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Penicillin and Macrolide Resistance Trends among *Streptococcus pneumoniae* Isolated in Latin America between 1998 and 2002: Report of SENTRY Antimicrobial Surveillance Program

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AMENDED ABSTRACT

Background: The importance of penicillin (PEN) and macrolide-resistant strains of *Streptococcus pneumoniae* (SPN) is recognized worldwide.
Methods: To detect increased resistance trends, a total of 1,606 SPN isolates were collected from distinct infectious sites in Latin American medical centers during 5 year-period of SENTRY Program (1998-2002). The isolates were susceptibility tested by reference broth microdilution methods according to NCCLS. Susceptibility (S) rates were calculated for PEN, erythromycin (ERY), and clindamycin (CL) yearly. Trend of S rates was ascertained for each compound by chi-square and/or chi-square for trend test.
Results: The number of SPN isolates tested and the percentage of S according to the antimicrobial agent, and the year of isolation can be observed below.

	Year (No. of isolates) % S				
Antimicrobial agent	1998 (312)	1999 (438)	2000 (270)	2001 (300)	2002 (286)
Penicillin	74.4	72.8	73.0	73.7	75.9
Erythromycin	85.6	88.8	86.7	84.3	87.1
Clindamycin	93.3	96.8	94.4	93.0	96.8[b]
PEN -S[a]	74.4	72.8	73.0	73.7	75.9
Erythromycin	93.1	94.4	88.3	89.1	91.2
Clindamycin	97.8	98.1	95.9	94.6	98.2
PEN -I[a]	15.7	13.7	15.2	13.0	13.3
Erythromycin	59.2	78.3	90.2	84.6	86.8[b]
Clindamycin	73.5	91.7	95.1	92.3	91.9[b]
PEN -R[a]	9.9	13.5	11.8	13.3	10.8
Erythromycin	71.0	69.5	71.9	57.5	58.1
Clindamycin	90.3	94.9	87.5	85.0	93.5

a. PEN -S, PEN susceptible; PEN -I, PEN intermediate; and PEN -R, PEN resistant.
b. $p < 0.05$

Conclusions: The rates of PEN-I and PEN-R remained stable during the period. The overall S rate to CL increased during the period mainly among PEN-I strains ($p<0.05$). In this category of isolates, ERY S rates also increased ($p<0.05$). Although the ERY percentage of resistance increased over the years among PEN-R SPN, this difference was not statistically significant.

INTRODUCTION

Streptococcus pneumoniae is a major bacterial pathogen causing respiratory tract infections, bacteremia, and meningitis especially in children and in the elderly. The emergence of antimicrobial resistance in this pathogen is a matter of major concern. Since penicillin resistance in *S. pneumoniae* was first reported in the mid-1960s, increasing resistance to this compound, and other antimicrobial agents, has been reported worldwide. Therefore, it is extremely important to understand the local epidemiology of *S. pneumoniae* in specific geographic settings, especially in developing countries, where invasive pneumococcal disease has a major impact among children. In this study we present data and assess trends on antimicrobial resistance among pneumococcal isolates from Latin American countries participating in the SENTRY Program.

METHODS

Study Design. The SENTRY Antimicrobial Surveillance Program monitors antimicrobial resistance patterns of predominant pathogens causing nosocomial and community-acquired infections through sentinel medical centers worldwide. In Latin America, participant laboratories were distributed throughout seven countries: Argentina, Brazil, Chile, Colombia, Mexico, Uruguay and Venezuela. The monitored pneumococcal infections included mainly community-acquired respiratory tract infections and bacteremia.

Bacterial Isolates. A total of 1,606 *S. pneumoniae* bacterial isolates were analyzed in this study. Only one isolate per patient was included in the analysis. The isolate was determined to be clinically significant based on the conclusions of the local physician. Isolates were acceptable from the lower respiratory tract (LRT) when isolated from high-quality sputum, tracheal aspirate, pleural fluid or bronchoalveolar lavage, and from the upper respiratory tract (URT) when isolated from nasopharyngeal aspirates, middle ear and sinus fluids. The isolates were identified at the participating institutions by the routine methodology in use at each laboratory. Upon receipt at the coordinating center (JMI Laboratories, North Liberty, Iowa), isolates were subcultured onto blood agar to ensure viability and purity. Confirmation of species identification was performed with Vitek (bioMerieux Vitek, Saint Louis, MO) or conventional methods, as required.

Antimicrobial Susceptibility. Antimicrobial susceptibility testing was performed using the reference broth microdilution method as described by the National Committee for Clinical Laboratory Standards. Antimicrobial agents were obtained from the respective manufacturers. Quality control was performed by testing *S. pneumoniae* ATCC 49619, *S. aureus* ATCC 29213, *E. faecalis* ATCC 29212, among other control strains. Comparisons of antimicrobial resistance rates between the years 1998 and 2002 were evaluated by chi-square test.

COMMENTS

- Similar to results from other surveillance programs performed in Latin America, the highest susceptibility rate to penicillin was recorded in Brazil (82.1%). Penicillin susceptibility results for other Latin American countries were also similar to those previously reported by other surveillance programs, ranging from 77.1% in Argentina to 48.3% in Mexico (Table 1).
- Only 13.3% of *S. pneumoniae* isolates overall showed erythromycin resistance (Table 1), and among those, 36.9% showed clindamycin co-resistance.
- Penicillin-resistance was generally higher among isolates from lower respiratory tract infections (15.2%) when compared to isolates from either upper respiratory tract (11.7%) or bloodstream infections (11.3%; Table 2).
- Overall, penicillin-non-susceptible isolates were more frequently isolated from bloodstream infections in children under five years of age.
- Although susceptibility rates for penicillin and erythromycin did not vary significantly during the study period (1998-2002), the overall clindamycin susceptibility rates increased from 93.3% in 1998 to 96.8% in 2002 ($p<0.05$). The increase was more noticable among penicillin-intermediate isolates (from 73.5 to 91.9%, $p<0.001$) (Table 3).
- There were also dramatic increases in the susceptibility to erythromycin among penicillin-intermediate strains in 2002 compared to 1998 (59.2% vs. 86.8%, $p<0.001$) (Table 3).
- The analysis of the changes occurring when the data was stratified according to age groups showed an overall tendency for susceptibility rates to increase among isolates in children and the elderly ($\geq$ 50 years of age; Table 4).
- The decrease in resistance rates to penicillin and clindamycin among isolates from these two groups (children and elderly) may be the result of the widespread use of pneumococcal vaccines since it covers the serotypes related to multi-drug resistance.

Table 1: In vitro antimicrobial susceptibility of *Streptococcus pneumoniae* isolated in Latin American medical centers – SENTRY Program Latin America, 1998-2002.

Country/antimicrobial agents	Cumulative % inhibited at (µg/mL) ≤0.06	0.12	0.25	0.5	1	2	4	8	MIC_{50}	MIC_{90}	% susc.[a]
Argentina (n=389)								[b]			
Penicillin	77.1	79.4	84.1	86.1	90.5	99.0	100.0	-	≤0.06	1	77.1
Erythromycin	-	-	86.4	87.7	89.5	91.3	92.8	93.1	≤0.25	2	86.4
Clindamycin	-	-	93.1	93.6	93.6	93.6	95.1	95.4	≤0.25	≤0.25	93.1
Brazil (n=413)											
Penicillin	82.1	87.0	91.4	93.1	94.1	99.6	99.8	-	≤0.06	0.25	82.1
Erythromycin	-	-	89.2	90.8	93.3	94.3	95.1	96.9	≤0.25	0.5	89.2
Clindamycin	-	-	95.7	95.9	96.1	96.1	97.3	97.8	≤0.25	≤0.25	95.7
Chile (n=579)											
Penicillin	66.1	71.8	77.4	78.9	80.3	88.6	99.3	-	≤0.06	4	66.1
Erythromycin	-	-	86.5	86.9	87.0	87.7	91.4	96.5	≤0.25	4	86.5
Clindamycin	-	-	96.9	96.9	97.1	97.1	97.8	97.9	≤0.25	≤0.25	96.9
Colombia (n=66)											
Penicillin	69.7	78.8	84.8	86.4	89.4	97.0	100.0	-	≤0.06	1	69.7
Erythromycin	-	-	86.4	87.9	89.4	92.4	92.4	92.4	≤0.25	2	86.4
Clindamycin	-	-	93.9	93.9	93.9	93.9	98.5	98.5	≤0.25	≤0.25	93.9
Mexico (n=29)											
Penicillin	48.3	51.7	65.5	75.9	82.8	100.0	100.0	-	0.12	2	48.3
Erythromycin	-	-	69.0	72.4	75.9	86.2	86.2	86.2	≤0.25	>8	69.0
Clindamycin	-	-	86.2	86.2	86.2	86.2	86.2	86.2	≤0.25	>8	86.2
Venezuela (n=52)											
Penicillin	76.9	84.6	90.4	92.3	98.1	100.0	100.0	-	≤0.06	0.25	76.9
Erythromycin	-	-	76.9	76.9	80.8	82.7	86.5	86.5	≤0.25	>8	76.9
Clindamycin	-	-	90.4	90.4	90.4	90.4	94.2	96.2	≤0.25	≤0.25	90.4
Total (n=1,606)											
Penicillin	73.8	78.6	83.5	85.7	88.0	95.4	99.7	-	≤0.06	2	73.8
Erythromycin	-	-	86.7	87.7	89.2	90.6	92.7	95.1	≤0.25	2	86.7
Clindamycin	-	-	95.1	95.3	95.4	95.4	96.7	97.0	≤0.25	≤0.25	95.1

a. Interpreted by NCCLS 2003.
b. - = Dilution not tested.

Table 2: Percentages of penicillin-intermediate and -resistant isolates according to country and site of infection - SENTRY Program, Latin America, 1998-2002.

Country	% of isolates (no. tested) Blood	LRT[a]	URT[b]	Total
Argentina	(89)	(51)	(249)	(389)
PEN – I	6.7	13.7	15.7	13.4
PEN - R	10.1	13.7	8.4	9.5
Brazil[c]	(75)	(25)	(390)	(491)
PEN – I	6.7	12.0	13.1	12.0
PEN - R	2.7	8.0	6.4	5.9
Chile[d]	(180)	(101)	(293)	(579)
PEN – I	18.9	5.9	13.7	14.2
PEN - R	16.7	18.8	21.8	19.7
Colombia	(33)	(6)	(27)	(66)
PEN – I	9.1	50.0	25.9	19.7
PEN - R	6.1	0.0	18.5	10.6
Mexico	(2)	(0)	(27)	(29)
PEN – I	50.0	-	33.3	34.5
PEN - R	50.0	-	14.8	17.2
Venezuela	(9)	(0)	(42)	(52)
PEN – I	22.2	-	21.4	21.2
PEN - R	0.0	-	2.4	1.9
Total	(338)	(184)	(1,028)	(1,606)
PEN – I	13.1	10.3	15.1	14.1
PEN - R	11.3	15.2	11.7	12.0

a. LRT, lower respiratory tract.
b. URT, upper respiratory tract.
c. The site of infection could not be identified for one isolate.
d. The site of infection could not be identified for five isolates.

Table 3: Yearly antimicrobial susceptibility of *S. pneumoniae* isolates to erythromycin and clindamycin according to their susceptibility to penicillin - SENTRY Program, Latin America, 1998-2002.

Antimicrobial agent	% susceptible strains 1998 (312)	1999 (438)	2000 (270)	2001 (300)	2002 (286)
Penicillin	74.4	72.8	73.0	73.7	75.9
Erythromycin	85.6	88.8	86.7	84.3	87.1
Clindamycin	93.3	96.8	94.4	93.0	96.8[b]
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Erythromycin	71.0	69.5	71.9	57.5	58.1
Clindamycin	90.3	94.9	87.5	85.0	93.5

a. PEN -S, penicillin-susceptible; PEN -I, pencillin-intermediate; and PEN -R, pencillin-resistant.
b. $p < 0.05$.

Table 4: Yearly variation of resistance rates stratified according to age group - SENTRY Program, Latin America, 1998-2002.

Age group/resistance phenotype	1998	1999	2000	2001	2002
0 - 5					
Penicillin-intermediate	0.0	22.1	26.2	19.5	15.3
Penicillin-resistant	20.0	17.8	14.3	14.6	17.3
Erythromycin-resistant	33.3	4.4	14.3	23.2	17.3
Clindamycin-resistant	13.4	0.0	2.4	8.5	1.9
6 - 49					
Penicillin-intermediate	9.1	0.0	9.0	6.6	11.2
Penicillin-resistant	4.5	8.0	6.0	10.9	9.5
Erythromycin-resistant	4.5	4.0	9.0	13.1	4.8
Clindamycin-resistant	0.0	2.0	0.0	7.6	0.0
≥ 50					
Penicillin-intermediate	12.5	15.6	9.1	10.2	11.5
Penicillin-resistant	0.0	14.3	18.2	14.7	4.9
Erythromycin-resistant	6.3	11.9	9.1	10.3	9.0
Clindamycin-resistant	6.3	3.6	4.6	5.1	4.1

CONCLUSIONS

- Penicillin resistance in *S. pneumoniae* continues to be a problem in Latin America, and seems to be clustered in specific age groups and geographic regions.
- Longitudinal antimicrobial surveillance programs can be valuable in guiding empiric therapy and in formulating conclusions about the changing values of therapeutic or preventative interventions on antimicrobial resistance rates.

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