Pharmacokinetic-Pharmacodynamic (PKPD) Modeling Characterizing Resistance for Predictions of Bacterial Kill *in vivo*

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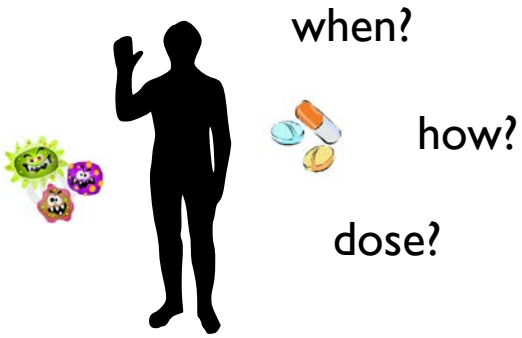
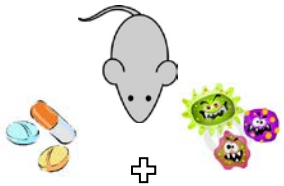
Introduction
Dose selection antibiotics



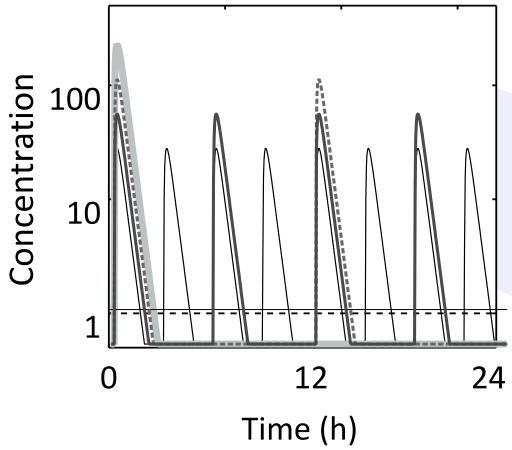
Difficulties:
Bacterial load
Variable susceptibility
Short term
Sudden onset
Emergence of resistance
Typically highly efficient comparators

Advantages:
Ability to study PD preclinically
-*in vitro*
-*in vivo* animal models

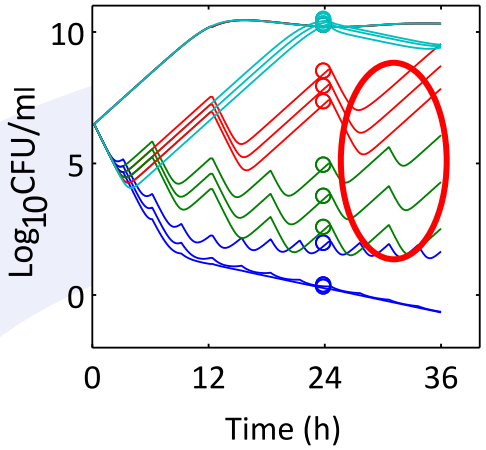
Introduction
PK/PD indices



PK

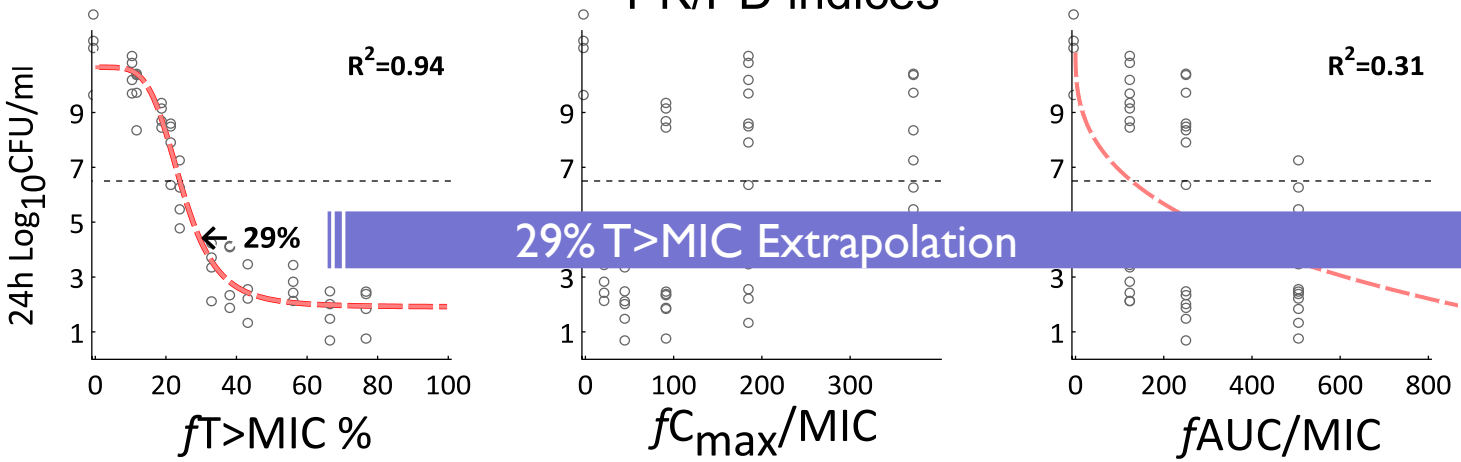


PD



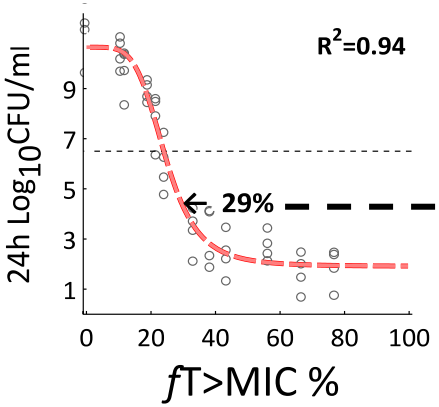
Regrowth?
Resistance?

PK/PD indices



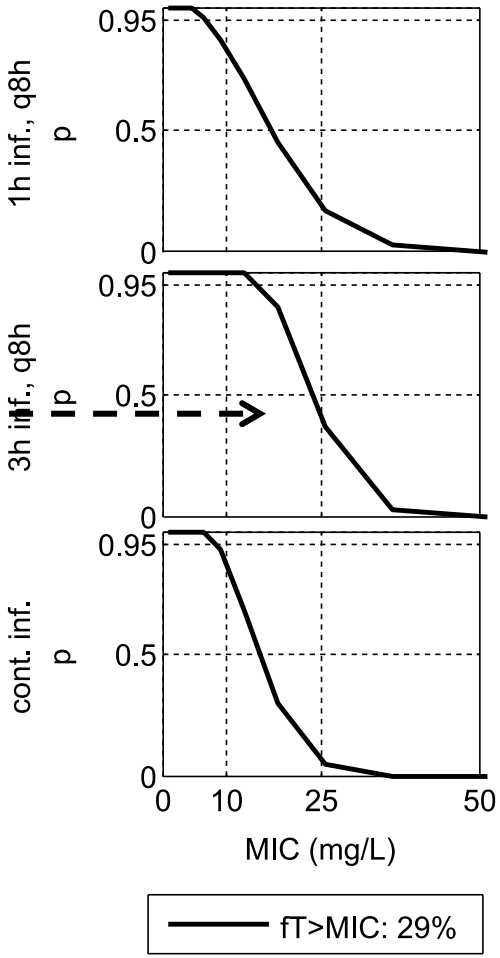
Introduction
Probability of target attainment (PTA)

Select target magnitude



Simulate pop-PK
total daily dose = 6g

Calculate PTA



3h infusion q8h
→ PTA 95%
MIC < 14mg/L

Dose

Same target and magnitude for different patient populations?

Same magnitude for bacterial strains with different susceptibility?

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Aims

- Describe bacterial kill and resistance using a previously developed PKPD-model

- Replicate an *in vivo* dose finding study (PK/PD indices)
  - Evaluate the predictability of the PKPD model
  - Compare dose predictions for a resistant and a susceptible strain

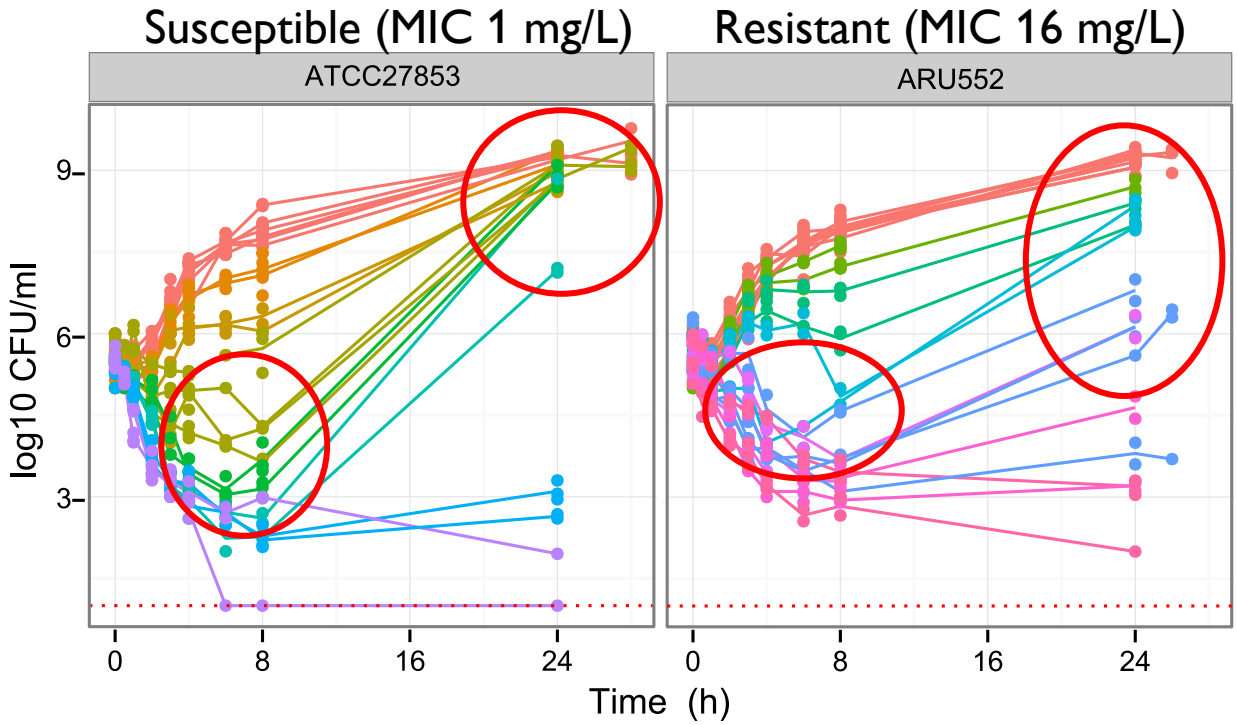
For *Pseudomonas aeruginosa* and meropenem

Meropenem *P. aeruginosa* PKPD model

In vitro time-kill data

2 strains *Pseudomonas aeruginosa:*
ATCC27853 (Susceptible), ARU552 (Resistant)

Meropenem: 0.05-3.2 x MIC (ATCC27853), 0.25-32 x MIC (ARU552)



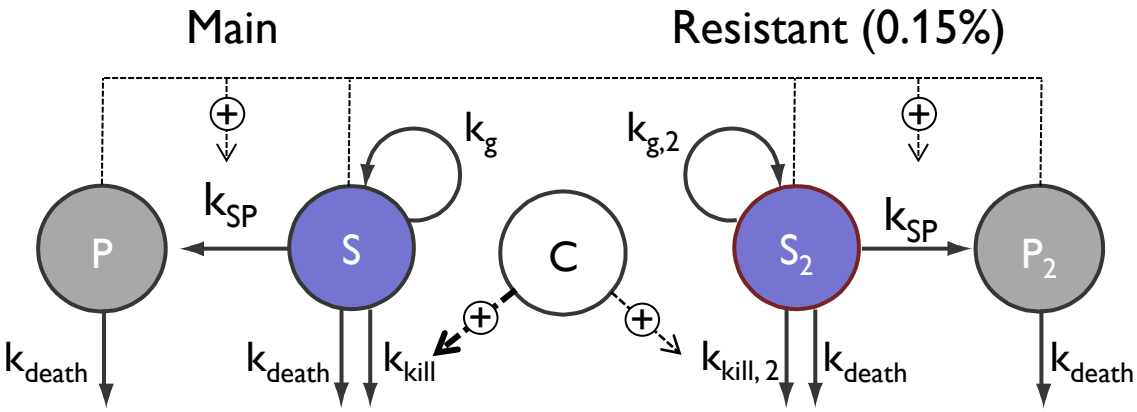
2 types of resistance:

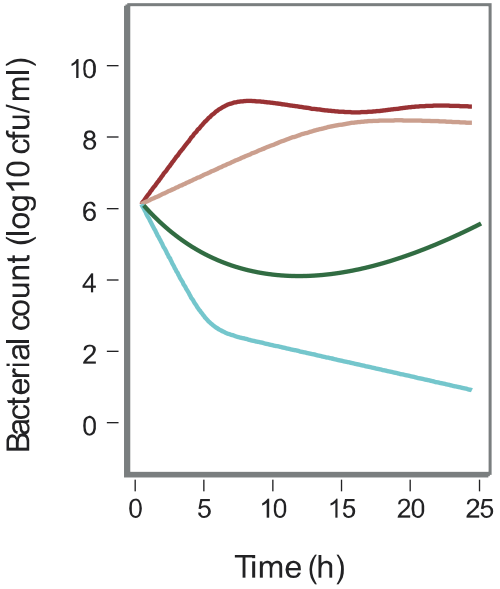
MIC classification
MIC 16 vs 1 mg/L

Selection by exposure
Regrowth during experiment due to resistance

Mohamed *et al.* in manuscript

Meropenem *P. aeruginosa* PKPD model
Structure



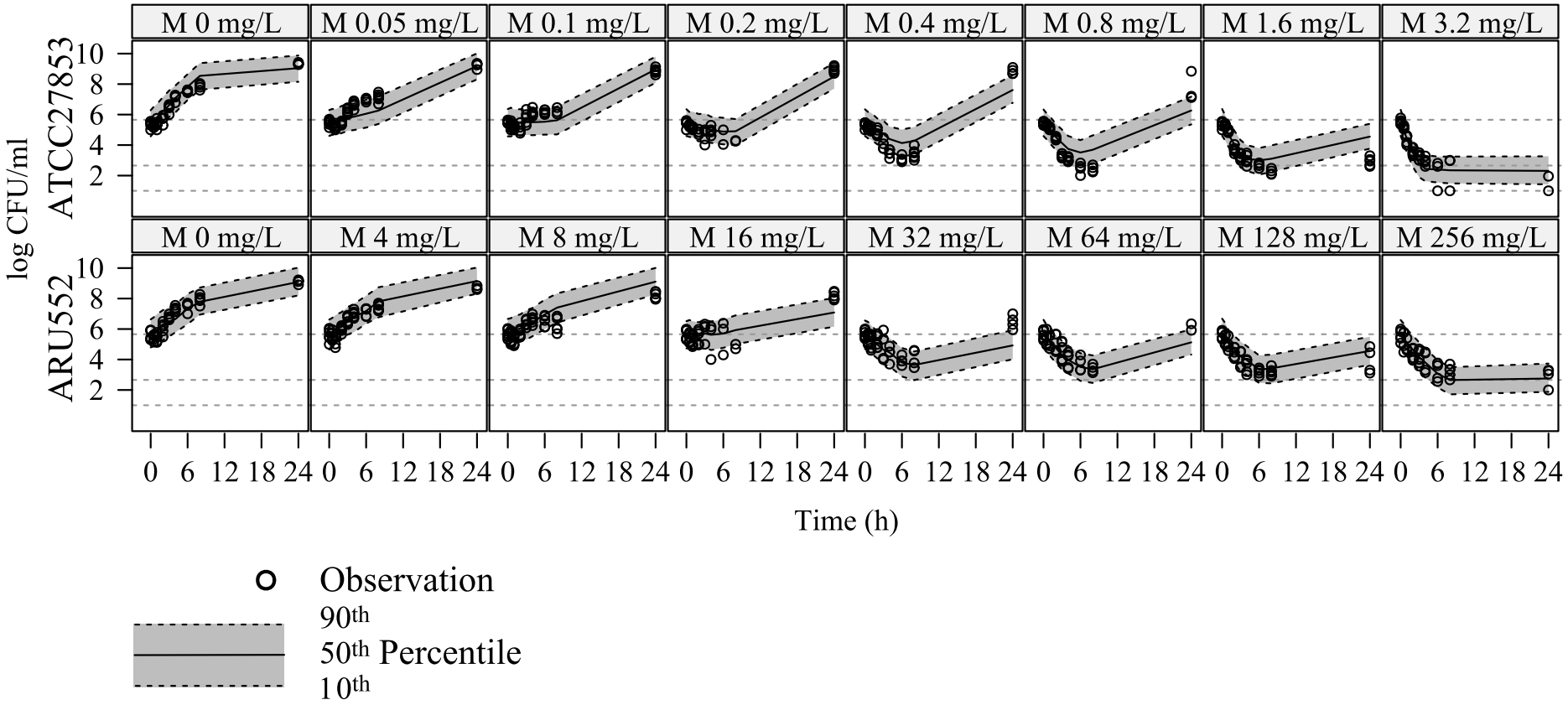


Concentration to suppress growth of main population:
ATCC 0.16 mg/L, ARU552 17 mg/L

Resistant subpopulation:
~20 times higher concentration for same effect
~50% reduced growth rate ARU552

Mohamed, *et al*. *In manuscript*

Meropenem *P. aeruginosa* PKPD model
VPC



Meropenem *P. aeruginosa* PKPD model
Predictions

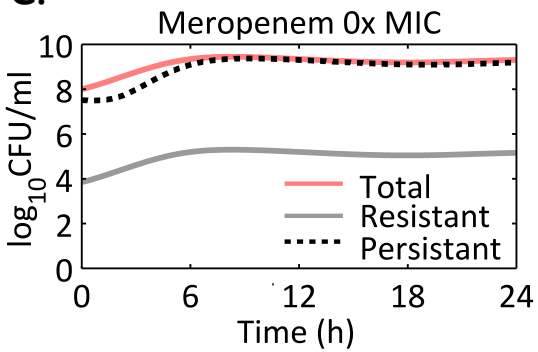
Selective pressure:

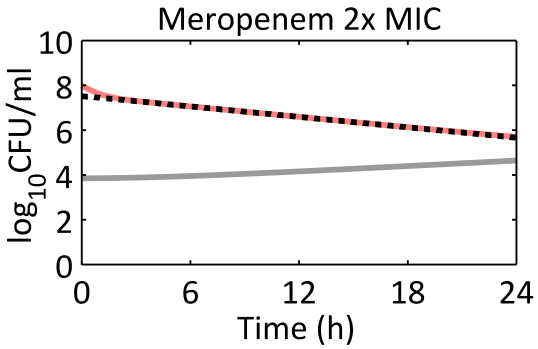
None
(0 x MIC)

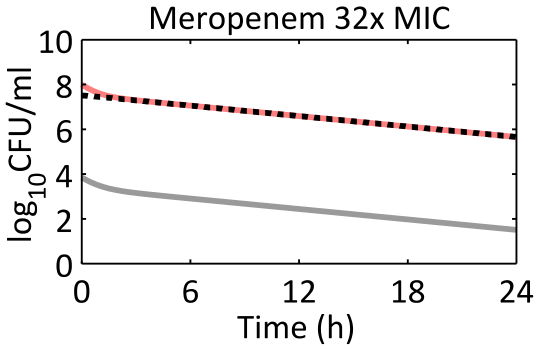
Mutant selective
(2 x MIC)

Mutant preventive
(32 x MIC)

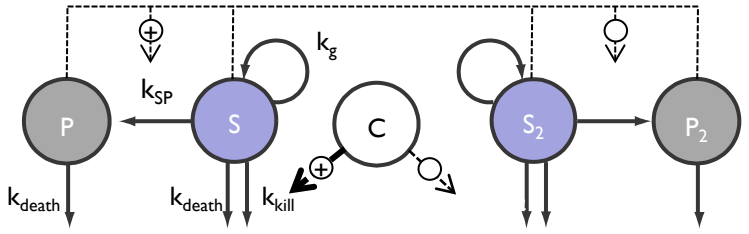
Prediction
ATCC27853







Total = Main + Resistant
Persistant = $P + P_2$



Meropenem *P. aeruginosa* PKPD model Predictions

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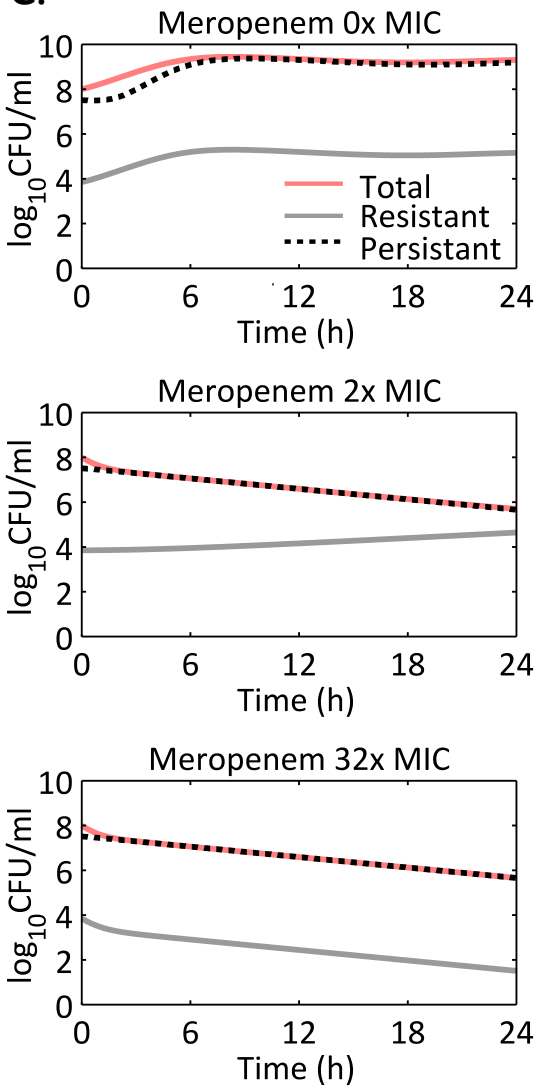
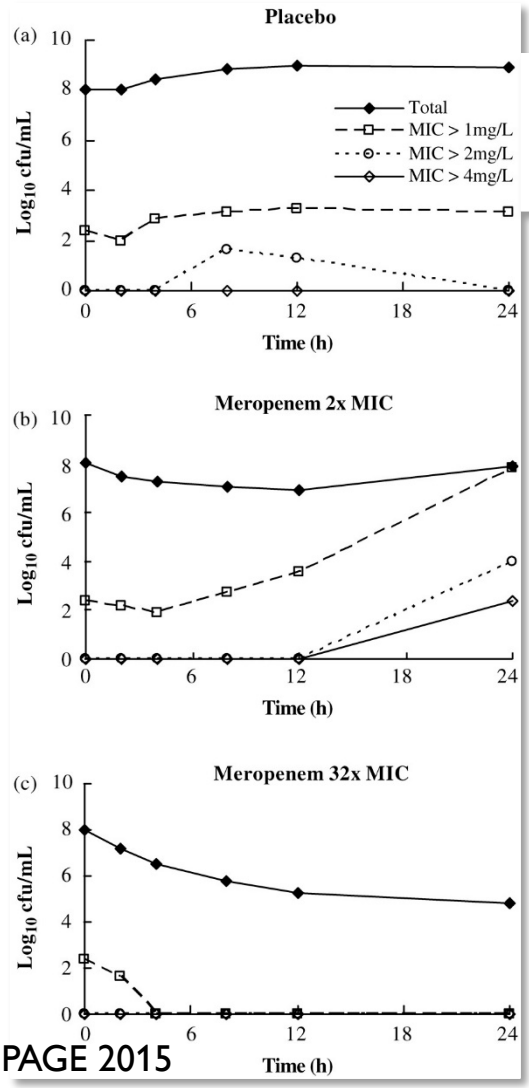
Prediction
ATCC27853

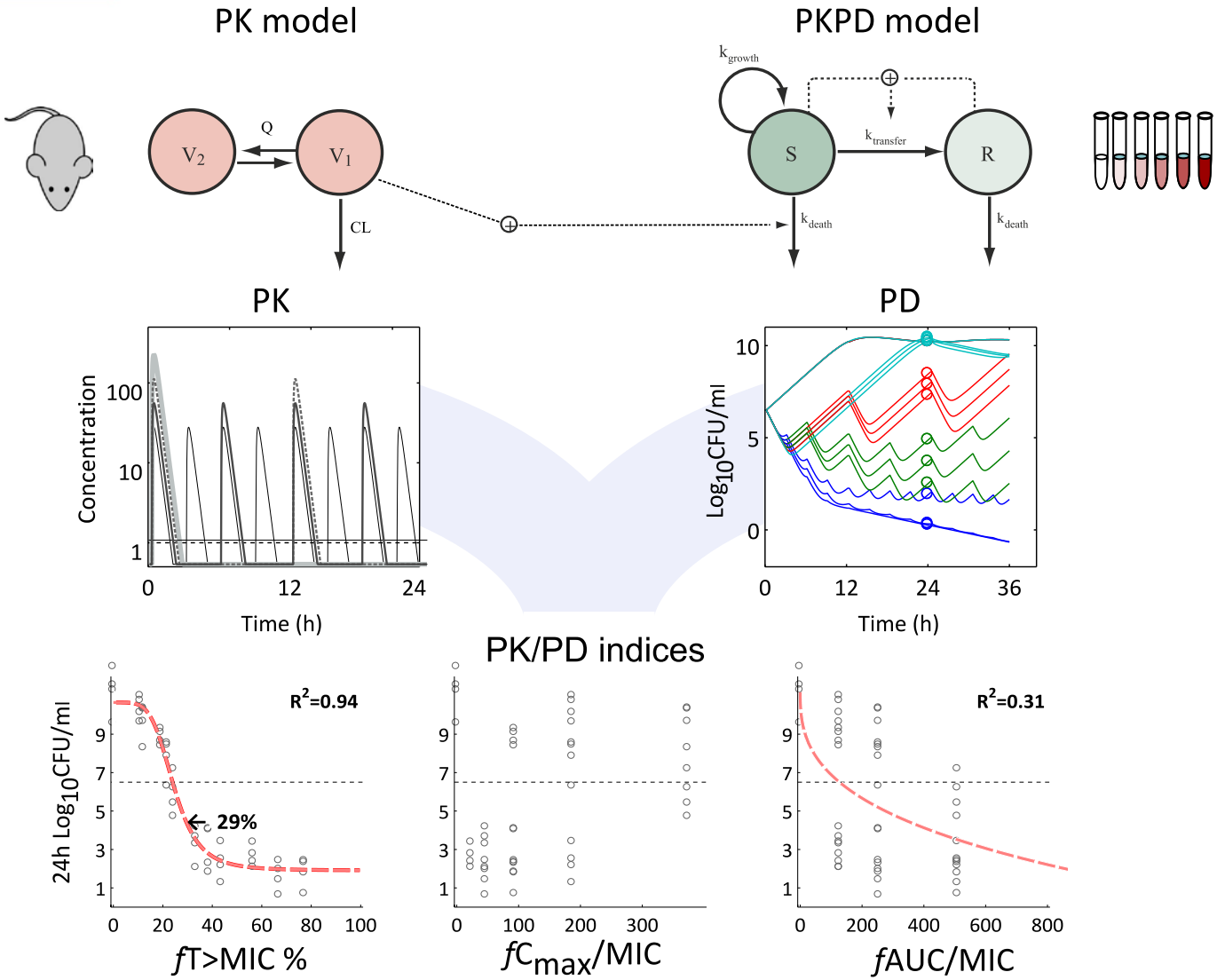


Tam *et al* 2005
ATCC27853



Tam et al. J. Antimicrob. Chemother. 2005

In silico, PK/PD indices

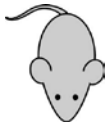


Predicting PK/PD indices Mouse

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Dec. 2010, p. 5298–5302 Vol. 54, No. 12
0066-4804/10/$12.00 doi:10.1128/AAC.00267-10

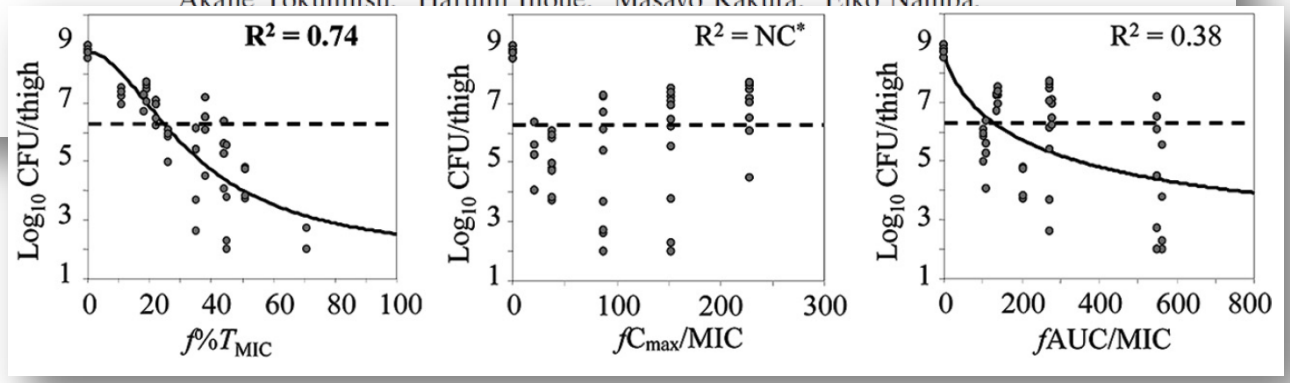
In Vivo Pharmacodynamic Activity of Tomopenem (formerly CS-023) against *Pseudomonas aeruginosa* and Methicillin-Resistant *Staphylococcus aureus* in a Murine Thigh Infection Model[▽]

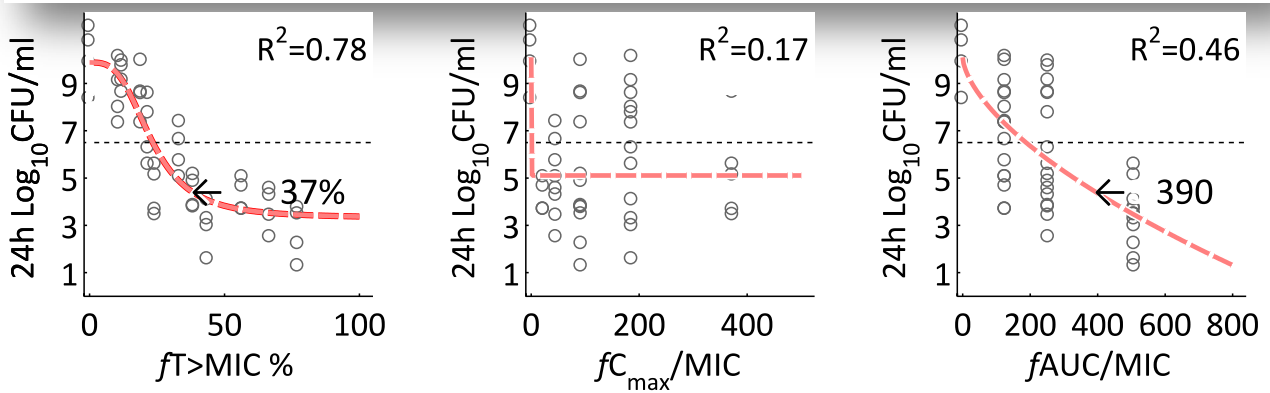
Kiyoshi Sugihara,[1]* Chika Sugihara,[1] Yoko Matsushita,[2] Naotoshi Yamamura,[2] Mitsutoshi Uemori,[3] Akane Tokumitsu,[1] Harumi Inoue,[1] Masayo Kakuta,[1] Eiko Namba,[1]



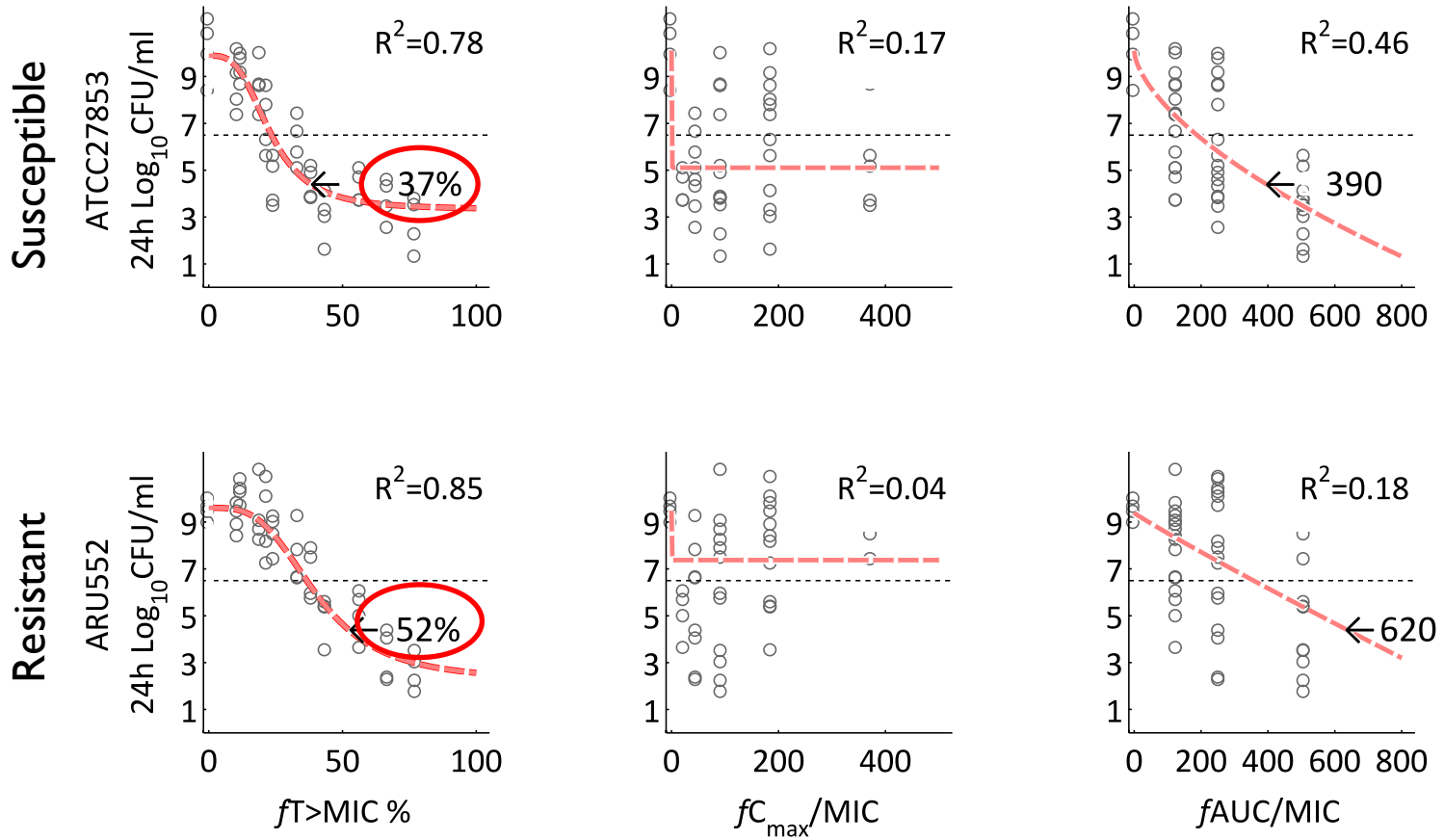
In vivo
(Sugihara *et al*,
AAC 2010)
P. aeruginosa 12467
MIC=2mg/L

Simulation
1-comp PK
(Katsube *et al*,
J. Pharm. Sci. 2008)
P. aeruginosa ATCC27853
MIC=1mg/L



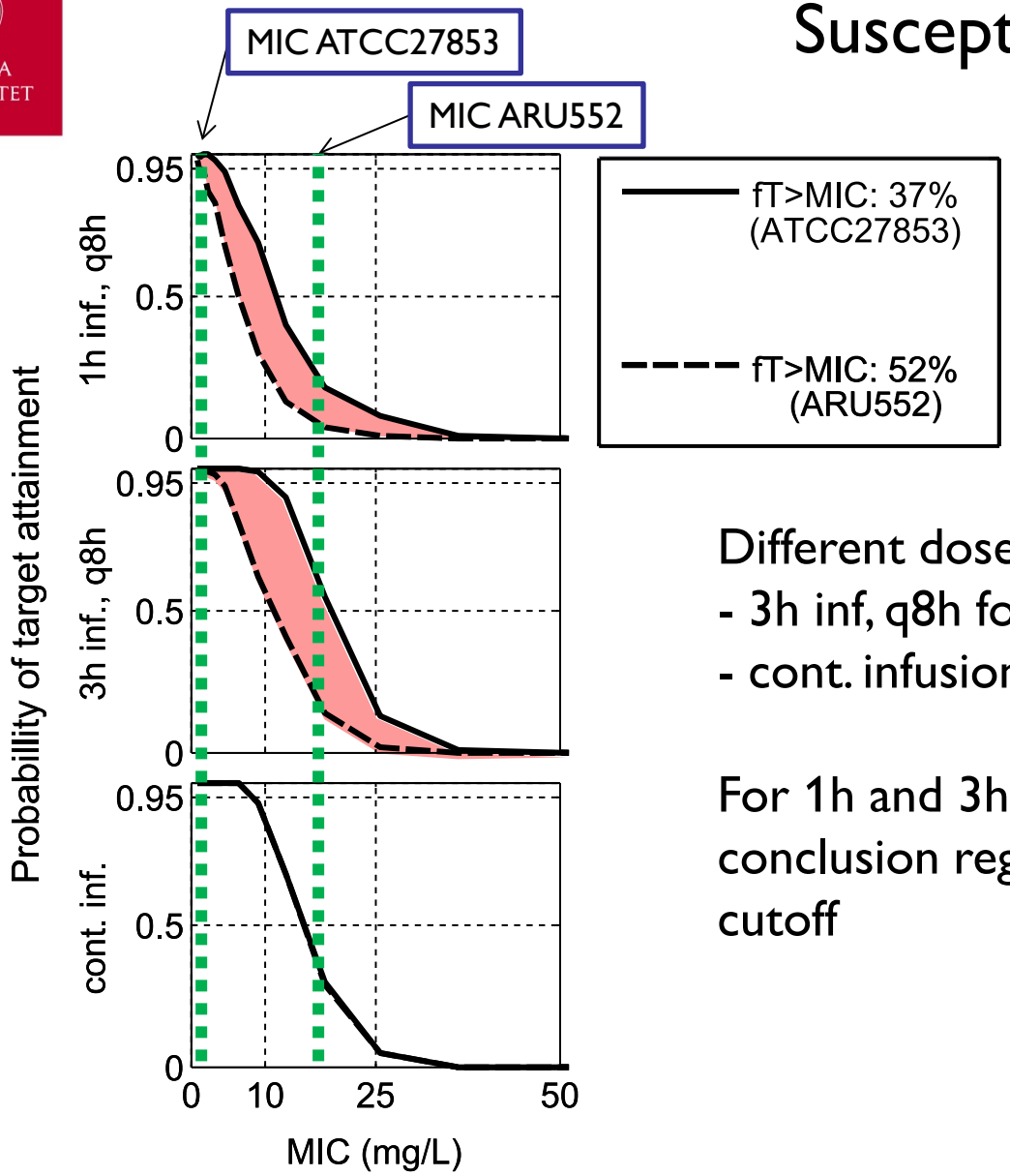


Predicting PK/PD indices
Susceptible vs. Resistant



37% to 52% →2-fold dose/MIC difference for q8h dosing regimen!

Probability of target attainment (PTA)
Susceptible vs. Resistant



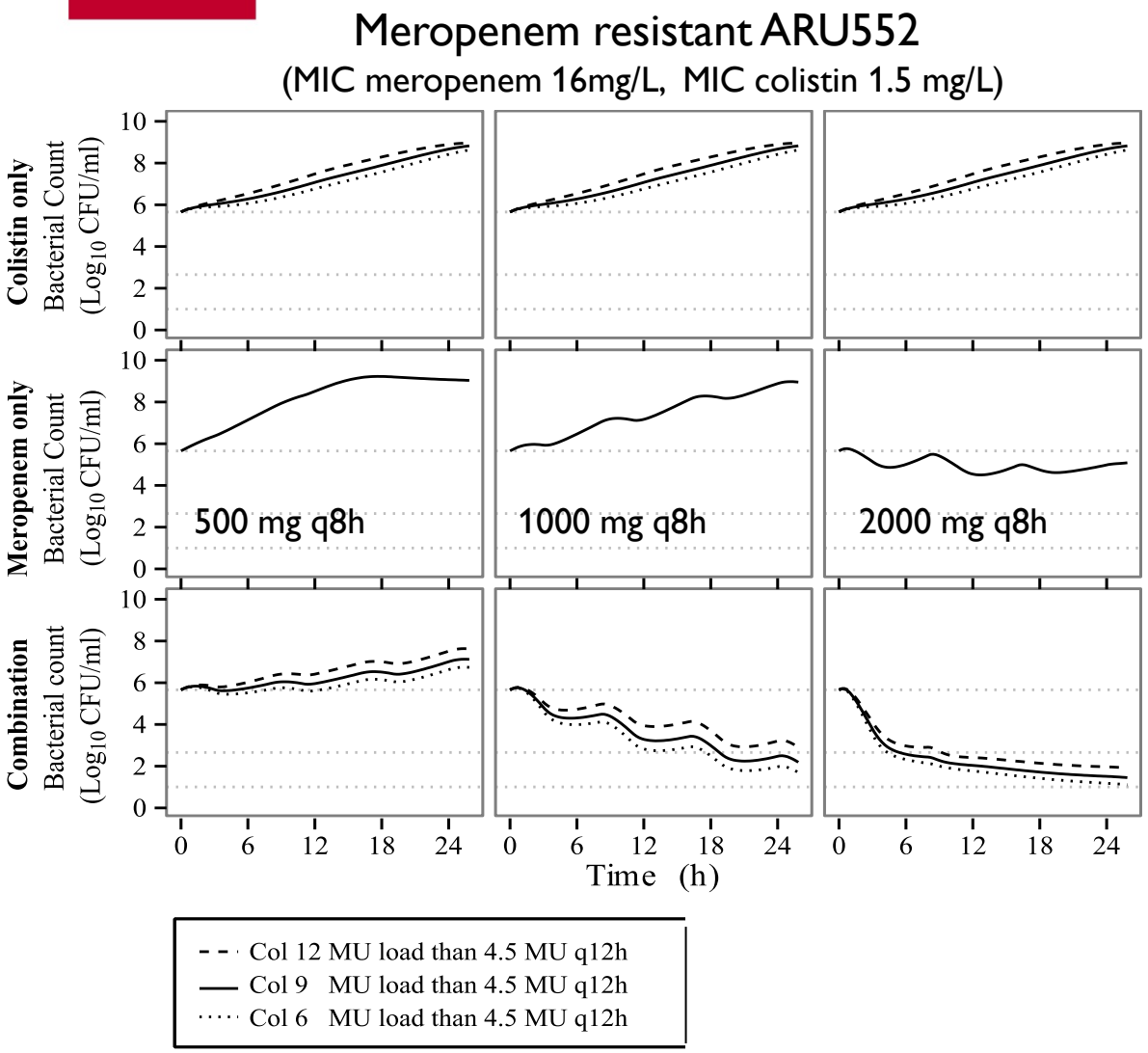
Different dose regimen selected
- 3h inf, q8h for 37% T>MIC
- cont. infusion for 52% T>MIC

For 1h and 3h infusion different conclusion regarding treatment cutoff

Total daily dose: 6g

Meropenem pop. PK by Li *et al*, JCP, 2006

Predict full time course
combination dose simulation



PKPD model of colistin and meropenem in combination against *P. aeruginosa*

Combination is predicted to achieve improved kill against meropenem resistant strain

Mohamed *et al.* in manuscript, PK Mer: Crandon *et al*, J. Intensive Care Med. 2011, PK Col: Mohamed *et al*, AAC, 2012

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Conclusions

- The PKPD model describes two types of resistance:
  - MIC classification
  - Regrowth from resistant subpopulation

- An *in vivo* dose finding study was replicated in simulation
  - The PK/PD index magnitude was MIC dependent
  - Dose selection differed between strains with different susceptibility

PKPD modeling and dose simulation offers a more powerful dose finding alternative!

Acknowledgments

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Co-authors Meropenem-Colistin PKPD model:

Ami F Mohamed, Matti Karvanen, Elisabet I Nielsen, Otto Cars, Lena E Friberg