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JMI Laboratories
North Liberty, IA, USA
www.jmilabs.com
319.665.3370
fax 319.665.3371
ronald-jones@jmilabs.com

Eight Year Summary of Community-Acquired *S. pneumoniae* Infections by the SENTRY Antimicrobial Surveillance Program (1997-2004): More Good News Than Bad!

RN JONES, DM JOHNSON, TR FRITSCHE, HS SADER, DJ BIEDENBACH
JMI Laboratories, North Liberty, IA, USA

SENTRY ANTIMICROBIAL SURVEILLANCE

AMENDED ABSTRACT

Background: For 8 consecutive years (1997-2004) the SENTRY Program has been monitoring community-acquired respiratory tract infections (CARTI) in >30 medical centers in North America (USA and Canada [CAN]). Changing patterns of resistance (R) and increased rates of multidrug-R (MDR) and fluoroquinolone-R (FQR) *S. pneumoniae* (SPN) have emerged and compromised the effectiveness of commonly used oral and parenteral antimicrobials.
Methods: 8,342 SPN isolates were tested by CLSI MIC methods against 25 - 31 antimicrobials over 8 years and 23 agents are reported here: penicillin (PEN), ceftriaxone (CTRI), erythromycin (ER), clindamycin (CM), tetracycline (TET) and trimethoprim/sulfamethoxazole (T/S) and seven comparator agents and 10 fluoroquinolones including ciprofloxacin (CIPRO), levofloxacin (LEVO) and gatifloxacin (GATI).
Results: Increased R was observed for most agents through 2001, followed by a significant decrease in 2002 likely due to moderation of drug-use and vaccine introduction. ER-R rates was higher than CM-R (*mef* pattern but decreasing from 71 to 58%). As CIPRO-R steadily increased then moderated; LEVO- and GATI-R (Canada > USA) remained stable as did FQR single-step QRDR mutations (CIPRO-R at ≥ 4 µg/ml) as confirmed by QRDR sequencing. Cefuroxime and cefpodoxime retained activity against PEN-I/R strains.

	% non-S							
Antimicrobial agent	1997	1998	1999	2000	2001	2002	2003	2004
PEN	27	31	33	34	36	30	33	38
CTRI	1	4	4	5	5	2	2	3
ER	14	20	25	27	30	26	29	31
CM	4	4	8	9	10	8	11	13
CIPRO[a]	1	1	2	4	4	3	5	2
LEVO	0.8	0.5	1	1	1	2	1	1
GATI	0.3	0.3	1	1	1	2	1	1
TET	11	13	18	18	19	15	18	15
T/S	25	29	33	35	35	31	31	33

a. MIC at ≥ 4 µg/ml.

Conclusions: Although a decline in MDR strains were observed in 2002, R rates increased in 2004 to the 2001 levels or greater for PEN, ER and CM. These results demonstrate the importance of comprehensive longitudinal surveillance programs in monitoring R as a guide to empiric CARTI therapy and epidemiologic interventions.

INTRODUCTION

S. pneumoniae is part of the normal flora of the nasopharyngeal tract and the leading cause of community-acquired respiratory tract infections (CARTI) including acute otitis media, pneumonia, sinusitis and acute exacerbations of chronic bronchitis. These CARTI account for the majority of clinic office visits and antimicrobial use in the United States. Over the last decade, an increase in resistant rates among *S. pneumoniae* to several classes of antimicrobial agents has occurred. Penicillin high-level resistance rates have increased to greater than 30% in some regions of the United States. Coinciding with the increase in penicillin resistance has been an increase in resistance to other classes of antimicrobial agents and the emergence of multidrug-resistant (MDR) *S. pneumoniae* has compromised the therapeutic effectiveness of commonly prescribed antibacterials. The increase and geographic variance in resistance rates has been associated with regional differences in antimicrobial usage and the spread of MDR clones. Recently (February 2000 in the United States, June 2001 in Canada), a heptavalent pneumococcal conjugate vaccine (PCV) was introduced. This PCV included the most common pneumococcal serotypes associated with invasive and antimicrobial non-susceptible infections in children. Studies have found that after only two years, the number of infections due to penicillin-non-susceptible strains has been significantly reduced.

The objective of this study was to analyze the current in vitro activity and spectrum of nine sentinel, orally-administered antimicrobials and 14 comparator agents available for treatment of CARTI caused by *S. pneumoniae* as a component of the SENTRY Antimicrobial Surveillance Program. In addition, we evaluated the current resistant trends based on the annual results obtained from 1997 to 2004.

MATERIALS AND METHODS

Bacterial isolate collection. A total of 8,342 contemporary *S. pneumoniae* CARTI isolates were collected from > 30 medical centers in North America during 1997 through 2004. Isolates were initially identified at the participating SENTRY Program laboratory site. Pure cultures were then transported on charcoal swabs to the central monitoring site (JMI Laboratories, North Liberty, IA). Upon arrival, to ensure purity and viability, the isolates were subcultured onto the appropriate media and incubated for 18 - 24 hours in 5% CO_2. After incubation, *S. pneumoniae* identification was determined based upon colony morphology and solubility to bile (2% sodium desoxycholate) or other procedures, as needed.

Determination of MIC values. Susceptibility testing was performed according to the reference broth microdilution method of the Clinical and Laboratory Standards Institute (CLSI, formerly National Committee for Clinical Laboratory Standards [NCCLS]). During the eight-year period, many broad-spectrum antimicrobial agents (25 - 31 drug/year) were analyzed for their activity; 23 of these are reported here. In brief, fresh colonies from an overnight subculture (< 24 hours) were suspended into 5 ml of cation-adjusted Mueller-Hinton broth to achieve a 0.5 McFarland turbidity standard suspension. 100 µl of this inoculum was pipetted into 10 ml of cation-adjusted Mueller-Hinton broth containing 3 - 5% lysed horse blood. 100 ml of this solution was then dispensed into validated dry-form panels (TREK Diagnostics, Cleveland, OH, USA) containing two-fold serial diluted antimicrobial agents for a target concentration of 5 x 10^5 CFU/ml. After incubation in ambient air for 20 - 24 hours, the panels were examined for visible growth to determine the MIC results. CLSI (2005) interpretive criteria was utilized in assigning susceptible/resistant breakpoints. Quality control (QC) of the panels was performed using the following organisms: *S. pneumoniae* ATCC 49619, *Haemophilus influenzae* ATCC 42947 and 49766, *Enterococcus faecalis* ATCC 29212, *Staphylococcus aureus* ATCC 29213, *Escherichia coli* ATCC 35218 and 25922, and *Pseudomonas aeruginosa* ATCC 27853. All QC results were within published CLSI limits.

RESULTS

- Most of the antimicrobial agents demonstrated an increase in non-susceptible rates through 2001, followed by a significant decrease in 2002 (Table 1).
- By 2004, resistance rates for penicillin, erythromycin and clindamycin were equal to or greater than those observed in 2001 (Table 1).
- Ceftriaxone (3% non-susceptible) was the most active among the ß-lactams and ß-lactam/inhibitor combinations tested, although cefepime had the lowest R rate (<1%); data not shown.
- Quinupristin/dalfopristin, rifampin and vancomycin were the most active agents by percentage susceptible results among the tested isolates.
- Erythromycin resistance rates were higher than clindamycin, the percentage of isolates demonstrating the *mefA* phenotype significantly decreased from 71 to 58% over the course of this surveillance. After the introduction of the pneumococcal conjugated vaccine, erythromycin-non-susceptible rates continued to rise, however, the presence of the *mefA* strains continues to decline (Figure 1).
- Among the fluoroquinolones that were tested for four or more years, the rank order of activity was: garenoxacin (0.2% non-susceptible) > gemifloxacin (0.6%) > gatifloxacin = levofloxacin = moxifloxacin (1.0%; Table 2).

Table 1. Antimicrobial activity of 13 selected agents tested against 8,342 strains of *S. pneumoniae* in the SENTRY Antimicrobial Surveillance Program (1997 - 2004).

	% I + R by year (no. tested)							
Antimicrobial	1997 (1,069)	1998 (1,093)	1999 (1,201)	2000 (1,100)	2001 (1,003)	2002 (1,098)	2003 (1,014)	2004 (764)
Penicillin	27/10[a]	31/14[a]	33/15[a]	34/19[a]	36/22[a]	30/17[a]	33/16[a]	38/19[a]
Amox/clav	5	3	3	7	8	6	6	10
Cefepime	2	2	2	3	4	3	3	5
Ceftriaxone	1	4	4	5	5	2	2	3
Cefuroxime	19	23	26	27	28	21	22	24
Erythromycin	14/13[a]	20/18[a]	25/24[a]	27/26[a]	30/24[a]	26/25[a]	29/28[a]	31/30[a]
Clindamycin	4	4	8	9	10	8	11	13
Quin/dalfo	0	0	0	0	0	0	0	0
Chloramphenicol	4	6	10	8	9	5	4	3
Rifampin	1	0	1	0	1	1	1	0
Tetracycline	11	13	18	81	19	15	18	15
Trim/sulfa	25	29	33	35	35	31	31	33
Vancomycin	0	0	0	0	0	0	0	0

a. % I + R/% R only.

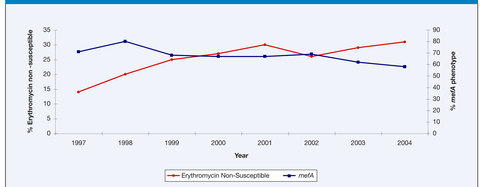
- During the latter years of the eight-year period, gatifloxacin- and levofloxacin-resistant rates remained stable, while ciprofloxacin resistance increased slightly until 2001 before declining. This shows a varying pattern of first-step mutants beginning in 2002 (Table 2).

Table 2. Antimicrobial activity of ten fluoroquinolones tested against 8,342 strains of *S. pneumoniae* in the SENTRY Antimicrobial Surveillance Program (1997 - 2004).

	% non-susceptible by year (no. tested)							
Antimicrobial (no. tested)	1997 (1,069)	1998 (1,093)	1999 (1,201)	2000 (1,100)	2001 (1,003)	2002 (1,098)	2003 (1,014)	2004 (764)
Ciprofloxacin (8,342)[a]	0.7	0.7	1.6	3.5	4.1	3.2	4.9	2.1
Garenoxacin (6,031)[b]	-	-	0.2	0.1	0.2	0.1	0.1	0.2
Gatifloxacin (8,342)	0.3	0.3	1.0	0.9	1.1	1.5	0.9	1.0
Gemifloxacin (3,026)	-	-	-	-	0.9	1.1	0.0	0.5
Grepafloxacin (1,093)	-	0.3	-	-	-	-	-	-
Levofloxacin (8,341)	0.8	0.5	1.1	0.9	1.1	1.5	1.1	1.0
Moxifloxacin (4,979)	-	-	-	0.9	1.0	1.3	0.8	0.9
Sitafloxacin (384)[b]	-	-	-	-	-	0.0	-	-
Sparfloxacin (1,453)	2.0	-	-	-	-	2.6	-	-
Trovafloxacin (3,363)	0.3	0.3	0.9	-	-	-	-	-

a. Resistance rates are based on Chen et al. criteria (1999) at ≥ 4 µg/ml.
b. Investigational fluoroquinolone. A breakpoint of ≤ 1 µg/ml as susceptible was used for comparison purposes only.

Figure 1: Relationship of macrolide resistance rates and frequency of occurrence of *mefA* phenotype of resistance in *S. pneumoniae* (USA).



CONCLUSIONS

- Although a decrease in the prevalence of MDR *S. pneumoniae* was observed in 2002, coinciding with the introduction of the pneumococcal vaccine, resistance rates for some agents have returned to 2001 levels or greater by 2004.
- Further studies are needed to analyze the breadth of the impact of the pneumococcal vaccine (i.e. serological evaluations of clinical isolates to detect any changes in the prevalence of clonal resistant serotypes) and prescription practice on the changing patterns of pneumococcal resistance.
- The continued monitoring of resistance rates to guide clinicians in empiric CARTI antimicrobial therapy that is provided by comprehensive longitudinal surveillance programs is imperative. The SENTRY Program will continue to provide these services.

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