A1-673 Changes in *Streptococcus pneumoniae* population profiles after exposure to fluoroquinolones in prolonged dosing simulations

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Introduction

- The risk of emergence of resistance (EoR) to fluoroquinolones (FQ) in *Streptococcus pneumoniae* remains a clinical and public health concern.
- Existing evidence suggests that multiple factors determine the antibacterial effect (ABE) of FQs on *S.pneumoniae* in pre-clinical infection models: these include fAUC/MIC ratio, bacterial inoculum, bacterial resistance mechanism and perhaps between drug differences within the FQ class.
- Prolonged antibiotic exposures in pharmacokinetic /pharmacodynamic (pK/pD) models allow for resistant sub-populations to emerge and for example, difference between dosing regimens to become more clear.
- *S.pneumoniae* is a technically difficult organism to study in *in vitro* pre-clinical models as drug induced changes in population profiles are small and it is difficult to maintain bacterial viability beyond 48h.
- An *in vitro* pK model was used to study the ABE and changes in population profiles of 4 *S.pneumoniae* strains with raised MICs but different mechanisms of resistance over 96h.

Methods

- Four strains of *S.pneumoniae* were used (Table 1).
- Free drug serum concentrations associated with doses of levofloxacin (levo) 750mg 24hrly po (Cmax 6mg/L, t½ 8h) and moxifloxacin (moxi) 400mg 24hrly po (Cmax 2mg/L, t½ 8h) were simulated.
- Low (initial inoculum 10^6 CFU/ml) and high (initial inoculum 10^8 CFU/ml) were used.
- A dilutional in vitro model was used to simulate the drug concentrations. 100% BHI broth was used in all experiments.
- EoR was assessed by recovery on blood agar plates containing MICx4 concentrations of levo or moxi.

Results

- Against SMH 21843 (wild type) moxi resulted in clearance from the model at both high and low inocula. Levo produced clearance at the low inoculum but not the high. No colonies were recovered on MICx4 containing plates up to 96h for either agent (Figure 1).

Results

Table 1: *S.pneumoniae* strains and drug exposures modelled

Strain	Mechanism of resistance	MIC (mg/L)		fAUC-$_{24}$/MIC	
		Levofloxacin	Moxifloxacin	Levofloxacin	Moxifloxacin
21843	None	1.5	0.38	42	63
21850	Efflux	0.75	0.38	84	63
21812	parC	1.5	0.5	42	48
37917	gyrA	6	2	10.5	12

Fig.1 ABE of moxi and levo against S.pneumoniae SMH 21843 (WT)

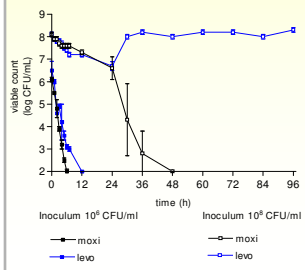
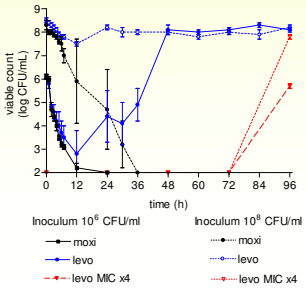


Fig. 2 ABE of moxi and levo against S.pneumoniae SMH 21850 (efflux)



- Against SMH 21850 (efflux) moxi resulted in clearance from the model at both inocula. Levo failed to produce clearance with either inoculum but produced a 3-5 log reduction in bacterial counts up to 30h. No colonies were recovered on MICx4 plates with moxi, however, with both inocula at 96h, levo resistant colonies were isolated (Figure 2).
- Against SMH 21812 (parC) neither agent resulted in clearance from the model at either inoculum. At the low inoculum early kill followed by regrowth and EoR with both agents. (Figure 3a). At the high inoculum neither agent had an ABE and there was some EoR with both agents (Figure 3b).
- Against SMH 37917 (gyrA) neither agent had an ABE at either inoculum and there was no EoR (Figure 4).

Fig. 3a ABE of moxi and levo against *S.pneumoniae* strain 21812 (parC) at low inoculum (10^6)

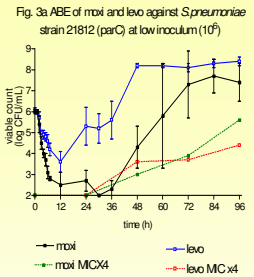


Fig. 3b ABE of moxi and levo against S.pneumoniae strain 21812 (parC) at high inoculum 10^8cfu/mL

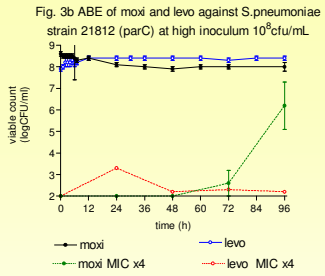
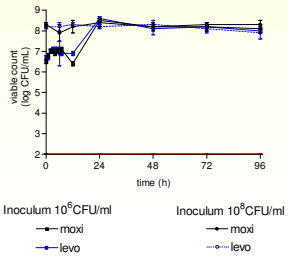


Fig. 4 ABE of moxi and levo against *S.pneumoniae* strain 37917 (gyrA)



Conclusions

- The strains with moxi MIC ≤0.5mg/L and levo MIC ≤1.5mg/L, have markedly different patterns of ABE and risk of EoR depending on the underlying mechanism (none, efflux or parC). EoR occurred with levo only with the efflux strain and both FQ with the parC strain.
- As expected, the low drug exposures with SMH 37917, gyrA mutation were associated with poor ABE and low risk of resistance.
- Bacterial inoculum and mechanism of resistance, in addition to MIC and drug exposure, determine the ABEs of moxi and levo against *S.pneumoniae* strains.

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