A-033
ASM 2007
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Trends in Antimicrobial Resistance (R) Among USA Isolates of *S. pneumoniae* (SPN): A Decade of Experience from the SENTRY Antimicrobial Surveillance Program

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SENTRY ANTIMICROBIAL SURVEILLANCE

AMENDED ABSTRACT

Background: The SENTRY Program, the oldest continuously-active surveillance network, routinely monitors SPN isolated from community-acquired respiratory tract infections (CA-RTI; 1997-date). Changes in antimicrobial and vaccine use or other confounding variables have markedly altered SPN-R patterns in this stable USA sample base (30 sites; 12,259 isolates).

Methods: Since 1997 (10 years), SPN has been collected in a prevalence design. All susceptibility (S) tests were performed by CLSI broth microdilution methods against >25 antimicrobials/year; often including new investigational agents. R mechanisms were evaluated by PCR, gene sequencing and CLSI-recommended phenotypic tests. Serotyping was performed pre- and post-vaccine (VAC) introduction on 352 strains in both sampling groups.

Results:

	% R by commonly tested antimicrobials:[a]								
Year (no. tested)	PEN	3GC	CP	ER	CC	(CIP)	LEV	TET	T/S
1997 (1,363)	14.0	1.0	1.3	13.1	3.2	(1.5)	0.3	9.3	23.6
1998 (1,399)[b]	12.9	1.1	0.4	16.8	3.7	(2.2)	0.2	10.7	26.2
1999 (1,486)[b]	14.9	2.1	0.1	22.6	6.9	(1.5)	0.9	15.5	30.1
2000 (1,356)	17.3	1.8	0.1	24.9	7.3	(3.8)	0.6	16.4	29.1
2001 (1,126)	22.6	2.0	0.6	28.7	8.3	(2.7)	0.4	16.8	32.7
2002 (1,256)	16.7	1.7	0.4	24.7	7.1	(2.8)	1.3	13.3	26.1
2003 (1,009)[b]	16.3	1.3	0.5	27.0	9.6	(4.9)	0.6	15.3	26.4
2004 (1,026)[b]	17.8	0.9	0.8	28.8	10.1	(1.8)	0.8	15.7	25.9
2005 (1,206)	15.3	0.9	0.2	31.6	11.8	(3.0)	0.7	16.6	24.5
2006 (1,250)	15.2	1.0	0.2	32.3	15.4	(3.7)	0.6	19.9	20.9

a. PEN = penicillin; 3GC = ceftriaxone or cefotaxime (1997-1999); CP = cefepime; ER = erythromycin; CC = clindamycin; (CIP) = ciprofloxacin at ≥4 µg/ml; LEV = levofloxacin; TET = tetracycline; and T/S = trimethoprim/sulfamethoxazole.
b. Serotyped populations (704 strains).

The R patterns and rates have varied by drug: chloramphenicol (2.7-9.1% R), ceftriaxone (CTRI; 0.9-2.1% R), and CP (0.1-1.3% R) generally low and stable; and PEN, ERY, CC, TET and T/S-R increased from 1997 to 2001, then decreased but increased later. ER-R rose by 19.2% and CC-R by 12.2%, as did the MLS_B-R pattern (22.0-47.7%). LEV-R varied from 0.2-1.3%, highest in 2002. CIP-R (QRDR mutants) showed limited increases (1.5-4.9% overall). Post-VAC R rate changes were documented by decreased isolation of multi-R VAC serotypes (68 to 29%), with 19f persisting (21 to 18%) and a marked increase of 19 not f (3 to 20%).

Conclusions: Most SPN-R patterns persisted in this monitored decade of results; greatest for older ß-lactams, MLS_B class agents, TET and T/S. CP, 3GCs, new quinolones and selected parenteral agents (glycopeptides, oxazolidinones; data not shown) retained near complete S rates.

INTRODUCTION

The SENTRY Antimicrobial Surveillance Program has been a continuously-active global surveillance network from 1997 to present. Isolates of *Streptococcus pneumoniae* have been collected according to site of infection: primarily from community-acquired respiratory tract infections (CA-RTI), bacteremia, and pneumonia in hospitalized patients.

CA-RTI, including otitis media, acute bacterial sinusitis, acute exacerbations of chronic bronchitis and community acquired pneumonia, are the largest source of pneumococci. These infections occur mostly among the very young and elderly; and are a leading cause of morbidity, mortality and increased health care cost.

Antimicrobial resistance among SPN is a serious problem for both ß-lactams and macrolides. Changes in antimicrobial use, the use of the 7-valent pneumococcal conjugate vaccine (PCV7), or other confounding variables have markedly altered *S. pneumoniae* resistance patterns among the sample pneumococci found in the stable USA SENTRY Program population base.

We report here 10 years of *S. pneumoniae* pathogens isolated in USA medical centers. These include a subset of serotyped isolates monitored before and after the introduction of PCV7.

MATERIALS AND METHODS

During the time period of 1997-2006 (10 years), 12,477 *S. pneumoniae* were collected using the SENTRY platform from medical centers in the USA. Seventy-two percent of the total isolates were collected from upper and lower respiratory tract infections and the majority of the remaining isolates were derived from bloodstream infections or hospitalized pneumonia patients. Isolates were transported to the central laboratory (JMI Laboratories, North Liberty, IA, USA) where identifications were confirmed by colony morphology, solubility to bile (2% sodium desoxycholate) and/or other procedures as needed. Resistance mechanisms were evaluated by PCR, gene sequencing and CLSI-recommended phenotypic tests. All isolates were stored at -70ºC until processed.

Susceptibility testing was performed by reference broth microdilution methods using dry-form panels (TREK Diagnostics, Cleveland, OH) with >25 antimicrobial agents per year, often including new investigational agents. When indicated, confirmation of MIC results was performed using Etest (AB BIODISK, Solna, Sweden). Quality control was performed with the following organisms: *S. pneumoniae* ATCC 49619, *Haemophilus influenzae* ATCC 49247 and 49766, *Enterococcus faecalis* ATCC 29212, *Staphylococcus aureus* ATCC 29213, *Escherichia coli* ATCC 35218 and 25922 and *Pseudomonas aeruginosa* ATCC 27853. All methods and interpretive criteria were those published by CLSI (M7-A7, 2006 and M100-M17, 2007).

Serotyping was performed pre- and post-vaccine introduction (VAC) on a subset of 704 strains from children <6 years of age (85.1%) and adults (18->65 years; 14.9%) across 9 CDC census zones. The collection was divided into 352 pre-VAC (1998-1999) and 352 post-VAC (2003-2004). Serotyping was performed by the University of Iowa Hygienic Laboratory (Iowa City, IA, USA) using reagents obtained from Statens Serum Institute (Copenhagen, Denmark) via MiraVista Diagnostics (Indianapolis, IN, USA).

RESULTS

- After a marked decrease in resistance rates in 2002, most antimicrobial agents returned to previous rates of resistance occurrence through 2006 with some surpassing the 2001 peak (Table 1).
- Among the ß-lactams and ß-lactam/enzyme inhibitor combinations tested, ceftriaxone was the most active with resistance rates ranging from 0.9 to 2.1% and cefepime from 0.1 to 1.3% with 10 year net % resistance changes of 0.0 and -1.1, respectively (Table 1).
- Quinupristin/dalfopristin, vancomycin, and linezolid were the most active agents with nearly 100% susceptibility (data not shown).
- Erythromycin and clindamycin resistance has 10 year increases of 19.2 and 12.2%, respectively (Table 1). The prevalence of the ermB phenotype increased proportionately to macrolide resistance with a significant escalation in 2006 (Figure 1).
- Among fluoroquinolones, levofloxacin has demonstrated a stable resistance rate, changing only 0.3% over 10 years. There is evidence that QRDR mutations (ciprofloxacin MIC's ≥4 µg/ml; Chen et al, 1999) are increasing by 2.5% in 10 years monitored.
- The current CLSI *S. pneumoniae* resistance breakpoint for penicillin (≥2 µg/ml) suggests a gradual decrease in resistance from 2001 to 2006. However, the proposed non-meningitis CLSI breakpoints (S/I/R at 2/4/8 µg/ml) demonstrates an increasing trend at ≥4 µg/ml (non-susceptible) with minimal resistance (<1%) if this breakpoint becomes ≥8 µg/ml (Figure 2).

Table 1. Resistance Rates of common antimicrobials tested against *S. pneumoniae* from USA medical centers, SENTRY Program 1997-2006.

	% Resistant by year (total isolates)										
Antimicrobial agent (breakpoint)	1997 (1,363)	1998 (1,399)	1999 (1,486)	2000 (1,356)	2001 (1,126)	2002 (1,256)	2003 (1,009)	2004 (1,026)	2005 (1,206)	2006 (1,250)	10 Year Changes
Penicillin (≥2 µg/ml)	14.0	12.9	14.9	17.3	22.6	16.7	16.3	17.8	15.3	15.2	+1.2
Amoxacillin/clavulanate (≥8 µg/ml)	5.0	1.9	1.4	2.9	4.4	3.4	4.5	4.7	6.8	7.8	+28
Ceftriaxone (≥4 µg/ml)	1.0	1.1	2.1	1.8	2.0	1.7	1.3	0.9	0.9	1.0	0.0
Cefepime (≥4 µg/ml)	1.3	0.4	0.1	0.1	0.6	0.4	0.5	0.8	0.2	0.2	-1.1
Erythromycin (≥1 µg/ml)	13.1	16.8	22.6	24.9	28.7	24.7	27.0	28.8	31.6	32.3	+19.2
Clindamycin (≥1 µg/ml)	3.2	3.7	6.9	7.3	8.3	7.1	9.6	10.1	11.8	15.4	+12.2
Chloramphenicol (≥8 µg/ml)	4.2	5.5	9.1	8.2	8.2	4.5	3.2	2.7	4.0	-[a]	-0.2
Ciprofloxacin[b]	1.5	2.2	1.5	3.8	2.7	2.8	4.9	1.8	3.0	3.7	+2.5
Levofloxacin (≥8 µg/ml)	0.3	0.2	0.9	0.6	0.4	1.3	0.6	0.8	0.7	0.6	+0.3
Tetracycline (≥8 µg/ml)	9.3	10.7	15.5	16.4	16.8	13.3	15.3	15.7	16.6	19.9	+10.6
Trim/sulfa[c] (≥4/76 µg/ml)	23.6	26.2	30.1	29.1	32.7	26.1	26.4	25.9	24.5	20.9	-2.7

a. - = not tested.
b. Ciprofloxacin breakpoint at ≥4 µg/ml indicates possible QRDR mutations (Chen et al.,1999).
c. Trimethoprim/sulfamethoxazole.

- Pre- (1998-1999) and post-PCV7 (2003-2004) serotyping illustrates major changes in serotype frequency (Figure 3). The multi-drug resistant (MDR) vaccine serotype strain frequencies decreased 39.2% although 19F (the most prevalent of resistant serotypes) only decreased 3.1%. There was a marked increase in the non-vaccine serotype 19 not F of 17.4%, a serotype also associated with a MDR pattern.

Figure 1. Correlation of macrolide resistance rates and prevalence of the ermB phenotypes among 10 years of USA *S. pneumoniae*.

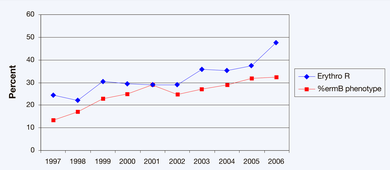


Figure 2. Comparison of current versus newly proposed CLSI penicillin breakpoints for *S. pneumoniae* (SENTRY Program USA 1997-2006).

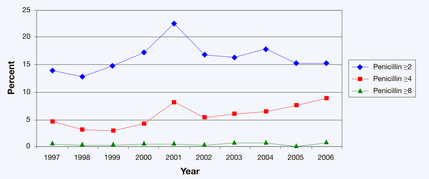
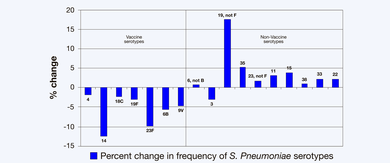


Figure 3. Percent change in *S. pneumoniae* serotype frequency of occurrence pre- and post-vaccine.



CONCLUSIONS

- Cefepime, ceftriaxone, and levofloxacin, as well as newer quinolones and selected parenteral agents (glycopeptides and oxazolidinones) remain viable options for treatment of pneumococcal infections in the USA. All retained near complete susceptibility rates.
- The most significant increases of resistance in the USA occurred among members of the MLS_B class of antimicrobial agents.
- Penicillin may return as a viable treatment option for *S. pneumoniae* if proposed CLSI non-meningitis breakpoints, (susceptible at ≤1 or ≤2 µg/ml) are adopted.
- The PCV7 vaccine had a significant effect on pneumococcal resistance rates in the USA as the frequency of vaccine serotypes were replaced by non-vaccine serotypes. Similar results have been noted from PROTEKT US. Despite the introduction of PCV7, resistance rates persist for older ß-lactams, MLS_B class agents, tetracyclines, and trimethoprim/sulfamethoxazole.
- Continued surveillance will be important to monitor the continuously changing resistance rates and to adjust treatment guidelines for this frequently occurring, often empirically treated pathogen.

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