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# A population-based assessment of the disease burden of consolidated pneumonia in hospitalized children under five years of age

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**KEYWORDS**
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**Summary**
*Background:* Population-based studies on childhood community-acquired pneumonia are scarce in Latin America. Pneumococcal epidemiology is poorly defined, hence the World Health Organization recommended standardized chest radiograph interpretation to improve the approach to bacterial pneumonia. Therefore, our study aimed to estimate the burden of pneumonia in hospitalized children.
*Methods:* A three-year surveillance study was carried out in four hospitals covering a population of 229 128 inhabitants of whom 10.2% were under five years of age. Clinical records and digitization of their chest radiographs were obtained. A pediatrician and a pediatric radiologist blinded to the clinical diagnosis interpreted the digital images.
*Results:* Of 2034 patients, 826 (40.6%) had consolidated pneumonia, 941 (46.3%) had non-consolidated pneumonia, and 267 (13.1%) had no pneumonia. Children under two years of age predominated (66.9%). The average annual incidence rate for consolidated pneumonia over the three-year study period was $1175/10^5$. Eighteen invasive *Streptococcus pneumoniae* were isolated from patients with consolidated pneumonia and two from those with non-consolidated pneumonia. Respiratory syncytial virus was evenly distributed between both X-ray groups.
*Conclusions:* Patients younger than two years of age predominated, being the main targets for anti-pneumococcal conjugated vaccines. Incidence rates provided evidence of the burden of consolidated pneumonia for childhood, estimating the potential benefits of vaccination.


## Introduction

Pneumonia is the major cause of morbidity and mortality from pneumococcal infection, especially in developing countries.[1] Population-based studies on community-acquired pneumonia

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in childhood are scarce in Latin America and *Streptococcus pneumoniae* epidemiology is poorly defined due to the low sensitivity of bacteriologic diagnostic methods. To overcome this problem the World Health Organization (WHO) recommended standardized chest radiograph interpretation as an epidemiological tool to provide a reasonable approach to bacterial pneumonia.[2] In addition, to assure comparability of data among population-based studies on pneumonia burden and results from vaccine field trials performed in different countries, a generic protocol was proposed by the WHO in collaboration with the Communicable Disease Center (CDC). This protocol was adopted in several Latin American countries, including Uruguay, in order to assess the burden of consolidated pneumonia in hospitalized children under five years of age, and the proportion preventable by vaccination with a *S. pneumoniae* conjugated vaccine.[3] In Uruguay, this estimation was facilitated because ten years of anti-*Haemophilus influenzae* type b (Hib) vaccination had dramatically controlled Hib pneumonia, and consequently it was possible to assume that most of the remaining bacterial pneumonia cases were due to *S. pneumoniae*.[4,5] Also, bacteremic pneumonia has been monitored since 1994, providing data on serotype frequency and antibiotic susceptibility of invasive isolates.[6,7]

## Methods

A three-year population-based prospective study (June 2001—May 2004) was carried out in the municipalities of Paysandú and Salto in Uruguay, covering a population of 229 128 inhabitants of whom 23 445 (10.2%) were under five years of age. These populations represent 7.1% and 8.3% of the total national population, respectively.

Patients were enrolled in four hospitals (two public and two private). Those eligible for enrollment were patients with acute lower respiratory tract infections for whom a chest X-ray was performed on admission to confirm a clinically suspected case of pneumonia. Excluded from the study were bronchiolitis and asthma/bronchial hypersensitivity cases for whom no X-ray was ordered.

A research nurse checked the pediatric ward admission book daily looking for children under five years of age. The medical charts of the patients were reviewed and relevant data were abstracted onto a standardized form including age, sex, previous hospitalizations, recent antibiotic-treated episodes, underlying conditions, selected respiratory signs and symptoms, antibiotherapy, duration of hospitalization, and outcome.

Digitization of the analog chest X-rays was also performed. A pediatrician and a pediatric radiologist, blinded to the patients' clinical diagnoses, interpreted the digital images according to the WHO criteria: alveolar consolidation or pleural effusion, non-consolidated pneumonia with mild interstitial/perihilar changes, and no pneumonia. By a table of random numbers, 10% of the digitized chest X-rays were identified and referred to an international panel of experts for quality evaluation.

Selected variables from the standardized form were compared between children with consolidated and non-consolidated pneumonia.

Bacterial and viral etiologies were routinely investigated during three winter months, three days per week. During the three study years, blood or pleural fluid specimens were cultured by standard methods for isolation of invasive pneumococci. At the National Reference Laboratory, identification of *S. pneumoniae* isolates was confirmed, serotypes determined by 'quelling' reaction, and susceptibility to antibiotics (penicillin, third generation cephalosporins, trimethoprim—sulfamethoxazole, vancomycin) assessed according to the National Committee for Clinical Laboratory Standards. Viral antigens for five respiratory viruses (respiratory syncytial virus (RSV), influenza A and B, parainfluenza 3, and adenovirus) were investigated by direct immunofluorescence (Light Diagnostics, Respiratory Panel, CA, USA) in cells of nasopharyngeal aspirates during the last two study years.

Data were entered into Epi Info 6.4, which was also employed for statistical analysis.

To calculate the annual incidence rate of chest X-ray documented consolidated pneumonia cases, the number of cases enrolled in one year (numerator), was divided by the number of population at risk in the area (denominator), and the result multiplied by 100 000. Non-parametric variables were evaluated by Chi-square test and results were considered significant when $p < 0.05$. The kappa coefficient was used to measure the degree of agreement between the interpretation of the local readers and the reference panel of experts. This project was approved by the Pediatric Committee of Ethics from the Pediatric Institut Prof L.A. Morquio.

## Results

Between June 2001 and May 2004, 2034 children were eligible for enrollment: 668, 662, and 704 patients per year. The majority of the inpatients were cared for at public hospitals, while a minority were admitted to private services, 97.1% and 2.9%, respectively. Most of the families lived in urban areas (82.2%), but their homes were located in areas where dwelling conditions and poverty predisposed the children to illness. Only 363 patients lived in rural areas (17.8%).

Table 1 shows the age distribution of all the enrolled patients. Of these 54.5% were male. Their median age was one year (range 0—4) with predominately children younger than 24 months (66.9%), of whom 38.3% were aged less than 12 months.

The standardized radiograph interpretation of 2034 patients indicated that 826 (40.6%) had consolidated pneumonia, 941 (46.3%) had non-consolidated pneumonia, and 267 (13.1%) had no pneumonia. Agreement between the interpretation of the local readers and those of the panel of experts showed a kappa coefficient of 0.58, which validated the study results.

**Table 1** Age distribution of children aged less than five years hospitalized with community-acquired pneumonia

| Age (in months) | Cases (*n*) | % | Accum. % |
|---|---|---|---|
| 0—5 | 381 | 18.7 | 18.7 |
| 6—11 | 399 | 19.6 | 38.3 |
| 12—23 | 581 | 28.6 | 66.9 |
| 24—35 | 312 | 15.3 | 82.2 |
| 36—59 | 361 | 17.8 | 100.0 |
| Total | 2034 | 100.0 | |

**Table 2** Total enrolled cases, consolidated pneumonia, and non-consolidated pneumonia by age of the patients

| Age (months) | Cases (*n*) | CP (*n*) | % | Empyema (*n*) | Non-CP (*n*) | % | No P (*n*) | % |
|---|---|---|---|---|---|---|---|---|
| 0—5 | 381 | 110 | 28.9 | 4 | 185 | 48.6 | 86 | 22.5 |
| 6—11 | 399 | 143 | 35.8 | 7 | 203 | 50.9 | 53 | 13.3 |
| 12—23 | 581 | 266 | 45.8 | 15 | 273 | 47.0 | 42 | 7.2 |
| 24—35 | 312 | 140 | 44.9 | 16 | 132 | 42.3 | 40 | 12.8 |
| 35—59 | 361 | 167 | 46.3 | 12 | 148 | 40.9 | 46 | 12.8 |
| Total | 2034 | 826 | 40.6 | 54 | 941 | 46.3 | 267 | 13.1 |

CP, consolidated pneumonia; non-CP, non-consolidated pneumonia; no P, no pneumonia.

Table 2 presents the age distribution of consolidated and non-consolidated pneumonia cases: the number of consolidated pneumonia cases increased with age, as did complications (54 cases with empyema; 6.5%), while non-consolidated pneumonia predominated in patients aged 0—11 months.

Although incidence rates of consolidated pneumonia varied annually, its variation was not statistically significant. As shown in Table 3, incidence rates changed according to age group. In every surveillance year, the highest incidence rates were recorded among patients aged less than 24 months, predominately in the 12—23 months age group.

Of 462 blood or pleural effusion cultures, 20 *S. pneumoniae* isolates (one per patient) were identified (4.3%). Eighteen of the isolates corresponded to patients with consolidated pneumonia, and two to non-consolidated pneumonia patients. Eleven isolates were available for typing and for antibiotic susceptibility testing. Nine were serotype 14 with reduced susceptibility to penicillin ($\geq$1.0 μg/mL) and to trimethoprim—sulfamethoxazole; one was serotype 5 and one was 18C, both susceptible to penicillin.

Viral antigens were recognized in 81 out of 228 nasopharyngeal aspirates (35.5%). The percentages of viral detection were similar in both radiographic groups: 38 RSV, three influenza A and one influenza B in consolidated pneumonia cases (18.4%) and 36 RSV, two parainfluenza 3, and one influenza B in non-consolidated pneumonia cases (17.1%).

**Table 3** Incidence rates of consolidated pneumonia in children by age group and study years

| Age (months) | Population at risk[a] | Period | | | | | |
|---|---|---|---|---|---|---|---|
| | | Jun 01—May 02 | | Jun 02—May 03 | | Jun 03—May 04 | |
| | | Freq. CP | Rate/$10^5$ | Freq. CP | Rate/$10^5$ | Freq. CP | Rate/$10^5$ |
| 0—11[b] | 4786 | 81 | 1692 | 84 | 1755 | 88 | 1839 |
| 12—23 | 4610 | 81 | 1757 | 93 | 2017 | 92 | 1996 |
| 24—35 | 4825 | 48 | 995 | 51 | 1057 | 41 | 850 |
| 36—59 | 9224 | 50 | 542 | 68 | 737 | 49 | 531 |
| Total | 23 445 | 260 | 1109 | 296 | 1263 | 270 | 1152 |

CP, consolidated pneumonia.
[a] National Statistic Institute (INE), 1996 Census.
[b] INE do not provide separate data for 0—5 and 6—11 months.

**Table 4** Severity-associated variables in consolidated pneumonia and in non-consolidated pneumonia

| Variables | Consolidated pneumonia | | Non-consolidated pneumonia | | *p* Value |
|---|---|---|---|---|---|
| | *n* | % | *n* | % | |
| Fatalities | 5/826 | 0.6 | 1/941 | 0.11 | NS |
| 2nd line antibiotic[a] | 60/826 | 7.3 | 16/941 | 1.7 | <0.001 |
| White blood cell count[b] | 346/826 | 41.9 | 209/941 | 22.2 | <0.001 |
| Hospitalization duration[c] | 317/826 | 38.4 | 291/941 | 30.9 | NS |
| Days in intensive care[d] | 17/826 | 2.1 | 10/941 | 1.1 | NS |
| Bacteremic pneumonia[e] | 18/273 | 6.6 | 2/189 | 1.1 | 0.004 |

[a] Third generation cephalosporins or/and vancomycin.
[b] WBC count >15 × $10^9$ cells/L.
[c] Hospitalization duration >5 days.
[d] Intensive care >6 days.
[e] *Streptococcus pneumoniae* isolated from blood or pleural effusion (one per patient).

Co-morbidity was present in 771 patients (38.0%), of which malnutrition and anemia was the most prevalent (409; 53.0%), followed by asthma/bronchial hypersensitivity (164; 21.3%) and neurologic disabilities (94; 12.2%).

Severity of the cases was evaluated comparing six variables as recorded among patients with consolidated and non-consolidated pneumonia (Table 4). Second line antibiotic therapy, white blood cell count above $15 \times 10^9$/L, and invasive *S. pneumoniae* isolation predominated among patients with consolidated pneumonia ($p < 0.05$).

Six children died: five were aged under 12 months and one belonged to the 2—4 year-old age group. Co-morbidity was present in four of the fatalities (one asthma and three cerebral palsy) and five of the patients had consolidated pneumonia.

## Discussion

Awareness of the health impact of pneumonia in childhood is of paramount importance in the decision-making for its prevention. This disease is rarely mentioned by national sanitary authorities as a health problem, although a recent publication confirmed that 19% of deaths in children under five years of age are due to pneumonia.[8] Consequently, the problem became a priority for the Division of Vaccines and Immunization of the Pan American Health Organization (PAHO), in order to prepare for the introduction of an appropriate conjugate vaccine to reduce pneumococcal mortality and severe morbidity in children younger than five years of age. Efforts were addressed to collect population-based data on the burden of pneumonia in children from the region. Research was based on the WHO generic protocol, and supported by PAHO in Argentina, Brazil, and Uruguay, and sponsored by the industry in Argentina (Córdoba) and in Chile (Santiago). A radiographic marker suggestive of bacterial pneumonia was advocated, similar to the one used in conjugated vaccine trials for evaluating the efficacy of anti-*S. pneumoniae* conjugate vaccines.[9,10]

Uruguay has also contributed, building a three-year evidence base on the burden of consolidated pneumonia in Paysandú and Salto. Patients under two years of age predominated (66.9%), pointing to the urgent need for a nine-valent conjugate vaccine that would provide a coverage of 78% for pneumonia in these children. This coverage would increase by 10% if serologic cross-reactivity with serotypes included in the vaccine were taken into account.[11,12]

This study enabled us to estimate annual incidence rates for different age groups that represented 8.3% of the national population aged 0—59 months. The highest annual incidence rates of consolidated pneumonia ranged from $1757/10^5$/year to $2017/10^5$/year among patients aged 12—23 months, confirming the need to protect them. The PAHO-supported study recorded similar incidence rates in Argentina (Pilar, Buenos Aires, and Concordia, Entre Ríos).[13] Also based on the WHO generic protocol, studies from Chile and Brazil showed lower incidence rates. In Santiago the rate was $928/10^5$/year and in Goiania patients aged 0—23 months the incidence rate was $758/10^5$/year.[14]

As patients with consolidated pneumonia, and those cases complicated with empyema increased with age, potential limitations to the vaccine effectiveness could occur as optimal results were obtained for children under 24 months of age.[15] Therefore, children with risk factors, aged 2—14 years, could benefit from the 23-valent *S. pneumoniae* polysaccharide vaccine.[16,17]

Etiological information on pneumonia cases has provided some valuable insights. Invasive *S. pneumoniae* isolation has mainly been achieved in patients with presumed bacterial pneumonia.[18] The almost even distribution of the viral etiologies among patients with consolidated and non-consolidated pneumonia could be explained by the increasing recognition of mixed infections, due to co-circulation of respiratory viruses and *S. pneumoniae* as well as other non-investigated bacterial pathogens.[19—22]

This study aimed to establish the local burden of pneumococcal disease and to assess the potential vaccine impact to justify its introduction in Uruguay. Nevertheless the results shown only include hospitalized cases. Meningitis and other invasive pneumococcal diseases should also be considered; even if they are quantitatively less relevant they involve high mortality and sequelae.[23] Ambulatory treated pneumococcal cases as well as pneumococcal diseases in school-aged children cannot be ignored when predicting the effectiveness of a vaccine.[24] As 46.6% of the enrolled patients belonged to families in poverty, and socioeconomic improvements are difficult to achieve in a short period of time, vaccination appears to be the best measure for health equity.[25,26] Thus high priority should be given to the development of an affordable pneumococcal conjugate vaccine suitable for the protection of Latin American children.

In spite of the limitations of this study, the information obtained is valuable because it provides much-needed population-based data for Uruguay. Besides enhancing the efforts of multidisciplinary groups, a surveillance network has been developed that is able to generate scientific evidence to support decisions concerning the use of vaccines to control pneumonia and other invasive diseases, and to evaluate the impact of vaccination programs.

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*Conflict of interest:* No conflict of interest to declare.

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