In vitro susceptibility of *S. pneumoniae* to solithromycin (SOL) in collections with an elevated proportion of isolates resistant to levofloxacin (LVX) and moxifloxacin (MXF).

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Introduction

There is currently an urgent need to develop new antibiotics active against strains resistant to currently used molecules. In the present context of respiratory tract infections, the main target organism, as far as resistance is concerned, remains *Streptococcus pneumoniae*, which has developed mechanisms conferring reduced susceptibility to β-lactams and full resistance to macrolides and fluoroquinolones (1). Solithromycin (SOL) is a novel fluoroketolide currently in Phase III of clinical development for respiratory tract infections in comparison with moxifloxacin (MXF). Our aim was to assess its *in vitro* activity against *S. pneumoniae* isolates collected from patients for whom resistance to β-lactams, macrolides and fluoroquinolones was expected to be higher than in the general population based on medical history of previous infections having necessitated multiple previous antibiotic treatments.

Materials and Methods

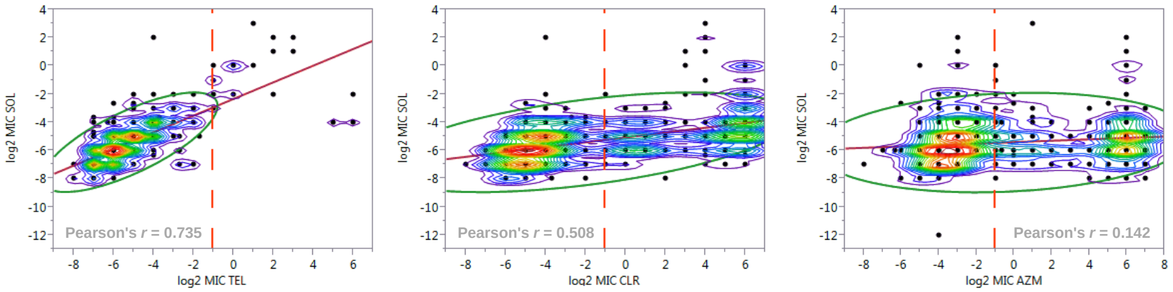
732 isolates were selected (i) in Belgium from patients with a clinically-confirmed diagnostic of community acquired pneumonia (CAP; n=336) or chronic obstructive pulmonary disease (COPD; n=107) (see refs. 2 and 3 for the methods of collection of these samples), suffering from respiratory tract infection (RTI; n=186; selected amongst isolates received by the Belgian Institute of Public Health, Brussels), or diverse infections (n=14); and (ii) in Germany from patients with invasive pneumococcal infections (IPI; n=89) and for whom samples had been received by the German Centre for *pneumococci* (Aachen).

MICs of SOL, MXF and other antibiotics currently approved for the treatment of respiratory tract infections and/or CAP were determined by microdilution in cation-adjusted Mueller-Hinton broth supplemented with horse blood, using *S. pneumoniae* strain ATCC 49619 as quality control and with re-identification of each isolate by the optochin test.

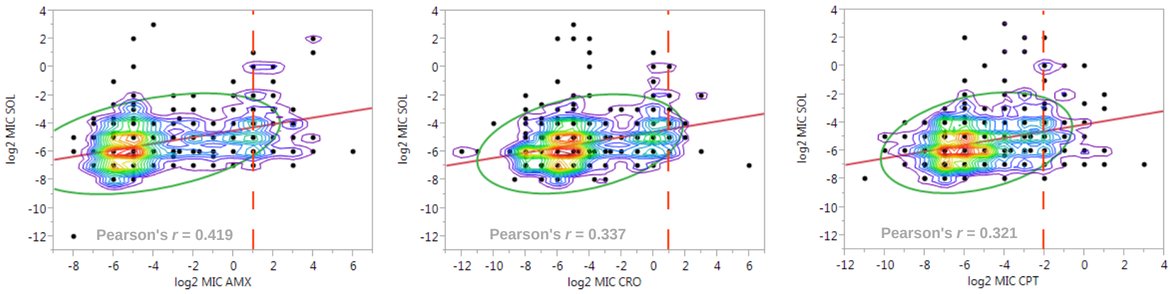
Categorization of strains as susceptible or resistant was made using EUCAST interpretive criteria for all antibiotics except for SOL for which no breakpoint has been set up so far. To gain insight into the potential cross-resistance between SOL and the other antibiotics, two-dimensional graphs were constructed and the correlation between SOL MICs and the MICs of each comparator assessed by linear fit, bivariate normal ellipse (0.95 overlap), and quantile density contour coincidence (0.1 to 0.9) analysis using JMP software (version 10.0.2; see ref. 4).

Results

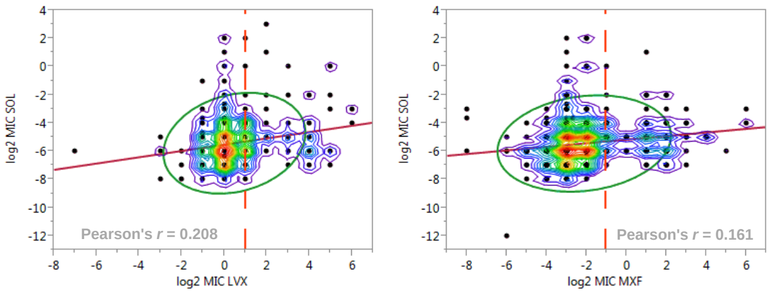
Correlation with telithromycin (TEL), clarithromycin (CLR) and azithromycin (AZM)



Correlation with amoxicillin (AMX), ceftriaxone (CRO) and ceftaroline (CPT)



Correlation with levofloxacin (LVX) and moxifloxacin (MXF)



the vertical **dotted red vertical line** shows the R breakpoint of EUCAST for each comparator

Linear Fit
Bivariate Normal Ellipse P=0.950
.1 .2 .3 .4 .5 .6 .7 .8 .9 Quantile Density Contours

How to read and interpret these data ?

1. Each black dot corresponds to a given test dilution (conventional $\log_2$ progress).
2. The coloured lines show the proportion of strains at the corresponding MIC (from red [many] to blue [few]; dots not surrounded by a coloured line correspond to MICs with only a few isolates. See Table for MIC_{50} and MIC_{90} for each antibiotic.
3. The oval green line surrounds 95% of all tested isolates.
4. The slope of the correlation line gives an indication as how resistance to the comparator affects the MIC of SOL (cross-resistance) across all isolates. The Pearson's *r* coefficient gives an indication of the level of correlation (1 = perfect correlation; 0 = no correlation).
5. Isolates with MICs for the comparator to the right of the dotted red vertical line must be categorized as resistant to the corresponding antibiotic (for example, very few isolates are resistant to telithromycin whereas a large proportion of isolates is resistant to clarithromycin; the Table shows the percentage of susceptible and resistant isolates).

	mg/L (figures **in bold red** indicate MIC values > the "R" EUCAST breakpoint)								
	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 (%)								
S		95.8 %	66.6 %	53.5 %	82.0%	86.3%	95.8%	88.4%	87.0%
R		2.9%	29.8%	35.4%	5.0%	0.8%	4.2%	11.6%	13.0%

References

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Summary and Conclusions

In this collection of clinical isolates of *S. pneumoniae* enriched in strains resistant to antibiotics currently used to treat respiratory tract infections (or CAP), solithromycin shows no cross resistance with the comparators, except for telithromycin (but for which (i) resistance rates are very low, and (ii) MICs are usually 1 $\log_2$ dilution higher that those of solithromycin). Solithromycin may, therefore, stand as a potentially useful antibiotic to substitute for commonly recommended antibiotics in areas and/or environments where resistance of *S. pneumoniae* to these agents will limit their use.