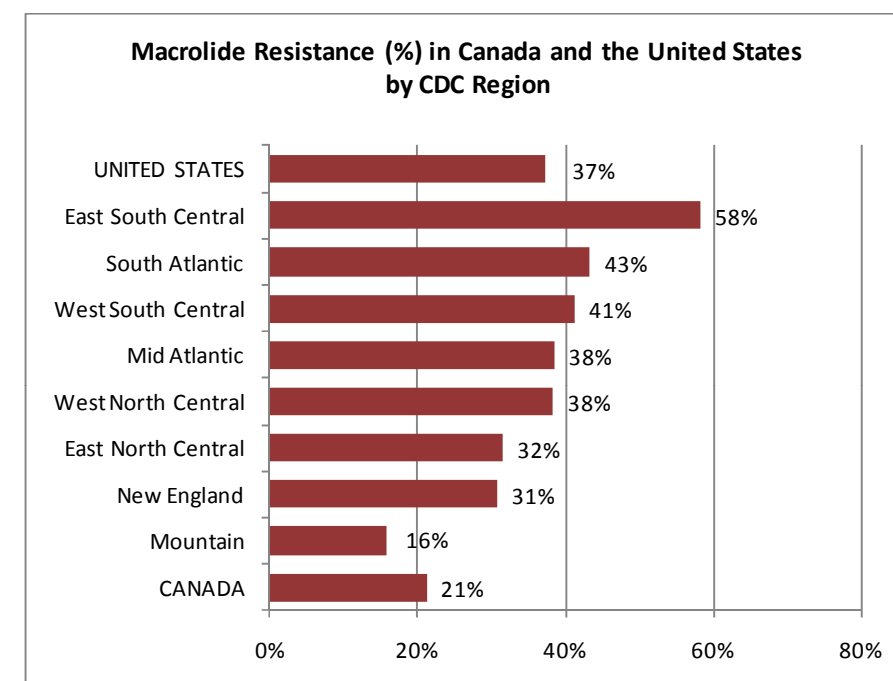


Revised Abstract

Objective: Macrolide resistance rates against *S. pneumoniae* have risen steadily for the past decade in North America. The Tigecycline Evaluation and Surveillance Trial (TEST) is an ongoing global surveillance designed to follow trends in antimicrobial activity. As part of the TEST program this report evaluates the current macrolide resistance rates in the United States and Canada and the *in vitro* activity of tigecycline against these isolates from 2008 to 2010. **Methods:** 940 clinical isolates were collected in the United States (n=808) and Canada (n=132) from 149 investigative sites. Clinical isolates were identified to the species level at each participating site and confirmed by the central laboratory. Minimum Inhibitory Concentrations (MICs) were determined by the local laboratory using sponsor supplied broth microdilution panels and interpreted according to CLSI and FDA (tigecycline) guidelines. **Results:** Tigecycline MIC₅₀, MIC₉₀, and % susceptible were 0.015, 0.03 mcg/ml and 96%, respectively, against both macrolide-susceptible and macrolide-resistant *S. pneumoniae* in this study. Regional macrolide-resistant rates for the US (and CDC regions) and Canada are as follows:



Conclusions: Overall, the macrolide resistance rate was 35% for *S. pneumoniae* from the United States (37%) and Canada (21%). Macrolide resistance varied from a low of 16% in the Mountain states to a high of 58% in the East South Central states of Alabama, Kentucky, Mississippi, and Tennessee. Tigecycline was highly active *in vitro* against this North American collection of *S. pneumoniae* without regard to macrolide resistance with over 96% of all isolates susceptible.

Introduction

Infections due to *S. pneumoniae* continue to evolve worldwide and are a major cause of morbidity and mortality. Resistance in *S. pneumoniae* not only to penicillin but also to cephalosporins, macrolides, TMP-SMX, fluoroquinolones and tetracycline is well documented.

This study was undertaken to document the current extent of macrolide-resistance and the *in vitro* activity of tigecycline against *Streptococcus pneumoniae* with macrolide-resistant determinants from diverse populations in North America. This study is part of the larger ongoing global Tigecycline Evaluation and Surveillance Trial (TEST).

Materials & Methods

- All isolates were derived from blood, CNS, respiratory, sinuses, sputum, middle ear, and other defined sources. Only one isolate per patient was accepted into the study.
- Between 2008 and 2010, 149 cumulative sites participated in the TEST program in the United States and Canada. For this report, 940 isolates of *S. pneumoniae* were identified to the species level and MICs determined at each participating laboratory.
- All organisms were deemed clinically significant by local participant criteria. Isolate inclusion was independent of medical history, antimicrobial use, age or gender. All sites identified each study isolate utilizing local laboratory site criteria.
- Antimicrobial Susceptibility Testing**
- Minimum inhibitory concentrations (MICs) were determined by the Clinical and Laboratory Standards Institute (CLSI) recommended broth microdilution testing method [1]. All antimicrobial agents were supplied by the panel manufacturers, MicroScan (Siemens Medical Solutions Diagnostics, West Sacramento, CA, USA) and Sensititre (TREK Diagnostic Systems, Cleveland, OH). MIC interpretive criteria followed guidelines published by the CLSI and the most recent United States Food and Drug Administration package insert for tigecycline where applicable [2,3].
- Quality controls (QC) were performed by each testing site on each day of testing 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 [2].

References

- Clinical Laboratory Standards Institute. 2009. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard—Eight Edition. CLSI Document M07-A08. Wayne, PA.
- Clinical Laboratory Standards Institute. 2011. Performance Standards for Antimicrobial Susceptibility Testing. Twenty-First Informational Supplement. CLSI Document M100-S21. Wayne, PA.
- Tygacil®, 2011. Tigecycline FDA prescribing information. Pfizer, Inc., Collegeville, PA.
- Zhanel GG, Palatnick L, Nichol KA, Bellyou T, Low DE, Hoban DJ. *Antimicrobial resistance in respiratory tract Streptococcus pneumoniae isolates: results of the Canadian Respiratory Organism Susceptibility Study, 1997 to 2002. Antimicrob Agents Chemother.* 2003 Jun;47(6):1867-74. Erratum in: *Antimicrob Agents Chemother.* 2003 Aug;47(8):2716.
- Jones RN, Pfaller MA. *Macrolide and fluoroquinolone (levofloxacin) resistances among Streptococcus pneumoniae strains: significant trends from the SENTRY Antimicrobial Surveillance Program (North America, 1997-1999).* J Clin Microbiol. 2000 Nov;38(11):4298-9.

Acknowledgements

We gratefully acknowledge the contributions of the investigators, laboratory personnel, and all members of the Tigecycline Evaluation and Surveillance Trial group. This study was sponsored by Pfizer Inc. IHMA is a clinical research organization that has been contracted by Pfizer Inc. to manage the TEST program.

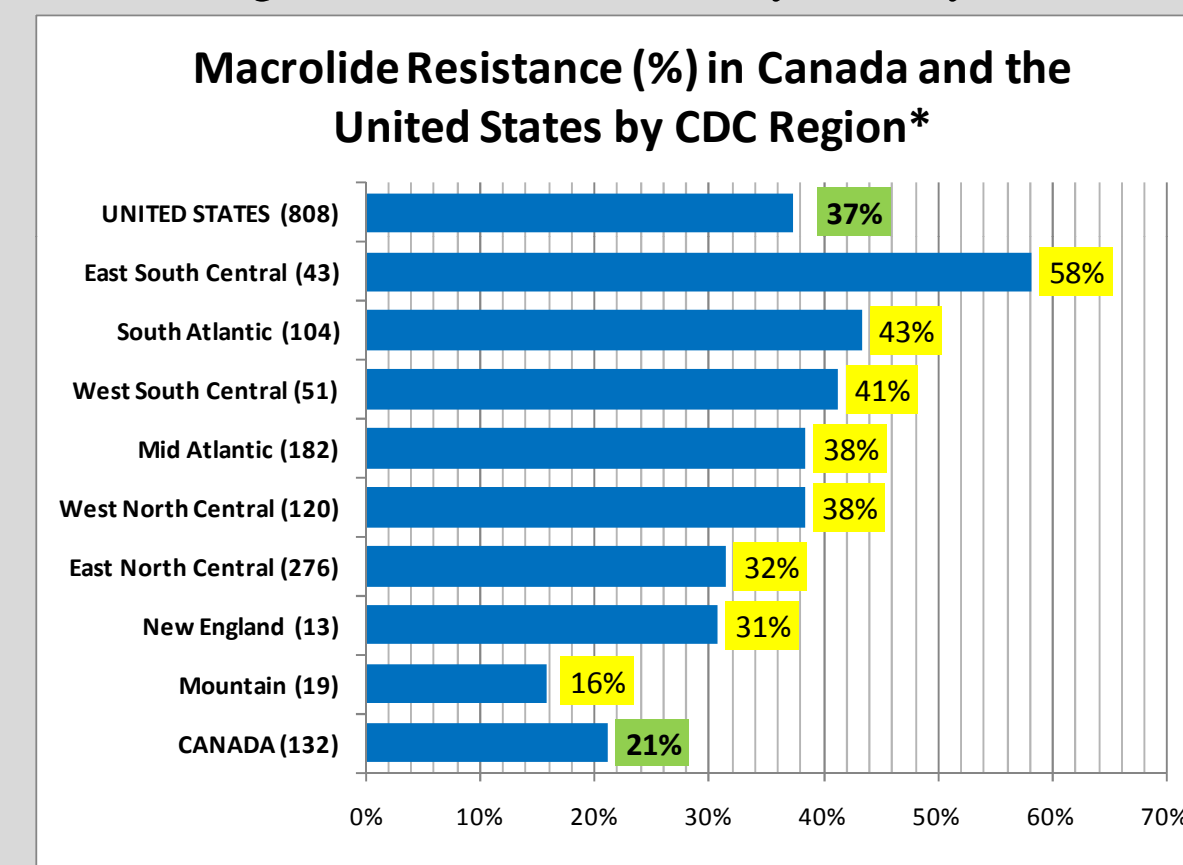
Results

Table 1. *In vitro* activity of tigecycline and comparators against 940 *S. pneumoniae* in the United States and Canada, 2008-2010.

Drug	MIC (mcg/ml)		%Sus*	%Int	%Res
	MIC ₅₀	MIC ₉₀			
Tigecycline	0.015	0.03	96.5	3.5 non-susceptible	
AmoxClav	≤0.03	4	87.5	3.4	9.9
Ceftriaxone	≤0.03	1	91.8	7.2	1.0
Erythromycin	0.12	>64	64.3	0.7	35.0
Levofloxacin	1	1	99.3	0.3	0.4
Meropenem	≤0.12	1	81.3	6.7	12.0
Penicillin	≤0.06	4	62.6	20.5	16.9

* Interpretive criteria are defined according to CLSI breakpoints in M100-S21 (2011), where available. Tigecycline breakpoints defined by the FDA (Tygacil®, 2011). Non-susceptible means no breakpoint other than susceptible is defined. **Boldfaced font** for %Sus > 90% is used for emphasis.

Figure 1. Macrolide-resistance rate (%) for 940 isolates of *S. pneumoniae* according to CDC Regions and summarized by country, 2008-2010.



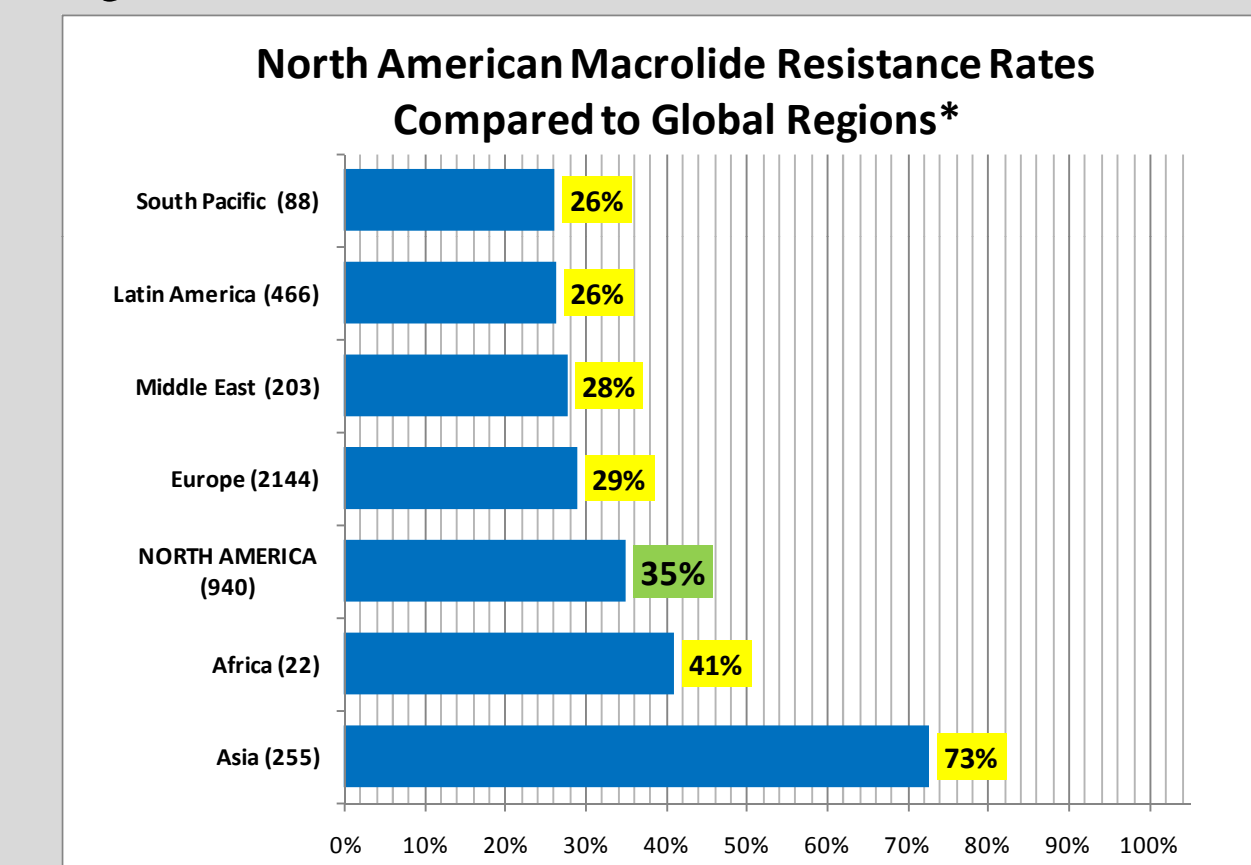
*Macrolide-resistance based upon the susceptibility to erythromycin (≥1 mcg/ml).

Table 2. *In vitro* activity of tigecycline and comparators against 329 macrolide-resistant *S. pneumoniae* in the United States and Canada, 2008-2010.

Drug	MIC (mcg/ml)		%Sus*	%Int	%Res
	MIC ₅₀	MIC ₉₀			
Tigecycline	0.015	0.03	96.1	3.9 non-susceptible	
AmoxClav	0.5	8	69.3	7.0	23.7
Ceftriaxone	0.25	2	79.3	18.5	2.2
Erythromycin	64	> 64	0	0	100
Levofloxacin	1	1	99.4	0.3	0.3
Meropenem	≤0.12	1	57.5	13.3	29.2
Penicillin	0.5	4	26.1	34.7	39.2

* Interpretive criteria are defined according to CLSI breakpoints in M100-S21 (2011), where available. Tigecycline breakpoints defined by the FDA (Tygacil®, 2011). Non-susceptible means no breakpoint other than susceptible is defined. **Boldfaced font** for %Sus > 90% is used for emphasis.

Figure 2. Macrolide-resistance rate (%) for North America compared to other global TEST regions, 2008-2010.



*Macrolide-resistance based upon the susceptibility to erythromycin (≥1 mcg/ml). North America defined as Canada and United States only.

Conclusions

- The current macrolide-resistance rate for the 940 *S. pneumoniae* collected from the North American investigative sites in this study stands at an overall 35%. Macrolide-resistance rates have increased approximately 50% in North America in the last decade from 23% in 2000 and almost 100% in Canada from 11% in 2003 to 21% in this study [4, 5].
- Tigecycline had the lowest MIC₉₀ value of all study drugs regardless of macrolide susceptibility with an MIC₉₀ value of 0.03 mcg/ml against macrolide-resistant strains. The *in vitro* activity of tigecycline against macrolide-resistant *S. pneumoniae* in this study was comparable or superior to all reported agents, including amoxicillin-clavulanic acid, ceftriaxone, and levofloxacin.
- The *in vitro* activity of tigecycline in this study suggests that tigecycline is a potent antimicrobial agent that may be beneficial in the treatment of infections due to difficult to treat macrolide-resistant *S. pneumoniae*.