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Streptococcus pneumoniae serotype 19A in Latin America and the Caribbean 2010–2015: A systematic review and a time series analysis

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ABSTRACT

Background: This systematic review aims to describe the prevalence, trends, and antibiotic resistance of *Streptococcus pneumoniae* serotype 19A (*Spn*19A) that causes invasive and non-invasive diseases in children <5 years in Latin-American and Caribbean countries.
Methods: We searched for published (between January 2010 and February 2016) observational and clinical studies within the region including effectiveness and impact on *Spn*19A after pneumococcal conjugate vaccine (PCV) introduction. We calculated prevalence estimates by country and standardized the frequency of isolates to conduct an interrupted time series analysis for selected countries and to assess the potential changes in disease trends, overall and for *Spn*19A.
Results: We identified and reviewed full-text of 89 publications and included 59 in the analysis. Data from the laboratory surveillance network, SIREVA, were included in 43 (74%) of the invasive pneumococcal disease reports. There are differences in the sensitivity, representativeness, and heterogeneity of laboratory surveillance. There has been and overall reduction in the trend and number of invasive *S. pneumoniae* isolates in children <5 years after PCVs introduction. To date, the prevalence of *Spn*19A has increased, however, there has been no observed change in the trend.
Conclusions: This updated systematic review provides evidence of a reduction in the total number of invasive pneumococcal disease isolates after the introduction of PCVs in the region but cannot yet conclude a change in the trend of *Spn*19A disease.

1. Introduction

The introduction of pneumococcal conjugate vaccines (PCVs) [1–3] has shown to dramatically reduce and sustain lower vaccine serotypes (VT) of invasive pneumococcal disease (IPD) rates in vaccinated targeted and non-targeted age groups [1–4]. VT isolates have also reduced in non-IPD acute otitis media (AOM) and became very low in the nasopharynges of vaccinated children [5,6]. Vaccination programs have also reduced the incidence of multi-drug resistant (MDR) IPD [1,7].

However, phenomena identified as serotype replacement has caused an increase in the frequency of IPD, non-IPD and nasopharyngeal carriage by non-vaccine serotypes (NVT) after the implementation of PCV [8].

Streptococcus pneumoniae serotype 19A (*Spn*19A) became the most prevalent NVT after the introduction of 7-valent PCV (PCV7) and was suggested to have caused an increase in the rate of MDR strain development [7,9]. However, in regions where PCV7 [10] and 13-valent PCV (PCV13) [11] were not available *Spn*19A incidence still rose. This increase in serotype *Spn*19A, therefore, may have been occurring independently and the use of PCVs had somehow accelerated or reinforced this trend.

In 2010, new PCVs were in the process of being implemented in the EPI in Latin American and Caribbean countries (LAC). We published a systematic review of published and unpublished *Spn*19A data from observational and randomized clinical studies (between 1990 and 2010) for children <6 years within the LAC region [12]. In the meantime, according to the Pan American Health Organization (PAHO), as of September 2015, 34 territories within the region offer PCVs in their Expanded Programs on Immunization (EPI) [13].

We aimed to update our previous review by including all data collected (published and unpublished) between 2010 through 2015 and describing the prevalence, incidence, and penicillin susceptibility of *Spn*19A in children <5 years. We also used a time series methodology that characterizes the *Spn*19A prevalence over time before and after PCV implementation.

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2. Methods

2.1. Search strategy and eligibility criteria

We used PubMed, EMBASE, Latin American and Caribbean Health Sciences Information, and SCOPUS to conduct the review search. The searches included epidemiological, observational, and clinical studies reporting efficacy, effectiveness and the impact against pneumococcal disease, and active surveillance and laboratory surveillance reports. Table S1 details the specific search terms used. The searches were limited to data published between January 2010 and February 2016 and covered all LAC countries without language restrictions. The targeted age group was children <5 years.

The search incorporated snowballing techniques and included summaries of recent meetings on infectious diseases. Regional experts in the field and authors were also contacted to obtain missing or extra information when needed.

For the inclusion and exclusion criteria for publications reporting non-IPD studies we reviewed international standards and accepted laboratory techniques [14,15]. Table S2 lists the selected definitions used.

2.2. Study selection

We first screened for inclusion by the title and abstract of all hits identified through database searching and other sources before removing any duplicates. For the remaining, potentially eligible, articles we reviewed the summaries and full-text to assessed whether the inclusion criteria were met or not. All researchers participated in both steps, and disagreements were resolved by consensus.

2.3. Data collection process and data items

Data for the total number of *S. pneumoniae* and *Spn*19A isolates were extracted using an electronic spreadsheet (Table S3). Two reviewers extracted the serotype distribution data for IPD, non-IPD and nasopharyngeal carriage. When available, we collected data on *Spn*19A penicillin susceptibility for IPD meningitis and non-IPD meningitis, pneumococcal disease prevalence and the number of cases per 100,000 children <5 years, and PCVs impact and effectiveness estimates.

We avoided the duplication of data between reports and manuscripts, identified for invasive isolates, by only adding available cases from the SIREVA Project databases (via the PAHO website) for years 2010–2013 [16–19]. Personal communication with the SIREVA country coordinators was done to obtain data for 2014 and 2015.

2.4. Risk of bias within individual studies

Selection bias was limited by reducing the heterogeneity of samples; most data for invasive isolates were from the SIREVA network. Qualitative assessment of the selected articles was conducted by the reviewers using the STROBE (Strengthening the Reporting of Observational studies in Epidemiology) checklist of essential items for IPD, AOM and nasopharyngeal carriage reporting articles [20] (Table S3).

2.5. Descriptive analysis

Prevalence estimates were calculated using the number of *Spn*19A isolates (from IPD, non-IPD, AOM and nasopharyngeal carriage) as the numerator and the total number of *S. pneumoniae* reported for each study as the denominator. *Spn*19A proportions and rates, among groups and periods, were compared using a Z-test and unadjusted 2-sided p-values were estimated using 0.05 as the cut-off.

Publications disclosing vaccine efficacy or effectiveness against *Spn*19A, as well as those reporting pneumococcal disease trends for this serotype before and after PCVs introduction were summarized.

2.6. Time series analysis

We standardized reporting across countries by estimating the total and the number of *Spn*19A annual IPD cases per 100,000 children <5 years using country-specific population estimates from UNICEF [21] (Table S4). We fitted the model for countries that had reported the highest number of *S. pneumoniae* isolates before and after the introduction of PCVs [22,23] (Table S5).

An interrupted time series analysis was used that involved a model fitting yearly rates before PCV introduction for each country and using an ordinary least-squares regression-based approach. We excluded the transition period defined as the year when the vaccination program began adjusted to the vaccine coverage reported by PAHO. The expected rates for the post-vaccination period were modeled based on the pre-vaccination period data for Argentina (2006–2012), Chile (2006–2011), and Uruguay (2006–2008). We calculated the percentage difference, with 95% confidence intervals (CI), to compare the observed and predicted rates for the whole post-vaccination period.

3. Results

3.1. Study selection

After removing the studies with duplicate data and articles that did not meet the inclusion criteria, 89 remained (from 1582) and received a full-text review. We removed another 30 after review and analyzed 59 articles in total (Fig. 1) [24]. The main reasons for exclusion were studies which did not report serotype distribution or that the data was duplicated (Table S6).

3.2. Study characteristics

Forty-three studies reported on IPD [12,16–19,25–62], of which 26 used data from SIREVA [12,27–51] and 11 used data from other sources [52–62] (Tables 1 and S7). Eighteen publications reported on non-IPD data: six focused on AOM [33,59,63–66] and 12 on nasopharyngeal carriage [67–78] (Table 2).

Among 37 studies for IPD (excluding the six SIREVA bulletins), 19 were retrospective and/or laboratory-based surveillance case series, and 18 were literature reviews or prospective/enhanced active surveillance (Table S8).

Similarly, the 18 studies for AOM and nasopharyngeal carriage were 11 prospective and seven cross-sectional studies, using cases with clinically or laboratory confirmed disease in eight (Table S8).

3.3. Spn19A

The SIREVA data, reported between 2010 and 2015, comprised of 6307 serotyped IPD isolate cases, of those, 742 (11.8%) were *Spn*19A (Table 3). The non-SIREVA data reported 768 IPD isolates, 41 (5.3%) of which were *Spn*19A (Table 4). When added together, there is a total of 7075 IPD isolates, of which 783 (11.1%) were *Spn*19A. No differences were observed for *Spn*19A prevalence between SIREVA and non-SIREVA data ($p > 0.05$).

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