



## Impact of vaccination during an epidemic of serogroup C meningococcal disease in Salvador, Brazil

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### ABSTRACT

To combat rising incidence of serogroup C meningococcal disease in the city of Salvador, Brazil, the Bahia state immunization program initiated routine childhood immunization with meningococcal C conjugate vaccine (MenC) in February 2010, followed by mass MenC vaccination of city residents 10–24 years of age from May through August 2010. We analyzed trends in incidence of reported cases of meningococcal disease and serogroup distribution among meningococcal isolates identified in hospital-based surveillance in Salvador from January 2000 to December 2011 and estimated vaccine effectiveness using the screening method. Annual incidence of serogroup C meningococcal disease increased from 0.1 cases per 100,000 population during 2000–2006 to 2.3 in 2009 and 4.1 in 2010, before falling to 2.0 per 100,000 in 2011. Estimated coverage of mass vaccination reached 80%, 67% and 41% among 10–14, 15–19 and 20–24 year olds, respectively. Incidence in 2011 was significantly lower than average rates in 2008–2009 among children <5 years, but reductions among 10–24 year olds were not significant. Among 10–24 year olds, a single dose of MenC vaccine was 100% effective (95% confidence interval, 79–100%) against serogroup C meningococcal disease. Low coverage in the population targeted for mass vaccination may have limited impact on ongoing transmission of serogroup C meningococcal disease despite high vaccine effectiveness.

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### 1. Introduction

Epidemics of bacterial meningitis caused by *Neisseria meningitidis*, the meningococcus, were first reported in Brazil in 1920 [1]. Meningococcal epidemics since the 1970s have been associated with serogroups B and C (the last meningococcal A epidemic in Brazil occurred in 1974) [2]. Following the predominance of meningococcal serogroup B during the 1990s, serogroup C outbreaks emerged throughout Brazil after 2000, gradually replacing B as the most prevalent serogroup [3,4]. With the rising incidence and high associated case-fatality of meningococcal serogroup C disease among young children and the availability of effective conjugate vaccines, several state and local governments purchased

meningococcal serogroup C polysaccharide–protein conjugate vaccines (MenC) for routine infant immunization or outbreak control in targeted age groups.

From 2007 to 2009, meningococcal serogroup C disease increased substantially in the state of Bahia, with a five-fold increase in the number of cases reported in the capital, Salvador. In 2009, 194 cases of meningococcal disease (1.5 cases per 100,000 population) with 50 deaths (39% case-fatality) were reported to the Bahia state health department, with 50% of the cases and 48% of the deaths occurring in Salvador [5]. Meningococcal serogroup C conjugate vaccine was introduced into the routine childhood immunization schedule of the state of Bahia in February 2010, with a two-dose primary immunization series (at 2 and 4 months) followed by a booster dose in the second year of life. All children younger than five years in the state of Bahia were eligible to receive at least one dose of MenC conjugate vaccine. During the first semester of 2010, unusually high numbers of meningococcal disease cases and deaths among persons older than 10 years occurred in the city of Salvador, leading the state immunization program to

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conduct mass vaccination (a single dose) of city residents 10–24 years of age from May to August 2010. We analyzed data from meningitis surveillance and immunization programs to evaluate the impact of vaccination on rates of meningococcal disease among vaccinated age groups and those not targeted for vaccination.

## 2. Methods

### 2.1. Surveillance for meningococcal disease

Reporting of suspected cases of meningitis is mandatory in Brazil. Suspected cases of meningitis are reported by public and private health facilities to municipal and state health departments using standardized case report forms from the national Notifiable Diseases Information System [*Sistema de Informação de Agravos de Notificação* (SINAN)]. Case report forms include patient identification, age, gender, clinical signs and symptoms, samples collected, diagnostic tests performed, antibiotic susceptibility and cerebrospinal fluid (CSF) evaluation. Suspected meningococcal disease includes the presence of fever, intense headache, profuse vomiting, neck stiffness, clinical signs of meningeal irritation (Kernig or Brudzinski), convulsions or petechial or purpurial rash. In infants, clinical signs may include irritability, persistent crying and bulging fontanelle. Clinical presentation of meningococcal disease is reported as meningitis, meningococemia or meningitis with meningococemia based on physician diagnosis and laboratory findings. Confirmed cases of meningococcal disease are defined by isolation of meningococci or positive antigen detection tests in blood, CSF or normally sterile fluid specimens from suspected cases. For surveillance purposes, suspected cases may also be classified as confirmed based on epidemiologic link to a laboratory-confirmed case, or by identification in Gram stain of gram-negative diplococci in a patient with suggestive symptoms and petechial or purpurial rash.

### 2.2. Vaccination against meningococcal serogroup C disease

Brazil's national immunization program provides vaccines included in the recommended immunization schedule through the Unified Health System [*Sistema Unico de Saúde* (SUS)], Brazil's public health system. State governments have autonomy to purchase and provide vaccines not included in the national immunization program through the state immunization program. Bahia, with a population of 13.6 million inhabitants, ranks fourth most populous among Brazil's 27 states (including the Federal District) and had an annual estimated health budget of US\$ 1.5 billion in 2010 [6]. In February 2010, MenC-tetanus toxoid conjugate vaccine (MenC-TT, Neisvac-C<sup>®</sup>, Baxter Vaccines) was introduced into the routine infant immunization schedule in the state of Bahia, Brazil, with financing from the state government. After August, 2010, infants began receiving MenC-CRM<sub>197</sub> conjugate vaccine (Novartis Vaccines), which was provided to all states for universal infant immunization through Brazil's national immunization program. The recommended schedule in all state immunization programs was two doses in the first year of life (either at 2 and 4 months or 3 and 5 months of age), followed by one dose in the second year of life (at 12 or 15 months). Catch-up vaccination was provided for children younger than two years of age in most states. In the state of Bahia, catch-up vaccination included children younger than five years; one dose of MenC was recommended for those at least 12 months of age in February 2010.

In addition, the state of Bahia purchased 1,876,863 doses of MenC-TT in 2010 to control the epidemic of meningococcal serogroup C disease in Salvador, the state capital and most populous city (estimated population 2,676,606, 21% of the state population).

MenC-TT vaccine was used for mass vaccination of persons 10–19 years old in May and June 2010. In August 2010, the state government received 447,983 doses of MenC-CRM<sub>197</sub> from Brazil's national immunization program, which were used for mass vaccination of persons 20–24 years with a single dose. Children 5–9 years of age were not vaccinated.

MenC vaccination was offered at 52 vaccination posts throughout the city. Vaccination was offered on Saturday and Sunday at the beginning of each phase to minimize disruption of normal vaccination services. Social mobilization focused on the first two days of vaccination for each age group. Due to poor turnout among 20–24 year olds in 2010, vaccination was offered for persons in this age group during the second weekend in February 2011, and at large universities the following week.

MenC doses administered by age group at each vaccination post were reported to the immunization unit of the Salvador municipal health department. For children younger than five years, MenC doses administered were also registered in the information system of the national immunization program according to whether the dose was the first, second or third dose for a child. We estimated coverage with at least one dose of MenC vaccine among children younger than five years using number of administered doses registered as the first dose in the information system of the national immunization program (<http://pni.datasus.gov>, accessed May 24, 2012). We estimated coverage with one dose of MenC vaccine among persons 10–24 years of age by dividing the number of administered doses registered in summary sheets for MenC vaccination campaigns by the estimated population of the target age group in the city of Salvador. Population estimates for Salvador from the 2010 census were obtained from the Brazilian Institute of Geography and Statistics (IBGE), the Brazilian census bureau.

### 2.3. Laboratory methods

*N. meningitidis* isolated from patients with meningococcal disease were sent to the Central Public Health Laboratory for the state of Bahia or the Molecular Biology Research Laboratory at the Gonçalo Moniz Research Center at the Oswaldo Cruz Foundation in Salvador for characterization using serogroup-specific antisera (Difco Laboratories, Detroit, MI, USA), as described previously [7,8].

### 2.4. Statistical analysis

For suspected meningitis cases, annual reporting rates for 2000–2011 were calculated by dividing the yearly number of suspected meningitis cases among city residents reported to the state health department by the estimated population of Salvador, Brazil. Similarly, annual cumulative incidence of confirmed meningococcal serogroup C disease was calculated by dividing the number of serogroup C cases in each age group by the corresponding population of Salvador. Rates were not adjusted for the proportion of confirmed meningococcal disease of unknown serogroup. We obtained population estimates for the city of Salvador from IBGE and used 2000 census data and intercensus projections from the census bureau to calculate rates for 2001 through 2007; for 2008 through 2011, we used the 2010 census estimate of the population. For confirmed meningococcal serogroup C disease, we calculated age-specific relative risk (RR) and corresponding 95% confidence intervals contrasting incidence in 2011 to average pre-vaccine incidence in 2008 and 2009. For 2011, we estimated vaccine effectiveness (VE) of one dose of MenC vaccine among 10–24 year olds using the screening method [9], as  $(1 - \text{odds ratio [OR] of vaccination among confirmed meningococcal C cases to the population}) \times 100$ . Exact confidence intervals for the OR were used to estimate the lower 95% confidence limit for vaccine effectiveness.

### 3. Results

Following seven years from 2000 to 2006 of declining reporting rates of suspected meningitis cases in the city of Salvador, suspected meningitis rates increased substantially during 2007 through 2010, reaching 14.9 suspected meningitis cases per 100,000 population (Fig. 1). Confirmed cases of meningococcal disease followed a similar pattern, falling from 74 confirmed cases in 2000 to a low of 15 in 2004 and then increasing rapidly from 2008 through 2010. From 2000 through 2006, meningococcal serogroup was identified for isolates from 127 (45%) of 281 confirmed cases (Fig. 1); 105 (83%) were serogroup B, 20 (16%) were serogroup C and 2 (1%) were other serogroups (A [ $n = 1$ ] and W135 [ $n = 1$ ]). From 2007 through 2011, serogroup was determined for 335 (77%) of 437 meningococcal cases, and serogroup C replaced B as the most prevalent serogroup identified among confirmed cases of meningococcal disease (Fig. 1).

Based on cases with known serogroup, cumulative incidence of serogroup C meningococcal disease in the city of Salvador was 0.1 cases per 100,000 population per year from 2000 through 2006 (Fig. 2) with 1 death (case-fatality, 5%). In 2007, 13 cases (0.45 cases/100,000 population) of serogroup C meningococcal disease were identified with 2 deaths (case-fatality, 15%); in 2008, 53 cases (1.8 cases/100,000 population) were identified with 4 deaths (8%) and in 2009, 69 cases (2.3 cases/100,000 population) with 10 deaths (14.5%). From 2007 to 2009, children younger than five years old accounted for 34 (25%) of 135 cases (incidence, 4.8 cases/100,000 children <5 per year; Fig. 3) and 4 (25%) of 16 deaths. Among 10–24 year olds, there were 43 (32%) cases (5.2 cases/100,000 population/year) and 3 deaths.

MenC vaccine was introduced into the routine infant immunization schedule in the city of Salvador in February 2010, with a catch-up vaccination campaign for all children younger than 5 years. In the first month, 87,111 doses of MenC were administered to children <5 years, reaching an estimated 44% coverage of the target population with at least one dose. By December 2010, an estimated 92% of children younger than 5 years had received at least one dose of MenC vaccine (Table 1).

In the first six months of 2010, cases of meningococcal disease continued to increase, with 93% of 63 cases among persons 10–24 years of age. The state health department purchased an additional MenC vaccine and conducted mass vaccination in three phases of persons 10–24 years of age. The first phase, targeting 10–14 year olds, began May 30; 160,554 (93%) of 172,624 MenC doses administered in this age group were applied in the first weekend of the campaign, reaching 75% of the target population. The second phase, targeting those 15–19 years began June 12; 145,249 (96%) of 151,884 MenC doses administered in this age group were applied in the first weekend. The third phase, targeting 20–24 year olds, was delayed until August 14; only 68,362 (67%) of 102,565 MenC doses administered in this age group were applied in the first weekend. At the end of the third phase, coverage with at least one dose of MenC had reached 80% among 10–14 year olds, 67% among 15–19 year olds, and 40% among 20–24 year olds (Table 1). An additional opportunity for 20–24 year olds was provided on February 12–13, 2011, during which 28,647 MenC doses were administered in this age group.

To evaluate the short-term effect of MenC vaccination, we contrasted age-specific incidence of meningococcal serogroup C disease in 2011 to average incidence in 2008–2009 for targeted and non-targeted age groups for MenC vaccination (Table 2). Among children <5, incidence of serogroup C meningococcal disease fell from 7.5 cases per 100,000 per year during 2008–2009, to 4.0 in 2010 and 2.0 per 100,000 in 2011, and was significantly lower in 2011 than during 2008–2009. Among 10–24 year olds, rates of serogroup C disease were lower in 2011 than in 2010, but were

not significantly lower than during 2008–2009 before mass vaccination. Similarly, rates of serogroup C disease among children 5–9 years and adults 25 years and older who were not targeted for vaccination fell in 2011 but were not significantly different from rates during 2008 to 2009 (Table 2). During 2011, there were 55 confirmed cases of serogroup C meningococcal disease and 21 were eligible for MenC vaccination; 4 case-patients were <5 years ( $2 < 1$  year of age) and 17 were 10–24 years old, none had received MenC vaccine. Based on the surveillance data, the effectiveness of a single dose of MenC vaccine for prevention of serogroup C meningococcal disease was 100% (95% confidence interval, 79–100%).

### 4. Discussion

The introduction of MenC conjugate vaccine for infants in the state of Bahia coincided with increasing incidence of meningococcal serogroup C disease. The capital city of Salvador experienced historic numbers of cases in older children and adults; the resulting panic and demand for MenC vaccine quickly consumed available supplies in the private sector, even at approximately US\$ 100/dose. In 2010, the Bahia state government invested US\$ 30 million to purchase MenC vaccines, including US\$ 10 million to purchase vaccine for the city of Salvador. MenC vaccine was offered at no charge through the state immunization program; however, because supplies were limited, vaccine was offered only to persons in age groups that experienced the highest disease incidence.

A single dose of MenC vaccine after the first year of life has been shown to be highly effective for preventing both epidemic and sporadic meningococcal disease [10–13]. The decision to offer a single dose of MenC vaccine to children 1–4 years old and individuals 10–24 years of age during the epidemic in Salvador was based on local epidemiology, resource constraints and experience with MenC vaccines during meningococcal serogroup C epidemics in the United Kingdom and other countries [4,11,12,14]. For infants, the state health department prioritized available MenC vaccine to provide two doses to prevent disease in the first year of life, followed by a booster in the second year of life. Administrative data suggested good uptake of MenC vaccine among young children, although surveys were not conducted to determine what proportion of children completed recommended schedules. However, cases of meningococcal serogroup C disease continued to occur among persons who were eligible for vaccination, prompting an investigation of vaccine effectiveness. The results of this study identified no confirmed cases of meningococcal serogroup C disease in vaccinated or partially vaccinated individuals through December 2011, consistent with the high effectiveness of MenC conjugate vaccines observed in the United Kingdom, Quebec, Spain and other settings [10,15–17]. Reasons for non-vaccination among case patients who were eligible to receive MenC vaccine need to be investigated to inform future vaccination strategies. Offering MenC vaccine over an extended period of time might have helped achieve coverage targets; national vaccination campaigns against influenza A(H1N1) and rubella in Brazil achieved coverage targets among persons 20–29 years old by providing multiple opportunities for vaccination over an extended period [18,19].

The increase in serogroup C meningococcal disease in Salvador, Brazil, was characterized by elevated attack rates among adolescents and young adults, as well as young children, with high case-fatality, similar to patterns of epidemic meningococcal disease described in other settings [10,15,16]. Data from surveillance for meningococcal disease, especially the availability of population-based data to compare disease incidence by age group in the city of Salvador [7], helped prioritize limited vaccine supplies. The increase of meningococcal serogroup C disease in Salvador followed a shift from predominance of serogroup B to serogroup C

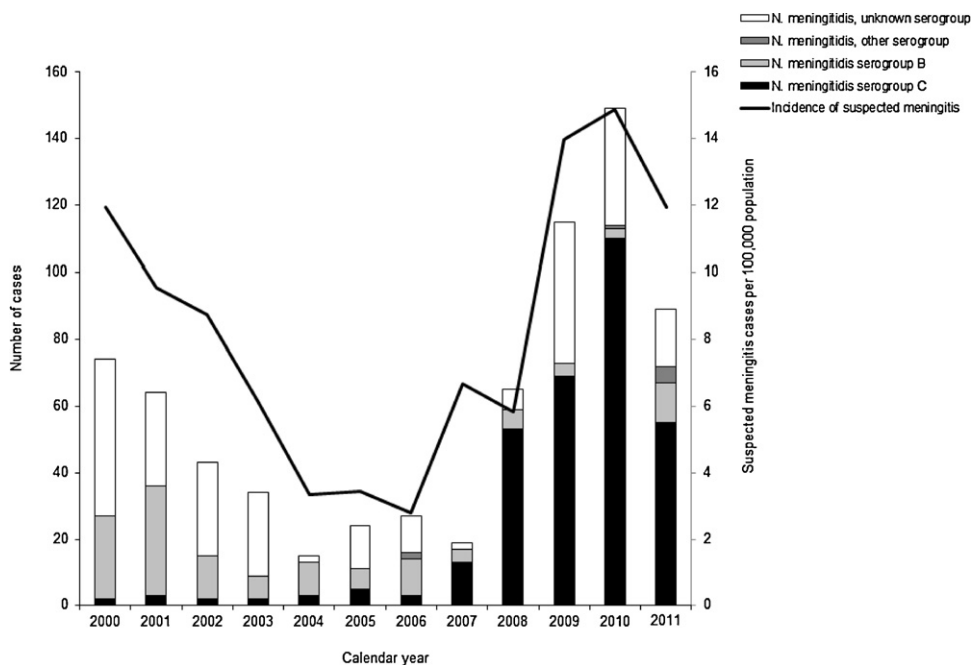


Fig. 1. Reporting rates of suspected meningitis cases and frequency of confirmed meningococcal disease, according to serogroup of isolate, among residents of Salvador, Brazil, 2000–2011.

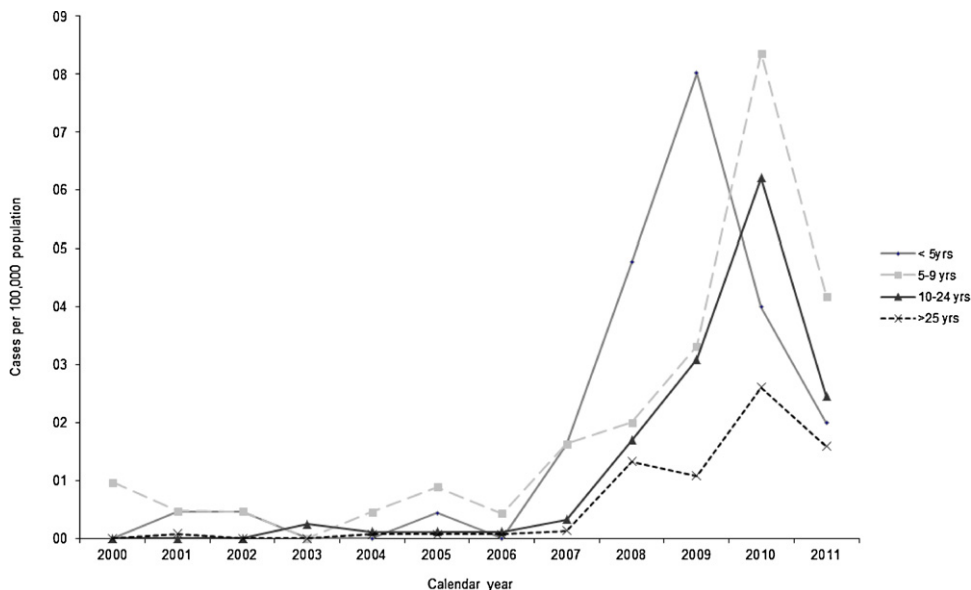


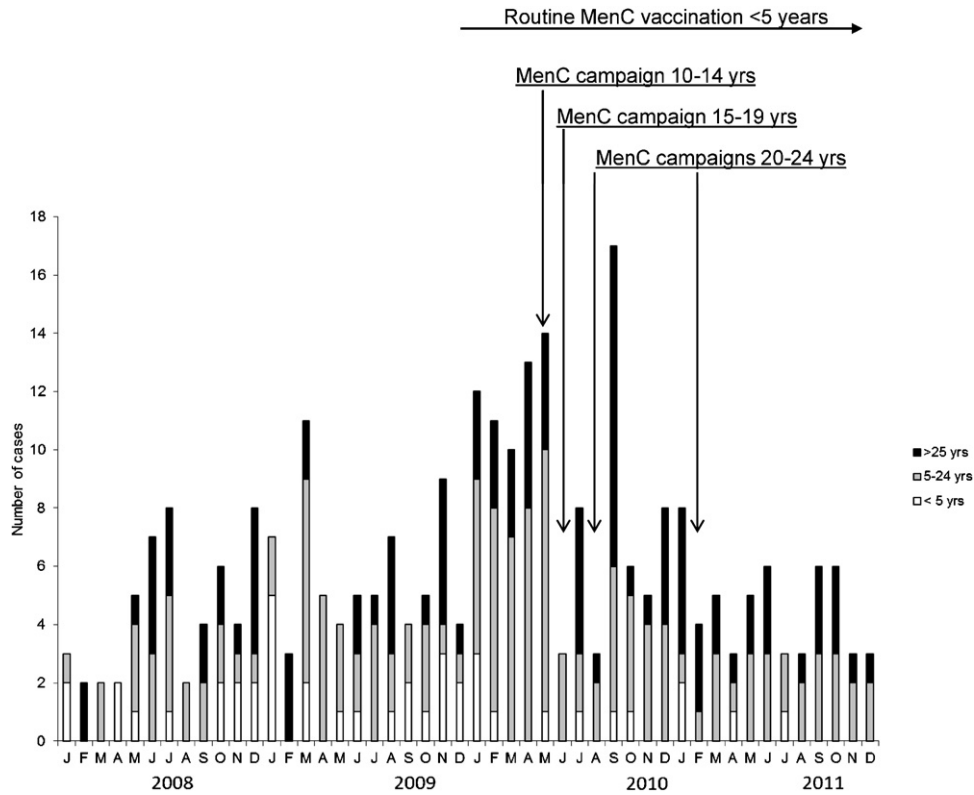
Fig. 2. Reported incidence of meningococcal serogroup C disease among residents of the city of Salvador, Brazil, according to age category, 2000–2011.

**Table 1**  
Number of MenC vaccine doses administered and estimated coverage of target population for routine and catch-up immunization of children and mass vaccination of persons 10–24 years of age in the city of Salvador, Brazil, 2010.

Age group, years	Population	Time period	Number of MenC doses administered	% of target population
<5	200,272	February–December 2010	184,600 <sup>a</sup>	92.2
10–14	214,814	May–August 2010	172,624	80.4
15–19	225,379	June–August 2010	151,884	67.4
20–24	252,066	August 2010	102,565 <sup>b</sup>	40.7

<sup>a</sup> Excludes doses registered as second or third doses.

<sup>b</sup> Excludes doses administered in February 2011.



**Fig. 3.** Confirmed cases of meningococcal serogroup C disease among residents of the city of Salvador, Bahia, by age group of case patient, January 2008 through December 2011.

first described in São Paulo in southeast Brazil [3], and spreading throughout the country [4]. While the emergence of a virulent serogroup C clone belonging to sequence type 103 complex may have contributed to epidemics in Brazil, steadily increasing incidence of serogroup C meningococcal disease has been reported from the greater São Paulo metropolitan area since the late 1980s [3]. Further, meningococcal epidemics may occur due to a variety of factors; shifts of predominant serogroup have been identified in other settings in Brazil without occurrence of epidemics [20]. For example, serogroup C meningococci belonging to the sequence type 103 complex have been identified in Salvador since 1996 (J. Reis, unpublished data). This clone has been associated with epidemics of meningococcal disease in Europe and other regions since 2000 [3,21]. Natural cycles in meningococcal disease complicate

efforts to document short-term impact of vaccination. Continuous surveillance in Brazil for meningococcal disease and strain characterization is needed to establish a baseline for vaccine impact assessments.

This study is subject to a number of limitations. First, cases of meningococcal disease may have been missed or not reported to the health department, isolates were not obtained for all episodes of meningococcal disease for serotyping and MenC vaccination may not have been correctly recorded in case report forms. Cases of serogroup C disease in vaccinated individuals may have been missed, however, active case investigations did not identify confirmed meningococcal disease (regardless of serotype) in vaccinated or partially vaccinated individuals. Second, improvements in surveillance and determination of serogroup for confirmed cases

**Table 2**  
Cumulative incidence of confirmed meningococcal serogroup C disease by time period and age group, Salvador, Brazil, 2008–2011.

Age group, years	Population	Beginning of vaccination	2008–2009 <sup>a</sup>		2010		2011		Relative risk <sup>b</sup> 2011 vs. 2008–9 (95% CI)
			Cases	Incidence per 100,000	Cases	Incidence per 100,000	Cases	Incidence per 100,000	
<5	200,272	February–10	30	7.49	8	3.99	4	2.00	0.27 (0.09–0.75)
5–9	161,475	N/A	13	4.03	18	11.15	9	5.57	1.38 (0.59–3.23)
10–14	214,814	May–10	20	4.66	15	6.98	5	2.33	0.5 (0.18–1.33)
15–19	225,379	June–10	10	2.22	13	5.77	5	2.22	1 (0.34–2.92)
20–24	252,066	August–10	10	1.98	15	5.95	7	2.78	1.4 (0.53–3.67)
25–29	297,758	N/A	7	1.18	13	4.37	9	3.02	2.57 (0.95–6.90)
30–39	476,921	N/A	12	1.26	17	3.56	8	1.68	1.33 (0.54–3.26)
40–49	392,966	N/A	15	1.91	9	2.58	4	1.15	0.6 (0.19–1.8)
50+	445,694	N/A	5	0.56	2	0.45	4	0.90	1.6 (0.42–5.9)

<sup>a</sup> Pre-vaccine comparison period defined as January 2008–December 2009. Average annual incidence during the pre-vaccine period was calculated as the total number of cases divided by twice the estimated population in 2010.

<sup>b</sup> Relative risk (RR) compares cumulative incidence in 2011 versus annual incidence during pre-vaccine period (2008–2009).

contributed to higher detection rates of serogroup C disease. However, the replacement of serogroup B and emergence of a dominant serogroup C clone suggested a true increase in serogroup C disease during the period. To control for improvements in surveillance, we calculated relative risks over a short period with high detection rates. We analyzed unadjusted rates, without redistribution of cases of unknown serotype; therefore, rates are minimum estimates of serogroup C disease incidence during the period. Third, meningococcal disease incidence was not stable during the pre-vaccine period and comparisons of age-specific relative risk of disease were based on few cases. For calculation of relative risk, we chose a pre-vaccine period when rates of serogroup C disease were increasing, potentially leading to an overestimation of vaccine impact. In addition, declining incidence of serogroup C disease in 2011 among non-targeted groups suggested that factors other than MenC vaccination may have contributed to lower rates. Differentiation between vaccine impact and secular trends was complicated by natural variability in meningococcal disease [20,22]. Finally, we did not account for MenC vaccination in the private sector. If individuals at lower risk of disease were more likely to be vaccinated, vaccine effectiveness (specifically, the lower confidence limit) may have been overestimated. However, persons of lower socioeconomic status may have been more likely to receive MenC vaccine than persons of higher status during the campaign, when MenC vaccine was offered at public clinics.

The state of Bahia was the second Brazilian state to introduce MenC conjugate vaccine for infants; later the same year, MenC was added to recommended infant immunizations provided by Brazil's national immunization program. Nationally, catch-up vaccination with a single dose of MenC was offered only for children <2 years old. To date, mass vaccination of older children and young adults to control epidemic disease has only been conducted in the city of Salvador. Surveillance for meningococcal disease needs to be improved. Ongoing surveillance will inform vaccination strategies in other parts of the state and throughout Brazil, as well as to monitor the long-term effectiveness of a single dose of MenC vaccine in this population.

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