

C2-926

ICAAC 2003
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Recent Declines in β -Lactam and MLS_B Resistances Among *S. pneumoniae* and Age-Related Effects: Report from the SENTRY Antimicrobial Surveillance Program (North America, 1997 - 2002)



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AMENDED ABSTRACT

Background: The SENTRY Program has monitored emerging resistance (R) in *S. pneumoniae* (SPN) since 1997. Consistent increases in penicillin (PEN), erythromycin (ER) and clindamycin (CC) R have been documented each year, however year 2002 results indicate a shift to greater susceptibility (S). Details of this change were analyzed to determine patient populations and other demographics contributing to these reductions in R.

Methods: Among 16,489 community-acquired respiratory tract (CARTI) pathogens processed from North America (NA) (1997 - 2002), a total of 6,562 SPN (1001 - 1201/year from > 30 sites) were tested by reference broth microdilution method against 27 - 32 drugs/year. All tests were interpreted by NCCLS criteria (2003) for S, R and intermediate (I). SPN was recovered from 38 - 42% of CARTI samples, similar to that of *H. influenzae* (39 - 42%) and 2-fold greater than *M. catarrhalis* (18 - 22%) that remained unchanged over the six year period.

Results: The results follow in the table:

Year	% by category				
	PEN (I + R)	PEN (R)	ER (I + R)	CC (I + R)	M-phenotype
1997	26.6	14.8	13.8	4.2	69.6
1998	30.9	15.0	19.6	6.3	68.1
1999	32.8	14.9	24.7	7.7	68.8
2000	34.1	18.7	27.0	8.7	67.8
2001	36.3	21.9	30.3	10.0	67.0
2002	30.5	16.7	26.1	7.7	70.5

The extreme age groups (0-5 and \geq 65 years) showed the greatest reduction in R to PEN, ER and CC with minimal change occurring in isolates from those 6-64 years.

Conclusions: The increase in PEN S was mainly associated with a decrease in the occurrence of isolates with high level R (MIC, \geq 2 μ g/ml). The net increase in S to macrolides and lincosamides was due to a simultaneous reduction in the MLS_B phenotype (ER- and CC-R) and a lesser magnitude increase in the M-phenotype (ER-R and CC-S). The potential impact of vaccine usage and prescription discipline on changes to the susceptibility pattern of SPN in NA should be further investigated.

INTRODUCTION

Penicillin resistance among *S. pneumoniae* has increased continuously in the USA in the last decade. Additionally, penicillin-resistant strains have become increasingly more resistant to other antimicrobial agents. Rates may vary according to the geographic region and in some areas more than one-third of *S. pneumoniae* isolates have resistance to penicillin. Resistance rates may also vary according to patient age group, the higher rates have usually been found in children and in the elderly. The continuous increase in the resistance rates among pneumococci has been attributed to several factors, mainly the dissemination of resistant clones and local or national patterns of antimicrobial use. Moreover, the influence of the increasing use of the pneumococcal conjugate vaccine on the pneumococcal resistance rates has not been fully evaluated. Since the vaccine has shown to be highly effective against invasive disease in young children and elderly people, and the serotypes included in the 7- or 23-valent vaccines account for most penicillin-resistant or multi-resistant clones causing infection in the USA, we may expect a reduction in resistant pneumococci as the vaccine becomes widely used.

The objective of this presented study was to evaluate the contemporary in vitro activity and spectrum for leading orally administered antimicrobials available for the treatment of community-acquired respiratory tract infections (CARTI) caused by *S. pneumoniae* as a component of the SENTRY Antimicrobial Surveillance Program. In addition, we evaluated the current resistance trends based on the annual results obtained from 1997 to 2002 and the influence of patient age on *S. pneumoniae* susceptibility patterns during the monitored 6-year period (16,489 isolates).

MATERIALS AND METHODS

Bacterial isolate collection. A total of 16,489 contemporary CARTI isolates were gathered from > 40 medical centers (approximately 35/year) in North America during 1997 to 2002. Isolates were identified by the originating laboratories and pure cultures were then forwarded in a semisolid transport medium containing charcoal to a central monitoring site (JMI Laboratories, North Liberty, IA). Upon arrival, isolates were subcultured onto appropriate media to ensure viability and purity, and incubated in a 3 - 5% CO₂ environment. *S. pneumoniae* isolates were identified by examination of typical colonial characteristics and use of the bile (2% sodium desoxycholate) solubility test.

Determination of MICs. Susceptibility testing utilizing the National Committee for Clinical Laboratory Standards (NCCLS) reference broth microdilution method was performed with a battery of broad-spectrum antimicrobial agents (27 - 32 drug/year): penicillin, amoxicillin/clavulanic, numerous oral cephalosporins, macrolides, ampicillin, clindamycin, ciprofloxacin and levofloxacin will be presented here. Colonies from fresh (< 24 hours) subcultures were used to

MATERIALS AND METHODS (Continued)

prepare a suspension equal to a 0.5 MacFarland turbidity standard. Using an autoinoculator, 100 μ l of the inoculum suspension was diluted in an appropriate broth for delivery of 5 x 10⁶ CFU/well. Cation-adjusted Mueller-Hinton broth with lysed horse blood for *S. pneumoniae* was dispensed into the wells of validated panels (TREK Diagnostics, Cleveland, Ohio, USA). Panels were incubated in ambient air for 20 - 24 hours. MIC endpoints were determined as a lack of visible growth as outlined in the NCCLS approved standard. Interpretive criteria used were those of NCCLS M100-S13. Daily quality control was performed by the routine testing of ATCC strains including *S. pneumoniae* ATCC 49619.

Impact of age on susceptibility profiles. Demographic information obtained with each isolate was grouped by subset analysis into three age classes (0 - 5 years, 6 - 64 years and \geq 65 years) and compared with trends in antimicrobial susceptibility patterns, specifically examining results for β -lactam and macrolide agents during each of the last three years under study.

RESULTS

- S. pneumoniae* was isolated from 38 - 42% of community-acquired respiratory tract infections, varying by year (p >0.05). The rates of occurrence for *H. influenzae* and *M. catarrhalis* were 39 - 42% and 18 - 22%, respectively.
- Resistance rates among *H. influenzae* and *M. catarrhalis* CARTI isolates remained stable over the last six respiratory disease seasons. Ampicillin-resistant (β -lactamase-positive) *H. influenzae* averaged 29%, slightly less in the last three years. β -lactamase production by *M. catarrhalis* isolates consistently exceeded 95% of strains (Table 1).
- A consistent trend toward increasing resistance in *S. pneumoniae* to β -lactams and MLS_B agents was observed from 1999 through 2001 (Figure 1). However, in 2002 the non-susceptible rates for penicillin and erythromycin decreased 5.8 and 4.3%, respectively. In contrast, levofloxacin resistance increased from 0.9 in 2000 to 1.4% in 2002 (Table 1).

- The other β -lactams (oral agents amoxicillin/clavulanate, cefdinir, cefuroxime axetil) also showed improved spectrums versus *S. pneumoniae* in 2002 (Table 1).

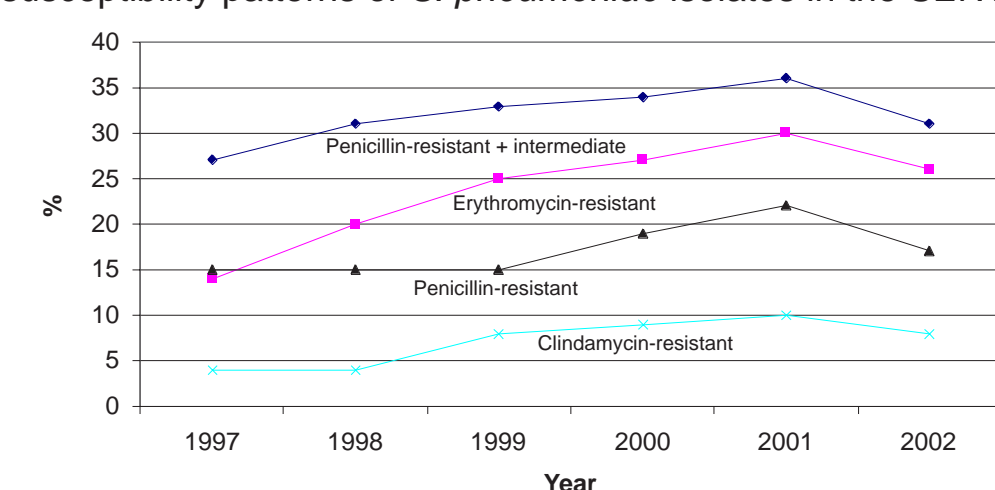
- Age group related changes in resistance for 2002 were most evident in the young (0 - 5 years) and the elderly (\geq 65 years) with susceptibility increases for β -lactams. Macrolides showed a decrease in susceptibility for the young children (-2.1% for erythromycin) compared to favorable increases in susceptibility for the isolates from adult patients (Table 2).

- Table 3 shows the resistance variation among 2001 and 2002 pneumococcal isolates by age and level of penicillin susceptibility. The greatest decrease in resistance occurred among the elderly patient isolates and the proportion of high-level resistant strains (penicillin MIC, \geq 2 μ g/ml).

- Changes in 2002 for MLS_B resistance phenotypes indicated an increase in *mef* A, efflux M-phenotypes in the children (60.9 to 67.4%) and in the elderly (69.2 to 74.3%), see Table 4.

- These changes in resistance appear to correspond to literature cited expansion of the use of pneumococcal vaccines in the most effected populations of patients illustrated in this report (0 - 5 and \geq 65 years).

Figure 1: Trends in the susceptibility patterns of *S. pneumoniae* isolates in the SENTRY Program (1997 - 2002).



RESULTS

Table 1. Activity and susceptibility rates for 6-7 selected antimicrobial agents against *H. influenzae*, *M. catarrhalis*, and *S. pneumoniae* in the SENTRY Program-North America (2000-2002).

Organism/Antimicrobial	2000 ^a		2001 ^a		2002 ^a	
	MIC ₅₀ /MIC ₉₀	%S/R	MIC ₅₀ /MIC ₉₀	%S/R	MIC ₅₀ /MIC ₉₀	%S/R
<i>H. influenzae</i> (no. of isolates)	(1,198)		(1,077)		(1,163)	
Ampicillin	\leq 0.5/>4	72.5/26.5	\leq 0.5/>4	75.2/24.0	\leq 0.5/>4	73.2/25.9
Cefdinir	0.25/0.5	99.0/ ^b	0.25/1	97.1/-	0.25/1	98.8/-
Cefuroxime axetil	1/2	99.0/0.0	1/4	97.8/0.3	1/2	99.5/0.1
Amoxicillin/clavulanate	0.5/1	100.0/0.0	0.5/1	99.7/0.3	0.5/1	100.0/0.0
Clarithromycin	8/16	85.3/1.2	8/16	84.0/2.6	8/16	83.5/2.2
Ciprofloxacin	\leq 0.015/ \leq 0.015	99.9/-	\leq 0.03/ \leq 0.03	100.0/-	\leq 0.03/ \leq 0.03	100.0/-
<i>M. catarrhalis</i> (no. of isolates)	(525)		(589)		(574)	
Penicillin ^c	>4/>4	4.4/95.6	>4/>4	4.6/95.4	>4/>4	4.7/95.3
Cefdinir	0.12/0.25	100.0/-	0.12/0.25	100.0/-	0.12/0.25	100.0/-
Cefuroxime axetil	1/2	99.6/0.0	1/2	99.8/0.0	1/2	99.5/0.0
Amoxicillin/clavulanate	\leq 0.25/ \leq 0.25	100.0/0.0	0.12/0.25	100.0/0.0	0.12/0.25	100.0/0.0
Clarithromycin	\leq 0.25/ \leq 0.25	100.0/0.0	\leq 0.25/ \leq 0.25	100.0/0.0	\leq 0.25/ \leq 0.25	100.0/0.0
Ciprofloxacin	0.03/0.03	100.0/-	\leq 0.03/0.06	100.0/-	\leq 0.03/0.06	100.0/-
<i>S. pneumoniae</i> (no. of isolates)	(1,101)		(1,001)		(1,098)	
Penicillin	\leq 0.03/2	65.9/18.7	\leq 0.03/2	63.7/21.9	\leq 0.03/2	69.5/16.7
Cefdinir	0.12/>4	71.8/25.7	0.12/>4	71.4/25.6	0.06/4	78.5/20.5
Cefuroxime axetil	\leq 0.06/8	72.9/23.2	\leq 0.06/8	72.3/24.2	\leq 0.06/4	78.6/19.1
Amoxicillin/clavulanate	\leq 0.25/2	92.9/3.1	\leq 0.06/2	92.4/3.9	\leq 0.06/2	94.1/3.4
Erythromycin	\leq 0.25/4	73.0/26.2	\leq 0.25/16	69.7/29.4	\leq 0.25/8	74.0/24.7
Clindamycin	\leq 0.25/ \leq 0.25	91.3/8.1	\leq 0.12/0.25	90.0/9.6	\leq 0.06/ \leq 0.06	92.3/7.3
Ciprofloxacin ^d	1/2	(3.6)	1/2	(3.9)	1/2	(3.2)
Levofloxacin	1/1	99.0/0.9	1/1	99.1/0.9	1/1	98.5/1.4

a. MIC₅₀ and MIC₉₀ in μ g/ml at which 50 and 90% of the isolates, respectively, were inhibited. % S, percent of isolates susceptible and % R, percent of isolates resistant using NCCLS criteria.
b. Interpretive criteria not established by the NCCLS.
c. MIC $<$ 0.06 negative β -lactamase production; MIC $>$ 0.06 is positive for β -lactamase production.
d. Resistance rates in parenthesis are based on Chen et al. criteria (1999) at \geq 4 μ g/ml.

Table 2. Susceptibilities of select antimicrobials tested against *S. pneumoniae* isolates from North America (2001-2002) listed by patient age group.

Antimicrobial/ (Age group-years)	2001		2002		Net change in % susceptible rate
	No. of isolates	% Susceptible ^a	No. of isolates	% Susceptible ^a	
Cefdinir					
(0-5)	125	56.0	167	64.1	+8.1
(6-64)	578	75.4	614	80.9	+5.5
(\geq 65)	291	70.4	307	78.8	+8.4
Ceftriaxone					
(0-5)	125	88.0	167	94.0	+6.0
(6-64)	578	96.2	614	97.9	+1.7
(\geq 65)	291	94.8	307	98.9	+3.9
Penicillin					
(0-5)	125	48.8	167	55.1	+6.3
(6-64)	578	66.3	608	71.5	+6.2
(\geq 65)	291	65.3	307	73.6	+8.3
Erythromycin					
(0-5)	125	63.2	167	61.1	-2.1
(6-64)	578	71.1	612	77.5	+6.4
(\geq 65)	291	69.8	307	73.9	+4.1
Clindamycin					
(0-5)	125	85.6	167	87.3	+1.7
(6-64)	578	90.5	604	93.0	+2.5
(\geq 65)	291	90.7	307	93.3	+2.6

a. Criteria for susceptibility applied from NCCLS tables.

Table 3. Change in the rate of penicillin resistance among *S. pneumoniae* isolates from North America (2001 to 2002) listed by patient age group.

Age group	% Intermediate			% Resistant		
	2001	2002	Variation	2001	2002	Variation
0-5	16.8	16.8	0.0	34.4	28.1	-6.3
6-64	15.2	14.7	-0.5	18.5	13.8	-4.7
\geq 65	11.7	10.4	-1.3	23.0	16.0	-7.0

Table 4. Change in macrolide resistance phenotype occurrence among *S. pneumoniae* isolates from North America (2001 to 2002) listed by patient age group.

Age group /Phenotype	% of resistance patterns by year	
	2001	2002
0-5 Years		
MLS _B ^a	39.1	32.6
M ^b	60.9	67.4
6-64 Years		
MLS _B ^a	32.9	31.1
M ^b	67.1	68.9
\geq 65 Years		
MLS _B ^a	30.8	25.7
M ^b	69.2	74.3

a. MLS_B resistance phenotype, representing resistance to macrolides, lincosamides, and streptogramin B agents. Conferred by methylation of a single adenine in the bacterial 50s ribosome (*erm* genes).
b. M-phenotype representing resistance to macrolides, but not clindamycin, which involves a macrolide efflux pump (*mef*).

CONCLUSIONS

- Resistance to penicillin and other β -lactams among *S. pneumoniae*, decreased in 2002 for the first time in the six-year interval driven by a reduction in high-level resistant isolates.
- Macrolide resistance decreased in 2002 via combined decreases in all MLS_B phenotypes, but showed a slight increase in the M-phenotype strains (69.6%).
- Reductions in resistance was greatest in age groups at the extremes of life, e.g. 0 - 5 and \geq 65 years.
- Resistance reductions appears to be related in time to pneumococcal vaccination success in the two targeted age groups.
- Further investigations are urged into the continued impact of vaccine usage and prescription discipline on pneumococcal resistance rates in CARTI and hospitalized patients with pneumonia.

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