

## Revised Abstract

**Background:** Even with decreases in antibiotic consumption, 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 Europe against macrolide-resistant *S. pneumoniae* during the years of 2004 to 2008. **Methods:** 1246 clinical isolates of *S. pneumoniae* were collected from 320 investigative sites from 24 countries in the Europe. 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 EUCAST guidelines. **Results:** Summary data for the 354/1246 (28.4%) macrolide-resistant strains are as follows:

Drug	Macrolide-Resistant <i>S. pneumoniae</i> (n=354)			
	MIC <sub>50</sub>	MIC <sub>90</sub>	%Sus	%Res*
Tigecycline	0.03	0.12	na	na
AmoxClav	0.06	2	95.5	1.4
Ceftriaxone	0.12	1	79.7	0.8
Imipenem	≤0.12	0.5	99.5	0.5
Levofloxacin	0.5	1	99.2	0.8
Linezolid	≤0.5	1	100.0	0.0
Meropenem	0.25	1	99.3	0.7
Minocycline	2	8	38.1	56.5
Penicillin	0.25	2	43.2	6.2

\*Macrolide-resistant: erythromycin ≥1 mg/L; na = breakpoints not defined

**Conclusions:** Tigecycline demonstrated the lowest MIC<sub>50</sub> and MIC<sub>90</sub> *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 tetracyclines. 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 glycylyclines 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 *in vitro* activity of tigecycline against *Streptococcus pneumoniae* with macrolide-resistant determinants in a diverse global population. 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 320 investigative sites in 24 European countries. 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.
- 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 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 published guidelines published by EUCAST where available. Where EUCAST interpretive criteria were not available, breakpoints were used as defined the Clinical and Laboratory Standards Institute [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 [7].

## 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 1,246 *S. pneumoniae* in Europe.

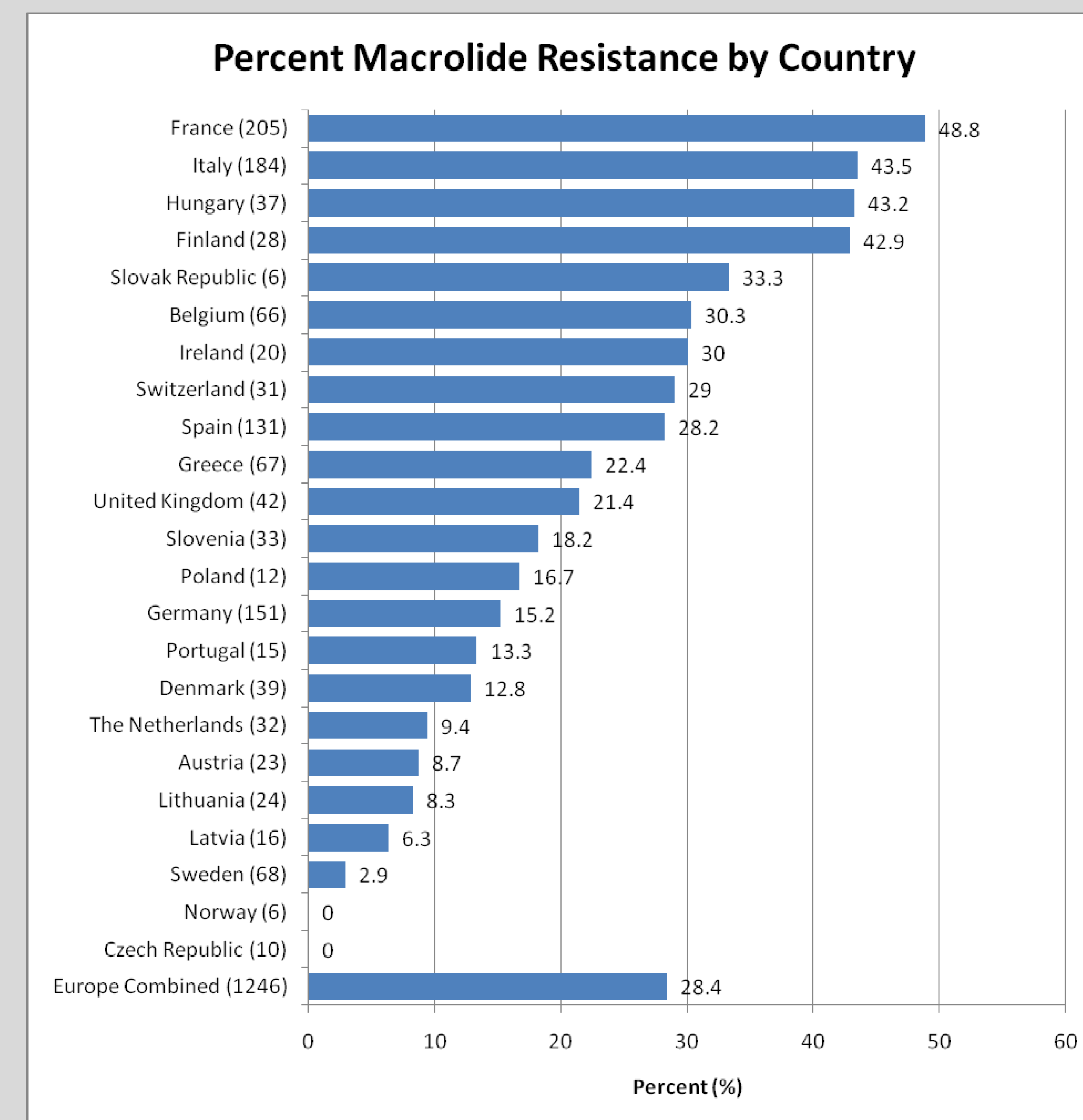
Drug	MIC (mg/L)		%Sus*	%Res
	MIC <sub>50</sub>	MIC <sub>90</sub>		
Tigecycline	0.03	0.12	na	na
AmoxClav	≤0.03	1	98.1	0.6
Ceftriaxone	≤0.03	0.5	90.7	0.5
Erythromycin	0.12	>64	71.3	28.4
Imipenem	≤0.12	0.25	99.6	0.4
Levofloxacin	0.5	1	99.5	0.5
Linezolid	≤0.5	1	100.0	0.0
Meropenem	≤0.12	0.5	99.6	0.4
Minocycline	≤0.25	4	76.9	20.1
Penicillin	≤0.06	1	71.7	2.1

\*Interpretive criteria are defined according to EUCAST guidelines (March, 2009), where available. Where no EUCAST guidelines exist, CLSI breakpoints are used (M100-S19, 2009). na = breakpoints not available.

Table 2. Frequency distribution of tigecycline and comparators against 354 macrolide-resistant *S. pneumoniae* in Europe.

Drug/N/Cum%	MIC (mg/L)														
	<0.08	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	≥128
Tigecycline	11	90	144	57	46	4	2								
	3.1	28.5	69.2	85.3	98.3	99.4	100.0								
AmoxClav			165	31	18	16	26	40	41	10	6	1			
			46.6	55.4	60.5	65.0	72.3	83.6	95.2	98.0	99.7	100.0			
Ceftriaxone			135	37	35	23	51	59	11	3					
			38.1	48.6	58.5	65.0	79.4	96.0	99.2	100.0					
Erythromycin							1	6	13	38	18	21	122	135	
							0.3	2.0	5.6	16.4	21.5	27.4	61.9	100.0	
Imipenem			149	39	24	4									
			68.7	86.6	97.7	99.5									
Levofloxacin			1	5	15	176	146	8	1		1	1			
			0.3	1.7	5.9	55.6	96.9	99.2	99.4		99.7	100.0			
Linezolid						224	127	3							
						63.3	99.2	100.0							
Meropenem			66	11	28	29	2					1			
			48.2	56.2	76.6	97.8	99.3					100.0			
Minocycline			113	22	19	47	70	66	17						
			31.9	38.1	43.5	56.8	76.6	95.2	100.0						
Penicillin			153	24	31	31	37	56	20	1	1				
			43.2	50.0	58.8	67.5	78.0	93.8	99.4	99.7	100.0				

Figure 1. Macrolide-resistant rate (%) for 1,246 isolates of *S. pneumoniae* categorized by country.\*



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

## Conclusions

- The current macrolide-resistant rate for the 1,246 *S. pneumoniae* collected from the European investigative sites in this study stands at an overall 28.4%. Macrolide-resistant *S. pneumoniae* rates ranged from a low 2.9% to 48.8% in institutions studied where there were 20 or more isolates evaluated. Four countries, France, Italy, Hungary and Finland are approaching parity with macrolide-susceptible and -resistant strains with resistant rates in excess of 40%.
- Tigecycline had the lowest MIC<sub>90</sub> value of all study drugs at 12 mg/L and exhibited no apparent cross-resistance with either macrolide-resistant determinants (erythromycin) or minocycline, inhibiting all strains at 0.5 mg/L.
- The *in vitro* activity of tigecycline was comparable to imipenem, 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*.