Vaccine 35 (2017) 2025–2033

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Impact of meningococcal C conjugate vaccination four years after introduction of routine childhood immunization in Brazil

Ana Lucia Andrade [a,*], Ruth Minamisava [b], Lisia Moura Tomich [a], Ana Paula Lemos [c], Maria Cecilia Gorla [c], Maria Cristina de Cunto Brandileone [c], Carla Madga S. Domingues [d], Camile de Moraes [d], Gabriela Policena [a], Ana Luiza Bierrenbach [a,e], Meningococcal Study Group

[a] Institute of Tropical Pathology and Public Health, Federal University of Goiás, Rua 235, s/n, Setor Universitário, Goiânia, Goiás CEP 74605-050, Brazil
[b] School of Nursing, Federal University of Goiás, Rua 227, s/n, Setor Leste Universitário, Goiânia, Goiás CEP 74605-080, Brazil
[c] Laboratory for Meningitis, Pneumonia and Pneumococcal Infection, Center of Bacteriology, Adolfo Lutz Institute, Secretary of Health of State of São Paulo, Avenida Dr. Arnaldo, 355, Cerqueira Cesar, São Paulo, São Paulo CEP 01246-902, Brazil
[d] National Immunization Program, Secretariat for Health Surveillance, Ministry of Health, Esplanada dos Ministérios, Bloco G, Brasília, Federal District CEP 70058-900, Brazil
[e] Research and Education Institute (IEP), Hospital Sírio-Libanês, São Paulo, Brazil

ARTICLE INFO

Article history:
Received 3 November 2016
Received in revised form 3 March 2017
Accepted 6 March 2017
Available online 18 March 2017

Keywords:
Neisseria meningitidis
Invasive meningococcal disease
Serogroup C meningococcal disease
Meningococcal vaccines
Vaccination impact
Surveillance
Data linkage
Interrupted time-series analysis

ABSTRACT

Background: Routine infant immunization with meningococcal C conjugate (MCC) vaccination started in Brazil in November 2010, scheduled at three and five months plus a booster at 12–15 months of age. No catch-up was implemented. We assessed the impact of vaccination on meningococcal C disease (MenC) four years after vaccination start in the National Immunization Program.

Methods: We performed an ecological *quasi*-experimental design from 2008 to 2014 using a deterministic linkage between the National Notification and the National Reference Laboratory databases for meningitis. We conducted an interrupted time-series analysis considering Brazil except for Salvador municipality, because an epidemic of serogroup C disease occurred in this city, which prompted a mass vaccination campaign with catch-up for adolescents in 2010. Observed MenC rates in the post-vaccination period were compared to expected rates calculated from the pre-vaccination years. Results for Salvador were presented as descriptive data. An additional time-series analysis was performed for the state of São Paulo.

Results: A total of 18,136 MenC cases were analyzed. The highest incidence rates were observed for infants aged <12 months and no second incident peak was observed for adolescents. For Brazil, MenC rates were reduced by 67.2% (95%CI 43.0–91.4%) for infants <12 months of age, 92.0% (77.3–106.8%) for the age-group 12–23 months, and 64.6% (24.6–104.5%) for children aged 2–4 years. For children 5–9 years old, MenC rates reduced 19.2% (9.5–28.9%). Overall, 955 MenC cases were averted in Brazil in individuals aged <40 years after MCC vaccination. Results from São Paulo State, mirror the patterns seen in Brazil.

Conclusion: After four years of infants and toddlers vaccination start, MenC invasive disease reduced in the target population. This investigation provide a robust baseline to ascertain how much the upcoming catch-up dose in 12–13 years of age will accelerate the decrease in MenC incidence rates among youths in Brazil.

1. Introduction

Neisseria meningitidis infections are an important public health problem, causing considerable mortality throughout the world, especially in infants and young children [1]. Meningococcal C conjugate (MCC) vaccination was first introduced in the United Kingdom in 1999, at two, three and four months followed by catch-up and a booster dose among the adolescent population in an attempt to reach a sustained indirect protection. Enormous success was achieved with this immunization strategy [2]. Taking advantage of the lessons learned from the UK program, in the last decade several industrialized countries have introduced MCC vaccination on their routine immunization programs [3,4]. All of them eventually implemented catch-up campaigns or adolescent doses

* Corresponding author at: Instituto de Patologia Tropical e Saúde Pública, Rua 235, s/n, Setor Universitário, Goiânia, Goiás CEP 74605-050, Brazil.
E-mail address: alssandrade@gmail.com (A.L. Andrade).

http://dx.doi.org/10.1016/j.vaccine.2017.03.010
0264-410X/

to reduce carriage and transmission of the organism in the population. The body of evidence accumulated so far on MCC vaccination is derived from industrialized countries, where invasive meningococcal disease (IMD) incidence rates have been observed to peak both in infants and adolescents.

In Brazil, notification rates of IMD caused by *N. meningitidis* as high as 7.0/100,000 inhabitants were reported for children under two years old during 2009 and 2010 [5]. A significant shift from serogroup B to serogroup C was observed from 2002 onwards, when serogroup C became the most frequent capsular type. A major virulent clonal complex 103 (CC103) has been a prevalent genotype associated with the serogroup C epidemic in the 2000 and several outbreaks have been identified [6–9]. The increasing frequency of serogroup C, coupled with several outbreaks of CC-103, prompted the introduction of routine MCC vaccination in November 2010, so that Brazil was the first country in Latin America to introduce this vaccine in its National Immunization Program (NIP). The vaccine was scheduled at three and five months, with a booster dose at 12 months of age [10]. Unlike industrialized countries such as The Netherlands, Spain, and UK [11–13], no catch-up campaign was implemented for older age-groups.

All meningitis cases are of mandatory notification into the National Information System for Notifiable Diseases (Sinan) of Brazil. The National Reference Laboratory for Meningitis, Adolfo Lutz Institute (IAL) records data on pathogen identification and capsular typing of invasive isolates [14]. Brazilian data on *N. meningitidis* have been published by independent studies, each assessing either notifications reported to Sinan or isolates data included in the IAL database [15–17]. Preliminary analysis using only data from Sinan two years after routine MCC vaccination introduction showed a decrease in 50% on IMD incidence rates in children target for immunization with no impact on unvaccinated individuals. We have to be careful when interpreting such results, as the study was performed in the early post-vaccination period, with no stratification by serogroups, and did not account for trends and seasonal components [17].

In this paper, we report the nationwide impact of MCC vaccination after four years of its introduction into the NIP, using a time-series analysis, controlling for secular trends and seasonality, using both notification and laboratory data combined through a linkage procedure.

2. Methods

2.1. Study design and population

In this ecological quasi-experimental study, an interrupted time-series analysis was conducted to measure the impact of MCC vaccination in the prevention of MenC invasive disease in Brazil using national data from 2008–2014. Brazil is a country of continental proportions with an estimated population as 190,732,694 inhabitants in 2014. Two sets of time-series analysis were performed: one for Brazil as a whole but excluding the city of Salvador (2,902,927 inhabitants in 2014) [18] and another for the State of São Paulo (44,035,304 inhabitants in 2014) [19] (Fig. 1).

Salvador is the third most populous city of Brazil. Before the introduction of MCC vaccination by the NIP, an epidemic of serogroup C disease occurred in this city in 2010, reaching high rates of MenC disease. This prompted the local government to initiate a MCC mass vaccination campaign targeting children less than 5 years of age and individuals 10–24 years until August 2010 (Table 1). Therefore, data from Salvador were excluded because vaccination was carried out in extended age groups in response to an outbreak focused in the city.

A high-quality meningitis surveillance system is critical for evaluating the impact of any MCC vaccination program. Although meningitis is a disease of mandatory notification in Brazil, completeness of the national surveillance system occurring in the public or private healthcare during the study period cannot be guaranteed. The meningitis surveillance program of the São Paulo state, the most populous state of the country, is considered of high quality, with rigorous active case search and identification of the etiologic agent. Analysis of the impact of MCC vaccination in the São Paulo state was carried out to support the analysis of national trends, i.e., to assure the quality of data provided by Sinan and IAL.

2.2. Data sources

Individual information on IMD cases were obtained from two National databases for the period of 2008–2014:

(1) National Information System for Notifiable Diseases (Sinan). All IMD notified cases are confirmed by laboratory or clinical/epidemiological criteria [20]. Data collected through this system include patient identification, demographic, clinical and microbiological information. Only data from 2008 onwards were included in the analysis because Sinan upgraded its operational system in 2007 and, for some months of this year, the two systems were running in parallel, which generated duplicate records. Also, in the previous system, there was no information on capsular groups, and MenC is the focus of our analysis.
(2) Adolfo Lutz Institute Reference Laboratory Database (IAL). The IAL is the national reference laboratory for Bacterial Meningitis, located in the city of São Paulo, that receives IMD isolates for serogrouping and other tests collected by the epidemiological surveillance network of public and private hospitals, and public health laboratories from all geographic regions of the country.

MCC coverage rates were provided by the NIP. Coverage rates are only estimated for the primary schedule, which corresponds to the two doses received in the first year of life. The formula is calculated by dividing the number of second doses administered by the target population, multiplied by 100 [11,16,21] (Table 1). A child is only recorded as having received the second dose if the first dose has been administered.

2.3. Linkage procedures

In order to identify and exclude eventual duplicate records from the same episode of disease within and between both databases, we applied a three-step process in which firstly an in-house deterministic record linkage algorithm. Similar linkage algorithms have been validated in other studies that used data from Brazilian health information systems [22–24]. Sinan and IAL databases were then combined by means of another in-house deterministic record linkage algorithm [5,23], tailored to the data available in both databases. Manual review was also used to confirm whether duplicate cases that were similar but not identical for the variables name and dates belonged to the same patient, and episode of disease. Repeated records were discarded. Matched records with missing information in Sinan on disease etiology and serogrouping had such details completed with IAL data. Description of the linkage algorithm is available at Supplemental material.

2.4. Case definitions

IMD cases reported to Sinan and IAL are clinically classified as meningococcal meningitis, meningococcemia or meningococcemia combined with meningococcal meningitis [20]. Confirmed IMD cases include only cases identified by laboratory criteria: Gram-

Fig. 1. Geographical location of the study areas.

Table 1
Meningococcal C conjugate vaccination schedules and coverage rates for Brazil, São Paulo state, and Salvador.

Region	Men-C vaccination schedules	Vaccination start	Vaccine	Vaccination coverage rates[a], %				
				2010	2011	2012	2013	2014
Brazil								
Routine immunization	3, 5, 12 m	Nov 2010	MenC-CRM197 (Novartis Vaccines)	26.9	100.0	96.2	99.7	95.8
São Paulo State								
Routine immunization	3, 5, 12 m	Nov 2010	MenC-CRM197 (Novartis Vaccines)	10.8	100.0	98.7	100.0	97.4
Salvador								
One-time only catch-up campaign[b]	<5 yrs	Feb 2010	MenC-TT (Neisvac-C®, Baxter Vaccines)	92.2				
	10–14 yrs	May-Aug 2010	MenC-TT (Neisvac-C®, Baxter Vaccines)	80.4				
	15–19 yrs	Jun-Aug 2010	MenC-TT (Neisvac-C®, Baxter Vaccines)	67.4				
	20–24 yrs	Aug 2010	MenC-CRM197 (Novartis Vaccines)	40.7				
Routine immunization	3, 5, 12 m	Nov 2010	MenC-CRM197 (Novartis Vaccines)	100.0	95.4	92.7	93.8	86.9

[a] For routine immunization, coverage rates are estimated for the primary schedule, which corresponds to two doses received in the first year of life [11,16,21].
[b] Mass vaccination outside the target age.

staining, culture, latex, contraimmune-electrophoresis and PCR tests. IMD due to serogroup C (main focus of our analysis) is confirmed by serogrouping, contraimmune-electrophoresis, latex agglutination, and PCR. Only IMD records with information on serogroup C were included in the analysis.

2.5. Data analysis

Data management was performed in STATA v.13, and data analysis in R (www.r-project.org/). Annual average rates of MenC during the pre-vaccination period were depicted for Brazil (except for Salvador) and São Paulo state for the following age-groups: less than 12 months, 12–23 months, 2–4 years, and then every 5 years.

The interrupted time-series analysis was carried out only for Brazil (except for Salvador) and São Paulo state. For this analysis, we defined the pre-vaccination period from January 2008 to December 2010, the transition period from January to December 2011, and the post-vaccination period from January 2012 to December 2014. The duration of these pre- and post-vaccination periods has been considered enough for accurate measurement of disease burden trends [25]. The transition period was excluded from the analysis, as it was the period when vaccine coverage rates increased from zero to over 90% in the target age-group for Brazil and São Paulo state. We used bimonthly notification rates and the exponential smoothing methods of Holt-Winters [26]. Secular trends were assessed by linear regression and Cox-Stuart tests, and seasonal variations by Kruskal-Wallis tests. Models were then adjusted for the effects of secular trends and seasonality by including indicator variables representing calendar years and months, respectively. The effect of vaccination was included in the models as a binary variable (0 = pre; 1 = post vaccination) [27]. Predicted rates for the post-vaccination period, representing those that would be expected if the vaccination program had not been introduced, were modeled based on the pre-vaccination period data. Observed and predicted rates for the post-vaccination period were compared for the following age-groups: less than 12 months, 12–23 months, 2–4 years, 5–9 years, 10–19 years, 20–24 years, 25–29 years, 30–39 years, and ≥40 years. We also separately evaluated the age-group of 6–9 years, since those aged 12–23 months in 2010 reached 5 years in 2014, while those aged 6–9 years could only have been affected indirectly by herd effect.

The impact of MCC vaccination was measured as an absolute reduction in number of cases (averted cases) and as a relative rate reduction, after discounting the effects of the temporal aspect of time-series data (linear trends and seasonal components). Averted cases were calculated as the difference in between the observed and the predicted cumulative numbers in the post-vaccination period. Relative reductions were calculated as the observed cumulative rates divided by the predicted cumulative rates minus one. Observed bimonthly meningococcal serogroup C rates per 100,000 inhabitants for the whole study period and predicted rates for the post-vaccination period were plotted for each age-groups. Because the number of cases for Salvador was relatively small, with zero cases in several months, we could not run a separate time-series analysis of city of Salvador alone. Instead, we presented annual rates (per 100,000 inhabs) by age-group for Salvador, São Paulo state and Brazil (except for Salvador).

3. Results

From 2008 to 2014, Sinan had a total of 213,709 records of bacterial meningitis, from which 8134 (3.8%) were duplicated records that were excluded from analysis. Of the remaining 205,575 cases, 17,161 (8.3%) were IMD cases, of which 12,321 (71.8%) were laboratory confirmed. During the same period, IAL had a total of 4505 *N. meningitidis* records. After cleaning this database, 482 (10.7%) repeated records and 212 (4.7%) non-viable strains were excluded, remaining 3811 records.

When the Sinan cases and IAL cases were combined, a total of 18,136 IMD cases were available for analysis. There were 2836 (15.6%) cases that were common to both databases, 975 (5.4%) cases from IAL that had not been notified to Sinan and 14,325 cases from Sinan that had not been recorded in the IAL database. Of the total 18,136 IMD cases, 326 (2%) had no age information, all of them from the IAL database, and 13,341 (73.6%) were IMD cases that had the *N. meningitidis* etiology confirmed cases by laboratory criteria, being 7217 (54.1%) due to capsular group C; the São Paulo state contributed with the majority (50.6%) of bacterial isolates from IAL. Among 13,341 IMD confirmed as *N. meningitidis* cases by laboratory criteria, 6528 (48.9%) were from São Paulo state, and 501 (3.8%) were from Salvador city.

In the pre-vaccination period, the highest annual incidence rates of MenC meningitis for both Brazil (except for Salvador) and São Paulo state were observed for infants less than 12 months of age, and no second incidence peak was observed for adolescents (Fig. 2). São Paulo state presented high annual MenC rates per 100,000 inhabitants for individuals aged <12 months (13.96), 12–23 months (7.72), 2–4 years (5.89), 5–9 years (2.77), and 10–19 years (1.58).

Fig. 3 clearly indicates reductions of MenC annual rates in the city of Salvador after vaccination, which occurred not only among individuals targeted for the campaign (<5 years, 10–24 years of age) but also for those aged ≥30 years old, who did not receive the MenC vaccine.

Overall, a total of 2600 IMD cases (data not shown) and 955 MenC cases were averted at the post-vaccination period (2012–2014) in Brazil (except for Salvador) for individuals <40 years of age. Observed and predicted trends of MenC rates can be visualized in Fig. 4. Observed rates in the post-vaccination period were much lower than the predicted ones for children less than 10 years of age.

MCC vaccination impact in Brazil except for Salvador was observed among children aged <10 years old (Table 2). There was a statistically significant impact on age-groups target by the NIP, with a relative reduction of 67.2% in cases among children under 12 months (95%CI 43.0–91.4%); $p < 0.001$); 92% reduction among 12–23 months (95%CI 77.3–106.8%; $p < 0.001$); and 64.6% reduction among children 2–4 years (95%CI 24.6–104.5%; $p < 0.001$). In addition, we noticed a 19.2% reduction in children aged 5–9 years (95%CI 9.5–28.9%, 9.5; $p = 0.039$). However, performing the analysis only for children aged 6–9 years of age (i.e. excluding children aged 5 years who might have benefited from the direct effect), no statistically significant impact was noted (5.2% reduction, 95%CI −78.3 to 67.9, $p = 0.581$). Similar results of the impact of MCC vaccination were noticed in the analysis performed with data from São Paulo state (Table 2).

4. Discussion

This is the first nationwide study showing the impact of MCC vaccination on MenC disease. Among vaccinated target age-groups, MenC reductions were similar to results found by other countries where MCC vaccination has been introduced [12,28,29]. The impact of the vaccination was also observed in children aged 5–9 years, even though the magnitude of the effect was only 19%, which is less than that observed elsewhere where teenage as well as infant vaccination programs have been introduced [29–34]. Moreover, no statistically significant effect was observed when analysis was repeated only for children aged 6–9 years, i.e. excluding the 5 year olds who could have received the vaccine when aged

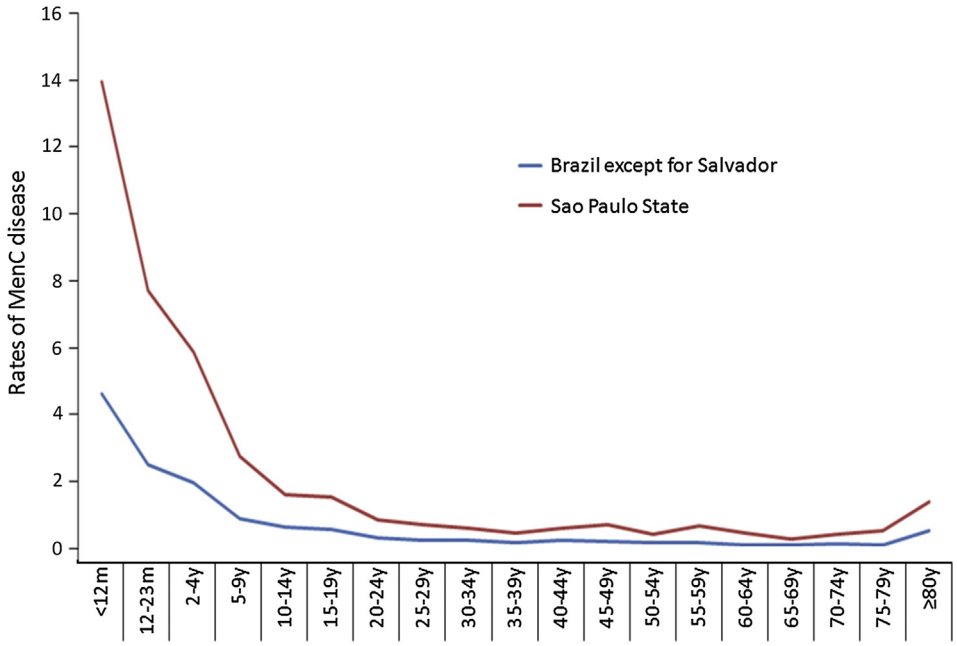

Fig. 2. Average annual rates of invasive MenC cases during the 3-year pre-vaccination period by age-group. Brazil (blue line), and Brazil except for Salvador (red line), 2008–2010. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

12–23 months in 2010. Even though only a small proportion of children aged 5 years had actually been vaccinated in the studied cohort, they were the ones with highest rates of MenC within the age-group of 5–9 years [35,36].

We believe that the observed MenC reductions in Brazil, excluding the city of Salvador, were mostly due to the direct effect of the vaccination. It is important to note that no major nationwide interventions happened in the same period the MCC vaccination, which could have influenced our results. Policies for epidemic surveillance and outbreak response have remained practically unchanged throughout the study period. The only implemented changes were that the MCC vaccine substituted the A/C polysaccharide vaccine for use in children above 2 years of age. The MCC vaccine had been introduced in Brazil for outbreak response since 2003, but until 2011 it was only being used for children under 2 years of age.

This investigation also provided the opportunity to address the MCC vaccination effects in a country harboring outbreaks of a hypervirulent lineage, sequence type (ST) - 103 clonal complex (CC103). Overall, we estimated that more than 1000 MenC cases have been prevented by MCC vaccination in Brazil.

Prior to the introduction of MCC vaccination by the NIP, the city of Salvador faced an epidemic of MenC invasive disease, which prompted a local vaccination campaign in 2010 for individuals with less than five years and from 10 to 24 years of age. Evaluation of the short-term effect of MCC vaccination among children with less than five years of age in this city found a decreasing incidence of MenC invasive disease, from 7.5 cases per 100,000 per year during 2008–2009 to 2.0 per 100,000 in 2011 [15]. Results of a parallel case-control study showed an overall vaccine effectiveness of 98% [21]. The rapid reduction in MenC cases in Salvador is a consequence of the catch-up vaccination strategy adopted in 2010. As such, apart from direct protection, indirect protection was probably induced by the introduction of routine infant vaccination, concurrently with the mass vaccination of individuals up to 24 years of age, reducing carriage and transmission of the organism in unvaccinated individuals, as evidenced by the fact that there were observed burden reductions in age-groups outside those targeted during the campaign.

Lessons on dynamics of *N. meningitidis* carriage and disease, and successful experiences from developed countries provide important evidence for regions that intend to introduce MCC vaccination. To optimize the indirect effect of meningococcal vaccination and to decrease the overall number of cases and disease outbreaks, previous studies have strengthened the need to vaccinate not only infants but also adolescents, the segment of the population that usually harbor the highest rates of meningococcal carriage [37–39]. These studies, however, have been done in industrialized countries, and the overall population impact is likely to depend on setting characteristics, including the burden of MCC invasive disease in the pre-vaccination period. The local epidemiology on carriage and disease transmission should be the driver influencing each country's best vaccination schedule strategy. In this way, an important shortcoming in interpreting the current findings is the absence of adequate local carriage data before MCC program implementation by the NIP. As far as the age distribution of meningococcal carriage is concerned, there is unfortunately only poor evidence in the country, and none of them from the pre-vaccination period [40–42]. These studies have identified that there are still MenC carriage among adolescents and adult age-groups in the early years after the introduction of the routine infant vaccination.

The robustness of our findings was confirmed using data exclusively from São Paulo state, which relies on an organized and effective surveillance system for meningitis, thereby increasing our confidence on the Brazilian MCC vaccination impact results. However, as an observational ecological study, our study has some limitations. The effects of vaccination after vaccine licensing assessed by observational studies may present bias and confounding due to the lacking of random allocation and masking which are controlled for during pre-licensure randomized controlled trials of a vaccine [43]. Even though it would be desirable to use other meningococcal serogroups as comparison groups, their absolute and relative burden were much smaller in Brazil in the pre-vaccination period, so that the small bimonthly rates of these other serogroups, particularly when analyzed by the several age-groups, precluded using them as a control group.

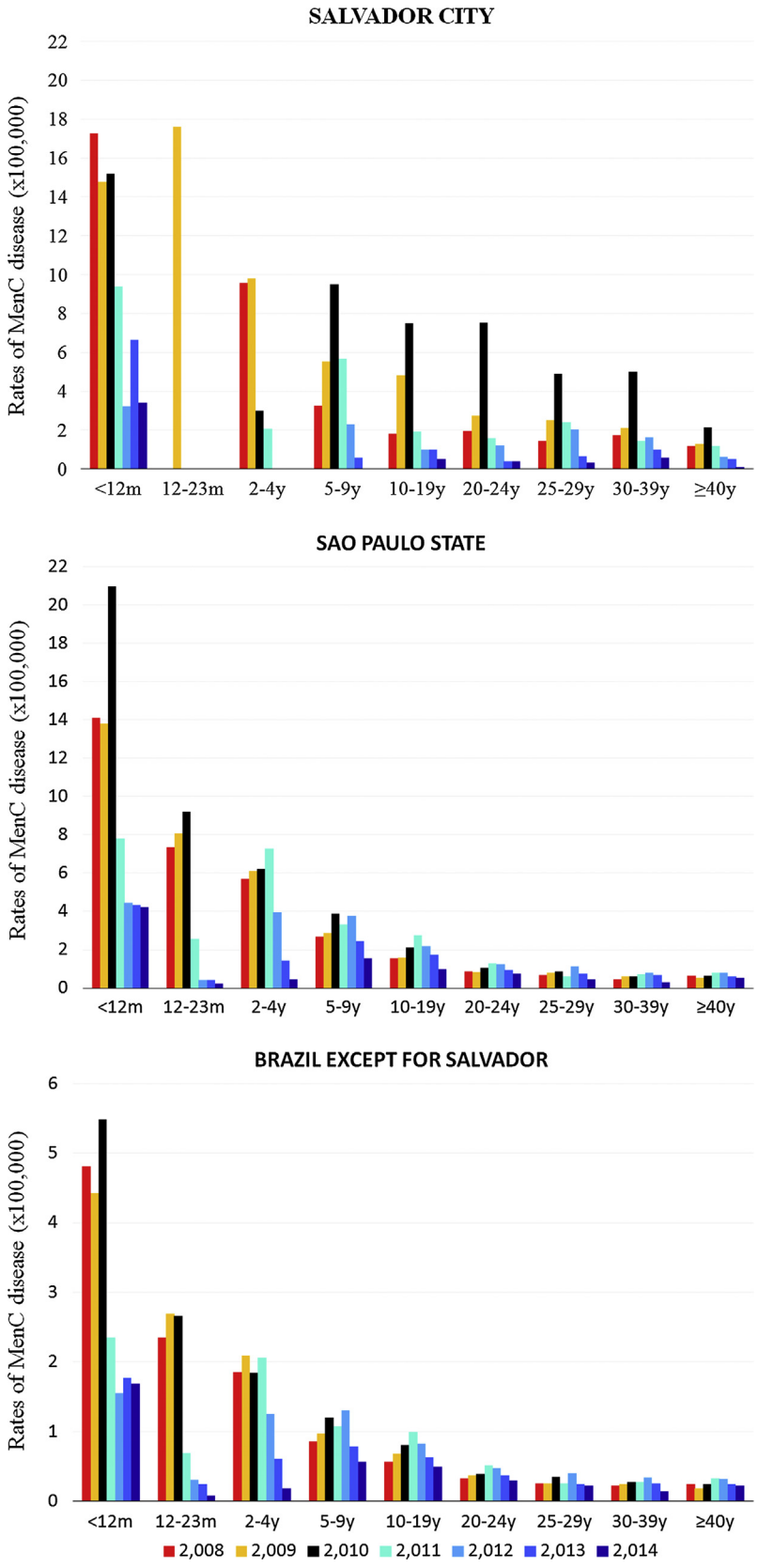

Fig. 3. Annual rates of MenC invasive disease for Brazil (except for Salvador), São Paulo state and Salvador city according to age-groups and years, 2008–2014. For Salvador, catch-up campaign was performed for children aged <5 years (Feb/2010), 10–14 years (May–Aug 2010), 15–19 years (Jun–Aug 2010), and 20–24 years (Aug/2010). In November 2010, the National Immunization Program introduced routine infant MCC vaccination.

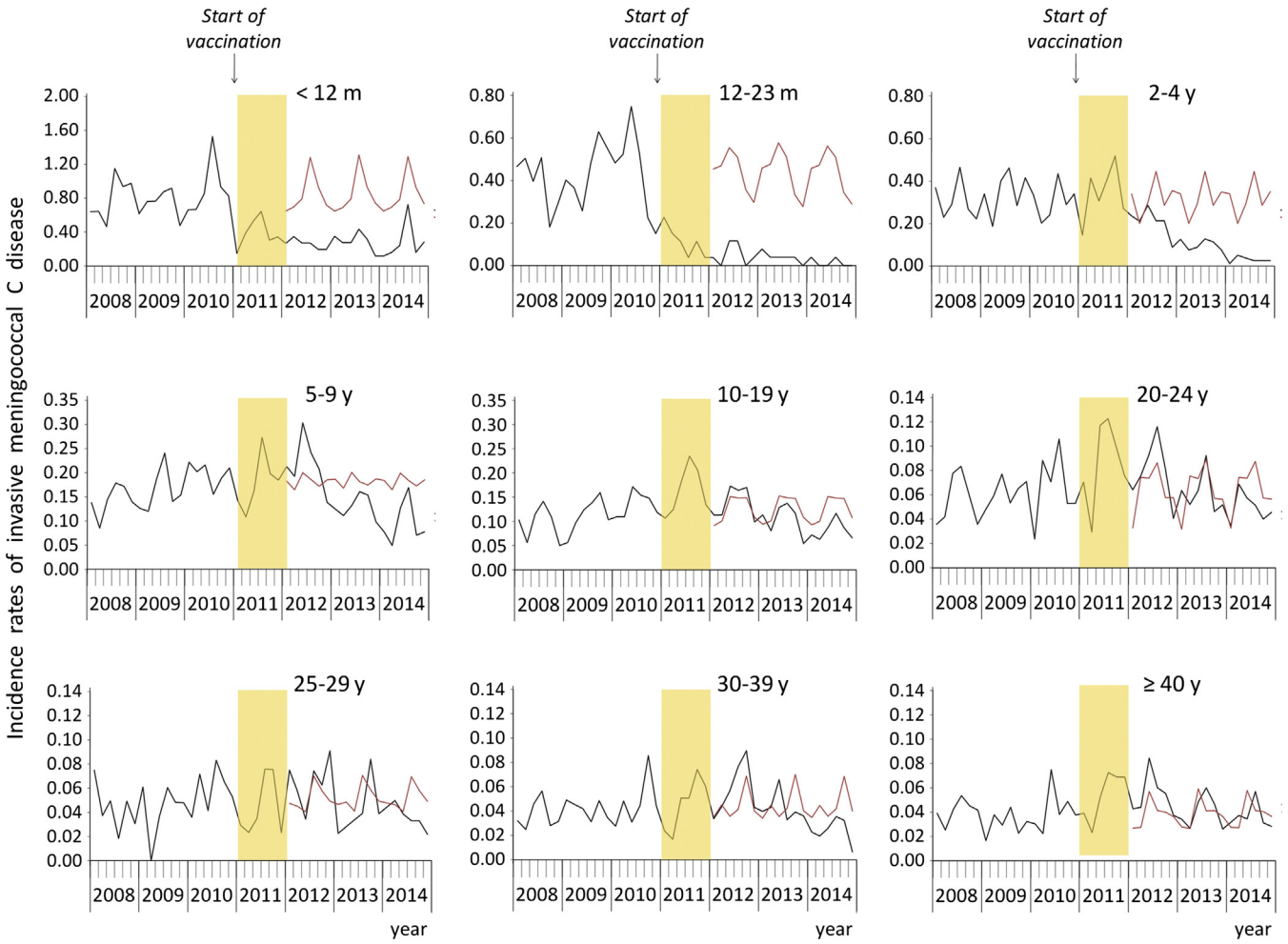

Fig. 4. Trends in observed (black lines) and predicted (red lines) bimonthly incidence rates of MenC invasive disease. Interrupted time-series analysis for Brazil except for Salvador, January 2008–December 2014. The National Immunization Program introduced routine infant MCC vaccination in November 2010. The yellow bar represents the transition period (year 2011), which was excluded from the time-series analysis. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Comparison of our findings with other studies is not straightforward. In addition to different methodological approaches applied to assess the impact of MCC vaccination, other reasons hamper the comparison of our results with studies conducted by others, such as differences in the MCC vaccine introduced in the countries, MCC coverage rates, length of time evaluated after the vaccination introduction, and vaccination schedules. Even so, MenC invasive disease reductions in Brazil ranging from 65% to 92% in the target population, four years after vaccination, have a similar magnitude to results shown by Netherlands (86%), Germany (51%), and England (66%) after, respectively, 4, 13 and 11 years of routine immunization with MCC vaccine [28,33,34].

The current Brazilian experience with MCC vaccination may provide essential epidemiological information for policy makers at neighboring countries, since data on MenC epidemiology is neither consistent nor uniform at Latin America [44]. Unlike many other countries, Brazil did not present a second age peak incidence in adolescence of MenC invasive disease [45]. The different epidemiology of IMD among adolescents in Brazil may be at least partially explained by the smoking patterns of this population and the overall warmer climate conditions of the country [42,46]. In particular, studies have linked cigarette smoking with an increased risk of meningococcal carriage among adolescents [46,47]. A comprehensive survey conducted in 2013/2014 in Brazil evaluated 74,589 adolescents and found current tobacco use in 5.7% of study participants [48], much lower than the prevalence observed in other regions, such as US (17%), UK (20%), and several Latin American countries [49–51]. Previous studies indicated that students residing on campus are more likely to be carriers and are at higher risk of IMD, probably due to social mixing patterns [52,53]. However, different from other countries, many undergraduate students in Brazil still live with their parents or extended family. These data highlight important differences in the epidemiology of IMD in Brazilian adolescents compared to Europe, North America and many neighboring countries.

In conclusion, after four years of infants and toddler immunization in Brazil, we found a reduction of MenC rates in individuals in the vaccine target population. The Brazilian government has just approved the gradual introduction of MCC vaccination among adolescents in the national immunization schedule [54]. Starting in 2017, the following cohorts will be included: 12–13 years of age (2017), 11–12 years of age (2018), 10–11 years of age (2019), and 9–10 years of age (2020). Therefore, the results of this investigation will certainly contribute as a robust baseline to ascertain how much this catch-up dose will accelerate the decrease in MenC incidence rates among adolescents in Brazil.

Table 2
Impact of MCC vaccination on rates of MenC invasive disease in Brazil. Interrupted time series analysis, 2008–2014.

Age-group	Probable vaccination schedule	Predicted		Observed		Averted invasive meningococcal C		Relative reduction		
		Number	Rate 10^5	Number	Rate 10^5	Number	Rate 10^5	%	95%CI	p-value
Brazil except for Salvador										
<12 m	2 + 0	387	15.28	127	5.01	260	10.27	−67.20	−91.40; −43.00	0.000
12–23 m	2 + 0 or 2 + 1	200	7.92	16	0.63	184	7.29	−92.00	−106.80; −77.30	0.000
2–4 yrs	2 + 1	451	5.76	162	2.04	289	3.72	−64.60	−104.50; −24.60	0.000
5–9 yrs	None	471	3.28	381	2.65	90	0.63	−19.20	−28.90; −9.50	0.039
10–19 yrs	None	752	2.25	654	1.96	98	0.29	−12.90	−59.80; +34.00	0.132
20–24 yrs	None	199	1.15	197	1.14	2	0.01	−0.90	−80.50; +78.70	0.940
25–29 yrs	None	167	0.94	153	0.86	14	0.08	−8.50	−87.40; +70.40	0.461
30–39 yrs	None	243	0.80	225	0.74	18	0.06	−7.50	−99.10; +84.10	0.588
≥40 yrs	None	473	0.69	534	0.79	−61	−0.1	14.50	−49.10; +78.10	0.256
São Paulo State										
<12 m	2 + 0	275	54.41	66	13.04	209	41.37	−76.00	−103.00; −49.10	0.000
12–23 m	2 + 0 or 2 + 1	127	26.05	5	1.02	122	25.03	−96.10	−107.90; −84.30	0.000
2–4 yrs	2 + 1	281	18.41	91	5.87	190	12.54	−68.10	−115.70; −20.50	0.000
5–9 yrs	None	287	10.36	216	7.77	71	2.59	−25.00	−30.50; −19.50	0.005
10–19 yrs	None	374	5.74	321	4.92	53	0.82	−14.30	−83.20; +54.60	0.185
20–24 yrs	None	106	2.89	108	2.95	−2	−0.06	2.10	−99.10; +103.20	0.893
25–29 yrs	None	96	2.43	94	2.38	2	0.05	−2.10	−138.30; +134.20	0.908
30–39 yrs	None	123	1.77	122	1.75	1	0.02	−1.1	−105.00; +102.80	0.956
≥40 yrs	None	300	1.86	311	1.94	−11	−0.08	4.3	−69.70; +78.30	0.735

Observed rates from the pre-intervention period (2008–2010) were used to predict rates for the post-intervention period (2012–2014). The year of 2011 was excluded from the analysis. Averted cases/rates (absolute reductions) were calculated as predicted minus observed cases/rates. The interrupted time-series analysis was based on exponential smoothing Holt-Winters additive model. Presented numbers and cumulative rates refer to the 3-year post-intervention period (2012–2014). Observed post-vaccination rates were used to compare to that predicted ones, which would have been expected if MCC vaccination had not been introduced in the National Immunization Program. Relative reduction refers to the 3-year (2012–2014) post-vaccination period. Relative reduction in rates of MenC was calculated as the observed rates divided by the predicted cumulative rates in the post-vaccination period minus one.

Ethical approval

This study was approved by the Research Ethics Committee of the Universidade Federal de Goiás (protocol # 162.53), with a waiver of the requirement for informed consent. Nominal information was used only for record-linkage purposes.

Funding sources

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Contributors

ALA conceived the idea of the study, contributed to the study design and coordination of the study, RM and ALB contributed to the study design, analysis and interpretation of the results. CM, CMSD, and LMT collected epidemiological data and interpreted the results. MCCB, APL, and MCG did the laboratory work, and contributed to interpretation of the data. EBC run the analysis and prepared the figures. GP performed the linkage of databases. CWC contributed with the analysis and interpretation of the findings. All authors gave valuable advice and critically revised the manuscript. All authors read and approved the final version of the manuscript.

Conflict of interests

ALA, has received research and travel grants from GlaxoSmithKline. She has also served on ad-hoc advisory boards for Pfizer. RM has received travel grant from GlaxoSmithKline. MCCB and APL have received travel grants and personal fees from Novartis, and travel grants from GlaxoSmithKline, outside the submitted work. MCG have received travel grants and personal fees from Novartis, outside the submitted work. EBC, CMSD, CM, LT, ALB, GB, and CWC declare no competing interests.

Acknowledgments

This investigation was supported by the Ministry of Health of Brazil (grant # 01/2012). ALA (grant # 313286/2014-0), and MCCB (grant # 304211/2014-1) are fellowship of the National Council for Scientific and Technological Development (CNPq).

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2017.03.010.

References

[1] Stephens DS, Greenwood B, Brandtzaeg P. Epidemic meningitis, meningococcaemia, and *Neisseria meningitidis*. Lancet 2007;369:2196–210. http://dx.doi.org/10.1016/S0140-6736(07)61016-2.
[2] Maiden MC, Ibarz-Pavon AB, Urwin R, Gray SJ, Andrews NJ, Clarke SC, et al. Impact of meningococcal serogroup C conjugate vaccines on carriage and herd immunity. J Infect Dis 2008;197:737–43. http://dx.doi.org/10.1086/527401.
[3] Borrow R. Advances with vaccination against *Neisseria meningitidis*. Tropical Med Int Health: TM & IH 2012;17:1478–91. http://dx.doi.org/10.1111/j.1365-3156.2012.03085.x.
[4] Bowley J. MenC conjugate vaccine in Europe – schedules, protection and outcomes. http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=2519 [cited 2017 Feb 07].
[5] Azevedo LC, Toscano CM, Bierrenbach AL. Bacterial meningitis in Brazil: baseline epidemiologic assessment of the decade prior to the introduction of pneumococcal and meningococcal vaccines. PLoS ONE 2013;8:e64524. http://dx.doi.org/10.1371/journal.pone.0064524.
[6] de Lemos AP, Yara TY, Gorla MC, de Paiva MV, de Souza AL, Goncalves MI, et al. Clonal distribution of invasive *Neisseria meningitidis* serogroup C strains circulating from 1976 to 2005 in greater Sao Paulo, Brazil. J Clin Microbiol 2007;45:1266–73. http://dx.doi.org/10.1128/JCM.02510-06.
[7] Gorla MC, de Lemos AP, Quaresma M, Vilasboas R, Marques O, de Sa MU, et al. Phenotypic and molecular characterization of serogroup C *Neisseria meningitidis* associated with an outbreak in Bahia, Brazil. Enfermedades infecciosas y microbiologia clinica 2012;30:56–9. http://dx.doi.org/10.1016/j.eimc.2011.07.022.

[8] Iser BP, Lima HC, de Moraes C, de Almeida RP, Watanabe LT, Alves SL, et al. Outbreak of *Neisseria meningitidis* C in workers at a large food-processing plant in Brazil: challenges of controlling disease spread to the larger community. Epidemiol Infect 2012;140:906–15. http://dx.doi.org/10.1017/S0950268811001610.

[9] Liphaus BL, Cappeletti-Goncalves-Okai MI, Silva-Delemos AP, Gorla MC, Rodriguez-Fernandes M, Pacola MR, et al. Outbreak of *Neisseria meningitidis* C in a Brazilian oil refinery involving an adjacent community. Enferm Infecc Microbiol Clin 2013;31:88–92. http://dx.doi.org/10.1016/j.eimc.2012.05.009.

[10] Brazil. [Introduction of meningococcal C vaccine (conjugated) in the childhood vaccination calendar]. http://www.sgc.goias.gov.br/upload/links/arq_626_menig.pdf [cited 2017 Feb 07].

[11] de Greeff SC, de Melker HE, Spanjaard L, Schouls LM, van Derende A. Protection from routine vaccination at the age of 14 months with meningococcal serogroup C conjugate vaccine in the Netherlands. Pediatr Infect Dis J 2006;25:79–80. http://dx.doi.org/10.1097/01.inf.0000195594.41449.c6.

[12] Larrauri A, Cano R, Garcia M, Mateo S. Impact and effectiveness of meningococcal C conjugate vaccine following its introduction in Spain. Vaccine 2005;23:4097–100. http://dx.doi.org/10.1016/j.vaccine.2005.03.045.

[13] Trotter CL, Andrews NJ, Kaczmarski EB, Miller E, Ramsay ME. Effectiveness of meningococcal serogroup C conjugate vaccine 4 years after introduction. Lancet 2004;364:365–7. http://dx.doi.org/10.1016/S0140-6736(04)16725-1.

[14] Brazil. [Portaria n° 70 de 23 de dezembro de 2004]. DOU. http://www.suvisa.ba.gov.br/sites/default/files/laboratorio_central_documentos/imagem/2012/05/09/Portaria%2070%202004.pdf [cited 2017 Feb 07].

[15] Cardoso CW, Pinto LL, Reis MG, Flannery B, Reis JN. Impact of vaccination during an epidemic of serogroup C meningococcal disease in Salvador, Brazil. Vaccine 2012;30:5541–6. http://dx.doi.org/10.1016/j.vaccine.2012.06.044.

[16] Kupek E, Puricelli RC, Westrupp MH. Effectiveness of a mass immunization campaign against serogroup C meningococci in children in the federal state of Santa Catarina, Brazil. Braz J Infect Dis: Off Publ Braz Soc Infect Dis 2001;5:324–31. http://dx.doi.org/10.1590/S1413-86702001000600006.

[17] Safadi MA, Berezin EN, Arlant LH. Meningococcal disease: epidemiology and early effects of immunization programs. J Pediatr Infect Dis Soc 2014;3:91–3. http://dx.doi.org/10.1093/jpids/piu027.

[18] DATASUS. [Health information. Resident population]. http://tabnet.datasus.gov.br/cgi/tabcgi.exe?ibge/cnv/poptbr.def [cited 2017 Feb 07].

[19] DATASUS. [Health information. Projection of the states population by sex and age groups: 2000–2030]. http://tabnet.datasus.gov.br/cgi/tabcgi.exe?ibge/cnv/projpopuf.def [cited 2017 Feb 07].

[20] Brazil. [Guideline on Health Surveillance]. http://portalsaude.saude.gov.br/images/pdf/2014/novembro/27/guia-vigilancia-saude-linkado-27-11-14.pdf [cited 2017 Feb 07].

[21] Cardoso CW, Ribeiro GS, Reis MG, Flannery B, Reis JN. Effectiveness of meningococcal C conjugate vaccine in salvador, Brazil: a case-control study. PLoS ONE 2015;10:e0123734. http://dx.doi.org/10.1371/journal.pone.0123734.

[22] Dusetzina SB, Tyree S, Meyer AM, Meyer A, Green L, Carpenter WR. Linking data for health services research: a framework and instructional guide. https://www.ncbi.nlm.nih.gov/books/NBK253313/ [cited 2017 Feb 07].

[23] Oliveira GP, Bierrenbach AL, Camargo KRJ, Coeli CM, Pinheiro RS. Accuracy of probabilistic and deterministic record linkage: the case of tuberculosis. Rev Saude Publica 2016;50:49. http://dx.doi.org/10.1590/S1518-8787.2016050006327.

[24] Pacheco AG, Saraceni V, Tuboi SH, Lauria LM, Moulton LH, Faulhaber JC, et al. Estimating the extent of underreporting of mortality among HIV-infected individuals in Rio de Janeiro, Brazil. AIDS Res Hum Retroviruses 2011;27:25–8. http://dx.doi.org/10.1089/aid.2010.0089.

[25] WHO. Measuring impact of *Streptococcus pneumoniae* and *Haemophilus influenzae* type b conjugate vaccination. Geneva, Switzerland. http://apps.who.int/iris/bitstream/10665/75835/1/WHO_IVB_12.08_eng.pdf [cited].

[26] Snedecor G, Cochran W. Statistical methods. 8th ed. Iowa City: Iowa State University Press; 1989.

[27] Venables WN, Ripley BD. Modern applied statistics with S. 4th ed. New York: Springer; 2002.

[28] Bijlsma MW, Bekker V, Brouwer MC, Spanjaard L, van de Beek D, van der Ende A. Epidemiology of invasive meningococcal disease in the Netherlands, 1960–2012: an analysis of national surveillance data. Lancet Infect Dis 2014;14:805–12. http://dx.doi.org/10.1016/S1473-3099(14)70806-0.

[29] Sadarangani M, Scheifele DW, Halperin SA, Vaudry W, Le Saux N, Tsang R, et al. The impact of the meningococcal serogroup C conjugate vaccine in Canada between 2002 and 2012. Clin Infect Dis: Off Publ Infect Dis Soc Am 2014;59:1208–15. http://dx.doi.org/10.1093/cid/ciu597.

[30] de Waure C, Miglietta A, Nedovic D, Mereu G, Ricciardi W. Reduction in *Neisseria meningitidis* infection in Italy after meningococcal C conjugate vaccine introduction: a time trend analysis of 1994–2012 series. Hum Vaccines Immunother 2016;12:467–73. http://dx.doi.org/10.1080/21645515.2015.1078951.

[31] Garrido-Estepa M, Leon-Gomez I, Herruzo R, Cano R. Changes in meningococcal C epidemiology and vaccine effectiveness after vaccine introduction and schedule modification. Vaccine 2014;32:2604–9. http://dx.doi.org/10.1016/j.vaccine.2014.03.010.

[32] Gunaratnam P, Massey P, Durrheim D, Torvaldsen S. Invasive meningococcal disease in elderly people, New South Wales, Australia, 1993 to 2012. West Pac Surveill Response J: WPSAR 2013;4:4–10. http://dx.doi.org/10.5365/WPSAR.2013.4.4.001.

[33] Hellenbrand W, Elias J, Wichmann O, Dehnert M, Frosch M, Vogel U. Epidemiology of invasive meningococcal disease in Germany, 2002–2010, and impact of vaccination with meningococcal C conjugate vaccine. J Infect 2013;66:48–56. http://dx.doi.org/10.1016/j.jinf.2012.09.008.

[34] Martin NG, Sadarangani M, Pollard AJ, Goldacre MJ. Hospital admission rates for meningitis and septicaemia caused by *Haemophilus influenzae*, *Neisseria meningitidis*, and *Streptococcus pneumoniae* in children in England over five decades: a population-based observational study. Lancet Infect Dis 2014;14:397–405. http://dx.doi.org/10.1016/S1473-3099(14)70027-1.

[35] Brazil. [Information system of the national immunization program (SI-PNI)]. http://pni.datasus.gov.br/inf_estatistica_cobertura.asp [cited 2017 Feb 07].

[36] IBGE. [Synopsis of the 2010 demographic census]. http://biblioteca.ibge.gov.br/visualizacao/livros/liv49230.pdf [cited 2017 Feb 07].

[37] Borrow R, Abad R, Trotter C, van der Klis FR, Vazquez JA. Effectiveness of meningococcal serogroup C vaccine programmes. Vaccine 2013;31:4477–86. http://dx.doi.org/10.1016/j.vaccine.2013.07.083.

[38] Vetter V, Baxter R, Denizer G, Safadi MA, Silfverdal SA, Vyse A, et al. Routinely vaccinating adolescents against meningococcus: targeting transmission & disease. Expert Rev Vaccines 2016;15:641–58. http://dx.doi.org/10.1586/14760584.2016.1130628.

[39] Christensen H, May M, Bowen L, Hickman M, Trotter CL. Meningococcal carriage by age: a systematic review and meta-analysis. Lancet Infect Dis 2010;10:853–61. http://dx.doi.org/10.1016/S1473-3099(10)70251-6.

[40] Weckx L, Puccini RF, Machado AMO, Gonçalves MG, Tuboi SH, Barros ENC, et al. Cross-sectional study assessing *Neisseria meningitidis* carriage in a 1–24-year-old population in Embu das Artes (Sao Paulo, Brazil). In: 9th world congr world soc pediatr infect dis. Rio de Janeiro: WSPID. PS0675. Poster session. p. 40.

[41] Cassio de Moraes J, Kemp B, de Lemos AP, Outeiro Gorla MC, Lemes Marques EG, Ferreira Mdo C, et al. Prevalence, risk factors and molecular characteristics of meningococcal carriage among Brazilian adolescents. Pediatr Infect Dis J 2015;34:1197–202. http://dx.doi.org/10.1097/INF.0000000000000853.

[42] Nunes AM, Ribeiro GS, Ferreira IE, Moura AR, Felzemburgh RD, de Lemos AP, et al. Meningococcal carriage among adolescents after mass meningococcal C conjugate vaccination campaigns in Salvador, Brazil. PLoS ONE 2016;11:e0166475. http://dx.doi.org/10.1371/journal.pone.0166475.

[43] Chen RT, Orenstein WA. Epidemiologic methods in immunization programs. Epidemiol Rev 1996;18:99–117.

[44] Ruttimann RW, Gentile A, Parra MM, Saez-Llorens X, Safadi MA, Santolaya ME. A consensus statement: meningococcal disease among infants, children and adolescents in Latin America. Pediatr Infect Dis J 2014;33:284–90. http://dx.doi.org/10.1097/INF.0000000000000228.

[45] Castelblanco RL, Lee M, Hasbun R. Epidemiology of bacterial meningitis in the USA from 1997 to 2010: a population-based observational study. Lancet Infect Dis 2014;14:813–9. http://dx.doi.org/10.1016/S1473-3099(14)70805-9.

[46] MacLennan J, Kafatos G, Neal K, Andrews N, Cameron JC, Roberts R, et al. Social behavior and meningococcal carriage in British teenagers. Emerg Infect Dis 2006;12:950–7. http://dx.doi.org/10.3201/eid1206.051297.

[47] Yazdankhah SP, Kriz P, Tzanakaki G, Kremastinou J, Kalmusova J, Musilek M, et al. Distribution of serogroups and genotypes among disease-associated and carried isolates of *Neisseria meningitidis* from the Czech Republic, Greece, and Norway. J Clin Microbiol 2004;42:5146–53. http://dx.doi.org/10.1128/JCM.42.11.5146-5153.2004.

[48] Figueiredo VC, Szklo AS, Costa LC, Kuschnir MC, da Silva TL, Bloch KV, et al. ERICA: smoking prevalence in Brazilian adolescents. Rev Saude Publica 2016;50(Suppl. 1):12s. http://dx.doi.org/10.1590/S01518-8787.2016050006741.

[49] Jamal A, Homa DM, O'Connor E, Babb SD, Caraballo RS, Singh T, et al. Current cigarette smoking among adults - United States, 2005–2014. MMWR Morb Mortal Wkly Rep 2015;64:1233–40. http://dx.doi.org/10.15585/mmwr.mm6444a2.

[50] ASH. Action on Smoking and Health. Smoking statistics. London, UK. http://ash.org.uk/files/documents/ASH_108.pdf [cited 2017 Feb 07].

[51] Muller F, Wehbe L. Smoking and smoking cessation in Latin America: a review of the current situation and available treatments. Int J Chron Obstr Pulm Dis 2008;3:285–93.

[52] Harrison LH, Dwyer DM, Maples CT, Billmann L. Risk of meningococcal infection in college students. JAMA 1999;281:1906–10.

[53] Neal KR, Nguyen-Van-Tam JS, Jeffrey N, Slack RC, Madeley RJ, Ait-Tahar K, et al. Changing carriage rate of *Neisseria meningitidis* among university students during the first week of term: cross sectional study. BMJ 2000;320:846–9. http://dx.doi.org/10.1136/bmj.320.7238.846.

[54] Brazil. [Information on changes to the national vaccination calendar for the year 2017]. http://portalsaude.saude.gov.br/images/pdf/2016/outubro/20/Nota-Informativa-311-Calendario-Nacional-de-Vacinacao-2017.pdf [cited 2017 Feb 07].