

Revised Abstract

Background: Even with decreases in antibiotic consumption in Canada, non-β-lactam resistant rates against *S. pneumoniae* are on the rise. The Tigecycline Evaluation Surveillance Trial (T.E.S.T.) program is an ongoing global surveillance designed to follow trends in antimicrobial activity. This report evaluates tigecycline activity in United States and Canada against macrolide-resistant *S. pneumoniae* during the time from 2004 to 2008. **Methods:** 2943 clinical isolates were collected from 485 investigative sites in the United States and Canada. 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 supplied broth microdilution panels and interpreted according to CLSI guidelines. **Results:** Summary data for the 961 (32.7%) macrolide-resistant strains are as follows:

Drug	Macrolide-Resistant <i>S. pneumoniae</i> (n=961)				
	MIC ₅₀	MIC ₉₀	%Sus	%Int	%Res
Tigecycline	0.03	0.12	na	na	na
AmoxClav	0.25	4	77.5	13.5	8.9
Ceftriaxone	0.25	1	84.1	11.3	4.6
Erythromycin	64	>64	0.0	0.0	100.0
Imipenem	0.25	1	46.6	44.7	8.6
Levofloxacin	0.5	1	98.5	0.3	1.1
Linezolid	≤0.5	1	100.0	0.0	0.0
Meropenem	≤0.12	1	53.4	1.9	44.8
Penicillin	0.5	4	20.5	43.6	35.9

na = breakpoints not defined

Conclusions: Tigecycline demonstrated the lowest MIC₅₀ and MIC₉₀ *in vitro* values of all study drugs against macrolide-resistant *S. pneumoniae*. Tigecycline *in vitro* activity suggests that tigecycline may be active against this important clinical pathogen and resistant phenotype.

Introduction

Tigecycline is a member of a new class of antimicrobial agents, the glycolcyclines. This synthetic analogue of the tetracyclines exhibits antibacterial activity that is both bacteriostatic and, in certain instances, bactericidal with killing activity that is as much as fourfold better than vancomycin and daptomycin [1, 2] against certain pathogens. The development of tigecycline is important in that it and other glycolcyclines are active against bacterial strains carrying either or both of the two major forms of tetracycline resistance: efflux and ribosomal protection. A single chemical modification of tigecycline overcomes the two molecularly distinct forms of resistance while maintaining activity against susceptible gram-positive, gram-negative, aerobic, and anaerobic bacteria [3].

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. New guidelines for the management of in-patient and out-patient community acquired pneumonia have recently been published [4].

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 Trials (T.E.S.T.) program.

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.
- Clinical isolates were collected and tested between January 2004 and December 2008 from 485 investigative sites in the United States and Canada. Isolates were identified to the species level and tested at each site by the 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.
- Minimum inhibitory concentrations (MICs) were determined by the Clinical and Laboratory Standards Institute (CLSI) recommended broth microdilution testing method [5]. Tigecycline was supplied by Wyeth Pharmaceuticals (Collegeville, PA, USA). All other agents were supplied by the panel manufacturers, MicroScan (Dade Behring Inc., West Sacramento, CA, USA) and Trek (TREK Diagnostic Systems, Cleveland, OH). The following antimicrobial agents were included on the panels with their dilution ranges (expressed in mg/L): amoxicillin/clavulanic acid (0.12/0.06-32/16); ceftriaxone (0.06-64); imipenem (0.06-16); linezolid (0.5-8); levofloxacin (0.008-8); meropenem (0.12-16); minocycline (0.5-16); tigecycline (0.008-16); penicillin (0.06-8); and piperacillin/tazobactam (0.06/4-128/4). MIC interpretive criteria followed guidelines published by the CLSI [6]. There are currently no breakpoints established for tigecycline against pneumococci.
- 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 (2009) guidelines [6].

References

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Acknowledgements

This study was sponsored by a grant from Wyeth Pharmaceuticals. We gratefully acknowledge the contributions of all investigators, laboratory personnel and from the entire Tigecycline Evaluation Study Trials program group.

Results

Table 1. *In vitro* activity of tigecycline and comparators against 2,943 *S. pneumoniae* in the United States and Canada.

Drug	MIC (mg/L)		%Sus	%Int	%Res (n)
	MIC ₅₀	MIC ₉₀			
Tigecycline	0.03	0.06	na	na	na
AmoxClav	≤0.03	2	92.2	4.8	3.1
Ceftriaxone	≤0.03	1	93.8	4.5	1.8
Erythromycin	0.12	64	66.7	0.6	32.7 (961)
Imipenem	≤0.12	0.5	72.0	24.2	3.8
Levofloxacin	0.5	1	99.1	0.2	0.6
Linezolid	≤0.5	1	100.0	0.0	0.0
Meropenem	≤0.12	1	79.9	1.1	18.9
Penicillin	≤0.06	2	57.8	27.9	14.3

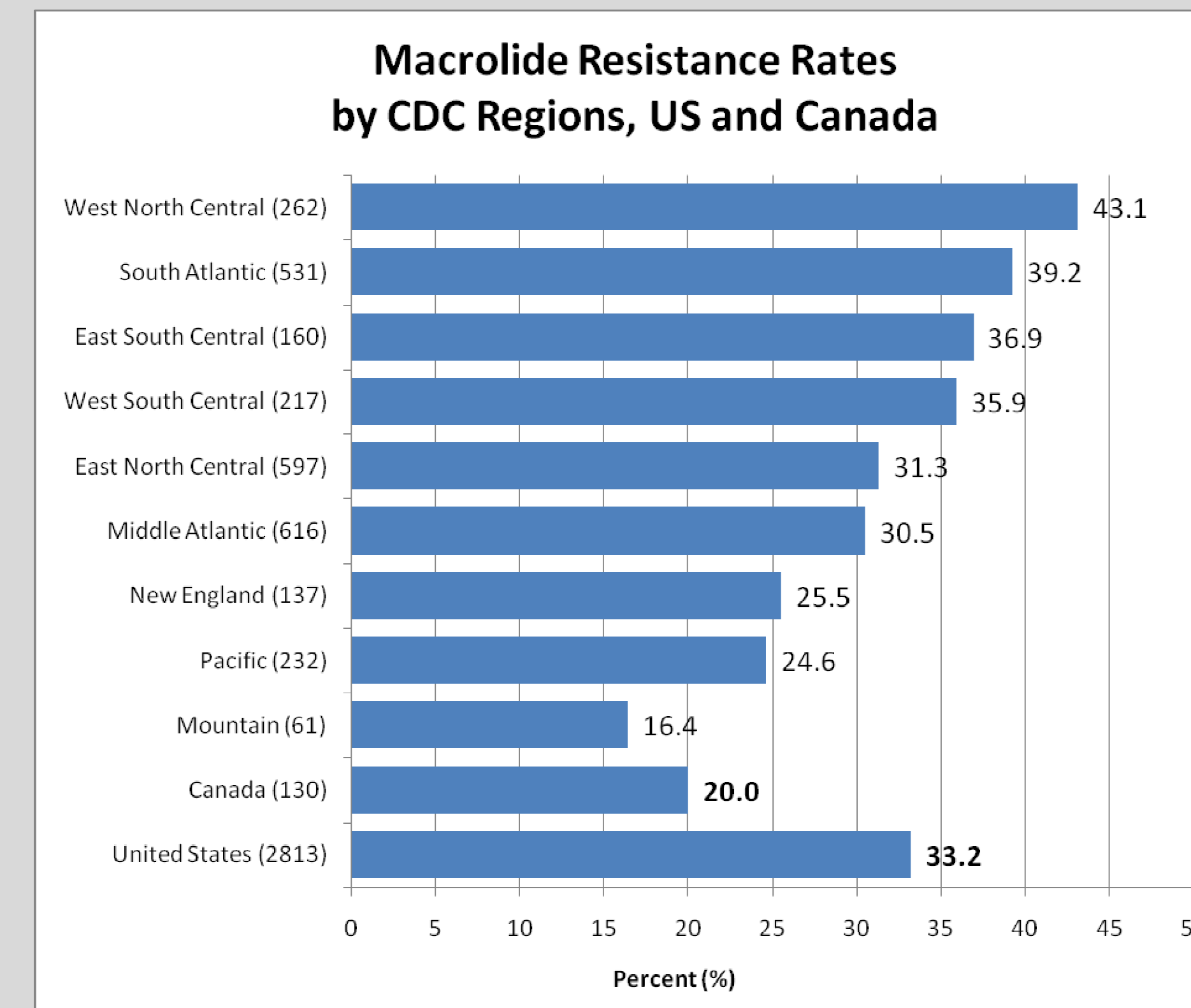
*Interpretive criteria are defined according to CLSI breakpoints (M100-S19, 2009).

na = breakpoints not available.

Table 2. Frequency distribution of tigecycline and comparators against 961 macrolide-resistant *S. pneumoniae* in the United States and Canada.

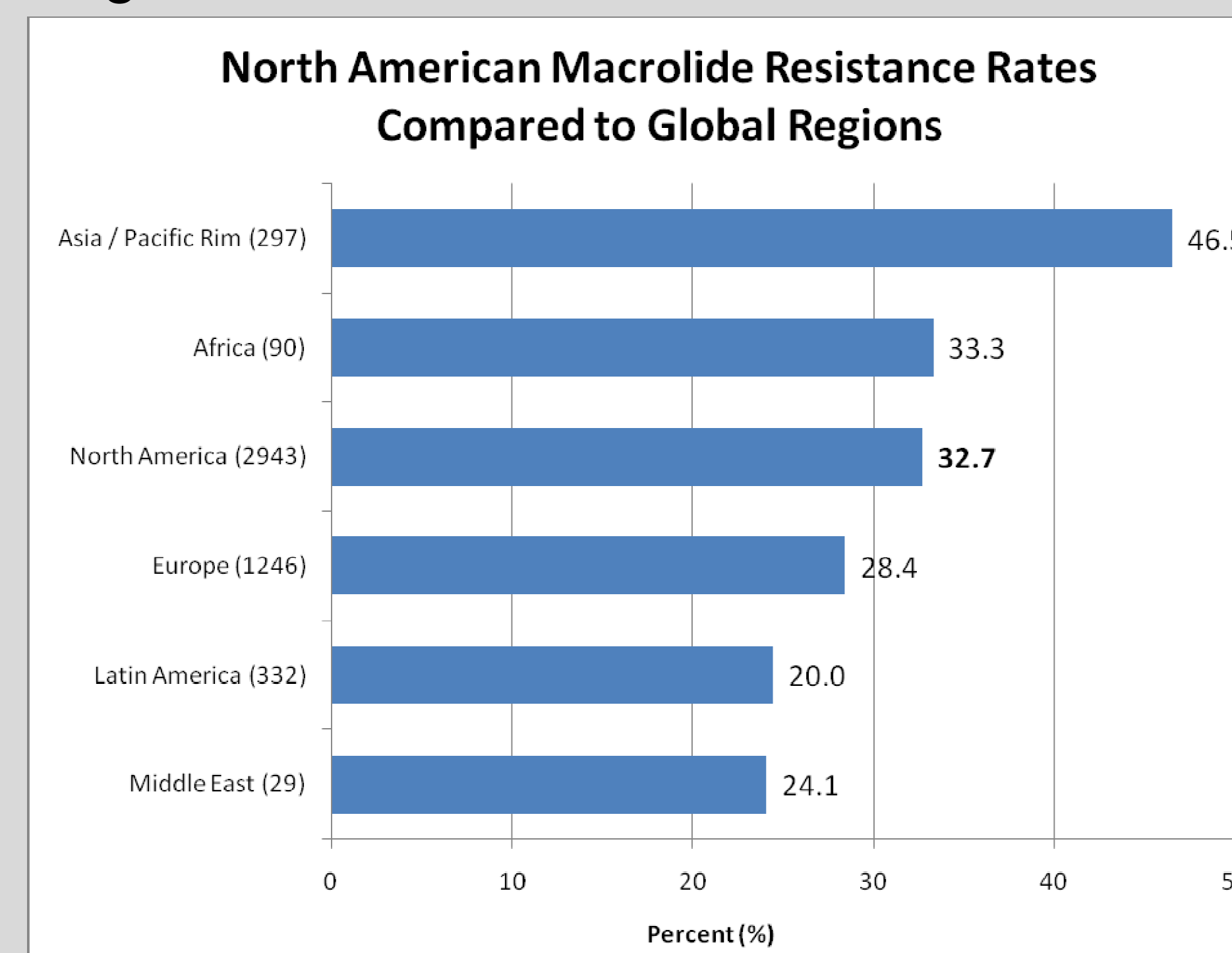
Drug/ NICum%	MIC (mg/L)														
	≤0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	≥128
Tigecycline	47	282	429	103	91	7	1	1							
AmoxClav	4.9	34.2	78.9	89.6	99.1	99.8	99.9	100							
Ceftriaxone	22.9	32.2	41.8	50.2	57.6	67.1	77.5	91.1	99.5	100					
Erythromycin	19.3	32.0	43.0	54.1	66.3	93.0	97.1	99.6	100						
Imipenem			260	156	150	64	4	1					2		
Levofloxacin			40.8	65.3	88.9	98.9	99.5	99.7	100						
Linezolid			9	10	31	45.4	43.9	4	3	3	7	1			
Meropenem			0.9	2.0	5.2	52.4	98.1	98.5	98.9	99.2	99.9	100			
Penicillin			562	390	9										
PipTazo			50.9	57.4	69.8	97.5	99.7	100							
			165	21	40	90	7	1							
			197	108	132	81	98	163	162	18	2				
			20.5	31.7	45.5	53.9	64.1	81.1	97.9	99.8	100				
			409	105	93	165	174	14	1						
			42.6	53.5	63.2	80.3	98.4	99.9	100						

Figure 1. Macrolide-resistant rate (%) for 1,961 isolates of *S. pneumoniae* according to CDC Regions and summarized by country.*



*Macrolide-resistance based upon the susceptibility of erythromycin (resistance ≥1 mg/L)

Figure 2. Macrolide-resistant rate (%) for North America compared to other Global Regions.*



*Macrolide-resistance based upon the susceptibility of erythromycin (resistance ≥1 mg/L)

Conclusions

- The current macrolide-resistant rate for the 2,943 *S. pneumoniae* collected from the North American investigative sites in this study stands at an overall 32.7%. Macrolide-resistance is increasing at alarming rates with increases of approximately 50% in North America in the last decade (23%, Jones, 2000) and almost 100% in Canada from 11% (Zhanel, 2003) to 20% in this study.
- Macrolide-resistance rates in the Asia/Pacific Rim countries (47%) are approaching parity with macrolide-susceptible rates.
- Tigecycline had the lowest MIC₉₀ values of all study drugs regardless of macrolide susceptibility with MIC₉₀ values of 0.12 mg/L against all macrolide-resistant strains and inhibiting all but a single strain at 0.5 mg/L. The *in vitro* activity of tigecycline was comparable or superior to amoxicillin-clavulanic acid, ceftriaxone, levofloxacin, and linezolid against all macrolide-resistant *S. pneumoniae* in this study.
- 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*.