INTRODUCTION

- Antibiotic resistance, one of the greatest threats to humans, is exacerbated by suboptimal antibiotic dosing regimens
- *Pseudomonas aeruginosa* (Pa) is a Priority 1 bacterial pathogen (WHO)
- Lung infections due to Pa are a main driver of mortality in cystic fibrosis (CF)\(^1,2\)
- 'One size fits all dosing has been ineffective in these exacerbations, mainly due to presence of biofilms and hypermutable, multidrug-resistant Pa strains\(^3,4\)

**URGENT change in antibiotic dosing is essential**

OBJECTIVES

- To evaluate inhaled dosing regimens of aztreonam (AZT) and tobramycin (TOB), in monotherapy and combination, against challenging Pa CF clinical isolates in a dynamic in vitro biofilm model.
- To characterize this experimental data through mechanism-based mathematical modelling.

METHODS

- Two multidrug-resistant, hypermutable clinical isolates from patients with CF, exposed to treatment for 168h (n=2±SEM)
- Biofilm model (Fig. 1) simulated the pharmacokinetics of inhaled AZT and TOB as observed in lung fluids of patients with CF (t\(_{1/2}=3h\))\(^5\)
- Concentrations of the AZT (75mg, every 8h) and TOB (300mg, every 12h) dosing regimens quantified by LC-MS/MS
- Total viable and resistant counts quantified at 8 and 5 time points
- Counts mathematically modelled (Fig. 2)

RESULTS

**Figure 1. Biofilm model experimental set up**

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**Figure 2. Simplified mechanism-based model (MBM) structure**

**Figure 3. Microbiological response of CW5 and CW13 biofilm bacteria**

- Total viable counts
  - Reproducible results (Fig. 3) demonstrate synergy, ≥2 log\(_{10}\) CFU/cm\(^2\) more bacterial killing than the best performing monotherapy AND a ≥2 log\(_{10}\) CFU/cm\(^2\) decrease from the initial inoculum, by the combination (orange) against both isolates
  - After initial killing, regrowth of both monotherapies, AZT (pink) and TOB (blue), to the control (black) occurred by 168h

- Resistant counts
  - Both monotherapies amplified resistance (Fig. 3), with counts greater than the baseline resistance that is shown in the control population
  - Monotherapies resulted in the total viable bacterial population at 168h showing increased resistance
  - The combination suppressed resistance compared to the control

MBM

- The simultaneously modelled biofilm data was well characterised by the model (Fig. 3)
- The combination was modelled with the inclusion of mechanistic synergy

CONCLUSIONS

As well as performing synergistically, the inhaled AZT and TOB combination was required to suppress resistance against both Pa clinical isolates from patients with CF. The MBM could be utilised to inform translation of regimens to *in vivo* or ultimately clinical studies in the future. This MBM could be extended with the use of population pharmacokinetics to adjust the dosing regimen for a patient based on their specific characteristics that affect the antibiotic pharmacokinetics in the lungs. This could also be paired with identifying bacterial characteristics which impact the antibiotic exposure in the lung fluid. This promising combination regimen warrants further investigation.