Comparison of United States Regional Rates of Penicillin Non-susceptible *S. pneumoniae*: TEST 2004-2006 versus 2008-2010

PR031

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Revised Abstract

Background: The proportion of penicillin non-susceptible (PenNS) *Streptococcus pneumoniae* (SPN) varies by country and region. We determined changes over time in U.S. regional variations of PenNS strains, as well as the current activity of tigecycline (TIG), amoxicillin-clavulanic acid (AUG), ceftriaxone (CAX), levofloxacin (LVX), linezolid (LZD), and vancomycin (VAN) against these isolates using data from the Tigecycline Evaluation and Surveillance Trial (TEST). **Methods:** From 2004-2006 and 2008-2010, 3,624 SPN isolates were collected in 184 U.S. hospitals. MICs were determined by broth microdilution and interpreted per CLSI guidelines (FDA breakpoints for TIG). **Results:** In 2008-2010, tigecycline had the lowest MIC_{90} (mcg/ml) against PenNS strains at 0.06, followed by VAN at 0.5, LVX and LZD at 1, and CAX and AUG at 2 and 8, respectively. Regional changes in % PenNS SPN isolates between 2004-2006 and 2008-2010 are shown below.

U.S. region	2004-2006 All SPN n	2004-2006 PenNS n	2004-2006 PenNS %	2008-2010 All SPN n	2008-2010 PenNS n	2008-2010 PenNS %	Gain/loss %	p**
Pacific	210	66	31.4	- *	-	-	-	-
Mountain	86	32	37.2	25	7	28.0	-9	0.48
East North Central	513	208	40.5	290	109	37.6	-3	0.45
East South Central	156	94	60.3	44	27	61.4	1	1
West North Central	262	125	47.7	129	37	28.7	-19	**0.0003**
West South Central	251	120	47.8	52	27	51.9	4	0.65
Mid-Atlantic	609	248	40.7	197	83	42.1	1	0.39
New England	147	50	34.0	13	3	23.1	-11	0.55
South Atlantic	519	253	48.7	121	59	48.8	0	1
All regions	2753	1196	43.4	871	352	40.4	-3	0.12

* No sites participated; ** Fisher's exact test was used to compare % PenNS between the two time periods

Conclusions: The slight decrease in the overall U.S. PenNS SPN rate was not statistically significant (p>0.05). Half the individual regions showed a decrease, but only the change in West North Central was statistically significant. TIG, LVX, LZD, and VAN displayed excellent activity unaffected by PenNS phenotype.

Introduction

The emergence and spread of resistance to commonly used antibiotics has complicated the treatment of infections caused by *Streptococcus pneumoniae*. Penicillin-non-susceptible *S. pneumoniae* (PenNS SPN) were uncommon in the United States until the 1990s, when the rates of antibiotic resistance rapidly increased. The prevalence of PenNS SPN varies among geographic regions and among hospitals within a geographic region [1].

Since 2004, the Tigecycline Evaluation and Surveillance Trial (TEST) has determined the *in vitro* activity of tigecycline and other commonly prescribed antimicrobials against gram-negative and gram-positive species. As part of this ongoing program, this study was designed to evaluate the *in vitro* activity of tigecycline and comparators against *S. pneumoniae* in different United States surveillance regions as defined by the Centers for Disease Control. Regional *in vitro* activity and susceptibility differences were recorded for tigecycline, amoxicillin-clavulanic acid, azithromycin, ceftriaxone, clindamycin, meropenem, levofloxacin, linezolid, penicillin, and vancomycin for the time periods 2004-2006 and 2008-2010.

Materials & Methods

- Isolates were derived from blood, respiratory tract, and various other infection sources. Only one isolate per patient was accepted into the study. Clinical isolates were collected in 2004-2006 and 2008-2010 from 184 medical centers in the United States. Isolates were identified to the species level and tested at each site by the participating laboratory.
- Organism collection, transport, confirmation of organism identification, and development and management of a centralized database were coordinated by Laboratories International for Microbiology Studies (LIMS), a division of International Health Management Associates, Inc., located in Schaumburg, IL, USA.
- Minimum inhibitory concentrations (MICs) were determined by the Clinical and Laboratory Standards Institute (CLSI) recommended broth microdilution testing method [2]. Tigecycline was supplied by Pfizer, Inc. (Collegeville, PA, USA). All other agents were supplied by the panel manufacturers MicroScan (Siemens Medical Solutions Diagnostics., West Sacramento, CA, USA) and TREK (TREK Diagnostic Systems, Cleveland, OH).
- Quality control (QC) of broth microdilution panels followed manufacturers' and CLSI guidelines using *S. pneumoniae* ATCC 49619. Results were included in the analysis only when corresponding QC isolates tested within the acceptable range according to CLSI guidelines [3].
- MIC interpretive criteria followed published breakpoints defined by CLSI [3] and the United States Food and Drug Administration (FDA) package insert for tigecycline [4]. Penicillin non-susceptibility was defined using breakpoints for oral administration of penicillin (0.06/0.12-1/2 mcg/ml).
- The two-tailed Fisher's exact test was used to compare % PenNS SPN between the two time periods as well as between the regions and the national average.

References

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Acknowledgements

We gratefully acknowledge the contributions of the investigators, laboratory personnel, and all members of the Tigecycline Evaluation Surveillance Trial program group. This study was sponsored by Pfizer Inc.

Results

Figure 1: Proportion of penicillin non-susceptible *S. pneumoniae* in U.S. regions, 2008-2010.

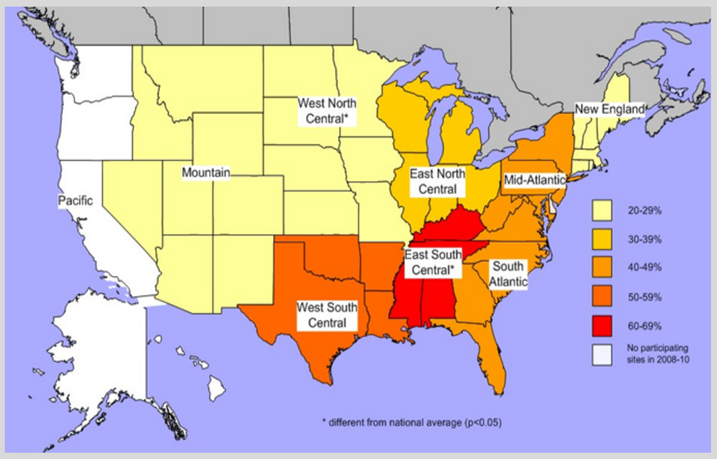

Figure 2: Change in proportion of penicillin non-susceptible *S. pneumoniae* in U.S. regions, 2004-2006 versus 2008-2010.

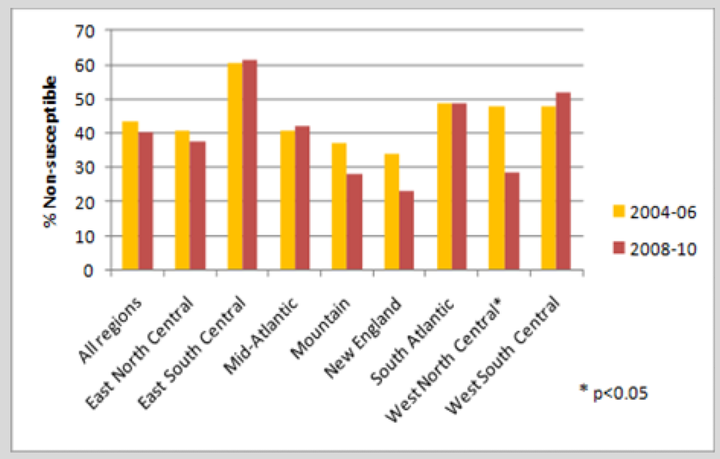

Table 1: Comparison of regional proportions of penicillin non-susceptible *S. pneumoniae*, 2004-2006 versus 2008-2010.

Region	2004-2006 All SPN n	2004-2006 PenNS n	2004-2006 PenNS % (95% CI)	2008-2010 All SPN n	2008-2010 PenNS n	2008-2010 PenNS % (95% CI)	Gain/loss %	p**
Pacific	210	66	31.4 (25.2-37.7)	- *	-	-	-	-
Mountain	86	32	37.2 (27.0-47.4)	25	7	28.0 (10.4-45.6)	-9	0.48
East North Central	513	208	40.5 (36.3-44.8)	290	109	37.6 (32.0-43.2)	-3	0.45
East South Central	156	94	60.3 (52.6-67.9)	44	27	61.4 (47.0-75.8)	1	1
West North Central	262	125	47.7 (41.7-53.8)	129	37	28.7 (20.9-36.5)	-19	**0.0003**
West South Central	251	120	47.8 (41.6-54.0)	52	27	51.9 (38.3-65.5)	4	0.65
Mid-Atlantic	609	248	40.7 (36.8-44.6)	197	83	42.1 (35.2-49.0)	1	0.39
New England	147	50	34.0 (26.4-41.7)	13	3	23.1 (0.2-46.0)	-11	0.55
South Atlantic	519	253	48.7 (44.5-53.1)	121	59	48.8 (39.9-57.7)	0	1
All regions	2753	1196	43.4 (41.6-45.3)	871	352	40.4 (37.1-43.7)	-3	0.12

* No sites participated; ** Fisher's exact test was used to compare % PenNS between the two time periods; CI: confidence interval

Table 2: *In vitro* activity of tigecycline and comparators against all *S. pneumoniae*, 2008-2010.

Region	Drug	MIC_{50}	MIC_{90}	%S	%I	%R
All regions (n=871)	AmoxClav	≤ 0.03	4	86.8	3.7	9.5
	Azithromycin	0.12	64	62.5	0.7	36.8
	Ceftriaxone	≤ 0.03	1	91.7	7.4	0.9
	Clindamycin	0.06	> 64	80.2	0.1	19.7
	Levofloxacin	1	1	99.2	0.3	0.5
	Linezolid	1	1	100	--*	--*
	Meropenem	≤ 0.12	1	80.6	6.9	12.5
	Penicillin	≤ 0.06	4	59.6	22.7	17.7
	Tigecycline	0.015	0.06	96.1	--*	--*
	Vancomycin	0.5	0.5	100	--*	--*

%S: % susceptible; % I: % intermediate; %R: % resistant; AmoxClav: amoxicillin-clavulanic acid;
* Only a susceptible breakpoint is defined for this drug against S. pneumoniae.

Table 3: *In vitro* activity of tigecycline and comparators against penicillin non-susceptible *S. pneumoniae*, 2008-2010.

Region	Drug	MIC_{50}	MIC_{90}	%S	%I	%R
All regions (n=352)	AmoxClav	1	8	67.3	9.1	23.6
	Azithromycin	64	> 64	29.7	0.9	69.4
	Ceftriaxone	0.5	2	79.6	18.2	2.3
	Clindamycin	0.12	> 64	56.6	0.3	43.1
	Levofloxacin	1	1	98.9	0.6	0.6
	Linezolid	1	1	100	--*	--*
	Meropenem	0.25	1	52.0	17.1	31.0
	Penicillin	1	4	0	56.3	43.8
	Tigecycline	0.015	0.06	96.3	--*	--*
	Vancomycin	0.5	0.5	100	--*	--*

%S: % susceptible; % I: % intermediate; %R: % resistant; AmoxClav: amoxicillin-clavulanic acid;
* Only a susceptible breakpoint is defined for this drug against S. pneumoniae.

Conclusions

- Overall in the United States, the proportion of penicillin non-susceptible *S. pneumoniae* showed a slight decrease from 43.4% to 40.4% between 2004-2006 and 2008-2010. This is encouraging even if not statistically significant.
- A decrease was also found in half of the individual U.S. regions, however only the change in West North Central was statistically significant. None of the increases (found in three regions) were statistically significant.
- The proportions of penicillin non-susceptible *S. pneumoniae* in different regions in 2008-2010 ranged from 23.3% in New England (albeit with a very small sample size) and about 28% in the Mountain and West North Central regions to 51.9% in West South Central and 61.4% in East South Central. Some of these differences were statistically significant as assessed by non-overlapping confidence intervals. Only West North Central and East South Central were statistically significantly different from the overall U.S. average (p<0.05).
- In 2008-2010, tigecycline, linezolid, levofloxacin, and vancomycin showed excellent activity (>96% susceptible) against *S. pneumoniae* regardless of phenotype. Less than 80% of PenNS SPN were susceptible to the other antimicrobials tested.