Epidemiology of Pediatric Pneumococcal Meningitis and Bacteremia in Latin America and the Caribbean

A Systematic Review and Meta-analysis

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Background: Pneumococcal meningitis and bacteremia pose a significant disease burden in Latin America and the Caribbean (LAC).

Methods: To perform a systematic review of studies of pediatric pneumococcal meningitis and non-pneumonia, non-meningitis pneumococcal bacteremia in LAC, we conducted an exhaustive search from 2000 to 2010 in electronic databases and grey literature. Pairs of independently selected reviewers assessed the quality and extracted the studies’ data. A STROBE-based checklist was used to assess the risk of bias in observational studies. Meta-analyses were performed.

Results: Of 1218 retrieved studies, 39 were included. In children <5 years, the pooled 95% confidence interval (CI) percentage of pneumococcal etiology out of cases studied with cerebrospinal fluid/blood cultures was 6.0% (95% CI: 3.3–9.5) for meningitis and 8.0% (95% CI: 5.3–12.4) for bacteremia. The incidences per 100,000 children were 4.7 (95% CI: 3.2–6.1) and 3.9 (95% CI: 2.0–5.9) for pneumococcal meningitis and non-pneumonia, non-meningitis bacteremia, respectively. The mortality was 8.3 (95% CI: 0.0–21.0) and 0.5 (95% CI: 0.3–0.6) per 100,000 for meningitis and sepsis, respectively. The case fatality ratio was 33.2% (95% CI: 21.3–46.2) for meningitis and 29.0% (95% CI: 21.9–36.8) for sepsis. The pooled serotype distribution from SIREVA surveillance data showed that 14, 6B, and 19F were the most frequent serotypes, all included in licensed vaccines.

Conclusion: Pneumococcal meningitis and bacteremia are important causes of morbidity and mortality in LAC children <5 years of age. This systematic review provided evidence about the burden of pneumococcal disease and the serotype distribution to assess the impact of the pneumococcal vaccines and to assist decision makers in the region.

Key Words: Pneumococcal meningitis, Pneumococcal bacteremia, burden of disease, costs, serotype distribution

Infections with Streptococcus pneumoniae represent a major cause of hospitalizations and deaths worldwide, leading to high health-care system costs. The World Health Organization estimates that approximately 1 million children die each year from pneumococcal disease, and these potentially preventable deaths occur primarily in developing countries.1–4

Child mortality reduction is 1 of the 8 Millennium Development Goals, adopted in 2000 by world leaders. In Latin America and the Caribbean (LAC), it is estimated that 2 children die every hour from pneumococcal disease.5 In the present study, we focused on meningitis and also on non-pneumonia, non-meningitis pneumococcal invasive disease, but we simplified this term for the reader as bacteremia. In the region of the Americas, O’Brien et al6 estimated for the year 2000 that pneumococcal meningitis was responsible of 9500 cases, 1300 deaths. The estimations for bacteremia (strictly non-pneumonia, non-meningitis pneumococcal invasive disease) were 55, 400 cases (most of which were sepsis) and 4300 deaths. We also collected serotype distribution data because this information is essential for assessment of the potential impact of vaccines.7

The World Health Organization has recommended that pneumococcal vaccines be prioritized for incorporation into national immunization programs, particularly in countries with a high child mortality.8,9 However, significant time has usually elapsed since the approval of the vaccine in the developed world and its widespread use in developing countries. Nowadays, 18 countries in LAC have introduced the vaccine: Argentina, the Bahamas, Barbados, Brazil, Chile, Colombia, Costa Rica, Ecuador, El Salvador, Guyana, Honduras, Mexico, Nicaragua, Panama, Paraguay, Peru, Trinidad and Tobago and Uruguay.10 Most countries with universal vaccination programs in 2010–2011 replaced the 7-valent vaccine with the 10-valent vaccine or the 13-valent vaccine.11 Despite this, pneumococcal disease continues to be an important health problem in the region. PAHO commissioned our institution, through the ProVac Initiative,12 to provide an updated epidemiologic picture of confirmed pneumococcal meningitis and bacteremia burden in children of LAC.

MATERIALS AND METHODS

We performed a systematic review and meta-analysis of observational studies of microbiologically confirmed pneumococcal meningitis or bacteremia in LAC. We searched Cochrane CENTRAL, specialized registers of the Cochrane Infectious Diseases Group, MEDLINE, EMBASE and LILACS from January 2000 to December 2010 (see text document, Supplemental Digital Content 1, http://links.lww.com/INF/B892, for detailed search strategies). We also performed a generic and academic Internet search. An annotated search strategy for grey literature was included to obtain information from relevant sources, like reports of Ministries of Health, the PAHO, the World Health Organization, institutional reports, databases containing regional proceedings or congresses’ annals, reference lists of included studies and consulting experts and societies related to the topic. We followed the MOOSE guidelines13 and the PRISMA statement for reporting systematic reviews and
meta-analyses. The authors from selected articles were contacted to obtain missing or additional information when it was needed. We included the control arms of controlled trials and cohort, case-control, surveillance, cross-sectional and case-series studies. There were no language restrictions. Systematic reviews and meta-analysis with original data were also included for quantitative synthesis. Studies were included when at least 20 cases of pneumococcal meningitis or 20 cases of non-pneumonia, non-meningitis (NPNM) bacteremia were reported in Latin American children from 0 to 60 months of age. Studies with patients’ enrolment before 1995 were excluded. If data were duplicated or data subsets appeared in >1 publication, the study with larger sample size was used.

Outcome measures included incidence, mortality, percentage of cases with culture-confirmed pneumococcal etiology, case fatality ratio (CFR) and percentage of meningitis and bacteremia from all pneumococcal disease, as well as pneumococcal serotypes. We also explored data on use of resources, such as length of hospitalization, use of supportive care, number of ambulatory visits, school days lost, parents work absenteeism and reported direct costs per episode, both for the families and the government. For incidence estimates, we considered only those prospective studies who applied active surveillance. As SIREVA network estimates the serotypes distribution through passive surveillance, this information is unsuitable for incidence meta-analysis.

Screening and Data Abstraction
Pairs of reviewers (A.C., M.R., N.E., J.I.R. and S.G.M.) independently screened each title and abstract of all identified citations and selected potentially eligible studies. Another pair then independently evaluated full-text versions of all potentially eligible articles to evaluate whether they met inclusion criteria. Any discrepancies were resolved by consensus in both phases.

Assessment of Risk of Bias
Pairs of reviewers (A.C., M.R., N.E., J.I.R., and S.G.M.) independently evaluated the methodological quality of studies included in the systematic review. The risk of bias for observational studies was assessed by a modified checklist of essential items stated in the STROBE statement (Strengthening the Reporting of Observational studies in Epidemiology) and reported by Fowkes and Fulton and Sanderson et al. We used an algorithm to estimate a summary risk of bias considering 6 criteria: methods for selecting study participants, methods for measuring exposure and outcome variables, methods to control confounding, design-specific sources of bias and comparability among groups, statistical methods and declaration of conflict (see text document, Supplemental Digital Content 2, http://links.lww.com/INF/B893). Disagreements were solved by consensus.

Statistical Analyses
Information from prospective studies was not combined with regional surveillance system information (SIREVA II) for meta-analysis and was reported separately, because of preliminarily observed heterogeneity in methodologies and subject selection. To analyze our data, we conducted proportion and percentage meta-analyses. We applied an arcsine transformation to stabilize the variance of proportions following the Freeman-Tukey variant of the arcsine, square-root of transformed proportions method. The pooled proportion was calculated as the back-transformation of the weighted mean of the transformed proportions, using inverse arcsine variance weights for the fixed and random effects model. The estimates and its confidence interval (95% CI) were calculated using the DerSimonian-Laird weights for the random effects model. We calculated the I² statistic as a measure of the proportion of the overall variation in the proportion that was attributable to between-study heterogeneity. StatsDirect and Comprehensive Meta-analysis were used for all analyses. All costs were expressed in the year reported currency in United States dollar (USS) and we also converted the total costs in International Dollars 2012 (I USS 2012) using purchasing power parity exchange rates. The international dollar is a hypothetical currency that is used as a means of translating and comparing costs from 1 country to the other using the common reference point of the USS.

RESULTS
The bibliographic search retrieved 1218 records after duplicates were removed. After the selection process, 39 studies were included, 32 for the qualitative synthesis of meningitis and 15 for bacteremia (see text document, Supplemental Digital Content 3, http://links.lww.com/INF/B894, for the flow diagram). Of the 39 included studies, 11 carried a low risk of bias, 23 moderate and 5 high/very high as assessed through the methods described previously. The main weakness of the studies included in the last category was selection bias (see text document, Supplemental Digital Content 3, http://links.lww.com/INF/B894, for main characteristics and risk of bias of included studies). Five studies in children aged from 0 to 59 months were included for meningitis and 3 for bacteremia could be used for meta-analysis of the percentage of pneumococcal etiology of all cases studied with cerebrospinal fluid/blood cultures. For meningitis, the pneumococcal etiology was 6.0% (95% CI: 3.3–9.5) and for bacteremia 8.0% (95% CI: 5.3–12.4; Fig. 1).

Eight studies of meningitis and bacteremia (Fig. 2 and 5) could be used for meta-analysis of incidence by age range. The pooled incidence of culture-confirmed pneumococcal meningitis was 4.6/100,000 (95% CI: 3.18–6.05) in children between 0 and 59 months and 8.3/100,000 (95% CI: 0.0–17.2) in children from 0 to 23 months (Fig. 2). However, the incidence was 4- to 11-fold in the 0–23 months versus 0–59 months age groups when only studies assessing both age ranges are included. For this estimation, we included information from 7 countries (Argentina, Brazil, Cuba, Dominican Republic, Jamaica, Chile and Costa Rica).

The pooled incidence of pneumococcal bacteremia was 3.9/100,000 (95% CI: 2.0–5.9) in children between 0 and 59 months (95% CI: 2.0–5.8) and 5.8/100,000 (95% CI: 0.0–15.9) in children from 0 to 23 months (Fig. 3). For this estimation, we included information from 3 countries (Argentina, Chile and Costa Rica).

The pooled mortality because of culture-confirmed pneumococcal meningitis and sepsis/periitonitis in children between 0 and 59 varied from 1.8 to 14.9% (95% CI: 0.0–21.0) and 0.5% (95% CI: 0.3–0.6) per 100,000 children, respectively. Out of all patients presenting bacteremia without a focus, only 1 with terminal leukemia died.

The pooled CFR in the age group between 0 and 59 months was 33.2 (95% CI: 21.3–46.2) for meningitis and 29.3% (95% CI: 19.9–39.7) for bacteremia. The CFRs ranged from 12% in Trottman 2009 to 60% in Reis et al. The sensitivity analysis excluding Reis et al showed a pooled CFR of 29.3% (95% CI: 19.9–39.7). The CFR was 29.0 (95% CI: 21.9–36.8) for sepsis and 0.0% (95% CI: 0.0–1.5) for bacteremia without sepsis. The distribution by age range is provided in Table 1.

The pooled percentage of meningitis and bacteremia out of all PID by year (see Table 2) and by country conflict (see text document, Supplemental Digital Content 4, http://links.lww.com/INF/B895) were calculated using data from the regional surveillance database SIREVA.

The most frequent serotype isolated in children with meningitis in the region was serotype 14 in 28.5% of the samples (95%...
CI: 24.1–33.1) followed by serotype 5, in 15% (95% CI: 5.8–27.4) and serotype 6B in 14.2% (95% CI: 7.7–22.3). Regarding bacteremia, the most frequent serotype isolated in the region was serotype 14 in 29.3% of the samples (95% CI: 24.5–34.3) followed by serotype 6B, in 10.6% (95% CI: 7.2–14.5) and serotype 19F in 7.3% (95% CI: 5.5–9.0; Supplemental Digital Content 4, http://links.lww.com/INF/B895).

Regarding use of resources, 8 studies identified included data from Argentina, Brazil, Colombia, Chile, Uruguay and the LAC region globally. The pooled mean length of stay per pneumococcal meningitis case was 15 days (95% CI: 12.6–17.5). There were no available data regarding length of stay per bacteremia case. Detailed results regarding direct, indirect and total costs are provided in Supplemental Digital Content 5, http://links.lww.com/INF/B896. The minimum total cost estimated for meningitis came from Brazil (833 IÚ$S 2012) and the maximum from Chile (10,538 IÚ$S 2012) with a median of 3459 IÚ$S 2012. The minimum total cost for hospitalized bacteremia came

FIGURE 1. Pooled percentage of pneumococcal etiology out of all cases studied with cerebrospinal fluid/blood cultures in Latin American children, during 2000–2010.

DISCUSSION

Pneumococcal infections are the leading cause of death from a vaccine preventable illness in children aged <5 years. Our study analyzed for this age group the burden of Pneumococcal meningitis and NPNM Pneumococcal bacteremia in LAC during years 2000–2010. The pooled incidence in children aged <5 years was 4.7 per 100,000 children and 3.9 per 100,000 children in pneumococcal meningitis and NPNM bacteremia, respectively. The countries most represented were Brazil, Chile and Argentina.

In both groups, the higher incidence was particularly observed in children <2 years of age. In United States, the mean annual incidence of pneumococcal meningitis reported was 10.2/100,000 individuals during 1998–1999 and in Europe around 2002–2005.8,9

<table>
<thead>
<tr>
<th>TABLE 1. Pooled and Single Estimates of Crude Mortality and Case Fatality Ratio Because of Pneumococcal Meningitis and Bacteremia in Latin-American Children by Age Range</th>
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<td>Age Range</td>
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<td>Mortality</td>
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*No of studies/substudies means the number of available rows for each country and for each year inside age subgroups.
†Single studies result used in Meta-Analysis.
TABLE 2. Pooled Percentage of Meningitis and Bacteremia Out of All Pneumococcal Invasive Disease, by Year (SIREVA Reports From 2000 to 2009)

<table>
<thead>
<tr>
<th>Year</th>
<th>No of studies/substudies</th>
<th>Meningitis % (95% CI)</th>
<th>Bacteremia % (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>2000</td>
<td>1642 (19)</td>
<td>33.9 (22.2–46.8)</td>
<td>8.9 (1.2–22.6)</td>
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<tr>
<td>2001</td>
<td>1667 (20)</td>
<td>38.6 (28.9–51.3)</td>
<td>8.7 (1.1–22.5)</td>
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<td>2002</td>
<td>1660 (20)</td>
<td>39.1 (26.7–52.3)</td>
<td>9.6 (1.8–22.5)</td>
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<tr>
<td>2003</td>
<td>1696 (20)</td>
<td>37.8 (28.6–49.5)</td>
<td>7.6 (1.2–18.9)</td>
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<tr>
<td>2004</td>
<td>1724 (20)</td>
<td>35.1 (23.8–47.3)</td>
<td>11.0 (2.3–24.9)</td>
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<tr>
<td>2005</td>
<td>1574 (20)</td>
<td>37.8 (26.3–50.0)</td>
<td>10.9 (3.9–21.0)</td>
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<tr>
<td>2006</td>
<td>1406 (19)</td>
<td>34.4 (21.5–48.5)</td>
<td>15.0 (5.8–27.4)</td>
</tr>
<tr>
<td>2007</td>
<td>1424 (20)</td>
<td>30.6 (20.3–41.9)</td>
<td>17.7 (9.0–28.6)</td>
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<tr>
<td>2008</td>
<td>1508 (20)</td>
<td>27.6 (20.4–35.5)</td>
<td>17.5 (10.7–25.7)</td>
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<tr>
<td>2009</td>
<td>1341 (20)</td>
<td>29.6 (20.5–39.5)</td>
<td>15.9 (8.2–25.5)</td>
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* No of studies/substudies means the number of available rows for each country for each year inside age subgroups.

10.4 per 100,000 individuals in the same age group and in both regions the highest age-associated incidence of invasive pneumococcal diseases occurred in children aged <2 years.\(^{63,64}\) The difference with our study could probably be related to underreporting of pneumococcal disease in many countries of the region and differences in surveillance programs and methodologies.

Meningitis in children of <1 year of age is associated with a high risk of death (10–15%), and neurologic sequelae (30%).\(^{65}\) Ruvinsky et al\(^{66}\) found that during the first year of life, meningitis and bacteremia are even more frequent than pneumonia. However, in children >1 year, pneumonia becomes the most frequent condition.

The mortality in children aged <5 years of age was higher in meningitis compared with the mortality in sepsis, whereas the mortality in bacteremia without focus was almost zero. Two landmark reviews, O’Brien et al\(^{6}\) and Valenzuela et al,\(^{67}\) have covered the topic; however, our literature search was run more than 4 and 5 years later, respectively, and therefore we included many more studies than these reviews. We found lower incidence and mortality for both conditions studied, in part because of use a more precise estimation of denominators of children-years and in part, because new studies were included.

The CFR was 33.2%, 29.0% and 0.0% for meningitis, sepsis and bacteremia without sepsis, respectively. These figures were two-thirds of those obtained by O’Brien et al\(^{6}\) This is surprising since O’Brien et al\(^{6}\) considered not only LAC but also the entire region of the Americas including lower CFR from United States.\(^{35.3}\) Reis et al\(^{35}\) reported the highest CFR (60%). As the secretary of health for the topic; however, our literature search was run more than 4 and 5 years later, respectively, and therefore we included many more studies than these reviews. We found lower incidence and mortality for both conditions studied, in part because of use a more precise estimation of denominators of children-years and in part, because new studies were included.

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The difference between the CFRs reported can be related to differences in patient populations or attributed to the fact that only severe cases were registered in the surveillance system or to differences between the countries’ healthcare systems. In 1993, a coordinated passive surveillance laboratory network for serotype distribution and antimicrobial resistance patterns for the Region of the Americas was established by the PAHO, through its special Program for Vaccines and Immunizations and the regional System for Vaccines (SIREVA). According to SIREVA Network Report, the highest proportions of meningitis of all PID reported were seen in Paraguay, Bolivia and Argentina, and for bacteremia the countries with the highest prevalence were Chile, Panama and Venezuela (see Text document, Supplemental Digital Content 4, http://links.lww.com/INF/B895). We believe that these differences are most likely because of surveillance methods than to true differences in the epidemiology of disease caused by pneumococcus. Additionally, the passive surveillance based on results from sterile specimens taken from hospitalized children is prone to selection bias, because it tends to report the more severe cases. Passive or retrospective studies may underestimate the true incidence of invasive S. pneumoniae infections as blood cultures and chest radiographs are often not routinely performed. The prior use of antibiotics may also contribute to underestimation and it may also be related with poorly sensitive method of blood culture to detect the real burden of invasive pneumococcal disease (IPD) cases. Several studies reported in LAC countries a sensitivity of blood culture to detect pneumococcal pneumonia of <10%,\(^{36,34,69}\) The addition of non-culture methods, as polymerase chain reaction (PCR) testing, to routinely performed culture analysis may improve the estimated burden of disease. Arguedas reported, in a prospective epidemiologic surveillance study, an IPD incidence rate for culture positive only of 33.7/100,000 per year. The addition of the cases confirmed by PCR increases this IPD incidence rate to 46.0/100,000 per year.\(^{70}\) These incidence rates were higher than in a retrospective study in hospitalized patients performed previously in the same country where the incidence of IPD in children <2 years of age was only 2.9 per 100,000.\(^{71}\) Real-time PCR was incorporated into routine public health surveillance of culture negative bacterial meningitis in Sao Paulo, Brazil since the year 2007. The addition of RT-PCR to routine microbiologic methods increased the yield for detection of S. pneumoniae by 52%.\(^{72}\) On the other hand, a systematic review concluded that currently available methods for PCR with blood samples for the diagnosis of IPD lack the sensitivity and specificity necessary for clinical practice.\(^{73}\) It is important to highlight that this method is not widespread available in LAC countries. Analyses should be conducted to assess the performance of PCR before putting in practice such novel costly technologies.

Some reports from LAC informed decreased burden of IPD after universal immunization with the 2 new conjugated vaccines: 13-valent and 10-valent. In Uruguay, from 2009 to 2011, the incidence of hospitalized children with pneumonia declined 59%.\(^{74}\) In 2010, Brazil introduced a 10-valent pneumococcal conjugate vaccine (PCV10) to its National Immunization Program. During the first year post-vaccination period, the rates of hospitalization for pneumonia decreased from 38% to 49% in the 3 cities with high PCV10 vaccination coverage.\(^{74}\)

Pirez et al\(^{75}\) compared in Uruguay the annual hospitalization rates for community-acquired pneumonia (CAP) and pneumococcal CAP in children <14 years of age before (2005–2007) and after implementation of universal vaccination for children <2 years of age (2009). The rates decreased 56% and 48%, respectively, and also a significant reduction in pneumococcal meningitis of 59%. The reduction was lower for pneumococcal CAPs respect to CAPs which might be related with low rate of pneumococcal isolation among pneumonia. Other reason for underestimation is the fact than blood cultures and chest radiographs are often not routinely performed in all countries.\(^{70}\)

The pneumococcal serotypes showed regional variability, but the most frequent pneumococcal serotypes reported by SIREVA in the region during 2006–2009 for meningitis were 14, 5 and 6B and for bacteremia 14, 6B and 19F (Supplemental Digital
Serotype 19A has increased as cause of disease worldwide, irrespective of the inclusion of PCV7 in countries’ vaccination schedules. It emerged as a predominant invasive pneumococcal serotype because of its capacity to colonize the nasopharynx and its antibiotic resistance and has become the most important emergent serotype worldwide. In our study, the serotype 19A for meningitis and bacteremia accounts for only 2.3% and 4.8% out of all serotypes reported in SIREVA respectively for each condition, probably because these pooled estimates included a long time window period (2000–2009). The serotypes 1 and 5 were also a common cause of disease in emergent and developed countries. Serotype 6A is responsible for a considerable portion of disease caused by the serotype 6. The immunologic cross-reactivity between serotype 6A and 6B may be responsible for the reduction of IPD caused by the serotype 6A after the introduction of PCV7.

It is important to highlight that the 2009 serotype data included Uruguay and Costa Rica which began to introduce the PCV into their National Immunization Program in 2008 and 2009, respectively. However, excluding this countries did not change the serotype ranking.

Eight of the included papers estimated the direct and indirect costs of meningitis or bacteremia direct and indirect costs showing a great variability. The median total cost of a meningitis episode was 3459 IUSS 2012 and for a bacteremia episode was 2132 IUSS 2012 for inpatients and 108 IUSS 2012 for outpatients. The meta-analyzed estimated length of stay in meningitis was 15 days (95% CI: 12.6–17.5) and this is one of the most important drivers of the total costs. The variations in costs among different countries from the region found in our study may well reflect differences in the costs of treatment and health services or cost estimation methodologies.

The limitation of our systematic review includes the scarcity of studies of adequate methodological quality in the region, since most information came from non-representative samples. Proper active population-based systematic surveillance for PID is needed to overcome the underreporting, particularly for ambulatory cases. Another caveat is that confirmed cases represent only a fraction of total cases and our results could not be directly extrapolated to unconfirmed cases but for the studied conditions both estimations are probably similar. A meta-analysis could not be conducted for health resource use because data were not available from most of the LAC countries.

Even considering these limitations, there is a need of new data necessary to perform policy and cost-effectiveness analysis for the region. Using the same methods as O’Brien et al and the most recent LAC’s population <5 years figures, we estimated for this region annually 3583 (95% CI: 2466–4962) incident cases of pneumococcal meningitis and 1189 (95% CI 763–1655) deaths because of this condition. We also estimated 2100 (95% CI: 1050–3149) incident cases of pneumococcal sepsis and 609 (95% CI: 460–773) deaths because of this condition. This kind of updated estimation could be a useful resource not only to investigate the pneumococcal disease economic burden but also to facilitate decision making to face this problem, such as the introduction of pneumococcal vaccination programs.

In LAC, pneumococcal meningitis and NPNM bacteremia are important causes of mortality and morbidity in children <5 years and particularly among children <2 years old in the region. This work was aimed to contribute to the knowledge of the burden of culture-confirmed pediatric pneumococcal meningitis and bacteremia in Latin America and the Caribbean and serotype distribution of these pneumococcal infections, which in turn are relevant in providing valuable information for economic evaluations and projections after the introduction of PCVs in LAC. We provided comprehensive information about frequency of IPD, serotype distribution and costs that are key for decision makers in the region.

It is necessary to continue to monitor pneumococcal serotypes and antibiotic resistance throughout the region so that adjustments can be made accordingly, to the pneumococcal vaccination schemes included in the national immunization programs of each country in LAC.

ACKNOWLEDGMENTS

The authors are deeply indebted to Daniel Comandé for his efforts with the electronic searches.

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Erratum

Methicillin-resistant *Staphylococcus aureus* Empyema Necessitatis in a Breast-fed Neonate: ERRATUM

In the article appearing on page 668, volume 33, issue 6, the order of authors is incorrect. The authors should appear in the following order: Julia Rosebush, DO, Ryan Summers, MD, Joseph Snitzer, MD, Robert Jerris, PhD, Sarah Satola, PhD, and Paul Spearman, MD. Paul Spearman, MD is the final, senior author.

REFERENCE