

Changes in United States Regional Variations in Penicillin Resistant Rates Against *Streptococcus pneumoniae*, 1999 to 2006

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REVISED ABSTRACT

Background: The percentage rates of penicillin-resistant (PenR) *S. pneumoniae* (SPN) vary by country and region. The purpose of this study was to determine changes in regional variations, if any, of PenR and PenNS strains of SPN, and the current activity of tigecycline (TIG), amoxicillin-clavulanic acid (AC), ceftriaxone (CFX), levofloxacin (LEV), linezolid (LNZ) and vancomycin (VAN) to penicillin-resistant isolates.

Methods: 1,694 clinically relevant isolates of SPN were collected from patients in 137 hospitals from 2004 - 2006. MIC's to all agents tested were determined by broth microdilution and interpreted following CLSI guidelines. Regions are defined by the CDC. **Results:** PenNS rate was 41.8% for all regions varying from a high of 61.5% (East South Central) to a low of 23.2% (Pacific). PenR decreased in all regions but one (New England) with a corresponding increase in PenR rates in most regions. Tigecycline and vancomycin had the lowest MIC₉₀s (mcg/ml) against PenR SPN at 0.5 followed by LEV and LNZ at 1 and CFX and AC at 2 and 8, respectively.

Regions	Pen I+R (%) 1999-2000*	Pen I+R (%) 2004-2006	Net (%) Gain/(Loss)
All Regions	n=4,751 41	n=1,694 41.8	0.8
East North Central	38.7	40.5	1.8
East South Central	53.3	61.5	8.2
Middle Atlantic	36.9	37.9	1
Mountain	41.1	38.7	(2.4)
New England	26.1	33.3	7.2
Pacific	34.6	23.2	(11.4)
South Atlantic	47.9	46.8	(1.1)
West North Central	37.1	41.5	4.4
West South Central	47.5	46.9	(0.6)

*Bouchillon et al (2001), ASM General Meeting, May 2001 [2].

Conclusion: PenNS for SPN has remained constant since 1999 but PenR has generally shifted from Pacific regions eastward. VAN, LNZ, LEV and TIG MIC₉₀ values remain unaffected by penicillin phenotypes.

INTRODUCTION

Resistance among common gram-positive pathogens, notably *Streptococcus pneumoniae*, has compromised the therapeutic effectiveness of commonly employed antimicrobials. Since first reported in 1965, there has been a significant rise of penicillin resistance in *S. pneumoniae*. This is a significant problem since both multiple drug resistance and increased mortality are associated with high levels of penicillin drug resistance (>4 mcg/ml). Penicillin non-susceptible *S. pneumoniae* have likewise increased rapidly over the last 8 years from 10.9% to as high as 46.9% in controlled surveillance studies and have been shown to vary from country to country and region to region. While quinolone MICs have typically remained low, surveillance studies are beginning to show a rise in *S. pneumoniae* isolates with quinolone non-susceptible and resistant MICs.

The T.E.S.T. program determined the in vitro activity of tigecycline compared to most commonly prescribed broad spectrum antimicrobials against gram-negative and gram-positive species collected from 205 hospitals globally from 2004 to 2006. As part of this ongoing program, this study was designed to evaluate the in vitro activity of tigecycline and seven antimicrobial agents against *S. pneumoniae* in geographically diverse population centers within the United States. Regional in vitro activity and susceptibility differences were recorded for tigecycline, amoxicillin-clavulanic acid, ceftriaxone, imipenem, levofloxacin, linezolid, penicillin and vancomycin.

MATERIALS & METHODS

- T.E.S.T program isolates were derived from blood, respiratory tract, skin, wound, fluids and few other defined sources. Only one isolate per patient was accepted.
- Clinical isolates (n=1,694) were collected from 2004 to 2006 from 137 medical centers within the United States.
- Custom broth microdilution panels were supplied by MicroScan (Dade Behring, West Sacramento, CA, USA) with the following antimicrobial agents and concentrations (expressed in mcg/ml): tigecycline (0.008-16); amoxicillin-clavulanic acid (0.12-32); levofloxacin (0.008-8); ceftriaxone (0.06-64); imipenem (0.06-16); linezolid (0.5-8); penicillin (0.06-8); and vancomycin (0.12-32).
- MIC interpretive criteria followed published guidelines established by the CLSI where applicable [6]. MIC interpretive criteria for tigecycline followed published guidelines established by the FDA where applicable [7].
- Isolates were identified to genus and species by the local laboratory. Each site tested the isolates using broth microdilution.
- Quality control of broth microdilution panels followed manufacturer's and CLSI guidelines using the following ATCC strains: *Staphylococcus aureus* ATCC 29213; *Enterococcus faecalis* ATCC 29212; and *Streptococcus pneumoniae* ATCC 49619.
- The collection and transportation of organisms, confirmation of identification, and construction and management of a centralized database were conducted and coordinated by Laboratories International for Microbiology Studies (LIMS), a subsidiary of International Health Management Associates, Inc. (IHMA, Schaumburg, IL, USA).

REFERENCES

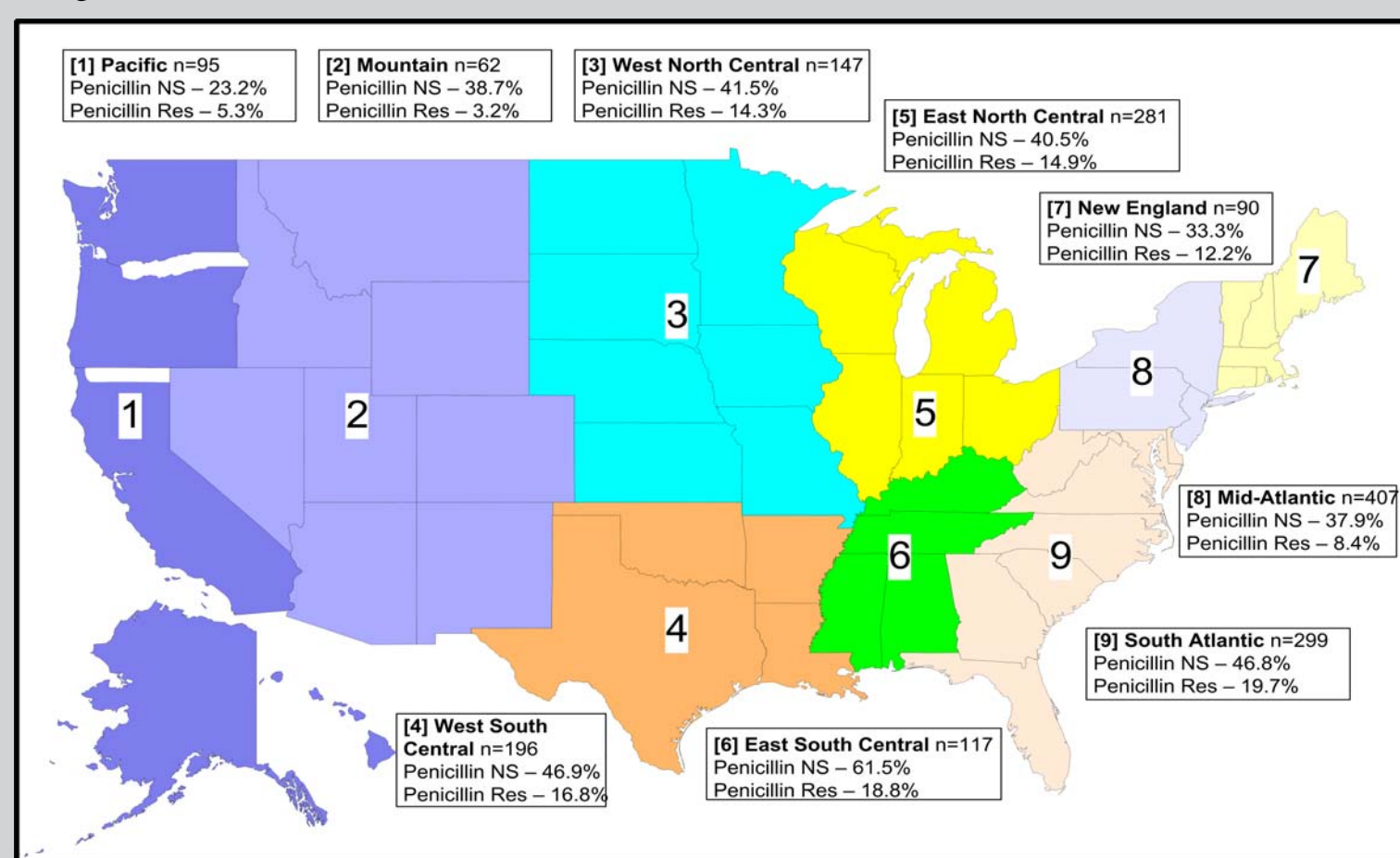
- Sahm DF, et al. Analysis of Ciprofloxacin activity against *Streptococcus pneumoniae* after 10 years of use in the United States. Antimicrob Agents Chemother 2000; 44(9):2521-4.
- Bouchillon SK, Hoban DJ, Johnson J, Stevens TM, Wagner DJ, 2001. Quinolone, Beta-Lactam and Macrolide Activity against *S. pneumoniae* from Hospitalized Patients in the United States Irrespective of Regional Resistance Patterns General Meeting (5/20/2001 through 5/24/2001).
- Fiekin Dr, et al. Mortality from invasive pneumococcal pneumoniae in the era of antibiotic resistance, 1995-1997. Am J Public Health 2000; 90(2):223-9.
- Doern GV, et al. Antimicrobial resistance with *Streptococcus pneumoniae* in the United States, 1997-1998. Emerg Infect Dis 1999; 5(6):757-65.
- Thornsberry C, et al. Resistance surveillance of *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis* isolated in the United States, 1997-1998. Antimicrob Chemother 1999; 44(6):749-59.
- CLSI, Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard—Sixth Edition, in Document M7-A7. 2006: Clinical Laboratory Standards Institute (CLSI), 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA.
- CLSI, Performance Standards for Antimicrobial Susceptibility Testing, in Document M100-S16. 2006: Clinical Laboratory Standards Institute (CLSI), 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA.
- Tygacil, Product Insert. 2005: Wyeth Pharmaceuticals, Inc., Philadelphia, PA, USA.

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RESULTS

Figure 1. Geographic map of penicillin resistance and non-susceptibility (%) for 1,694 isolates of *Streptococcus pneumoniae* from 137 centers in the United States categorized by CDC Regions*; 2004 through 2006.



*Surveillance regions as defined by the United States Centers for Disease Control.

Figure 2. Relative shift in penicillin non-susceptible rates in the various CDC regions from 2000 to 2006.

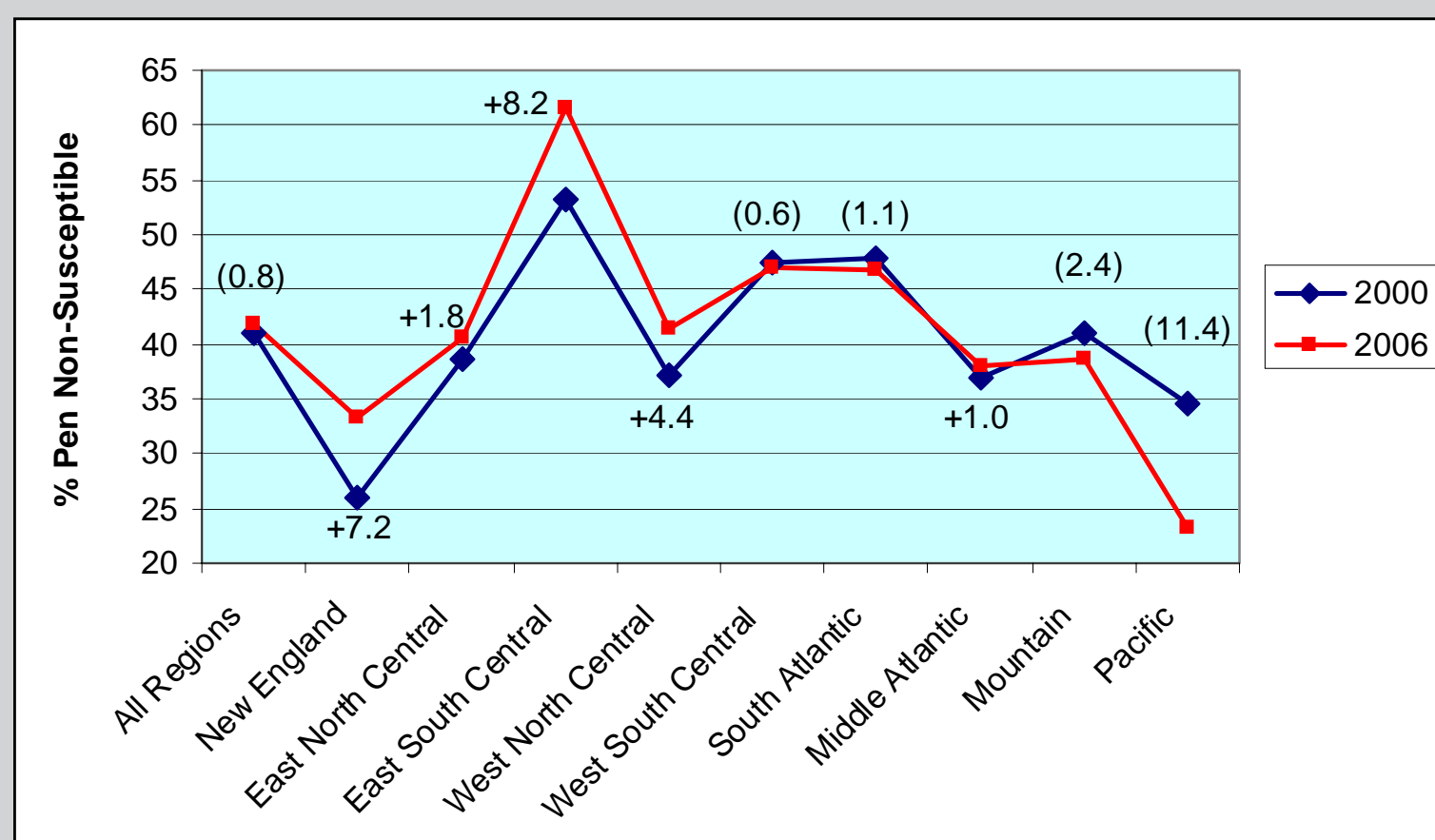


Table 1. Comparative in vitro activity of tigecycline against *Streptococcus pneumoniae* from the United States categorized by CDC Regions.*

Demographics	Drug	%Sus	%Int	%Res	MIC (mcg/ml)	
					MIC ₅₀	MIC ₉₀
All Regions (n=1,694)	Tigecycline	na	na	na	0.03	0.5
	AmoxClav	93.4	4	2.5	≤0.03	2
	Ceftriaxone	97.3	1.4	1.3	≤0.03	1
	Imipenem	60.2	36.2	3.6	≤0.12	0.5
	Levofloxacin	99.8	0.2	0	0.5	1
	Linezolid	100	0	0	≤0.5	1
	Penicillin	58.1	28.3	13.5	≤0.06	2
	Vancomycin	100	0	0	0.25	0.5
	East North Central (n=281)	Tigecycline	na	na	na	0.03
AmoxClav		91.1	5.3	3.6	≤0.03	2
Ceftriaxone		97.2	2.1	0.7	≤0.03	1
Imipenem		60.5	37.4	2.1	≤0.12	0.5
Levofloxacin		99.6	0.4	0	0.5	1
Linezolid		100	0	0	≤0.5	1
Penicillin		59.4	25.6	14.9	≤0.06	2
Vancomycin		100	0	0	0.25	0.5
East South Central (n=117)		Tigecycline	na	na	na	0.03
	AmoxClav	93.2	6	0.9	≤0.03	2
	Ceftriaxone	94	5.1	0.9	0.06	1
	Imipenem	45.3	48.7	6	0.25	0.5
	Levofloxacin	99.1	0.9	0	1	1
	Linezolid	100	0	0	≤0.5	1
	Penicillin	38.5	42.7	18.8	0.25	2
	Vancomycin	100	0	0	0.25	0.5
	Middle Atlantic (n=407)	Tigecycline	na	na	na	0.03
AmoxClav		94.3	3.7	2	≤0.03	2
Ceftriaxone		98.3	1	0.7	≤0.03	0.5
Imipenem		73.4	22.9	3.7	≤0.12	0.5
Levofloxacin		100	0	0	0.5	1
Linezolid		100	0	0	≤0.5	1
Penicillin		62.2	29.5	8.4	≤0.06	1
Vancomycin		100	0	0	0.25	0.5
Mountain (n=62)		Tigecycline	na	na	na	0.06
	AmoxClav	98.4	1.6	0	≤0.03	0.5
	Ceftriaxone	100	0	0	≤0.03	0.5
	Imipenem	61.3	37.1	1.6	≤0.12	0.5
	Levofloxacin	100	0	0	1	1
	Linezolid	100	0	0	≤0.5	1
	Penicillin	61.3	35.5	3.2	≤0.06	1
	Vancomycin	100	0	0	0.25	0.5
	New England (n=90)	Tigecycline	na	na	na	0.06
AmoxClav		93.3	4.4	2.2	≤0.03	2
Ceftriaxone		97.8	1.1	1.1	≤0.03	1
Imipenem		54.4	41.1	4.4	≤0.12	0.5
Levofloxacin		100	0	0	0.5	1
Linezolid		100	0	0	≤0.5	1
Penicillin		66.7	21.1	12.2	≤0.06	2
Vancomycin		100	0	0	0.25	0.5
Pacific (n=95)		Tigecycline	na	na	na	0.06
	AmoxClav	97.9	1.1	1.1	≤0.03	0.5
	Ceftriaxone	100	0	0	≤0.03	0.5
	Imipenem	68.4	30.5	1.1	≤0.12	0.5
	Levofloxacin	100	0	0	0.5	1
	Linezolid	100	0	0	≤0.5	1
	Penicillin	76.8	17.9	5.3	≤0.06	1
	Vancomycin	100	0	0	0.25	0.5
	South Atlantic (n=299)	Tigecycline	na	na	na	0.06
AmoxClav		92.6	4	3.3	≤0.03	2
Ceftriaxone		94.6	2	3.3	0.06	1
Imipenem		51.5	44.4	4.1	≤0.12	0.5
Levofloxacin		100	0	0	0.5	1
Linezolid		100	0	0	≤0.5	1
Penicillin		53.2	27.1	19.7	≤0.06	2
Vancomycin		100	0	0	0.25	0.5
West North Central (n=147)		Tigecycline	na	na	na	0.03
	AmoxClav	89.8	6.1	4.1	≤0.03	4
	Ceftriaxone	97.3	0.7	2	≤0.03	1
	Imipenem	57.8	38.1	4.1	≤0.12	0.5
	Levofloxacin	100	0	0	0.5	1
	Linezolid	100	0	0	≤0.5	1
	Penicillin	58.5	27.2	14.3	≤0.06	2
	Vancomycin	100	0	0	0.25	0.5
	West South Central (n=196)	Tigecycline	na	na	na	0.03
AmoxClav		95.4	2	2.6	≤0.03	2
Ceftriaxone		99	0	1	0.06	1
Imipenem		54.6	41.3	4.1	≤0.12	0.5
Levofloxacin		99.5	0.5	0	1	1
Linezolid		100	0	0	≤0.5	1
Penicillin		53.1	30.1	16.8	≤0.06	2
Vancomycin		100	0	0	0.25	0.5

*Susceptibility breakpoints are defined by CLSI document M100-S16, 2006, where available. na = not available. Tigecycline breakpoints for *S. pneumoniae* are undefined.

CONCLUSIONS

- This study demonstrates an overall penicillin non-susceptible rate of 41% with a penicillin-resistant rate of 13.5% in the United States.
- The penicillin non-susceptible rate of 41% has not changed from 2000 to 2006, but the rates have shifted among the various CDC regions. The highest rates have always been seen in the Southern regions and have either stayed the same as in the West South Central (47%) and South Atlantic (47%) or risen to higher levels as seen in the East South Central states (62%). The lowest penicillin non-susceptible rates are now seen in the New England (33%) and Pacific regions (23%).

- All *S. pneumoniae* isolates in this study were susceptible to linezolid and vancomycin with >99% susceptible to levofloxacin. No levofloxacin-resistant isolates were seen.
- At 0.03 mcg/ml and 0.5 mcg/ml, the tigecycline MIC₅₀ and MIC₉₀ values were comparable to linezolid, vancomycin and levofloxacin. MIC₅₀ and MIC₉₀ values for tigecycline were consistent among the various CDC regions, varying not more than +/- 1 doubling dilutions.
- This study demonstrates the leveling of penicillin non-susceptibility rates in the United States over the past six years and sets baseline in vitro activity for the monitoring of the new glycolglycyl, tigecycline, against *S. pneumoniae* in the United States.