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Long-term surveillance of invasive pneumococcal disease: The impact of 10-valent pneumococcal conjugate vaccine in the metropolitan region of Salvador, Brazil

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CDC disclaimer

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CRediT authorship contribution statement

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2023.12.055.

Abstract

Background: In 2010, Brazil introduced the ten-valent pneumococcal conjugate vaccine (PCV10) in the national infant immunization program. Limited data on the long-term impact of PCV10 are available from lower-middle-income settings. We examined invasive pneumococcal disease (IPD) in Salvador, Bahia, over 11 years.

Methods: Prospective laboratory-based surveillance for IPD was carried out in 9 hospitals in the metropolitan region of Salvador from 2008 to 2018. IPD was defined as *Streptococcus pneumoniae* cultured from a normally sterile site. Serotype was determined by multiplex polymerase chain reaction and/or Quellung reaction. Incidence rates per 100,000 inhabitants were calculated for overall, vaccine-type, and non-vaccine-type IPD using census data as the denominator. Incidence rate ratios (IRRs) were calculated to compare rates during the early (2010–2012), intermediate (2013–2015), and late (2016–2018) post-PCV10 periods in comparison to the pre-PCV10 period (2008–2009).

Results: Pre-PCV10, overall IPD incidence among all ages was 2.48/100,000. After PCV10 introduction, incidence initially increased (early post-PCV10 IRR 3.80, 95% CI 1.18–1.99) and then declined to 0.38/100,000 late post-PCV10 (IRR 0.15; 95% CI 0.09–0.26). The greatest reductions in the late post-PCV10 period were observed in children aged ≤2 years, with no cases (IRR not calculated) and those ≥60 years (IRR 0.11, 95% CI 0.03–0.48). Late post-PCV10, significant reductions were observed for both PCV10 serotypes (IRR 0.02; 95% CI 0.0–0.15) and non-PCV10 serotypes (IRR 0.27; 95%CI 0.14–0.53). Non-PCV10 serotypes 15B, 12F, 3, 17F, and 19A became predominant late post-PCV10 without a significant increase in serotype-specific IPD incidence compared to pre-PCV10.

Conclusion: Significant declines in IPD, including among adults not eligible for vaccination, suggest direct and indirect protection up to nine years after PCV10 introduction, without evidence of significant replacement disease. Continued surveillance is needed to monitor changes in non-vaccine serotypes and inform decisions about introducing higher valent PCVs.

Keywords

Invasive pneumococcal disease; Pneumococcal conjugate vaccine; *Streptococcus pneumoniae* ; 10-valent pneumococcal conjugate vaccine

1. Introduction

Streptococcus pneumoniae frequently colonizes the human nasopharynx and may spread in the respiratory tract, causing non-invasive pneumococcal disease, or through the bloodstream to other sites, leading to invasive pneumococcal disease (IPD) such as meningitis, septicemia, or bacteremic pneumonia [1]. In Brazil, invasive pneumococcal disease (IPD) represents an important public health problem, mainly affecting children and the elderly [2]. In the period before the introduction of the 10-valent pneumococcal vaccine, 2007–2009, the average incidence rate of pneumococcal meningitis among children under five years of age was 2.3 cases/100,000 inhabitants [3].

The serotypes that historically most frequently caused pediatric IPD globally in the 1990s (4, 6B, 9 V, 14, 18C, 19F, and 23F) were included in the seven-valent conjugate vaccine (PCV7, Prevnar, Pfizer) and licensed in 2000 [4]. Higher-valent PCVs became available in 2009, including 10-valent (PCV10, Synflorix, GSK) and 13-valent (PCV13, Prevenar, Pfizer) [5]. PCV10 conjugated to a non-typeable *Haemophilus influenzae* protein D conjugate vaccine contains the PCV7 serotypes, as well as serotypes 1, 5, and 7F. PCV13 contains all PCV10 serotypes, plus serotypes 3, 6A, and 19A [6]. A 10-valent vaccine PNEUMOSIL® (PCV10-SII) from Serum Institute of India with slightly different serotypes from GSK-PCV10 received WHO prequalification in 2019 [7]. More recently, 15-valent (PCV15) (Merck Sharp & Dohme Corp.) and 20-valent vaccines (PCV20, Wyeth Pharmaceuticals LLC, a subsidiary of Pfizer Inc.) have been licensed by the U.S. Food and Drug Administration [8].

PCVs are now widely in use worldwide, including most low-income countries [9]. Studies in various countries have consistently demonstrated a dramatic decline in vaccine-type IPD following PCV introduction, through both direct and indirect effects [10–12]. This reduction was partially offset in some countries using 7-valent PCV by increases in IPD due to serotype 19A (which is included in PCV13, and in all newly formulated PCVs) [13]. Continuous monitoring of PCV impact on vaccine-type and non-vaccine-type IPD is important for quantifying the benefits of PCV and informing vaccine policy decisions. Limited data are available on the long-term impact of PCV10 in the context of low- or middle-income countries.

The Brazilian government introduced PCV10 in March 2010 [14,15]. The initial schedule was three primary doses at ages 2, 4, and 6 months plus a booster dose at 12 to 15 months of age [15]. In addition, catch-up vaccination was offered for children between 7 and 11 months of age (two doses) plus a booster at 12–15 months of age; children between 12 and 23 months were offered a single catch-up dose and no booster. Based on evidence of vaccine impact and effectiveness from countries using 2 primary doses plus 1 booster, in 2016, the schedule was changed to 2 primary doses at 2 and 4 months, and a booster dose for children at age 12–18 months [16].

Following PCV10 introduction in Brazil, declines in vaccine-type IPD incidence ranging from 41.3% to 87.4% were observed in young children [17–19], as well as considerable indirect effects, with a 50.4% decline in vaccine-type IPD among persons aged ≥ 65 years [19]. Nevertheless, the latest published data on PCV10 impact in Brazil cover a period of up to only 5 years following the introduction of PCV10 [17–20]. Longer-term data on PCV10 impact and currently circulating strains are needed to guide decisions about new formulation and higher-valent PCVs.

2. Material and Methods

2.1. Study setting

The metropolitan region of Salvador is a large urban setting located in northeastern Brazil, and encompasses 13 municipalities, with a population size of 3.5–3.9 million inhabitants [21] with a stagnant poverty rate around 30% [22]. The health facilities in the metropolitan

region of Salvador are organized into 12 health districts with 13 Emergency Care Units (UPA) and 30 hospitals (including private and public facilities). Estimated coverage of three or more PCV10 doses among children aged 6–48 months ranged from 66.4% in 2011 to 82.9% in 2018 [23].

2.2. Pneumococcal Disease Surveillance

Laboratory-based surveillance for IPD was conducted at the Couto Maia Institute (ICOM), the Paediatric Centre Professor Hosannah de Oliveira (CPPHO) and the Cerebrospinal Fluid Laboratory (SINPEL). ICOM is the main reference hospital for infectious diseases in the metropolitan region of Salvador since 1996 [24], and CPPHO is the pediatric unit of the Federal University of Bahia Hospital. Culture of sterile samples collected from patients admitted at these facilities are processed at on-site microbiology labs. In addition, SINPEL performs cerebrospinal fluid (CSF) culture for patients admitted to seven hospitals in the metropolitan region of Salvador. Together, these nine hospitals represent more than 90% of the total IPD cases reported to the State Secretary of Health (unpublished data). IPD cases were defined by identification of pneumococcus from a normally sterile site (CSF, blood, or pleural fluid) from a patient admitted to any of the participating hospitals. Cultures were ordered at the discretion of the attending physician; standardized clinical case definitions were not used. The study team reviewed laboratory records 5 days a week to identify new culture isolations of *S. pneumoniae* among hospitalized patients. At the ICOM, a standardized data entry form was used to extract demographic and clinical information from medical records of IPD cases.

Pneumococcal isolates from all sites were sent to the Laboratory of Pathology and Molecular Biology at the Gonçalo Moniz Institute, Oswaldo Cruz Foundation (LPBM-IGM/FIOCRUZ) for confirmation and capsular serotyping. Confirmation of *S. pneumoniae* was performed using standard bacteriological techniques, including Gram stain, colony morphology on agar media with 5% of sheep blood, optochin susceptibility (5 μg Oxoid disks), and bile solubility [25].

Serotyping was performed using a previously described 8-sequential multiplex PCR method [26]. Isolates with negative or unresolved PCR serotyping results were subjected to Quellung reaction testing for capsular type definition at the U.S. Centers for Disease Control and Prevention (CDC).

2.3. Statistical analyses

Epi-Info Version 3.5.1 (CDC, Atlanta, GA) was used for data entry and statistical analysis. The pre-vaccine period was defined as the 2-year period 2008–2009, while the post-PCV10 period was divided into early (2010–2012), intermediate (2013–2015), and late (2016–2018) periods. Serotypes were classified according to the serotype content of pneumococcal vaccines: PCV10-type serotypes (1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, and 23F), PCV13 serotypes (PCV10 types plus 3, 6A, and 19A), PCV15 serotypes (PCV13 types plus 22F and 33F), PCV20 serotypes (PCV15 plus 8, 10A, 11A, 12F, and 15B), and PCV10-SII types (1, 5, 6A, 6B, 7F, 9V, 14, 19A, 19F, and 23F). All PCV10 related serotypes (e.g., 6A, 19A) were considered as non-vaccine serotypes. Overall, PCV10-type and non-PCV10-type IPD

incidence was calculated using the number of cases identified from participating hospitals as the numerator and age-stratified population estimates for the Salvador metropolitan region from the census provided by the Brazilian Institute of Geography and Statistics as the denominator [21]. The incidence of IPD was calculated for each year from 2008 through 2018. Additionally, IPD incidence rate in each of the post-PCV10 periods was compared to that of the pre-PCV10 period using incidence rate ratios (IRRs) with 95% confidence intervals (CI). Cases lacking serotype information were considered as non-vaccine serotypes.

2.4. Ethical approval

This study was approved by the National Committee for Ethics in Research (CONEP), Brazilian Ministry of Health (no. 1.667.451), the Institutional Review Board of IGM-FIOCRUZ. This activity was reviewed by CDC and was conducted consistent with applicable federal law and CDC policy[§] ([§]See e.g., 45C.F.R. part 46, 21C.F.R. part 56; 42 U.S.C. §241 (d); 5 U.S.C. §552a; 44 U.S.C. §3501 et seq). A waiver of informed consent was granted by the institutional review board because the research involves only minimal risk.

3. Results

From 2008 through 2018, a total of 299 cases of IPD were identified, including 195 from ICOM, 13 from CPPHO, and 91 from SINPEL. Overall, 116 (38.8%) were isolated from blood and 183 (61.2%) from CSF.

The annual incidence rates of overall IPD ranged from 1.45/100,000 inhabitants (2008) to 0.21/100,000 inhabitants (2018), with highest rates during 2010–2011 (Table 1, supplementary Fig. 1). In the pre-vaccine period (2008–2009), 95 cases were identified, yielding an incidence of 2.48 cases/100,000 inhabitants (Table 1). In the early post-PCV10 (2010–2012), the incidence increased to 3.8 cases/100,000 inhabitants, (IRR 1.53; 95% CI 1.18–1.99) then subsequently declined until reaching an incidence of 0.38 cases/100,000 inhabitants in the late post-PCV10 period (2016–2018), (IRR 0.15: 95% CI 0.09–0.26). Similar patterns were observed over time when stratified by age group (with the exception of no increase observed in the early post-PCV10 period for ages 5–24 years). The greatest declines in IPD incidence relative to the pre-PCV10 period were observed in children aged ≤ 2 years (IRR for intermediate post-PCV10 0.12; 95% CI 0.03–0.53, and 0 cases in the late post-PCV10 period) and adults aged ≥ 60 years (IRR for late post-PCV10 period 0.11; 95% CI 0.03–0.48).

Among 299 isolates, 278 (93%) were available for serotyping, including 90/95 (95%) from the pre-PCV10 period and 188/204 (92%) from the post-PCV10 period. In the pre-PCV10 period, 52.2% (47/90) of IPD cases were due to PCV10 serotypes; in the early, intermediate, and late post-PCV10 periods, 47.3% (61/129), 10.8% (5/46), and 7.7% (1/13) were PCV10 serotypes, respectively. The incidence of IPD due to PCV10 serotypes in the pre-PCV10 period was 1.23 per 100,000 inhabitants increasing to 1.69 per 100,000 inhabitants in the early post-PCV10 period (IRR 1.38 95%CI [0.94–2.02]). The incidence during the intermediate (0.13 per 100,000 inhabitants; IRR 0.10 [95%CI 0.04–0.26]) and late (0.03 per

100,000 inhabitants; IRR 0.02 [95%CI 0.00–0.15]) post-PCV10 periods were significantly lower compared to the pre-PCV10 period.

Overall, 24 distinct pneumococcal serotypes were identified in the pre-PCV10, 30 in the early post-PCV10, 21 in the intermediate post-PCV10, and 9 in the late post-PCV10 periods. The most common PCV10 serotypes in the pre-PCV10 period were 14 (11/90, 12.2%), 23F (11/90, 12.2%), 6B (8/90, 8.8%), and 19F (8/90, 8.8%). In the late post-PCV10 period, the only PCV10 serotype identified was serotype 4, one case in an adult aged 36 years (supplementary Table 1). Non-PCV10 serotype 3 rose during the PCV10 years from 0.16 cases per 100,000 inhabitants increasing to 0.25 per 100,000 inhabitants in the early post-PCV10 period (IRR 1.59 95%CI [0.57–4.48]) then reduced to 0.13 and 0.05 in the intermediate and late post-PCV10 periods, respectively. No significant changes were observed in the serotype-specific incidence of IPD due to the most common non-PCV10 serotypes, with the exception of serotype 12F, which had a significant increase in the early-post PCV10 period (IRR 3.89 95%CI [1.09–13.96]) but no significant difference compared to pre-PCV10 was observed in the intermediate or late-post PCV10 periods (Table 2).

During the pre-PCV period, the proportion of IPD cases due to PCV10-SII, PCV13, PCV15, and PCV20 serotypes was 54.4% (49/90), 68.8% (62/90), 68.8% (62/90), and 75.5% (68/90), respectively (Fig. 1). In the late post-PCV10 period, the corresponding proportions were 7.7% (1/13), 30.7% (4/13), 30.7% (4/13), and 76.9% (10/13), respectively.

4. Discussion

Over 9 years following PCV10 introduction, we observed a decline of 84.7% and 98.0% in overall IPD and PCV10-type IPD, respectively, in the metropolitan region of Salvador. The reduction was seen in all age groups including adults, which may reflect indirect vaccine effects. We also observed an unexpected decline in non-vaccine-type IPD, which could have resulted from changes in surveillance over time or the impact of other (non-vaccine) factors. In the post-PCV period, the distribution of serotypes was more diverse, with no evidence of replacement disease. Higher-valent newer PCVs, particularly PCV20, could offer better serotype coverage for the remaining burden of IPD. These data contribute to a growing body of evidence of long-term PCV10 impact on IPD in middle-income countries.

Several studies employing hospital-based surveillance or population-based data from other regions of Brazil have shown declines in IPD following PCV10 introduction (17–19,27). However, these studies differ with respect to study population, case definitions, and period since PCV10 introduction. An early investigation conducted at the national level using time-series analysis aimed to predict trends in post-vaccination IPD rates. This analysis utilized data from the National Surveillance System for notifiable diseases (SINAN) from 2008 through 2013. The findings revealed a significant decrease of 41.3% in PCV10 types of IPD, following the administration of PCV10, mostly in children aged 2–23 months [17]. A study conducted at the University Hospital of São Paulo (HU-USP), the most populous city in the Americas located in the southeast region of Brazil, reported that overall IPD hospitalization rates among children aged < 2 years decreased from 20.30 to 3.97 cases/1,000 admissions and PCV10-type IPD fell from 16.47 to 0.44 cases/1,000 admissions within two years

after PCV10 introduction [18]. In the state of Paraná, southern Brazil, early post-PCV10 surveillance data (2010–2011) indicated a decline in pneumococcal meningitis incidence due to PCV10 serotypes, especially in children aged ≤ 2 years (from 6.01 to 2.49 cases/100,000 inhabitants) [27]. A national laboratory-based surveillance study that examined IPD rates up to five years after PCV10 introduction in Brazil reported a decline in PCV10-type IPD of 83.4% in children aged 2 months through 4 years, and 53.4% in adults aged ≥ 65 years [19]. The present study encompassing nine years post-PCV10 introduction provides additional evidence of a sustained impact of PCV10 on IPD in Brazil, particularly among children in the first two years of life.

Our findings of reduced PCV10-type IPD incidence in older age groups after PCV10 introduction are consistent with other studies reporting indirect effects from PCV vaccination of infants [12,28]. A meta-analysis using data from 34 different countries found that following PCV7 introduction, vaccine-type IPD in all age groups (including non-vaccine eligible age groups) reduced about 90% within approximately nine years; based on available data the model predicted a similar pattern of reduction in PCV13 unique serotypes following transition from PCV7 to PCV13 [12]. However, data on indirect PCV effects from low- and middle-income countries are more limited. Our data covering a nine-year period following PCV10 introduction in Brazil suggest a robust population-level reduction in PCV10-type IPD. Most low- and middle-income countries do not currently recommend PCV for adults, and instead rely on high coverage in the childhood vaccination program and indirect PCV effects, so that vaccine-type disease in adults will be reduced. Data from this study and other assessments of indirect effects can inform evidence-based decisions about adult pneumococcal vaccination.

As expected, an increased diversity of non-PCV10 serotypes was found after PCV introduction. Some of the non-PCV10 types identified in the present study, including 12F, 3, 6A, 8, 17F, and 15B, have been a common cause of IPD in other settings after PCV introduction [11,29]. Yet despite changes in serotype distribution, there was no significant increase in IPD due to non-PCV10 serotypes, including serotype 19A. IPD due to serotype 19A increased in many settings following PCV7 introduction [30]. PCV10 was thought to potentially offer cross-protection against 19A disease based on immunogenicity data [31]. Although some early studies suggested possible declines in 19A disease or effectiveness of PCV10 against 19A disease [32], overall evidence has not shown PCV10 impact on 19A disease [19,33,34] Furthermore, evidence of increased prevalence of 19A carriage after introduction of PCV10 has been documented in different settings [35–38]. We observed a 76% reduction in IPD due to serotype 19A in the late post-PCV10 period compared to pre-vaccine baseline; however, this reduction is similar to the reduction in all non PCV10-type IPD (73%), suggesting that the observed declines in 19A disease are likely attributable to non-vaccine factors.

The study has several limitations. The study does not account for other (non-PCV10) factors that could influence the burden of pneumococcal disease over time, such as changes in the prevalence of HIV, nutritional status, socioeconomic status, or access to healthcare (i.e. treatment of non-invasive pneumococcal infections before they become invasive). Changes in the sensitivity of the surveillance system also likely impacted the observed IPD incidence.

During the early post-PCV10 period, laboratory surveillance was enhanced, as the State of Bahia was one of the sentinel points for evaluating PCV10 effectiveness [14]. More active surveillance likely led to an increased detection of IPD cases during the early period of PCV10 introduction (2010–2012), as reflected in the high IRRs for this period. During the subsequent period (2013–2018), surveillance was more passive and may reflect under-ascertainment of IPD, which could exaggerate the apparent impact of PCV10 during the intermediate- and late-post-PCV10 periods. It is possible that some patients were missed because they were treated in hospitals that were not part of the IPD surveillance network. In addition, since patient recruitment was based on CSF/blood culture result, ascertainment of IPD cases may have been affected by the previous use of antimicrobials agents. Another limitation is predominance of meningitis cases (61.2%), reflecting an under-ascertainment of bacteremic pneumonia cases.

In conclusion, the study adds to a growing evidence base of the considerable health benefits resulting from the inclusion of PCV10 in the Brazilian immunization program. The incidence of PCV10-type IPD has fallen across all age groups, with no cases identified in children under two years of age in the late-post-PCV10 period. The incidence of non-PCV10 type IPD also declined, suggesting that non-vaccine factors are contributing to a reduced IPD burden. Out of the remaining cases during the late-post PCV10 period, newly formulated and higher valent vaccines have the potential to prevent more IPD cases.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Joice Neves Reis Pedreira reports financial support was provided by Brazilian National Research Council. Joice Neves Reis Pedreira reports financial support was provided by Foundation for Research Support of Bahia State. Joice Neves Reis Pedreira reports financial support was provided by National Institutes of Health. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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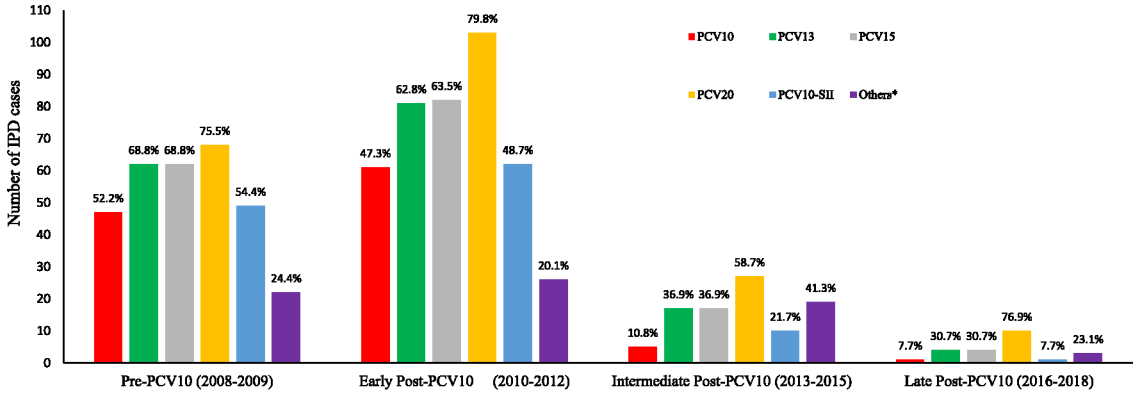

PCV10 serotypes: 14 (*n*=30), 23F (*n* =22), 6B (*n*= 21), 19F (*n*= 15), 18C (*n* =10), 4 (*n*= 10), 7F (n= 5), 9V (*n*= 1)
PCV13 serotypes: PCV10 serotypes + 3 (*n* =22), 6A (*n* =16), 19A (*n* =13)
PCV15 serotypes: PCV13 serotypes + 22F (*n* =1), 33F (*n* =0)
PCV20 serotypes: PCV15 serotypes + 8 (*n* =7), 10A (*n* =4), 11A (*n* =4), 12F (*n* =19), 15B (*n* =9)
PCV10-SII serotypes: 14 (*n*=30), 23F (*n* =22), 6B (*n*= 21), 6A (*n* =16), 19F (*n*= 15), 19A (*n* =13), 7F (n= 5), 9V (*n*= 1)
***Others serotypes: 9N (n=8); 6C (n=7); 7C (n=6); 16F, 20, 28A, 34 (*n*= 4, each); 13, 15A, 18A (*n*= 3, each); 18B, 21, 24F, 38 (*n*= 2, each); 35B, 10F, 11F, 15C, 23A, 23B, 31, 9A, NT (*n*= 1, each);**

Fig. 1.

Number of IPD cases in the metropolitan region of Salvador according to vaccine period, stratified by vaccines compositions.

Table 1

Incidence of IPD cases in the Salvador metropolitan region (Bahia-Brazil), from 2008 to 2018, stratified by age and PCV10 vaccine serotype.

Age group (years)	Pre-PCV10 (2008–2009)		Early Post-PCV10 (2010–2012)			Intermediate Post-PCV10 (2013–2015)				Late Post-PCV10 (2016–2018)	
	N° of cases	Cases per 100,000 pop.	N° of cases	Cases per 100,000 pop.	IRR (95% CI)	N°. of cases	Cases per 100,000 pop.	IRR (95% CI)	No. of cases	Cases per 100,000 p°p.	IRR (95% CI)
All IPD cases (*n* = 299)											
≤ 2	23	12.56	38	26.25	2.09 (1.25-3.51)	2	1.28	0.10 (0.02-0.43)	0	0.00	NA
3-4	2	1.59	8	8.49	5.33 (1.13-25.12)	0	0.00	NA	2	1.93	1.21 (0.17-8.59)
5-24	20	1.49	12	1.00	0.68 (0.33-1.38)	5	0.38	0.26 (0.10-0.69)	2	0.15	0.10 (0.02-0.44)
25-59	25	1.32	51	2.74	2.08 (1.29-3.35)	27	1.34	1.01 (0.59-1.74)	7	0.34	0.26 (0.11-0.60)
≥ 60	15	5.27	26	8.30	1.57 (0.83-2.97)	11	3.24	0.61 (0.28-1.34)	2	0.58	0.11 (0.03-0.48)
Total *	95	2.48	137	3.80	1.53 (1.18-1.99)	52	1.33	0.54 (0.38-0.75)	15	0.38	0.15 (0.09-0.26)
Cases due to PCV10 serotypes (*n* = 114)											
≤2	12	6.55	23	15.89	2.43 (1.21-4.87)	0	0.00	NA	0	0.00	NA
3-4	1	0.80	6	6.37	8.00 (0.96-66.46)	0	0.00	NA	0	0.00	NA
5-24	11	0.82	5	0.42	0.51 (0.18-1.47)	0	0.00	NA	0	0.00	NA
25-59	12	0.63	16	0.86	1.36 (0.64-2.87)	4	0.20	0.31 (0.10-0.97)	1	0.05	0.08 (0.01-0.59)
≥ 60	5 1.76	11	3.51	2.00 (0.69-5.75)	1	0.29	0.17 (0.02-1.43)	0	0.00	NA	
Total *	47	1.23	61	1.69	1.38 (0.94-2.02)	5	0.13	0.10 (0.04-0.26)	1	0.03	0.02 (0.0-0.15)
Cases due to non-PCV10 serotypes (*n* = 164) **											
<2	10	5.46	11	7.60	1.39 (0.59-3.28)	2	1.28	0.23 (0.05-1.07)	0	0.00	NA
3-4	1	0.80	2	2.12	2.67 (0.24-29.41)	0	0.00	NA	2	1.93	2.42 (0.22-26.69)
5-24	7	0.52	7	0.59	1.13 (0.39-3.21)	5	0.38	0.74 (0.23-2.33)	2	0.15	0.29 (0.06-1.41)

Age group (years)	Pre-PCV10 (2008–2009)		Early Post-PCV10 (2010–2012)			Intermediate Post-PCV10 (2013–2015)				Late Post-PCV10 (2016–2018)	
	N° of cases	Cases per 100,000 pop.	N° of cases	Cases per 100,000 pop.	IRR (95% CI)	N°. of cases	Cases per 100,000 pop.	IRR (95% CI)	No. of cases	Cases per 100,000 p°p.	IRR (95% CI)
25-59	11	0.58	32	1.72	2.96 (1.49-5.87)	22	1.09	1.87 (0.91-3.87)	5	0.24	0.42 (0.15-1.21)
≤ 60	10	3.51	14	4.47	1.27 (0.56-2.86)	6	1.77	0.50 (0.18-1.38)	2	0.58	0.17 (0.04-0.76)
Total *	43	1.12	68	1.88	1.68 (1.15-2.46)	41	1.05	0.93 (0.61-1.43)	12	0.30	0.27 (0.14-0.51)
Age group			2008-2009			2010-2012		2013-2015			2016-2018
≤ 2 years			183,150			144,752		156,131			159,618
3-4 years			125,581			94,176		103,824			103,799
5-24 years			1,345,002			1,194,765		1,298,750			1,315,043
25-59 years			1,894,396			1,861,869		2,021,484			2,044,738
≥60 years			284,679			313,340		339,679			343,242
All ages *			3,832,808			3,608,902		3,919,868			3,966,440

* The total number of cases includes some cases lack in age information in the pre-PCV10 period (n= 10) and post-PCV10 period (n=11).

** Cases lacking serotype information occurred in the pre-PCV10 period (n=5) and post-PCV10 period (n=16).

NA: Not applied.

Note: Population average number used for incidence calculation in each period and age groups.

Table 2

Incidence of the most common non-PCV10 serotypes causing IPD cases in the metropolitan region of Salvador (Bahia-Brazil) according to PCV10 period.

	Pre-PCV10 (2008–2009)		Early Post-PCV10 (2010–2012)			Intermediate Post-PCV10(2013–2015)			Late Post-PCV10 (2016–2018)		
Serotypes	**N° of Cases**	**Cases per 100,000 pop**	**N° of Cases**	**Cases per 100,000 pop**	**IRR (95% CI)**	**N° of Cases**	**Cases per 100,000 pop**	**IRR (95% CI)**	**N° of Cases**	**Cases per 100,000 p°p**	**IRR (95% CI)**
3	6	0.16	9	0.25	1.59 (0.57-4.48)	5	0.13	0.81 (0.25-2.67)	2	0.05	0.32 (0.06-1.58)
8	0	0.00	4	0.11	NA	3	0.08	NA	0	0.00	NA
6A	5	0.13	5	0.14	1.06 (0.31-3.67)	5	0.13	0.98 (0.28-3.38)	0	0.00	NA
6C	2	0.05	0	0.00	NA	4	0.10	1.96 (0.36-10.68)	0	0.00	NA
7C	1	0.03	5	0.14	5.31 (0.62-45.45)	0	0.00	NA	0	0.00	NA
9N	3	0.08	2	0.06	0.71 (0.12-4.24)	3	0.08	0.98 (0.20-4.84)	0	0.00	NA
12F	3	0.08	11	0.30	3.89 (1.09-13.96)	4	0.10	1.30 (0.29-5.83)	1	0.02	0.32 (0.03-3.06)
15B	1	0.03	3	0.08	3.19 (0.33-30.63)	2	0.05	1.96 (0.18-21.57)	3	0.07	2.86 (0.30-27.53)
17F	4	0.10	0	0.00	NA	1	0.03	0.24 (0.03-2.19)	1	0.02	0.24 (0.03-2.14)
19A	4	0.10	6	0.17	1.59 (0.45-5.65)	2	0.05	0.49 (0.09-2.67)	1	0.02	0.24 (0.03-2.14)