Laboratory-Based Surveillance of *Streptococcus pneumoniae* Invasive Disease in Children in 10 Latin American Countries

A SIREVA II Project, 2000–2005

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Background: For the last 14 years the Pan American Health Organization has been promoting surveillance of invasive pneumococcal disease in Latin American children for better understanding of the disease tendencies regarding capsular types circulation in each country and susceptibility to antimicrobials.

Methods: Laboratory-based surveillance data from 10 Latin American countries collected from 2000 to 2005 were analyzed, including serotype distribution and susceptibility to beta-lactam antibiotics.

Results: Although 61 different capsular types were identified during the 6-year surveillance, 13 serotypes accounted for 86% of all isolates. These were consistently the most prevalent throughout the study period with serotype 14 predominating. Diminished susceptibility to penicillin was detected in 38% of all *Streptococcus pneumoniae* isolates, with the highest prevalence in Dominican Republic and Mexico. Decreased susceptibility to penicillin increased in Brazil and Colombia whereas decreased high resistance rates was recorded in Chile.

Conclusions: These data indicate that 10 countries of the Region continue to have high quality laboratory-based surveillance for pneumococcal disease thus generating valuable information so that healthcare decision makers may prioritize interventions. The heptavalent vaccine will potentially cover from 52.4% to 76.5% of strains causing invasive pneumococcal disease and the 13 valent from 76.7% to 88.3%.

Key Words: *Streptococcus pneumoniae*, surveillance, serotypes, beta lactam susceptibility, children, Latin America, invasive disease

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For 14 years the Pan American Health Organization has been encouraging Latin American countries to conduct appropriate surveillance on invasive pneumococcal disease in children less than 6 years of age to provide a better understanding of the disease causing tendencies of the most common capsular types circulating in each country. This strategy should provide high quality and reliable data for the composition of an ideal vaccine for the region. The worldwide increase in the rates of antibiotic resistance, especially to penicillin was also considered as an integral part of the data generated in the surveillance. The Sistema Regional de Vacunas (SIREVA) project has been the first multicenter, international laboratory-based surveillance study to focus on *Streptococcus pneumoniae* causing invasive disease in Latin American children. The project began in 1994, and the data generated in 6 countries until 2000 have already been published.[1–5] The aim of this study is to present the surveillance data from 10 Latin American countries from 2000 to 2005. The analysis includes the distribution of capsular types and susceptibility to beta-lactam antibiotics. The results of these analyses are then compared with the composition of the licensed heptavalent pneumococcal conjugated vaccine and the 10- and 13-valent vaccines which are being tested in clinical trials.

MATERIALS AND METHODS

Participating Countries and National Reference Laboratories

The description of participating centers has already been done.[1,2,4,6] Countries with at least 400 isolates during the selected

period were included Argentina, Brazil, Chile, Colombia, Cuba, the Dominican Republic, Mexico, Paraguay, Uruguay, and Venezuela. The Reference Centers were responsible for the confirmation, serotyping, and antimicrobial susceptibility testing of every invasive pneumococcal isolate included in the study.

Strain Collection

Isolates were obtained from children less than 6 years of age with invasive pneumococcal disease: pneumonia, defined using the World Health Organization clinical criteria, without radiologic results,[2,4] meningitis, sepsis, or bacteremia without focus, febrile syndrome, arthritis, peritonitis, abscesses, and cellulitis. *S. pneumoniae* was isolated from normally sterile body sites. Demographic data were collected from each patient and initial clinical diagnosis.[2,4] The referral of invasive pneumococcal isolates to the reference laboratories was voluntary.

S. pneumoniae, Confirmation, Serotyping, and Susceptibility to Beta-Lactams

A common protocol was established for the isolation and identification of *S. pneumoniae* isolates.[7] Serogrouping or serotyping was carried out by the Quellung reaction using antisera from the Statens Serum Institute (Copenhagen, Denmark) according to the Sistema Regional de Vacunas Procedures Manual.[7] All isolates were tested for sensitivity to 1 μg oxacillin disk, by the disk diffusion method. For isolates with diminished susceptibility to penicillin (DSP) minimal inhibitory concentrations (MICs) to penicillin and third generation cephalosporins were determined by broth microdilution method or agar dilution method, according to CLSI guidelines.[8–10] *S. pneumoniae* ATCC 49619 was used as a control strain and the interpretation for penicillin and for third generation cephalosporins was based on 2006 and 2008 CLSI guidelines.[8–11]

External Quality Assurance (EQA) Program

Serotyping and antimicrobial susceptibility testing were validated by a program coordinated by the National Centre for Streptococcus in Canada and by 2 Subregional laboratories (1) Institute Adolfo Lutz in Brazil for Argentina, Chile, Cuba, Dominican Republic, Paraguay, Uruguay, and Venezuela; (2) Instituto Nacional de Salud in Colombia for Mexico.[6]

Analysis of Circulating Capsular Types Included in Some Conjugate Vaccines

To predict the potential benefit of pneumococcal conjugate vaccines, the degree of agreement between the serotypes causing invasive pneumococcal disease in Latin American children ≤2 years was compared with those contained in the 7 valent vaccine (serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F),[12] and the 10 valent (the 7 valent plus 1, 5, 7F) and the 13 valent (the 10 valent plus 3, 6A, 19A).[13] The analysis was also performed by country, disease, and DSP.

Statistical Analysis

For the analysis, only 1 isolate per patient was considered. Data were consigned and verified with Epi-Info 6.1.[14] Variables were described using proportions, means, or medians depending on their level of measurement. Confidence intervals were calculated for proportions and means with a confidence level of 95%. Yearly serotype proportion was compared using chi square (χ^2) with IC 95% or Fisher exact test when small samples precluded using χ^2 Therefore P values should be interpreted as a suggestion that serotype prevalence had or had not shown significant changes during the period 2000 to 2005. However, significant changes would not be interpreted as trends.

A comparative study of the distribution of 8 capsular types, 1, 5, 6B, 9V, 18C, 19A, 23F, and 14, selected by epidemiological significance, in 2 different periods 1994–1999[5] and 2000–2005 was done in 6 countries using χ^2. A similar analysis was done for DSP. Means were compared using Kruskal-Wallis test.

RESULTS

Pneumococcal Isolates

Between January 2000 and December 2005, a total of 8993 pneumococcal invasive isolates were collected. The study included 475 health centers. The yearly distribution of isolates was homogeneous; in Argentina the mean number was 156 (range, 115–225), Brazil 327 (270–353), Chile 333 (288–358), Colombia 107 (94–122), Dominican Republic 69 (57–87), México 121 (104–161), Paraguay 79 (64–93), and Venezuela 67 (54–91). In Cuba 140 (63–224), but the number of isolates decreased in the last 2 years and in Uruguay 95 (45–138) a progressive increase was observed since 2003. The isolates belonged to 4950 (58.5%) male and 3509 (41.5%) female patients, ratio 1.4:1 (in Chile the ratio was 1.9:1 and in Mexico 0.7:1). Regarding age, 76.8% of patients were ≤2 years.

Invasive Isolates by Country, Diagnosis, and Source

The data are shown in Table 1. Regarding sources, 4145 (46.1%) isolates were recovered from blood cultures, 3024 (33.6%) from cerebrospinal fluid, 1412 (15.7%) from pleural fluid, 137 (1.5%) from bronchial aspirates, and 275 (3.1%), from other sterile fluids.

Serotype Distribution Among Invasive Isolates by Year and Country

Capsular typing of 8756 (97.4%) isolates yielded 61 of 91 serotypes described. Distribution of the 13 more frequent serotypes

TABLE 1. Distribution of *Streptococcus pneumoniae* Invasive Isolates by Country and Diagnosis, 2000–2005

Diagnosis	%										
	Argentina n = 936	Brazil n = 1963	Chile n = 2,003	Colombia n = 647	Cuba n = 842	DR* n = 415	Mexico n = 728	Paraguay n = 477	Uruguay n = 575	Venezuela n = 407	Total n = 8993
Pneumonia	55.4	26.9	13.5	39.1	25.5	57.6	38.0	76.1	74.1	45.9	36.4
Meningitis	26.1	61.9	10.9	41.9	74.5	40.2	27.1	17.2	12.7	29.3	35.7
Sepsis/bacteremia	7.2	2.0	73.7	17.3	0.0	2.2	27.3	6.3	10.6	24.8	24.0
Other†	11.3	9.2	1.9	1.7	0.0	0.0	7.6	0.4	2.6	0.0	3.9

*Dominican Republic.

†Other invasive disease: 41 (20.6%) septic arthritis, 58 (29.2%) peritonitis, 30 (15.1%) cellulitis, 15 (7.5%) osteomyelitis, 14 (7.0%) abscesses, and 41 (20.6%) from another 9 conditions with less than 10 cases each; in 149 (1.7%) cases the data were not available.

TABLE 2. Serotype Distribution of *Streptococcus pneumoniae* From Invasive Isolates in 10 Latin American Countries, 2000–2005

Serotype	% Year of Diagnosis						Total n = 8756*	$P^{\ddagger}$
	2000 n = 1407	2001 n = 1455	2002 n = 1446	2003 n = 1511	2004 n = 1545	2005 n = 1392		
14	27.7	28.9	27.8	29.3	28.2	31.5	28.9	0.32
6B	9.2	10.9	10.7	7.4	8.7	8.2	9.2	0.005‡
1	8.2	6.5	5.0	5.5	8.8	11.1	7.5	<0.001‡
5	6.8	4.1	4.3	8.1	9.9	8.0	6.9	<0.001‡
18C	6.1	6.3	6.1	6.8	6.2	4.2	6.0	0.07
19F	6.7	6.8	6.0	6.0	5.0	5.2	6.0	0.22
23F	5.1	5.4	6.5	4.0	3.4	3.7	4.7	<0.001‡
6A	4.4	3.6	4.1	3.1	2.9	4.2	3.7	0.14
19A	3.5	3.0	3.9	4.1	3.6	4.1	3.7	0.57
7F	3.7	3.1	3.2	3.7	3.0	3.4	3.3	0.83
9V	2.2	3.3	3.0	2.7	3.6	2.4	2.9	0.17
3	2.3	1.6	1.8	2.2	2.6	1.9	2.1	0.46
4	2.3	1.4	2.1	0.9	1.7	0.9	1.5	0.001
Other§/NT¶	11.7	15.3	15.6	16.0	12.3	11.1	13.7	—

*Two hundred isolates from Chile and 37 from Dominican Republic, without serotyping.
†χ^2.
‡Indicates statistical significance.
§Forty-eight different capsular types.
¶NT indicates nontypable.

TABLE 3. Distribution of *Streptococcus pneumoniae* Isolates by Susceptibility to Penicillin and Serotype

Serotype	n	% Penicillin		
		Susceptible	Intermediate	Resistant
14	2530	32.2	33.6	34.2
23F	408	40.9	35.3	23.8
19A	323	44.3	48.0	7.7
6B	804	46.6	42.3	11.1
19F	522	47.1	28.0	24.9
9V	253	68.4	9.9	21.7
6A	324	75.0	23.5	1.5
4	135	91.9	5.9	2.2
18C	523	93.1	4.8	2.1
7F	292	94.5	4.5	1.0
1	656	97.0	2.1	0.9
3	182	97.3	2.2	0.5
5	605	100.0	0.0	0.0
Others*	1199	81.2	11.3	7.3
Total	8756	62.2	22.1	15.7

*Forty-eight different capsular types.

by year is shown in Table 2. They represented 86.3% of the isolates circulating in the countries studied.

The results of the comparative study of the distribution of 5 capsular types are consigned in Figure (Supplemental Digital Content 1, http://links.lww.com/A1132).

Capsular Types and Invasive Disease by Country

Four capsular types 14, 1, 5, and 6B, accounted for 64.7% of pneumonia isolates and 6 for meningitis 14, 6B, 18C, 19F, 23F, and 5, which represented 64.3% of isolates; whereas for other invasive diseases, 7 serotypes 14, 6B, 18C, 19F, 1, 6A, and 19A accounted for 64.5% of the isolates. (Table, Supplemental Digital Content 2, http://links.lww.com/A1133).

Beta-Lactam Susceptibility by Year, Country, Invasive Disease, and Capsular Type

Important differences in the proportion of DSP (CLSI, 2006), were seen among countries. (Analysis by year and country is included in Fig., Supplemental Digital Content 3, http://links.lww.com/A1134). For pneumonia, sepsis and bacteremia, 38.8% of isolates showed DSP (21.5% intermediate and 17.3% high), and for meningitis, total DSP was 30.5% (19.3% intermediate and 11.2 high).

The analysis of the global data with the 2008 CLSI criteria showed that for pneumonia 4.1% of isolates showed intermediate resistance (MIC, 4 μg/mL) (range, 0.6% in Argentina to 16.8% in México) and 0.8% high resistance (MIC, $\geq$8 μg/mL) (only 1.9% in Cuba and 8.4% in Mexico). For meningitis 30.5% of the isolates should be considered resistant (MIC, $\geq$0.125 μg/mL).

The DSP distribution of the isolates, by capsular type show that serotypes 14, 23F, 19A, 6B, and 19F represented 85.1% of DSP in the countries studied (Table 3).

Comparing these results with earlier data from 6 countries during 1994–1999[2] some differences were observed (Fig., Supplemental Digital Content 4, http://links.lww.com/A1135).

For third generation cephalosporins, ceftriaxone, or cefotaxime, data were available from 8906 (99%) isolates. Only 9% of the isolates recovered from pneumonia were resistant (7.1% intermediate and 1.9% high); however, 14.3% ($P < 0.001$) of the isolates recovered from meningitis were resistant (12.6% with intermediate resistance and 1.7% with high resistance).

External Quality Assurance Program

Results for serotyping and antimicrobial susceptibility were over 90% for the 2 subregional laboratories[6] as well as for the 7 laboratories assigned to them.

Percentage of Capsular Types Included in the Conjugate Vaccines Circulating in the 10 Countries

The agreement of the 7-, 10-, and 13-valent pneumococcal current available vaccines with isolates causing invasive disease in children <2 years is shown in Table 4.

TABLE 4. Percentage of Capsular Types Included in the Conjugate Vaccines Circulating in the 10 Countries in Children ≥2 Years, by Disease and Country

Disease	Vaccines	% Countries										Total
		Argentina	Brazil	Chile	Colombia	Cuba	DR*	Mexico	Paraguay	Uruguay	Venezuela	
Pneumonia	7 valent	69.9	70.0	59.3	70.1	66.0	76.9†	62.9	57.9	56.4	56.2†	63.4
	10 valent	83.9	82.4	79.7	81.8	86.4†	84.0	71.6†	80.1	81.5	76.6	81.6
	13 valent	91.9	92.9	91.1	94.1	95.1	95.3	77.6†	85.7	93.6	97.1†	91.8
Meningitis	7 valent	55.7	68.5	59.3	61.6	69.9	75.8†	61.2	43.5	32.8†	68.0	65.1
	10 valent	77.6	77.6	73.5	78.9	89.9†	86.7	65.7†	68.1	70.1	88.3	79.3
	13 valent	82.9	86.0	83.2	86.1	96.8†	95.8	76.9	75.4	74.6†	93.2	87.4
Total‡	7 valent	59.1	68.9	59.3	65.3	68.9	76.5†	62.0	54.9	52.4†	61.3	64.2
	10 valent	81.7	78.9	76.7†	79.2	88.3†	85.1	68.4	77.6	79.6	81.7	80.4
	13 valent	88.9	87.9	87.3	89.6	96.3†	95.5	77.2†	83.6	90.4	95.4	89.5

Seven valent (4, 6B, 9V, 14, 18C, 19F, 23F), 10 valent (+1, 5, 7F), 13 valent (+3, 6A, 19A).
*Dominican Republic.
†Indicates the percentage range.
‡Pneumonia + meningitis.

DISCUSSION

With a visionary project, for the last 14 years the Pan American Health Organization has been coordinating pneumococcal surveillance studies in the Region.[1,2,4,6] The EQA program has support the reliability of data originated in the region as well as the comparison of data across countries. This EQA program is unique for developing countries.[6]

The rationale concerning blood cultures, the treatment of patients with antibiotics before taking samples and the characteristics of each national laboratory network are different. Therefore the proportion of clinical diagnosis varied between countries, with pneumonia predominating in 5 countries, meningitis in 4, and bacteremia in 1. Similar trends were observed in 6 countries participating in the surveillance during 1994–1999.[2] The number of bacteremia cases reported in Chile can be explained by the rationale concerning blood cultures prevalent in Chile.[15]

Although even 61 different capsular types were identified during the 6-year surveillance of the 10 countries; 13 serotypes accounted for 86.3% of the isolates, and these were consistently the most prevalent serotypes throughout the study period. Serotype 14 was the most important pediatric serotype worldwide in 8 of the 10 countries. Moreover, an increase observed in Brazil, Colombia, and Chile may be of special concern because of its association with DSP, and the spread of a resistant clone Spain 9V ST156 variant 14. This clone has been described in 8 countries Argentina, Chile Colombia, Mexico, Uruguay, and Brazil,[3] Dominican Republic and Paraguay (J. Sánchez and G. Chamorro, personal communication). The success of this clone with different variant serotypes as 14, 6B, and 9A between others has been well documented.[16,17]

Statistically significant changes in frequency were seen only with serotypes 6B, 1, 5 23F, and 4, but these changes did not affect the final data. Recent reports emphasize the short-term variations in serotype prevalence, especially serotypes 1 and 5, even sometimes showing a cyclical pattern.[13] This epidemiologic situation was observed for serotype 1 simultaneously in Argentina, Chile, Colombia, and Uruguay, with 2 peaks at the beginning and at the end of the study period. The same situation also happened with serotype 5 in Uruguay.

Overall, 4 capsular types accounted for 63.5% of pneumonia isolates, as did 6 capsular types for meningitis and 7 for other invasive diseases; serotype 14 was the primary cause in all 3 categories. A stronger association was observed for serotypes 14, 1, 19A, and 3 with pneumonias and for serotypes 6B, 18C, 19F, and 23F with meningitis. Several studies have explored the invasiveness of pneumococci and it has been found that it varies according to the capsular type.[18,19]

Diminished susceptibility was detected in 37.8% of *S. pneumoniae* isolates, with the highest prevalence in Dominican Republic and Mexico. During the observation period an increase in resistance was observed in Brazil[20] and Colombia. The only country in which a decrease in high-level resistance is observed was Chile. This change could have been the result of a strict control over the use of antimicrobials in the community since September 1999.[21] Differences in penicillin susceptibilities between countries in the same continent have also been reported in Europe.[22] In general, total resistance in pneumonia, sepsis, and bacteremia cases was higher than in meningitis cases. Meanwhile, third-generation cephalosporins remain a treatment option for meningitis for Latin American countries since only 14.3% of isolates were resistant.

According to the new breakpoints established by CLSI for *S. pneumoniae* recovered from respiratory disease,[11] the susceptibility to penicillin in the region is 95.1%, which represents an excellent option to treat this pathology. These data are essential for the establishment of evidence-based guidelines for the treatment of pneumococcal invasive disease.

Penicillin resistance is associated with a few capsular types.[2,3,22–25] Among the isolates from the 10 countries, serotypes 14, 23F, 19A, 6B, and 19F were the most frequent types showing DSP. Similar trends have been observed in the previous surveillance.[2] Capsular type 19A is becoming highly significant in the United States after using heptavalent conjugate vaccine as the leading replacement type.[26–29] In our data, the frequency of capsular type 19A varies from 5.9% in Venezuela, 5.8% in Mexico to 0.9% in Colombia, although 55.7% of pneumococci capsular type 19A have DSP (48.0% intermediate level and 7.7% high level resistance).

Our data show that the percentage of capsular types included in the heptavalent vaccine circulating in Latin American countries varies from 52.4% in Uruguay to 76.5% in the Dominican Republic. This situation is similar to the one observed in Africa and Thailand[12,30] and emphasizes the need to developed vaccines that will be effective against serotypes predominant in the target population. To support this fact, a conjugated vaccine with 9 capsular types including serotypes 1 and 5 has proved to be effective in The Gambia.[31] During 2010 a new 10-valent conjugate vaccine with additional serotypes 1, 5, and 7F is expected to be available. The percentage of capsular types represented in our

countries will range from 76.7% in Chile to 88.3% in Cuba. This increment is mainly consequence of the addition of serotypes 5 and 1, ranking third and fourth in frequency in our data. The 13-valent conjugate vaccine, by the addition of serotypes 3, 6A, and 19A, would increase even more the percentage of serotypes represented.

The pneumococcal population worldwide is now being subject to a selective pressure of a highly immunogenic heptavalent conjugate vaccine.[23] One of the results of this pressure has been the replacement phenomena, well documented for serotype 19A.[32–36] We also have to remember the restriction imposed by the high cost of the pneumococcal conjugate vaccines. In 1 study carried out in Colombia it was concluded that vaccination could be a less cost-effective intervention than improving children's nutrition (Fernando de la Hoz, personal communication).

Information about the burden of disease is crucial to making decisions and evaluating the impact of vaccination. Active surveillance studies have been taken place recently in Argentina,[37] Brazil,[38] and Uruguay.[39]

The Region now has reliable and quality data regarding the *S. pneumoniae* capsular types, which have caused invasive disease in children less than 6 years old as well as information about their susceptibility to beta lactam antibiotics.[40] This information is of paramount importance to healthcare decision makers to enable them to prioritize public health interventions coupled with the post intervention surveillance data to evaluate their impact. Alongside the data generated, all from reference laboratories in the region have been strengthening their ability to conduct and lead national and international research activities.

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