Clinical and economic burden of pneumonia among adults in Latin America

Raul E. Isturiz a,⁎, Carlos M. Luna b, Julio Ramirez c

⁎ Corresponding author. Tel.: +58 212 551 7889; fax: +58 212 552 0626.
E-mail address: risturiz7@hotmail.com (R.E. Isturiz).

1. Introduction

Lower respiratory tract infections (LRTIs), which include community-acquired pneumonia (CAP), are a leading cause of mortality worldwide, causing 1.6 million deaths annually in adults aged >59 years. Streptococcus pneumoniae is the most common pathogen implicated in CAP. In developed regions of the world, LRTIs have been reported to account for 4% of overall deaths, while in Latin America, mortality due to LRTIs has been reported as 6%. LRTIs in persons aged >65 years were the third most frequent cause of death in 31 Latin American countries during the period 2001 to 2003. In comparison, pneumonia was found to be only the eighth leading cause of death in the USA.

In aging adults, the burden of CAP is of even greater concern when considering that the number of persons aged >60 years globally is projected to triple, from 673 million in 2005 to 2 billion by 2050. This will be most apparent in developing regions of the world, where this age group is projected to increase from 64% (2005) to 80% (2050) of the total population. The 50 least developed countries will realize a more than 200% increase in their populations, from 0.8 billion in 2007 to 1.7 billion by 2050, compared with developed regions, which are projected to remain stable at a population of 1.2 billion.

CAP poses a considerable health problem worldwide and is responsible for a substantial clinical and economic burden and the utilization of health care resources. This review examines the etiology, incidence, hospitalization, morbidity and mortality, antibiotic resistance, costs associated with care, and the potential benefits of pneumococcal vaccination in the reduction of CAP in Latin American adults.

2. Methods

A review of the scientific literature using the US National Institutes of Health, National Library of Medicine (MEDLINE) database was conducted to ascertain the clinical and economic burden of CAP among adults in Latin America. A broad search strategy employing the MeSH (medical subject heading) major topic ‘pneumonia’ was used to ensure the initial capture of all relevant publications published during the period January 1970 through August 2008. To further identify potentially relevant data, the Boolean operator ‘AND’ was then used with each of these additional search terms: community acquired, hospital acquired, health care associated, and ventilator associated. Variations of
these terms were also included. These results were filtered to identify adult subjects using age delimiters of adult, adult disease, adulthood, and aged. Finally, the search results were filtered to include only those cases identified by the United Nations as composing the geographic region of Latin America and the Caribbean.

The search was limited to primary articles focusing on the epidemiology, etiology, hospitalization, morbidity and mortality, antibiotic resistance, and clinical and economic impact of CAP in adults in Latin America. Additional references were identified through review of the bibliographies of retrieved articles. Although the search period began with 1970, no relevant primary articles regarding adult CAP in Latin America prior to 1997 were identified. There were no language restrictions.

Supplemental sources of data were identified via Web sites of the US Census International Database, the Pan American Health Organization, and 12 Latin American health agencies (Appendix).

2.1. Inclusion criteria

Primary articles that focused on the etiology, mortality, antibiotic resistance, and clinical and economic burden of CAP in adults in Latin America were included in this review. Studies that included data on persons aged <17 years were included only if the data between adults and children were separated; only data from adults were included in this review.

2.2. Exclusion criteria

Specific exclusions were review articles, articles that reported solely on persons aged <17 years, and geographic regions other than Latin America.

3. Results

3.1. Etiology

In a database derived by the Community-Acquired Pneumonia Organization in 2005 to determine clinical outcomes of CAP among adults in Latin America, *S. pneumoniae* was demonstrated to be the most common pathogen implicated in adult CAP, accounting for 35% of cases in which an organism was identified. The second most commonly identified organism was *Staphylococcus aureus* in 17% of culture-positive cases. *Haemophilus influenzae* was also an important cause of CAP, identified as the causative agent in 23.2% of adult pneumonia cases in the Regional System for Vaccines II (SIREVA II) study between 2000 and 2005. Fifty-three percent of patients with CAP in Latin America were treated for atypical pathogens. The most frequently occurring atypical pathogens were *Mycoplasma pneumoniae* (13%), *Chlamydia pneumoniae* (6%), and *Legionella pneumophila* (3%). In Argentina and Chile, viruses were the second most common pathogens. Parainfluenza virus types 1–3, influenza virus types A and B, adenoviruses, and respiratory syncytial virus caused approximately 6–26% of CAP. In a multicenter clinical trial conducted in five Latin American countries (Argentina, Brazil, Chile, Mexico, and Uruguay), *S. pneumoniae* was detected in 40% of positive sputum cultures and *M. pneumoniae* was detected in 16% of patients. Mixed organisms accounted for 8.6% of CAP infections.

3.2. Incidence

The incidence of pneumonia in the Latin American region is substantial, however pneumonia is generally not considered to be a reportable disease, and only estimations of the number of annual cases have been made. In countries with the most available data, 120 000 annual cases (Argentina), 170 000 annual cases (Chile), and 1 920 000 annual cases (Brazil) have been estimated.

Detailed incidence rates for Brazilian adults aged ≥50 years hospitalized with CAP during the period 2000 to 2007 have been reported. These data showed that hospitalization for CAP decreased 25.3% for persons aged 50–59 years (400–299 per 100 000 population) and 19.5% for persons aged 60–69 years (651–524 per 100 000 population). In older age groups incidence rates increased 5.2% for persons aged 70–79 years (1134–1193 per 100 000 population) and 33.0% for persons aged ≥80 years (2177–2895 per 100 000 population) (Table 1).

3.3. Hospitalizations

The most detailed available hospitalization data was also for Brazil. During the 2000 to 2007 period, 1 524 376 hospital admissions for pneumonia for adults aged ≥50 years were reported in Brazil (Table 2). As to be expected with the decreased incidence rates previously shown, the number of hospitalizations decreased 17% for persons aged 50–59 years (50 000–41 480) and 11.4% for persons aged 60–69 years (53 230–47 154). The number of hospitalizations increased 15.3% for persons aged 70–79 years (51 265–59 095) and 45.3% for persons aged ≥80 years (39 884–57 936). CAP was the second most frequent reason for hospital admission in Brazil in 2003.

A prospective study of 84 patients in five Latin American countries (Argentina, Brazil, Chile, Mexico, and Uruguay) showed that 50–52.8% of CAP patients were admitted to the hospital. This high rate of hospitalization increases the economic burden of CAP through utilization of more expensive health care resources.

### Table 1

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>2000</th>
<th>2001</th>
<th>2002</th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
</tr>
</thead>
<tbody>
<tr>
<td>50–59</td>
<td>400</td>
<td>358</td>
<td>316</td>
<td>309</td>
<td>330</td>
<td>296</td>
<td>299</td>
<td>299</td>
</tr>
<tr>
<td>60–69</td>
<td>651</td>
<td>586</td>
<td>517</td>
<td>526</td>
<td>599</td>
<td>526</td>
<td>526</td>
<td>524</td>
</tr>
<tr>
<td>70–79</td>
<td>1134</td>
<td>1096</td>
<td>1013</td>
<td>1076</td>
<td>1241</td>
<td>1115</td>
<td>1130</td>
<td>1193</td>
</tr>
<tr>
<td>≥80</td>
<td>2177</td>
<td>2162</td>
<td>2078</td>
<td>2256</td>
<td>2716</td>
<td>2556</td>
<td>2684</td>
<td>2895</td>
</tr>
</tbody>
</table>

### Table 2

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>2000</th>
<th>2001</th>
<th>2002</th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
</tr>
</thead>
<tbody>
<tr>
<td>50–59</td>
<td>50 211</td>
<td>45 445</td>
<td>40 616</td>
<td>40 064</td>
<td>43 431</td>
<td>39 940</td>
<td>40 960</td>
<td>41 480</td>
</tr>
<tr>
<td>60–69</td>
<td>53 230</td>
<td>48 564</td>
<td>43 368</td>
<td>44 556</td>
<td>51 310</td>
<td>46 226</td>
<td>46 812</td>
<td>47 154</td>
</tr>
<tr>
<td>70–79</td>
<td>51 265</td>
<td>50 200</td>
<td>46 800</td>
<td>49 935</td>
<td>58 693</td>
<td>53 989</td>
<td>56 305</td>
<td>59 095</td>
</tr>
<tr>
<td>≥80</td>
<td>39 884</td>
<td>40 081</td>
<td>38 936</td>
<td>42 713</td>
<td>51 949</td>
<td>50 011</td>
<td>53 107</td>
<td>57 936</td>
</tr>
</tbody>
</table>
and contrasts with the rest of the world, where 80% of CAP patients are treated as outpatients.\textsuperscript{15} In a retrospective study in Argentina that assessed 436 patients admitted to 12 hospitals, 30% were admitted to the intensive care unit (ICU).\textsuperscript{19}

3.4. Mortality

In Argentina, CAP-related mortality averaged 13.3% in two studies of hospitalized patients (1998–1999 and 2000–2001).\textsuperscript{13} In Brazil, pneumonia was the leading cause of death among respiratory diseases at all ages and the fourth leading cause of death in adults, causing 26,394 deaths in 1996.\textsuperscript{15} Mortality due to respiratory diseases at all ages and the fourth leading cause of death in adults, pneumonia was the leading cause of death among those aged \( >60\) years. Also in Brazil, hospital mortality rates increased between 1998 (2.0%) and 2003 (2.9%).\textsuperscript{18}

In Chile, CAP mortality among adults aged 20–64 years was 14.8 per 100,000 population\textsuperscript{20} and was 17 times higher at 258.8 per 100,000 population for adults aged \( >65\) years.\textsuperscript{5} For hospitalized patients aged \( >65\) years, mortality ranged from 7.6–9.8% (in-hospital) to 12.4–13.1% (30-day follow-up),\textsuperscript{21,22} with an ICU mortality of 20%.\textsuperscript{21}

3.5. Antibiotic resistance

Penicillin-resistant \textit{S. pneumoniae} is an increasingly important pathogen worldwide. An independent study conducted in Brazil revealed substantial increases in penicillin resistance in strains of \textit{S. pneumoniae} – a 300% increase in high resistance and a 61% increase in intermediate resistance from 1998 to 2003.\textsuperscript{23}

Two major surveillance studies of \textit{S. pneumoniae} resistance conducted in Latin America are the SENTRY Antimicrobial Surveillance Program and the SIREVA II Surveillance Program. The SENTRY Antimicrobial Surveillance Program was conducted in seven countries (Argentina, Brazil, Chile, Colombia, Mexico, Uruguay, and Venezuela) from 1997 to 2001, during which 1561 isolates were collected from subjects with CAP for assessment of antimicrobial resistance rates for \textit{S. pneumoniae}. The majority of the isolates (87%) were recovered from Argentina, Brazil, and Chile,\textsuperscript{24} and most were collected from the respiratory tract (77%). Almost half of the isolates were obtained from middle-aged and older adult patients – 24% of the subjects were in the group aged 41–64 years and 24% were aged \( >65\) years. Rates of penicillin resistance were 15.5% in adults aged 41–60 years and 11.3% in those aged \( >65\) years and, along with erythromycin resistance, did not vary significantly over the years studied. For all age groups, penicillin resistance ranged from 2.8% in Venezuela to 25% in Mexico, demonstrating a marked variability across the region.\textsuperscript{24} The mean rate of penicillin-resistant \textit{S. pneumoniae} was 39%.\textsuperscript{25}

The World Health Organization (WHO) and the Pan American Health Organization jointly conducted the SIREVA II \textit{S. pneumoniae} Surveillance Program through a network of 20 participating hospitals and sentinel laboratories in Latin American countries. The program gathered data on the distribution of serotypes and susceptibility of \textit{S. pneumoniae} between 2000 and 2005.\textsuperscript{26} Results on \textit{S. pneumoniae} susceptibilities to penicillin and ceftriaxone in 2005 from countries who collected at least 60 isolates from adults are shown in Table 3.\textsuperscript{26} Resistance rates to chloramphenicol, erythromycin, and trimethoprim–sulfamethoxazole (SXT) were also evaluated during the SIREVA II study period. Where reported, \textit{S. pneumoniae} generally remained susceptible, in adults, to chloramphenicol and erythromycin.\textsuperscript{26} However, high levels of resistance to SXT were observed for the adult population from 2000 to 2005: 33–54.5% in Brazil, 11.2–30.2% in Chile, 19.6–35.8% in Colombia, 14.3–40.0% in adults aged \( >60\) years in Cuba, and 23.5–55.6% in Mexico, where resistance by \textit{S. pneumoniae} to SXT in persons aged \( >60\) years almost doubled from 2000 to 2005 (from 23.5–53.8%).\textsuperscript{26} Resistance to erythromycin was also high in Mexico at 10.0–46.2% and more than doubled during the surveillance period. It is also noteworthy that although the sample sizes were small (\( n = 13\) for each age group), 30.8% of isolates retrieved from CAP patients aged 15–60 years and 15.4% from patients aged \( >60\) years in Mexico showed intermediate resistance to ceftriaxone in 2005.\textsuperscript{26} These data underscore the importance of continued surveillance and judicious use of antibiotics in treating pneumococcal infections and the need to implement adult vaccination programs to reduce the rate of antibiotic use.

The SIREVA II initiative also studied the distribution of \textit{S. pneumoniae} serotypes in Latin America and the Caribbean. Serotypes 1, 3, and 14 were responsible for the highest proportion of pneumococcal disease in adults (Figure 1).\textsuperscript{8}

4. Discussion

The incidence of CAP and prevalence of pathogens in CAP vary throughout Latin America. CAP in the Latin American region is not subject to epidemiological monitoring, and there are minimal reliable data on its incidence and etiology among adults. Further, the literature on CAP in Latin America has focused on pediatric populations, and the impact of CAP in adults may be under-recognized and under-reported.

Data on CAP among adults in Latin America have primarily been reported from those countries that are more developed and have greater financial resources – Argentina, Brazil, Chile, and Mexico. Data on CAP among adults in Latin America from other countries...
were often incomplete or derived from a small number of cases. Further, the etiology of CAP is difficult to assess from published studies in Latin America because of variations in screening, variations in the inclusion or exclusion criteria for age and co-morbidities, differences in methodology, and the use of antibiotics prior to culture.

Microbiology testing is not routinely performed in clinical practice, and any evidence that it has clinical value is sparse in the literature. Obtaining microbial specimens to determine the etiological agent(s) involved in CAP becomes a major challenge in aged patients as more than 50% of these patients do not have a productive cough with expectoration at the time of diagnosis. Delays in initiating antibiotic treatment are linked to a greater risk of complications and death, particularly in those requiring hospitalization. Although empiric therapy should be rapidly initiated, microbiologic studies should be conducted to identify the causal agent and facilitate specific antimicrobial treatment for patients hospitalized with CAP and those who are at increased risk for death. There is no consensus in Latin America regarding the use of antimicrobial agents that cover atypical pathogens in the initial treatment of patients hospitalized with CAP. Only 53% of hospitalized CAP patients in Latin America received empiric therapy for typical and atypical pathogens in accordance with North American guidelines, compared with 91% of North American inpatients.

The emerging resistance among the causative pathogens of CAP adds to the economic burden of this disease by making it necessary to alter established therapeutic regimens. Penicillin resistance is often associated with cross-resistance to other antibiotics and multidrug-resistant strains may create a demand for newer antimicrobials, which are often more costly than existing therapies.

In January 2008, the Clinical and Laboratory Standards Institute revised the penicillin minimum inhibitory concentration (MIC) breakpoints for infections due to S. pneumoniae. The susceptibility breakpoints for penicillin administered parenterally for non-meningeal infections due to S. pneumoniae have been increased as follows: susceptible, 2 μg/ml; intermediate, 4 μg/ml; and resistant, ≥8 μg/ml. The breakpoints for penicillin-susceptible and resistant S. pneumoniae meningeal infections due to S. pneumoniae are ≤0.06 μg/ml and ≥0.12 μg/ml, respectively. The impact of applying the new breakpoints to the data derived from the SENTRY Antimicrobial Surveillance Program was demonstrated as follows: using the prior MIC breakpoint of ≤0.06 μg/ml, only 68% of S. pneumoniae isolates would be considered susceptible to penicillin, but according to the new breakpoint of ≤2 μg/ml, 93% of the isolates would be susceptible. Therefore, if data from the studies described in this review utilized the new breakpoints, the percentage of penicillin-resistant S. pneumoniae isolates would likely be lower and similar to the proportion of isolates susceptible to ceftriaxone (MICs susceptible, 1 μg/ml; 2 intermediate, 4 μg/ml; and resistant, ≥4 μg/ml) administered parenterally for non-meningeal infections (96%).

Although CAP has a major economic impact on health care systems worldwide, there are only limited data regarding this burden in Latin America. Moreover, there is no clear information contained in these studies on how the treatment of pneumococcal disease is calculated, and what is included in cost estimates. The data from one population is not applicable to other populations, and are not representative of the true cost of pneumococcal disease.

Pneumococcal vaccines are effective in reducing rates of invasive pneumococcal disease (IPD) and CAP due to S. pneumoniae and substantial preventive benefits can be achieved through their incorporation into national immunization programs (NIPs). A polysaccharide pneumococcal vaccination is recom-mended by the Advisory Committee on Immunization Practices (ACIP) for all persons aged ≥65 years and persons aged <65 years who are at high risk for pneumococcal infections. The H. influenzae b conjugate vaccine is implemented nearly universally throughout Latin America, but vaccination for S. pneumoniae, which causes more invasive and noninvasive diseases, has not been widely implemented. In the USA, nearly universal vaccination of children with the seven-valent pneumococcal conjugate vaccine (PCV7) resulted in an 18% decrease in the incidence of IPD in persons aged ≥65 years and reduced the incidence of IPD caused by antibiotic-resistant strains by 35%. PCV7 vaccination diminished levels of pneumococcal disease in both adults and unvaccinated children in addition to vaccinated children. In the USA in 2003, compared with 1998–1999, twice as many IPD cases were prevented through indirect effects via interruption of pneumococcal transmission than through the direct effect of vaccinating children. Despite these substantial indirect effects, many adults remain at risk for pneumococcal disease, and directly vaccinating adults within the context of a vaccine program is a sound public health strategy.

5. Conclusions

S. pneumoniae remains the leading cause of CAP and is associated with a high incidence of mortality in Latin American adults. As populations age, there is an increase in co-morbidities, increased susceptibility to infection, and a greater risk for hospitalization. Temporal variations in endemic pathogens and increasing antibiotic resistance diminish the therapeutic efficacy of existing treatment regimens, thus leading to a need for newer, more expensive antimicrobial agents.

Limited information on the epidemiology and etiology of CAP in Latin American adults makes it difficult to gain a perspective regarding the evolution of the disease in this region. Comprehensive surveillance and standardized reporting systems such as the SENTRY and SIREVA II programs will facilitate the monitoring of emerging resistance patterns, guide clinicians in the choice of appropriate treatment options, and improve outcomes for patients with CAP.

The lack of data on adult pneumococcal disease in this region may be a factor in the limited use of pneumococcal vaccination among adults. Incorporation of pneumococcal conjugate vaccines into NIPs will help the vaccine reach the most vulnerable populations and should be expanded to include adults.

Conflict of interest: Raul E. Isturiz: advisory board member and lecturer for Wyeth, Sanofi-Aventis USA and AstraZeneca; Carlos M. Luna: advisory board member for Wyeth, Bayer, and Pfizer, lecturer for Merck and AstraZeneca; Julio Ramirez: grant support from Cubist, Pfizer, Merck, and Wyeth, presentations for Cubist, Pfizer, and Ortho-McNeil.

Acknowledgements

The authors thank Excerpta Medica (Bridgewater, NJ, USA) for professional writing and editorial assistance that was funded by Wyeth Pharmaceuticals, Collegeville, PA, USA.

Appendix A. Appendix

Supplemental data sources

Pan American Health Organization (www.paho.org)
Latin American health agencies:
Argentina: National Administration of Foods, Drugs and Medical Technology (http://www.anmat.gov.ar)
Brazil: Ministry of Health (http://www.saude.gov.br)
Chile: Health Ministry of Chile, Institute of Public Health (http://www.ispch.cl)
Colombia: Ministry of Health (http://www.minsalud.gov.co)
Costa Rica: Ministry of Health (http://www.netsalud.sa.cr/cms)
Ecuador: Ministry of Public Health (http://www.msp.gov.ec)
Honduras: Ministry of Health (http://www.paho-who.hn/msa-lud)
Mexico: Ministry of Health (http://www.ssa.gob.mx)
Peru: Ministry of Health (http://www.digesa.sld.pe)

References