Review

Systematic review of pneumococcal disease costs and productivity loss studies in Latin America and the Caribbean

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ABSTRACT

Background: Pneumococcal disease is an important cause of morbidity and mortality associated with significant economic burden for healthcare systems and society.

Objectives: To systematically review pneumococcal disease cost of illness and productivity loss studies in the Latin America and Caribbean (LAC) region.

Methods: A search of relevant databases was performed till November 2011. A broad and sensitive search strategy was used consisting of medical subject headings (MeSH) terms for pneumococcal disease, healthcare costs and productivity loss studies. No language restriction was applied. Only papers from LAC region and child population were analyzed. Additional exclusion criteria included duplicate studies, and insufficient information about methods.

Results: A total of 1241 citations were retrieved. After applying the exclusion criteria, only 16 studies remained for analysis. There were 4 papers from Brazil, 3 from Argentina, 2 from Colombia, 2 from Mexico, 1 from Uruguay, 1 from Chile, and 3 analyzing a group of LAC countries. Only 4 were cost-of-illness studies, 11 were cost-effectiveness studies of pneumococcal vaccine and 1 study of the pneumococcal burden of disease. Methods used for quantifying health resource utilization and costing methods varied significantly among studies, as well as data sources considered. Productivity losses were considered in 8 studies, all of which used the human capital approach method. Pneumococcal disease cost estimates varied significantly depending on the pneumococcal syndromes considered, methods used, study perspective and type of costs included.

Conclusion: This systematic review reinforced the importance of standardization of methods for cost studies that can allow comparison and reproducibility in other settings. These estimates can be useful for future economic analysis conducted to support the decision making process on the introduction of new vaccines in LAC. However, caution must be taken, as methodological aspects of studies will result in estimates with varying levels of accuracy and external validity.

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1. Introduction

*Streptococcus pneumonia* is a leading cause of bacterial pneumonia, meningitis, and sepsis in children worldwide, and is responsible for approximately 11% of deaths in children under 5 years old [1]. Pneumococcal disease represents a significant economic burden for health care systems and society, constituting a public health priority.

The World Health Organization (WHO) recommends the introduction of pneumococcal conjugate vaccine into national immunization programs, especially in countries with high mortality rates in children under 5 years old [2]. It has been estimated that vaccination could prevent over half of all cases and deaths due to pneumococcal disease annually in the Latin America and Caribbean region (LAC) [3].

The introduction of new vaccines requires significant investment of resources and economic analyses are important to ascertain cost-effectiveness. Such analyses should take into account local epidemiological data; pneumococcal disease incidence; serotype distribution; vaccine efficacy; disease costs including costs of diagnosis, treatment and follow-up of cases; vaccine introduction program costs; and budget impact analysis. National decision makers are frequently constrained by the time and human resources needed to develop such economic analyses.

The Pan American Health Organization (PAHO) provides technical assistance for evidence-based decision making regarding new vaccine introduction in Latin America and the Caribbean, including development of economic analyses. PAHO’s ProVac Initiative was launched in 2006 with the objective to promote and strengthen technical capacity in countries to perform economic analyses regarding vaccine introduction, and to make critical assessments of all factors involved in the decision-making process, including technical, logistical, and financial criteria [4].

Cost-of-illness (COI) studies aim to identify and measure the total costs attributable to a particular disease and can include both direct (medical and non-medical) and indirect costs (e.g., productivity losses). Depending on methods used, type of costs included, and syndromes considered, COI estimates can vary significantly.

To date, COI studies assessing pneumococcal diseases have been conducted in several countries, using various methodologies. This article aims to systematically review such studies conducted in the LAC region, assessing the methods used in each of the studies and analyzing results in light of the methodological approach used.

2. Methods

The authors followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement and checklist for undertaking and reporting this systematic review [5]. Fig. 1 depicts the flow of information throughout the review, including the number of records identified, articles excluded and the reasons for exclusions, and the final number of articles included in the final review.

2.1. Literature search

As an initial step, published studies, guidelines, and clinical trials were searched in relevant databases. These included the Cochrane Central Register of Controlled Trials (CENTRAL); Embase, a biomedical database; the MEDLINE database of the United States National Medical Library; the Latin American and Caribbean Health Sciences Literature database (LILACS); and the Economic Evaluation Database of the United Kingdom National Health Service (NHS EED). Searches for relevant dissertations and theses available in the database of Brazilian academic dissertations and theses (“Banco de Teses”) were also conducted [6]. The date range for searches used November 2011 as the end date; there was no start date. No language restriction was applied. Search strategies were applied in English, Portuguese, and Spanish. The search strategy included a combination of free text terms and standardized terms from the medical subject headings (MeSH) for searches in English-language databases. For searches in LILACS, MeSH synonyms in Portuguese available in the “Descritores em Ciências da Saúde” (DeCS) database were used. MeSH terms used included: “Pneumococcal Infections”, “Cost of Illness”, “Cost and Cost Analysis”, “Absenteeism”, “Indirect Costs”, “Societal Costs”, “Productivity Loss”, “Work Impairment”, and “Presenteeism”.

2.2. Study selection

We considered the following inclusion criteria for studies in this systematic review: studies about economic evaluation or cost of illness, studies conducted in the LAC region, and studies assessing the economic burden of pneumococcal disease or the economic impact of pneumococcal vaccination programs. Studies conducted in countries outside the LAC region and in adult populations (18 years of age and older) were excluded from the analysis. All records retrieved in the literature search were initially screened by title and abstract. When eligibility for inclusion could not be determined after initial title/abstract review, full articles were obtained and independently reviewed by two reviewers. Duplicate studies were excluded. If eligibility was not consensual among reviewers, a third reviewer assessed the paper for final decision on inclusion.

2.3. Data extraction and analysis

Results were analyzed considering each study’s methodological aspects. The following information was extracted into standardized data retrieval forms: author; publication year; country; target population; type of study (economic evaluation or cost-of-illness study); type of analysis (cost-effectiveness, cost-utility or cost-benefit analysis, when applicable); study perspective; type of costs included (direct, indirect, or both); sources of unit costs; source of health care resource utilization data (primary data collection, database analysis, expert panel, or modeling); time horizon; and results including currency and year. For productivity loss estimates, methods of cost estimation (human-capital or friction-cost approach) and monetizing method were assessed.
Study perspectives considered included the following: (a) societal perspective, in which all medical and non-medical direct costs, as well as indirect costs incurred by health systems, patients, and their families were included in the analysis; (b) public health system perspective, in which only direct costs incurred by the public health system were included in the analysis; and (c) private health system perspective, in which only costs reimbursed by health insurance companies (usually direct medical costs) were included in the analysis.

Direct medical costs considered in the hospital setting included medications, diagnostic tests, surgeries, health professional fees, physiotherapy, parenteral nutrition, blood products, and ambulance transportation. In the outpatient setting the costs included were medications, diagnostic tests, and health professional fees. Direct medical costs also included the cost of long-term treatment costs, cochlear implants and other procedure-related costs, special education, caregiver time, and rehabilitation.

Non-medical costs included costs of transportation of patients and caregivers to and from the health care facilities. Indirect costs were defined as costs related to productivity losses and were based on the number of days off work (for the parent or caregiver) and income lost due to pneumococcal disease.

Syndromes/outcomes included were acute otitis media (AOM), all-cause pneumonia, pneumococcal pneumonia, meningitis (with or without sequelae), bacteremia, sepsis, and invasive pneumococcal disease (pneumococcal meningitis and sepsis).

By establishing purchasing power equivalence, where one international dollar purchases the same quantity of goods and services in all countries, PPP conversions allow cross-country comparisons of economic aggregates on the basis of physical levels of output, free of price and exchange rate distortions.

### 3. Results

A total of 1241 records were initially retrieved from the databases of published studies, guidelines and clinical trials. After initial title/abstract screening, only 22 articles were retrieved to be read in full. An additional 6 articles were further excluded, resulting in 16 papers included in the final analysis (Fig. 1). These studies were published between 2005 and 2011.

There were four papers on Brazil [9–12], three on Argentina [13–15], two on Colombia [16,17], two on Mexico [18,19], one on Uruguay [20], one on Chile [21], and three that analyzed groups of LAC countries [22–24]. The main characteristics of these studies are described in Tables 1 and 2.

In addition, two theses were initially identified from the Brazilian “Banco de Teses” database. One was deleted as it was a narrative review of cost estimation methods for economic evaluation of vaccination programs. One thesis was included in the final analysis [11].

#### 3.1. Study participants

Eight of the 16 studies assessed the economic impact of pneumococcal disease in children up to 5 years of age [9,10,12,15,20–24]. Different target age groups (2, 3, and 10 years old) were used in the remaining studies [11,13,14,16–19,21].

Cost-effectiveness studies (n = 11) were conducted considering hypothetical birth cohorts [9,10,12,14,15,17–20,23,24], and

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**Fig. 1.** Systematic review of pneumococcal disease costs and productivity loss studies in Latin America and Caribbean. PRISMA flowchart.

<table>
<thead>
<tr>
<th>Citations</th>
<th>Citations</th>
<th>Citations</th>
<th>Citations</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEDLINE/Pubmed</td>
<td>812</td>
<td>EMBASE</td>
<td>1366</td>
</tr>
<tr>
<td>All years</td>
<td>89</td>
<td>NHS EED</td>
<td>6</td>
</tr>
<tr>
<td>All years</td>
<td></td>
<td>LILACS</td>
<td></td>
</tr>
<tr>
<td>All years</td>
<td></td>
<td>Articles retrieved from other sources</td>
<td>1 Citation</td>
</tr>
</tbody>
</table>

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2.4. Currency units

Results are presented in both local currencies and US dollars, considering the year of the study. Official inflation rates of each country [7] and exchange rates for local currency to US dollars, considering the 2010 purchasing power parity (PPP), were used [8].
Table 1
Main characteristics of studies on pneumococcal disease costs and productivity loss in LAC.

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Country</th>
<th>Currency/year of reported results</th>
<th>Study design</th>
<th>Target population</th>
<th>Study perspective</th>
<th>Disease outcomes/syndromes considered</th>
<th>Health resources utilization data sources</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guzmán NA, 2005 [16]</td>
<td>Colombia</td>
<td>2002 US dollars</td>
<td>COI (prospective)</td>
<td>128 pneumonia cases (64 bacterial, 64 viral) 0–2 years old</td>
<td>Public health care system and societal</td>
<td>Pneumonia (bacterial and viral) (only hospitalizations)</td>
<td>Hospital databases (4 hospitals)</td>
</tr>
<tr>
<td>Guzmán NA, 2010 [17]</td>
<td>Colombia</td>
<td>2006 US dollars</td>
<td>CEA</td>
<td>Children with low birthweight 0–2 years old</td>
<td>Public health care system</td>
<td>All-cause AOM, all-cause pneumonia, meningitis, and invasive pneumococcal diseases</td>
<td>Sabin Institute report (physician and parent interviews) [3]</td>
</tr>
<tr>
<td>Constenla D, 2007 [22]</td>
<td>Brazil, Chile, Uruguay</td>
<td>2004 US dollars</td>
<td>COI Hospital: retrospective (90%); prospective (10%); ambulatory: prospective (100%)</td>
<td>753 children (166 Brazil, 400 Chile, 187 Uruguay) 0–5 years old</td>
<td>Public health care system</td>
<td>All-cause AOM, all-cause pneumonia, and pneumococcal meningitis</td>
<td>Prospective multi-center observational study; secondary databases</td>
</tr>
<tr>
<td>Constenla D, 2008 [23]</td>
<td>Brazil, Chile, Uruguay</td>
<td>2004 US dollars</td>
<td>CEA</td>
<td>Annual hypothetical birth cohort, followed up to 5 years</td>
<td>Societal</td>
<td>All-cause AOM, all-cause pneumonia, pneumococcal meningitis, and pneumococcal sepsis</td>
<td>Prospective multi-center observational study*; secondary databases</td>
</tr>
<tr>
<td>Sinha A, 2008 [24]</td>
<td>All LAC countries</td>
<td>2005 US dollars</td>
<td>CEA</td>
<td>Annual hypothetical birth cohort, followed up to 5 years</td>
<td>Societal</td>
<td>All-cause AOM, all-cause pneumonia, pneumococcal meningitis, and pneumococcal sepsis</td>
<td>Physician interviews (10 LAC countries); interviews with parents of sick children, secondary databases</td>
</tr>
<tr>
<td>Vespa G, 2009 [9]</td>
<td>Brazil</td>
<td>2006 US dollars</td>
<td>CEA</td>
<td>Annual hypothetical birth cohort, followed up to 5 years</td>
<td>Public health care system and societal</td>
<td>AOM with and without complications, pneumonia, pneumococcal sepsis, pneumococcal meningitis with or without disabilities</td>
<td>Physician interviews, WHO-CHOICE, Brazilian HMOs and MCOs</td>
</tr>
<tr>
<td>De Souza CPR, 2009 [10]</td>
<td>Brazil</td>
<td>2008 Brazilian reais</td>
<td>CEA</td>
<td>Annual hypothetical birth cohort, followed up to 5 years</td>
<td>Public health care system</td>
<td>AOM, pneumonia, and invasive pneumococcal diseases</td>
<td>Medical records of 300 hospitalized patients in Ribeirão Preto city</td>
</tr>
<tr>
<td>Lucarevski BR, 2010 [11]</td>
<td>Brazil</td>
<td>2009 Brazilian reais</td>
<td>COI (retrospective)</td>
<td>0–10 years</td>
<td>Public health care system</td>
<td>Pneumococcal meningitis (only hospitalizations)</td>
<td>Medical records, secondary databases</td>
</tr>
<tr>
<td>Sartori AM, 2012 [12]</td>
<td>Brazil</td>
<td>2004 Brazilian reais</td>
<td>CEA</td>
<td>Annual hypothetical birth cohort, followed up to 5 years</td>
<td>Public and private health care systems and societal</td>
<td>AOM, pneumonia, pneumococcal sepsis, and pneumococcal meningitis</td>
<td>Secondary databases</td>
</tr>
<tr>
<td>Larraz GG, 2010 [20]</td>
<td>Uruguay</td>
<td>2008 US dollars</td>
<td>CEA</td>
<td>Annual hypothetical birth cohort, followed up to 5 years</td>
<td>Public and private health care systems and societal</td>
<td>AOM, pneumonia, empyema, bacteremia–sepsis, meningitis without and with sequelae (neurologic and auditory)</td>
<td>Medical records of hospitalized patients; expert panel</td>
</tr>
</tbody>
</table>
3.2. Study design

There were 4 cost-of-illness (COI) studies [11,16,21,22], 11 cost-effectiveness analyses (CEA) of pneumococcal vaccine introduction [9,10,12,14,15,17–20,23,24] and 1 burden of disease study [13]. Productivity losses were estimated in eight studies [9,12,14–16,20,23,24] and costs associated with long-term sequelae were included in five studies [9,10,13,14,20].

All COI studies included in this review were observational studies. Two used prospective data collection [16,21], one was a mix of prospective and retrospective data collection [22], and one used retrospective data collection based on the review of medical charts and interviews with parents [11]. Two studies included only inpatient costs [11,16].

All CEA were based on modeling. None of them was conducted alongside a clinical trial or observational study specifically designed to assess both economic and clinical outcomes.

3.3. Perspectives

Regarding the analytic perspective, four studies considered the societal perspective [13,14,23,24]; one considered both societal and public health care system perspectives [9], seven considered only the public health care system perspective [10,11,16–19,22], one considered both the public and private health care systems perspectives [21], and three considered public, private, and societal perspectives [12,15,20].

3.4. Cost estimates

Table 3 describes the direct costs of the pneumococcal infection as originally presented by authors and in 2010 US (international) dollars. The mean cost estimates of all studies is also presented. As expected, costs varied by syndrome (Fig. 2). Acute otitis media (AOM) was the event with lower costs, although in recurrent and/or complicated AOM cases that required surgical procedures and/or hospitalization, cost estimates increased 7–39 times compared to non-complicated cases [10,13]. In one study conducted in selected LAC countries, health care costs (e.g., 10% in Brazil and 84% in Chile) and out-of-pocket expenses (86% in Brazil and 15% in Chile) were factors that contributed to huge differences in AOM costs [22].

Costs for hospitalized pneumonia cases were approximately 6–8 times higher than cases managed as outpatients [13]. The highest costs reported were attributed to pneumococcal meningitis, with the estimated annual costs of long-term meningitis sequelae reaching 3–5 times the costs of acute meningitis [13].

The costs per hospitalization varied by type of health facility, with significantly higher costs in public facilities when compared to public health facilities [12,14,15,20,21]. One study reported that hospitalization costs were 80% higher in private facilities compared to public ones [14].

3.5. Indirect costs

The main methodological characteristics of studies on pneumococcal disease indirect costs are presented in Table 2. All indirect cost studies considered the human-capital approach (HCA), and most (6 out of 8) used average country wages to estimate the cost of each unit of paid work time [9,12,14,20,23,24]. Two studies collected primary data of self-reported wages [15,16]. One study included government benefits for patients with meningitis long-term sequelae (i.e., deafness and/or neuromotor disabilities as a result of meningitis) [9].

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Table 2
Methodological characteristics of studies on pneumococcal disease costs and productivity loss in LAC, with indirect cost estimates.

<table>
<thead>
<tr>
<th>Author/year</th>
<th>Country</th>
<th>Collection of primary data</th>
<th>Absenteeism</th>
<th>Presenteeism</th>
<th>Inclusion of long-term losses</th>
<th>Methodological approach</th>
<th>Wage/income cost estimation</th>
<th>Productivity loss outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guzmán NA, 2005 [16]</td>
<td>Colombia</td>
<td>Yes (n = 100)</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>HCA</td>
<td>Self-reported wage</td>
<td>Lost days of paid work × wage</td>
</tr>
<tr>
<td>Constenla D, 2008 [23]</td>
<td>Brazil, Chile, Uruguay</td>
<td>Yes (n = 60)</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>HCA</td>
<td>Country mean wage</td>
<td>Mean hours × mean wage</td>
</tr>
<tr>
<td>Sinha A, 2008 [24]</td>
<td>LAC region</td>
<td>Yes (n = 60)</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>HCA</td>
<td>Country mean wage</td>
<td>Mean hours × mean wage</td>
</tr>
<tr>
<td>Vespa G, 2009 [9]</td>
<td>Brazil; experts</td>
<td>Yes; experts</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>HCA</td>
<td>Country minimum wage</td>
<td>Lost days of paid work × minimum wage</td>
</tr>
<tr>
<td>Sartori AM, 2012 [12]</td>
<td>Brazil</td>
<td>No; assumptions</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>HCA</td>
<td>Country mean wage (women)</td>
<td>Inpatient days × daily wage; outpatients × 5 days for pneumonia and 1 day for AOM × daily wage; outpatient visits × 2 × hourly wage; daily wage × 0.5 × daily wage; outpatient visits × 2 × hourly wage; daily wage × 2 × hourly wage</td>
</tr>
<tr>
<td>Larraz GG, 2010 [20]</td>
<td>Uruguay</td>
<td>No; assumptions</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>HCA</td>
<td>Country mean wage</td>
<td>Lost days of paid work × daily income</td>
</tr>
<tr>
<td>Giglio ND, 2009 [14]</td>
<td>Argentina</td>
<td>No; assumptions</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>HCA</td>
<td>Country mean wage</td>
<td></td>
</tr>
<tr>
<td>Urueña A, 2011 [15]</td>
<td>Argentina</td>
<td>Yes; secondary reference</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>HCA</td>
<td>Self-reported family income (divided by all the residents of the house)</td>
<td></td>
</tr>
</tbody>
</table>

LAC, Latin America and Caribbean region; HCA, human-capital approach; AOM, acute otitis media.

- Government benefits for disabled patients (sequelae).
- Average length of stay in hospital retrieved from government databases and the clinical course of disease treated in an ambulatory setting.
- Taking into account unemployment rates.
Table 3
Estimated direct costs by syndrome/disease outcomes, as originally presented and converted to 2010 US dollars.

<table>
<thead>
<tr>
<th>Author/year</th>
<th>Country</th>
<th>Currency/year of reported results</th>
<th>Study perspective</th>
<th>Acute otitis media (original currency/2010 USD)</th>
<th>All-cause pneumonia (original currency/2010 USD)</th>
<th>Pneumococcal pneumonia (original currency/2010 USD)</th>
<th>Pneumococcal meningitis (Original currency/2010 USD)</th>
<th>Bacteremia/sepsis (Original currency/2010 USD)</th>
<th>Sequelae (costs per year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constenla D, 2008 [23]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3 (Continued)

<table>
<thead>
<tr>
<th>Author/year</th>
<th>Country</th>
<th>Currency/year of reported results</th>
<th>Study perspective</th>
<th>Acute otitis media (original currency/2010 USD)</th>
<th>All-cause pneumonia (original currency/2010 USD)</th>
<th>Pneumococcal pneumonia (original currency/2010 USD)</th>
<th>Pneumococcal meningitis (original currency/2010 USD)</th>
<th>Bacteremia/sepsis (Original currency/2010 USD)</th>
<th>Sequelae (costs per year) (original currency/2010 USD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Giglio ND, 2010</td>
<td>Argentina</td>
<td>2007 USD</td>
<td>Public and private health care systems and societal Public and private health care systems</td>
<td>24/41</td>
<td>NA</td>
<td>104/180</td>
<td>1592/2740</td>
<td>Inpatient: 126/259</td>
<td>NA</td>
</tr>
<tr>
<td>All studies</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

This Table displays only public costs of all studies (private cost data not shown). Decimal values for currencies were rounded to the nearest integer. NA—not available

1 Costs of pneumococcal disease in Latin America countries
2 Economic impact of pneumococcal conjugate vaccination in Brazil, Chile and Uruguay
3 Medical costs per child.
4 Total direct cost per child including medical and non-medical costs.
5 With or without adenosidectomy or placement of tympanostomy tubes.
6 De Souza et al. [10] estimate for auditory sequelae costs considered only the cost of hearing aid and was not included in the calculation of average total costs.
7 Pneumonia meningitis and pneumococcal sepsis considered together as invasive pneumococcal disease.
8 Pneumonia with bacteremia.
9 Pneumonia with pleural effusion or empyema.
10 Based on unpublished estimates of resource use from a Delphi panel.
11 Direct medical costs of bacteremia and pneumonia were estimated based on 37 pneumonia and 20 bacteremia/sepsis cases in two intensive care units of a tertiary hospital without mention of pneumococcal etiology – Navarrete-Navarro S. Costos secundarios por infecciones nosocomiales en dos unidades pediátricas de cuidados intensivos. Salud Pública Méx 1999; 41(Suppl. 1):51–8. Costs of meningitis, AOM and outpatient pneumonia were obtained from an IMSS report – Instituto Mexicano del Seguro Social, Dirección de Planeación y Finanzas, Coordinación de Presupuestos, Contabilidad y Evaluación Financiera. Costs by diagnosis-related group for hospitalized cases. Mexico, D.F. IMSS; 2003.
12 Cost values are expressed only in 2010 USD and as a mean [min – max]. When the costs per event were not specified as out- or inpatient care, they were excluded from the mean calculation.
Two studies conducted in Brazil differ in these estimates because national country wages were obtained with a four-year interval. One did primary data collection [9], while the other adopted an assumption based on length of hospital stay of a sick child with an employed caregiver [12].

In the majority of studies the inclusion of productivity losses contributed to a smaller proportion of the total costs compared to direct costs with a wide variability (1.9–78.3%) [14,24]. In outpatient AOM and pneumonia cases, three studies reported indirect costs that were higher than direct costs due to productivity losses of the caregiver [9,12,20].

Estimated costs for productivity loss related to pneumococcal diseases are presented in Table 4 as originally described by the authors and in 2010 US dollars.

4. Discussion

This systematic review analyzed pneumococcal disease cost-of-illness and productivity loss studies in the LAC region. The methodology for collecting data about health resource utilization and their costs varied broadly among studies (retrospective and prospective primary data collection, government and hospital databases, international literature adaptation, physician and parent interviews, expert panels). Varying methods and data sources were used in the same studies, making it difficult to compare results between studies conducted in different countries and to extrapolate cost results from one setting to another.

Although there is no method that is the gold standard for cost-of-illness studies, those using micro-costing methodology, collecting primary data prospectively, and considering the societal perspective are considered to generate more accurate cost estimates [25]. Secondary databases were commonly used as data sources for health resource utilization and costs [9,11–14,19,24]. These included vital registries, census, population and household surveys, and administrative records. Many countries in LAC have health information systems that managers and policy makers use to plan and evaluate both performance and costs of health care programs and interventions. Although most of these databases are
### Table 4

Estimated indirect costs by syndromic disease outcomes, as originally presented in studies and converted to 2010 US dollars.

<table>
<thead>
<tr>
<th>Author/year</th>
<th>Country</th>
<th>Categorical diagnosis</th>
<th>Secondary cause</th>
<th>Lower respiratory infection</th>
<th>Expected years of life lost</th>
<th>Other sequelae</th>
<th>Multiresistant pneumococcal disease*</th>
<th>Cost per year</th>
<th>Cost of reported IPD results (original currency/2010 USD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brazil 2009 [16]</td>
<td>Brazil 910</td>
<td>Inpatient: 67/126</td>
<td>Brazil 792</td>
<td>-</td>
<td>-</td>
<td>241/900</td>
<td>241/900</td>
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*Costs were rounded to the nearest integer.
• Invasive pneumococcal disease (IPD) includes pneumococcal meningitis and pneumococcal sepsis.
• Costs per year. Costs per patient. Includes costs associated with hospitalizations due to acute respiratory infection in children in different public hospitals in Buenos Aires (Buenos Aires Health Authority) and Argentina (Buenos Aires Health Authority). Data from [2007] 105(1):5–11.

**Note:** Costs per operational costs are expressed only in 2010 USD and as a mean [min – max].
developed and used for administrative and reimbursement purposes, they are valuable sources of information on health care resource utilization and costs. A potential limitation of using such data sources is the quality of data input. Another limitation is that an estimated cost of illness may be an underestimate of true costs.

In addition to primary or secondary data collection, health care resource utilization estimates can be obtained using a "per protocol" or a guideline-oriented approach, in which a typical treatment course is developed by expert panels, and costs of each treatment component are then estimated using appropriate data sources to determine unit costs. This approach was used in many of the studies reviewed [9,13–15,18,20,24], indicating the lack of secondary data sources in many countries. This method relies on expert judgment for determining the average treatment, length, and proportion of patients receiving it. As such, it may represent either an over-or under-estimate of resource utilization.

In most studies conducted in LAC, pneumococcal meningitis is associated with higher costs compared to other pneumococcal syndromes requiring hospitalizations (pneumonia, bacteremia, sepsis). Some studies showed a huge variation in costs when they separated complicated cases from uncomplicated ones [11,15,20]. The cost estimates generated from primary data collection [10,11,20] and specialist opinions [15,18] were higher than those obtained from secondary databases [9,12–14,17,22–24].

Similar results were found for pneumococcal pneumonia and AOM episodes, with clear differences in cost estimates if complications occurred and/or hospitalization was needed. Most studies have separated the costs of a single AOM episode from recurrent and/or complicated cases, but without a clear definition of diagnosis criteria. Likewise, the highest cost estimates came from the two Mexican studies and were generated using information from an expert panel [18] and diagnosis-related group payment for hospitalized patients [19]. This latter study showed much higher cost estimates than the average. These values may have included all cases together (simple and complicated), but this cannot be confirmed.

Long term sequelae costs were indirectly estimated in five studies and there was a wide difference among them [9,10,13,14,20]. The occurrence of auditory and/or other neurologic sequelae increased the long-term costs for health systems and society. The comparison of these estimates is difficult, however, because some studies do not clearly describe the methodology for estimating costs related to sequelae [9,10]. One study based estimates on interviews conducted with five parents [14], another study used local expert opinion [20], and a third based its estimates on the authors’ assumption [13]. Furthermore there was no uniformity in the characterization of auditory sequelae (unilateral versus bilateral hearing impairment, severe hearing sequelae needing special education and cochlear implants, partial hearing loss versus deafness) and neurologic sequelae (neuromotor disabilities, seizure disorder).

All studies adopted the human-capital approach to estimate productivity loss based on work time lost (hours or days) multiplied by its costs. Some differences in indirect costs could be attributed to the methods used for assessing the value attributed to paid work time. The majority of studies obtained this information predominantly from average national wages [12,14,20,23,24]. By using the societal perspective, the inclusion of productivity loss costs contributed to a smaller proportion of the total costs compared to direct costs, although this percentage varied greatly from one study to another, and sometimes, in uncomplicated cases of AOM and pneumonia, indirect costs were higher than direct costs.

Even after adjusting for inflation and taking PPP into account, cost estimates presented in different studies are difficult to compare and there is not a single explanation for the broad variation.

In some cases the variation could be explained by the type of data source used (higher values for values obtained from expert panels and microcosting), inclusion of different types of costs (medical, non-medical, and societal costs), the perspective considered, and differences in the value of payments for health resources among countries. All studies were done in countries grouped as upper-middle-income (based on World Bank classifications [26]), so there is no reason to suggest that cost estimates differ because of income differences among countries.

The generalization of cost estimates from the published literature is difficult due to the important differences already described. In the absence of accurate cost estimates there are two reports that are available to the general public that can be used as a proxy for cost estimates in regional analysis. The first is the World Health Organization’s project “Choosing Interventions that are Cost Effective” (WHO-CHOICE) which provides estimates of the per diem cost of public hospitals, outpatient visits, and health center visits for 14 epidemiological categories based on geographical region and mortality stratum [27]. The second is a report by the Sabin Vaccine Institute (in collaboration with PAHO, US Centers for Disease Control and Prevention [CDC] and the Global Alliance for Vaccines and Immunizations [GAVI]) which estimated the burden and costs of pneumococcal disease in Latin America and the Caribbean for 2007 [3]. This report demonstrates the average regional costs due to treatment (in- and outpatient care) for pneumonia, meningitis, acute otitis media, and sepsis, and provides insight into the cost of pneumococcal disease by country income group (low income, lower-middle income, and upper-middle income).

5. Conclusion

This systematic review reinforces the need to standardize methodology for cost-of-illness studies in order to compare results and duplicate them in different settings. Estimates from standardized approaches will be useful for future economic analysis conducted to support the decision-making process on the introduction of new vaccines in countries where local pneumococcal epidemiologic and costing data are limited or not readily available. However, caution must be taken when reproducing these results in other settings, as methodological aspects of any given study will result in estimates with varying levels of accuracy.

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[7] Index Mundi Inflation rate (consumer prices); historical data graphs per year [Internet]. Available at: http://www.indexmundi.com/g/g.aspx?v=71&c=us&l=en [accessed 10.06.12].


