

Regional Variations in Penicillin Resistant Rates Against *Streptococcus pneumoniae*: The United States 2008

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B. Johnson¹, D. Hoban¹, M. Renteria¹, J. Johnson¹, R. Badal¹, S. Hawser², M. Hackel¹, S. Bouchillon¹, M. Dowzicky³

¹International Health Management Associates, Inc., Schaumburg, IL, USA
²International Health Management Associates Europe Sàrl, Epalinges, Switzerland
³Wyeth Pharmaceuticals, Collegeville, PA, USA

IHMA, Inc.
 2122 Palmer Dr.
 Schaumburg, IL
 60173
 Tel: 847.303.5003
 Fax: 847.303.5601

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), azithromycin (AZ), ceftriaxone (CFX), clindamycin (CD) levofloxacin (LEV), imipenem (IM), linezolid (LNZ), minocycline (MN), penicillin (PEN) and vancomycin (VAN) to pen-resistant isolates. **Methods:** 3739 clinically relevant isolates of SPN were collected from patients from 460 U.S. investigators from 2004 - 2008. 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 43.1% for all regions varying from a high of 59.7% (East South Central) to a low of 34.5% (Pacific). PenR decreased in all regions but one (New England) with a corresponding increase in PenR rates in most regions. Regional changes from a 1999-2000 study to 2004-2008 study are noted. Tigecycline and vancomycin had the lowest MIC₉₀s (mg/L) against PenR SPN at 0.06 and 0.5 respectively followed by LEV and LNZ at 1 and CFX and AC at 2 and 8, respectively.

Regions	Pen I-R (%) 1999-2000 n=4,751	Pen I-R (%) 2004-2008 n=1,610	Net (%) (Gain/Loss)
East North Central	38.7	38.7	0.00
East South Central	53.3	59.7	6.40
Middle Atlantic	36.9	40.5	3.60
Mountain	41.1	36.8	(4.30)
New England	26.1	37.4	11.30
Pacific	34.6	34.5	(0.10)
South Atlantic	47.9	47.8	(0.10)
West North Central	37.1	44.4	7.30
West South Central	47.5	47.8	0.30
All Regions	41	43.1	2.10

Conclusions: PenNS for SPN has remained relatively 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

Increasing resistance in *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 morbidity are associated with increased penicillin resistance. Penicillin non-susceptible *S. pneumoniae* have increased rapidly over the last 8 years from less than 10% to over 50% 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 in particular to ciprofloxacin.

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 2008. 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, azithromycin, ceftriaxone, clindamycin, imipenem, levofloxacin, linezolid, minocycline, 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=3739) were collected from 2004 to 2008 from 193 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 mg/L): tigecycline (0.008-16); amoxicillin-clavulanic acid (0.12-32); azithromycin (0.03 - 64), clindamycin (0.015 - 64), levofloxacin (0.008-8); ceftriaxone (0.06-64); imipenem (0.06-16); linezolid (0.5-8); minocycline (0.5-16), penicillin (0.06-8); and vancomycin (0.12-32).
- MIC interpretive criteria followed published guidelines established by the CLSI where applicable. MIC interpretive criteria for tigecycline followed published guidelines established by the FDA where applicable.
- 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 manufacturers 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

Figure 1. Relative shift in penicillin non-susceptible rates in the various CDC regions from 2000 to 2008.

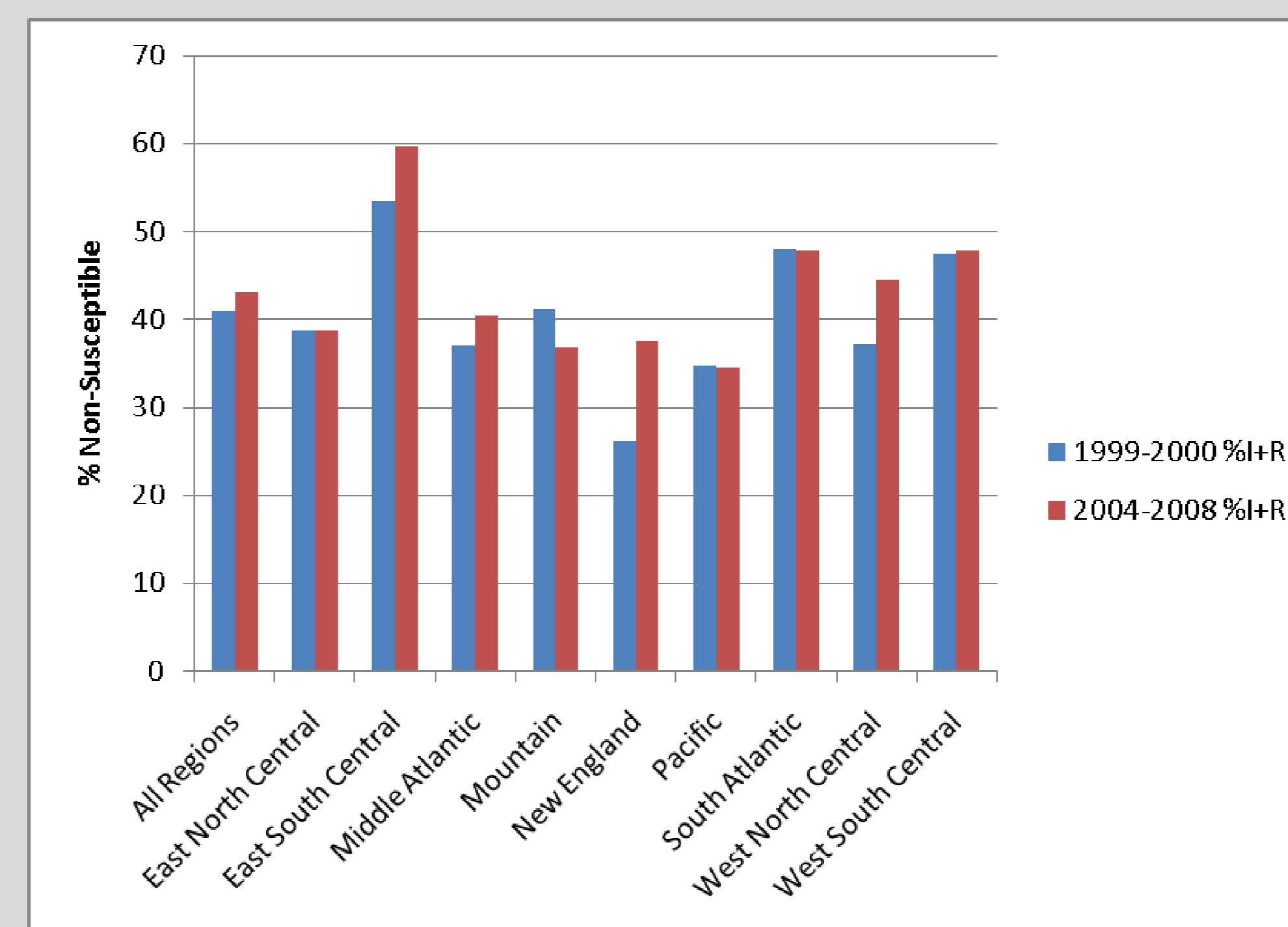


Table 1. *In vitro* activity of antimicrobials against 553 penicillin-resistant *S. pneumoniae* isolated in the United States from 2004-2008.

Drug	%Sus	%Int	%Res	MIC (mg/L)	
				MIC ₅₀	MIC ₉₀
Tigecycline	na	na	na	0.03	0.06
AmoxClav	45.4	32.2	22.4	4	8
Azithromycin	17.1	0.4	82.5	64	>64
Ceftriaxone	59.0	29.3	11.8	1	2
Clindamycin	41.9	0	58.1	>64	>64
Imipenem	10.5	66.3	23.2	0.5	1
Levofloxacin	98.7	0.4	0.9	1	1
Linezolid	100	0	0	≤0.5	1
Minocycline	na	na	na	2	4
Penicillin	0	0	100	2	4
Vancomycin	100	0	0	0.25	0.5

Conclusions

- This study demonstrates an overall penicillin non-susceptible rate for *S. pneumoniae* of 43.1% in the United States, with a penicillin-resistant rate of 14.8%.
- The overall penicillin non-susceptible rate of 43.1% has not changed significantly from 2000 to 2008, but the rates have shifted somewhat among the various CDC regions. The highest rates are seen in the East South Central region (59.7%), West South Central (47.8%) and South Atlantic (47.8%) and the lowest penicillin non-susceptible rates are seen in the Mountain (36.8%) and Pacific regions (34.5%). The New England region experienced the biggest increase in non-susceptibility.
- All *S. pneumoniae* isolates in this study were susceptible to linezolid and vancomycin, with >98% susceptible to levofloxacin and only 0.5% resistant.
- Tigecycline's MIC₉₀ of 0.12 mg/L for all pneumococci and 0.06mg/L for penicillin-resistant strains was the lowest among the antimicrobials tested.
- It is encouraging that overall non-susceptible rates have remained largely unchanged since 2000.

Table 2. *In vitro* activity of tigecycline and 10 comparators against *Streptococcus pneumoniae* from the United States, grouped by CDC Regions.^a

Demographics (n)	Drug	%Sus	%Int	%Res	MIC (mg/L)	
					MIC ₅₀	MIC ₉₀
All Regions (n=3739)	Tigecycline	na	na	na	0.03	0.12
	AmoxClav	91.7	4.9	3.3	≤0.03	2
	Azithromycin	66.5	0.8	32.9	0.12	>64
	Ceftriaxone	93.5	4.7	1.8	≤0.03	1
	Clindamycin	84.7	0.2	15.1	0.06	>64
	Imipenem	72.3	24.0	3.8	≤0.12	0.5
	Levofloxacin	99.2	0.3	0.5	0.5	1
	Linezolid	100.0	0.0	0.0	≤0.5	1
	Minocycline	na	na	na	≤0.25	4
	Penicillin	56.9	28.3	14.8	≤0.06	2
	Vancomycin	100.0	0.0	0.0	0.25	0.5
East North Central (n=741)	Tigecycline	na	na	na	0.03	0.12
	AmoxClav	91.6	4.9	3.5	≤0.03	2
	Azithromycin	68.3	1.0	30.7	0.12	>64
	Ceftriaxone	94.5	4.0	1.5	≤0.03	1
	Clindamycin	82.6	0.0	17.4	0.06	>64
	Imipenem	72.2	24.9	3.0	≤0.12	0.5
	Levofloxacin	99.2	0.3	0.5	0.5	1
	Linezolid	100.0	0.0	0.0	≤0.5	1
	Minocycline	na	na	na	≤0.25	4
	Penicillin	61.3	24.7	14.0	≤0.06	2
	Vancomycin	100.0	0.0	0.0	0.25	0.5
East South Central (n=248)	Tigecycline	na	na	na	0.03	0.12
	AmoxClav	89.1	6.0	4.8	0.06	4
	Azithromycin	63.1	0.0	36.9	0.12	>64
	Ceftriaxone	86.7	7.7	3.6	0.06	1
	Clindamycin	83.8	0.0	16.3	0.06	>64
	Imipenem	55.3	39.4	5.3	0.25	0.5
	Levofloxacin	98.8	0.4	0.8	0.5	1
	Linezolid	100.0	0.0	0.0	≤0.5	1
	Minocycline	na	na	na	≤0.25	4
	Penicillin	40.3	37.9	21.8	0.25	4
	Vancomycin	100.0	0.0	0.0	0.25	0.5
Middle (n=849)	Tigecycline	na	na	na	0.03	0.12
	AmoxClav	92.5	4.6	2.9	≤0.03	2
	Azithromycin	69.3	0.8	29.9	0.12	64
	Ceftriaxone	95.4	3.5	1.1	≤0.03	1
	Clindamycin	84.6	0.2	15.3	0.06	>64
	Imipenem	78.9	16.4	4.7	≤0.12	0.5
	Levofloxacin	99.2	0.5	0.4	0.5	1
	Linezolid	100.0	0.0	0.0	≤0.5	1
	Minocycline	na	na	na	≤0.25	4
	Penicillin	59.5	29.3	11.2	≤0.06	2
	Vancomycin	100.0	0.0	0.0	0.25	0.5
Mountain (n=117)	Tigecycline	na	na	na	0.03	0.12
	AmoxClav	95.7	1.7	2.6	≤0.03	1
	Azithromycin	83.6	0.0	16.4	0.06	32
	Ceftriaxone	96.6	2.6	0.9	≤0.03	0.5
	Clindamycin	98.4	0.0	1.6	0.06	0.06
	Imipenem	73.1	25.4	1.5	≤0.12	0.25
	Levofloxacin	100.0	0.0	0.0	0.5	1
	Linezolid	100.0	0.0	0.0	≤0.5	1
	Minocycline	na	na	na	≤0.25	4
	Penicillin	63.2	27.4	9.4	≤0.06	1
	Vancomycin	100.0	0.0	0.0	0.25	0.5
New England (n=174)	Tigecycline	na	na	na	0.03	0.06
	AmoxClav	93.1	3.4	3.4	≤0.03	2
	Azithromycin	73.7	2.2	24.1	0.12	64
	Ceftriaxone	93.1	4.0	2.9	≤0.03	1
	Clindamycin	88.3	0.7	10.9	0.06	64
	Imipenem	70.0	26.7	3.3	≤0.12	0.5
	Levofloxacin	98.9	0.6	0.6	0.5	1
	Linezolid	100.0	0.0	0.0	≤0.5	1
	Minocycline	na	na	na	≤0.25	4
	Penicillin	65.5	24.4	10.1	≤0.06	2
	Vancomycin	100.0	0.0	0.0	0.25	0.5
Pacific (n=255)	Tigecycline	na	na	na	0.03	0.12
	AmoxClav	95.7	3.1	1.2	≤0.03	1
	Azithromycin	75.0	0.4	24.6	0.12	>64
	Ceftriaxone	94.2	5.4	0.4	≤0.03	0.5
	Clindamycin	88.8	0.4	10.8	0.06	64
	Imipenem	81.9	16.7	1.4	≤0.12	0.5
	Levofloxacin	98.4	0.0	1.6	1	1
	Linezolid	100.0	0.0	0.0	1	1
	Minocycline	na	na	na	≤0.25	4
	Penicillin	65.5	24.4	10.1	≤0.06	2
	Vancomycin	100.0	0.0	0.0	0.25	0.5
South Atlantic (n=701)	Tigecycline	na	na	na	0.03	0.12
	AmoxClav	88.9	6.6	4.6	≤0.03	2
	Azithromycin	60.3	0.2	39.4	0.12	>64
	Ceftriaxone	90.4	6.6	3.0	0.06	1
	Clindamycin	82.3	0.6	16.9	0.06	>64
	Imipenem	72.0	24.4	3.6	≤0.12	0.5
	Levofloxacin	99.7	0.1	0.1	0.5	1
	Linezolid	100.0	0.0	0.0	≤0.5	1
	Minocycline	na	na	na	≤0.25	4
	Penicillin	52.2	27.7	20.1	≤0.06	2
	Vancomycin	100.0	0.0	0.0	0.25	0.5
West North Central (n=358)	Tigecycline	na	na	na	0.03	0.06
	AmoxClav	90.5	5.9	3.6	≤0.03	2
	Azithromycin	56.9	0.0	43.1	0.12	>64
	Ceftriaxone	94.1	4.2	1.7	≤0.03	1
	Clindamycin	82.1	0.0	17.9	0.06	>64
	Imipenem	68.9	25.4	5.7	≤0.12	0.5
	Levofloxacin	98.9	0.3	0.8	0.5	1
	Linezolid	100.0	0.0	0.0	1	1
	Minocycline	na	na	na	≤0.25	4
	Penicillin	55.8	28.3	15.1	≤0.06	2
	Vancomycin	100.0	0.0	0.0	0.25	0.5
West South Central (n=293)	Tigecycline	na	na	na	0.03	0.12
	AmoxClav	94.5	3.8	1.7	≤0.03	2
	Azithromycin	64.1	0.5	35.5	0.12	64
	Ceftriaxone	94.2	4.1	1.7	0.06	1
	Clindamycin	89.9	0.0	10.1	0.06	16
	Imipenem	65.0	32.0	3.0	≤0.12	0.5
	Levofloxacin	99.7	0.3	0.0	0.5	1
	Linezolid	100.0	0.0	0.0	1	1
	Minocycline	na	na	na	≤0.25	4
	Penicillin	52.2	31.7	16.0	≤0.06	2
	Vancomycin	100.0	0.0	0.0	0.25	0.5</