Mechanism-based modelling of meropenem plus tobramycin combination regimens against clinical hypermutable *Pseudomonas aeruginosa* in the hollow-fibre infection model.

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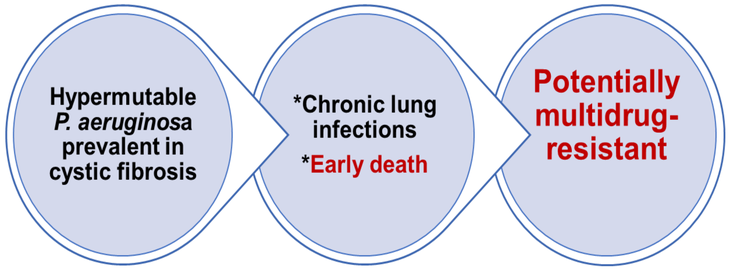
Background & Aim



Methods

Clinical isolates

- **CW8 :** Meropenem (MER) resistant, Tobramycin (TOB) resistant
- **CW44:** MER susceptible increased exposure, TOB susceptible

Data Generation

- Clinically relevant meropenem/tobramycin dosage regimens
- Epithelial lining fluid concentrations (ELF): Meropenem (30%), Tobramycin (50%)
- *In vitro* dynamic hollow-fiber infection model (HFIM)

Model development

- Mechanism-based mathematical modelling (MBM) of HFIM data
- Quantify bacterial killing and resistance suppression of HFIM data

Results

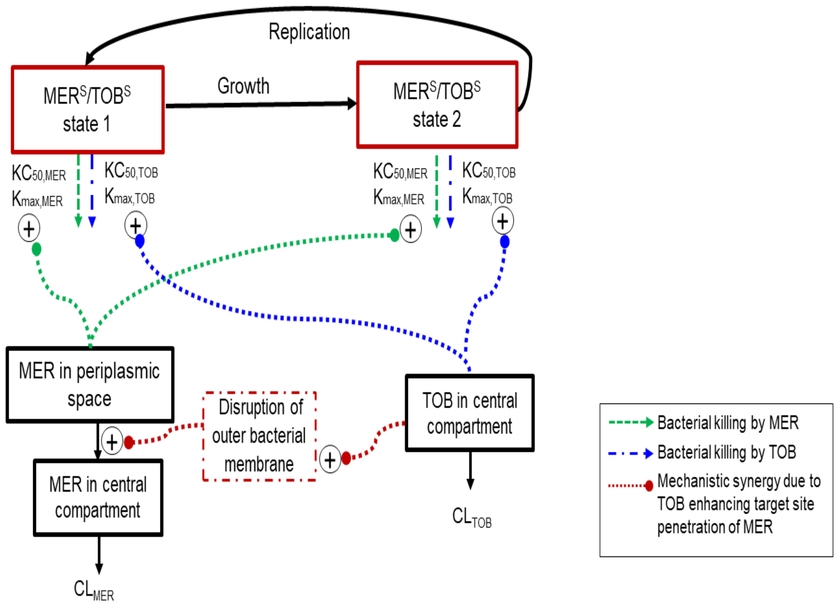


Fig.1: Structure of the final mechanism-based model for bacterial growth and killing by meropenem and tobramycin in mono- and combination therapies. The MER^R/TOB^I (meropenem resistant, tobramycin intermediate) and MER^I/TOB^R (meropenem intermediate, tobramycin resistant) subpopulations are not shown.

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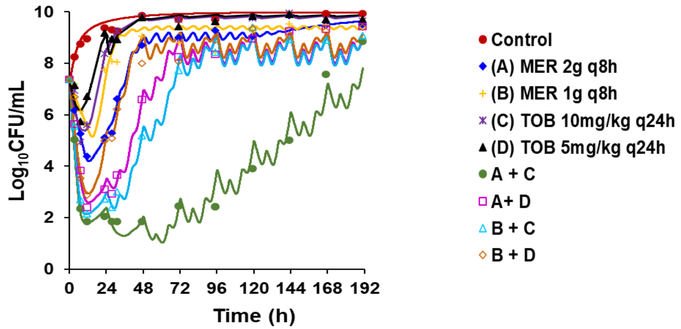
(A) CW8 (MIC$_{MER}$ 8 mg/L, MIC$_{TOB}$ 8 mg/L)



(B) CW44 (MIC$_{MER}$ 4 mg/L, MIC$_{TOB}$ 2 mg/L)

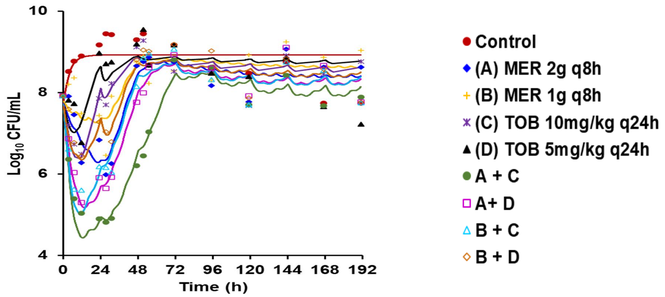


Fig.2: 8-day HFIM results of the total population viable count. Lines are MBM fits.

Conclusions

- Clinically relevant MER + TOB combination dosage regimens simulating ELF concentrations demonstrated synergistic killing against clinical hypermutable *P. aeruginosa isolates.*
- Further investigations for dose optimization are warranted.

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