IBGE]/DATASUS for each year throughout the study period [25] (Supplementary Table 1). Data on MenC vaccination coverage in vaccine-eligible infants and adolescents were obtained from the National Immunization Program Information System (SI-PNI) [29] as follows. For infants, data on the number of infants receiving the second dose of the primary series were available for the 2010–2018 period, while data on the number receiving the subsequent booster dose were only available from 2013 onwards; these data were available both at a nationwide and regional level. Coverage estimates for the percentage of infants receiving these vaccine doses were calculated using the relevant infant population projections. For adolescent vaccination coverage, data for the percentage of vaccine-eligible children receiving the single vaccine dose were supplied directly by the SI-PNI for the years 2017 (12 –13-year-olds) and 2018 (eligible 11 –14- year-olds).

2.3. Data analysis

Data were analyzed using descriptive and statistical analyses. The absolute numbers of confirmed MD cases reported in the SINAN system from 2005 to 2018 were tabulated, and stratified by outcomes of interest (incidence, mortality, age, serogroup and geographical region within Brazil). Mean annual incidence and mortality rates per 100,000 (with 95% confidence intervals [CIs]) were calculated and plotted over the study period for the overall population and for specific age-strata; in particular children and adolescents (<1 year; 1–4 years; 5–9 years; and 10–14 years). For the time-trend analysis, mean incidence and mortality rates for the pre- (2005–2009) and post-vaccination period (2011–2018) were calculated and compared. MD CFRs were also calculated as the annual number of MD deaths by year / annual number of MD cases [X100]).

For MD due to specific serogroups, annual numbers of cases and incidence rates were analyzed in a similar manner, although due to data availability (with little serogroup data available for the years 2005–2006), we considered the pre-vaccination period as 2007–2009 for the serogroup time-trend analyses. The Student's *t*-test was used to compare data with significance at $p < 0.05$. All data were stored and analysed using Microsoft Excel.

3. Results

3.1. MD incidence

From 2005 to 2018, a total of 31,108 MD cases were reported in SINAN. (Fig. 1**A**). The greatest case numbers occurred in the years 2005–2006 and 2010 (each with over 3,000 cases) after which we observed a sequential decline in case numbers in each subsequent year (falling to < 1200 cases in the years 2016–2018). Across

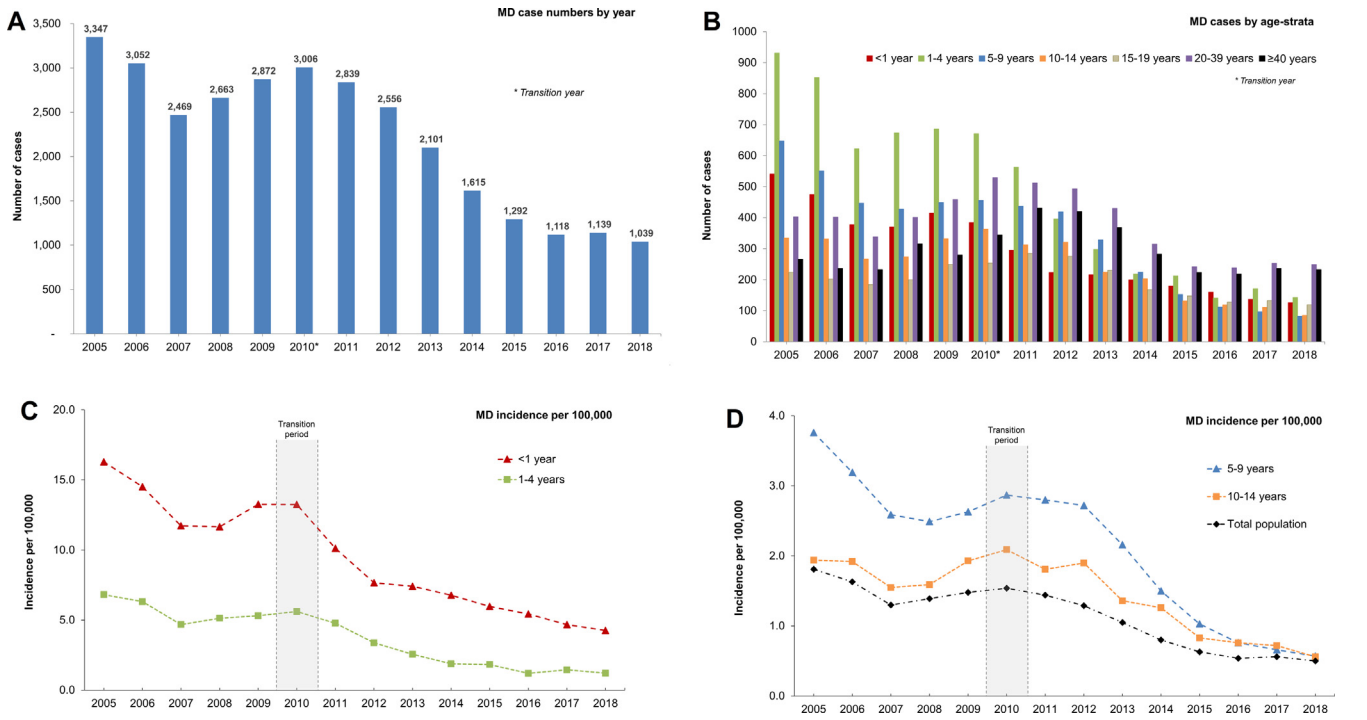

Fig. 1. Meningococcal disease in Brazil and trends in annual incidence rates (2005–2018). Annual number of cases in overall population (A) and in different age-strata (B). Incidence rates per 100,000 across the study period in infants (C) and in older children, adolescents and in the overall population (D); the light grey bar indicates 2010 as a transition year with introduction of MenC vaccination in the national immunization program. Abbreviations: MD, Meningococcal disease.

the study period, most MD cases occurred in subjects < 40 years of age, with greater numbers in younger age-groups; 4103 cases (13.2%) occurred in children aged < 12 months, and 6580 (21.2%) were reported in those between 1 and 4 years of age. In the latter years, disease in those aged 20–39 years was an important contributor to the overall MD burden (Fig. 1**B** and Supplementary Table 2).

A consistent trend of an overall decline in MD incidence rates since vaccine introduction in 2010 was observed. Incidence rates were substantially higher in younger children and greatest in those aged < 1 year and those aged 1–4 years prior to vaccine introduction (Fig. 2**C** and Supplementary Table 2). In infants (<1 year), incidence rates were highest in 2005 (16.29/100,000) with a

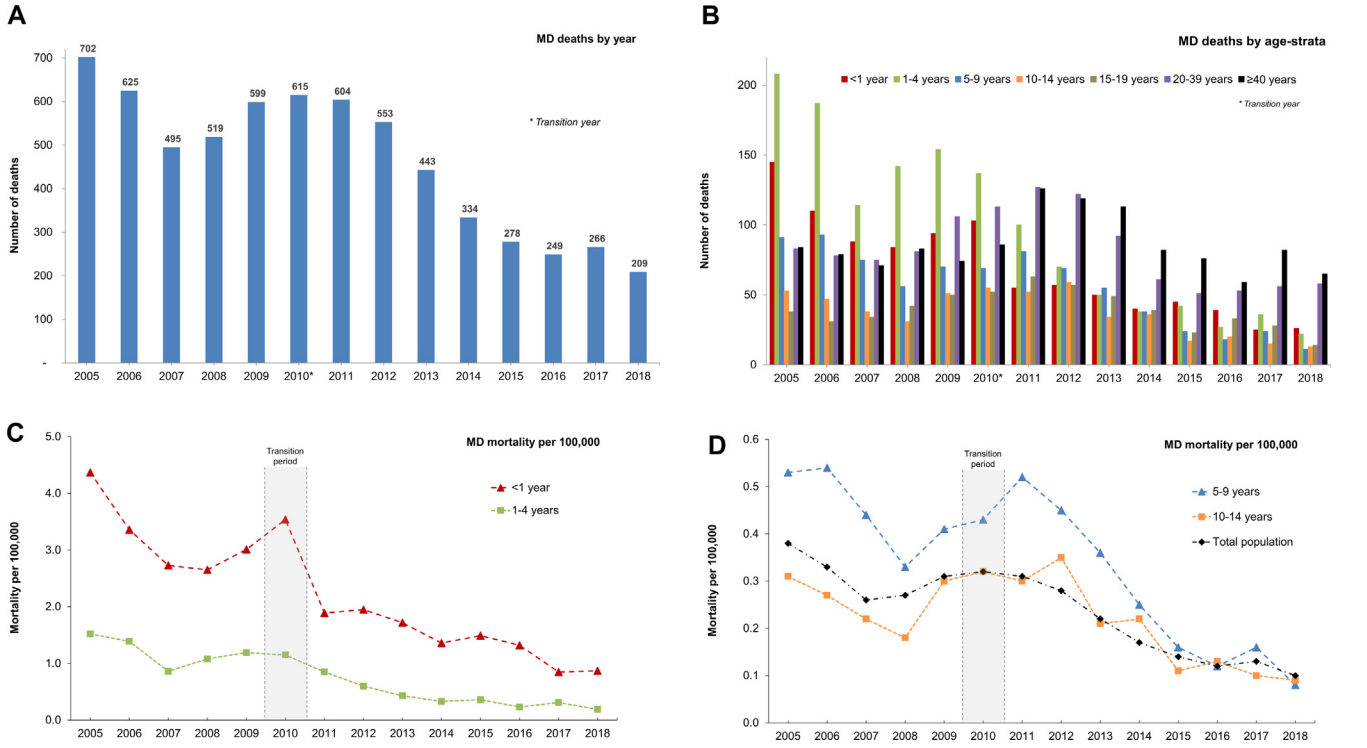

Fig. 2. Meningococcal disease mortality in Brazil and trends in annual mortality rates (2005–2018). Annual number of deaths in overall population (A) and in different age-strata (B). Mortality rates per 100,000 across the study period in infants (C) and in older children, adolescents and in the overall population (D); the light grey bar indicates 2010 as a transition year with introduction of MenC vaccination in the national immunization program. Abbreviations: MD, Meningococcal disease.

subsequent decline, from 13.27/100,000 in 2009 (the year prior to vaccine introduction) to 4.26/100,000 in 2018. Among 1–4-year olds, rates were also highest in 2005 (6.82/100,000) falling to 1.21/100,000 in 2018. A decline in incidence among children aged 5–9 years and adolescents aged 10–14 years was also observed. Consequently, incidence rates for the overall population also declined, from 1.81/100,000 in 2005 to 0.50/100,000 in 2018 (Fig. 2**D**).

This decline was reflected in the time-series analysis demonstrating substantial reductions in the estimated mean MD incidence rates for the period following vaccine introduction (2011–2018) compared with the pre-vaccination (2005–2009) period (Table 1 and Supplementary Table 2). In infants < 1-year old, mean annual incidence rates were 13.49/100,000 (95%CI 11.77–15.22) in the pre-vaccination period and 6.54/100,000 (95%CI 4.88–8.20) in the post-vaccination period (p < 0.001). In those aged between 1 and 4 years, mean annual incidence rates fell from 5.65/100,000 (95%CI 4.88–6.43) to 2.29/100,000 (95%CI 1.19–3.38) for these periods (p=<0.001). Significant reductions were also observed in children aged 5–9 years, and those aged 10–14 years; in the overall population, incidence rates fell from 1.52/100,000 (95%CI 1.35–1.70) to 0.85/100,000 (95%CI 0.53– 1.17; p = 0.001) (Table 1 and Supplementary Table 2).

3.2. MD mortality

In total, 6496 deaths due to MD were reported in DATASUS between 2005 and 2018 (Fig. 2**A** and Supplementary Table 3), of which 961 (14.8%) occurred in infants (<1 year) and 1327 (20.4%) in 1–4-year-olds. Similar to case numbers, an overall decline in number of deaths and in annual mortality rates was seen in the years following vaccine introduction, and with relatively fewer infant deaths (Fig. 2**B**). A consistent trend of declining MD mortality rates since vaccine introduction in 2010 was observed in all childhood age strata; in adolescents a decline was observed between 2015 and 2018 (Fig. 2**C and D**).

The time-series analysis showed significantly lower mean annual mortality rates in the period following vaccine introduction compared to the pre-vaccination period. In infants < 1 year, MD mortality rates were 3.22/100,000 (95%CI 2.61–3.83) in the pre-vaccination period and 1.43/100,000 (95%CI 1.07–1.80) in the post-vaccination period (p = 0.002).

Significant reductions in mortality rates in these period comparisons were also seen in children aged 1–4 years and in the 5–9 years age; in the overall population MD mortality rate fell from 0.31/100,000 (95%CI 0.27–0.35) to 0.18/100,000 (95%CI 0.11–0.25) in the post-vaccine introduction period (p = 0.004) (Table 1 and Supplementary Table 3).

Estimated CFRs for MD across the study period in the overall population was approximately 21%, and while these showed some fluctuation, there were no notable differences in any particular year or period. The CFRs were higher in infants < 1 year, with a mean CFR across 2005–2018 of 23.4% (Supplementary Table 4).

3.3. Meningococcal serogroups

Between 2007 and 2018 11,852 MD cases were serogrouped (via culture, PCR or antigen detection), representing 48.0% of all laboratory confirmed cases in this period. The majority of serogrouped cases belonged to serogroup C (71.1%, n = 8434), followed by B (19.9%, n = 2361) and W (6.3%, n = 748). Other serogroups (Y, A, 29E, X, and Z) were uncommon. The relative proportion of all MD cases that were serogrouped varied across the study period, increasing from 37.7% of all MD cases in 2007 to 54.3% in 2012, with a subsequent decline; in 2018, 47.4% of MD cases were serogrouped (Fig. 3**A**).

Table 1
Meningococcal disease incidence and mortality per 100,000 (2005–2018).

	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2005–2018*	Mean incidence/mortality rate		P-value†
																Pre-vaccination 2005–2009	Post vaccination 2011–2018	
Incidence rate																		
<1 year	16.29	14.52	11.73	11.66	13.27	13.25	10.13	7.67	7.42	6.78	5.98	5.43	4.68	4.26	8.98	13.49 (11.77–15.22)	6.54 (4.88–8.20)	**<0.001**
1–4 years	6.82	6.32	4.68	5.14	5.31	5.61	4.78	3.38	2.56	1.88	1.83	1.20	1.45	1.21	3.49	5.65 (4.88–6.43)	2.29 (1.19–3.38)	**<0.001**
5–9 years	3.76	3.19	2.59	2.49	2.63	2.87	2.80	2.72	2.16	1.50	1.03	0.76	0.66	0.57	2.00	2.93 (2.46–3.40)	1.53 (0.72–2.33)	**0.005**
10–14 years	1.94	1.92	1.55	1.59	1.93	2.09	1.81	1.90	1.36	1.26	0.83	0.76	0.72	0.56	1.41	1.79 (1.61–1.96)	1.15 (0.70–1.60)	**0.011**
Total population	1.81	1.63	1.30	1.39	1.48	1.54	1.44	1.29	1.05	0.80	0.63	0.54	0.55	0.50	1.14	1.52 (1.35–1.70)	0.85 (0.53–1.17)	**0.001**
Mortality rate																		
<1 year	4.37	3.36	2.73	2.65	3.01	3.54	1.89	1.95	1.72	1.36	1.49	1.32	0.85	0.87	2.22	3.22 (2.61–3.83)	1.43 (1.07–1.80)	**0.002**
1–4 years	1.52	1.39	0.86	1.08	1.19	1.15	0.85	0.60	0.43	0.33	0.36	0.23	0.31	0.19	0.75	1.21 (0.98–1.44)	0.41 (0.22–0.60)	**0.001**
5–9 years	0.53	0.54	0.44	0.33	0.41	0.43	0.52	0.45	0.36	0.25	0.16	0.12	0.16	0.08	0.34	0.45 (0.37–0.53)	0.26 (0.12–0.41)	**0.023**
10–14 years	0.31	0.27	0.22	0.18	0.30	0.32	0.30	0.35	0.21	0.22	0.11	0.13	0.10	0.09	0.22	0.26 (0.21–0.30)	0.19 (0.10–0.27)	0.139
Total population	0.38	0.33	0.26	0.27	0.31	0.32	0.31	0.28	0.22	0.17	0.14	0.12	0.13	0.10	0.24	0.31 (0.27–0.35)	0.18 (0.11–0.25)	**0.004**

Abbreviations: CI, Confidence interval.
* Mean incidence/mortality rate across the study period (2005–2018).
† Student's t–test for independent samples.

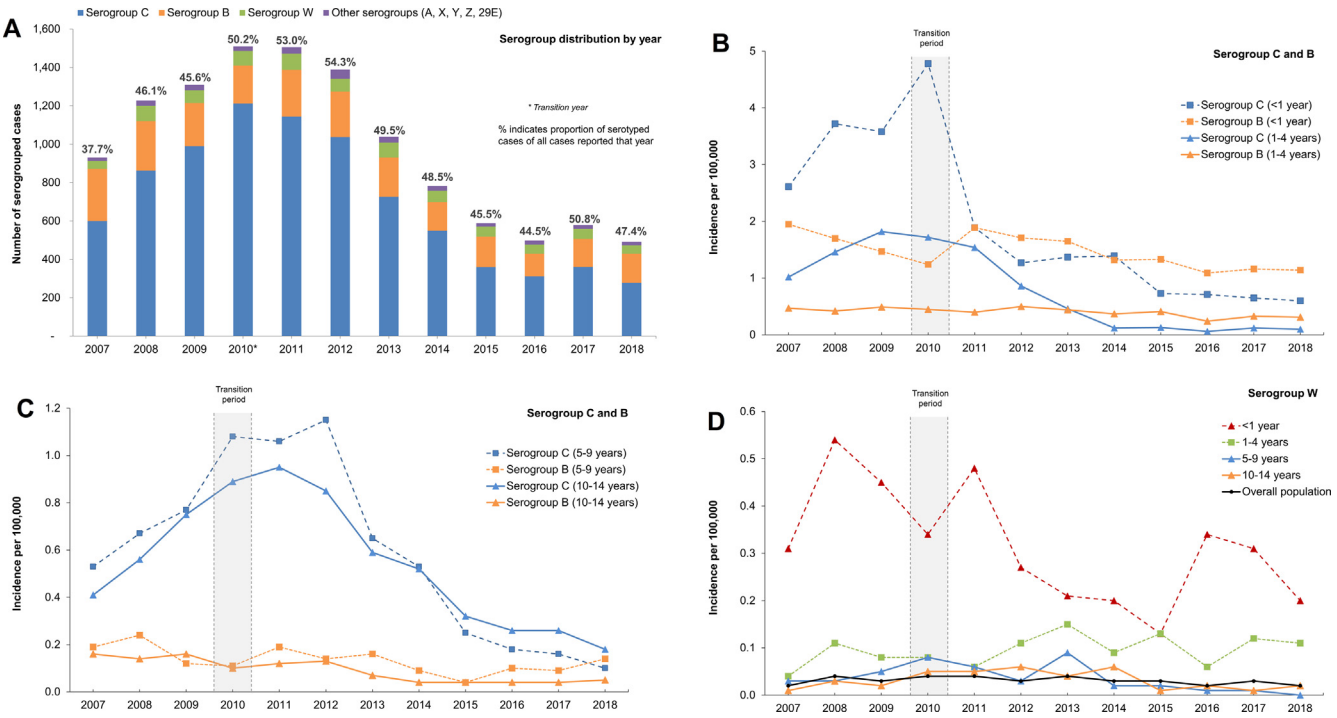

Fig. 3. Relative prevalence of N. meningitidis serogroups and incidence rates (2007–2018). (A) Annual number of cases due to specific serogroups; % indicates proportion of serotyped cases of all cases reported that year. Incidence rates per 100,000 of disease due to serogroups C and B in infants (B) and in older children and adolescents (C); the light grey bar indicates 2010 as a transition year with introduction of MenC vaccination in the national immunization program. (D) Disease due to serogroup W in different age strata (2007–2018).

Annual case numbers due to specific serogroups are shown in Supplementary Table 5. Serogroup C disease was the most frequently identified serogroup in each year between 2007 and 2015, although absolute numbers fell substantially between 2013 and 2018. A substantial decline in the incidence of MD due to serogroup C was observed in the years following vaccine introduction; mainly in infants < 1 year and children aged 1–4 years, with a similar trend seen in older children and adolescents. In contrast, the number of cases due to serogroup B and corresponding incidence rates were relatively stable across the study period in both younger age strata (Table 2 and Fig. 3**B and 3C** and Supplementary Table 6). Consequently, while serogroup C was the most frequent serogroup associated with disease in younger children between 2007 and 2011, the subsequent decline in absolute numbers is such that from 2012 onwards more disease in infants (<1 year) is due to serogroup B; and in children aged 1–4 years from 2014 onwards (**Supplementary Figure 3**).

In 2018, the incidence of MD due to serogroup C and B in infants < 1 year was 0.60/100,000 and 1.14/100,000 respectively (and 0.10/100,000 and 0.31/100,000 respectively in those aged 1–4 years). Serogroup W was the third most frequent serogroup, with 748 cases in the overall population reported across 2007–2018.

Incidence of serogroup W was generally low, although higher in infants < 1 year (Table 2 and Fig. 3**B and 3C** and Supplementary Table 6).

Time-series analysis showed a significant decline in MD incidence due to serogroup C in the post-vaccination period (2011–2018) compared with the 2007–2009 pre-vaccination period. In infants < 1 year, mean annual incidence rate fell from 3.30/100,000 (95% CI 2.77–3.83) to 1.08/100,000 (95% CI 0.67–1.49) (p = 0.011); and from 1.44/100,000 (95% CI 1.09–1.78) to 0.42/100,000 (95% CI −0.04–0.89) in children aged 1–4 years (p = 0.02). Non-significant reductions were also apparent in older children and in the overall population (Table 2). Significant reductions in serogroup B disease were also observed for these period comparisons in certain age-strata; 1–4 years; 10–14 years and in the overall population. For MD due to serogroup W the incidence remained relatively unchanged.

3.4. Brazilian regional variations in epidemiology

We evaluated MD incidence, mortality, and serogroup distribution in the overall population at a sub-national (regional) level. Some regional differences in epidemiology were observed. MD incidence and mortality rates were consistently higher in the Southeast than other regions across the study period. A consistent decline in incidence and mortality from 2005 to 2018 was observed in all regions (Fig. 4 and Table 3). In the time-series analysis, significant reductions in overall MD incidence rates were seen in each region; in the southeast, where incidence was highest, rates fell from 2.16 /100,000 (95%CI 1.98– 2.35) to 1.30/100,000 (95%CI 0.73–1.97; p = 0.007) (Table 3). Reductions in mortality rates in the period following vaccine introduction were also apparent in all regions, although non-significant in the Midwest. Mean CFRs across the study period in the overall population showed minor regional variation; generally lower in the South (19.2%) and Southeast (20.6%) and higher in the Midwest (23.2%).

MD incidence rates by causative serogroups in the different regions in the overall population are shown in Table 3 (with case numbers reported in Supplementary Table 8). Some regional variation was observed; the incidence of serogroup C was highest in the Southeast and the most substantial decline was also apparent in this region. The incidence of serogroup C disease was higher than serogroup B in all regions (**Supplementary Figure 4** and Table 3). Disease due to serogroup W was low, and declined in most regions from 2010 onwards, although a disease spike was observed in 2013 in the Midwest (and to a lesser extent in the

Table 2
Incidence rates for meningococcal disease due to serogroups C, B and W (2007–2018).

	Mean incidence rate (95% CIs)														
	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2007–2018*	Pre-vaccination 2007–2009†	Post vaccination 2011–2018	P-value‡
Men C																
<1 year	2.61	3.72	3.58	4.78	1.89	1.27	1.37	1.39	0.73	0.71	0.65	0.60	1.92	3.30 (2.77–3.83)	1.08 (0.67–1.49)	**0.011**
1–4 years	1.02	1.46	1.82	1.72	1.54	0.86	0.46	0.12	0.13	0.06	0.12	0.10	0.77	1.44 (1.09–1.78)	0.42 (-0.04–0.89)	**0.020**
5–9 years	0.53	0.67	0.77	1.08	1.06	1.15	0.65	0.53	0.25	0.18	0.16	0.10	0.59	0.66 (0.55–0.77)	0.51 (0.15–0.87)	0.389
10–14 years	0.41	0.56	0.75	0.89	0.95	0.85	0.59	0.52	0.32	0.26	0.26	0.18	0.54	0.57 (0.43–0.52)	0.49 (0.24–0.75)	0.585
Total population	0.32	0.45	0.51	0.62	0.58	0.52	0.36	0.27	0.18	0.15	0.17	0.13	0.35	0.43 (0.34–0.51)	0.30 (0.14–0.45)	0.172
Men B																
<1 year	1.95	1.70	1.47	1.24	1.89	1.71	1.65	1.32	1.33	1.09	1.16	1.14	1.47	1.71 (1.50–1.92)	1.41 (1.15–1.67)	0.156
1–4 years	0.47	0.42	0.49	0.45	0.40	0.50	0.44	0.37	0.41	0.24	0.33	0.31	0.40	0.46 (0.43–0.49)	0.38 (0.30–0.45)	**0.043**
5–9 years	0.19	0.24	0.12	0.11	0.19	0.14	0.16	0.09	0.04	0.10	0.09	0.14	0.13	0.18 (0.13–0.24)	0.12 (0.18–0.16)	0.190
10–14 years	0.16	0.14	0.16	0.10	0.12	0.13	0.07	0.04	0.04	0.04	0.04	0.05	0.09	0.15 (0.14–0.16)	0.07 (0.03–0.10)	**<0.001**
Total population	0.14	0.13	0.12	0.10	0.12	0.12	0.10	0.07	0.08	0.06	0.07	0.07	0.10	0.13 (0.12–0.14)	0.09 (0.07–0.11)	**0.008**
Men W																
<1 year	0.31	0.54	0.45	0.34	0.48	0.27	0.21	0.20	0.13	0.34	0.31	0.20	0.32	0.43 (0.33–0.53)	0.27 (0.17–0.36)	0.108
1–4 years	0.04	0.11	0.08	0.08	0.06	0.11	0.15	0.09	0.13	0.06	0.12	0.11	0.10	0.07 (0.04–0.10)	0.10 (0.07–0.13)	0.294
5–9 years	0.03	0.03	0.05	0.08	0.06	0.03	0.09	0.02	0.02	0.01	0.01	0.00	0.04	0.04 (0.03–0.04)	0.03 (0.00–0.06)	0.543
10–14 years	0.01	0.03	0.02	0.05	0.05	0.06	0.04	0.06	0.01	0.02	0.01	0.02	0.03	0.02 (0.01–0.03)	0.03 (0.01–0.05)	0.281
Total population	0.02	0.04	0.03	0.04	0.04	0.03	0.04	0.03	0.03	0.02	0.03	0.02	0.03	0.03 (0.02–0.04)	0.03 (0.02–0.04)	0.731

Abbreviations: CI, Confidence interval; MenB, meningococcal serogroup B; MenC, meningococcal serogroup C; MenW, meningococcal serogroup W.

* Mean incidence/mortality rate across the study period (2005–2018).

† Pre-vaccination period of 2007–2009 used due to absence of serogroup data for 2005/2006.

‡ Student's *t*-test for independent samples.

Northeast) (Table 3 and **Supplementary Figure 4**). In contrast, the incidence of serogroup W disease was substantially higher in the South, with a notable increase from 2012 to 2018, with a peak incidence in the general population of 0.11/100,000 in 2017 and 2018 (Table 3).

3.5. Vaccine coverage

After introduction to the NIP in 2010, initial vaccination coverage with MenC vaccine in infants was high; in 2012, second-dose uptake was > 95% nationwide and in all regions (except the North), then increased or remained stable between 2012 and 2015, and subsequently declined; with nationwide coverage falling from 99.7% in 2013 to 83% in 2018 (Table 4 and **Supplementary Figure 4**). Uptake of the toddler booster dose (given at 12–15 months of age) was also initially high. While data for the early years of MenC introduction was not available, coverage for this booster dose was 92.4% in 2013, although this declined in most subsequent years (with 76.8% coverage nationwide in 2018); some regional variation was observed, with uptake lower in the North. Uptake of adolescent vaccination in eligible age groups in the years following introduction in the NIP was low; only 19.5% of 12–13-year-olds were vaccinated in 2017 (and 14.3% of 11–14-year-olds in 2018).

4. Discussion

MD is an unpredictable disease with temporal variation in incidence and in the prevalence of specific causative serogroups, including periodic outbreaks. We evaluated MD incidence and mortality rates across 2005–2018 in Brazil, where MenC vaccination was introduced in 2010, and conducted a time-series analysis to compare incidence and mortality rates in the period following MenC vaccine introduction with rates in the pre- vaccination period (2005–2009).

We found that MD case numbers and incidence rates were greatest across 2005–2009 (although with some fluctuations in certain years) after which a year-on-year decline from 2011 to 2018 was observed. Across the study period, most cases occurred in children and adolescents, with approximately 35% involving children < 5 years across, although the prevalence of MD in younger children declined substantially following vaccine introduction. We found significant reductions in MD incidence rates in the post-vaccine introduction period compared to those in earlier years of the study, with incidence in the overall population falling from 1.5/100,000 in 2005–2009 to 0.8/100,000 in 2011–2018.

This was due to substantial rate reductions in younger children, which fell from 13.5 to 6.5 per 100,000 in infants aged < 1 year, and from 5.7 to 2.3 per 100,000 in children aged 1–4 years; significant reductions in the post-vaccine introduction period were also seen in children aged 5–9 years and those aged 10–14 years. We also found a notable decline in mortality following vaccine introduction, largely due to fewer deaths in infants aged < 1 year with a drop in mortality of 3.2 per 100,000 (2005–2009) to 1.4 per 100,000 (2011–2018).

Mortality rates also dropped substantially in older children (aged 1–4 years and 5–9 years). These mortality reductions would seem to be due to declining incidence following vaccine introduction, as the lethality rate (CFR of approximately 20% in the overall population) was relatively consistent across the study period.

The decline in MD incidence and mortality rates and reductions in the vaccination period comparisons observed at the national level in the overall population were also observed in all regions and in particular in the Southeast region. There, incidence and mortality were higher in the Southeast than in other regions throughout the study period, and the greatest numerical decline

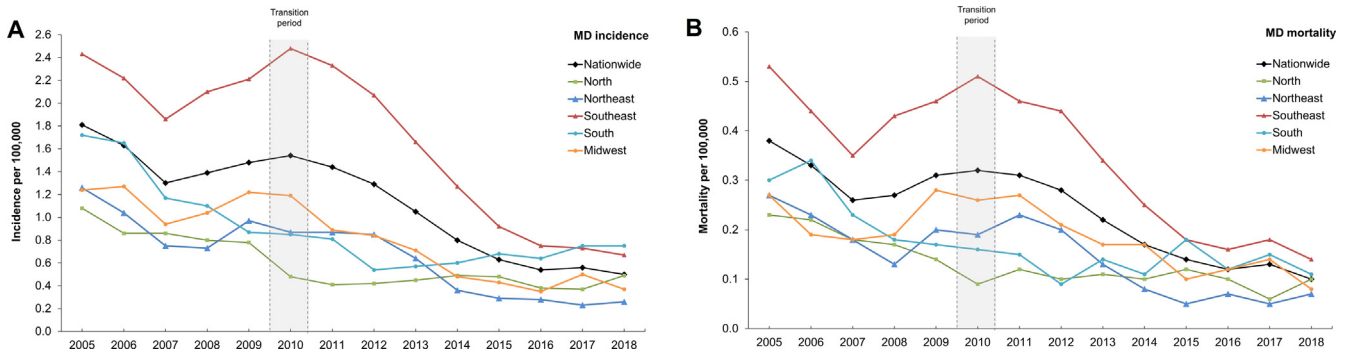

Fig. 4. Regional variations in epidemiology. MD incidence and mortality rates. The light grey bar indicates 2010 as a transition year with introduction of MenC vaccination in the national immunization program. Abbreviations: MD, Meningococcal disease.

in rates in the period following vaccine introduction were also observed in the Southeast (with rates in 2018 approaching those in the other regions).

Data at a national level for the overall burden of MD in Brazil is limited, as most studies have focused on specific serogroups or report incidences at a more local (regional, state, or metropolitan) level. Presa and colleagues have reported national and regional incidence rates for 2015 at the overall population level (using the same secondary data sources as we have used with similar results for that year), but did not report any longitudinal data [5]. In their study, chiefly focusing on strengths and limitations of the Brazilian MD epidemiological surveillance system, Ribeiro and colleagues reported on incidence and mortality across 2007–2017; they found a similar pattern of decline at a national and regional level as observed in the present study [27]. Our results provide an additional, detailed nationwide perspective on the temporal nature of the overall burden of MD (regardless of causative serogroup) in Brazil, both in the overall population and in different age-strata.

Our serogroup analyses suggest that much of the decline in incidence we observed is driven by a decline in disease due to serogroup C following introduction of infant MenC vaccination, although other factors (including a decline in serogroup B disease have played a role). We found that serogroup C accounted for 71% of all serogrouped cases and was the predominant serogroup each year in 2007–2011, albeit with substantial decline in numbers between 2013 and 2018. The greater prevalence of serogroup C is consistent with that reported by others in Brazil and elsewhere in Latin America [2,5,6]. At a national level, the incidence of serogroup C disease fell substantially in children < 5 years, so that in the most recent years serogroup B was the predominant serogroup in younger children.

These findings are broadly consistent with previous analyses from Brazil that report significant reductions in incidence rates of disease due to serogroup C in children aged < 5 years following vaccine introduction [23,24,30–33] as well as more recent data reporting a decline in serogroup B [34]. A national study by Moraes et al. evaluating incidence of serogroup C disease across Brazil between 2001 and 2013 reported a steady decline in incidence in children < 5 years since vaccine introduction [30]. That study found differences in incidence rates and vaccine impact; MenC incidence rates were far higher in the Southeast region than in other regions (at all age-strata and in every year), with greatest rate-reductions observed in the Midwest and Southeast regions [30]. More recently, in their national study (excluding Salvador) Andrade and colleagues reported significant reductions in the incidence of serogroup C disease in children < 1 year following vaccine introduction; from 15.28 per 100,000 in 2008–2010 to 5.01 per 100,000 in 2012– 2014, a 67.2% relative reduction, with significant rate-reductions also reported in children aged 1–4 years [24]. In addition, a national study by Bierrenbach et al reported reductions in mortality rates due to serogroup C of approximately 28% in children < 5 years between 2012 and 2015 compared with 2005–2009 [33].

In countries with more established meningitis vaccination programmes (including Canada, the United States, Australia, the United Kingdom and across Europe) similar declines in incidence rates (especially in children < 5 years) have been reported following MenC vaccine introduction [35–42]. In these countries, MenC infant vaccination was accompanied by a catch-up vaccination strategy for other age-groups (including older children, adolescents and young adults). This resulted in high rates of disease reduction, both in the target population and also in unvaccinated age-groups, who benefited indirectly through reduction in serogroup C carriage (herd protection) [43]. In contrast, in Brazil, where (with the exception of Salvador) no such catch-up campaign was employed, the reported benefits are seen chiefly in children eligible for MenC vaccination [24,30]. Our long-term impact data after eight years of infant MenC vaccination also confirms that significant reductions in disease due to serogroup C are also seen only in younger children < 5 years, with no evidence for any broader (herd protection) effect.

Turning to other serogroups, we found that case numbers and incidence rates for serogroup B disease were relatively stable, there was some evidence of a decline in recent years. In their recent analysis of the disease burden due to serogroup B in Brazil across 2001–2015, using similar data sources to those used in the present study, Chicuto et al. also reported on an overall decline in serogroup B disease, with the greatest decline between 2001 and 2009, after which incidence was more stable [34].

In the present study, while disease due to serogroups other than serogroups C and B was relatively infrequent (<10% of all causative serogroups), serogroup W remained an important cause of MD, particularly in infants (<1 year). We found increasing prevalence of serogroup W in the South in recent years, where increased circulation in specific states (Santa Catarina) has been reported, and where serogroup W was the most prevalent causative serogroup in 2018 [44]. Increasing incidence of serogroup W disease is recognised, both globally and in South America; in their recent analysis, Presa et al also reported on increasing prevalence of serogroup W disease in Brazil, and this has also been observed in Argentina and Chile [5,45–47].

We must note here that the incidence of MD due to specific serogroups we report are based upon serogroup information from only approx. 40–50% of cases. Moreover, the relative proportion of all MD cases with serogroup information shows substantial year-on-year variation, a pattern also reported by others evaluating MD burden in Brazil [5,34].

Table 3
Meningococcal disease incidence and mortality per 100,000 in the overall population by region (2005–2018).

	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2005–2018*	Mean incidence/mortality rate		
																Pre-vaccination 2005–2009†	Post vaccination 2011–2018	P-value‡
Incidence rate																		
North	1.08	0.86	0.86	0.80	0.78	0.48	0.41	0.42	0.45	0.49	0.48	0.38	0.37	0.49	0.60	0.88 (0.77–0.98)	0.44 (0.39–0.48)	**0.001**
Northeast	1.26	1.04	0.75	0.73	0.97	0.87	0.87	0.85	0.64	0.36	0.29	0.28	0.23	0.26	0.67	0.95 (0.76–1.15)	0.47 (0.24–0.71)	**0.006**
Southeast	2.43	2.22	1.86	2.10	2.21	2.48	2.33	2.07	1.66	1.27	0.92	0.75	0.73	0.67	1.69	2.16 (1.98–2.35)	1.30 (0.73–1.97)	**0.007**
South	1.72	1.65	1.17	1.10	0.87	0.85	0.81	0.54	0.57	0.60	0.68	0.64	0.75	0.75	0.91	1.30 (0.98–1.62)	0.67 (0.58–0.75)	**0.017**
Midwest	1.24	1.27	0.94	1.04	1.22	1.19	0.89	0.84	0.71	0.48	0.43	0.35	0.50	0.37	0.82	1.14 (1.02–1.27)	0.57 (0.39–0.76)	**0.0001**
Nationwide	1.81	1.63	1.30	1.39	1.48	1.54	1.44	1.29	1.05	0.80	0.63	0.54	0.55	0.50	1.14	1.52 (1.35–1.70)	0.85 (0.53–1.17)	**0.001**
Mortality rate																		
North	0.23	0.22	0.18	0.17	0.14	0.09	0.12	0.10	0.11	0.10	0.12	0.10	0.06	0.10	0.13	0.19 (0.16–0.22)	0.10 (0.08–0.12)	**0.003**
Northeast	0.27	0.23	0.18	0.13	0.20	0.19	0.23	0.20	0.13	0.08	0.05	0.07	0.05	0.07	0.15	0.20 (0.15–0.25)	0.11 (0.05–0.17)	**0.022**
Southeast	0.53	0.44	0.35	0.43	0.46	0.51	0.46	0.44	0.34	0.25	0.18	0.16	0.18	0.14	0.35	0.44 (0.39–0.50)	0.27 (0.16–0.38)	**0.007**
South	0.30	0.34	0.23	0.18	0.17	0.16	0.15	0.09	0.14	0.11	0.18	0.12	0.15	0.11	0.17	0.24 (0.18–0.31)	0.13 (0.11–0.16)	**0.026**
Midwest	0.27	0.19	0.18	0.19	0.28	0.26	0.27	0.21	0.17	0.17	0.10	0.12	0.14	0.08	0.19	0.22 (0.18–0.27)	0.16 (0.11–0.21)	0.064
Nationwide	0.38	0.33	0.26	0.27	0.31	0.32	0.31	0.28	0.22	0.17	0.14	0.12	0.13	0.10	0.24	0.31 (0.27–0.35)	0.18 (0.11–0.25)	**0.004**
Serogroup incidence rate																		
Men C																		
North			0.12	0.10	0.16	0.10	0.10	0.13	0.05	0.13	0.11	0.06	0.06	0.03	0.09	0.13 (0.10–0.16)	0.08 (0.05–0.11)	0.122
Northeast			0.10	0.20	0.30	0.40	0.33	0.34	0.22	0.09	0.05	0.05	0.04	0.03	0.18	0.20 (0.11–0.29)	0.15 (0.03–0.26)	0.522
Southeast			0.57	0.78	0.86	1.04	1.03	0.91	0.63	0.46	0.27	0.21	0.24	0.19	0.60	0.73 (0.60–0.87)	0.49 (0.20–0.78)	0.134
South			0.13	0.18	0.14	0.16	0.16	0.09	0.14	0.22	0.22	0.26	0.27	0.27	0.19	0.15 (0.13–0.17)	0.20 (0.15–0.26)	0.098
Midwest			0.29	0.47	0.43	0.50	0.34	0.22	0.17	0.14	0.11	0.10	0.26	0.17	0.27	0.40 (0.32–0.48)	0.19 (0.12–0.26)	**0.035**
Nationwide			0.32	0.45	0.51	0.62	0.58	0.52	0.36	0.27	0.18	0.15	0.17	0.13	0.35	0.43 (0.34–0.51)	0.30 (0.14–0.45)	0.172
Men B																		
North			0.13	0.07	0.05	0.02	0.04	0.04	0.02	0.02	0.01	0.01	0.02	0.01	0.04	0.08 (0.05–0.12)	0.02 (0.01–0.03)	0.133
Northeast			0.09	0.09	0.06	0.05	0.06	0.06	0.02	0.01	0.01	0.01	0.003	0.002	0.04	0.08 (0.07–0.09)	0.02 (0.00–0.04)	**0.003**
Southeast			0.16	0.14	0.14	0.15	0.17	0.18	0.18	0.13	0.14	0.09	0.13	0.15	0.15	0.15 (0.14–0.15)	0.15 (0.12–0.17)	0.888
South			0.26	0.26	0.22	0.14	0.18	0.12	0.11	0.07	0.10	0.07	0.07	0.10	0.14	0.25 (0.22–0.27)	0.10 (0.07–0.10)	**0.001**
Midwest			0.07	0.09	0.08	0.06	0.08	0.08	0.02	0.02	0.04	0.04	0.04	0.03	0.05	0.08 (0.07–0.09)	0.04 (0.02–0.06)	**0.006**
Nationwide			0.14	0.13	0.12	0.10	0.12	0.12	0.10	0.07	0.08	0.06	0.07	0.07	0.10	0.13 (0.12–0.14)	0.09 (0.07–0.11)	**0.008**
Men W																		
North			0.00	0.00	0.00	0.01	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	–	–	–
Northeast			0.00	0.00	0.00	0.00	0.02	0.01	0.02	0.01	0.01	0.01	0.01	0.01	0.01	0.001 (0.00–0.002)	0.01 (0.01–0.02)	**0.002**
Southeast			0.04	0.08	0.07	0.08	0.08	0.05	0.05	0.04	0.03	0.02	0.02	0.01	0.05	0.06 (0.05–0.08)	0.04 (0.02–0.06)	0.155
South			0.03	0.04	0.02	0.03	0.02	0.03	0.06	0.07	0.06	0.07	0.11	0.11	0.06	0.03 (0.02–0.04)	0.07 (0.04–0.09)	**0.014**
Midwest			0.01	0.01	0.01	0.01	0.01	0.03	0.05	0.02	0.01	0.01	0.01	0.01	0.02	0.01 (0.01–0.02)	0.02 (0.01–0.03)	0.311
Nationwide			0.02	0.04	0.03	0.04	0.04	0.03	0.04	0.03	0.03	0.02	0.03	0.02	0.03	0.03 (0.02–0.04)	0.03 (0.02–0.04)	0.731

Abbreviations: CI, Confidence interval; MenB, meningococcal serogroup B; MenC, meningococcal serogroup C; MenW, meningococcal serogroup W.

* Mean incidence/mortality rate across the study period (2005–2018 for overall MD incidence/mortality and 2007–2018 for serogroup specific incidence).

† Pre-vaccination period of 2007–2009 used due to absence of serogroup data for 2005/2006.

‡ Student's *t*-test for independent samples.

Table 4
MenC vaccine coverage in Brazil: national and by region (2010–2018).

		Vaccination coverage (%)								
		2010	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**	**2018**
National	D2*	26.9	105.7	96.2	99.7	96.4	98.2	91.7	86.6	83.0
	B†				92.4	88.6	87.9	93.9	81.8	76.8
	Adolescents‡								19.5	14.3
North	D2*	3.0	78.7	88.2	89.8	86.4	87.2	81.9	77.9	71.8
	B†				78.0	73.5	72.1	85.7	76.0	66.7
	Adolescents‡								17.7	12.4
Northeast	D2*	28.5	93.4	94.2	96.3	93.2	97.4	88.7	84.2	86.1
	B†				89.4	85.4	86.3	93.1	80.5	78.2
	Adolescents‡								17.1	12.0
Southeast	D2*	38.2	115.5	98.5	102.1	98.3	100.8	93.1	88.9	82.5
	B†				96.7	92.6	93.1	91.5	82.4	76.0
	Adolescents‡								20.6	14.2
South	D2*	4.8	121.6	98.9	103.8	100.6	101.5	94.5	90.8	85.0
	B†				94.9	92.2	90.2	99.6	85.9	81.6
	Adolescents‡								21.9	21.0
Midwest	D2*	10.1	115.1	98.9	107.1	104.4	97.4	103.2	88.5	86.2
	B†				97.1	93.8	85.1	109.5	84.4	80.8
	Adolescents‡								22.2	15.7

Abbreviations: D2, Doses one and two; B, Booster.
* D2 - Doses one and two given at three and five months.
† Booster given between 12 and 15 months (implemented in 2013) (data available from 2013 onwards).
‡ Adolescent dosing given between 11 and 14 years (implemented in 2016) administered to 12–13-year-olds (2017) expanded to include 11–14-year-olds in 2018.

This variation is apparent across a number of perspectives; at a national level, at a regional level, and also when evaluating causative serogroup data in individual age-strata. This presents some challenges to reporting prevalence and incidence of disease due to specific serogroups. The crude incidence rates we report represent substantial underestimates of their true incidence, both at a national and a regional level (and across all age-strata). Furthermore, as the proportion of MD cases that were serogrouped varies year on year, this also influences the relative incidence rates in different study years, and so direct comparisons of different years are subject to some uncertainty. This applies nationally, and regionally and for specific age-strata; overall, disparities in serogroup surveillance are such that direct year on year comparisons of incidence rates for any particular age-group (or region) is subject to considerable uncertainty, as is year on year comparisons of incidence rates for any particular region. Similar observations have also been made by others [5,34]. These aspects also impact upon our post-vaccination and pre-vaccination period comparisons. While others e.g. Moraes et al. in their study evaluating serogroup C disease have recognised this (and accounted for this by using a proportional redistribution methodology in which those unidentified serogroup cases were redistributed proportionate to the existing distribution for known serogrouped cases) [30]; we chose to report unadjusted incidence rates based upon the confirmed number of cases with identifiable causative serogroup data. Consequently, the incidence rates we report for serogroup C in the overall population at a national and regional level are underestimated and so are lower than those reported by Moraes et al. [30].

Efforts to improve MenC vaccine coverage in certain areas or populations with suboptimal coverage may lead to further reductions in infant morbidity and mortality. We evaluated coverage at regional levels, with coverage of 88–100% in the initial years since introduction for both the primary 2-dose series and for the booster dose. Some regional differences were observed, with lower initial uptake seen in the North and Northeast regions and higher uptake in the Southeast. The decline in coverage we found in the most recent years however, is a concern. Declining coverage is seen, nationally and in all regions, with the northern region showing lowest coverage rates in recent years.

Improving across all regions is important. It is anticipated that the introduction of MenC vaccine as a catch-up schedule in adolescents may bring additional reductions in MD in Brazil; data from countries with adolescent vaccine programmes have shown this strategy leads to reduced incidence of disease and reduced carriage of *N. meningitidis* in adolescents, and may contribute to herd protection of unvaccinated individuals, including unvaccinated infants [7,48,49]. In addition, more complete compliance to infant primary vaccination and subsequent booster dosing is critical if the full benefits of immunization are to be realised.

Our study has some limitations to consider. This is a retrospective study, using longitudinal data over a long timeframe. Data quality may have varied during the study period due to potential changes in the surveillance system and its underlying structure which can impact our results. In this study, we used secondary data sources (SINAN/DATASUS) and underreporting and inconsistency at a national and regional level are potential challenges, an issue recognised by other investigators using these resources in previous epidemiological studies [6,24,30,50]. As we describe above, incomplete serogroup reporting hampered our ability to fully evaluate rates of disease due to meningitis C and B; the case numbers and incidence rates we report for disease due to specific serogroups are an underestimation of the actual rates, and the prevalence of specific serogroups may not be wholly representative of the actual epidemiology. Efforts to increase serogroup reporting, to provide a more accurate epidemiological appraisal, are welcome.

For all analyses we report unadjusted results (i.e., we did not account for impact of any temporal/historical trend and effect of seasonality). In addition, as an ecological study, it was not possible to determine any association between MD cases in younger children and vaccination status which limits our ability to infer any direct association of vaccine impact. In addition, other factors e.g. public health interventions (including smoking reduction) and improved medical care could have contributed to the observed decline in incidence rates and mortality due to MD (although the overall trends suggest that vaccination has had an important influence in reducing MD rates). For our analyses at a regional perspective, our present data allowed only appraisal in the overall population rather than the impact on the younger age-strata at greatest risk of MD and where the benefits of vaccination are greatest. Finally, investigating the molecular epidemiology of specific serogroups was not an objective of this

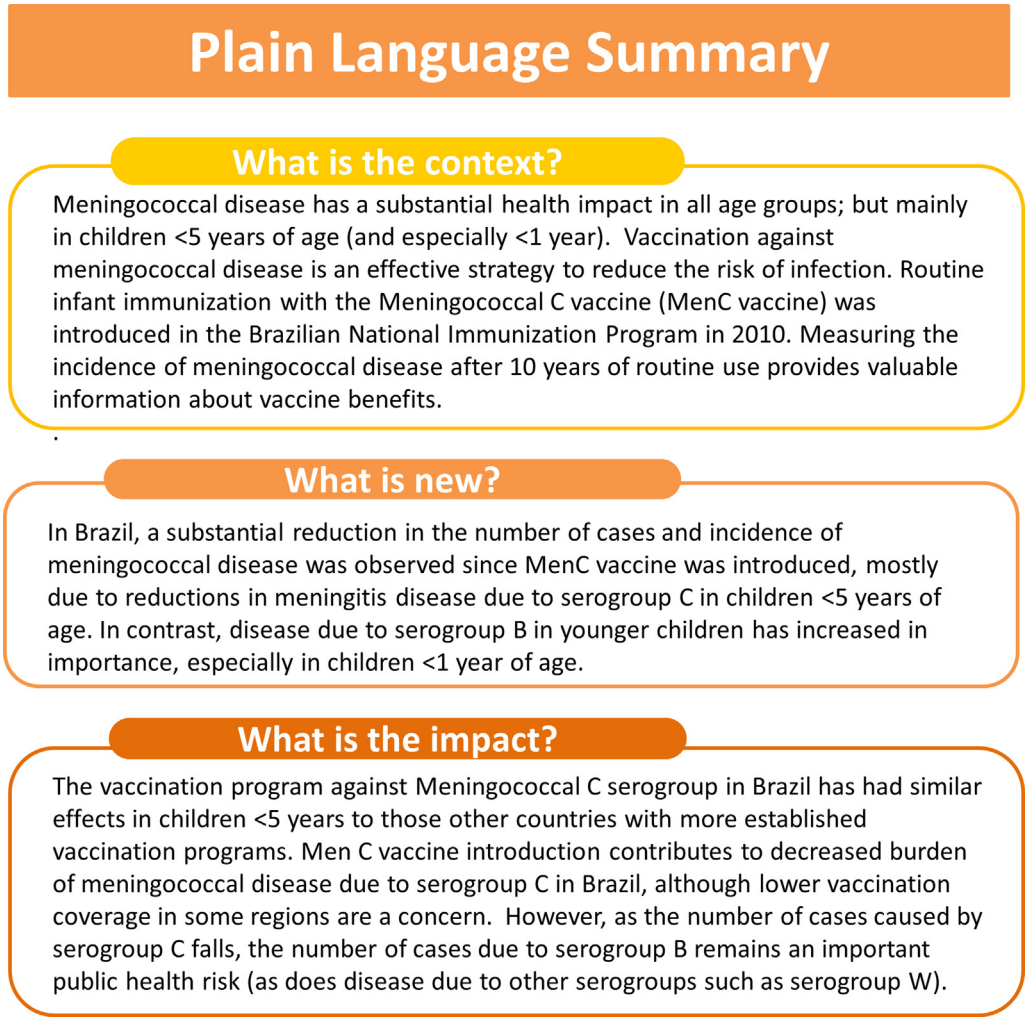

Fig. 5. Focus on the Patient. No legend.

study, and our data does not allow us to directly report on epidemiologic shifts in disease due to specific clonal complexes or genotypes. Recent data indicates that the prevalence of serogroup C disease due to CC103 (and in particular ST-3780) has increased in the period following MenC vaccine introduction, while the prevalence of other serogroup C clones (e.g., CC32, CC11 and CC8) have declined [51]. The MenW clone, CC11, associated with a high CFR [52] is an important cause of endemic MD in regions of Brazil such as the South [53]. It is anticipated that evaluation of the prevalence of specific clonal complexes associated with endemic MD and disease outbreaks will continue to evolve as an integral aspect of ongoing surveillance in Brazil [52].

Despite these limitations, the current study has a number of strengths that may deserve comment. We evaluated the overall burden of MD across Brazil between 2005 and 2018; our aim was to comprehensively report our data in full, as we hope that this complete reporting of raw unadjusted data may serve as a useful resource and reference point for others. We found evidence of substantial decline in MD cases, incidence rates, and deaths in the years following MenC vaccine introduction in the NIP. Fig. 5 presents a summary of the context, outcomes, and impact of this study for healthcare providers.

While these benefits are considerable, they can be improved by improving MenC vaccination coverage in all age groups and, in particular, the adolescent population. In addition, prevention of MD due to other serogroups (B and W) remains yet unaddressed in Brazil within the NIP.

In Chile, in response to the emergence of serogroup W as the predominant cause of MD, immunization with ACWY meningococcal conjugate vaccines (MenACWY) was introduced for children aged from 9 months through 4 years of age; initially in Santiago at the end of 2012, then nationwide in 2013 [47]. MenACWY was given to those aged < 2 years as a 2-dose schedule and for those aged $\geq$ 2 years as a single dose. Since 2014, all infants receive a single dose at 12 months of age. This strategy has led to reduction in the incidence of serogroup W disease in children < 5 years in recent years [47], although there has been no impact on older individuals where case numbers continued to increase [54]. MenACWY immunization has also been introduced in Argentina, in 2017, with infant vaccination given at 3, 5 and 15 months, and with adolescents receiving a single dose at 11 years of age [55]. The impact of this strategy has yet to be fully reported. A similar approach in Brazil could further reduce disease burden in the Brazilian population, as may vaccination initiatives against serogroup B. At the present time, the adolescent MenACWY immunization was introduced in the public health system in Brazil, with this vaccine now available through the NIP [56,57]. Future studies to evaluate the impact of its effects on the burden of the disease in the country are recommended.

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CRediT authorship contribution statement

Altacílio Aparecido Nunes: Conceptualization, Methodology, Data curation, Formal analysis, Writing - review & editing. **Ariane De Jesus Lopes De Abreu:** Conceptualization, Methodology, Data curation, Formal analysis, Writing - original draft, Writing - review & editing, Visualization. **Otavio Cintra:** Conceptualization, Methodology, Writing - review & editing. **Monica A.C.T. Cintra:** Methodology, Data curation, Formal analysis, Writing - review & editing. **Eduardo Barbosa Coelho:** Conceptualization, Methodology, Formal analysis, Writing - review & editing. **Eliana Nogueira Castro De Barros:** Conceptualization, Methodology, Data curation, Formal analysis, Writing - original draft, Writing - review & editing, Visualization.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: OC is an employee of the GSK group of companies and holds stock options in the GSK group of companies. ENCB was an employee of the GSK group of companies at the time of this study and owns restricted shares in the GSK group of companies. *AA* was an outsourced employee for the GSK group of companies at the time of this study. The institutions of *EBC, AAN, and MC* received funding from the GSK group of companies to support the costs of this study, and work disclosed in this manuscript, as well as funding outside the submitted work.

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Appendix A. Supplementary material

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