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The burden of pneumococcal disease in older children and adults in Latin America and the Caribbean

A systematic review

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Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the official views of the Centers for Disease Control and Prevention.

Abstract

Background: We explored the epidemiology of pneumococcal disease among persons ≥5 years in the region through a systematic literature review and analyses of regional laboratory-based surveillance data.

Methods: We analyzed data from the Adult Global Estimation of Disease Burden and Distribution of Serotypes of Serious Pneumococcal and Meningococcal Disease (AGEDD) project, which included literature published from 1990 to 2009. The AGEDD search was complemented with an updated search through mid-2012. Furthermore, the Pan American Health Organization's regional pneumococcal network (SIREVA II) provided surveillance data from 2006 to 2011 on the distribution of serotypes associated with invasive pneumococcal disease (IPD).

Results: Only four studies describing IPD incidence in the population aged ≥5 years were found. Highest IPD incidence occurred among people over 60 years of age and ranged from 9.4 to 60.0 per 100,000. Proportion of pneumonia cases associated with *S. pneumoniae* was reported in eight studies, ranged from 5.0% to 31.8%, and was highest in two studies using urine antigen detection testing. Proportion of meningitis cases associated with pneumococcal infection was reported in five studies and ranged from 3.3% to 64.3%. Proportion of infecting isolates with a serotype included in both the 10- and 13-valent pneumococcal conjugate vaccines was lower among elderly (≥65 years) than among younger persons.

Conclusions: An extensive review yielded limited and heterogeneous data, but available data suggest pneumococcal infection comprises an important proportion of community-acquired pneumonia and meningitis among persons ≥5 years. In the region, there is a sizeable proportion of IPD caused by vaccine serotypes.

Keywords

Streptococcus pneumoniae, pneumococcal infections, pneumonia, meningitis, pneumococcal vaccines, Latin America

Background

Streptococcus pneumoniae remains an important cause of pneumonia and invasive bacterial disease, primarily meningitis and sepsis. The greatest burden of disease occurs in low-and middle-income countries, and the risk of serious pneumococcal disease peaks at the extreme ages of life. Young children are at highest risk, but older adults and people with immuno-compromising conditions also suffer high rates of pneumococcal disease.[1] The burden of pneumococcal disease among children less than 5 years of age has been well characterized, both globally and in the region of Latin America and the Caribbean (LAC) [2,3]. However, fewer data are available on the incidence and mortality of pneumococcal disease among older children and adults, particularly in low- and middle-income countries[1].

Pneumococcal conjugate vaccines (PCV) have been available for use in routine infant immunization programs since 2000 and are an important tool in preventing illness and death due to *S. pneumoniae*. Starting in 2008, uptake of PCV in routine immunization programs has increased dramatically in LAC. As of September 2015, 34 of the 45 countries and territories in the LAC region have introduced PCV[4]. As the widespread use of PCV is expected to reduce the burden of pneumococcal disease among young children, the remaining pneumococcal disease burden among other high-risk groups, such as the elderly and immunocompromised, will become increasingly important[5]. PCV use in infants also has the potential to reduce the burden of pneumococcal disease in older children and adults through herd protection,[5,8] and quantifying a pre-PCV burden of disease is important for measuring indirect effects of PCV use in routine infant immunization. Furthermore, there are long-standing recommendations for use of a 23-valent polysaccharide pneumococcal vaccine (PPV23) in adults in LAC and globally,[1,9] and more recent recommendations for use of PCV in the United States among adults 65 years of age or older.[10] Data on pneumococcal disease burden in older children and adults are essential for evidence-based vaccine policies.

Methods

A systematic review of available literature was conducted to estimate the burden of invasive pneumococcal disease (i.e., meningitis, bacteremia, and sepsis) and pneumococcal pneumonia (including bacteremic and non-bacteremic) among people 5 years of age or older in the LAC region. We used secondary epidemiological information from two main sources. The first source was the database of the Adult Global Estimation of Disease Burden and Distribution of Serotypes of Serious Pneumococcal and Meningococcal Disease (AGEDD) project, a systematic literature review aimed at estimating the worldwide burden of pneumococcal disease among older children and adults.[11] The AGEDD literature search covered publications from 1980-2009 and included Medline, Embase, CINAHL, Global Health, and ISI Web of Knowledge databases. Search terms included the following key MeSH terms and their related combinations: "*Streptococcus pneumoniae*," "pneumococcal vaccines," "morbidity," "mortality," "death rate," "incidence," "prevalence," "surveillance," "disease burden," "adult," "elderly," "adolescent," "young adult," "meningitis," "pneumonia," "bacteraemia," and "sepsis."

All published studies providing data on pneumococcal disease in older children and adults from LAC were screened for potential inclusion in this analysis. Only those studies with primary data were selected for data abstraction. Abstracted data included the incidence of invasive pneumococcal disease and pneumococcal pneumonia, the proportion of pneumonia and meningitis associated with *S. pneumoniae* infection, and case fatality proportion (CFP) of pneumococcal disease. An updated literature search conducted by the Public Health Library and Information Center at the Centers for Disease Control and Prevention (CDC) used the same AGEDD search criteria for the inclusion of more recently published studies (2009-June 2012). For the updated search, six members of the research team abstracted information using a standardized electronic questionnaire built in the database software Microsoft Access™. Individual studies were assessed for quality and potential sources of bias during the data abstraction process. The internal validity of each study was evaluated for the following considerations: access to care, case ascertainment, death ascertainment, population denominator for incidence and mortality data, and laboratory testing. Studies characterized as having either a low or moderate risk of bias were included in the analysis due to the small number of studies available.

The second source of epidemiological information was the Pan American Health Organization/World Health Organization (PAHO/WHO) implemented laboratory surveillance network, the *Sistema de Redes de Vigilancia de los Agentes Responsables de Neumonias y Meningitis Bacterianas* (SIREVA II).[12] *S. pneumoniae* isolates are routinely gathered by the SIREVA II network from 20 countries in the LAC region. SIREVA II data are a convenience sample of isolates from patients with invasive pneumococcal disease. In each country, the national reference laboratories (NRLs) are responsible for serotyping *S. pneumoniae* isolates. Serotyping methods, including the use of the Quellung reaction and conventional and real-time polymerase chain reaction (PCR)

techniques, vary by country. Due to the network's quality assurance program, NRLs are required to send select isolates to regional reference laboratories (RRLs) for further serotyping and indirect quality control to validate regional data.

A descriptive analysis was carried out to summarize published data on the epidemiology of pneumococcal disease among individuals 5 years of age or older in the LAC region including the incidence of pneumococcal disease, the proportion of community-acquired pneumonia and meningitis associated with pneumococcus, and the case fatality of pneumococcal pneumonia and meningitis. Studies published before 1980 or those with 5 or fewer pneumococcal cases were excluded from the analysis of the proportion of pneumonia and meningitis associated with *S. pneumoniae*. When possible, a 95% confidence interval was estimated for each epidemiological parameter extracted. A pooled analysis of the proportion of pneumococcus in pneumonia and meningitis cases was carried out using the Freeman-Tukey transformation (arcsine square root transformation) to calculate the weighted summary proportion under the fixed and random effects model. Calculations were performed using MedCalc for Windows, version 15.0 (MedCalc Software, Ostend, Belgium).

SIREVA II data on serotype distribution were analyzed for all countries participating in the surveillance network from 2006 to 2011; however, data from countries and years in which PCV had already been introduced into the routine infant immunization program were excluded in order to provide a pre-PCV baseline. Data from the following countries were restricted to pre-PCV years: Brazil (2006-2010), Colombia (2006-2010), Costa Rica (2006-2009), Ecuador (2006-2010), El Salvador (2006-2010), Mexico (2006-2008), Panama (2006-2010), Peru (2006-2009), and Uruguay (2006-2008). Serotype distribution was described by age group, clinical syndrome, and regional area. LAC countries were grouped within six areas: 1) Andean, including Bolivia, Colombia, Ecuador, Peru, and Venezuela; 2) Brazil; 3) Caribbean, including Cuba, Dominican Republic, and the Caribbean Epidemiology Centre (CAREC); 4) Central America, including Costa Rica, El Salvador, Guatemala, Honduras, Nicaragua, and Panama; 5) Mexico; and 6) the Southern Cone, including Argentina, Chile, and Uruguay. The proportion of isolates with serotypes included in the 10- and 13-valent PCVs (PCV10 and PCV13, respectively) were described. The SIREVA II network also has the capacity to identify serotype coverage of the 23-valent pneumococcal polysaccharide vaccine (PPV23). However, PPV23 serotypes were reported as "others" and not disaggregated until 2011. Focusing on the pre-PCV baseline, the 2011-2012 SIREVA II reports were excluded from the analysis. SIREVA II regional reports are publically available at: http://www.paho.org/hq/index.php?option=com_content&view=article&id=5536&Itemid=3966&lang=en.

Results

Data from literature search

For the LAC region, 255 potentially relevant articles were screened and 71 full-text articles were reviewed for eligibility from both the AGEDD and supplemental searches (Figure 1). A total of 22 papers were included in the analysis; 19 articles were from the AGEDD search and 3 were from the updated literature search. The articles came from 5 LAC countries (Argentina, Brazil, Bolivia, Chile, and Cuba) and provided data on at least one of our outcomes of interest (e.g., pneumococcal disease incidence, CFP, or proportion of pneumonia or meningitis cases associated with *S. pneumoniae*) in persons ≥5 years old.

Data on the incidence of pneumococcal disease among patients aged 5 years or older were found in four studies (Table 1), including three studies from Chile[13-15] and one study from Brazil.[16] Invasive pneumococcal disease incidence reported in these studies ranged from 2.5 to 60.0 per 100,000, with variation across age groups and sites. Older adults (≥60 or 65 years, depending upon the study), had the highest rates, with incidences of 9.4 to 60.0 per 100,000. Of note, the age group distribution varied across studies as did the methods to ascertain cases. The study carried out in Brazil utilized administrative data from the Brazilian National Health System, and included discharge diagnosis codes (10th revision of the International Classification of Diseases) for pneumococcal sepsis, meningitis, and pneumonia. The three Chilean studies enrolled cases of invasive pneumococcal disease for which pneumococcal strains had been isolated from normally sterile fluids. All four studies used a population-based denominator estimated from census projections by national statistics agencies.

FIGURE 1. Flow diagram: selection of included studies.

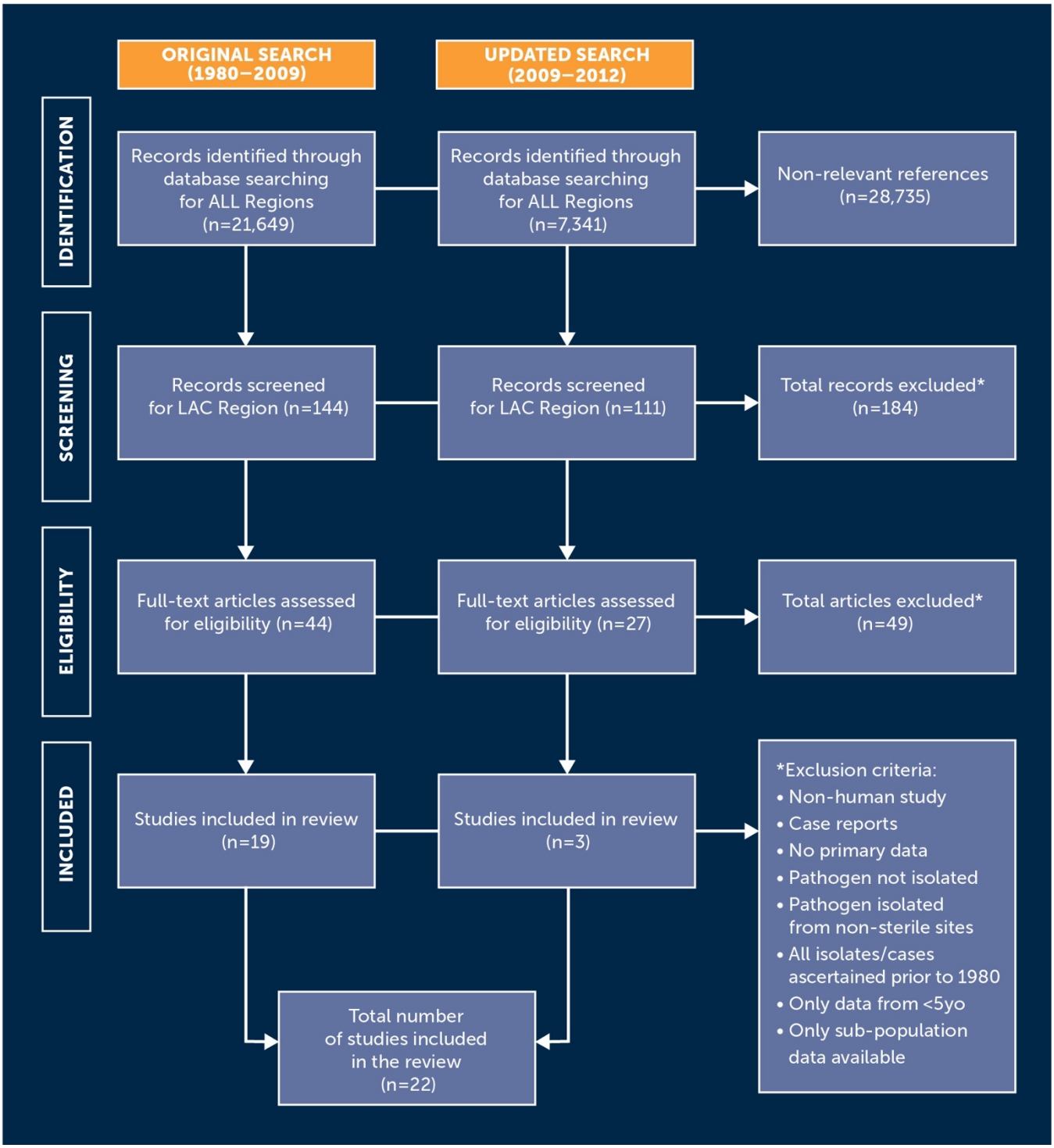


TABLE 1. Incidence of invasive pneumococcal disease among persons ≥5 years in LAC studies.

Study Reference	Country	Data Source	Time Period	Case Definition	Age Group (years)	Incidence (per 100,000)
[13]	Chile (Temuco)	Hospital-based Surveillance	1994–2004	Isolation of *S. pneumoniae* from blood or sterile fluid	5–64 65+	10.0 60.0
[14]	Chile (Metropolitan region of Santiago)	Hospital-based Surveillance	1994–2007	Isolation of *S. pneumoniae* from blood or sterile fluid	5–14	2.7
[15]	Chile (Santiago)	National Reference Laboratory, Hospital Laboratories, Hospital Discharge Data	2004–2006	Isolation of *S. pneumoniae* from blood or sterile fluid	15–44 45–64 65+	2.5 6.1 21.0
[16]	Brazil	Official Brazilian Hospital Discharge Database	2004–2006	ICD-10 codes: pneumococcal sepsis, meningitis, or pneumonia	5–9 10–14 15–19 20–39 40–49 50–59 60–69 70+	9.0 4.3 3.2 3.1 3.9 5.6 9.4 26.0

Note: LAC, Latin America and the Caribbean; ICD-10, International Classification of Diseases, Tenth Revision.

Proportion of community-acquired pneumonia cases associated with *S. pneumoniae* was estimated in eight studies (Table 2) conducted in Argentina (1 study), Bolivia (1 study), Brazil (1 study), and Chile (5 studies). All eight were hospital-based studies and defined community-acquired pneumonia on the basis of respiratory complaints along with radiographic findings. Pneumococcal infection was identified through blood culture (8 studies), sputum analysis (7 studies), and/or urinary antigen detection tests (2 studies). Proportion of community-acquired pneumonia cases associated with *S. pneumoniae* ranged from 5.0% to 31.8%, with a weighted mean of 16.4% (95% CI 10.9-22.8). This proportion was highest, 27.8% and 31.8% respectively (weighted mean 29.1%, 95% CI 23.6-35.0), in two studies that used urine antigen testing. Among studies that did not use urine antigen detection, the proportion of community-acquired pneumonia cases associated with *S. pneumoniae* ranged from 5.0% to 27.8% (weighted mean 12.8%, 95% CI 8.6-17.7).

TABLE 2. Proportion of community-acquired pneumonia associated with *S. pneumoniae* in LAC studies.

Study Reference	Country	Time Period	Study	CAP Diagnostic Criteria	Detection Methods	Age Group (years)	Total CAP Cases	*SP* Cases	*SP* Cases/ Total Cases (%)	95% CI of Proportion
[17]	Chile (Santiago)	1999–2001	Prospective	Cough, temp >37.8°C, respiratory distress, infiltrates on chest X-ray	Blood & sputum culture	16–92	460	46	10.0	7.5–13.0
[18]	Chile Santiago)	2003–2004	Prospective	Cough, temp >37.8°C, respiratory distress, infiltrates on chest X-ray	2 blood cultures & sputum culture	17–101	130	22	16.9	10.0–22.0
[19]	Chile (Santiago)	2003–2005	Prospective	Altered mental status, fever, acute respiratory symptoms, infiltrates on chest X-ray	2 blood cultures, sputum culture, urine antigen	17–101	176	49	27.8	22.0–35.0
[20]	Chile (Santiago)	2003	Retrospective	Cough, fever, respiratory distress, infiltrates on chest X-ray	Blood cultures	18–90	121	6	5.0	2.0–10.0
[21]	Brazil (Sumaré)	2005–2007	Prospective	Chest X-ray, one or more clinical symptoms	Blood culture, sputum culture, urine antigen	≥14	66	21	31.8	21.0–44.0
[22]	Argentina (Buenos Aires)	1997–1998	Prospective	Cough, temp >37.8°C, respiratory distress, infiltrates on chest X-ray	2 blood cultures & sputum culture	≥17	346	35	10.1	7.0–14.0
[23]	Bolivia (La Paz)	1981–1991	Retrospective	Fever, cough, chest pain, expectoration, infiltrates on chest X-ray	Blood & sputum culture	≥18	101	28	27.7	20.0–37.0
[24]	Chile (Puerto Montt)	2000–2001	Prospective	Cough, temp >37.8°C , respiratory distress, infiltrates on chest X-ray	2 blood cultures & sputum culture	≥15	200	24	12.0	8.0–17.0

Note: LAC, Latin America and the Caribbean; CAP, community-acquired pneumonia; SP, *S. pneumoniae*; CI, confidence interval.

Proportion of meningitis cases associated with *S. pneumoniae* was addressed in five studies conducted in Argentina (1 study), Brazil (2 studies), Chile (1 study), and Cuba (1 study) (Table 3). Four of these studies presented data on pneumococcal meningitis only for individuals under 20 years of age. The Cuban study included individuals 5 years of age or older. Proportion of meningitis cases associated with *S. pneumoniae* ranged from 3.3% to 64.3%, with a weighted mean of 14.3% (95% CI 8.4-21.5).

TABLE 3. Proportion of meningitis associated with *S. pneumoniae* in LAC studies.

Study Reference	Country	Time Period	Study	Meningitis Diagnostic Criteria	Detection Methods	Age Group (years)	Total Meningitis Cases	*SP* Cases	*SP* Cases/ Total Cases (%)	95% CI of Proportion
[25]	Chile	1988–1991	Prospective	Fever, meningism, CSF abnormalities	*S. pneumoniae* in CSF (Gram stain, isolation, & latex) or isolation from blood culture	5–15	14	9	64.3	38.0–96.0
[26]	Cuba	1993–1998	Retrospective	Fever, meningism	*S. pneumoniae* in CSF or blood culture, or latex agglutination	5–14 15-64 65+	1,598 2,591 741	52 244 129	3.3 9.4 17.4	2.0–4.0 8.0–11.0 15.0–20.0
[27]	Brazil	1987–2001	Prospective	No information	*S. pneumoniae* in CSF culture, blood, or latex agglutination	5–14	38	9	23.7	12.0–39.0
[28]	Argentina	2002–2006	Retrospective	Meningitis diagnosis at hospital discharge	Not clearly stated	5–16	51	7	13.7	6.2–25.2
[29]	Brazil	1997–1998	Prospective	Clinical signs of meningism, CSF abnormalities	*S. pneumoniae* isolated from CSF or blood, or latex agglutination	5–19 5–9 10–19	101 57 41	8 1 7	7.9 1.8 17.1	3.0–14.0 0.1–8.3 8.0-31.0

Note: LAC, Latin America and the Caribbean; *SP, S. pneumoniae*; CI, confidence interval; CSF, cerebrospinal fluid.

Six studies describing the CFP among people with pneumococcal pneumonia were found in the literature from LAC; all of these studies were conducted in Chile (Table 4). CFP ranged from 0.0% to 13.0%, with the lowest CFP (0.0%) found in studies with the lowest sample size (<10 patients). Two studies reported CFP values stratified by age groups,[17,32] and the data showed that individuals older than 75 years of age had higher CFP than younger persons (19.2% to 20.0% versus 2.0% to 7.7%, respectively). CFP among persons with pneumococcal

meningitis was evaluated in four studies, two from Brazil and two from Chile, and ranged from 9.9% to 57.9%. CFP in meningitis patients aged 60 to 89 years was 57.9%, which was six times higher than for children 5-15 years of age (Table 5).

TABLE 4. Case fatality proportion among cases of pneumococcal pneumonia in LAC studies.

Study Reference	Country	Time Period	Case Definition	Age Group (years)	Deaths	Cases	CFP (%)
[17]	Chile	1999–2001	*S. pneumoniae* isolation from blood or sputum	16–92 16–55 56–75 75–92	6 0 1 5	46 7 13 26	13.0 0.0 7.7 19.2
[19]	Chile	2003–2005	*S. pneumoniae* isolation from blood or sputum, or + urine antigen	17–101	3	49	6.1
[30]	Chile	1999–2001	*S. pneumoniae* isolation from blood or sputum	29–91	0	6	0.0
[14]	Chile	1994–2007	*S. pneumoniae* isolation from blood	5–14	4	232	1.7
[31]	Chile	1997–2002	*S. pneumoniae* isolation from blood	17–97	3	45	6.7
[32]	Chile	2002–2005	*S. pneumoniae* isolation from blood or sputum, or + urine antigen	16–92 16–74 75–92	13 2 11	151 96 55	8.6 2.0 20.0

Note: LAC, Latin America and the Caribbean; CFP, case fatality proportion.

TABLE 5. Case fatality proportion among cases of pneumococcal meningitis in LAC studies.

Study Reference	Country	Time Period	Case Definition	Age Group (years)	Deaths	Cases	CFP (%)
[25]	Chile	1988–1991	Isolation of *S. pneumoniae* from CSF culture or + latex agglutination	5–15	2	9	22.2
[33]	Brazil	1973–1982	Isolation of *S. pneumoniae* from CSF culture	7–15 15+	49 101	120 195	40.8 51.8
[14]	Chile	1994–2007	Isolation of *S. pneumoniae* from blood or CSF culture	5–14	7	71	9.9
[34]	Brazil	1989–1997	Isolation of *S. pneumoniae* from CSF culture	60–89	11	19	57.9

Note: LAC, Latin America and the Caribbean; CFP, case fatality proportion; CSF, cerebrospinal fluid.

Data from SIREVA II surveillance

Between 2006 and 2011, a total of 10,175 isolates with syndrome and age group data were submitted to SIREVA II (Table 6). Overall, 3,635 IPD isolates (35.7%) were from cases of meningitis and 6,540 (64.2%) were from non-meningitis cases, including pneumonia, sepsis, bacteremia, and others. On average, 67.0% of the invasive isolates submitted from 6 countries (Brazil, Cuba, Dominican Republic, El Salvador, Peru, and Venezuela) were from meningitis cases. Of meningitis cases reported, 23.4% occurred in children aged 5-14 years, 59.9% in adults

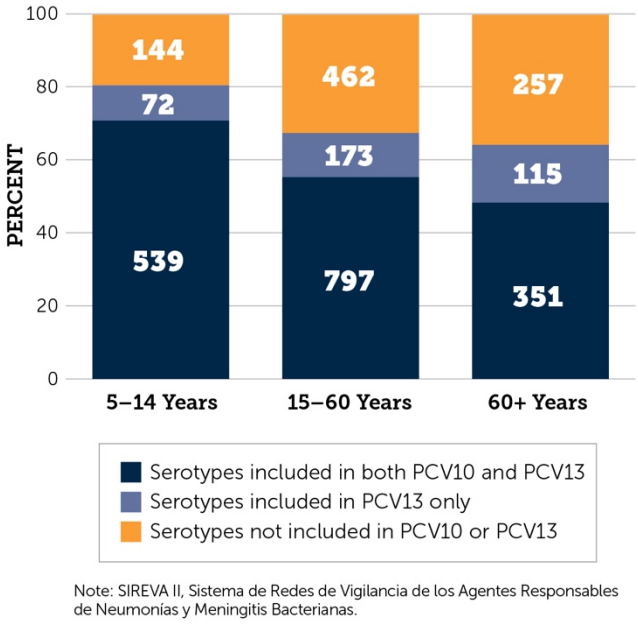
TABLE 6. Distribution of *S. pneumoniae* isolates by age and syndrome in LAC countries, SIREVA II 2006–2011.

Syndrome	5–14 (years)		15–59 (years)		60+ (years)		5–60+ (years)	
	Number of Isolates	Number of Isolates/ Total Isolates by Syndrome (%)	Number of Isolates	Number of Isolates/ Total Isolates by Syndrome (%)	Number of Isolates	Number of Isolates/ Total Isolates by Syndrome (%)	Total Isolates by Syndrome	Total Isolates by Syndrome/ Total Overall Isolates (%)
Meningitis	850	23.4%	2,178	59.9%	607	16.7%	3,635	35.7%
Pneumonia	850	25.8%	1,421	43.2%	1,018	31.0%	3,289	32.3%
Sepsis	161	20.8%	368	47.5%	246	31.7%	775	7.6%
Bacteremia	331	16.8%	934	47.5%	703	35.7%	1,968	19.3%
Others	166	32.7%	217	42.7%	125	24.6%	508	5.0%
							Total Over-all: 10175	100.0%

Note: LAC, Latin America and the Caribbean; SIREVA II, Sistema de Redes de Vigilancia de los Agentes Responsables de Neumonias y Meningitis Bacterianas.

aged 15-59 years, and 16.7% in adults 60 years or older. Of non-meningitis cases reported, 23.1% occurred in children aged 5-14 years, 45.0% in adults aged 15-59, and 32.0% in adults 60 years or older.

FIGURE 2. Serotype distribution of invasive pneumococcal disease isolates by age group, SIREVA II, 2006–2011.

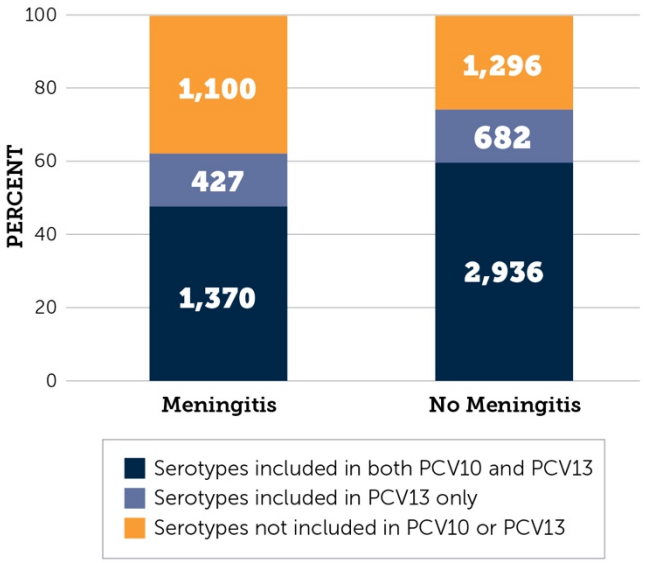


Note: SIREVA II, Sistema de Redes de Vigilancia de los Agentes Responsables de Neumonías y Meningitis Bacterianas.

Of the 10,175 available isolates, a total of 7,811 (76.8%) invasive pneumococcal disease isolates were collected during the pre-PCV period. For the analysis of serotype distribution by age group (Figure 2), only 2,910 isolates of the 7,811 pre-PCV isolates were disaggregated by age in SIREVA II reports and therefore included in the analysis. All 7,811 isolates were included in the analysis of serotype distribution by syndrome (Figure 3) and geographic area (Figure 4).

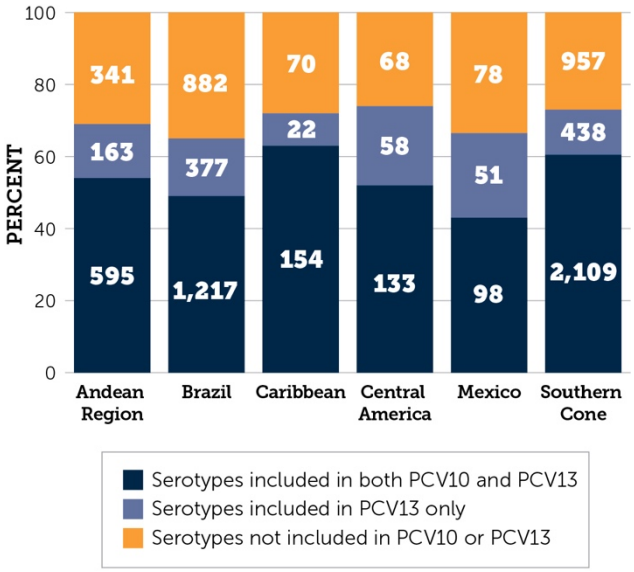
Figure 2 depicts the serotype distribution of these isolates by vaccine type (PCV10 and PCV13, PCV13 only, neither), stratified by age group. Overall, 58.0% of isolates represented serotypes contained in both vaccines and 12.4% represented serotypes included in PCV13 only. The highest proportion of isolates corresponding to vaccine

FIGURE 3. Serotype distribution of invasive pneumococcal disease isolates by syndrome, SIREVA II, 2006–2011.



Note: SIREVA II, Sistema de Redes de Vigilancia de los Agentes Responsables de Neumonías y Meningitis Bacterianas.

FIGURE 4. Serotype distribution of invasive pneumococcal disease isolates by geographic area, SIREVA II, 2006–2011.



Note: SIREVA II, Sistema de Redes de Vigilancia de los Agentes Responsables de Neumonías y Meningitis Bacterianas.

serotypes was observed in children aged 5-14 (71.4% in both PCV10 and PCV13, 9.5% in PCV13 only). Among adults ≥60 years old, 35.5% of isolates were non-PCV serotypes.

Figure 3 depicts the serotype distribution of invasive pneumococcal disease isolates stratified by clinical syndrome. Serotypes included in both PCV10 and PCV13 represented 47.3% of meningitis isolates and 59.7% of non-meningitis isolates. Serotypes included in only PCV13 represented 14.7% of meningitis isolates and 13.9% of non-meningitis isolates.

Figure 4 depicts the serotype distribution of invasive pneumococcal disease isolates stratified by geographic area in the LAC region. The area contributing the most isolates was the Southern Cone (n=3504), followed by Brazil (n=2476), and the Andean region (n=1099). The proportion of isolates that were non-PCV serotypes was highest for Brazil (35.6%), followed by Mexico (34.4%), Andean (31.0%), Caribbean (28.5%), Southern Cone (27.3%), and Central America (26.3%).

Discussion

This extensive effort to gather evidence on the burden of pneumococcal disease in older children and adults in LAC yielded very limited and heterogeneous data. Only four studies, representing only two countries (Chile and Brazil) and utilizing different methodologies, provided incidence estimates of pneumococcal disease. Given the paucity of data and inability to directly compare studies, it was not possible to conduct a meta-analysis or generate a population-based estimate of the burden of pneumococcal disease in the LAC region. Furthermore, the primary source of data was hospitalized patients across the studies. This may have biased the analysis towards more severe disease, since hospital-based case ascertainment does not represent the full spectrum of pneumococcal disease burden and severity. For assessing case fatality proportion, fatal cases may be missed if patients die before enrollment, thus biasing the analysis towards a lower case fatality proportion. Regarding SIREVA II, surveillance data are biased according to the types of specimens that are submitted to the network. Since several countries submit mainly cerebrospinal fluid (CSF) isolates, the serotype distribution may be biased towards meningitis cases and not accurately reflect the serotypes causing all invasive disease. The reviewed data do, however, provide some useful insight into the proportion of pneumonia and meningitis caused by *S. pneumoniae*, as well as the pneumococcal serotypes most commonly reported among adults and older children with invasive pneumococcal disease in LAC.

We found a high degree of variability in the proportion of pneumonia and meningitis associated with *S. pneumoniae,* with estimates ranging from 5.0% to 31.8% for community-acquired pneumonia and 3.3% to 64.3% for meningitis. Differences in laboratory methods certainly contributed to the variation in results across individual studies. For community-acquired pneumonia, the proportion in which *S. pneumoniae* was isolated was almost 2 times higher in studies that used pneumococcal urine antigen testing (29.1% versus 16.4%). This finding is consistent with the overall AGEDD study, which reported that, for each case of pneumococcal pneumonia identified by blood or sputum culture, urine antigen testing identified an additional 0.87 cases.[11] The sensitivity of urine antigen testing for detecting pneumococcal pneumonia has been estimated to be 70.0% to 80.0% for bacteremic pneumococcal pneumonia[35,36] and 52.0% to 78.3% for non-bacteremic pneumococcal pneumonia.[37] Thus, even the 29.8% of community-acquired pneumonia cases found to be pneumococcal among studies using urine antigen testing is likely underestimating the true burden of pneumococcal pneumonia among older children and adults in LAC. Notably, none of the meningitis studies used antigen detection or molecular diagnostic techniques, which suggests an underestimation of pneumococcal etiology in the proportion of meningitis cases. Adding other techniques to bacteriological methods, such as immunochromatographic tests and polymerase chain reaction, may increase the identification of pneumococcus among culture-negative meningitis cases.[38,39]

Differences in case definition also likely led to variability in results, and complicate direct comparison across studies. For example, the study that found the highest proportion of meningitis cases associated with *S. pneumoniae* (64.3%), started with a case definition of fever, meningism, and CSF abnormalities; most other studies had case definitions based on clinical signs without consideration of laboratory results. The case definitions used for pneumonia studies generally relied on a combination of clinical signs and abnormalities on chest radiograph. However, interpretation of chest radiographs can be quite variable.[40] Guidelines for standardized interpretation of pediatric chest radiographs were developed by WHO as an epidemiologic tool for measuring bacterial pneumonia in children less than 5 years old.[41] No such guidelines exist for older children and adults. However, a study in Guatemala found that applying the same guidelines for interpretation of adult chest radiographs could identify adults more likely to have pneumococcal pneumonia.[42] Standardized definitions for studying community-acquired pneumonia and meningitis in adults could help improve the quality and comparability of studies on the burden of pneumococcal disease among older children and adults.

The LAC region has a relatively rich source of data on pneumococcal serotypes causing invasive disease. SIREVA II data show that, among older children and adults, the proportion of invasive pneumococcal disease cases associated with PCV serotypes is highest among children aged 5-14 years (71.4%) and lowest among persons aged ≥60 years (48.5%). Studies from North America and Europe have not noted such differences in serotype coverage between older children, adults, and the elderly.[43,44] PCV serotypes were also recovered more frequently from patients with invasive non-meningitis syndromes than from patients with meningitis in the current analysis for LAC, which is similar to findings from a hospital-based surveillance study in Uruguay.[45] However, since some countries submit predominantly meningitis isolates, the proportion of vaccine serotypes among meningitis versus non-meningitis cases may be confounded by regional differences in serotype distribution. The predominance of meningitis isolates might also skew the overall serotype distribution (including by age group and by region), as pneumonia isolates are under-represented, despite pneumonia representing the greatest burden of serious pneumococcal infections. Furthermore, SIREVA II lacks detailed epidemiological and clinical data, does not have a defined population denominator, and does not mandate submission of isolates – all of which limit interpretation of the data. Despite such limitations, the large number of isolates that SIREVA II collects provides important insight on serotype coverage of pneumococcal vaccines among older children and adults in LAC.

Data on isolate serotype distribution with respect to inclusion in PPV23 could not be assessed from SIREVA II for our period of analysis. PPV23 has been available for several decades for prevention of pneumococcal disease in older children and adults. Data on the efficacy of PPV23 are conflicting, however it seems to protect against invasive pneumococcal disease among healthy young adults and provide some degree of protection against invasive pneumococcal disease in the elderly.[1,46,47] Two economic studies have concluded that the use of PPV23 in Colombia and Brazil is likely to be cost effective at a price of US$8.00 per dose.[9,48] PPV23 is used among

high-risk populations by several countries in the LAC region [49], but there are no published studies evaluating its impact.

Clinical trials of PCV in adults have shown it to be protective against pneumonia in adults ≥65 years of age,[10,50] and against repeat episodes of invasive pneumococcal disease among HIV-infected adults.[51] In 2014, the U.S. Advisory Committee on Immunization Practices (ACIP) recommended the routine use of PCV13 in series in with PPV23 for prevention of pneumococcal disease among people ≥65 years of age in the United States.[10] ACIP had previously recommended use of PCV13 among immunocompromised adults[52] and older children.[53] In 2014, PAHO's Technical Advisory Group (TAG) on vaccine-preventable diseases discussed the use of PCV in adults, and concluded that countries may consider use of PCV13 among high-risk adults.[54] The TAG also emphasized that that routine vaccination of children with PCV should be the highest priority for reducing pneumococcal disease burden and that PCV use in healthy adults would depend on the results of studies of PCV effectiveness, cost-effectiveness, and herd protection.

Consideration of PCV use in adults must take into account indirect protection afforded through routine vaccination of infants and mediated by reductions in nasopharyngeal carriage of vaccine serotypes.[5,6] For the 7-valent PCV (PCV7), herd protection has been demonstrated in developing[55] and developed countries,[56] and there is emerging evidence of this effect for PCV10 and PCV13.[57-60] In the United States and England, there has been a considerable reduction of PCV7 and PCV13 serotypes causing invasive pneumococcal disease among older people not targeted for vaccination following the implementation of vaccine recommendations for children.[57,59] In Kenya, a reduction in nasopharyngeal carriage of PCV10 serotypes has been observed in non-vaccinated people >5 years old following the implementation of routine vaccination in children.[60] However, the magnitude of decreased transmission provided through herd protection varies by different factors, such as age group, syndrome, number of years since vaccine introduction, and vaccination schedule.[56] Even though most countries in the LAC region have introduced universal childhood vaccination with PCVs, there are currently no published studies assessing the impact of herd protection in the region. Additional research evaluating the indirect effects of PCV in older children and adults is needed to guide evidence-based policy decisions regarding PCV in adults.

Conclusions

Despite limited data on pneumococcal disease burden for older children and adults in LAC, available evidence suggests that pneumococcus causes an important proportion of community-acquired pneumonia and meningitis. In addition, data from SIREVA II indicate that a substantial proportion of invasive pneumococcal disease cases in older children and adults were caused by PCV serotypes prior to the introduction of PCV. The uptake of PCV in routine infant immunization programs in LAC[4,61] was rapid and preceded that in Africa and Asia by several years; monitoring the indirect impact of PCV in this region could provide essential data to guide the use of PCV in countries that have not yet introduced it. Strengthening surveillance for pneumococcal disease among older children and adults in the LAC region is important in order to better characterize the burden of disease, to monitor the indirect effects of PCV introduction in infant immunization programs, and to guide vaccine policy decisions in the region and worldwide.

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