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Combined effect of PCV10 and meningococcal C conjugate vaccination on meningitis mortality among children under five years of age in Brazil

Ana Luiza Bierrenbach [a], Ruth Minamisava [b], Airlane Pereira Alencar[c], Gizelton Pereira Alencar[d], and Ana Lucia Andrade [e]

[a]Research and Education Institute (IEP), Hospital Sirio-Libanes, Sao Paulo, Sao Paulo, Brazil; [b]School of Nursing, Federal University of Goias, Goiania, Goias, Brazil; [c]Department of Statistics, Institute of Mathematics and Statistics, Sao Paulo University, Sao Paulo, Sao Paulo, Brazil; [d]Department of Epidemiology, Faculty of Public Health, University of Sao Paulo, Sao Paulo, Sao Paulo, Brazil; [e]Institute of Tropical Pathology and Public Health, Federal University of Goias, Goiania, Goias, Brazil

ABSTRACT

The 10-valent pneumococcal conjugate vaccine (PCV10) was introduced in the Brazilian National Immunization Program in March 2010, scheduled at 2, 4, and 6 months, with a booster at 12–15 months of age. The meningococcal C conjugate vaccine (MCC) was introduced in November 2010, scheduled at 3 and 5 months, with a booster dose at 12–15 months of age and no catch-up for older age groups. In this interrupted time-series analysis study, we used Brazilian mortality data from 2005 to 2015 for children under five years of age (excluding data from the state of Bahia) to assess the combined impact of these vaccines on the overall burden of meningitis mortality among children aged 0–23 months and 2–4 years, as defined using meningitis and meningococcemia specific International Classification of Diseases - tenth revision codes. Secular trends and seasonality were taken into account. We found significant reductions for both age groups relative to those observed for the comparison group of diseases, with immediate effects after the transition period (2010-2011) of 29.2% and 27.5% for children aged 0–23 months and 2–4 years, respectively. These immediate effects were sustained throughout the post-vaccination period (2012–2015). In total, 337 deaths were averted by the combined effect of both vaccines, 238 (95%CI 169-319) for children aged 0–23 months and 99 (95%CI 56–144) for those aged 2–4 years. These results add strong evidence in support of investments in these vaccines by low and middle-income countries.

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Meningococcal meningitis; pneumococcal meningitis; mortality; interrupted time series analysis; vaccination

Introduction

Bacterial meningitis is a severe disease associated with a high mortality and neurological sequelae. For children aged 1–59 months, 115,000 meningitis deaths were estimated to happen worldwide in 2015.[1] *Haemophilus influenzae* type b (Hib), *Streptococcus pneumoniae* and *Neisseria meningitidis* are the three most common causes of meningitis. Remarkable reductions in meningitis disease burden have been documented in high-income countries where polysaccharide-protein conjugate vaccines for these pathogens have been introduced,[2–4] but not many dedicated impact studies have been carried out in low and middle-income countries.[5–10]

In Brazil, Hib conjugate vaccine was incorporated into the National Immunization Program (NIP) in 1999, with sustained high coverage. Since then, Hib meningitis has become a relatively rare disease,[11,12] and Hib carriage rates are low in healthy children under five years of age.[13,14] An analysis of the mandatory meningitis notification data of the 2000-2010 period showed that out of the total number of bacterial meningitis (excluding tuberculosis), 31.7% were due to *Neisseria meningitidis*, 12 % to *Streptococcus pneumoniae*, 2% to Hib type b, 4.3% to other bacteria and 50% had no bacteria specified.[15]

The 10-valent pneumococcal conjugate vaccine (PCV10) was introduced in the Brazilian NIP in March 2010, scheduled at 2, 4, and 6 months of age, with a booster at 12–15 months of age. Epidemiological studies have shown direct and indirect effects of the vaccine in pneumonia hospitalizations and invasive pneumococcal disease (IPD) outcomes,[16–19] as well as reductions of carriage rates among toddlers,[14,20] and otitis-media.[21–25] There have also been studies showing the effect of PCV10 on meningitis using notification data in Brazil.[9,10] Incidence of notified pneumococcal meningitis cases has decreased in the country from 3.70 in 2007 to 1.84/100,000 in 2012, and mortality from 1.30 to 0.40/100,000, with the highest impact in the 6–11 month age group.[10]

The meningococcal C conjugate vaccine (MCC) was introduced in the Brazilian NIP in November 2010, scheduled at three and five months, with a booster dose at 12–15 months of age and no catch-up for older age groups.[26] In 2009 and 2010, notification rates of invasive meningococcal disease (IMD) were as high as 7.0/100,000 for children under two years old.[15] A virulent clonal complex (CC103) has been identified as a prevalent genotype, responsible for outbreaks and epidemics in the country.[27–30] In an early impact study performed two years after vaccine

CONTACT Prof. Ana Lucia Andrade, MD alssandrade@gmail.com Department of Community Health Institute of Tropical Pathology and Public Health, Federal University of Goias, Rua 235, s/n, Setor Universitario, Goiania, Goias, CEP 74605-050, Brazil.

Table 1. Numbers and rates of meningitis deaths, by year and age group. Brazil, 2005–2015.

	Pre-vaccination period						Transition period			Post-vaccination period				
Age-groups	2005	2006	2007	2008	2009	Mean	2010	2011	Mean	2012	2013	2014	2015	Mean
0–23 months														
Number	423	412	349	337	317	367.6	283	180	231.5	186	163	156	146	162.8
Rate[a]	7.80	7.73	6.65	6.53	6.24	6.99	5.67	3.66	4.67	3.85	3.43	3.34	3.17	3.45
2–4 years														
Number	146	126	95	113	114	118.8	104	80	92.0	69	52	39	52	52.8
Rate[a]	1.73	1.52	1.17	1.41	1.45	1.46	1.34	1.05	1.20	0.92	0.71	0.54	0.72	0.72

[a]rates per 100,000 population.

introduction, a decrease of 50% was observed in meningococcal notification rates for vaccinated children irrespective of serogroup.[31] A time-series analysis study performed with a combination of notification and laboratory IMD data up to 2014 reported decreases of 67.2%, 92% and 64.6% for the age groups of under 12 months, 12–23 months and 2 4 years of age, respectively.[32] Another study using notification data corroborated these findings showing reduction in IMD rates of 65.2% for children under one year of age and of 46.9% for children aged 1–4 years.[33] No studies have yet been carried out in the country to measure the effect of the MCC vaccine on mortality outcomes.

Since PCV10 and MCC vaccines are important public-health interventions that have been particularly implemented aiming to prevent deaths,[5,34] and since not many meningitis deaths in our country have had their etiological agents identified and/or officially notified, we thought it was important to measure the impact of these vaccines on the overall burden of meningitis mortality, i.e. not only on the subset of deaths for which the causative agents had been identified. As the two vaccines were introduced with a time span of less than a year and time-series studies require the availability of data for sufficient periods of time after vaccine introduction,[34] we had to measure their combined impact on the prevention of meningitis deaths, and for that we performed an interrupted time-series analysis using data reported to the National Mortality Information System (SIM) from 2005 to 2015 for children under five years of age.

Results

In Brazil, there were 3,941 bacterial meningitis deaths during the study period: 2,432 in the pre-vaccination (2005 to 2009), 647 in the transition period (2010 and 2011) and 862 in the post-vaccination period (2012 to 2015). Table 1 shows the annual numbers and rates for each of the two study age groups along the study period.

Out of the 2,432 meningitis deaths that occurred in the pre-vaccination period, the distribution of International Classification of Diseases - tenth revision (ICD-10) codes was: 761 (31.3%) = G00.9 – Bacterial meningitis, unspecified; 511 (21%) = G03.9 – Meningitis, unspecified; 481 (19.8%) = A39.4 – Meningococcemia, unspecified; 282 (11.6%) = G00.1 – Pneumococcal meningitis, 205 (8.4)% = A39.0 – Meningococcal meningitis, 191 (7.9%) = A39.2 – Acute meningococcemia, and 1 (<0.1%) = A39.3 – Chronic meningococcemia. There was a clear preference for the use of the most unspecified codes. Table 2 shows the distribution of ICD-10 codes by year, along the whole study period.

Table 3 shows, for each age group, the estimates obtained with the time-series analysis. The "immediate effect" refers to the percentage of change in rates right after the transition period, defined as from January 2010 to December 2011. There was a decrease in the meningitis death rates that happened concomitantly to an increase of a smaller magnitude in the comparison death rates. Even though these changes *per se* were not statistically significant for the age group of 2–4 years (p-value=0.217), for the age group of 0–23 moths there was a decrease of 25.7% in the meningitis death rates (p-value=0.007) and, for both the age groups, the relative changes were statistically significant. But the "immediate effect" is just a snapshot of what happened right after the transition period, so that it is also important to consider if there were changes in the trends of the death rates and if they were differential for meningitis and for the other diseases. The "trend without vaccination effect" and "trend with vaccination effect" refer to annual percentage of change in rates estimated respectively without and with the vaccination effect. For the age group

Table 2. Distribution of meningitis deaths – ICD-10 codes, by year. Brazil, 2005-2015.

	Pre-vaccination period					Transition period		Post-vaccination period				
Codes[a]	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	Total
A39.0	52	42	30	45	36	41	29	28	23	11	19	356
A39.2	41	48	29	36	37	39	18	16	15	13	15	307
A39.3	0	0	0	1	0	1	0	0	0	0	0	2
A39.4	125	83	88	91	94	89	42	47	38	37	28	762
G00.1	50	65	60	51	56	58	29	22	27	26	15	459
G00.9	185	179	146	128	123	80	78	69	60	58	69	1,175
G03.9	116	121	91	98	85	79	64	73	52	50	51	880
Total	569	538	444	450	431	387	260	255	215	195	197	3,941

[a]A39.0 = Meningococcal meningitis, A39.2 = Acute meningococcemia, A39.3 = Chronic meningococcemia, A39.4 = Meningococcemia, unspecified, G00.1 = Pneumococcal meningitis, G00.9 = Bacterial meningitis, unspecified and G03.9 = Meningitis, unspecified.

Table 3. Time-series model estimates of the impact of PCV10 and meningococcal C vaccination on meningitis deaths, by year and age group. Brazil 2005-2015.

	Meningitis			Comparison group[a]			Relative change	
Outcomes	Estimate	95% CI	p	Estimate	95% CI	p	Estimate	p
0–23 months								
Immediate effect[b]	−25.7%	−39.8%; −8.3%	0.007	4.9%	2.0%; 7.9%	0.001	−29.2%	<0.001
Trend without vaccination effect[c]	−5.8%	−8.7%; −2.8%	<0.001	−2.5%	−3.0%; −2.1%	<0.001	−3.4%	0.008
Trend with vaccination effect[d]	−6.7%	−12.6%; −0.5%	0.036	1.1%	0.4%; 1.8%	0.003	−7.7%	0.004
Comparison of pre-post trends			0.790			<0.001		
2–4 years								
Immediate effect[b]	−23.9%	−50.6%; 17.1%	0.217	4.9%	−4.1%; 14.9%	0.299	−27.5%	0.038
Trend without vaccination effect[c]	−4.7%	−10.7%; 1.7%	0.147	−1.6%	−3.1%; −0.1%	0.043	−3.2%	0.085
Trend with vaccination effect[d]	−10.4%	−21.7%; 2.6%	0.112	−3.5%	−5.7%; −1.2%	0.003	−7.1%	0.073
Comparison of pre-post trends			0.419			0.163		

[a]deaths due to all causes except respiratory, neurological, external and ill-defined conditions
[b]impact on the rates of meningitis death right after the transition period (January 2010 to December 2011)
[c]annual trend during the pre-vaccination period
[d]annual trend during the post-vaccination period

of 0–23 months, there were decreasing trends of meningitis death rates (−5.8%), which magnitude increased with vaccination (−6.7%), even though the difference in between the two trends was not statistically significant ("comparison of pre-post trends" – p-value=0.790). For the age group of 2–4 years, there were also decreasing trends of meningitis death rates (−4.7%), which magnitude increased with vaccination (−10.4%), but neither the pre- and post-trends or the difference in between them reached statistical significance (p-value = 0.419).

As for the trends of the comparison death rates, for the age group of 0–23 months, there were decreasing trends (−2.5%), which reverted to slightly increasing trends with the vaccination (1.1%), and the difference in between the two trends was statistically significant (p-value<=0.001). Trends of the comparison death rates with and without vaccination effect were different from the corresponding trends of the meningitis death rates (p-values = 0.008 and 0.004, respectively). For the age group of 2–4 years, there were decreasing trends of the comparison death rates (−1.6%), which increased in magnitude with vaccination (−3.5%), even though the difference in between the trends was not statistically significant (p-value=0.163). The differences between the pre and post trends of the comparison and the meningitis death rates did not reach statistical significance (p-values = 0.085 and 0.073, respectively). (Table 3)

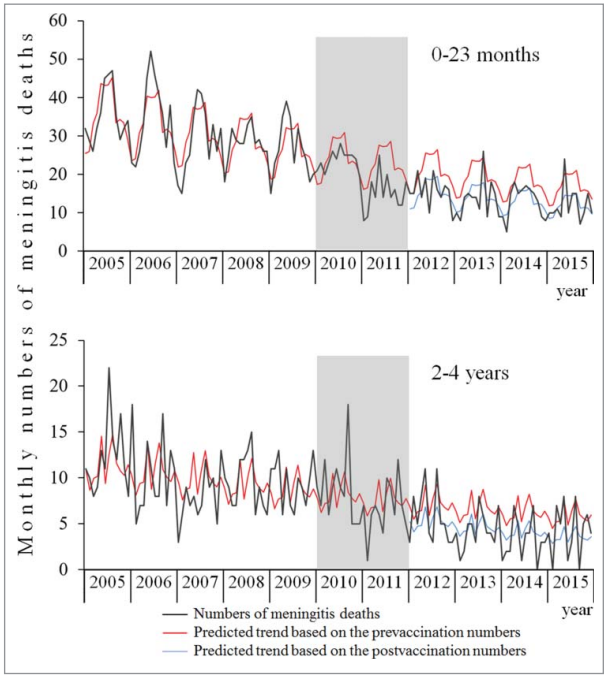

Figure 1. Monthly numbers of deaths for meningitis over the study period for each age group. Brazil 2005-2015. Gray bars represent the year of the introduction of PCV10 and meningococcal C vaccination (year 2010) and the transition period (year 2011), which were excluded from the time-series analysis.

Figure 1 shows, for each age group, monthly numbers of meningitis deaths over the study period. The black line indicates the observed numbers, the red line indicates the predicted numbers based on pre-vaccination data and the blue line indicates the predicted numbers based on pre- and post-vaccination data. Importantly, there is a small but significant gap in between predicted numbers based on pre- and post-vaccination trends, which does not seem to widen or to shrink over the post-vaccination years, for both age groups. The corresponding trends for the comparison deaths is shown in Figure 2.

Considering the predicted number of 1,199 meningitis deaths for the post-vaccination period, we estimated that a total of 337 meningitis deaths were averted in Brazil except Bahia for individuals aged less than 5 years (Table 4).

Discussion

The combined introduction of PCV10 and MCC vaccines in the childhood immunization program in Brazil was associated with a significant nationwide decline in meningitis deaths among children younger than 5 years of age. The combined effect of the introduction of the two vaccines was perceived immediately after the transition period, and was sustained throughout the post-vaccination period. These results add strong evidence in support of investments in these vaccines by low and middle-income countries.

The combined effect of these vaccines on meningitis deaths as assessed using mortality databases and ICD codes has not been measured in other studies, preventing strict comparisons of our results. However, our results are consistent with those from Grando and colleagues that compared the pre and post-vaccination periods using data from the Brazilian national notification system and found reductions in pneumococcal

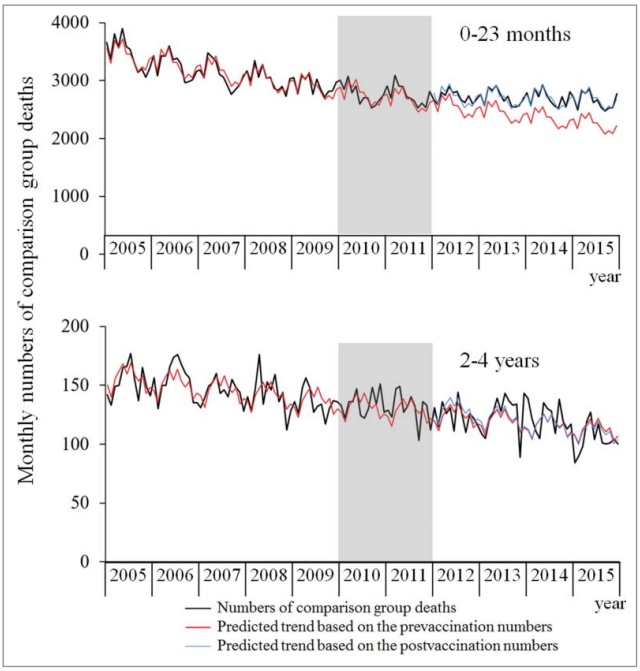

Figure 2. Monthly numbers of deaths for the comparison group over the study period for each age group. Gray bars represent the year of the introduction of PCV10 and meningococcal C vaccination (year 2010) and the transition period (year 2011), which were excluded from the time-series analysis.

meningitis deaths varying from 65.1% to 56.8% and 55.4% for children under 1 year, from 1 to 2 years and from 2 to 3 years of age.[10] Hirose and colleagues, using similar data from Paraná state in Brazil, found a reduction of 75.5% for children under 2 years of age.[9]

An evaluation of the impact of both pneumococcal seven-valent conjugate vaccine and the quadrivalent meningococcal conjugate vaccine on meningitis mortality was also conducted in USA. A population-based observational was performed by Castelblanco and colleagues (2014), who used data from hospital discharges on bacterial meningitis from 1997 to 2010, based on ICD coding across all hospitals in the USA within the HealthCare Cost Utilization Project network.[3] They found that mortality due to pneumococcal meningitis decreased with a risk ratio of 0,57 in between the pre- and post-PCV7 vaccination introduction, but called attention to the fact that these results were temporally associated with changes in the clinical management of such cases, as the addition of adjunctive dexamethasone to antibiotic treatment in bacterial meningitis became routine practice in 2004, after it was endorsed by the Infectious Diseases Society of America guidelines.

Table 4. Number of observed, predicted and averted number of meningitis deaths in the post-vaccination period[b], by age group. Brazil 2005-2015.

			Averted deaths[b]	
Age groups	Observed	Predicted	median	percentiles
0–23 months	651	889	238	169; 319
2–4 years	211	310	99	56; 144

[a]from 2005 to 2009.
[b]the median averted number of deaths and the 2.5 and 97.5 percentiles were obtained after 1000 simulations of the "pre" and "post" models of the predicted monthly number of deaths for 2012-2015.

We can also compare our results with those from von Mollendorf and colleagues (2017) in South Africa, where PCV7 was introduced in April 2009 and replaced by PCV13 in June 2011. They used data from the national laboratory-based surveillance to estimate the national burden of severe pneumococcal disease. They estimated a reduction of 240 pneumococcal meningitis deaths (170-310) for children < 1 year and 70 (40-90) for children aged 1-4 years when comparing the periods from 2005-2008 (pre PCV) and 2012-2013 (post PCV). In absolute numbers, their results are very similar to ours, in spite of the differences in baseline diseases burden, including a higher burden of HIV prevalence.[8]

In a publication authored by the International Vaccine Access Center in 2017 that aimed to assess the performance, effectiveness and impact of the PCV products, evaluating the impact of PCV10 and PCV13 on mortality is considered of high priority for policy decision-makers. However, the authors point out that such studies are among the most technically difficult to conduct, not only because of the relative rarity of mortal outcomes but also because of the many other interventions that can affect the mortality rate other than vaccine introduction, and these confound the conclusions from mortality analyses.[35]

Nevertheless, we believe that the reductions in meningitis deaths observed here could be mostly attributable to the direct protection induced by the vaccines. First, we believe that there were no major concomitant public-health interventions that could have such an effect on meningitis death rates. Access to health, both to primary and to emergency care services, has been increasing as a result of dedicated governmental programs, but the increase has been gradual over the last decades.[36] We also believe it unlikely that major differences in treatment and intensive care support provided to meningitis cases have changed much during the study transition period, so suddenly and so broadly in the country.[37] There were also no important changes to the SIM or the coding of causes of deaths that we believe could have affected the assignment of the underlying causes of death of such prominently hospital-based occurrence.[38] To our knowledge there were also no disruptions to the meningitis mandatory notification system over the study period, or to the national reference laboratories responsible for the identification of the etiologic agents. In any case, in this paper we presented trends of meningitis deaths alongside those of deaths due to the comparison group of diseases, which were also taken into consideration in order to calculate the combined effect of the vaccines on meningitis deaths. By so doing, we were aiming to reduce the confounding effect of possible co-interventions on our conclusions.[39]

Secondly, we were able to find significant effects even though we used a somewhat unspecific meningitis cause of death definition. Studies using routine surveillance data, such ours, depend on the accuracy of CID coding, that is, on the extent to which these codes actually indicate the underlying cause of death. On the one hand, we may have missed meningitis deaths that were wrongly classified as other causes, like sepsis, for example. In this regard, we can affirm that throughout the study period the mortality information system used the same process to select the underlying cause of death, following international recommendations.[40] On the other hand, we most

likely included some meningitis deaths due to other etiologic agents. However, we do believe that the etiological agents targeted by the two vaccines (vaccine-specific pneumococcal serotypes and to the meningococcal serogroup C) caused many, if not most, of the meningitis deaths reported to the SIM, particularly in the pre-vaccination period. *Streptococcus pneumoniae* and *Neisseria meningitidis* were the most common bacteria reported to the Brazilian compulsory meningitis notification database in the years prior to vaccine introduction.[15] In 2008 and 2009, among invasive pneumococcal disease in the national reference laboratory database, PCV10 serotypes accounted for 58.8% of isolates with serotype information and the proportion was much higher for individuals from 2 months to under 5 years of age, 77.2%.[18] In 2010, among lab-confirmed meningococcal meningitis notifications of all ages, capsular subgroup C accounted for 61.7% of isolates.[15] Had we used only ICD-10 codes that related to pneumococcal and meningococcal deaths, higher effects could be expected, but it would be methodologically impossible to measure these effects using time-series analysis given the very low monthly rates of such reported deaths. It is worthwhile mentioning the sharp decrease in IPD pneumococcal vaccine-types in children after PCV10 introduction.[18] Similarly, Men C rates were significantly reduced in children less than 5 years old after MCC vaccination.[32,33]

Lastly, the reductions estimated in our study is not likely to be attributable to secular declines or seasonality changes, as our analysis were adjusted for these aspects.[41]

In summary, this time-series analysis provides evidence of reductions of meningitis deaths following the introduction of PCV10 and MCC vaccines in the Brazilian NIP. This finding has important global health policy implications, as the main motivation for introduction of such vaccines has been the potential to prevent deaths.

Methods

Study design and population

This is an interrupted time-series analysis study using mortality data for children under five years of age from Brazil, but excluding data from the state of Bahia. Brazil is a Latin-American middle-income country with an estimated population of 204,482,459 inhabitants in 2015.[42]

The reason for excluding the state of Bahia (15,203,934 inhabitants in 2015) from the analysis of Brazil relates to an epidemic of serogroup C meningococcal disease that occurred in 2010 in its state capital, the city of Salvador, and that prompted the local government to initiate a MCC mass vaccination campaign. This epidemic took place before the introduction of the MCC vaccination by the NIP. Rates reached 15.2 per 100,000 for children less than 12 months of age and 7.5 per 100,000 for individuals aged 10–19 years. The vaccination campaign began in February 2010 targeting all children less than 5 years of age from the state of Bahia. As meningococcal disease continued to spread among older children and teenagers in Salvador, in this city the campaign was progressively extended to individuals of 10 to 24 years of age until August of the same year.[43] As both the epidemic and its dedicated mass vaccination campaign interfere with the time-series analysis assumption that disease rates would remain the same in a population had it not been for the studied intervention, it was decided to exclude the state of Bahia from the analysis of the data. Therefore, all results will be presented using data from Brazil except Bahia state.

Data source

Information on meningitis deaths was obtained from SIM for the period of 2005 to 2015. Data are based on death certificates, which are completed by physicians. SIM has case-based data on age, sex, cause of death and residence of the deceased. Its coverage and information quality have rapidly increased over the last two decades. Coverage has been over 95% since 2000.[44] The Secretariat of Health Surveillance, Ministry of Health in Brazil, manages the system.

Case definitions

The main outcome was deaths due to meningitis, which were defined as those that had the following ICD-10 codes: A39.0 (Meningococcal meningitis), code A39.2 (Acute meningococcemia), A39.3 (Chronic meningococcemia), A39.4 (Meningococcemia, unspecified), G00.1 (Pneumococcal meningitis), G00.9 (Bacterial meningitis, unspecified), and G03.9 (Meningitis, unspecified), listed on the underlying cause of death field of the mortality records. Among patients classified as having meningococcemia (selected codes A39.2, A39.3 and A39.4), there may be some that did not have clinically apparent or laboratory confirmed meningitis, but we are assuming that most of them would have had meningitis with meningococcemia.[15] Additionally, among patients classified as having unspecified meningitis (selected codes G00.9 and G03.9), there may some that had other etiologies, but we are assuming that most of them would have had either meningococcal or pneumococcal agents. Importantly, code A87 that refers to viral meningitis was also excluded from our case definition.

The comparison outcome was defined as deaths due to all causes except respiratory, neurological, external and ill-defined conditions, assuming that their rates over time would not be much influenced by the vaccines introduction, but would otherwise be affected by the same set of causal relations as the main outcome of interest.[39] These deaths were defined as those that had all ICD-10 codes listed on the underlying cause of death field, except those under chapters VI (Disease of the Nervous System: G00-G99), X (Disease of the respiratory system: J00-J99), XVIII (Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified) and XX (External causes of morbidity: V00-Y99).

Data analysis

Two age groups were considered: 0–23 months and 2–4 years. Numbers and rates (per 100,000 population) of meningitis and comparison deaths were described by month or year and age group. Denominators were monthly or yearly population estimates obtained by exponential regression using 2000 and 2010 census data for each age group.

For the time-series analysis, the pre-vaccination period was defined from January 2005 to December 2009, the transition period from January 2010 to December 2011, and the post-vaccination period from January 2012 to December 2015. The length of these pre- and post-vaccination periods has been considered enough for accurate measurement of disease burden trends.[34] The transition period of two years represents the period when coverage rates increased from zero to over 90% for MCC vaccination and over 80% for PCV10 vaccination in the target age group. For the post-vaccination period, coverage rates ranged from 96.2%-98.2% for meningococcal vaccination and from 88.4%-94.2% for PCV10 vaccination.[45]

A quasi-Poisson generalized linear model with a logarithmic link function and an offset equal to the log of the population divided by 100,000 was fit to the monthly number of deaths due to meningitis and to the control group of diseases, for both age groups.[41,46] This model is similar to the Poisson distribution, but corrects the standard errors of the estimators for possible under and over dispersion, which were observed with the analyzed data. In this setting, the linear predictor for the mean death rate depends on the month (included as a dummy variable), an intercept and a secular trend that may change after the vaccination period. The transition period was not included in the model. The fitted model allowing for the vaccination effect is from now on called "post" and the one without the vaccination effect is called "pre". This model allows for the estimation of four outcomes: (1) the "immediate effect" which is the percentage change in rates immediately after the vaccination (i.e. right after the transition period), (2) the "trend without vaccination effect", which is the annual percentage change in rates before the vaccination and (3) the "trend with vaccination effect", which is the annual percentage change in rates after the vaccination and (4) the "comparison of pre and post trends", which is the a p-value of a test that compares the equality of these trends before and after the vaccination. As the models were fit separately for the two age groups considering deaths due to meningitis and to the control group of disease, it was also possible to compare these outcomes in between them.

The model goodness of fit was evaluated using the deviance residual and the assumptions of independence and homoscedasticity of the standardized residuals did not appear to be violated.

The estimates of each "pre" and "post" models were used to simulate 1000 time-series of the monthly number of deaths from 2012-2015, using the fitted models. Based on these simulations, for each of the age groups, the forecast of the median estimate of averted deaths of the post-vaccination period was presented with their corresponding interval, calculated using the 2.5 and the 97.5 percentiles of the simulated counts.

Data management was performed in STATA-13 (Statacorp, College Station, Texas, USA). The models were fit using the MASS library available in the R software (www.r-project.org).

Abbreviations

Hib	*Haemophilus influenzae* serotype b
ICD-10	International Classification of Diseases tenth revision
IPD	invasive pneumococcal disease
IMD	invasive meningococcal disease
MCC	meningococcal C conjugate vaccine
NIP	National Immunization Program
PCV10	10-valent pneumococcal conjugate vaccine
PCV7	7-valent pneumococcal conjugate vaccine
PCV13	13-valent pneumococcal conjugate vaccine
SIM	National Mortality Information System

Disclosure of potential conflicts of interest

ALA has received research and travel grants from GlaxoSmithKline (GSK) and Pfizer. She has also served on ad-hoc advisory boards for GSK and Pfizer. RM has received travel grant from GSK. ALB, APA and GPA declare no competing interests.

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Authors' contributions

ALB and ALA: conceived the idea of the study and contributed to the study design. RM contributed to data management. APA and GPA contributed to the statistical analysis. ALA coordinated the study. All authors contributed to the interpretation of the findings and critically revised the manuscript. All authors approved the final version of the manuscript.

Ethical approval

The 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.

ORCID

Ana Luiza Bierrenbach http://orcid.org/0000-0002-6837-0636
Ruth Minamisava http://orcid.org/0000-0001-9352-5567
Ana Lucia Andrade http://orcid.org/0000-0002-5911-5158

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