

Recent Antimicrobial Resistance Increases among *S. pneumoniae* in Four Geographic Regions:  
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## Abstract

**Background:** Consistent trends toward greater resistance (R) rates for  $\beta$ -lactams and macrolides have been documented in *S. pneumoniae* (SPN) by several regional surveillance programs. We summarize R rates for 5 commonly used antimicrobial classes against 12,560 SPN isolated in USA, Europe (EU), Latin America and Asia Pacific (APAC) regions of a [global](#) program (2007-2009).

**Methods:** SPN were susceptibility (S) tested by CLSI broth microdilution methods in 2 monitoring reference laboratories against penicillin (PEN), amoxicillin/clavulanate (AC), ceftriaxone (CRO), cefepime (CPM), erythromycin (ERY), clindamycin (CC), levofloxacin (LEV) and ciprofloxacin (CIP); interpreted by M100-S20 (2010) breakpoint criteria. CIP MIC at  $\geq 4$   $\mu\text{g/ml}$  indicate QRDR mutational events. All isolates were from lower respiratory tract sources in 2007-2009.

**Results:** Year-to-year increasing R was noted. R averages across the 3 most recent years showed low  $\beta$ -lactam S, worst in APAC nations followed by USA (AC-R, 16.0%). No agent was  $>80\%$  active against SPN from APAC except LEV (98.0% s). In USA, CRO- and CPM-S was at 90% and PEN had a coverage (%S) range of only 60.2 (PEN oral-dose) to 86.4% (PEN high-dose). ERY (R range, 25.0-77.9%) and CC (6.5-59.0%) had limited in vitro potency with cMLS<sub>B</sub>-R at 27.6-75.7% (53.6% in USA). CIP-R results noted potential QRDR mutation rates of 2.8-5.3%, highest in EU (see [Table 1](#)).

**Conclusions:** Decreasing contemporary S (63.4-90.6%) among SPN markedly limits utility of recommended first-line CAP agents (CRO, AC, ERY) in USA; only fluoroquinolones show  $>95\%$  coverage. Alternative treatments are urgently needed as therapy for emerging multidrug-R SPN worldwide.

## Introduction

The SENTRY Antimicrobial Surveillance Program has been a continuously-active global resistance surveillance network for more than a decade. Isolates of *Streptococcus pneumoniae* have been collected stratified by 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 bacterial pneumonia (CABP), continue to be the largest source of pneumococcal isolates. These diseases occur commonly among the very young and elderly; and are the leading cause of infectious disease admissions leading to morbidity, mortality and increased health care cost.

Antimicrobial resistance among *S. pneumoniae* is a serious problem for numerous antimicrobial agents, but especially for the frequently utilized  $\beta$ -lactams and macrolides. Changes in antimicrobial use, the introduction of the 7-valent pneumococcal conjugate vaccine (PCV7), or other confounding variables have markedly altered *S. pneumoniae* resistance patterns among the sampled pneumococci tabulated in the stable SENTRY Program United States (USA) database. We report here the 12-year summary of *S. pneumoniae* pathogens isolated in USA medical centers. These results include two subset of serotyped isolates monitored before and after the PCV7 use and another 2008 sample. Also the results for the last three (3) surveillance years in four geographic regions (USA, Europe, Latin America, Asia-Pacific) were compared for susceptibility testing differences among commonly utilized antimicrobial agents.

## Methods

**Organism sampling.** During the time period of 1998-2009 (12 years), a total of 14,934 *S. pneumoniae* were collected using the SENTRY Program platform from medical centers across 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 bacteremias or hospitalized pneumonia patients. Because of consistent sampling methods, demographic (e.g. age distribution of patients) and clinical (e.g. ratio of bloodstream to respiratory specimen sources) parameters were similar across each of the 12 study years. Isolates were transported to the central reference laboratory (JMI Laboratories, North Liberty, Iowa, USA), where identifications were confirmed by colony morphology, solubility to bile (2% sodium desoxycholate) and/or other molecular procedures, as needed. Resistance mechanisms were evaluated by PCR, gene sequencing and Clinical and Laboratory Standards Institute (CLSI)-recommended phenotypic tests.

Similarly, the lower respiratory tract samples for 2007-2009 (8,560 strains) from the four monitored geographic regions were tested against key antimicrobials (8) commonly used for CABP or HABP. Presented results represent the total isolates tested over the 3-year sampling period.

**Susceptibility tests and serotyping.** Susceptibility testing was performed by reference CLSI (2009 and 2010) broth microdilution methods using panels produced by TREK Diagnostics (Cleveland, Ohio, USA) with more than 30 antimicrobial agents per year, often including new investigational agents. 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 interpretive criteria were those published by CLSI in M100-S20 (2010).

Serotyping was performed pre- and post-PCV7 introduction on a subset of 704 strains from children  $<6$  years of age (85.1%) and adults (18- $>65$  years; 14.9%) across nine CDC Census Regions. The collection was divided into 352 pre-PCV7 (1998-1999) and 352 post-PCV7 (2003-2004). Serotyping was performed by the University of Iowa Hygienic Laboratory (Iowa City, Iowa, USA) and Case Western Reserve University at University Hospitals Case Medical Center (M.R. Jacobs; Cleveland, Ohio, USA) for an additional subset of year 2008 isolates (Jacobs et al., 2010) using reagents obtained from Statens Serum Institute (Copenhagen, Denmark) and/or MiraVista Diagnostics (Indianapolis, Indiana, USA).

## Results

• Across all three years (2007-2009) in the inter-regional analysis, increasing resistance rates were noted for listed agents ([Table 1](#), year-to-year data not shown) and the highest  $\beta$ -lactam resistance rates were observed in the APAC Region followed by the USA.

• No agent was  $>80\%$  active versus *S. pneumoniae* in APAC except levofloxacin (98.0% susceptible). Macrolides (erythromycin) and clindamycin coverage was generally poor, ranging from 25.0-77.9% resistance and 6.5-59.0% resistance, respectively. The cMLS<sub>B</sub>-resistance phenotype varied from 27.6% (Latin America) to 75.7% (APAC), see [Table 1](#).

• Ciprofloxacin resistance ( $\geq 4$   $\mu\text{g/ml}$ ; Chen et al., criteria) indicates QRDR mutation rate of 2.8-5.3% for the 4 regions, highest in Europe ([Table 1](#)).

• For the USA ([Table 2](#)) isolates of *S. pneumoniae*,  $\beta$ -lactams showed decreasing susceptibility rates (1998-2001), and then an increase from 2002-2003 followed by a decline of 93.8 to 82.7%, 94.7 to 84.1% and 97.4 to 87.5% for amoxicillin/clavulanate, penicillin and ceftriaxone, respectively. Improved susceptibility in 2002-2003 was attributed to initial serotype switching patterns following PCV7 introduction.

• A variable susceptibility profile for tetracyclines and trimethoprim/sulfamethoxazole (TMP/SMX) was observed in the USA, where significant ( $p>0.05$ ) increases in non-susceptibility were noted, particularly from 2006 through 2009 at 4.5 to 6.3%; and a decreased susceptibility of 13.3 and 8.1% over all years for tetracyclines and TMP/SMX, respectively ([Table 2](#)). In contrast, fluoroquinolone activity as measured by levofloxacin susceptibility, ranged from 98.7% (2002) to 99.8% (1998) with an overall decrease in susceptibility of only 0.6% in the 12 monitored years.

**Table 1.** Comparative activity of eight antimicrobial agents tested against 8,560 *S. pneumoniae* isolated during the SENTRY Antimicrobial Surveillance Program (four geographic regions; 2007-2009).

Antimicrobial (Susceptible breakpoint) <sup>a</sup>	% non-susceptible by region:			
	USA	Europe	Latin America	APAC <sup>b</sup>
Penicillin ( $\leq 0.06$ $\mu\text{g/ml}$ ) <sup>c</sup>	39.8	27.0	35.6	60.4
Penicillin ( $\leq 2$ $\mu\text{g/ml}$ ) <sup>d</sup>	13.6	5.9	5.8	22.7
Amoxicillin/clavulanate ( $\leq 2$ $\mu\text{g/ml}$ )	16.0	6.6	8.1	19.8
Ceftriaxone ( $\leq 1$ $\mu\text{g/ml}$ )	9.4	6.0	5.5	24.8
Cefepime ( $\leq 1$ $\mu\text{g/ml}$ )	9.5	5.6	3.3	20.8
Erythromycin ( $\leq 0.25$ $\mu\text{g/ml}$ )	36.6	31.4	25.0	77.9
Clindamycin ( $\leq 0.25$ $\mu\text{g/ml}$ )	19.6	20.3	6.5	59.0
Levofloxacin ( $\leq 2$ $\mu\text{g/ml}$ )	0.6	1.4	0.5	2.0
Ciprofloxacin ( $\geq 4$ $\mu\text{g/ml}$ ) <sup>e</sup>	(3.4)	(5.3)	(2.8)	(4.3)

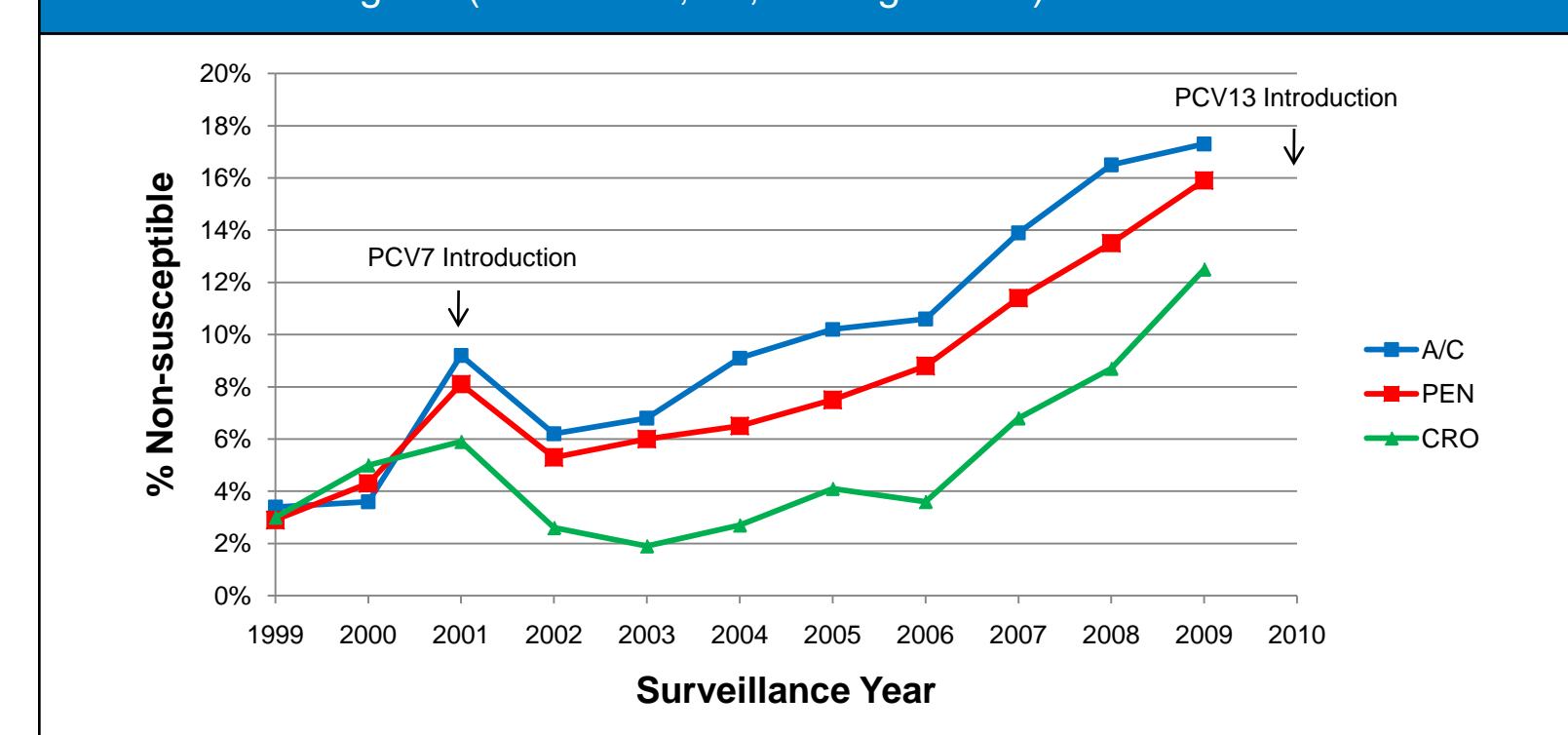
a. CLSI interpretive criteria [2010].  
b. APAC = Asia-Pacific region.  
c. Breakpoints as applied for therapy of meningitis or when using oral penicillin V [CLSI M100-S20, 2010].  
d. Breakpoint for intravenous penicillin G at doses of 12 million U per day (non-meningitis infections).  
e. Criteria proposed by Chen et al [1999] suggesting the presence of mutations in the quinolone resistance determining region (QRDR).

**Table 2.** Trends in susceptibility rates for nine antimicrobial agents tested against 14,934 *S. pneumoniae* isolated in the United States SENTRY Antimicrobial Surveillance Program; 1998-2009).

Year (no. tested)	% susceptible by agent (MIC breakpoint in $\mu\text{g/ml}$ ) <sup>a</sup>									
	A/C ( $\leq 2$ )	PEN ( $\leq 0.06$ )	PEN ( $\leq 2$ )	CRO ( $\leq 1$ )	ERY ( $\leq 0.25$ )	TC ( $\leq 0.25$ )	TMP/SMX ( $\leq 2$ )	LEV ( $\leq 2$ )	CIP ( $\geq 4$ )	
1998 (1,399)	97.1	71.6	96.8	97.0	82.2	96.2	88.8	73.8	99.8	2.2
1999 (1,486)	96.6	67.6	97.1	97.0	76.5	92.9	84.5	66.5	99.1	1.5
2000 (1,356)	93.4	66.5	95.7	95.0	74.3	92.3	83.6	67.3	99.3	3.8
2001 (1,126)	91.8	63.1	91.9	94.1	70.6	91.4	83.2	62.9	99.6	2.7
2002 (1,255)	93.8	68.7	94.7	97.4	74.1	92.4	86.7	70.1	98.7	2.8
2003 (1,008)	93.2	67.1	94.0	98.1	72.3	89.9	83.9	69.4	99.2	4.9
2004 (1,026)	90.9	64.0	93.5	97.3	70.5	89.4	86.2	67.1	99.2	1.7
2005 (1,206)	89.8	64.6	92.5	95.9	67.7	87.9	82.9	70.4	99.1	3.0
2006 (1,250)	89.4	65.4	91.2	96.6	67.2	83.7	80.0	72.0	99.1	3.7
2007 (1,241)	86.1	62.4	88.6	93.2	67.4	82.5	78.3	71.2	99.7	2.8
2008 (1,209)	83.5	59.6	86.5	91.3	63.2	80.0	77.3	67.1	99.4	4.0
2009 (1,372)	82.7	59.0	84.1	87.5	60.8	79.1	75.5	65.7	99.2	3.3

a. CLSI interpretive breakpoints (2010); A/C = amoxicillin/clavulanate, PEN = penicillin, CRO = ceftriaxone; CIP = ciprofloxacin (Chen et al., 1999), LEV = levofloxacin, TC = tetracycline, TMP/SMX = trimethoprim/sulfamethoxazole, ERY = erythromycin, and CC = clindamycin.

**Figure 1.** Profile of non-susceptibility rates (CLSI criteria) for three commonly used  $\beta$ -lactams (A/C = amoxicillin/clavulanate; PEN = penicillin, high-dose; and CRO = ceftriaxone) tested against *S. pneumoniae* isolates from the SENTRY Antimicrobial Surveillance Program (1998-2009; 14,934 organisms).



## Conclusions

- This update of SENTRY Program results from USA isolates of *S. pneumoniae* documents striking ( $p<0.05$ ) declines in susceptibility rates for key  $\beta$ -lactams ([Figure 1](#)) and other antimicrobials in the last five years (-4.7 to -8.8% for all drugs except the fluoroquinolones, see [Table 2](#)).
- Inter-regional variations can be marked with highest  $\beta$ -lactam and MLS<sub>B</sub>-resistance rates observed in the APAC region.
- Rational use of empiric therapy for suspected pneumococcal infections must consider application of contemporary in vitro susceptibility data, and the realization that fluoroquinolones must assume a greater therapeutic role, as well as some investigational cephalosporins that remain active against pneumococci at achievable clinical concentrations (Patel et al., 2009).
- Also, will the introduction of Prevnar 13 alter these escalating resistance rates?; and if so, reduce the alarming number of MDR strains.

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