

# Nineteen-years of pneumococcal invasive disease surveillance in a children's hospital in Mendoza, Argentina

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## ABSTRACT

Five hundred and thirty-seven children admitted to Hospital Dr. Notti and diagnosed with invasive pneumococcal disease between 1993 and 2011 were studied. Their median age was 19 months (range= 0-192 months); 34.82% were <1 year old and 23.46%, ≥60 months old. Pneumonia with or without effusion (48.04%) and meningitis (29.05%) were the most predominant conditions, with a case fatality rate of 6.14%. Identified serotypes corresponded to 14, 5 and 1 in 56.86% of cases. Sensitivity to penicillin was observed in 99.74% of non-meningeal strains, while sensitivity to ceftriaxone was found in 98.08% of meningeal strains. Risk factors in pneumonia with effusion were associated to age ≥60 months old, RR: 1.47 (1.06-2.04),  $p=0.02$ , to serotype 5, RR: 2.57 (1.71-3.87),  $p=0.0001$ , and to serotype 1, RR: 1.86 (1.17-2.96),  $p=0.014$ ; in the case of meningitis, risk factors were mainly associated to age <1 year old, RR: 2.35 (1.87-3.06),  $p=0.0000$ , and to serotype 18C, RR: 2.19 (1.3-3.7),  $p=0.024$ .

**Conclusion.** *Streptococcus pneumoniae* was a major problem in infants younger than one year old, who predominantly developed meningitis which caused half of deaths, and in children older than 60 months old, who had a prevalence of pneumonia with effusion. Most cases were sensitive to penicillin and ceftriaxone.

**Key words:** invasive pneumococcal disease, serotypes, antibiotic sensitivity, risk factors.

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## INTRODUCTION

*Streptococcus pneumoniae* (*Spn*) causes vaccine-preventable diseases with a high mortality rate.<sup>1</sup> A review of data from Latin America and the Caribbean collected between 1990 and 2006 showed that between 12 000 and 28 000 children younger than 5 years old could die every year because of this disease.<sup>2</sup>

Serotypes that cause most invasive pneumococcal diseases (IPDs) show variations

in terms of geographic regions and type of disease,<sup>3</sup> in addition to changes in antimicrobial susceptibility, specially to penicillin and third-generation cephalosporins.<sup>4</sup> In Argentina, according to data collected by the Surveillance System for Bacterial Agents Responsible for Pneumonia and Meningitis (SIREVA), 2012, 79.2% of identified meningitis strains and 100% of non-meningeal strains were sensitive to penicillin in children younger than 5 years old. In the case of ceftriaxone, 94.3% were sensitive in meningitis, with an intermediate sensitivity (IS) of 5.7%, while 98.5% were sensitive in non-meningeal conditions, with an IS of 1.5%.<sup>5</sup>

In 2012 (Resolution 502/2011), Argentina introduced the 13-valent pneumococcal conjugate vaccine (PCV13) to the immunization schedule for infants as of 2 months old.<sup>6</sup> Knowing the epidemiology of IPD, the distribution of serotypes and antimicrobial susceptibility is essential to assess the potential impact of an immunization program.

## OBJECTIVES

To describe the epidemiological characteristics of hospitalized patients with IPD and to detect risk factors for IPD.

## POPULATION AND METHODS

Observational, analytical and retrospective study conducted between January 1993 and December 2011.

All patients with confirmed IPD diagnosis admitted to Hospital Pediátrico Dr. Humberto Notti, Mendoza, were selected. Confirmed IPD was defined as isolation of *Spn* in typically sterile liquid and a compatible clinical presentation.

Medical records were reviewed using the files from the Department of Microbiology, and a form was filled in with demographic data, clinical presentation, underlying disease, isolation site of *Spn*, antibiotic susceptibility, serotype, and case fatality rate.

During the study, serotyping was conducted using the Neufeld-Quellung test at the Department of Clinical Bacteriology INEI-ANLIS Dr. Carlos Malbrán, while the minimum

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inhibitory concentration (MIC) for penicillin and ceftriaxone was established using the E Test; values were adjusted according to cut-off points established by the Clinical and Laboratory Standards Institute (CLSI) in 2008.<sup>5</sup>

Quantitative outcome measures were expressed as median and range, and qualitative outcome measures, as percentage.

An univariate analysis was performed using the Epidat software, version 3.1, to assess risk factors for IPD, which reported the relative risk (RR), the 95% confidence interval (95% CI), and a significant *p* value <0.05.

The study was approved by Hospital Dr. H. Notti Ethics Research Committee and it was not necessary to sign an informed consent. The confidentiality of patient's identity was warranted.

## RESULTS

Five hundred and thirty-seven children with IPD were included, with an annual mean proportion of 18.53 cases every 10 000 hospital discharges (range: 7.82/10 000-35.66/10 000).

Table 1 shows some of the clinical characteristics of the studied population.

Considering all patients, 34.82% (n: 187) were ≤11 months old; 19.36% (n: 104) were between 12 and 23 months old; 10.80% (n: 58) were between 24 and 35 months old; 6.70% (n: 36) were between 36 and 47 months old; 4.84% (n: 26) were between 48 and 59 months old; and 23.46% (n: 126) were ≥60 months old.

Clinical presentations by age group are shown in Figure 1.

An underlying disease was present in 4.10% (n: 22) of children, distributed as nephrotic syndrome: 8; neoplasm: 7; immunodeficiency: 2; HIV: 1; cochlear implant: 1; cerebrospinal fluid (CSF) fistula: 1; chronic lung disease: 1; and heart disease: 1.

According to the records, no subject had a history of pneumococcal vaccine or hospital-acquired IPD.

Through serotyping, 255 strains (47.5%) were identified. Serotypes 14, 5 and 1 accounted for 56.86% (n: 145) of all serotypes. Of the serotypes identified, 88% (225/255) are included in the PCV13. No circulating serotypes corresponded to serotypes 3 and 4. Serotype distribution by age group is shown in Figure 2.

Among meningitis cases, 89.10% (n: 139) of strains were sensitive to penicillin; 98.08% (n: 153) were sensitive to ceftriaxone, and 0.26% (n: 1)

had an IS. Among non-meningeal cases, 99.74% (n: 380) were sensitive to penicillin, with an IS of 0.26% (n: 1); while 0.26% (n: 1) resulted in an IS to ceftriaxone.

Of all serotypes, 6.67% (n: 17) were resistant to penicillin, distributed as 14 (n: 8), 6B (n: 3), 19F (n: 2), 18C (n: 1), 9V (n: 1), 23F (n: 1), 23B (n: 1), with an IS to ceftriaxone of 1.18% (n: 3), accounted as serotypes 14 (n: 2) and 23F (n: 1).

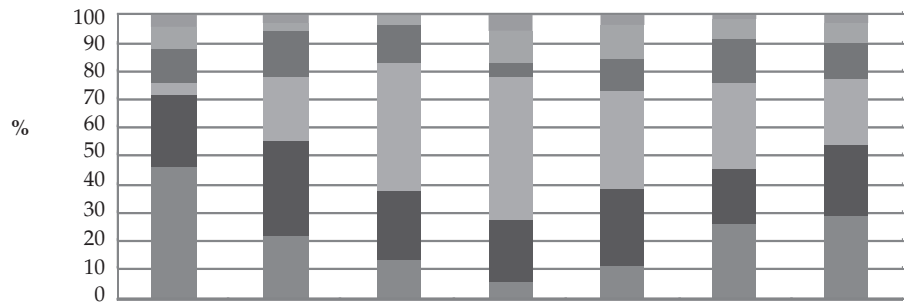
Table 2 shows an analysis of the relative risk for each clinical presentation, by age, with no adjustment for comorbidities.

In infants younger than 1 year old, a significant association to serotypes 19F: RR: 2.01 (95% CI: 1.35-3.0), *p*: 0.01, and 19A: RR: 2.48 (95% CI: 1.86-3.30), *p*: 0.0021 was observed. In children ≥60 months old, such association was found with serotype 1: RR: 3.05 (1.77-5.26), *p*: 0.0004. For cases of pneumonia with effusion, an association was found with serotypes 5: RR: 2.57 (95% CI: 1.71-3.87), *p*: 0.0001, and 1: RR: 1.86 (95% CI: 1.17-2.96), *p*: 0.014. For cases of meningitis, an association was found with serotype 18C: RR: 2.19 (95% CI: 1.3-3.7), *p*: 0.024.

TABLE 1. Characteristics of hospitalized patients diagnosed with invasive pneumococcal disease

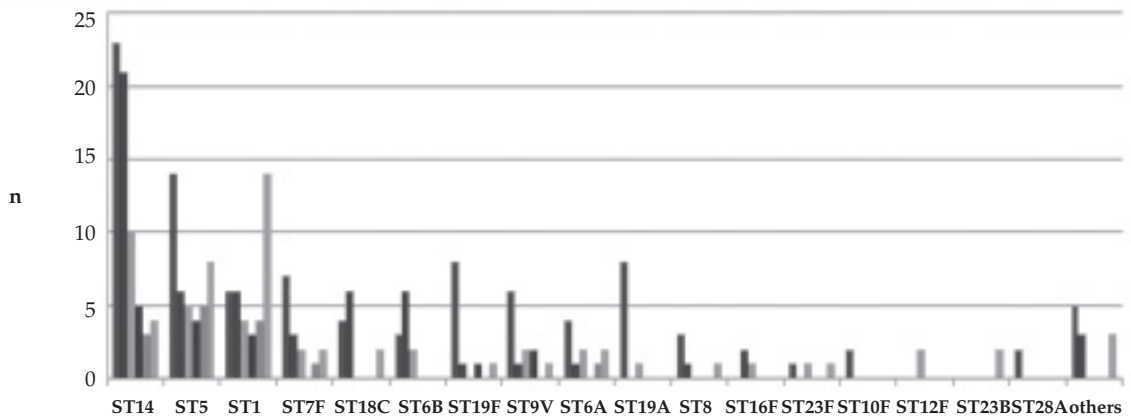
N= 537	
Median age, months (range)	19 (0-192)
Boys, n (%)	305 (56.8)
<b>Clinical presentations</b>	
Meningitis, n (%)	156 (29.05)
Pneumonia, n (%)	136 (25.32)
Pneumonia with effusion, n (%)	122 (22.72)
Bacteremia, n (%)	71 (13.22)
Sepsis, n (%)	36 (6.70)
Cellulitis, n (%)	8 (1.49)
Arthritis, n (%)	6 (1.12)
Primary peritonitis, n (%)	2 (0.37)
<b>Underlying disease</b>	
Total, n (%)	22 (4.10)
Median age, months (range)	60 (4-195)
<b>Case fatality rate</b>	
Overall, n (%)	33 (6.14)
Due to meningitis, n (%)	18 (54.54)
Due to sepsis, n (%)	8 (24.24)
Due to pneumonia, n (%)	7 (21.21)

FIGURE 1. Clinical presentation by age group



	0-11 m.o.	12-23 m.o.	24-35 m.o.	36-47 m.o.	48-59 m.o.	≥ 60 m.o.	Total
Other	8	8	8	8	8	8	8
Sepsis	15	15	15	15	15	15	15
Bacteremia	22	17	8	2	3	19	71
Pneumonia with effusion	8	23	26	18	9	38	122
Pneumonia	47	35	14	8	7	25	136
Meningitis	87	23	8	2	3	33	156

FIGURE 2. Serotype distribution by age group



	ST14	ST5	ST1	ST7F	ST18C	ST6B	ST19F	ST9V	ST6A	ST19A	ST8	ST16F	ST23F	ST10F	ST12F	ST23B	ST28A	Others
00 to 11 m.o.	23	14	6	7	4	3	8	6	4	8	3	0	1	2	0	0	2	5
12 to 23 m.o.	21	6	6	3	6	6	1	1	1	0	1	2	0	0	0	0	0	3
24 to 35 m.o.	10	5	4	2	0	2	0	2	2	1	0	1	1	0	2	0	0	0
36 to 47 m.o.	5	4	3	0	0	0	1	2	0	0	0	0	0	0	0	0	0	0
48 to 59 m.o.	3	5	4	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0
>60 m.o.	4	8	14	2	2	0	1	1	2	0	1	0	1	0	0	2	0	3

ST: serotype.

\* Others with a ST: 11, 12, 16A, 18A, 18B, 2, 20, 35F, 42, 7C, 15B.

A case fatality risk was observed in sepsis: RR: 4.45 (95% CI: 2.16-9.15),  $p$ : 0.0008; meningitis: RR: 3.46 (95% CI: 1.67-7.16),  $p$ : 0.0007; and serotype 18C: RR: 3.37 (95% CI: 1.21-10.54),  $p$ : 0.05.

## DISCUSSION

This was a hospital-based study, and considering that approximately half of IPD cases require hospitalization,<sup>7,8</sup> and that no outpatients with fever were included, the actual burden of IPD may have been underestimated. For this reason, prevalent conditions were meningitis and pneumonia with and without effusion, with a low frequency of bacteremias.<sup>9</sup> This was also a limitation when analyzing the relative risk of having a certain age in relation to the different clinical presentations since the study included only seriously ill children.

Notwithstanding, and consistent with the literature from Latin America and the Caribbean,<sup>2,10</sup> a higher incidence was observed in boys younger than 1 year old, showing an association with a higher risk of meningitis (RR: 2.35 [1.87-30.6],  $p$ = 0.0000) and serotypes 19F and 19A. It is worth noting that, in the group  $\geq 60$  months old, the percentage of IPD was high and showed a significant association with serotype 1 and pneumonia with effusion, which was also observed in other studies on wider age groups.<sup>11</sup>

When compared to other sites<sup>10,12</sup> the percentage of subjects with an underlying disease was low, possibly in relation to the lesser complexity of hospitalized patients.

It should be noted that most strains were sensitive to ceftriaxone in meningeal conditions, and to penicillin in non-meningeal processes.

TABLE 2. Relative risk for each clinical presentation by age, with no adjustment for comorbidities

Clinical presentation	Age	N	RR	CI (95%)	P
Meningitis (N: 156)	<1 year old	87	2.35	1.87-3.06	0.0000
	<2 years old	110	2.02	1.49-2.72	0.000
	<3 years old	118	1.67	1.21-2.3	0.006
	<4 years old	120	1.34	0.97-1.85	NS
	<5 years old	123	1.14	0.82-1.58	NS
	>5 years old	33	0.87	0.63-1.21	NS
Pneumonia (N: 136)	<1 year old	47	0.98	0.72-1.34	NS
	<2 years old	82	1.28	0.95-1.73	NS
	<3 years old	96	1.29	0.93-1.98	NS
	<4 yearsold	104	1.28	0.95-1.81	NS
	<5 yearsold	111	1.36	0.92-2.00	NS
	>5 yearsold	25	0.73	0.49-1.07	NS
Pneumonia with effusion (N: 122)	<1 yearold	8	0.13	0.06–0.26	0.000
	<2 yearsold	31	0.28	0.19–0.41	0.000
	<3 yearsold	57	0.47	0.34–0.64	0.000
	<4 yearsold	75	0.63	0.46–0.86	0.004
	<5 yearsold	84	0.67	0.48–0.93	0.02
	>5 yearsold	38	1.47	1.06–2.04	0.02
Others* (N: 123)	<1 yearold	45	1.07	0.78–1.48	NS
	<2 yearsold	68	1.04	0.76-1.42	NS
	<3 yearsold	78	0.93	0.67-1.28	NS
	<4 yearsold	86	0.91	0.66-1.28	NS
	<5 yearsold	93	0.95	0.66–1.36	NS
	>5 yearsold	30	1.05	0.73–1.75	NS

NS: not significant. RR: relative risk. CI: confidence interval.

Based on these data, it is relevant to continue using these antibiotics in *Spn* infections.

One of the limitations of this study was that it did not analyze the length of stay, progression or sequelae. However, the study recorded the case fatality rate, an indicator of disease severity, its value was considered intermediate when compared to other regions,<sup>7,10,12</sup> an a risk four times higher for sepsis and three times higher for meningitis and serotype 18C.

Serotypes 14, 5 and 1 accounted for more than half of all identified serotypes, as observed in most Latin American countries.<sup>2,5,9,13</sup> Although serotypes 3 and 4, which are included in the PCV13, were not found in our cases, the vaccine does include most circulating serotypes related to resistance, except for 23B, which is less prevalent. Therefore, it is expected that the PCV13, recently introduced in Argentina, will achieve a major reduction in IPDs, as documented in other countries that introduced the 7-valent pneumococcal conjugate vaccine (PCV7).<sup>14,15</sup> For this reason, it is important to continue collecting data on IPDs, both at a national and regional level, and considering the different variations.

## CONCLUSIONS

IPD is a major problem among children in Mendoza, specially infants younger than 1 year old, in whom meningitis was predominant, and in children older than 60 months old, who showed a higher occurrence of pneumonia with effusion. A small percentage of patients had comorbidities, and more than half of all deaths were caused by meningitis. Most *Spn* cases were sensitive to penicillin and ceftriaxone. ■

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