Prospective epidemiologic surveillance of invasive pneumococcal disease and pneumonia in children in San José, Costa Rica

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A B S T R A C T

Background: Streptococcus pneumoniae (SP) is the leading cause of vaccine-preventable death in children <5 years of age, globally. This surveillance determined incidence rates of invasive pneumococcal disease (IPD), clinical and chest radiograph-confirmed pneumonia (CXR + Pn); and SP serotype distribution and antimicrobial susceptibility in children in San José, Costa Rica.

Methods: This was a 2-year prospective, population-based surveillance conducted in 2007–2009 in children aged 28 days to 36 months presenting to participating healthcare centers. Eligibility criteria for study inclusion were as follows: temperature > 38.0°C within 24 h and/or clinical suspicion of IPD or pneumonia.

Results: 8801 subjects were enrolled. Median age: 14.5 months. A total of 25 children had invasive pneumococcal disease with S. pneumoniae isolated from nonduplicate cultures (22) or detected solely by PCR and a clinical picture consistent with IPD (3). Sources of positive cultures (some children had >1 positive culture) were: blood (20), pleural fluid (4), and cerebrospinal fluid (3). Of the 3 cases detected solely by PCR, 2 were from cerebrospinal fluid and 1 from pleural fluid. The overall IPD incidence rates for culture-positive only cases for children aged 28 days to <3 years was 33.7/100,000 per year for years 1 and 2 combined. Age stratification of culture-positive only subjects showed a peak during year 1 (106.8/100,000) in children 28 days to <6 months of age group, and in year 2 (45.5/100,000) in children 12 months to <24 months of age group. Most common serotypes were 14 (28.6%), followed by 3, 4, 6A, 19A, and 22F (9.5% each). Of 22 nonduplicate IPD isolates, 42.9% were penicillin- and trimethoprim/sulfamethoxazole nonsusceptible isolates. Consideration of PCR-positive cases increases the incidence of IPD for children aged 28 days to <3 years to 46.0/100,000. Overall incidence of clinical pneumonia and CXR + Pn was 1968/100,000 and 551/100,000, respectively.

Conclusions: There is a considerable burden of IPD and pneumonia in children in San José. These epidemiologic data serve as a baseline to evaluate the effectiveness of the incorporation of new conjugate pneumococcal vaccines into the National Immunization Program in Costa Rican children.

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1. Introduction

Streptococcus pneumoniae (SP) is a major cause of serious disease, and is the leading cause of vaccine-preventable deaths in children <5 years of age, globally [1]. Knowledge of the epidemiology of pneumococcal disease and its serotype distribution is essential to assess the potential impact of implementing a vaccination program with pneumococcal conjugate vaccine (PCV) in children. Surveillance data from countries that have incorporated the heptavalent pneumococcal conjugate vaccine (PCV7) into their routine pediatric immunization schedules have shown a significant decline in the incidence of invasive pneumococcal disease (IPD) and mucosal diseases such as nonbacterial pneumonia and otitis media [2,3]. In addition, an important contribution has been the decrease in disease observed in the unvaccinated population (indirect or herd effect) by reduced transmission of vaccine serotypes...
from vaccinated children to the unvaccinated population [4,5]. Data collected before the introduction of PCVs into a country’s universal immunization program are critical for comparison of baseline information with post-implementation data. Such comparisons allow an objective assessment of the vaccine’s impact, on both vaccine and non-vaccine serotypes.

Data from prospective surveillance studies are essential to assess the incidence of IPD in children, and more accurately reflect the true burden of disease than information from passive studies, particularly in countries where blood cultures and chest radiographs are not routinely performed. Prospective data on incidence of IPD [6,8] and pneumonia in Latin America are limited [6–9]; this is the first of such studies from Central America.

The Latin American Epidemiologic Assessment of Pneumococci (LEAP) was a population-based study of IPD and pneumonia in children aged 28 days to 36 months conducted in three countries – Brazil, Colombia, and Costa Rica. The objectives of this study were to determine the incidence of IPD and pneumonia (clinical and chest X-ray-confirmed [CXR + Pn]); to describe the serotype distribution of S. pneumoniae isolates causing IPD; and to determine the antimicrobial susceptibility of invasive S. pneumoniae strains isolated.

Here, we report results from a population of infants and young children in San José, Costa Rica, before the introduction of PCV7 into the National Immunization Program (NIP). Our study data may serve as the baseline for assessing the impact of PCV7 introduction into this NIP on the burden of IPD caused by S. pneumoniae, and for monitoring the dynamics of serotypes. As there are now 2 more pneumococcal conjugate vaccines available in Latin America (PCV10 and PCV13), and the World Health Organization (WHO) has recommended pneumococcal vaccination as a priority for all countries, future surveillance will be critical to evaluate optimal vaccination strategies for regions and countries.

2. Materials and methods

This was a prospective, population-based surveillance study conducted by the Instituto de Atención Pediátrica (IAP) and the Caja Costarricense de Seguro Social in San José, Costa Rica from 20 April 2007 through 19 April 2009. IPD and pneumonia are not routinely under surveillance in San José, and blood culture is not routinely collected for cases with suspicion of IPD or pneumonia. Therefore, an extensive effort was made to build a comprehensive surveillance network to actively capture all outpatients and inpatients with clinical suspicion of IPD and/or pneumonia in both public and private health sectors.

The surveillance area comprised 5 of the counties within the province of San José (Central San José, Desamparados, Aserría, Alajuelita and Escazú). Seven districts adjacent to Central San José (Merced, Hospital, La Uruca, Mata Redonda, Pavas, Hatillo, and San Sebastián) were selected because of their geographical proximity, annual birth rates and conformity between the clinics and hospitals where the children are required by the Social Security System to go for treatment.

The study design and informed consent were approved by the Ethics Committee of the Universidad de Ciencias Médicas, Caja Costarricense de Seguro Social, and Hospital Cima San José. Informed consent was obtained from the parents or legal guardians of all participants.

Children residing in the surveillance areas aged 28 days to 36 months who presented (or were referred to a participating health-care center) with temperature ≥ 39.0 °C and/or clinical suspicion of an invasive S. pneumoniae infection or clinical signs and symptoms of pneumonia as determined by the treating physician were eligible. Children were evaluated by their treating physicians and, if enrolled, assigned a study-specific physician, available 24 h a day throughout the study, who was summoned via a telephone call center specific to this study. The study physician’s role was to obtain blood for culture prior to initiation of antibiotic therapy, whenever possible, but all treatment decisions and treatments remained the responsibility of the treating physicians.

During enrolment, data collected from all enrolled children included: demographic information; baseline diagnosis; history of receipt of a conjugate (PCV) or polysaccharide (PPS) pneumococcal vaccine; and absence/presence of factors known to be associated with IPD. Upon enrolment, a blood sample for culture was collected. Specimens from other sterile sites (pleural, joint, and cerebrospinal fluids [CSF], among others) were collected as per routine medical practice. All samples were cultured for bacteria at the Laboratorio de Investigaciones Clínicas in San José or a local hospital laboratory. Identification of bacterial pathogens, together with antimicrobial susceptibility testing using the E-test technique according to standard methodology, and interpreted in accord with Clinical and Laboratory Standards Institute (CLSI) 2007, was performed at Laboratorio de Investigaciones Clínicas in San José. If S. pneumoniae was detected in a participant, a subculture of the isolate was always transferred to the Laboratorio de Investigaciones Clínicas in San José for confirmation and antimicrobial susceptibility testing. A central laboratory (Soroka University Medical Center, Beer-Sheva, Israel) confirmed the identification of all S. pneumoniae isolates and performed serotyping (using type-specific sera by the Quellung reaction). In addition, PCR testing was performed on non-blood sterile fluids at the study sponsor’s laboratory (Vaccine Research East and Early Development, Pearl River, NY).

A chest radiograph was performed in children with suspected pneumonia, preferably at the time of presentation, but accepted within 72 h of study enrolment. All radiographs were examined by a single pediatric radiologist. The presence of lobar consolidation and/or pleural effusion, or other findings suggestive of an infection, was documented as abnormal. Radiographs were interpreted according to WHO guidelines [10].

Diagnostic and outcomes information (recovery or death, and for patients diagnosed with meningitis, neurologic outcome) was collected for all subjects whose culture(s) yielded S. pneumoniae, subjects who were hospitalized and/or whose inclusion criteria included clinical suspicion of meningitis. Standardized definitions were used for the diagnoses. IPD was defined as the isolation of S. pneumoniae from a sterile body site. Pneumococcal meningitis was defined as CSF whose culture was positive for S. pneumoniae or, upon examination of the Gram stain had Gram-positive cocci in pairs, and/or yielded a positive latex-agglutination test and/or a positive PCR test for S. pneumoniae in subjects with CSF compatible with meningitis. Clinical pneumonia (Clin Pn) was defined as children who received a diagnosis by the treating physician based on clinical signs/symptoms consistent with pneumonia. Chest radiograph-confirmed pneumonia (CXR + Pn) was defined according to WHO guidelines.

2.1. Epidemiologic measurements

Primary epidemiologic endpoints included the yearly incidence rate of IPD and serotype distribution of invasive S. pneumoniae isolates. IPD incidence was calculated as the number of non-duplicate culture-positive samples divided by the number of children between the ages of 28 days and 36 months residing in the study surveillance area. Calculation of nonduplicate culture-positive and PCR-positive samples was also calculated as above.

Secondary epidemiologic endpoints included incidence rates of Clin Pn and CXR + Pn, antimicrobial resistance of pneumococcal isolates, serotype distribution of resistant isolates, assessment of neurologic sequelae in subjects with pneumococcal meningitis.
Calculation of pneumonia incidence rates used the same methodology described below for IPD. In addition, identification of pathogens other than S. pneumoniae in sterile site cultures was a secondary outcome that has been presented separately and will not be presented here.

The percent coverage of S. pneumoniae serotypes included in currently licensed 7-valent, 10-valent, and 13-valent PCVs was evaluated. Cross-protection for other serotypes within a specific serogroup (i.e., protection against serotype 6A due to inclusion of serotype 6B, or protection against serotype 6C due to inclusion of serotype 6A in PCV13) was not assumed.

2.2. Statistical analysis

All analyses were conducted separately for each study year (year 1 and year 2) and for both study years combined. The 2-year combined incidence rate represented an annualized rate. IPD, clinical pneumonia, and CXR + Pn cumulative incidence rates were stratified by age group (i.e., 28 days to <6 months; 6 months to <12 months; 12 months to <24 months; 24 months to <36 months), and by gender.

IPD incidence rates were computed per year, per 100,000 children in the at-risk population, with 95% confidence intervals (CI) based on the Poisson distribution [11]. The frequency distribution of IPD cases per serotype is summarized and breakdowns of the serotype distribution by age, gender, and final diagnosis are provided. The serotype frequency distribution is described for all serotypes identified and is analyzed by serotypes included in PCV7, PCV10, and PCV13.

In this study, the numerator (cases) for study calculations was the number of cases in the population at risk (children aged 28 days to less than 36 months residing in the surveillance area during the study years). The denominator came from census estimates of population of children in this age group living in the San José study surveillance area during the study years.

Individuals could be enrolled in the study more than once provided that the presenting illnesses reflected independent episodes and that informed consent was obtained for each event. Each enrollment was considered a separate subject/episode and analyzed accordingly. Unless otherwise noted, the child/episode was the unit of analysis.

3. Results

3.1. Baseline characteristics and disposition of study subjects

A total of 8801 children from the target population (children 28 days to 36 months of age living in the study surveillance area) of 65,285, were included in this study over the 2-year period. Demographic characteristics included: median age, 13.0 months; 54.7% of children were male; birth weight (mean ± SD, 3146 ± 555 g). The age distribution of enrolled subjects was: 20.7% (28 days to <6 months); 27.2% (6 months to <12 months); 33.1% (12 months to <24 months); 18.9% (24 months to <36 months). Among patient characteristics known to be risk factors for IPD, the most common were urban area residence (99.7%); smokers in the household (37%); antibiotic use in the past 7 days (13%); premature birth classified as <37 weeks (8%); daycare attendance (6%); and history of reactive airway disease (5%).

3.2. Identification of IPD cases

A blood sample for culture was collected from >97% of subjects. S. pneumoniae was isolated from 27 of the 8993 cultures obtained and 11 of 91 specimens sent for PCR. Sources of positive cultures were: blood (20), pleural fluid (4), and cerebrospinal fluid

(3). Among 91 non-blood sterile body fluid samples tested by PCR, 11 were positive for S. pneumoniae; of these, 3 were from subjects who also had positive cultures and 8 were from subjects whose cultures did not yield S. pneumoniae; sites for PCR-positive-only isolates were CSF (7) and pleural fluid (1).

Cases were identified as having a positive culture or a positive PCR with clinical picture consistent with IPD. Thus, a total of 25 IPD cases were identified: 22 from subjects with 27 cultures positive for S. pneumoniae (some subjects had >1 positive culture) and 3 subjects positive by PCR testing (5 subjects with a positive PCR in CSF did not have a clinical picture of meningitis, thus were not included in the IPD cases).

3.3. IPD incidence rates

Among children 28 days to <36 months of age, the IPD incidence rates for culture-positive only cases for years 1 and 2 combined was 33.7/100,000 per year; year 1 was 39.6/100,000 per year; year 2 was 27.8/100,000. The addition of the cases confirmed by PCR increases the IPD incidence rate for years 1 and 2 combined to 46.0/100,000 per year; year 1 was 39.6/100,000 and year 2 was 52.4/100,000 (Fig. 1). Age-stratified analysis of IPD incidence rates for culture-positive only cases suggested different peak IPD incidence by year; the peak in year 1 was for the 28 days to <6 months group (106.8/100,000 per year); the peak in year 2 was for the 12 months to <24 months group (45.5/100,000 per year). By diagnosis, the IPD incidence rates for culture-positive only subjects were: pneumococcal pneumonia 12.2/100,000; bacteremia 9.2/100,000; sepsis 6.1/100,000; meningitis 4.6/100,000 and peritonitis 1.5/100,000 (although SP was not isolated from the peritoneum, one subject was identified as having peritonitis with a positive blood culture and signs and symptoms compatible with peritonitis) (Table 1). Addition of the PCR-positive cases (2 meningitis and 1 pneumococcal pneumonia) would increase the incidence rates to 7.7/100,000 and 13.8/100,000, respectively.

3.4. Meningitis

Meningitis was diagnosed from culture-positive CSF samples in 3 subjects (13.6% of IPD cases): 2 cases in year 1 (6.1/100,000), and 1 in year 2 (3.1/100,000). These subjects were aged 53 days, 129 days, and 161 days, respectively. Neurologic sequelae were observed in two of these subjects: both showed cognitive disability; one also showed developmental delay. CSF characteristics of 2 culture-negative/PCR-positive samples were consistent with meningitis; neither had abnormal neurologic status.
Clinical pneumonia was diagnosed in 1285 of 8801 subjects enrolled (14.6%): 501 cases (11.8%) in year 1 and 784 cases (17.2%) in year 2. Incidence of clinical pneumonia by age is shown in Fig. 2. A peak incidence in both years was found in children aged 28 days to <6 months and the combined incidence in years 1 and 2 was 4459/100,000. The number of clinical pneumonia cases varied during the year: the peak numbers of cases occurred during July through October (Fig. 2).

Chest radiographs were obtained in 1248 of 1285 (97.1%) subjects diagnosed with clinical pneumonia. Of 1248 chest radiographs obtained, CXR + Pn was confirmed in 360, a positivity rate of 28.8%. Lobar consolidation was observed in 356 (98.9%) radiographs, pleural effusion in 5 (1.4%), and both lobar consolidation and pleural effusion in 1 (0.3%). When stratified by age group, similar proportions of children in each age group were shown to have abnormal radiographs: 29.7% in children 28 days to <6 months of age; 31.3% in 6 to <12 months; 36.6% in 12 to <24 months; and 34.2% in 24 to <36 months.

CXR + Pn incidence rates stratified by age are shown in Fig. 3. The peak incidence by age differed in years 1 and 2; during year 1, the peak was seen in children 6 months to <12 months of age (745/100,000) and in year 2 the peak was in children aged 28 days to <6 months (1644/100,000). For years 1 and 2 combined, the peak incidence was 1180/100,000 in children aged 28 days to <6 months. The highest numbers of cases occurred during August through November (Fig. 4).

### Table 1
Incidence rates by IPD diagnosis for culture-positive subjects and by study year.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Number of cases</th>
<th>Number in at-risk population</th>
<th>Incidence rate per 100,000 (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumococcal meningitis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year 1</td>
<td>2</td>
<td>32,849</td>
<td>6.09 (0.74–21.99)</td>
</tr>
<tr>
<td>Year 2</td>
<td>1</td>
<td>32,436</td>
<td>3.08 (0.08–17.18)</td>
</tr>
<tr>
<td>Years 1 and 2</td>
<td>3</td>
<td>65,285</td>
<td>4.60 (0.95–13.43)</td>
</tr>
<tr>
<td>Sepsis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year 1</td>
<td>2</td>
<td>32,849</td>
<td>6.09 (0.74–21.99)</td>
</tr>
<tr>
<td>Year 2</td>
<td>2</td>
<td>32,436</td>
<td>6.17 (0.75–22.27)</td>
</tr>
<tr>
<td>Years 1 and 2</td>
<td>4</td>
<td>65,285</td>
<td>6.13 (1.67–15.69)</td>
</tr>
<tr>
<td>Peritonitis*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year 1</td>
<td>1</td>
<td>32,849</td>
<td>3.04 (0.08–16.96)</td>
</tr>
<tr>
<td>Year 2</td>
<td>0</td>
<td>32,436</td>
<td>0.00 (0.00–11.37)</td>
</tr>
<tr>
<td>Years 1 and 2</td>
<td>1</td>
<td>65,285</td>
<td>1.53 (0.04–8.53)</td>
</tr>
<tr>
<td>Pneumococcal pneumonia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year 1</td>
<td>4</td>
<td>32,849</td>
<td>12.18 (3.32–31.18)</td>
</tr>
<tr>
<td>Year 2</td>
<td>4</td>
<td>32,436</td>
<td>12.33 (3.36–31.57)</td>
</tr>
<tr>
<td>Years 1 and 2</td>
<td>8</td>
<td>65,285</td>
<td>12.25 (5.29–24.15)</td>
</tr>
<tr>
<td>Bacteremia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year 1</td>
<td>4</td>
<td>32,849</td>
<td>12.18 (3.32–31.18)</td>
</tr>
<tr>
<td>Year 2</td>
<td>2</td>
<td>32,436</td>
<td>6.17 (0.75–22.27)</td>
</tr>
<tr>
<td>Years 1 and 2</td>
<td>6</td>
<td>65,285</td>
<td>9.19 (3.37–20.00)</td>
</tr>
</tbody>
</table>

* S. pneumoniae isolated from blood in subject with clinical diagnosis of peritonitis.
Table 2
Serotype distribution of *S. pneumoniae* isolates from culture-positive children aged 28 days to <36 months of age.

<table>
<thead>
<tr>
<th>Serotype</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Years 1 and 2 combined</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total cohort (<em>N</em>=13); available for serotyping (<em>N</em>=13)</td>
<td>Total cohort (<em>N</em>=9); available for serotyping (<em>N</em>=9)</td>
<td>Total cohort (<em>N</em>=22); available for serotyping (<em>N</em>=21)</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>14</td>
<td>3</td>
<td>23.1</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>7.7</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>7.7</td>
<td>1</td>
</tr>
<tr>
<td>6A</td>
<td>2</td>
<td>15.4</td>
<td>0</td>
</tr>
<tr>
<td>19A</td>
<td>0</td>
<td>0.0</td>
<td>2</td>
</tr>
<tr>
<td>22F</td>
<td>1</td>
<td>7.7</td>
<td>1</td>
</tr>
<tr>
<td>6B</td>
<td>1</td>
<td>7.7</td>
<td>0</td>
</tr>
<tr>
<td>7C</td>
<td>1</td>
<td>7.7</td>
<td>0</td>
</tr>
<tr>
<td>9V</td>
<td>1</td>
<td>7.7</td>
<td>0</td>
</tr>
<tr>
<td>15B</td>
<td>1</td>
<td>7.7</td>
<td>0</td>
</tr>
<tr>
<td>23F</td>
<td>1</td>
<td>7.7</td>
<td>0</td>
</tr>
</tbody>
</table>

* There were no serotype results in year 2 for one subject because the *S. pneumoniae* culture died before serotyping could be performed.

3.6. Serotype distribution of *S. pneumoniae* isolates

Of the 22 non-duplicative *S. pneumoniae* cultures from IPD subjects, 21 were available for serotyping. Serotype 14 was the most common, representing 28.6% of the isolates, followed by serotypes 3, 4, 6A, 19A, and 22F (9.5% each); other serotypes each represented 4.8% of isolates (Table 2). The percentages of serotypes covered by PCV7, PCV10, and PCV13 among the non-duplicative isolates obtained from cultures were 52.4%, 52.4%, and 81.0%, respectively. Serotypes covered by PCV13, but not by PCV7 or PCV10, were 3, 6A, and 19A. Serotypes not covered by any of these 3 PCVs represented a total of 4 (19.1%) isolates and were 7C (n=1), 15B (n=1), and 22F (n=2).

Serotypes of 3 IPD cases that were identified by PCR were as follows: 6B (1), 14 (1), and non-13 valent (1). Including these cases, the percentages of serotypes covered by PCV7, PCV10, and PCV13 were 54.2%, 54.2%, and 79.2%, respectively.

3.7. Antimicrobial resistance rates of invasive *S. pneumoniae* isolates

Of 22 non-duplicative IPD isolates, 21 were available for antimicrobial resistance testing. A wide range of antimicrobial agents was tested and highest rates of nonsusceptibility were seen for trimethoprim/sulfamethoxazole (42.9%), penicillin (42.8%) and erythromycin (28.6%) (Table 3). Serotypes exhibiting penicillin nonsusceptibility were: 6A, 6B, 14, 19A, and 23F. Both serotype 19A isolates were penicillin-nonsusceptible and 66.7% of the serotype 14 isolates demonstrated penicillin nonsusceptibility. Coverage of penicillin-nonsusceptible isolates by PCV7 was 66.7%, by PCV10 66.7%, and by PCV13 100%.

3.8. Case fatality rates

No subject with IPD died during the study period. Among children with pneumonia, 1 subject of the 1285 (0.08%) diagnosed with clinical pneumonia died, and 1 subject of the 360 (0.28%) diagnosed with CXR + Pn died.

4. Discussion

This study is the first prospective population-based surveillance for IPD and pneumonia in children from Central America. The incidence rates of IPD among children aged 28 days to <36 months (46.0/100,000 for culture- and PCR-positive children) were much greater than the rates from a retrospective study of hospitalized patients aged 0–11.4 years in Costa Rica from 1995 to 2001 where the incidence of IPD in children <2 years of age was 2.9/100,000) [12]. The difference in incidence rates reflects the more effective design of prospective studies over passive, hospital-based surveillance studies. The main limitation of passive or retrospective studies for evaluating the incidence of *S. pneumoniae* infections is the fact that blood cultures and chest radiographs may not be performed routinely, which may result in an underestimation of the true disease burden. Furthermore, both inpatients and outpatients must be included to obtain the best estimate of disease burden. Inclusion of PCR testing, in addition to routinely performed culture analysis, may improve the estimated burden of disease.

The overall IPD rates for culture-positive subjects in the current study in children aged 28 days to <36 months of age are of similar magnitude to those found in the other LEAP countries: Goiânia, Brazil (55/100,000) and Bogota, Colombia (76/100,000). Also, the highest rates for IPD in Costa Rica were seen in children <24 months of age, as observed in the studies from Brazil and Colombia. We identified a significant burden of pneumonia in children in San José. The annualized incidence of Cln Pn and of CXR + Pn over the 2 years was high, with rates of 1968/100,000 and 551/100,000, respectively. These rates are lower than those for children of the same age in the other LEAP countries, as well as those in other prospective studies of children 2–23 months of age in Argentina [6] and Chile [13], and <5 years of age in Uruguay [8]. Even among the age group with the highest pneumonia incidence rates, children aged 28 days to <6 months, the rates (Clin Pn 4459/100,000 and CXR + Pn 1180/100,000) were lower than those seen in the same age group in the other LEAP countries. We speculate that the lower incidence rates of IPD and pneumonia in Costa Rican children may be attributed to the high compliance rate with yearly influenza vaccination in high-risk children ≤4 years of age and adults >65 years [14]. The compliance rate with influenza vaccination in 2004 was 88% for high-risk children 6 months to 5 years of age and 98% for adults >65 years. In contrast, the influenza vaccination rate in Colombia in 2005 was 10% for children 6–18 months of age with respiratory diseases or living in poor areas [15]. In Brazil an estimated 7% of children received influenza vaccines in 2007 and 2008 [16].

In our study, cases of IPD showed a peak in March through April; this seasonal presentation occurs toward the end of the dry (warm) season in Costa Rica (December through April). However, the cases of clinical pneumonia and CXR + Pn did show a peak in August through October during the rainy season. This observation is consistent with data previously observed in Costa Rican children with *S. pneumoniae* otitis media in which most cases were observed...
Table 3
Antimicrobial susceptibility of invasive S. pneumoniae isolates.

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>Year 1 (N=13)</th>
<th>Year 2 (N=9)</th>
<th>Years 1 and 2 combined (N=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Susceptible</td>
<td>Int.</td>
<td>Resistant</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>%d</td>
<td>n</td>
</tr>
<tr>
<td>Penicillin</td>
<td>8</td>
<td>61.5</td>
<td>5</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>8</td>
<td>61.5</td>
<td>5</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>9</td>
<td>69.2</td>
<td>0</td>
</tr>
<tr>
<td>TMP/sulfamethoxazole</td>
<td>7</td>
<td>53.8</td>
<td>1</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>13</td>
<td>100.0</td>
<td>0</td>
</tr>
</tbody>
</table>

TMP/sulfamethoxazole

4 No resistance was found for amoxicillin, levofloxacin, or vancomycin.
5 In year 2, one subject had at least 1 culture that did not have susceptibility results. Therefore, nonmissing serotypes (N=8).
6 For subjects with multiple cultures, the most resistant result was counted.
7 Percentages were based on denominator of each row within each year. Denominator was nonmissing susceptibility values for each antimicrobial.

during the rainy season (May through November) [17]. The monthly profiles of our pneumonia cases may reflect a seasonality of pneumonia, as reported in other countries [18,19].

Our data on serotype distribution are in accordance with SIREVA data, which demonstrate that serotype 14 is the most common serotype responsible for IPD in children <5 years of age in Latin America. The next most common serotype observed in this study was serotype 3, a non-PCV7 serotype previously reported among the most common serotypes in Costa Rican children with otitis media [20–23]. Serotype 3 is associated with serious invasive disease, particularly necrotizing pneumonia and empyema, as well as with increased mortality [4,21,24–27]. Although there were only two cases of serotype 19A disease, both were noted in year 2, possibly indicating an increase in this serotype’s importance following partial introduction of PCV7 in year 2004 in children cared for by private pediatricians (approximately 20% of Costa Rican children).

IPD caused by serotype 19A has increased globally, both in countries that have PCV7 as part of their NIPs as well as in countries prior to PCV7 implementation. The use of antibiotics with long half-lives has also been associated with an increase in serotype 19A disease [27]. The highest PCV coverage in the present study occurred for PCV13 (81.0% among the nonduplicative isolates; 100% of penicillin-nonsusceptible isolates) because this vaccine includes serotypes 19A and 3. Serotypes 1 and 5, classically associated with IPD in Latin America were not identified during the study period, which may reflect their characteristic epidemic pattern with sudden increases followed by decreases in incidence [6,22,28].

Antimicrobial resistance to penicillin and trimethoprim/sulfamethoxazole was relatively common in these isolates, and the serotypes associated with resistance are the ones that have demonstrated resistance globally. No resistance was found for amoxicillin, ceftriaxone, levofloxacin, or vancomycin. Of interest, the two 19A isolates were penicillin-nonsusceptible.

A limitation of this study is the generalizability from the study population in seven districts of San José to the overall Costa Rican population. These results may not represent children in more rural areas that may have a lower socioeconomic status than this population. If we assume that socioeconomic class is inversely related to the risk of pneumonia [29], then the incidence estimates from this study may be an underestimate of the true pneumococcal disease burden for Costa Rican children in areas with lower socioeconomic class. Furthermore, a surveillance study such as this one will not capture all potential subjects presenting at the clinics, which may result in an underestimation of disease burden. Other factors that could contribute to such an underestimation include prior use of antibiotics, which might decrease the likelihood of isolating S. pneumoniae; in this study, prior antibiotic use was not uncommon (13.4%).

In conclusion, S. pneumoniae causes a considerable burden of IPD and pneumonia in children aged 28 days to 36 months of age in San José. This study was conducted before the introduction of PCV7 into the Costa Rican NIP, which started in January 2009. Therefore, these epidemiologic data will serve as a baseline to evaluate the impact of the introduction of PCV7 on the burden of S. pneumoniae disease in Costa Rican children. Continued surveillance is essential to identify the serotype distribution following PCV7 introduction and to determine the optimal vaccination strategy for the country.

Conflicts of interest statement

Adriano Arguedas, Arturo Abdelnour, Carolina Soley, Elias Jimenez, Ana Lucia Jimenez, Nurith Porat, Ron Dagan report no financial conflicts of interest relevant to this manuscript. Darmendra Ramcharran reports that, at the time of the LEAP study, he worked with Via Research LLC on the Pfizer sponsored study and is currently an employee of Pfizer Inc. Sharon Gray and Gayl L Rodgers are also employees of Pfizer Inc.

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