

Revised Abstract

Background: *S. pneumoniae* continues to be an important cause of community acquired pneumonia and bacteremia globally. Macrolides constitute an important first or second line antibiotic choice for community acquired SPN infections. This study describes the prevalence of macrolide resistance in European SPN 2009/2010 and the activity of relevant comparator antibiotics against *Streptococcus pneumoniae* of various phenotypes. **Methods:** 1101 clinical isolates of SPN were collected from European countries between 2009 and 2010 from a variety of clinical sources including blood and the lower respiratory tract. MICs were determined and interpreted by broth microdilution according to EUCAST and FDA (tigecycline) guidelines. **Results:** The following table reports the percent susceptible and MIC₉₀ (mg/L) of SPN including resistant phenotypes.

Drug	All SPN		PSSP		PISP		PRSP		Macro R SPN	
	% S	MIC ₉₀	% S	MIC ₉₀	% S	MIC ₉₀	% S	MIC ₉₀	% S	MIC ₉₀
Azithromycin	71.1	64	83.2	64	43.5	>64	30.6	>64	0	>64
Ceftriaxone	87.7	1	99.9	0.06	67.0	1	8.2	2	71.6	2
Clarithromycin	71.7	64	83.5	32	45.1	>64	30.6	>64	1.0	>64
Clindamycin	81.7	>64	90.4	0.25	61.7	>64	53.1	>64	36.1	>64
Levofloxacin	99.5	1	99.9	1	98.5	1	98	1	98.7	1
Linezolid	100	1	100	1	100	1	100	1	100	1
Meropenem	100	0.5	100	≤0.12	100	0.5	100	1	100	1
Penicillin	70.8	2	100	≤0.06	0	1	0	4	41.8	4
Tigecycline	99.6	0.03	99.6	0.03	99.6	0.03	100	0.03	99.7	0.03
N	1101		779		253		49		299	

Conclusions: Linezolid, meropenem, tigecycline and levofloxacin were the most active agents against SPN including both penicillin and macrolide resistant phenotypes with % susceptible >98%. In Europe in 2009-2010 28.6% of SPN were resistant to the macrolides azithromycin or clarithromycin.

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. New guidelines for the management of in-patient and out-patient community acquired pneumonia have recently been published [1-3].

This study was undertaken to document the current extent of macrolide-resistance and the *in vitro* activity of tigecycline against *S. pneumoniae* with macrolide-resistant determinants from a multi-center European population. This study is part of the larger ongoing global Tigecycline European Surveillance Trial (TEST) 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 2009 and December 2010 from 228 cumulative investigative sites in 24 European countries. Isolates were identified to the species level and MICs determined 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 [4]. Tigecycline was supplied by Pfizer Pharmaceuticals (Collegetown, 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): Azithromycin (0.03- 64); clarithromycin (0.015-64); clindamycin (0.015-64); ceftriaxone (0.03-64); linezolid (0.5-8); levofloxacin (0.008-8); meropenem (0.12-16); tigecycline (0.008-16); and penicillin (0.06-8). MIC interpretive criteria followed guidelines published by the EUCAST [5], where available. Tigecycline breakpoints are defined in Federal Drug Administration (FDA) product information [6].
- 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 (2011) guidelines [7].

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Results

Table 1. *In vitro* activity of tigecycline and comparators against 1,101 *S. pneumoniae* from Europe, 2009-2010.

Organism	Drug	(mg/L)			%Sus	%Int	%Res
		EUCAST (≤S I ≥R)*	MIC ₅₀	MIC ₉₀			
<i>S. pneumoniae</i> (n=1101)	Azithromycin	≤0.25 0.5 ≥1	0.06	64	71.1	0.3	28.6
	Ceftriaxone	≤0.5 1-2 ≥4	≤0.03	1	87.7	11.4	1.0
	Clarithromycin	≤0.25 0.5 ≥1	0.03	64	71.7	0.3	28.0
	Clindamycin	≤0.5 ≥1	0.06	>64	81.7	–	18.3
	Levofloxacin	≤2 ≥4	1	1	99.5	–	0.6
	Linezolid	≤4 ≥8	1	1	100	–	0
	Meropenem	≤2 ≥4	≤0.12	0.5	100	–	0
<i>S. pneumoniae</i> Penicillin-Sus (n=779)	Penicillin	≤0.06 0.12-2 ≥4	≤0.06	2	70.8	24.8	4.5
	Tigecycline	≤0.06 – –	0.015	0.03	99.6	–	–
	Azithromycin	≤0.25 0.5 ≥1	0.06	64	83.2	0	16.8
	Ceftriaxone	≤0.5 1-2 ≥4	≤0.03	0.06	99.9	0.1	0
	Clarithromycin	≤0.25 0.5 ≥1	0.03	32	83.5	0.1	16.4
	Clindamycin	≤0.5 ≥1	0.06	0.25	90.4	–	9.6
	Levofloxacin	≤2 ≥4	1	1	99.9	–	0.1
<i>S. pneumoniae</i> Penicillin-Int (n=253)	Linezolid	≤4 ≥8	1	1	100	–	0
	Meropenem	≤2 ≥4	≤0.12	≤0.12	100	–	0
	Penicillin	≤0.06 0.12-2 ≥4	≤0.06	≤0.06	100	0	0
	Tigecycline	≤0.06 – –	0.015	0.03	99.6	–	–
	Azithromycin	≤0.25 0.5 ≥1	8	> 64	43.5	1.2	55.3
	Ceftriaxone	≤0.5 1-2 ≥4	0.25	1	67.0	30.4	2.6
	Clarithromycin	≤0.25 0.5 ≥1	4	> 64	45.1	0.8	54.2
<i>S. pneumoniae</i> Penicillin-Res (n=49)	Clindamycin	≤0.5 ≥1	0.06	> 64	61.7	–	38.3
	Levofloxacin	≤2 ≥4	1	1	98.5	–	1.5
	Linezolid	≤4 ≥8	1	1	100	–	0
	Meropenem	≤2 ≥4	0.25	0.5	100	–	0
	Penicillin	≤0.06 0.12-2 ≥4	0.5	2	0	100	0
	Tigecycline	≤0.06 – –	0.015	0.03	99.6	–	–
	Azithromycin	≤0.25 0.5 ≥1	64	> 64	30.6	0.0	69.4
Macrolide-Res (n=299)	Ceftriaxone	≤0.5 1-2 ≥4	2	2	8.2	83.7	8.2
	Clarithromycin	≤0.25 0.5 ≥1	32	> 64	30.6	–	69.4
	Clindamycin	≤0.5 ≥1	0.25	> 64	53.1	–	46.9
	Levofloxacin	≤2 ≥4	1	1	98	–	2
	Linezolid	≤4 ≥8	1	1	100	–	0
	Meropenem	≤2 ≥4	1	1	100	0	0
	Penicillin	≤0.06 0.12-2 ≥4	4	4	0	0	100.0
Tigecycline	≤0.06 – –	0.015	0.03	100	–	–	

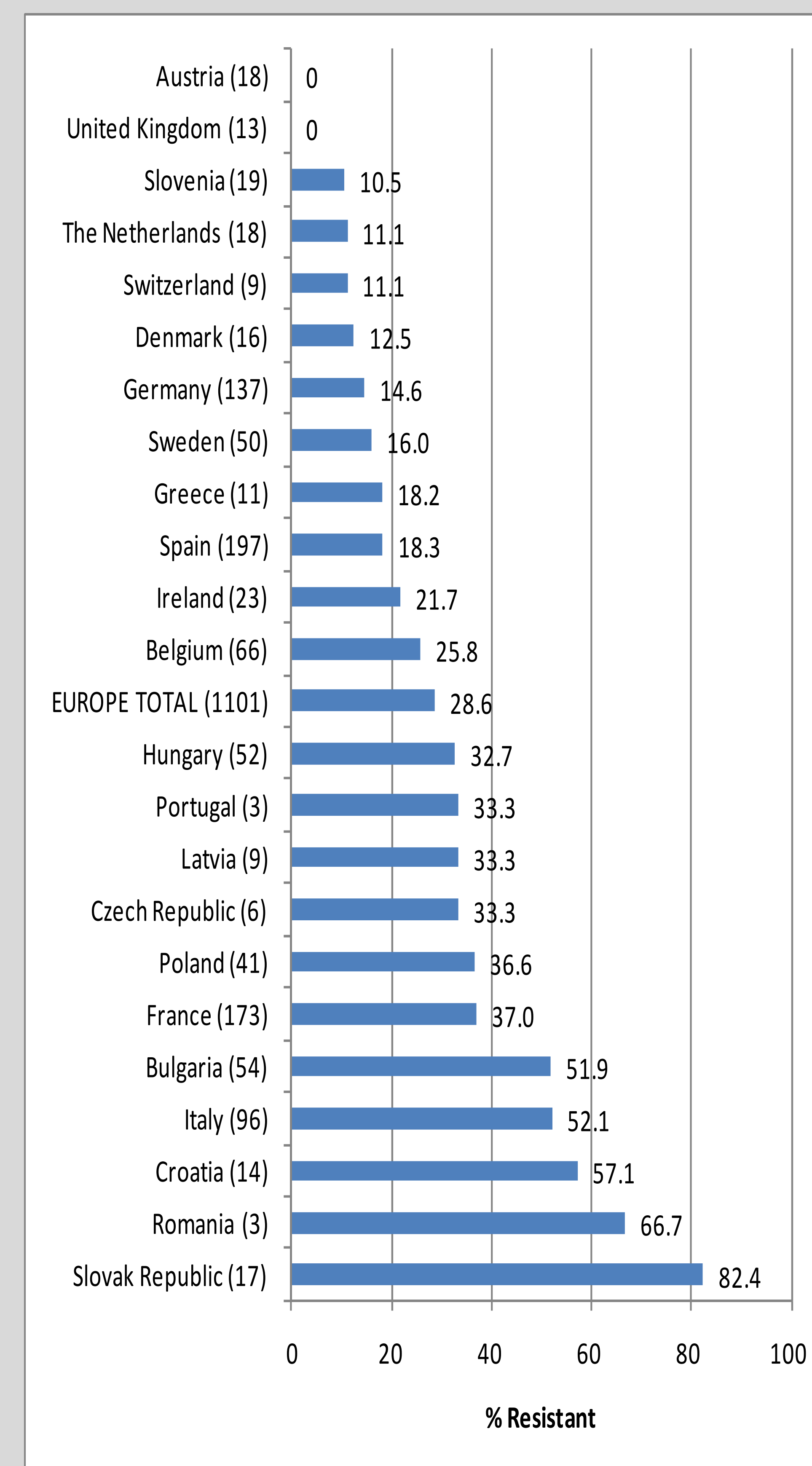
* Interpretive criteria are defined according to EUCAST breakpoints (Jan 2011), where available; Tigecycline breakpoints defined by FDA (Tygacil®, 2010); – Breakpoint not defined.
Note: *S. pneumoniae* n=1045 for azithromycin, clindamycin, and clarithromycin.

Table 2. *In vitro* activity of tigecycline and comparators against 299 macrolide-resistant *S. pneumoniae* from Europe, 2009-2010.

Organism	Drug	(Mg/L)			%Sus	%Int	%Res
		EUCAST (≤S I ≥R)*	MIC ₅₀	MIC ₉₀			
<i>S. pneumoniae</i>	Azithromycin	≤0.25 0.5 ≥1	64	>64	0	0	100
Macrolide-Res (n=299)	Ceftriaxone	≤0.5 1-2 ≥4	0.12	2	71.6	26.8	1.7
	Clarithromycin	≤0.25 0.5 ≥1	64	>64	1.0	1.0	98.0
	Clindamycin	≤0.5 ≥1	>64	>64	36.1	–	63.9
	Levofloxacin	≤2 ≥4	1	1	98.7	–	1.3
	Linezolid	≤4 ≥8	1	1	100	–	0
	Meropenem	≤2 ≥4	≤0.12	1	100	–	0
	Penicillin	≤0.06 0.12-2 ≥4	0.25	4	41.8	46.8	11.4
Tigecycline	≤0.06 – –	0.015	0.03	99.7	–	–	

* Interpretive criteria are defined according to EUCAST breakpoints (Jan 2011), where available; Tigecycline breakpoints defined by FDA (Tygacil®, 2010); – Breakpoint not defined. Macrolide resistance determined by azithromycin susceptibility.

Figure 1. European macrolide-resistant rates (%) for *S. pneumoniae* categorized by country.*



*Macrolide-resistance based upon the susceptibility to azithromycin (resistant ≥1 mg/L)

Conclusions

- The current macrolide-resistant rate for the 1,101 *S. pneumoniae* collected from the global TEST investigative sites in this study stands at an overall 28%.
- Macrolide-resistance rates for *S. pneumoniae* vary widely from country to country in Europe. Macrolide-resistance rates ranged from a low of 0% in Austria and the United Kingdom to 82% in the Slovak Republic, although the numbers collected from each of the countries is low and may skew the data. For countries with n's >50, the macrolide-resistant rates ranged from 14.6% in Germany to 52% in Italy.
- Levofloxacin, linezolid, and meropenem demonstrated percents susceptible of >98% for all isolates including penicillin- and macrolide-resistant isolates. Tigecycline demonstrated potent *in vitro* activity against all *S. pneumoniae*, including both penicillin- and macrolide-resistant isolates, with percents susceptible of 100% and 99.7%, respectively, using the FDA breakpoint of 0.06 mg/L since breakpoints for tigecycline against *S. pneumoniae* remain undefined by EUCAST.
- 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*.