Status of Pneumococcal Pneumonia in a Public Hospital over a Period of 12 Years

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Abstract

Aim: To characterize some clinical features of children hospitalized with invasive pneumococcal pneumonia, and to determine the prevalent serotypes and antimicrobial susceptibility patterns of the clinical isolates.

Methods: Invasive pneumococcus strains were isolated from children admitted with pneumonia, and were characterized by serotype and antimicrobial susceptibility testing.

Results: A total of 101 pneumococcal isolates from children up to 13 years of age who were hospitalized with pneumonia from April 1999 to April 2010 were analyzed. The median age (18 months), and the median period of admission (11 days) were higher in patients with pleural effusion (21 months and 13 days), compared with uncomplicated cases (15 months and five days, respectively). Pleural effusion was detected in 76 cases (75.2%), most common among children older than two years (80.6%; 29/36 versus 72.3%; 47/65). The main source of isolates was pleural fluid (59.4%; 47/65). The predominant serotypes included 14, 1, 5, 19A, 6B, 9V, 3, 6A and 18C. Resistance to penicillin was detected in 3% of the isolates and 2% were resistant to ceftriaxone, both at an intermediate level.

Conclusions: The rate of resistance to penicillin (and to ceftriaxone) was low, thereby emphasizing its importance in treating non-meningeal invasive forms of the disease; the hypothetical coverage of the PCV10 and PCV13 vaccines was 80.1% and 95.6% in children up to two years old, respectively. Younger children were the most affected (median age of 18 months), and pleural effusion, which was present in 75.2% of cases, was most common in older children (median age of 21 months).

Keywords

Pneumonia; Pneumococcus; Children

Introduction

Pneumococcal invasive disease refers to infection of normally sterile sites with pneumococcus, including pneumonia, meningitis and bacteraemia, among others [1]. Pneumococcal pneumonia is one of the most common forms of pneumococcal disease, and is the result of bacterial infection facilitated by exposure to host and environmental risk factors [1,2]. This disease primarily affect children up to one year of age living in less developed and developing countries [1,3,4]. Parapneumonic effusion occurs in 0.6%-2% of children with pneumonia of bacterial etiology [3,5], and in up to 12% [6] to 50% [7] of children admitted to hospital with invasive pneumococcal pneumonia. Studies performed throughout the world identify pneumococcus as the most common bacterial agent causing pneumonia, responsible for 30% [2] to 85% [7] of cases. Different values are reported depending on the methodology and evaluation conditions, such as patients’ age, disease type and severity, hospitalization status, season of the year, concomitant outbreak caused by other pathogens (e.g., influenza), vaccine coverage in the population and the number and type of tests performed [7]. In cases of probable bacterial etiology, pneumococcus is detected through blood culture in approximately 4%-14% of adults and in 12%-16% of children, under the age of two [3].

Most children presenting with pneumonia do not need to be hospitalized; however, the most severe cases do require in-patient care [6,8]. Penicillin is the treatment of choice for several pneumococcal diseases; however, due to the increasing prevalence of penicillin-resistant strains beginning in the 1980s, alternative treatments have been suggested [9]. Given the good response to treatment with β-lactam drugs (penicillin or ampicillin) among patients with invasive pneumococcal disease (except meningitis), even when caused by strains exhibiting minimal inhibitory concentrations (MIC) up to 2.0 μg/mL, a new sensitivity classification scheme was adopted [9-11].

The prevention of pneumococcal invasive disease is mainly based on active immunization. Vaccines containing capsular polysaccharides of different serotypes conjugated to a protein carrier have been licensed since 2000: PCV7 containing antigens from serotypes 1, 4, 6B, 9V, 14, 18C, 19F and 23F; PCV10 containing extra antigens from serotypes 1, 5 and 7F; and PCV13, which includes the three additional serotypes 3, 6A and 19A [1,12]. The PCV10 vaccine licensed in June 2009 by the National Health Surveillance Agency (ANVISA), Brazil, was included in the schedule of the National Immunization Program (PNI) of the Ministry of Health for the universal vaccination of children up to two years of age, beginning in April 2010 (Official Gazette, Supplement of 08/22/2009). To evaluate the epidemiological impact of the vaccine in the Brazilian population, continuous laboratory surveillance studies and an expansion of clinical surveys are needed to provide scientific data for this new scenario.

The SIREVA (Sistema Regional de Vacunas) and SIREVA II project implemented by the PAHO (Pan American Health Organization) in 1993 with the participation of Brazil is a laboratory surveillance program, in which the serotype profiles and in vitro resistance patterns of invasive pneumococcal strains are analyzed among other characteristics [13]. Since April 1999, the General Hospital of the Federal University of Uberlândia (HC-UFU) has participated in the SIREVA II by sending pneumococcal strains isolated at the Clinical Analyses Laboratory to the Adolfo Lutz Institute (IAL) in São Paulo, SP, Brazil.

The aim of this work was to evaluate some clinical characteristics (age, gender, duration of admition and presence of effusion) of patients...
admitted to HC-UFU with invasive pneumococcal pneumonia, and to determine the prevalent serotypes and antimicrobial susceptibility patterns of the clinical pneumococcal isolates.

Case Series and Methods

A prospective laboratory surveillance study, in which laboratory data on serotype and the in vitro antimicrobial susceptibility of invasive pneumococci strains were obtained from patients admitted to HC-UFU is described here. The index (or primary) case was a *Streptococcus* strain isolated from clinical samples (e.g., blood and pleural fluid) at the Division of Bacteriology of the Clinical Analyses Laboratory of HC-UFU. The specimens were obtained aseptically and processed (isolated and identified), according to internationally accepted procedures [14]. Strains identified as *S. pneumoniae* were forwarded to IAL for species confirmation, serotyping and assessment of in vitro antimicrobial sensitivity, and then lyophilized in 20% nonfat milk and cataloged [14]. Serotyping was performed using the Neufeld Quellung reaction, according to a previously described protocol using polyclonal antibodies [14].

Antimicrobial susceptibility was evaluated at IAL by the standard technique [15-17]. Strains resistant to oxacillin (inhibition zone $\leq 19 \text{ mm}$) were assayed to determine the MIC for penicillin and ceftriaxone by the broth microdilution method, and were considered to be sensitive or resistant, according to the criteria of the Clinical and Laboratory Standards Institute (CLSI), 2010 [15,16]. Strains sensitive to oxacillin (inhibition zone $> 20 \text{ mm}$) were considered sensitive to penicillin, and were not assayed for MIC, according to the CLSI 2010 recommendation [16]. Cut-off values for penicillin and ceftriaxone [16] were applied for results (MIC) obtained throughout the study and maintained in the database.

Demographic and clinical data were obtained in real time after laboratory identification of a *Streptococcus* strain, and were included in a previously drafted individual record. Patients were monitored until hospital discharge. The diagnosis of pneumonia and pleural effusion, and the decision to hospitalize were determined by the medical staff according to well-established criteria [18]. Briefly, the clinical diagnosis of pneumonia depended on the presence of an acute manifestation of cough and fast breathing (age dependent); the association of chest in drawing and inability to drink, among other signs and symptoms, indicates severe illness and required immediate hospitalization [4,18,19]. The radiological diagnosis of pneumonia was based on the appearance of alveolar infiltration (dense fluffy consolidation) of a portion of a lobe or the entire lung, usually containing air bronchograms, and occasionally associated with pleural effusion [20-23]. Moderate pleural effusion ($\geq 1 \text{ cm rim}$ on lateral decubitus $\times > 5$ or PA $\times > 5$; or $\text{PA} = 5$; or $\text{PA} = 5$) associated with respiratory distress were submitted to pleural tap, and eventually drained; large effusions ($\geq 5$ or PA $\times > 5$; or $\text{PA} = 5$; or $\text{PA} = 5$) were drained [6,20].

HC-UFU is a public university hospital, and is part of the Unified Health System (SUS). This hospital’s capacity is approximately 520 active beds, and because it is a regional reference hospital, most of these beds are occupied by patients with the most severe illnesses.

Data were obtained from patients admitted from April 1999 to April 2010, and the results were subjected to descriptive statistical analysis. A single pneumococcus isolate per patient per hospital admission was considered.

The study was approved by the Research Ethics Committee (CEP/UFU) protocols 032/00 and 058/10.

Results

The study population consisted of children up to 13 years old admitted with a diagnosis of pneumonia caused by an invasive *S. pneumoniae* strain registered in the local SIREVA database. Because this is a laboratory surveillance study, the index case refers to the bacteria (*S. pneumoniae*) recovered in the laboratory, and thereafter, data from the patients’ individual records were obtained. The cases were admitted through the emergency department (ED), and all of them had clinical and radiological evaluation.

Of the 335 *S. pneumoniae* strains sent to IAL from 1999 to 2010, 196 (58.5%) were isolated from patients with pneumonia, of which 110 (32.8%) were obtained from children up to 13 years old. Of these 110 samples, 101 were analyzed, because in nine cases, the records were incomplete. The number of children admitted per year varied from four in 2008 and 2010 to 18 in 2000, with a mean of 9.6 children up to 13 years and 5.5 children up to two years old. Fifty-three patients (52.5%) were males. Ages ranged from one month to 151 months, with a mean of $28 \pm 28.3$ months and median of 18 months (P25=12 months and P75=34 months). The predominant age range was from 13 to 24 months (35 patients); 63 patients (64.4%) were up to two years old, and 93 patients (92.1%) were up to five years old. The median period of admission was 11 days, higher amongst children with pleural effusion (13 days), than amongst those without pleural effusion (five days).

Pneumonia was clinically diagnosed in 25 cases (24.8%; 25/101), and pneumonia with pleural effusion was diagnosed in 76 cases (75.2%; 76/101); of these, 47 (61.8%; 47/76) were up to two years old. Pleural effusion was most commonly detected in children older than two years (80.6%; 29/36), compared with younger children (72.3%; 47/65). The median age (18 months) was higher in children with pleural effusion (21 months), than in those with uncomplicated disease (15 months).

The source for *S. pneumoniae* recovery in culture was pleural fluid in 59.4% (60/101), and blood in 40.6% (41/101) of cases. In 21.8% (22/101) of cases, bacteria were recovered from both sources; however, only one sample per patient was sent to IAL for analysis.

The serotypes obtained are presented in descending order of frequency and age group in Table 1, and by nosology in Table 2. There was a trend for serotypes 1, 5, 19A, 6B, 9V, and 23F to predominate in children younger than two years (80.6%; 29/36), compared with younger children (72.3%; 47/65). The median age (18 months) was higher in children with pleural effusion (21 months), than in those with uncomplicated disease (15 months).

Intermediate resistance (IR) to penicillin (MIC $> 4 \mu g/mL$) was detected in three pneumococcus samples (3% rate; two isolates of serotype 14 and one of serotype 19A); two of these isolates had simultaneous IR (MIC=$2 \mu g/mL$) to ceftriaxone (2% rate; both of serotype 14). None of these strains was resistant to penicillin (MIC $\leq 8 \mu g/mL$) [11], or ceftriaxone (MIC $\geq 4 \mu g/mL$) [17]. Resistance rates to the other antimicrobials were 81.2% for co-trimoxazole, 17.8% for tetracycline, 11.9% for erythromycin and 11.9% for clindamycin. Resistance to levofloxacin, chloramphenicol, rifampicin or vancomycin was not detected for any pneumococcus strain.

Multiresistance, defined as simultaneous resistance to three or
Table 1: List of serotypes in decreasing order of frequency, distributed by age group, obtained from patients up to 13 years old presenting with pneumococcal pneumonia from 1999 to 2010. General Hospital of the Federal University of Uberlândia (Hospital de Clínicas da Universidade Federal de Uberlândia), Uberlândia, MG, Brazil.

<table>
<thead>
<tr>
<th>Age (months)</th>
<th>Serotype</th>
<th>≤ 24 m (%)</th>
<th>25-60 m (%)</th>
<th>61-156 m (%)</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>34 (52.3)</td>
<td>14 (51.6)</td>
<td>--</td>
<td>--</td>
<td>48 (47.5)</td>
</tr>
<tr>
<td>1</td>
<td>2 (3.1)</td>
<td>4 (6.5)</td>
<td>3 (8.9)</td>
<td>9 (8.9)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>5 (7.7)</td>
<td>2 (7.5)</td>
<td>1 (7.9)</td>
<td>8 (7.9)</td>
<td></td>
</tr>
<tr>
<td>19A</td>
<td>4 (6.2)</td>
<td>2 (6.5)</td>
<td>--</td>
<td>6 (5.9)</td>
<td></td>
</tr>
<tr>
<td>6B</td>
<td>4 (6.2)</td>
<td>1 (5.4)</td>
<td>--</td>
<td>5 (4.9)</td>
<td></td>
</tr>
<tr>
<td>9V</td>
<td>4 (6.2)</td>
<td>1 (5.4)</td>
<td>--</td>
<td>5 (4.9)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>4 (6.2)</td>
<td>-</td>
<td>-</td>
<td>4 (3.9)</td>
<td></td>
</tr>
<tr>
<td>6A</td>
<td>2 (3.1)</td>
<td>1 (3.2)</td>
<td>-</td>
<td>3 (2.9)</td>
<td></td>
</tr>
<tr>
<td>18C</td>
<td>-</td>
<td>2 (2.2)</td>
<td>1</td>
<td>3 (2.9)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1 (1.5)</td>
<td>-</td>
<td>1</td>
<td>2 (1.5)</td>
<td></td>
</tr>
<tr>
<td>10A</td>
<td>1 (1.5)</td>
<td>-</td>
<td>1</td>
<td>2 (1.5)</td>
<td></td>
</tr>
<tr>
<td>23F</td>
<td>2 (3.1)</td>
<td>-</td>
<td>-</td>
<td>2 (1.5)</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>-</td>
<td>-</td>
<td>1 (0.9)</td>
<td>1 (0.9)</td>
<td></td>
</tr>
<tr>
<td>9N</td>
<td>-</td>
<td>1 (1.1)</td>
<td>-</td>
<td>1 (0.9)</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>1 (1.5)</td>
<td>-</td>
<td>-</td>
<td>1 (0.9)</td>
<td></td>
</tr>
<tr>
<td>NT</td>
<td>1 (1.5)</td>
<td>-</td>
<td>-</td>
<td>1 (0.9)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>65 (100)</td>
<td>28 (100)</td>
<td>8 (100)</td>
<td>101 (100)</td>
<td></td>
</tr>
</tbody>
</table>

NT: Non Typeable

Table 2: List of pneumococcal serotypes in decreasing order of frequency, distributed by nosology, obtained from patients up to 13 years old presenting with pneumococcal pneumonia from 1999 to 2010. General Hospital of the Federal University of Uberlândia (Hospital de Clínicas da Universidade Federal de Uberlândia), Uberlândia, MG, Brazil.

<table>
<thead>
<tr>
<th>Nosology</th>
<th>Serotype</th>
<th>Pneumonia (%)</th>
<th>Pleural effusion (%)</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>13 (52)</td>
<td>35 (46.2)</td>
<td>48 (47.5)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1 (4)</td>
<td>8 (10.8)</td>
<td>9 (8.9)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>1 (4)</td>
<td>7 (9.2)</td>
<td>8 (7.9)</td>
<td></td>
</tr>
<tr>
<td>19A</td>
<td>-</td>
<td>6 (9.2)</td>
<td>6 (9.9)</td>
<td></td>
</tr>
<tr>
<td>6B</td>
<td>2 (8)</td>
<td>3 (4.6)</td>
<td>5 (4.9)</td>
<td></td>
</tr>
<tr>
<td>9V</td>
<td>4 (16)</td>
<td>1 (1.5)</td>
<td>5 (4.9)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>-</td>
<td>4 (6.2)</td>
<td>4 (3.9)</td>
<td></td>
</tr>
<tr>
<td>6A</td>
<td>1 (4)</td>
<td>2 (1.5)</td>
<td>3 (2.9)</td>
<td></td>
</tr>
<tr>
<td>18C</td>
<td>-</td>
<td>3 (3.1)</td>
<td>3 (2.9)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>-</td>
<td>2 (3.1)</td>
<td>2 (1.5)</td>
<td></td>
</tr>
<tr>
<td>10A</td>
<td>1 (4)</td>
<td>1</td>
<td>2 (1.5)</td>
<td></td>
</tr>
<tr>
<td>23F</td>
<td>2 (8)</td>
<td>-</td>
<td>2 (1.5)</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>-</td>
<td>1 (1.5)</td>
<td>1 (0.9)</td>
<td></td>
</tr>
<tr>
<td>9N</td>
<td>-</td>
<td>1 (1.5)</td>
<td>1 (0.9)</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>-</td>
<td>1</td>
<td>1 (0.9)</td>
<td></td>
</tr>
<tr>
<td>NT</td>
<td>-</td>
<td>1 (1.5)</td>
<td>1 (0.9)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>25 (100)</td>
<td>76 (100)</td>
<td>101 (100)</td>
<td></td>
</tr>
</tbody>
</table>

NT: Non Typeable

more different classes of antimicrobials, was detected in 11 strains, all with the same pattern: simultaneous resistance to erythromycin, tetracycline and co-trimoxazole (serotype 14 in nine of the isolates and 19A in the other two); IR to penicillin was detected in only one of the isolates (serotype 19A).

According to standard recommendations [3,9,21], the drugs most commonly used were crystalline penicillin or ampicillin (70 occasions, associated with oxacillin twice) and ceftriaxone (25 occasions, associated with vancomycin thrice). In 13 occasions, the empirical drug was changed; in ten of them, the crystalline penicillin or ampicillin was changed by ceftriaxone; none according to cultures.

No patients have received the PCV vaccine.

Discussion

The ages of patients were generally similar to those reported in other studies. The predominant age range was from 13 to 24 months, and the percentage of cases in children under the age of five was consistent with recent studies of children admitted with community-acquired pneumonia (69% to 82.5%) [7,22-24]; however, the median age of 18 months was lower than the previously reported median ages of 23 months to 33 months [7,22,24]. The lower age of children admitted with invasive pneumococcal pneumonia (median age of 15 months in uncomplicated forms) reinforces the importance of using effective vaccines beginning in the first year of life.

The number of pleural effusion cases was high (75.2%; 76/101), when compared with other studies (9% to 27%) [22,23]; as well was the percentage of pneumococcus recovery from pleural fluid (59.4%; 60/101), compared with other studies conducted in Brazil and other countries with positive blood culture in 4% and 7% [22,23] to 60% and 70% [12,24]. Such diverse values are most likely due to different methodologies and evaluation conditions, such as patient age, disease type and severity, hospitalization status, season of the year, broad vaccine coverage of the population and the number and type of tests performed [7].

Parapneumonic effusion has been reported in 0.6%-2% of children with pneumonia caused by bacterial infection [3,5], and in 12% to 50% of children admitted with invasive pneumococcal pneumonia [6,7]. These values are lower than the 75.2% found in the present study. The prevalence of pleural effusion in older children compared with uncomplicated cases has been previously reported by Grijalva et al. [25], who evaluated the incidence of pneumonia associated with empyema in an ecological study conducted in the USA from 1996 to 2007. The authors reported rates of 7.9% in children under two years, and 16.8% in children from two to four of age, among cases caused by pneumococcus [25]. Recovery of bacteria from cultures of pleural fluid has been described at rates of 20% to 80% [7,26], which is a range that includes the value of 59.4% obtained in the present study. The median duration of admission (11 days) was higher than other reports (three days [23], and five days [7,22]).

The prevalence of pleural effusion, the recovery of bacteria from cultures of pleural fluid, and the median duration of admission were high in this study because the hospital serves as a regional reference center and admits the most severe cases, and probably because of a selection of patients with pleural effusion. The methodology adopted in this study (laboratory surveillance instead of clinical surveillance) tends to exclude patients with pneumonia and negative culture, and select patients with effusion and positive culture (the index case is the pneumococcus recovered in culture).
Serotype 14 is the most commonly isolated serotype in children presenting with invasive pneumococcal disease, and in the present study, this serotype was recovered from approximately half of the patients under the age of five. Serotypes 1 and 5, which are notoriously virulent, were most commonly recovered in patients with pleural effusion (approximately 10% versus 4%). Serotype 3, detected in the present study only in patients presenting with pleural effusion, and has been associated with complicated forms of pneumonia [27]. Among the pneumococcus serotypes that most commonly cause pneumonia, serotypes 1 and 3 have been associated with complicated forms of the disease in children [28]. In several communities and countries that have universal vaccination programs using the conjugated 7-valent vaccine, serotypes 1, 3, and 19A (which are not part of the vaccine) have been increasingly implicated in invasive forms of pneumonia associated with empyema in both children and adults [25,28,29]. There are three possibilities to explain this increase of the serotype 19A [30,31]: the expansion of a clone that existed before the introduction of the vaccine (ex: ST199, ST63), the introduction of a new clone (ex: ST230, ST695) and the capsular switching.

An association between serotypes 14, 1, 19A and 3 and pneumonia was observed in this (66.2% of the isolates; Table 2), and in a previous study (63.5%) [32]. Similar to the data presented here, another study reported a higher prevalence of serotypes 14, 3 and 6B in those under the age of two, and of serotypes 1 and 5 in older patients [24]. However, in the present study, serotype 5 predominated in children under the age of two, and interestingly, this serotype was last detected in 2003 in a patient 6.6 years of age presenting with pneumonia and pleural effusion. In fact, a decreasing trend in the frequency of serotype 5 over time has been confirmed by national surveys: from 13% in 2000 to 2010 [13], the frequency of the 13 most commonly isolated serotypes reflects, with slight differences, the profile of serotypes obtained in the Uberlândia study: 14>1>6B>3>5>6A/C=9V=19A=23F>19F>18C=7F>4.

In the present study, the resistance rates for co-trimoxazole, erythromycin and clindamycin were 81.2%, 11.9% and 11.9%, respectively. These values are higher than the previously reported rates of 69.7% [13] and 71.4% [24], for co-trimoxazole and 7.2% [13] for erythromycin, and well above the rate of 2.8% found for erythromycin and clindamycin in national surveys [24]. The multiresistance rate of 10.9% observed in the present study is similar to the 9.5% rate detected in a survey of 8993 strains collected in ten Latin American countries from 2000 to 2005 [34], and higher than the 4.7% rate among the 107 cases evaluated by Yoshioka et al. [24].

The results obtained in the present study agree with the current recommendation of using crystalline penicillin for treating invasive pneumococcal pneumonia. In fact, there are reports on the success of crystalline penicillin (200,000 U/kg/day) [10,35], and ampicillin (100 mg/kg/day [36] to 150 mg/kg/day [10,35]), for treating children hospitalized with pneumonia caused by strains with MICs to penicillin up to 4 μg/mL. It is important to notice that in none of the ten occasions in which the initial empiric antibiotic (penicillin or ampicillin) was changed toceftriaxone, it was according to the result of culture and susceptibility test.

Therefore, it is reasonable to conclude that the rate of resistance to penicillin is low, supporting its use in treating invasive non-meningeal forms of the disease. The rate of resistance to co-trimoxazole is high, calling into question the use of this drug in treatment of severe forms of hospitalized pneumococcal disease. The hypothetical coverage of PCV10 and PCV13 in children under the age of two is 80.1% and 95.6%, and in children younger than five is 81.9% and 95.9%, respectively. We also observed that in this study population, the frequency of pleural effusion was high, with a higher prevalence being observed in older children (median of 21 months).

Nevertheless, the present study has several limitations, given that it was based on laboratory surveillance combined with epidemiological and clinical data. First, care should be taken when extrapolating these results to the non-hospitalized population, where uncomplicated mild and moderate pneumonia predominates; moreover, HC-UFU admits the most severe cases of the disease, because it is a regional reference center. This fact is reflected in the percentage of children admitted with pleural effusion (75.2% of the cases), similar to other studies reporting severe cases [23,24]. Finally, the study’s sample size was relatively small.

Although the sample size was small, it consisted of a 12-year historical series. The benefits of the study are broad and indirect because it characterizes the children admitted with moderate or severe pneumococcal pneumonia, confirms the elevated sensitivity of pneumococcus to β-lactam drugs, and allows the calculation of coverage rates for vaccines that include pneumococcus serotypes causing pneumonia in the studied population. The latter benefit is particularly promising, given that the study is based on a historical series representative of the pre-vaccine period, thereby allowing comparison with periods after implementation of the PCV10 vaccination in the PNI schedule by April 2010.

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