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Antibiotic susceptibility of *Streptococcus pneumoniae* in the US in 2014

Keedy K, Li J, Nenninger A, Sheets A, Fernandes P, Tillotson G
Cempra, Inc., Chapel Hill, NC 27517

Glenn Tillotson
Cempra, Inc.
6320 Quadrangle Drive, Bldg. 4
gtillotson@cempra.com
984-999-0106

INTRODUCTION

Solithromycin was designed primarily to overcome macrolide-resistant streptococci, including multidrug-resistant (MDR) *Streptococcus pneumoniae*. Macrolides exert their effect by inhibiting protein synthesis, specifically through inhibition of the 50S ribosomal subunit (1). Solithromycin (formerly CEM-101) is a fourth-generation macrolide and the first fluoroketolide in Phase III clinical development. Intravenous, oral capsules, and a pediatric suspension have been developed for the treatment of moderate to moderately-severe community-acquired bacterial pneumonia (CABP). Solithromycin has demonstrated potent activity against *S. pneumoniae*, including MDR and macrolide-resistant strains and genotypes (2,3-5). Interestingly, unlike older macrolides, solithromycin exhibits bactericidal activity when tested against macrolide-susceptible streptococci and many other pathogens (2). Solithromycin interacts with three distinct sites on the bacterial ribosome, thereby limiting the emergence of resistant strains (6). In contrast, the older macrolides, such as erythromycin and azithromycin, interact at a single site

S. pneumoniae is the predominant causative agent of CABP. The introduction of the seven-valent pneumococcal conjugate vaccine (PCV7) into the United States childhood vaccine schedule in 2000, followed by the PCV13, in combination with the PPSV23 vaccine in the high risk adults, combined with the selective pressure of antimicrobial use, have been associated with the emergence of MDR strains outside of vaccine coverage. These observations highlight the changing landscape of circulating clones of *S. pneumoniae* and the prevalence of antimicrobial resistance in this species, which support the need for maintained antimicrobial resistance surveillance. Moreover, non-vaccine serotypes are replacing serotypes covered in current vaccines. Indeed, non-encapsulated strains of *S. pneumoniae* (NESp) such as ST344 and ST448 may be the cause of invasive and non-invasive infections. NESp strains are frequently resistant to a range of commonly prescribed antibiotics including penicillin and azithromycin (7). Solithromycin has also demonstrated activity comparable to azithromycin against *Haemophilus influenzae*, and very potent activity against *Moraxella catarrhalis*, beta-hemolytic streptococci, *Legionella pneumophila*, *Mycoplasma pneumoniae* (including macrolide-resistant strains), and *Chlamydophila pneumoniae*.

This study reports the incidence of antibiotic susceptibility among 2014 surveillance isolates of *S. pneumoniae* from the nine CDC Census divisions. We also show the macrolide-resistance trend over 6 years in the US.

MATERIALS AND METHODS

A total of 4,567 non-replicative CABP *S. pneumoniae* United States isolates collected prospectively between the years 2008 to 2014 were investigated in this study. The number of unique isolates per year is as follows: 765 in 2008, 796 in 2009, 925 in 2010, 1369 in 2011, and 715 in 2014. These isolates were recovered consecutively from patients with respiratory tract infections (RTI), bloodstream infections (BSI) and other infection types.

Isolates were identified by the submitting laboratories and confirmed by JMI Laboratories (North Liberty, Iowa, US) using standard bacteriologic algorithms and methodologies, including the use of Vitek Identification Systems (bioMerieux), matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF-MS), and DNA sequencing based methods, when required.

Isolates were tested for susceptibility by broth microdilution methods, according to the recommendations of CLSI (8,9). MIC interpretations were based on CLSI breakpoint criteria (8,9). Macrolide resistance rates were based on erythromycin and/or azithromycin and/or clarithromycin MICs as available (in 2014 only azithromycin data was collected).

RESULTS

The antimicrobial susceptibility patterns of US isolates for *S. pneumoniae* in 2014 are shown in **Table 1**. These are expressed as MIC_{50}, MIC_{90}, MIC range, and % S, %I or %R based on approved CLSI breakpoints. Solithromycin does not have approved breakpoints, therefore only MICs are presented. **Figure 1** shows the distribution of MICs for azithromycin and solithromycin for 2014. The resistance breakpoint for azithromycin is ≥ 2 µg/mL, thus 48% of isolates are considered macrolide-resistant. IDSA guidelines for treatment of CABP recommend alternative class(es) of antibiotic be considered for empirical therapy when the local, high-level resistance rate (≥16 µg/mL) exceeds 25%. **Table 2** shows the rates of azithromycin and high-level macrolide resistance by CDC Census division as well as azithromycin and penicillin co- resistance for 2014. Overall, azithromycin resistance exceeded 30% in all of the nine CDC divisions, with high-level resistance >25% in 8 of 9 divisions. *S. pneumoniae* resistance to both azithromycin and penicillin was highest in the East South Central division. **Figure 2** illustrates the overall and high-level macrolide resistance data by US Census Divisions. **Figure 3** shows the increasing rate of azithromycin resistance in the US from 2008-2014.

Table 1: Activity of solithromycin and comparators when tested against *S. pneumoniae* isolated in the US in 2014

Antimicrobial Agent	MIC (µg/mL)			Interpretation[a]		
	MIC_{50}	MIC_{90}	Range	%S	%I	%R
Solithromycin	0.008	0.25	0.002 — 1	-	-	-
Azithromycin	0.25	>32	0.03 — >32	51.3	0.3	48.4
Amoxicillin-Clavulanate	≤1	4	≤1 — >8	88.4	4.2	7.4[b]
Ampicillin	≤0.25	4	≤0.25 — >8	-	-	-
Ceftriaxone	≤0.06	1	≤0.06 — 8	80.8	11.9	7.3[c]
				92.7	6.0	1.3[b]
Clindamycin	≤0.25	>2	≤0.25 — >2	80.8	1.3	17.9
Linezolid	1	1	≤0.12 — 2	100.0	-	-
Moxifloxacin	≤0.12	0.25	≤0.12 — >4	98.3	1.4	0.3
Penicillin	≤0.06	2	≤0.06 — 8	57.2	29.5	13.3[d]
				57.2	-	42.8[e]
				92.7	6.3	1.0[f]
Tetracycline	≤0.5	>8	≤0.5 — >8	75.2	0.7	24.1
Trimethoprim-Sulfamethoxazole	≤0.5	>4	≤0.5 — >4	69.1	12.2	18.7
Vancomycin	0.25	0.5	≤0.12 — 1	100.0	-	-

a. Criteria as published by CLSI [2015]; "-" = breakpoints not available to interpret; b. Using Non-Meningitis breakpoints; c. Using Meningitis breakpoints; d. Using Oral breakpoints; e. Using Parenteral, Meningitis breakpoints; f. Using Parenteral, Non-Meningitis breakpoints

Table 2: *Streptococcus pneumoniae* resistance by CDC Census Division in 2014

US Census Division	# of Isolates	Macrolide-Resistance[a]	Macrolide- and Penicillin-Resistance	High-level Macrolide Resistance
New England	81	43.2%	11.1%	30.9%
Mid-Atlantic	117	46.2%	15.4%	35.0%
East North Central	112	44.6%	10.7%	33.9%
West North Central	87	44.8%	9.2%	25.3%
South Atlantic	94	53.2%	14.9%	34.0%
East South Central	44	56.8%	25.0%	43.2%
West South Central	97	62.9%	13.4%	38.1%
Mountain	16	31.3%	6.3%	12.5%
Pacific	67	40.3%	6.0%	31.3%
US TOTAL	715	48.4%	12.6%	33.1%

a. Macrolide-resistance rates are based on azithromycin MICs

Figure 1: Distribution of azithromycin and solithromycin activity against *S. pneumoniae* isolated in the US in 2014

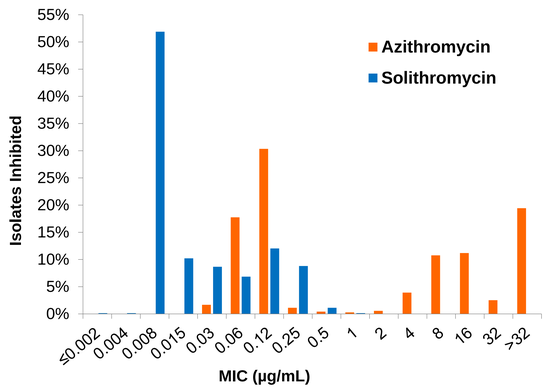


Figure 2: Distribution of macrolide resistance for *S. pneumoniae* across the US in 2014

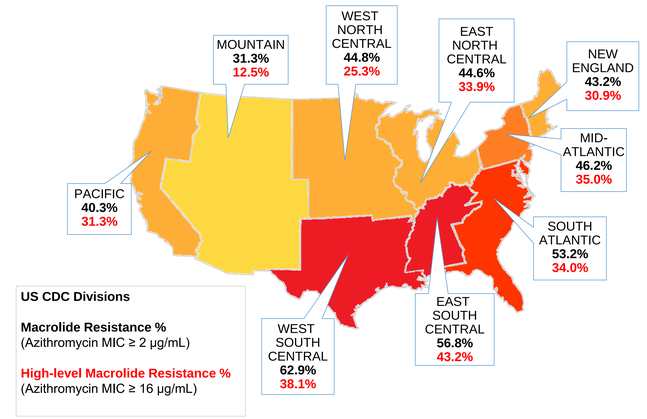
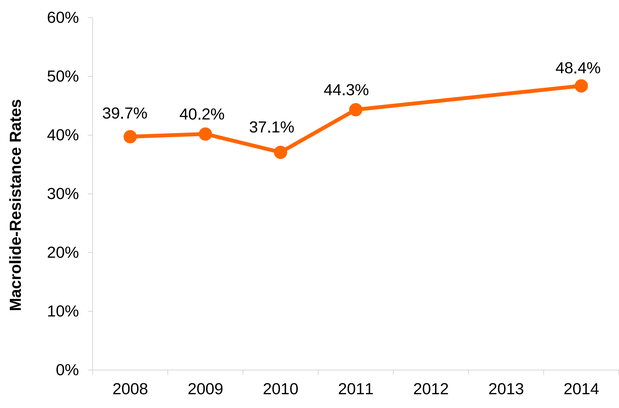


Figure 3: Changes in macrolide resistance in *S. pneumoniae* in US, 2008-2014



CONCLUSIONS

- *S. pneumoniae* is the most common bacterial cause of CABP. It is also a frequent pathogen in other respiratory tract infections.
- Antibiotic resistance in *S. pneumoniae* is a significant clinical challenge as highlighted by the CDC's list of threatening pathogens, with *S. pneumoniae* in the "Urgent" category.
- Almost all community-acquired respiratory tract infections are empirically treated. In the US, a macrolide (such as azithromycin), amoxicillin/clavulanate or a respiratory fluoroquinolone (usually levofloxacin), are the most frequent agents prescribed. Current agents each have their weaknesses, whether it be inconsistent activity against *S. pneumoniae*, lack of activity against atypical species, or unpredictable safety and tolerability.
- Macrolide resistance in *S. pneumoniae* is continuing to increase in the US.
- There are regional differences but overall almost half of strains tested were macrolide resistant (azithromycin MIC ≥ 2 µg/mL) with high-level macrolide resistance (azithromycin MIC ≥16 µg/mL) being reported in 8 of the 9 CDC census divisions, leading to a national average of 33% high-level macrolide resistance.
- Both low and high-level macrolide resistance have been reported to cause clinical failures and other negative outcomes including longer hospital stays and higher costs.
- Solithromycin shows activity against all macrolide-resistant strains of *Streptococcus pneumoniae* isolated, irrespective of the location in the US.

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