Vaccine xxx (2017) xxx–xxx

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

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ARTICLE INFO

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

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

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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-

Please cite this article in press as: Andrade AL et al. Impact of meningococcal C conjugate vaccination four years after introduction of routine childhood immunization in Brazil. Vaccine (2017), http://dx.doi.org/10.1016/j.vaccine.2017.03.010