

***In vitro* susceptibility of *S. pneumoniae* to solithromycin (SOL) in Belgian and German collections with an elevated percentage of isolates resistant to macrolides and fluoroquinolones**

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Objectives: SOL, a novel fluoroketolide, is developed for respiratory tract infections with MXF as comparator (Phase III). Our aim was to assess its *in vitro* activity against *S. pneumoniae* isolates collected from patients for whom an elevated percentage of strains resistant to macrolides and fluoroquinolones could be expected based on previous antibiotic treatments.

Methods: 732 isolates were collected between 2007 and 2012 from patients (i) in Belgium with (a) clinically-confirmed community-acquired pneumonia (CAP; n=336), (b) respiratory tract infections (RTI; n=186), (c) clinically-confirmed exacerbations of chronic bronchitis (AECB; n=107), (d) miscellaneous (n=14) and (ii) in Germany from patients with invasive pneumococcal disease (IPD; n=89). MICs of SOL, LVX, MXF, macrolides and beta-lactams (see Table) were determined by microdilution in cation-adjusted Mueller-Hinton broth supplemented with horse blood, using *S. pneumoniae* strain ATCC 49619 as quality control and after re-identification of isolates by the optochin test. Cross-resistance between SOL and the other antibiotics assessed by linear fit, bivariate normal ellipse analysis (0.90 overlap), and quantile density contour coincidence (QDCI; 0.1 to 0.9) using JMP software (version 10.0.2).

Results: The table shows the results observed for the combined collections

	mg/L ^a								
	SOL	TEL	CLR	AZM	AMX	CRO	CPT	LVX	MXF
MIC ₅₀	0.0156	0.0156	0.0625	0.125	0.0312	0.0312	0.0156	1	0.125
MIC ₉₀	0.0625	0.125	64	64	2	1	0.25	16	4
	Susceptible / Resistant (%) ^b								
S	c	95.8 %	66.6 %	53.5 %	82.0%	86.3%	95.8%	88.4%	87.0%

R	c	2.9%	29.8%	35.4%	5.0%	0.8%	4.2%	11.6%	13.0%
<p>(a) SOL: solithromycin; TEL: telithromycin, CLR: clarithromycin; AZM: azithromycin; AMX: amoxicillin; CRO: ceftriaxone, CPT: ceftaroline, LVX: levofloxacin; MXF: moxifloxacin.</p> <p>(b) EUCAST 2014 interpretive criteria (mg/L); TEL, CLR, AZM: S ≤ 0.25, R > 0.5; AMX, CRO: S ≤ 0.5, R > 2; CPT: S ≤ 0.25, R > 0.25; LVX: S ≤ 2, R > 2; MXF: S ≤ 0.5, R > 0.5 (http://www.eucast.org).</p> <p>(c) 97.7% of isolates with MIC < or = to 0.25 mg/L and 1.8% > 0.5 mg/L</p>									

The elevated percentages of LVX and MXF resistant isolates were driven by the Belgian RTI (10.3 and 14.1%) and AECB (8.4 and 13.3%), and the German IPD (53.5 and 58.1%) collections (vs. only 3.0 and 0.6% for the Belgian CAP collection). SOL MIC₉₀ (mg/L) were 0.125 (RTI), 0.0625 (AECB), 0.0625 (IPD) and 0.0312 (CAP). No or only weak cross resistance was observed between SOL and each of the antibiotics studied (see the Figure for SOL vs LVX and vs MXF).

Conclusions: SOL shows an essentially unaltered activity in collections where resistance is high to macrolides and is creeping for fluoroquinolones (and also, but to a lesser extent, for AMX and CPT). Continuous surveillance of SOL susceptibility in isolates from these patient populations is warranted.

Figure: Cross resistance between SOL and LVX (left) and SOL and MXF (right) with contour analysis.

