

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) varies by country and region. Earlier studies have documented U.S. regional variations in PenR SPN. 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 pen-resistant isolates. **Methods:** 2,443 clinically relevant isolates of SPN were collected from patients in 193 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 42.4% for all regions varying from a high of 60.3% (East South Central) to a low of 32.3% (Pacific and New England). PenR decreased in all regions but one (New England) with a corresponding increase in PenI rates in most regions. Regional changes from a 1999-2000 study to 2004-2006 study are noted. Tigecycline had the lowest MIC₉₀ (mcg/mL) against PenR SPN at 0.25, followed by vancomycin 0.5, and then 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
East South Central	60.3	60.3	7
South Atlantic	47.9	47.9	0
West North Central	37.1	45.7	8.6
West South Central	47.5	45.1	-2.4
Middle Atlantic	36.9	39.7	2.8
East North Central	38.7	39.6	0.9
Mountain	41.1	36.3	-4.8
Pacific	34.6	32.3	-2.3
New England	26.1	32.3	6.2
All Regions	41	42.4	1.4

Conclusion: PenNS for SPN has remained essentially constant since 1999, but PenR has generally shifted from Pacific regions eastward. VAN, LNZ, LEV and TIG MIC₉₀ values remain unaffected by pen 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 substantial diminishment of penicillin susceptibility in *S. pneumoniae*. This is a significant problem since both multiple drug resistance and increased mortality are associated with penicillin minimal inhibitory concentrations (MICs) >4 mcg/ml. Penicillin non-susceptible *S. pneumoniae* have increased rapidly in some geographical areas 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 over 320 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 other defined sources. Only one isolate per patient was accepted.
- Clinical isolates (n=2,443) were collected from 2004 to 2006 from 193 medical centers within the United States.
- Custom broth microdilution panels were supplied by MicroScan (Dade MicroScan, Sacramento, CA, USA) with the following antimicrobial agents and concentrations (expressed in mcg/ml): amoxicillin/clavulanic acid (0.03-8); ampicillin (0.06-16); piperacillin/tazobactam (0.25-16); levofloxacin (0.06-32); ceftriaxone (0.03-64); linezolid (0.5-8); penicillin (0.06-8); imipenem (0.06-16); minocycline (0.25-8); tigecycline (0.008-16); and vancomycin (0.12-32).
- MIC interpretive criteria followed published guidelines established by the CLSI where applicable [6].
- 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)*.
- Flekin 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.
- Thornberry 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-S17*. 2007: 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. Rates of *S. pneumoniae* penicillin non-susceptibility (pen-intermediate plus pen-resistant) in United States surveillance regions as defined by Centers for Disease Control - 2006.

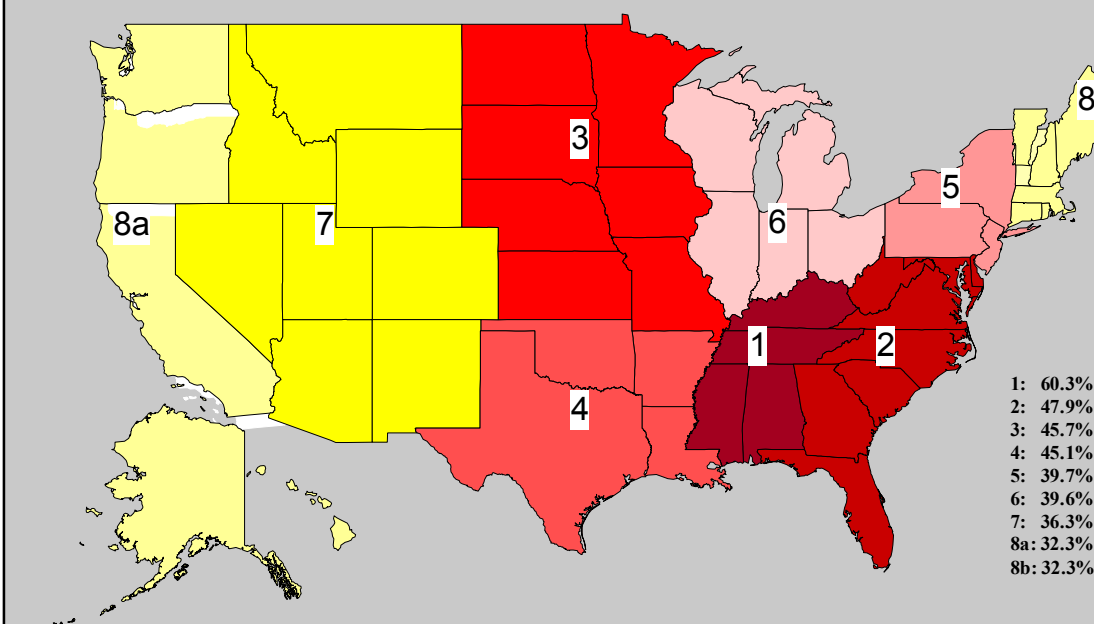


Figure 2. Relative shift in penicillin non-susceptible rates in the various CDC regions from 2000 to 2006.

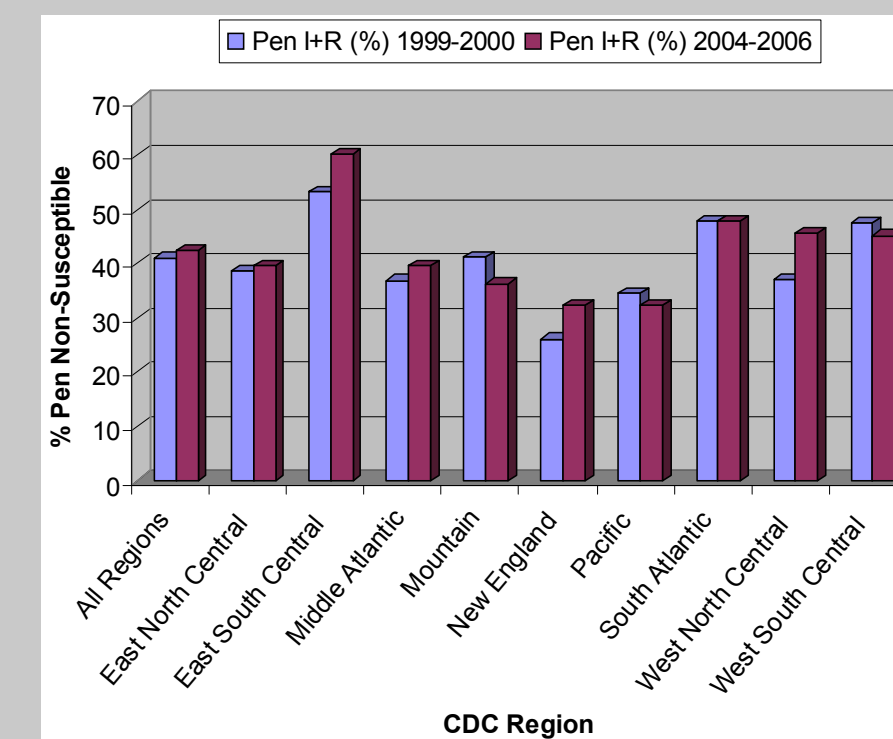


Table 1. In vitro activity of antimicrobials against 316 penicillin-resistant *S. pneumoniae* isolated in the United States from 2004-2006.

Drug				MIC (mcg/ml)	
	%Sus	%Int	%Res	MIC ₅₀	MIC ₉₀
Tigecycline	na	na	na	0.03	0.25
AmoxClav	50	30.1	19.9	2	8
Ceftriaxone	77.5	12.3	10.1	1	2
Imipenem	5.5	70	24.5	0.5	1
Levofloxacin	99.7	0.3	0	1	1
Linezolid	100	0	0	≤0.5	1
Penicillin	0	0	100	2	4
Vancomycin	100	0	0	0.25	0.5

Table 2. In vitro activity of tigecycline and 7 comparators against *Streptococcus pneumoniae* from the United States, grouped by CDC Regions.^a

Demographics	Drug				MIC (mcg/ml)	
		%Sus	%Int	%Res	MIC ₅₀	MIC ₉₀
All Regions (n=2,443)	Tigecycline	na	na	na	0.03	0.25
	AmoxClav	93.7	3.7	2.6	≤0.03	2
	Ceftriaxone	95.9	2.6	1.4	≤0.03	1
	Imipenem	71.9	24.9	3.2	≤0.12	0.5
	Levofloxacin	99.8	0.2	0	0.5	1
	Linezolid	100	0	0	≤0.5	1
	Penicillin	57.6	29.7	12.6	≤0.06	2
	Vancomycin	100	0	0	0.25	0.5
East North Central (n=470)	Tigecycline	na	na	na	0.03	0.12
	AmoxClav	93	4.5	2.6	≤0.03	2
	Ceftriaxone	98.5	1.3	0.2	≤0.03	0.5
	Imipenem	71.9	25.1	3	≤0.12	0.5
	Levofloxacin	100	0	0	0.5	1
	Linezolid	100	0	0	≤0.5	1
	Penicillin	60.4	27.9	11.7	≤0.06	2
	Vancomycin	100	0	0	0.25	0.5
East South Central (n=136)	Tigecycline	na	na	na	0.03	0.25
	AmoxClav	92.6	5.1	2.2	≤0.03	2
	Ceftriaxone	94.1	3.7	2.2	0.06	1
	Imipenem	46.2	48.1	5.8	0.25	0.5
	Levofloxacin	99.3	0.7	0	0.5	1
	Linezolid	100	0	0	≤0.5	1
	Penicillin	39.7	44.9	15.4	0.12	2
	Vancomycin	100	0	0	0.25	0.5
Middle Atlantic (n=571)	Tigecycline	na	na	na	0.03	0.12
	AmoxClav	93.3	4	2.6	≤0.03	2
	Ceftriaxone	97.9	1.6	0.5	≤0.03	1
	Imipenem	78.1	17	4.9	≤0.12	0.5
	Levofloxacin	99.8	0.2	0	0.5	1
	Linezolid	100	0	0	≤0.5	1
	Penicillin	60.2	29.4	10.3	≤0.06	2
	Vancomycin	100	0	0	0.25	0.5
Mountain (n=80)	Tigecycline	na	na	na	0.03	0.5
	AmoxClav	98.8	1.3	0	≤0.03	0.5
	Ceftriaxone	98.8	0	1.3	≤0.03	0.25
	Imipenem	74.7	24	1.3	≤0.12	0.25
	Levofloxacin	100	0	0	1	1
	Linezolid	100	0	0	≤0.5	1
	Penicillin	63.8	31.3	5	≤0.06	1
	Vancomycin	100	0	0	0.25	0.5
New England (n=124)	Tigecycline	na	na	na	0.03	0.25
	AmoxClav	94.4	3.2	2.4	≤0.03	1
	Ceftriaxone	97.6	0.8	1.6	≤0.03	0.5
	Imipenem	70.7	26.1	3.3	≤0.12	0.5
	Levofloxacin	100	0	0	0.5	1
	Linezolid	100	0	0	≤0.5	1
	Penicillin	67.7	25.3	7	≤0.06	1
	Vancomycin	100	0	0	0.25	0.5
Pacific (n=158)	Tigecycline	na	na	na	0.03	0.25
	AmoxClav	97.5	1.9	0.6	≤0.03	1
	Ceftriaxone	97.5	2.5	0	≤0.03	0.5
	Imipenem	79.4	19	1.6	≤0.12	0.5
	Levofloxacin	100	0	0	1	1
	Linezolid	100	0	0	1	1
	Penicillin	67.7	25.3	7	≤0.06	1
	Vancomycin	100	0	0	0.25	0.5
South Atlantic (n=472)	Tigecycline	na	na	na	0.03	0.25
	AmoxClav	90.9	5.1	4	≤0.03	2
	Ceftriaxone	93.2	3.4	3.4	0.06	1
	Imipenem	69.6	26.1	4.3	≤0.12	0.5
	Levofloxacin	100	0	0	0.5	1
	Linezolid	100	0	0	≤0.5	1
	Penicillin	52.1	29	18.9	≤0.06	2
	Vancomycin	100	0	0	0.25	0.5
West North Central (n=206)	Tigecycline	na	na	na	0.03	0.5
	AmoxClav	100	0	0	0.25	0.5
	Ceftriaxone	97.6	1	1.5	≤0.03	1
	Imipenem	68.4	25.9	5.7	≤0.12	0.5
	Levofloxacin	99.5	0.5	0	0.5	1
	Linezolid	100	0	0	1	1
	Penicillin	54.4	31.6	14.1	≤0.06	2
	Vancomycin	100	0	0	0.25	0.5
West South Central (n=226)	Tigecycline	na	na	na	0.03	0.12
	AmoxClav	95.6	2.2	2.2	≤0.03	2
	Ceftriaxone	97.8	0.9	1.3	≤0.03	1
	Imipenem	65.2	31.8	3	≤0.12	0.5
	Levofloxacin	99.6	0.4	0	1	1
	Linezolid	100	0	0	1	1
	Penicillin	54.9	29.2	15.9	≤0.06	2
	Vancomycin	100	0	0	0.25	0.5

^aSusceptibility breakpoints are defined by CLSI document M100-S17, 2007, where available; na = not available; Tigecycline breakpoints for *S. pneumoniae* are undefined.

CONCLUSIONS

- This study demonstrates an overall penicillin non-susceptible rate for *S. pneumoniae* of 42.4% in the United States, with a penicillin-resistant rate of 12.9%.
- The overall penicillin non-susceptible rate of 42.4% has not changed significantly from 2000 to 2006, but the rates have shifted somewhat among the various CDC regions. The highest rates have always been seen in the East South Central region, and the lowest penicillin non-susceptible rates are still seen in the New England and Pacific regions (both at 32.3%). The West North Central region experienced the biggest increase in non-susceptibility, from 37.1% to 45.7%.
- All *S. pneumoniae* isolates in this study were susceptible to linezolid and vancomycin, with >99% susceptible to levofloxacin. No levofloxacin-resistant isolates were seen.
- Tigecycline's MIC₉₀ of 0.25 mcg/ml for all pneumococci and for penicillin-resistant strains was the lowest among the antimicrobials tested.
- The reason for declining resistance rates has been speculated to be due to wide use of pneumococcal vaccines that have been effective at significantly reducing prevalence of strains with penicillin resistance; however, the reason for concomitantly increasing intermediate rates is not known at this time.
- It is encouraging that overall non-susceptible rates have remained largely unchanged since 2000 (1.4% increase nation-wide).