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REVISED ABSTRACT

Background: The percentage rates of penicillin-resistant (PenR) *S. pneumoniae* (SPN) vary 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 PenR isolates. **Methods:** 2,351 clinically relevant isolates of SPN were collected from patients in 187 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 31.0% (Pacific). PenR decreased in all regions but one (New England) with a corresponding increase in PenR rates in all regions. Regional changes from 1999-2000 to 2004-2006 are noted. Tigecycline and vancomycin had the lowest MIC₅₀s (mcg/ml) against PenR SPN at 0.25 and 0.5, respectively, followed by LEV and LNZ at 1, and CFX at 2.

Regions	Pen I+R (%) 1999-2000 n=1948/4751	Pen I+R (%) 2004-2006 n=996/2351	Net (%) Gain/Loss
All Regions	41	42.4	1.4
East North Central	38.7	40.1	1.4
East South Central	53.3	60.3	7
Middle Atlantic	36.9	40.2	3.3
Mountain	41.1	36.2	(4.9)
New England	26.1	32.3	6.2
Pacific	34.6	31	(3.6)
South Atlantic	47.9	46.6	(1.3)
West North Central	37.1	45.6	8.5
West South Central	47.5	45.3	(2.2)

Conclusion: PenNS for SPN has increased only slightly since 1999, with increases in levels of PenI in almost all regions accompanied by corresponding decreases in PenR levels. VAN, LNZ, LEV and TIG MIC₅₀ 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 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 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=1,694) were collected from 2004 to 2006 from 187 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 (0.03-8; levofloxacin (0.06-32); ceftriaxone (0.03-64); 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 [8].
- 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).

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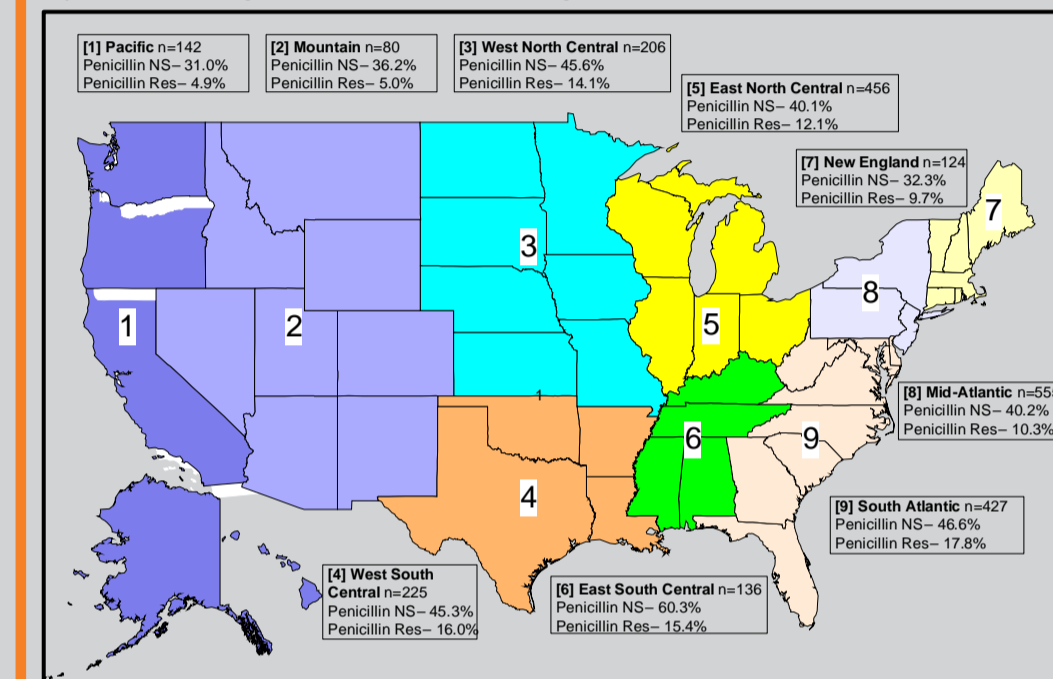
RESULTS

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=2,351)	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=456)	Tigecycline	na	na	na	0.03
AmoxClav		92.8	4.6	2.6	≤0.03	2
Ceftriaxone		96.9	2.9	0.2	≤0.03	0.5
Imipenem		73.6	24.5	1.9	≤0.12	0.5
Levofloxacin		100	0	0	0.5	1
Linezolid		100	0	0	≤0.5	1
Penicillin		59.9	28.1	12.1	≤0.06	2
Vancomycin		100	0	0	0.25	0.5
East South Central (n=136)		Tigecycline	na	na	na	0.03
	AmoxClav	92.6	5.1	2.2	≤0.03	2
	Ceftriaxone	93.4	4.4	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=555)	Tigecycline	na	na	na	0.03
AmoxClav		93.3	4	2.7	≤0.03	2
Ceftriaxone		95	4	1.1	≤0.03	1
Imipenem		81.5	15.3	3.2	≤0.12	0.5
Levofloxacin		99.8	0.2	0	0.5	1
Linezolid		100	0	0	≤0.5	1
Penicillin		59.8	29.9	10.3	≤0.06	2
Vancomycin		100	0	0	0.25	0.5
Mountain (n=80)		Tigecycline	na	na	na	0.03
	AmoxClav	98.8	1.3	0	≤0.03	0.5
	Ceftriaxone	98.8	0	1.3	≤0.03	0.25
	Imipenem	76	22.7	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
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	22.6	9.7	≤0.06	1
Vancomycin		100	0	0	0.25	0.5
Pacific (n=142)		Tigecycline	na	na	na	0.03
	AmoxClav	98.6	0.7	0.7	≤0.03	0.5
	Ceftriaxone	100	0	0	≤0.03	0.5
	Imipenem	78	20.3	1.7	≤0.12	0.5
	Levofloxacin	100	0	0	1	1
	Linezolid	100	0	0	1	1
	Penicillin	69	26.1	4.9	≤0.06	1
	Vancomycin	100	0	0	0.25	0.5
	South Atlantic (n=427)	Tigecycline	na	na	na	0.03
AmoxClav		92.5	3.7	3.7	≤0.03	2
Ceftriaxone		94.1	2.8	3	0.06	1
Imipenem		66.3	29.1	4.5	≤0.12	0.5
Levofloxacin		100	0	0	0.5	1
Linezolid		100	0	0	≤0.5	1
Penicillin		53.4	28.8	17.8	≤0.06	2
Vancomycin		100	0	0	0.25	0.5
West North Central (n=206)		Tigecycline	na	na	na	0.03
	AmoxClav	91.7	5.3	2.9	≤0.03	2
	Ceftriaxone	95.6	2.4	1.9	≤0.03	1
	Imipenem	72.5	24.4	3.1	≤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=225)	Tigecycline	na	na	na	0.03
AmoxClav		95.6	2.2	2.2	≤0.03	2
Ceftriaxone		96.9	1.3	1.8	≤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		54.7	29.3	16	≤0.06	2
Vancomycin		100	0	0	0.25	0.5

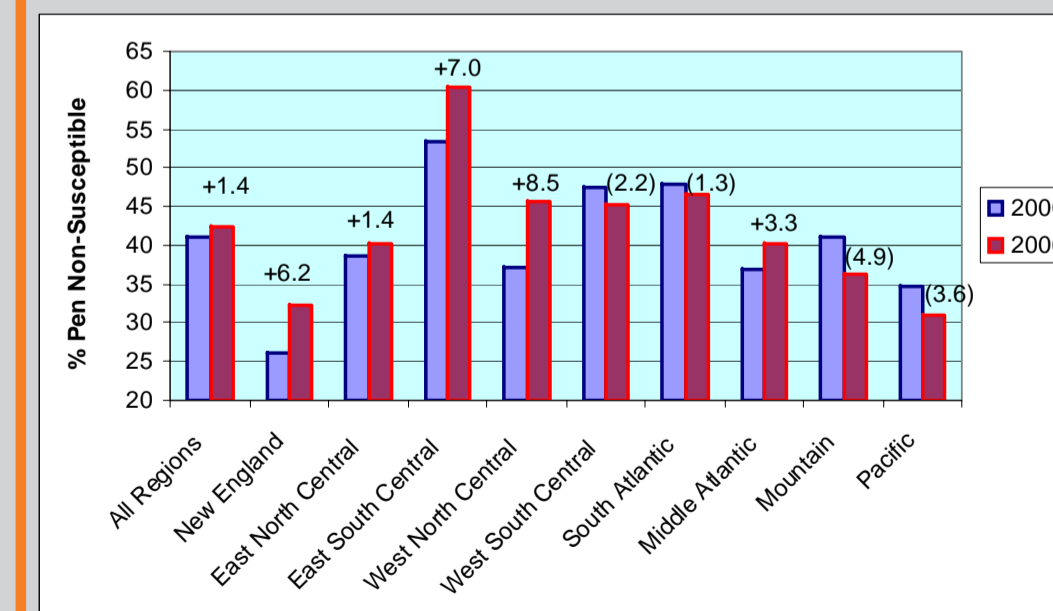
* Susceptibility breakpoints are defined by CLSI document M100-S16, 2006, where available. na = not available. Tigecycline breakpoints for *S. pneumoniae* are undefined.

Figure 1. Geographic map of penicillin resistance and non-susceptibility (%) for 2,351 isolates of *Streptococcus pneumoniae* from 187 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.



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 12.6%.
- 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 (32.3%) and Pacific regions (31.0%). The West North Central region experienced the biggest increase in non-susceptibility, from 37.1% to 45.6%.
- 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 was the lowest among the antimicrobials tested against *S. pneumoniae* from the United States.
- Although the reason for declining resistance rates and concomitantly increasing intermediate rates is not known at this time, it is encouraging that overall non-susceptible rates have remained largely unchanged.
- This study sets baseline in vitro activity for the monitoring of the new glycylicline, tigecycline, against *S. pneumoniae* in the United States.