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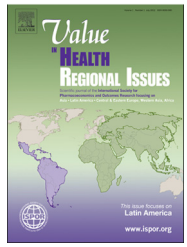

Burden of Culture-Confirmed Pediatric Pneumococcal Pneumonia in Latin America and the Caribbean: A Systematic Review and Meta-Analysis

Ariel Esteban Bardach, MD, PhD, MSc[1,*], *Lucila Rey-Ares, MD, MSc*[1], *María Calderon Cahua, MD, MSc*[1], *Agustín Ciapponi, MD, MSc*[1], *María Luisa Cafferata, MD*[1], *Gabriela Cormick, BSc, MSc*[1], *Ángela Gentile, MD*[2]

[1]*Institute for Clinical Effectiveness and Health Policy, National Scientific and Technical Research Council, Argentina;* [2]*Children's Hospital "Dr Ricardo Gutierrez", Buenos Aires, Argentina*

ABSTRACT

Background: Pneumococcal pneumonia (PP) causes almost one in five deaths in children younger than 5 years worldwide. In Latin America and the Caribbean (LAC), pneumonia causes 14% of all deaths. Although pneumococcal disease is a vaccine-preventable disease that accounts for a significant proportion of this burden, the decision-making process to introduce pneumococcal conjugate vaccines in official schedules is still complex in LAC. Confirmed PP cases and epidemiology are the basis for broader projections. **Objective:** To gather all the information available in the LAC region to assist decision makers. **Methods:** We performed a systematic review of studies of consolidating and culture-confirmed pediatric PP in LAC (2000–2016) using a generic academic Internet search and search engines without language restrictions. Pairs of reviewers independently selected and assessed the studies' methodological quality. We analyzed meta-information on pneumococcal serotypes available from the SIREVA laboratory-based surveillance system. **Results:** A total of 35 out of 750 initially identified studies were included. In the age group between 0 and 59 years, the incidence of culture-confirmed PP ranged from 10.2 to 43.0/100,000 children, with a pooled incidence of 20.4/100,000 children (95% confidence interval 0.0–123.2). Mortality ranged from 0.4 to 5.7/100,000 children, and the pooled mortality was 2.9/100,000 children (95% confidence interval 0.3–8.2). The pooled serotype distribution from surveillance data showed that serotypes 14, 1, and 6B were the most frequent serotypes in LAC, all included in licensed vaccines. **Conclusions:** Studies on confirmed pediatric PP were scarce in LAC in 2000 to 2016. Epidemiology indicators and health resource use are still poorly defined.

Keywords: child health, Latin America, pneumonia, *Streptococcus pneumonia*, systematic review.

Introduction

Reduction of child mortality was one of the eight Millennium Development Goals adopted in 2000 by world leaders. Because it is relatively common and severe, pneumococcal disease represents an important cause of morbidity, mortality, and health care system costs [1]. Pneumonia, an invasive pneumococcal disease, causes almost one in five deaths in children younger than 5 years worldwide, more than 1.6 million children each year. In Latin America and the Caribbean (LAC), pneumonia is responsible for the 14% of deaths in this age group [2].

A recent study reported that in the year 2009, *Streptococcus pneumoniae* infections led to 648,000 cases and 24,300 deaths because of pneumonia worldwide [3]. Furthermore, Valenzuela et al. [4] estimated an annual burden of 330,000 pneumonia cases among children younger than 5 years in LAC. The annual number of deaths due to pneumococcal disease reported in this region ranged between 12,000 and 28,000 [4].

Most pneumonia episodes are not bacteremic and pneumococcus is difficult to isolate because of its fastidious nature. The proportion of pneumonia cases tested, the proportion of tests positive for any pathogen, the assessment of antibiotic use before sample collection, and contamination rates, among other factors, are important issues not always reported by epidemiological studies. Despite low microbiological isolation, the epidemiology and health resource use of confirmed cases help develop burden of disease projections to evaluate the impact and effectiveness of pneumococcal conjugate vaccines (PCVs) with local data. In LAC, this type of information remains incomplete. The first data available came from the SIREVA network, a laboratory-based surveillance system driven by the Pan American Health Organization (PAHO) [5], gathering information retrieved from

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* *Address correspondence to:* Ariel Esteban Bardach, Institute for Clinical Effectiveness and Health Policy–National Scientific and Technical Research Council, Argentina Cochrane Center, Dr. Emilio Ravignani 2024, Buenos Aires C1414CPV, Argentina.

E-mail: abardach@iecs.org.ar

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hospitalized cases. SIREVA is based in a network of sentinel laboratories and hospitals that provide prospective information about distribution data serotypes and susceptibility to antibiotics of *S. pneumoniae*, *Haemophilus influenzae*, and *Neisseria meningitidis* as well as epidemiological information. Two other important pieces of research have also guided international policies in the last decade [3,6].

Although it is clear that pneumococcal disease is now vaccine-preventable and accounts for a significant proportion of the burden of disease, the decision-making process regarding the introduction of the different vaccines in official immunization schedules is still ongoing in the region, with budget and logistical constraints. High-quality and updated epidemiological evidence is needed to assess the current situation in the region as well as the potential impact of different vaccination strategies. The World Health Organization (WHO) [7] suggests performing economic evaluations before deciding to incorporate a new vaccine in national immunization schedules. Public health costs associated with the management of cases of pneumococcal disease are often under-reported and underestimated in the literature. Accurate estimates of these costs are needed to understand the true economic burden of pneumococcal disease and as inputs for the aforementioned evaluations. Although decision makers are primarily interested in data on effectiveness and disease burden, the high costs of the vaccine are likely to stimulate interest in information about the economic implications of its use.

The ProVac initiative is a country-led endeavor of PAHO, which aims to promote evidence-based decisions, making scientific evidence accessible to policymakers at the country level [8,9]. In LAC, PCV introduction started in 2008 and still continues. Most LAC countries now include PCV in their national schemes.

The aim of this study was to help address some of these existing knowledge gaps and to provide data on the burden use of resources including available direct costs and characteristics of pneumococcal disease in LAC that are necessary to guide prevention efforts and inform vaccine policy decisions.

Methods

We performed a systematic review and meta-analysis of observational studies of consolidating microbiologically confirmed pneumococcal pneumonia (C-PP) in LAC. We searched Cochrane CENTRAL, specialized registers of the Cochrane Infectious Diseases Group, MEDLINE, Embase, and LILACS from January 2000 to January 2016. We used the terms "pneumonia" and "*Streptococcus pneumonia*" and their variations in plain text, thesaurus, and terms from the Medical Subject Headings, adapting the search across databases (for detailed search strategies, see Appendix 1 in Supplemental Materials found at http://dx.doi.org/10.1016/j.vhri.2017.04.004). We also performed a generic and academic Internet search (Scopus and Google Scholar). An annotated search strategy for gray literature was included to obtain information from relevant sources, such as reports of regional ministries of health, PAHO, WHO, 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 guidelines of the Meta-analysis of Observational Studies in Epidemiology group [10] and the Preferred Reporting Items for Systematic Reviews and Meta- Analyses (PRISMA) statement for reporting systematic reviews and meta-analyses [11,12].

Authors from selected articles were contacted to obtain missing or additional information when 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-analyses with original data were also included for quantitative synthesis. Studies (or surveillance periods for SIREVA data) were included when at least 20 cases of C-PP were reported (so as to both be inclusive and avoid studies with very small number of observations). Studies with patients' enrollment before 1995 were excluded. If data were duplicated or data subsets appeared in more than one publication, the study with the larger sample size was used. A C-PP case in children younger than 5 years was defined as a febrile individual with cough, tachypnea, and decreased breath sounds over the affected area with radiologic pulmonary consolidation or without pleural effusion, with microbiologic confirmation of the presence of *S. pneumoniae* in blood or pleural effusion cultures or by latex agglutination. Studies focusing on special populations and chronically ill patients were excluded including patients with cystic fibrosis, ciliary dyskinesia, and other structural conditions. Data from the regional surveillance system SIREVA were retrieved because it represents the most suitable epidemiological source for serotypes in LAC because of its representativeness and laboratory quality standards [5,13]. SIREVA reports lack clinical details for PP samples, and thus all cases reported were included only for serotype analyses.

Outcome measures for C-PP included incidence, mortality, percentage of pneumonia cases with culture-confirmed pneumococcal etiology, serotype distribution, and case-fatality rate (CFR). We also explored data on use of resources (length of hospitalization, use of supportive care, number of ambulatory visits, school days lost, and parents work absenteeism reported both for the families and for the government) and costs. For incidence estimates we considered only those studies performed within the general population.

Screening and Data Abstraction

Two reviewers independently prescreened the titles and abstracts of all identified citations and selected potentially eligible studies. Two other reviewers 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

Six reviewers independently evaluated the methodological quality of studies included in the systematic review. The risk of bias for observational studies was assessed by the tool ROBINS-I, developed in 2016 by Sterne et al. [14]. We used the pre-intervention domains of this tool because no study included specific interventions. We reported a summary risk of bias considering five criteria: bias in selection of participants into the study, bias in the measurement of outcomes, bias due to confounding, bias due to missing data, and bias in selection of reported results (see Appendix 2 in Supplemental Materials found at http://dx.doi.org/10.1016/j.vhri.2017.04.004). Disagreements were solved by consensus. When overlapping information was identified, we selected the one with the largest data set to avoid double counting of cases.

Statistical Analyses

We conducted a meta-analysis of rates to estimate the incidence and mortality of C-PP. Because the follow-up period of the studies varied considerably, we based the calculation of incidence rates on person-years, dividing the number of new cases occurring during the follow-up period (the numerator) by the total person-time units (person-years) of the group at risk (the denominator). The person-time incidence rate, or incidence density rate, is an appropriate measure of incidence when follow-up periods are

unequal. To calculate pooled incidence rate ratios, we used the Comprehensive Meta-Analysis software package, version 2.2.021 (Biostat, Englewood, NJ). For serotypes we conducted a meta-analysis of proportions. We applied an arc-sine transformation to stabilize the variance of proportions following the Freeman-Tukey variant of the arc-sine square root of transformed proportions method [15]. The estimates and its confidence interval (95% CI) were calculated using the DerSimonian-Laird [16] weights for the random effects model, in which heterogeneity between studies was found. We calculated the I^2 statistic as a measure of the proportion of the overall variation in the proportion that was attributable to between-study heterogeneity. StatsDirect (StatsDirect Ltd., Cheshire, UK), Comprehensive Meta-Analysis, and STATA 13.0 (StataCorp LLC, College Station, TX) were used for all analyses.

Direct costs referred to the costs of the diagnosis and treatment of the clinical condition, and indirect costs included the costs of transportation, absenteeism, and other related expenditures. All costs were expressed in 2006 international dollars (I$); 2006 was the most common year of identified studies. The international dollar has the same purchasing power that the US dollar has in the United States. Costs in local currency units were converted to international dollars 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 one country to the other using the common reference point of the US dollar.

Results

The bibliographic search retrieved 750 studies after removing duplicates. After the first screening process, 150 studies were considered eligible and 53 studies remained after full-text screening. During the data extraction process, 19 studies were excluded (not being about pneumococcal etiology, or no data set available). As shown in Figure 1, with the addition of 1 personal communication, 35 studies remained for analyses (26 with epidemiological data [17–41] and 9 for costs and use of resources analysis [42–50]). Of the 26 studies used to perform meta-analyses, 7 studies carried a low risk of bias, 14 moderate risk, and 5 serious risk, as assessed through the methods described previously. No study in the present work included vaccinated children. We found some studies that did not discriminate between ages, providing data for the age group between 0 and 14 years. Even though our aim was to assess the epidemiology of C-PP in children younger than 5 years, we decided to include these 11 studies because the information gathered was scarce. Incidence and mortality rates were taken from five studies from Argentina [22,28], Uruguay [20],

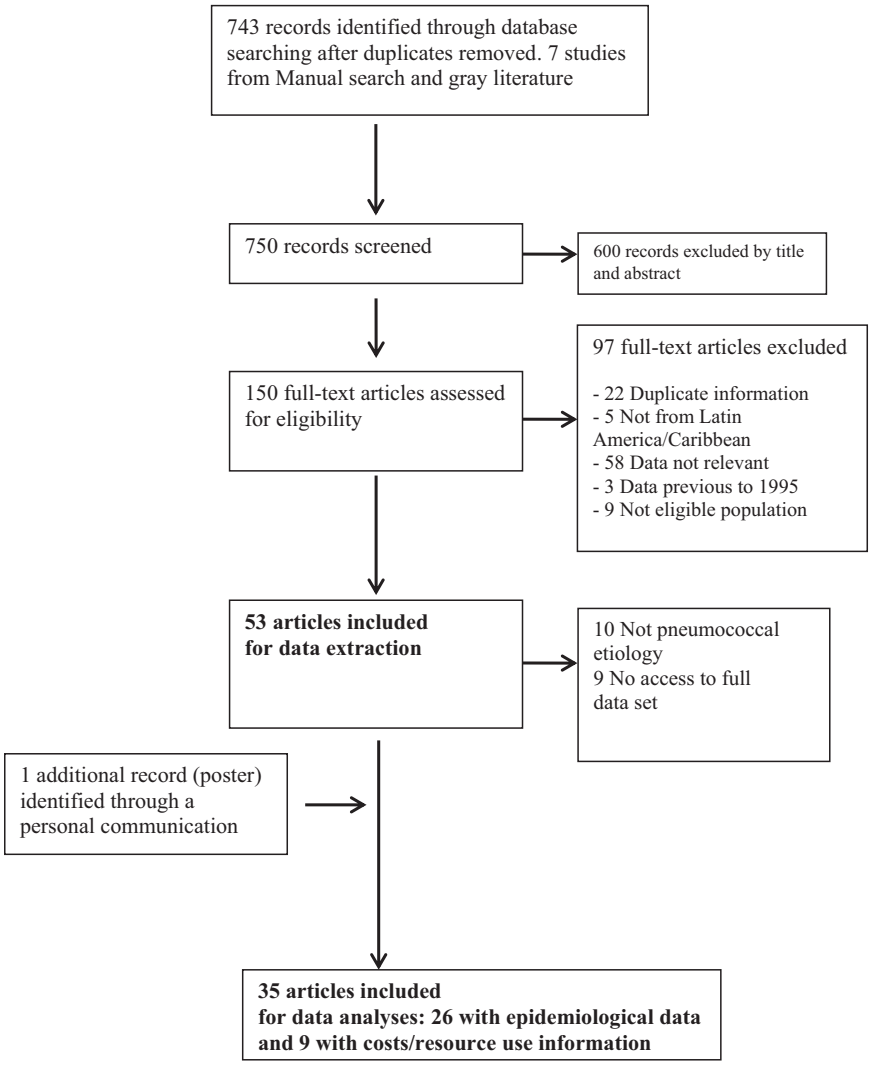

Fig. 1 – Flowchart of the systematic review.

Chile [24], and Colombia [19]. The Argentinean study was conducted in three cities [23,51–53], and we had access to the complete data set provided by Dr Gentile by late 2010. Most studies included were not population-based ones; they were useful for estimations of CFR [19,20,22,27,28,30,54] and confirmed pneumococcal etiology [17–19,21–23,25,26,28,29,31,32,35,36,38,39,41,54–56] (Table 1). Most meta-analyses performed carried I^2 indexes higher than 70%. Detailed information including figure outputs is available on demand.

Table 2 presents individual studies data of culture-confirmed PP from 2000 to 2016 by age group.

Children between 0 and 23 Months

For this group, only one study reported an incidence of 95.1/100,000 (95% CI 76.1–118.7) of culture-confirmed PP [28]. The pooled CFR in the age group between 0 and 23 months was 2.8% (95% CI 1.4–8.7) [20,27,28].

Children between 0 and 59 Months

The incidence of culture-confirmed PP for the group between 0 and 59 months ranged from 10.2 to 43.0/100,000 children, with a pooled incidence of 20.4/100,000 children (95% CI 14.0–27.9) [19,20,23,24]. Mortality ranged from 0.4 to 5.7/100,000 children and the pooled mortality was 2.9/100,000 children (95% CI 0.3–8.2) [19,20,23,24].

For the group 0 to 59 months, the individual studies' estimations for CFR are presented in Figure 2 and for pneumococcal etiology in Figure 3. The pooled CFR was 4.2% (95% CI 3.3–5.2) [20,23,24,30,54] and the proportion of pneumococcal etiology was 5.8% (95% CI 3.5–8.5) [17,18,21,23,25,26,28,29,41,54].

Children between 0 and 14 Years

For the age group of 0 to 14 years, the proportion of pneumococcal etiology was 20.1% (95% CI 2.8–47.6). Six studies [32–34,37,38,40] reported CFR data for children in a relatively wide age range, between 0 and 14 years. Because the data were heterogeneous and most of the cases within these data sets occurred in children younger than 5 years, we describe them individually. Gómez-Barreto et al. [33] report a CFR of 16% in 25 hospitalized children in Mexico during a period of 7 years. Hortal et al. [34] report a 7.6% CFR in 410 children hospitalized in a National Reference Children's Hospital in Montevideo, Uruguay, between 2000 and 2004. A previous study from the same institution carried out in 1999 reports a 3% CFR [32]. Pírez et al. [38] report a CFR of 5% in 76 children in Uruguay between 1999 and 2000. Ochoa et al. [37] report data of children hospitalized at 11 public hospitals in the city of Lima, Peru; the overall CFR during the 2-year study period (2006–2008) was 22.2%. Finally, a study from Costa Rica [40] reports a CFR of 14.4% between 1995 and 2001.

Serotype Surveillance

Using data from the regional surveillance database SIREVA, we performed a proportion meta-analysis for pneumococcal serotype frequency in C-PP for all countries together and one for each country for all available years (see Table 3). The most frequent serotype isolated in children's disease in the region was serotype 14 in 34.1% of the samples (95% CI 29.4–38.9), followed by serotype 1 in 10.9% (95% CI 9.2–12.8) and serotype 6B in 8.5% (95% CI 7.0–10.3). The 2013 update report [57] does not break serotype information by diagnosis and we were unable to get raw data.

Use of Resources

Regarding use of resources, studies identified included data from Argentina [42,45], Brazil [43,47,50], Chile [43,46], Mexico [49], Uruguay [43,44], and the LAC region [48]. The mean length of stay per PP case was 10 days (95% CI 7.7–12.3) and the mean number of visits per case was 2.8. The median direct costs for admitted patients were I$961.5 (interquartile range 804.5–2677.0); detailed results are provided in Table 4.

Discussion

S. pneumoniae is an important cause of pneumonia and invasive bacterial disease, primarily meningitis and sepsis, in both developed and developing countries. The burden of pneumococcal disease among children younger than 5 years is well established; the Sabin Vaccine Institute published a review of the epidemiological data of invasive and noninvasive pneumococcal disease among children in the LAC region [3,4]. This pediatric study estimated that the annual burden of pneumonia due to pneumococcal infection ranged from 980,000 to 1,500,000 for children younger than 5 years. Despite this publication, even in countries with good surveillance systems, there is a paucity of epidemiological data on the incidence, mortality, and costs of the disease. Quantifying the burden of disease is important because PCVs are increasingly being introduced into routine infant immunization programs and are reducing the burden of pneumococcal disease among young children, adolescents, as well as adults. Having a baseline in Latin America before vaccine introduction is important for cost and effectiveness assessments.

This study analyzes the burden of disease and epidemiological characteristics for children with culture-confirmed PP in LAC. The countries most represented were Argentina and Uruguay. The overall incidence of culture-confirmed PP found was 20.4/100,000 children (95% CI 1.4–27.9) in children younger than 5 years. Sgambatti et al. [58] report hospitalization rates of 1976 and 1,525/100,000 pre- and postvaccination in Goiania, Brazil.

Although previous reviews about pneumococcal disease exist in the literature [3,4], ours provides a significant update (up to January 2016) and includes a longer time frame to show the natural history of the serotype evolution according to clinical criteria, that is, the re-emerging 19A or 3 serotype as a cause of important disease in Latin America. In addition, we used conventional meta-analysis techniques for epidemiological parameters to complement our results with summary estimates.

The presence of significant alveolar consolidation is considered by most experts to be the most specific radiographic predictor of bacterial pneumonia available today, although viruses may also cause this pattern. Differences in observed incidence could be due to true differences in the patient populations studied or also due to differences in the way the disease is reported [59–61]. The estimation of the true burden of PP is thus possible only in the context of vaccine probe trials.

Estimating the total burden of pneumococcal disease represents a challenging task because standard diagnostic methods have a low sensitivity. Studies report low microbiological isolation, between 0.5% and 16%, in blood samples [62,63]. One of the LAC studies included in this meta-analysis found a similarly low rate of 7%. This known low sensitivity leads to information bias, and therefore observational studies and surveillance data heavily underestimate the true pneumococcal disease burden, reflecting only the tip of the iceberg, the most severe cases. It has been estimated by vaccine probe trials that all cases of clinical pneumonia prevented were more than 10 times greater than cases of all culture-confirmed pneumonia prevented. Notwithstanding these facts, the information presented is important and may be used as

Table 1 – Characteristics of studies included in the analysis of epidemiological outcomes and their summary risk of bias.

Reference	Cities, country	Study period	Study design	Admission status and age	Outcomes	Summary risk of bias
Asturias et al. [17]	Guatemala City, Guatemala	October 1, 1996, to January 31, 1999	Cross-sectional hospital-based study	Inpatients Children <5 y	Proportion of C-PP	Moderate
Bautista-Marquez et al. [18]	México	March 1, 2010, to June 1, 2011	Prospective study	Inpatients Children 0–59 mo	Proportion of C-PP	Low
Benavides et al. [19]	Colombia	November 16, 2006, to November 15, 2008	Hospital-based surveillance	Inpatients and outpatients Children from 28 d to 36 mo	Incidence Mortality CFR	Low
Bakir [30]	Buenos Aires, Argentina	January 1, 1993, to December 31, 1999	Case series	Inpatients Children 0–59 mo	CFR	Serious
Camou et al. [20]	Uruguay	January 1, 1994, to December 31, 2001	Hospital-based surveillance	Inpatients Children 0–60 mo	Incidence Mortality CFR	Moderate
Cardoso et al. [21]	Argentina, Dominican Republic, Brazil	June 1, 1998, to December 1, 2002	Cross-sectional hospital-based	Inpatients Children 3–59 mo	Proportion of C-PP	Moderate
Cirino et al. [31]	Sao Paulo, Brazil	November 1, 1986, to November 1, 1996	Retrospective study	Inpatients Children 0–14 y	Proportion of C-PP	Moderate
Ferrari et al. [32]	Uruguay	May 19, 1999, to September 19, 1999	Case series	Inpatients Children 0–14 y	CFR Proportion of C-PP	Serious
Gentile et al. [79]	Buenos Aires, Tucumán, Mendoza, and Santa Fe, Argentina	January 1, 2000, to December 31, 2009	Prospective cohort hospital-based	Inpatients Children 0–14 y	Proportion of C-PP	Moderate
Gentile [22]	Concordia and Parana y Pilar, Argentina	November 1, 2002, to October 31, 2004	Observational descriptive study	Inpatients Children 0–59 mo	Incidence Mortality CFR Proportion of C-PP	Moderate
Gentile et al. [41]	Pilar, Argentina	January 1, 2012, to December 31, 2013	Prospective population-based study	Inpatients and outpatients Children <5 y	Proportion of C-PP	Moderate
Gómez-Barreto et al. [33]	Mexico	January 1, 1997, to August 31, 2004	Retrospective cohort study hospital-based	Inpatients Children 0–14 y	CFR	Serious
Hortal et al. [80]	Montevideo, Uruguay	June 1, 2000, to December 1, 2004	Retrospective cohort study hospital-based	Inpatients Children 0–14 y	CFR	Low
Kunyoshi et al. [35]	Sao Paulo, Brazil	January 1, 2000, to December 31, 2002	Case series	Inpatients Children 0–14 y	Proportion of C-PP	Moderate
Lagos et al. [24]	Santiago, Chile	January 1, 1994, to December 31, 2007	Surveillance annual cohort	Inpatients Children 0–59 mo	Incidence Mortality CFR	Serious
Nacul et al. [25]	Recife, Brazil	June 1, 1994, to June 1, 1995	Randomized controlled trial	Ambulatory and hospitalized Children 6–59 mo	Proportion of C-PP	Low

continued on next page

Table 1 – *continued*

Reference	Cities, country	Study period	Study design	Admission status and age	Outcomes	Summary risk of bias
Nascimento-Carvalho et al. [36]	Salvador do Bahia, Brazil	September 1, 2003, to May 1, 2005	Prospective study	Ambulatory and hospitalized Children 0–14 y	Proportion of C-PP	Moderate
Nascimento-Carvalho et al. [26,55]	Salvador do Bahia, Brazil	September 1, 2003, to May 1, 2005	Cross-sectional	Inpatients Children 0–59 mo	Proportion of C-PP	Moderate
Ochoa et al. [37]	Lima, Peru	January 5, 2006, to April 30, 2008	Surveillance study hospital-based	Inpatients Children 0–14 y	CFR	Moderate
Grupo Multifuncional de Neumonias [29]	Lima, Cusco, Arequipa, and Puno, Peru	October 1, 2000, to December 31, 2001	Cross-sectional	Inpatients Children 0–59 mo	Proportion of C-PP	Moderate
Pírez et al. [54]	Montevideo, Uruguay	September1, 1997, to September 1, 1998	Cohort study hospital-based	Inpatients Children 0–59 mo	CFR Proportion of C-PP	Low
Pírez et al. [38]	Montevideo, Uruguay	May 19, 1999, to May 18, 2000	Cohort study hospital-based	Inpatients Children 0–14 y	CFR Proportion of C-PP	Moderate
Pírez et al. [27]	Montevideo, Uruguay	January 1, 1998, to December 31, 2005	Cohort study hospital-based	Inpatients Children 0–23 mo	CFR	Serious
Requejo and Cocoza [39]	Sao Paulo, Brazil	January 1, 2002, to December 31, 2002	Laboratory-based surveillance study	Inpatients Children 0–14 y	Proportion of C-PP	Moderate
Tregnaghi et al. [28]	Cordoba, Argentina	December 1, 1999, to November 30, 2002	Surveillance study primary and secondary care–based	Ambulatory and hospitalized Children 2–23 mo	Incidence CFR Proportion of C-PP	Low
Ulloa-Gutierrez et al. [40]	San José de Costa Rica, Costa Rica	January 1, 1995, to December 31, 2001	Surveillance study primary and secondary care–based	Inpatients Children 0–14 y	CFR	Low

CFR, case-fatality rate; C-PP, confirmed pneumococcal pneumonia.

Table 2 – Culture-confirmed PP individual studies epidemiological data from 2000 to 2016 by age group.

Study	Point estimate	95% CI	Number of subjects*	Summary risk of bias
		Age 0–23 mo		
Case-fatality rate (%)				
Benavides et al. [19]	0.1	0.0–0.05	1,721	Low
Camou et al. [20]	4.3	1.9–8.2	188	Low
Pírez et al. [27]	7.8	4.4-12.6	192	High
Tregnaghi et al. [28]	1.2	0.0–6.6	82	Low
		Age 0–59 mo		
Incidence (per 100,000)				
Benavides et al. [19]	32.0	20.9–46.9	81,173	Low
Camou et al. [20]	117.2	104.5–129.8	281,605	Moderate
Gentile [22]	43	27.9–58.1	72,101	Low
Lagos et al. [24]	13.6	12.8–14.4	7,452,653	High
Mortality (per 100,000)				
Benavides et al. [19]	3.7	0.8–10.8	81,173	Low
Camou et al. [20]	57	2.9–8.5	281,605	Moderate
Gentile [22]	2.8	0–6.6	72,101	Low
Lagos et al. [24]	0.6	0.5–0.8	7,452,653	High
Pneumococcal etiology (%)				
Asturias et al. [17]	4.3	2.9–6.1	700	Moderate
Bautista-Marquez et al. [18]	8.2	5.8–11.3	413	Low
Cardoso et al. [21]	11.1	9.9–12.3	2,566	Moderate
Gentile et al. [22,23]	4.8	3.3–6.7	646	Low
Gentile et al. [41]	1.3	0.3–2.3	308	Low
Nacul et al. [38]	6.4	4.3–8.9	472	Low
Nascimento-Carvalho et al. [26,55]	21.2	15.5–27.8	184	High
Grupo Multifuncional de Neumonias [29]	1.5	0.1–2.0	1,210	Moderate
Pírez et al. [54]	4.4	3.3–5.7	1,163	High
Tregnaghi et al. [28]	3.9	3.1–4.8	2,112	Low
Case-fatality rate (%)				
Bakir [30]	4.8	2.2–8.9	188	High
Gentile et al. [22,23]	6.5	0.8–21.2	31	Low
Pírez et al. [54]	3.9	0.5–13.5	51	High
Camou et al. [20]	4.8	2.8–7.8	330	Moderate
Lagos et al. [24]	3.7	2.6–5.0	1,013	High
		Age 0–14 y		
Pneumococcal etiology (%)				
Cirino et al. [31]	39.1	30.1–48.7	115	Moderate
Ferrari et al. [32]	10.7	7.5–14.8	307	High
Gentile et al. [78]	68	64.9–71.0	938	Moderate
Kunyoshi et al. [35]	18.2	11.8–26.2	121	High
Nascimento-Carvalho et al. [36]	0.8	0.5–1.3	2,246	High
Pírez et al. [27]	10.9	8.7–13.5	697	High
Requejo and Cocoza [39]	15.1	11.0–20.0	265	High
Case-fatality rate (%)				
Ochoa et al. [37]	14.6	6.1–27.8	48	Moderate
Hortal et al. [34]	7.6	5.2–10.6	410	High
Gómez-Barreto et al. [33]	16.0	0.5–36.1	25	Low
Pírez et al. [27]	10.5	0.7–19.7	76	High
Ferrari et al. [32]	3.0	0.1–15.8	33	High
Ulloa-Gutierrez et al. [40]	22.2	10.1–39.2	36	Low

CI, confidence interval; PP, pneumococcal pneumonia.
* Denominators may vary in each study for different outcomes.

input for economic evaluations and studies to draw projections of clinical cases and on the wider burden of disease, or on the impact and effectiveness of PCVs with local epidemiological information.

Regarding the CFR, we found estimates similar to those reported previously in children younger than 5 years (4.2% vs. 4%) [64]. We observed that CFR in children younger than 2 years is similar to that in the younger than 5 years group, showing the pediatric group the higher impact in mortality. These results are similar to those published in previous systematic reviews in LAC [6]. We did not find enough high-quality methodological studies to be able to perform a sensitivity meta-analysis to assess in which direction estimates might have biased the pooled results.

Worldwide, pneumonia has not been included among reportable diseases in the official systems. Traditionally, for bacterial pneumonia, laboratory surveillance systems have provided invaluable reports focusing on serotype distribution and

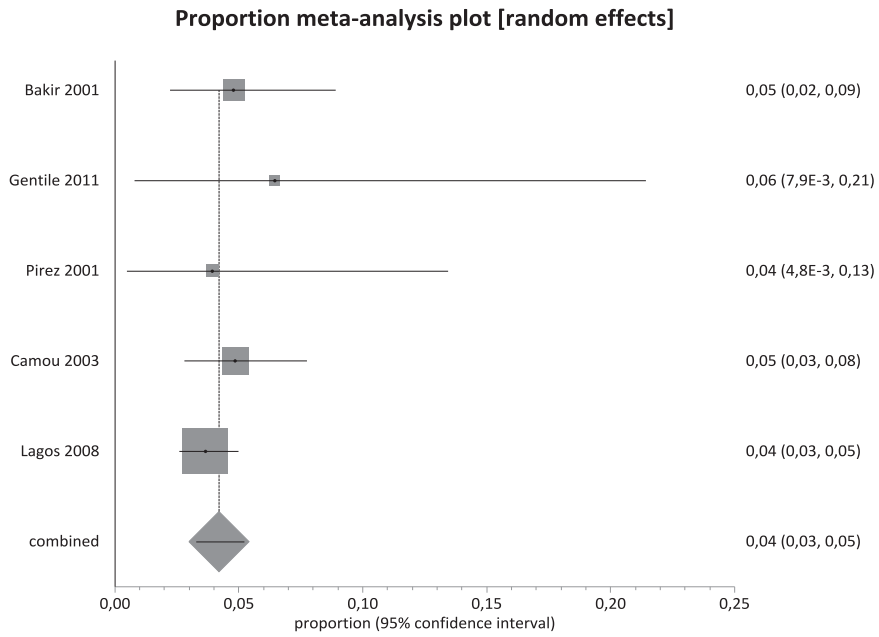

Fig. 2 – Forest plot of the case-fatality rate in children aged 0–59 mo.

emergence of antimicrobial resistance of selected isolates among hospitalized pneumonia cases. Three countries in Latin America (Argentina, Chile, and Uruguay) established population-based surveillance for x-ray–confirmed pneumonia, and data from some of these surveillance systems have recently been published [51,61]. It is, however, necessary to take into account that viruses in pediatric population may cause a consolidative radiological pattern.

In 1993, a coordinated passive surveillance laboratory network for serotype distribution and antimicrobial resistance patterns for the region of the Americas was established by PAHO through its special Program for Vaccines and Immunizations and the regional System for Vaccines (SIREVA). It conducts surveillance for invasive pneumococcal disease and for *Haemophilus influenzae* and *Neisseria meningitidis*. The activities started in six countries—Argentina, Brazil, Chile, Colombia, Mexico, and Uruguay—and from 2000 onward expanded to 300 sites in 22 countries.

This type of 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, mostly with unfavorable evolution and under-representing the mild and moderate spectrum of disease occurrence. A small number of studies included patients with complicated pneumonia, which could introduce selection bias in epidemiological results. This would be a topic of further analysis. Studies identified on costs and resource use did not include complicated cases.

Another limitation was the lack of population-based incidence estimates, because most studies were conducted in

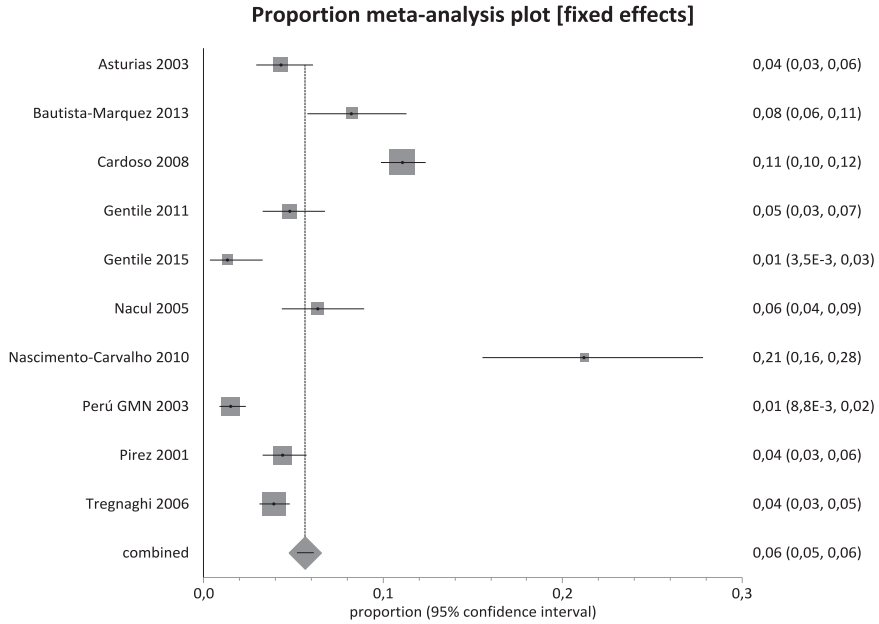

Fig. 3 – Forest plot of confirmed pneumococcal etiology proportion in pneumonias in children aged 0–59 mo.

Table 3 – Proportion meta-analysis of C-PP serotype frequency from several surveillance periods using SIREVA II information[*].

By country	Serotype, % (CI)						
	14	1	6B	5	19F	19A	6A
Overall	34.4 (29.6–39.4)	11.1 (9.3–13.1)	7.8 (6.4–9.4)	7.2 (4.9–9.8)	4.0 (2.5–5.8)	4.0 (3.3–4.8)	3.4 (2.6–4.3)
Argentina	31.0 (23.6–39.0)	13.5 (11.0–16.2)	5.4 (3.1–8.4)	15.6 (12.4–19.2)	1.8 (0.9–2.9)	5.2 (2.4–9.0)	2.1 (1.2–3.3)
Brazil	49.3 (45.5–53.1)	8.9 (4.0–15.5)	8.8 (6.3–11.5)	2.8 (0.9–5.9)	1.2 (0.5–2.1)	4.6 (3.1–6.3)	2.9 (0.7–6.7)
Chile	31.5 (27.1–36.0)	8.3 (4.3–13.3)	8.5 (1.6–20.0)	8.1 (3.5–14.5)	4.8 (3.0–7.1)	4.7 (2.8–6.9)	4.6 (2.1–8.0)
Colombia	40.2 (35.1–45.5)	13.4 (10.0–17.2)	9.4 (6.6–12.7)	5.6 (3.4–8.3)	2.2 (0.7–4.4)	2.2 (0.3–5.8)	6.2 (3.9–9.0)
Cuba	41.1 (0.7–99.1)	9.5 (6.0–13.8)	11.8 (7.9–16.4)	2.6 (0.9–5.1)	15.1 (10.6–20.1)	4.5 (2.1–7.6)	3.6 (1.5–6.5)
Ecuador	23.2 (11.8–37.2)	23.5 (6.6–46.7)	13.2 (5.9–23.0)	10.8 (2.1–24.9)	3.8 (0.0–15.9)	4.9 (0.9–11.9)	3.7 (0.0–13.4)
El Salvador	30.3 (13.7–50.2)	17.1 (4.8–34.8)	2.2 (0.3–12.0)	2.2 (0.3–12.0)	24.9 (8.3–46.7)	2.6 (2.2–20.6)	21.1 (3.7–47.6)
Mexico	13.9 (6.6–23.4)	3.7 (2.0–5.9)	13.2 (9.9–16.9)	1.6 (0.6–3.2)	16.7 (13.0–20.8)	4.2 (1.2–8.9)	5.3 (0.7–13.6)
Paraguay	36.1 (29.6–43.0)	13.4 (6.9–21.7)	5.4 (3.6–7.6)	17.6 (11.4–24.7)	0.8 (0.2–1.8)	2.3 (1.1–3.8)	2.1 (0.6–4.3)
Peru	35.9 (21.7–51.4)	3.7 (0.0–13.7)	12.7 (4.2–24.8)	4.0 (0.2–12.2)	9.8 (2.6–20.9)	1.3 (0.2–7.2)	7.5 (1.4–17.6)
Dominican Republic	56.4 (50.5–62.3)	9.0 (5.9–12.7)	7.1 (2.7–13.3)	2.2 (0.8–4.2)	1.1 (0.2–2.7)	2.9 (1.2–5.3)	3.6 (1.7–6.1)
Uruguay	34.2 (27.6–41.1)	18.8 (13.2–24.9)	4.2 (2.7–6.0)	9.8 (1.5–24.2)	1.2 (0.5–2.3)	4.0 (2.5–5.8)	1.3 (0.5–2.4)
Venezuela	35.5 (22.1–50.2)	9.7 (6.1–14.1)	9.5 (5.9–13.8)	15.1 (6.3–27.0)	4.8 (0.1–19.9)	8.3 (4.9–12.4)	2.7 (0.4–7.0)

CI, confidence interval; C-PP, confirmed *pneumococcal pneumonia*.

[*] Pooled estimates do not add up to 100% because each one comes from a different meta-analysis with variable numbers of surveillance periods.

Table 3 – Continue[*]

By country	Serotype, % (CI)							
	23F	9V	3	7F	18C	4	Other	No. of samples (no. of surveillance periods)
Overall	3.4 (2.3–4.7)	3.3 (2.7–4.1)	3.2 (2.3–4.2)	2.6 (1.8–3.5)	1.8 (1.0–2.7)	1.3 (0.9–1.6)	8.7 (6.7–11.0)	4267 (35)
Argentina	2.1 (1.2–3.4)	3.8 (0.8–9.0)	2.4 (0.6–5.4)	4.0 (2.4–6.1)	1.9 (0.7–3.7)	0.7 (0.2–1.5)	9.4 (5.2–14.7)	664 (3)
Brazil	2.8 (1.6–4.1)	3.0 (1.9–4.5)	5.6 (2.7–9.5)	1.3 (0.6–2.3)	1.2 (0.5–2.1)	0.8 (0.2–1.6)	6.1 (4.4–8.1)	660 (3)
Chile	3.6 (0.7–8.5)	1.1 (0.1–3.1)	0.9 (0.2–2.1)	5.6 (3.6–8.0)	3.1 (1.7–5.0)	2.7 (0.7–6.1)	11.8 (5.4–20.3)	414 (3)
Colombia	5.0 (2.9–7.5)	5.2 (2.2–9.3)	3.9 (2.1–6.2)	0.2 (0.0–0.9)	2.3 (1.0–4.1)	1.5 (0.5–3.0)	7.9 (3.7–13.4)	341 (3)
Cuba	5.4 (2.8–8.8)	3.6 (1.5–6.5)	2.2 (0.7–4.5)	7.2 (4.2–11.1)	17.8 (13.0–23.2)	1.7 (0.4–3.8)	5.9 (3.2–9.4)	216 (2)
Ecuador	2.4 (0.0–8.7)	3.8 (0.0–15.9)	2.4 (0.0–8.7)	0.9 (0.1–4.8)	0.9 (0.1–4.8)	0.9 (0.1–4.8)	15.2 (7.2–25.3)	57 (2)
El Salvador	2.2 (0.3–12.0)	2.6 (2.2–20.6)	2.2 (0.3–12.0)	6.8 (0.3–20.3)	2.2 (0.3–12.0)	2.2 (0.3–12.0)	6.4 (0.0–23.1)	21 (2)
Mexico	13.9 (8.5–20.4)	2.3 (0.2–6.6)	2.3 (0.5–5.6)	0.8 (0.2–2.0)	1.4 (0.4–2.8)	0.8 (0.2–2.0)	24.9 (20.6–29.6)	348 (3)
Paraguay	2.1 (0.7–4.3)	4.9 (3.2–7.0)	0.8 (0.2–1.7)	3.2 (1.8–4.9)	0.6 (0.1–1.5)	1.4 (0.5–2.8)	12.9 (10.1–16.0)	485 (3)
Peru	7.5 (1.4–17.6)	1.3 (0.2–7.2)	1.3 (0.2–7.2)	1.3 (0.2–7.2)	1.3 (0.2–7.2)	4.0 (0.2–12.2)	1.3 (0.2–7.2)	37 (2)
Dominican Republic	2.2 (0.8–4.2)	2.7 (1.0–5.4)	4.7 (2.5–7.6)	1.1 (0.2–2.7)	1.4 (0.4–3.2)	1.9 (0.6–3.8)	6.0 (3.5–9.1)	267 (3)
Uruguay	1.3 (0.0–5.0)	4.4 (2.8–6.3)	6.5 (4.6–8.7)	4.7 (2.0–8.6)	0.5 (0.1–1.2)	1.5 (0.7–2.7)	4.7 (3.1–6.7)	551 (3)
Venezuela	1.4 (0.3–3.5)	1.4 (0.3–3.5)	8.1 (4.8–12.1)	3.8 (1.6–6.8)	0.9 (0.1–2.6)	4.8 (0.1–19.9)	2.9 (1.1–5.6)	206 (3)

Table 4 – Information on resource use of PP in LAC, 2000–2016.

	Mean ± SD or median (Md)	95% CI or IQR	Number of studies
	Inpatients		
LOS	10 ± 2.7	7.7–12.3	5
Direct costs	961.5 (Md)	804.5–2677.0 (IQR)	9
Indirect costs	94 ± 21.2	64.6–123.4	2
	Outpatients		
Number of visits (per case)	2.8		1*
Direct costs	89.5 (Md)	61.0–241.0 (IQR)	4
Indirect costs	40 ± 5.7	32.2–47.8	2
	Both		
Direct costs	748.0 (Md)	272.1–1261.5 (IQR)	1*,†

Note. Costs were expressed in 2006 international dollars. Direct costs: medical—costs of laboratory tests, medications, supplies, facilities, and personnel; nonmedical direct costs—transportation to and from the medical facility, childcare, home care, time waiting for care, and time undergoing care. Indirect costs: caregiver productivity losses that may occur because of illness or death.
IQR, interquartile range; LAC, Latin America and the Caribbean; LOS, length of stay (in days); PP, pneumococcal pneumonia.
* Study's data as described in the source article.
† Three substudies.

selected subpopulations that may not be representative of the whole country, with variable risks of pneumococcal disease. This compromises the external validity of the results and hinders estimation of the serotype burden of pneumonia at the community level. Although a random effects model was selected in all cases to minimize heterogeneity, the combined point estimates should be taken with caution and the CIs should be considered the best approximation to the truth. This approach takes advantage of the strength of the meta-analytic technique, in which statistical precision is increased through weighting of the individual studies, thus yielding more informative results than a mere description of the dispersion parameters or the values obtained in each primary study.

Epidemiological behavior of PP may vary in LAC countries according to the year of introduction of PCVs, degree of coverage, or type of vaccine. PAHO/WHO hosts a detailed Web page with updated data on immunization in the Americas [65].

Data on temporal changes in the proportion of serotypes on the basis of SIREVA reports were published for Argentina. The comparison between 2000 to 2003 and 2004 to 2007 showed statistically significant changes in the frequency of serotypes 14, 1, and 19A: a decrease in serotype 14, and an increase in serotype 1 and in serotype 19A [66], in the absence of PCV introduction in the countries. In our study, serotypes 14, 1, and 6B were the most frequently isolated.

Regional SIREVA information on bacterial resistance showed that serotypes 6B, 9V, 14, 19F, and 23F, all present in the 7-valent PCV (PCV7), are those most frequently associated with nonsusceptibility to penicillin as well as serotypes 6A and 19A. All these serotypes are included in currently licensed pneumococcal vaccines. Serotype 19A has increased as a cause of disease worldwide [67,68], both in countries that have incorporated the PCV7 in their vaccination schedule and in those that have not. It was an important cause of invasive pneumococcal disease in the United States before the introduction of PCV7 [69]. It emerged as a predominant invasive pneumococcal serotype because of its capacity to colonize the nasopharynx and its antibiotic resistance, becoming the most important emergent serotype worldwide.

SIREVA information showed that serotype 19A represented 4.4% of all isolates during the period 2007 to 2008 and this percentage increased to 5% during the period 2008 to 2014 [5,13]. The serotypes 1 and 5, although more frequently associated with disease in developing countries, were cause of disease in emergent and developed countries [70]. The incidence of these serotypes may vary because of their tendency to cause outbreaks, especially for children older than 2 years [71–73]. In Argentina they represent around 10% to 25% of all the invasive pneumococcal disease. Nevertheless, there is information about serotype 1 as the cause of pneumonia with empyema [5,13,74,75]. Serotype 3, although less common, constitutes an important and increasing cause of invasive pneumococcal disease after vaccine introduction [75,76] and always represents an important cause of virulent otitis media and complicated pneumonia, especially because empyema and necrotizing pneumonia in older children are associated with serious disease and increasing mortality [75,76]. Serotype 6A is responsible for a considerable portion of disease caused by serotype 6 and is often associated with a lack of antibiotic susceptibility [77]. The immunologic cross-reactivity to serotype 6A, as a response to serotype 6B, may be responsible for the reduction in disease caused by serotype 6A after the introduction of PCV7.

As for use of resources, we identified data in nine studies originating mainly from Argentina, Brazil, Chile, and México. C-PP admissions lengthened about 10 days, costing roughly I $3000 on average, and the mean number of outpatient visits per case was 2.8. Direct costs of ambulatory visits were 10 times lower. No information was found regarding other health resource outcomes explored. The total cost of hospitalizations due to pneumonia in children in Lima was reported to be US $59.5 in one study [78].

Conclusions

This study gathered all published information available about the incidence, serotype distribution, mortality, lethality, and resource use of C-PP from 2000 to 2016 in LAC.

There is a significant need in the region of up-to-date local epidemiological data to perform disease burden, cost-effectiveness, and financial impact analysis to help the decision-making process, and these analyses should be based on the best available contextually relevant evidence. The present study helps to provide one key piece of information (C-PP epidemiology and mortality) that can serve as the basis for further projections on the region, to help decide what type of vaccine to include in the country's calendars and monitor their performance by measuring the future effectiveness of vaccines in each area.

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Supplemental material

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