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Timeliness and risk factors associated with delay for pneumococcal conjugate 10-valent routine immunization in Brazilian children

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ABSTRACT

Background: Vaccination coverage is the usual metrics to evaluate the immunization programs performance. For the 10-valent pneumococcal conjugate (PCV10) vaccine, measuring the delay of vaccination is also important, particularly as younger children are at increased risk of disease. Routinely collected administrative data was used to assess the timeliness of PCV10 vaccination, and the factors associated with delay to receive the first and second doses, and the completion of the PCV10 3 + 1 schedule.

Methods: A population-based retrospective cohort study was conducted with children born in 2012 in Central Brazil. Children who received the PCV10 first dose in public health services were followed-up until 23 months of age. Timeliness of receiving each PCV10 dose at any given age was defined as receiving the dose within 28 days grace period from the recommended age by the National Immunization Program. Log-binomial regression models were used to examine risk factors for delays of the first dose and the completion PCV10 3 + 1 schedule.

Results: In total, 14,282 children were included in the cohort of study. Delayed vaccination occurred in 9.4%, 23.8%, 36.8% and 39.9% children for the first, second, third and the booster doses, respectively. A total of 1912 children (12.8% of the cohort) were not adequately vaccinated at the 6 months of life; 1,071 (7%) received the second dose after 6 months of age, 784 (5.4%) did not receive the second dose, and 57 (0.4%) received the first dose after six months of life.

Conclusion: A considerable delay was found in PCV10 third and booster doses. Almost 2 thousand children had not received the recommended PCV10 doses at 6 months of age. Timeliness of vaccination is an issue in Brazil although high vaccination coverages.

1. Introduction

Streptococcus pneumoniae is a major cause of serious invasive diseases, such as meningitis, bacteremia, pneumonia, and cause of mortality worldwide among children in the first 5 years of life [1].

Pneumococcal conjugate vaccines (PCV) are recommended for routine immunization in infant as a public health priority to prevent pneumococcal disease and the spread of *S. pneumoniae* within the community. Currently, two PCV, PCV10 and PCV13, are available for use in children less than 2 years old. The World Health Organization (WHO) has recommended two PCV schedules: (i) 3 priming doses (3 + 0) or (ii) 2 priming doses plus 1 booster (2 + 1) [2]. The 3 + 1 schedule has also been used in some America countries (USA, Canada, and Brazil) [3,4]. The first dose can be administered as early as 6 weeks of age [2].

In 2010, Brazil introduced the PCV10 in the National Immunization Program (NIP) during March to September at 3 + 1 schedule [4], and since 2011 the rates of PCV10 vaccination coverage for 3-dose PCV10 primary series have been kept higher than 81% [5]. After the introduction of PCV10 vaccination in the NIP of Brazil, rates of hospitalization to pneumonia, invasive pneumococcal disease (IPD), and acute otitis media significantly decreased among children aged <2 years [6–12]. PCV10 vaccination has also reduced vaccine-type pneumococcal carriage in Brazil [13,14].

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Vaccination coverage rates are the most frequently used indicators for the evaluation and monitoring of immunization program performance [15,16]. However, high vaccination coverage rates may not have a direct correlation with disease protection. Instead, timely vaccination, i.e., receiving the PCV10 schedule in an age-appropriate fashion, is critical to protect the child against pneumococcal disease in early life when the child is vulnerable to vaccine preventable diseases; measuring timely vaccination is, therefore, more informative to monitor the risk of a child acquiring a disease [15,16]. For instance, although the sustainable high rates of PCV10 vaccination coverage, the burden of pneumonia and IPD in Brazil remains high in childhood [8,11].

In Brazil, vaccination coverage rates for PCV10 have been estimated by the NIP as the number of children who receive the third dose of PCV10 during the first year of age by the population under one year of age [17]. Coverage rates for the booster dose (available since 2013 only) have been estimated as the number of children who receive a PCV10 dose during the second year of age [17]. As such, official statistics provided by the NIP comprise only aggregate data, lacking any analysis of the age of children at vaccination, i.e., estimates of the timeliness for PCV10 vaccination.

Public and private sectors provide health care in Brazil. Public health care service is provided by the Unified Health System (SUS), which offers free care with universal coverage to all the population. Health care management is decentralized, and municipalities are responsible for most primary care services [18]. It is estimated that SUS accounts for about 77% of the outpatient consultations in the country [19]. In Brazil, selected municipalities have implemented computerized databases that record all vaccination doses administered by SUS, as well as all outpatient visits to public ambulatories. While these source of data constitute a worth piece of information on vaccination, they have been poorly explored in order to ascertain the timeliness of PCV10 vaccination. The municipality of Goiania is one of the few cities in the country that has a vaccination information system, which records vaccination doses at individual-level, online, making feasible the use of such data to evaluate the history of vaccination of each child.

A household survey conducted 6–8 months after PCV10 introduction in Goiania showed that 43% and 70% of children targeted for the NIP delayed the first and third PCV10 dose, respectively [20]. Taking the opportunity of the availability of a local vaccination information system, in this study we assessed the timeliness of childhood PCV10 vaccination administered by the NIP, and the factors associated with delay to receive the first dose and to complete the 3 + 1 schedule, 3 years of vaccination start. Considering that, since 2016 Brazil has shifted the PCV10 schedule from 3 + 1 to 2 + 1 we also evaluated the delay for receiving the second dose.

2. Methods

2.1. Study design and population

This was a population-based, retrospective birth cohort study conducted with children residing in the municipality of Goiania, located in the Central-West Region of Brazil. The population of Goiania was estimated at 1,333,767 inhabitants in 2012; 35,424 (2.7%) were children younger than 2 years old [21]; infant mortality was estimated as 12.9 deaths per 1000 born alive [22]. Almost 70% of the population of Goiania has SUS as the exclusive health care provider [19].

Children born in Goiania from January to December 2012 were eligible to participate in the study. Each child was followed-up in the VAS until 23 months of age. This follow-up time was chosen because, at the time of the study, the NIP recommended that PCV10 booster doses should be administered only up to the age of 23 months [4].

2.2. Data sources

For this investigation, we used two health information systems: the Vaccination Information System (VAS) and the Brazilian Live Birth Information System (SINASC). The VAS is an online administrative system of the municipality of Goiania, which has been implemented in 2010 to report vaccine uptake administered by SUS. In 2012, the VAS covered 67 (91.8%) out of the 73 vaccination rooms in Goiania. This system records individual-level information (individual name, mother's name, date of birth and address), gender, vaccine dose, and date of the vaccine uptake.

SINASC is a nationwide database that comprises data from all live births occurring in public and private hospitals, at home, or in other health facilities. SINASC gathers epidemiological data about the newborns, the mothers, their pregnancies and deliveries [18]. We used the SINASC database to identify children born in Goiania and to recover data on potential risk factors associated with PCV10 vaccination delay. Exposure variables obtained from SINASC were child's gender, child's birthweight (grams), maternal age (years), maternal education level (categorized as high school and above and up to elementary school), and number of prenatal visits (categorized as $\geqslant 7$, 4–6, and <4). In 2012, it was estimated that 99.6% of all live births in Goiania were registered on the SINASC database [23].

2.3. PCV10 vaccination

In the municipality of Goiania, PCV10 was introduced in June 2010 with a 3-dose primary series at 2, 4 and 6 months of age followed by a booster dose at 12 months of age (3 + 1 schedule) [4]. PCV10 coverage rates for the primary series in 2012 and for the booster dose in 2013 were 91.3% and 90.2%, respectively [5].

2.4. Deterministic record linkage between VAS and SINASC

Record linkage is a methodology used to identify whether separate records pertain to the same individual. In Brazil, no unique identifier number is available for each individual so as to facilitate the search of his/her name in different databases. We performed a deterministic linkage between VAS and SINASC records to identify children who were born in 2012 in Goiania and resided in the city. In the deterministic logic, the agreement on one or multiple given identifiers (patient's name, name of patient's mother, date of birth, address, telephone, etc.), assessed in a single step or in multiple steps, establishes the match status of the records. Identifiers may be fragmented by means of substringing or Soundex transformations. In the multi-step strategy, which was the one used in this analysis, records are combined in a series of progressively less restrictive steps, and pairs of records that fail to meet the first round of matching criteria are passed to a subsequent rounds of matching criteria for further comparison. Similar linkage algorithms have been validated in other studies that used data from Brazilian health information systems [24–26].

All records of the VAS were used in the linkage procedures, irrespective of the city of residence. Children were considered to use the public health system if they had been administered with at least one vaccine of the NIP. After the deterministic linkage procedures, we also conducted a manual review in search of eventual unmatched pairs. Matched children were considered residents of Goiania. Among those, there were some who did not have a record in the VAS for the first PCV10 dose. These children probably received this first dose and other vaccine doses in the private sector. These children were excluded from the study.

2.5. Definition of timely, delayed vaccination and completion of 3+1 schedule

Only valid doses were counted for ascertaining delay of PCV10 vaccination. In order to define what constituted "valid doses" we took into account NIP and WHO recommendations concerning the minimum acceptable age to receive each PCV10 dose: 6 weeks for the first dose, at least 4 weeks for the second and third doses, and at least 6 months between third and booster dose [2,4].

The NIP schedule recommends that PCV10 should be administered at the ages of 2 months (equal to 61 days of life in the study), 4 months (122 days), 6 months (183 days) and 12 months (365 days). Timely vaccinations were defined as receipt of a PCV10 dose within 28 days grace period from the recommended age [27–29]. Hence, a dose was defined as delayed if it was received 29 days after the recommended age. Specifically for the booster dose, we extended the grace period to 31 days in addition to the 28 days defined above, as proposed by others [30]. As such, the cut-offs that established if a vaccination dose was delayed were 90 days for the first dose, 151 days for the second dose, 212 for the third dose, and 425 days for the booster dose. Timely completion of PCV10 3 + 1 schedule was defined only for children who completed the full PCV10 series, i.e. those who completed the 3 + 1 schedule under the age of 425 days. Conversely, those who did not complete the 3 + 1 schedule before 425 days were considered as delayed.

2.6. Ethical approval

This study was approved by the Ethical Committee from the Federal University of Goiás (protocol #1.374.719).

2.7. Data analysis

We used birth and vaccination dates to determine the age of a child at vaccination. We assessed the median of age (in days), full range, and interquartile range (IQR) for each PCV10 dose. A few children had only the first and third dose recorded at VAS, but the second dose was missing. For these cases, we imputed the age of the second dose considering as if it had been administered exactly in between the first and third PCV10 dose.

Timely vaccination was calculated per vaccinated children receiving vaccinations within the grace period, and timely completion of the PCV10 3 + 1 schedule were calculated per vaccinated children receiving the completed full PCV10 series up to 425 days of life.

The delay for the two outcomes (first dose and completion of the 3 + 1 schedule) was dichotomized as a yes/no variable. Log-binomial regression models were used in simple and multiple regression analysis in order to derive risk ratios (RR) for the two outcomes studied. Multiple regression models were used to adjust for possible confounders and test for interactions. Stepwise backward procedures were used to remove exposure variables with P-values $\geqslant 0.2$ in Wald tests one by one from the models. The remaining variables were then successively removed based on their confounding effect and their contribution to the models. Variables whose removal from the model caused substantial changes (>10%) in the RRs were retained, as were variables whose removal incurred in significant likelihood ratio tests (P-values < 0.05). Likelihood ratio test was also used to test for interactions. The Akaike and Bayesian information criterion were used to determine the best-fit models. P-values < 0.05 were considered statistically significant for all analyses. All analyses were performed in Stata-13 software (Stata Corporation, Texas, USA).

Table 1
Characteristics of the cohort of 14,282 children born in 2012 in Goiania, Brazil.

Characteristics	N	%
Child		
Males[a]	7,174	50.2
Median birth weight (IQR), g	3195	(2900–3480)
Mother		
Median age (IQR), yrs	27	(22–31)
High school education or above[b]	13,568	97.8
$\geqslant$7 prenatal visits[c]	10,087	70.8

Abbreviations: IQR, interquartile range; g, grams; yrs, years.
Missing values.
[a] N = 1.
[b] N = 436.
[c] N = 44.

3. Results

3.1. Record linkage between VAS and SINASC

A total of 26,085 records were identified in the VAS, representing children born in 2012 and who had received at least one dose of any vaccine in the health facilities from SUS, regardless of the city of residence. In the SINASC database, 21,359 records were identified, representing children born in 2012 and who resided in Goiania. After excluding unmatched records from VAS (n = 8913) and from SINASC (n = 2601), 615 twins, and 3861 matched pairs with missing PCV10 first dose, we arrived at 14,282 matched pairs available for the analysis, representing children who were born and resided in Goiania and had received the PCV10 first dose.

3.2. Descriptive analysis

Characteristics of the cohort of 14,282 children are presented in Table 1. The cohort was equally distributed by sex. Overall, 75% of the children had birthweight $\geqslant$2900 g. Twenty-five percent of the mothers had $\leqslant$22 years of age. Almost all mothers had high school education or above and the majority had seven or more prenatal visits.

Table 2 shows the exact day of life that the children received the first, second, third and booster doses for the children with delay vaccination, and for timely vaccinated children. The proportion of children with delay for the first, second, third and the booster dose

Table 2
Age of the administration of each PCV10 dose in the cohort of children born in 2012 in Goiânia, Brazil.

Vaccine dose	N	Children vaccinated with delay			Children vaccinated on time		
		%	Median age[a] (IQR)	Full range[b]	%	Median age[a] (IQR)	Full range[b]
1st	14,282	9.4	99 (93;117)	90–351	90.6	64 (62;68)	42–89
2nd	13,498	23.8	168 (157.5;188.5)	151–362	76.2	128 (124;134)	87–150.5
3rd	12,151	36.8	231 (219;255)	212–364	63.2	192 (188;199)	127–210
Booster	10,469	39.9	440 (411;482)	425–730	60.1	377 (371;385)	365–393

Abbreviations: PCV10, 10-valent pneumococcal conjugate vaccine; IQR, interquartile range.
[a] Age in days.
[b] Minimum and maximum age in days.

was 9.4%, 23.8%, 36.8%, and 39.9%, respectively. Conversely, the proportion of children timely vaccinated was 90.6%, 76.2%, 63.2% and 60.1% for the first, second, third and booster doses, respectively.

A total of 1912 children (12.8% of the cohort) were not adequately vaccinated at the 6 months of life, since 1071 (7%) received the second dose after 6 months of age, 784 (5.4%) did not receive the second dose, and 57 (0.4%) received the first dose after six months of life. Among 14,282 children of the birth cohort, 50% of them received the booster before the age of 14 months.

Table 3 shows that among the 14,282 children who had received the first PCV10 dose, 66.8% (9547/14,282) completed the 3 + 1 schedule up to 23 months of age, regardless whether they received the vaccine on time or with delay. From these, 60.8% (5801/9547) completed it on time. Overall, 85.0% (12,147/14,282) of children received the 3-dose PCV10 primary series, 63.2% (7677/12,147) on time.

3.3. Factors associated with delay for the first dose and completion of PCV10 3+1 schedule

In multiple regression analysis, children who had a higher birthweight had a statistically significant lower risk to receive the first PCV10 dose with delay, but the RR was 0.99 only (Table 4). Mothers who had low education level and had less than seven prenatal visits were more likely to delay the first dose.

Among children who completed the PCV10 3 + 1 schedule, 39.2% (3746/9547) completed with delay. Table 5 shows the unadjusted analysis for risk factors associated with delay for the completion of PCV10 3 + 1 schedule. In the adjusted analysis, there was a positive interaction in between mothers' educational level and number of prenatal visits (p = 0.011), in which the mothers' lower educational level potentiated the effect of having had fewer prenatal visits in increasing the risk of non-completion of the 3 + 1 schedule (Table 6). Birthweight was not associated with delay for the completion of the 3 + 1 schedule.

Table 3
Number and proportion of PCV10 schedule received by 14,282 children. Goiânia, Brazil.

Received doses	n	%
3 + 1	9,547	66.9
3 + 0	2,600	18.2
2 + 1	715	5.0
1 + 0	577	4.0
1 + 1	207	1.4
2 + 0	636	4.5
Total	14,282	100.0

Abbreviation: PCV10, 10-valent pneumococcal conjugate vaccine.

4. Discussion

In this investigation, we found that children born and residing in the city of Goiania in Brazil had a considerable delay in receiving the third dose of PCV10 (36.8%) and the booster dose (39.9%). In addition, we also found that one third of children did not complete the 3 + 1 schedule during their first two years of life. Similar results were observed in the National survey on vaccination coverage carried out in 2007 which showed that 71.5% (95%CI: 67–75%) of children residing in Goiania completed the DTP fourth dose at 18 months of age [31].

Population-based studies on child with IPD and pneumonia conducted in Latin American countries showed that the highest burden of disease occurred from 7 to 12 months of age [32–34]. Studies have shown that two primary series and a booster is as effective as 3 + 1 and 3 + 0 schedules to provide good immunogenic response for preventing IPD and pneumonia in children [2,35]. In this sense, we found that almost 2 thousand children had not received the recommended number of vaccine doses at 6 months of age even though PCV10 were available for free and without discontinuity during the study period. These findings are a matter of concern taking into account that Brazil has recently adopted the 2 + 1 PCV10 schedule [36], and also that the higher incidence of IPD is in the second half of the first year of life.

The delay in receiving the PCV10 booster found in our study was higher than what has been observed in other countries where PCV has been introduced in routine pediatric immunization and sustainable high vaccination coverage have also been achieved [37,38]. In Norway, where a 2 + 1 schedule has been adopted, a study conducted with data from the National Immunization registry found that 21.9% of children received the booster PCV7/13 dose >31 days of the recommended age for vaccination [37]. In France, where PCV13 has been used in a 2 + 1 schedule, in a study using data from the computerized registries of several pediatricians, only 4% of children had delayed the booster dose, having defined a booster dose received at more than 2 months after the recommended age as being delayed [38]. Different definitions of delay of PCV vaccination, besides the existence of few similar pub-

Table 4
Unadjusted and adjusted analyses for risk factors associated with delay for the first PCV10 dose in a cohort of 14,282 children born in 2012 in Goiânia, Brazil.

Variables	Delay for the first PCV10 dose[a]				Unadjusted			Adjusted		
	Yes		No		RR	95%CI	P-value	RR	95%CI	P-value
	No.	%	No.	%						
Child's birth weight median (IQR), g	3150 (2800–3430)		3200 (2910–3485)		0.99	0.99–0.99	0.000	0.99	0.99–0.99	0.000
Mother's age median (IQR), yrs	26 (22–31)		27 (22–31)		0.99	0.98–1.00	0.252			
Mother's education level[b]										
High school or above	1,303	96.6	12,265	98.1	1.00			1.00		
Up to elementary school	46	3.4	232	1.8	1.74	1.32–2.28	0.000	1.57	1.19–2.05	0.001
Number of prenatal visits[c]										
⩾7	840	60.6	9,247	72.0	1.00			1.00		
4–6	399	28.7	2,728	21.2	1.50	1.34–1.69	0.000	1.45	1.29–1.63	0.000
<4	148	10.7	876	6.8	1.72	1.45–2.03	0.000	1.66	1.40–1.97	0.000

Abbreviations: PCV10, 10-valent pneumococcal conjugate vaccine; IQR, interquartile range; g, grams; yrs, years; RR, risk ratio; CI, confidence interval.
[a] The cut-off for delay was 90 days of life.
[b] Missing values, yes: N = 39; no: N = 397.
[c] Missing values, yes: N = 2; no: N = 42.

Table 5
Unadjusted analyses for risk factors associated with delay for the completion of PCV10 3 + 1 schedule in a cohort of 9,547 children. Goiânia, Brazil.

Variables	Completion for the 3 + 1 schedule with delay[a]				Unadjusted		
	Yes		No		RR	95%CI	P-value
	No.	%	No.	%			
Child's birth weight median (IQR), g	3200 (2920–3500)		3175 (2900–3475)		1.00	0.99–1.00	0.055
Mother's age median (IQR), yrs	27 (22–31)		27 (22–32)		0.99	0.99–1.00	0.518
Mother's education level[b]							
High school or above	3,563	97.9	5,515	98.4	1.00		
Up to elementary school	77	2.1	90	1.6	1.17	0.99–1.39	0.072
Number of prenatal visits[c]							
⩾7	2,675	71.6	4,311	74.6			
4–6	787	21.0	1,125	19.5	1.07	1.01–1.14	0.023
<4	276	7.4	344	5.9	1.16	1.06–1.28	0.002

Abbreviations: PCV10, 10-valent pneumococcal conjugate vaccine; IQR, interquartile range; g, grams; yrs, years; RR, risk ratio; CI, confidence interval.
[a] The cut-off for delay was 425 days of life.
[b] Missing values, yes: N = 106; no: N = 196.
[c] Missing values, yes: N = 8; no: N = 21.

Table 6
Adjusted analyses for risk factors associated with delay for the completion of PCV10 3 + 1 schedule in a cohort of 9,547 children. Goiânia, Brazil.

Variables	Adjusted		
	RR	95%CI	P-value
Child's birth weight median, g	1.00	1.00–1.00	0.057
Mother's education level * Number of prenatal visits[a]			
High school or above			
⩾7	1.00		
4–6	1.06	0.99–1.13	0.071
<4	1.14	1.03–1.25	0.012
Up to elementary school			
⩾7	0.90	0.69–1.18	0.456
4–6	1.59	1.27–2.00	0.000
<4	1.66	1.21–2.29	0.002

Abbreviations: PCV10, 10-valent pneumococcal conjugate vaccine; g, grams; RR, risk ratio; CI, confidence interval.
[a] Interaction between mother's education level and number of prenatal visits (⩾ 7, 4–6, < 4).

lications aimed at studying timeliness of vaccination for this vaccine prevent further comparisons of our findings [30,37].

The definition of delay in PCV vaccination has been the matter of some debate [30]. In a recent survey done in France with many experts in child vaccination, over 70% of pediatricians considered that for PCV vaccination, delayed second and booster doses were those administered after 15 days and 2 months of their respective recommended ages [30]. The grace period for the booster dose used in our investigation (up to 59 days) was higher than that used in the Norwegian study (up to 31 days) [37], however it was similar to that used in the French study [38]. The adoption of different PCV schedules across countries is an additional impediment when comparing studies on delay in PCV vaccination. Studies conducted in different countries with several vaccines suggest that the higher the number of doses, the higher the vaccination delays [15,39]. Since Brazil has just switched from 3 + 1 to 2 + 1 schedule, further studies should be conducted on delay in PCV10 vaccination [36].

There are scarce data from both developing and developed countries on the relationship of prenatal visits and childhood vaccination [40,41]. On the other hand, low birthweight and the caregiver education are commonly established as determinants of child timely vaccination in a number of reports for several immunobiologicals [39,42–44]. The present investigation shows an inverse relationship between prenatal visits and delay of the first dose. As regards the timely completion of the 3 + 1 schedule, prenatal visits played a stronger role for mothers with lower educational level. A study in India observed that higher number of prenatal visits increased the chance of a child being immunized against tuberculosis, diphtheria, pertussis, tetanus, polio, and measles [40]. A study conducted in the US observed that incorporating information on the importance of the immunization during the prenatal visits reduced delay in childhood vaccination [41].

We believe that in Brazil both the number of prenatal visits and the mothers' education levels are proxies for socio economic status and overall access to health care. Health system strengthening to ensure easy access to both prenatal and pediatric care are needed to families with poor socio economic levels together with more targeted information and communication strategies – in which pediatricians and other staff working on immunization centers certainly play a major role – so as to ensure the timely administration of vaccines.

This study has some limitations. First, our findings represent children users of SUS only and may not reflect the entire population of children of less than 2 years of age. Although SUS covers about 70% of the total population of Goiania, the delay in PCV10 vaccination might still be overestimated since PCV10 vaccination coverage and compliance with 3-dose PCV10 primary series is higher in private health insurance [20]. Second, the accuracy of the VAS data in representing all vaccination doses administered by SUS has never been previously determined. However, such dataset is indeed used as an administrative tool by the NIP, from where statistics are officially derived. Third, the VAS includes few individual-level variables. By performing the record linkage in between the database, we were able to retrieve from the live-birth database some variables potentially associated with delay in vaccination, which were not available from the VAS database, therefore improving the study of delay determinants. The lack of other socioeconomic variables hampered the detection of some determinants of delay in vaccination that have been identified for other vaccines in previous reports, such as BCG, DTP, and measles [15,45].

In summary, using an administrative online vaccination registry at population level we were able to measure the delay in PCV10 vaccination in Central Brazil. Our study shows that timeliness of vaccination is an issue in Brazil, which historically has high vaccination coverages [5]. The information provided by this investigation point to the need to monitor the delay in vaccination even in areas with high rates of PCV10 vaccination coverage.

Conflict of interest

ALA has received research grant from GlaxoSmithKline (GSK) and also grants from Pfizer and GSK for participation at meetings.

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Author contributions

ALS contributed to the study concept and design, participated of the analysis and interpretation of data, and carried out the initial draft of the manuscript. RM contributed to the concept and design of the manuscript, and made substantial contributions on analysis and interpretation of data. ALB participated of study design and data analysis, and provided critical reviews of the content of the manuscript. GMP enabled database preparation, and contributed to analysis and interpretation of data. GCP participated of database preparation, as well as data analysis and interpretation of the results. ETA contributed to the study design, interpretation of the results, and provided a critical revision of the manuscript. ALA prompted the initial concept and design of the manuscript, participated of data analysis and interpretation, and revised it critically for important intellectual content before submission. All authors approved the final version of the manuscript as submitted and agreed to be accountable for all aspects of the work.

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