“PK/PD” type of modelling approach to support time-kill data interpretation of cefoxitin for the treatment of *Mycobacterium abscessus*

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Mycobacterium abscessus

- ✓ Nontuberculosis mycobacteria
- ✓ Pulmonary infections

Koh W *et al*. 2002
Griffith *et al*. 2007

Mycobacterium abscessus

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- ✓ Pulmonary infections

- General treatment:
  Tri-antibiotic combination:
  one **macrolide** + **two antibiotics**
  from amikacin, cefoxitin, imipenem
  and linezolid (by ATS)

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  Tri-antibiotic combination:
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  and linezolid (by ATS)

- Treatment: long, costly, often associated with drug related toxicity and rapid development of drug resistance

Koh W *et al*. 2002
Griffith *et al*. 2007

Cefoxitin

- ✓ β-lactam antibiotic
- ✓ Time-dependent activity

Few challenges during in vitro experiments

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Few challenges during in vitro experiments

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- ✓ MIC determination after 3 days – misleading !

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Cefoxitin

- ✓ β-lactam antibiotic
- ✓ Time-dependent activity

Few challenges during *in vitro* experiments

- ✓ not stable over time
- ✓ MIC determination after 3 days – misleading !
- ✓ Time-kill kinetics assay for longer period > 1 day

Rominski *et al.* 2017

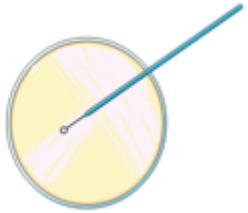
Study *in vitro* pharmacodynamics of FOX

Study *in vitro* FOX degradation over time

PK/PD type modeling approach to correct for degradation

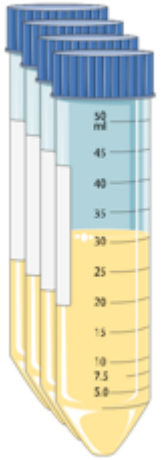
Rominski *et al.* 2017

Experimental Design



Mycobacterium abscessus
CIP104536

cefoxitin



Time kill kinetics assay

Sampling up to 8 days

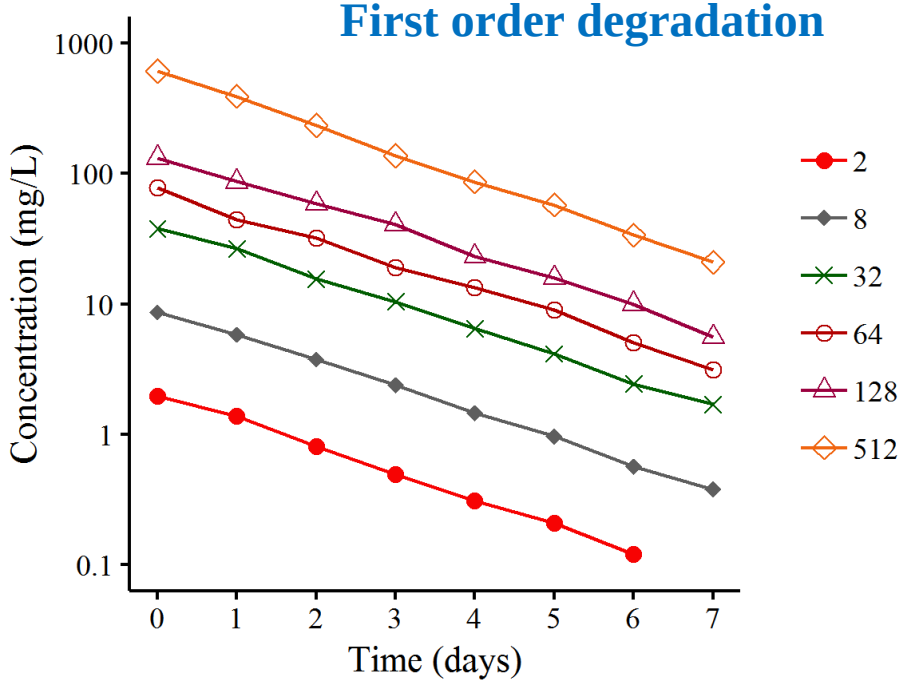
Bacterial count

Concentration measurement using LC-MS/MS

PK/PD type modeling approach

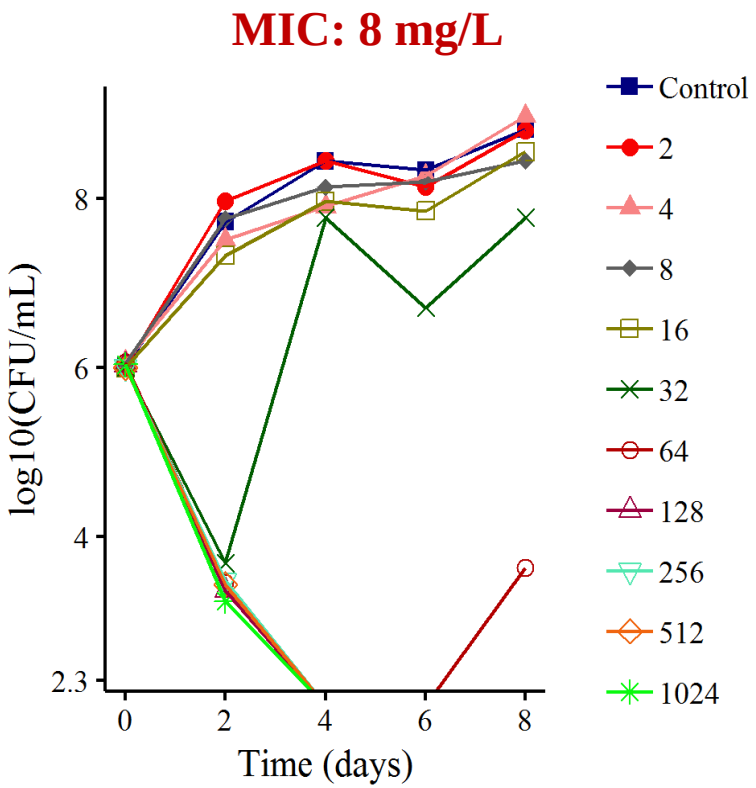
FOX degradation

$t_{1/2}$ = 1.5 days
First order degradation



Concentrations: mg/L

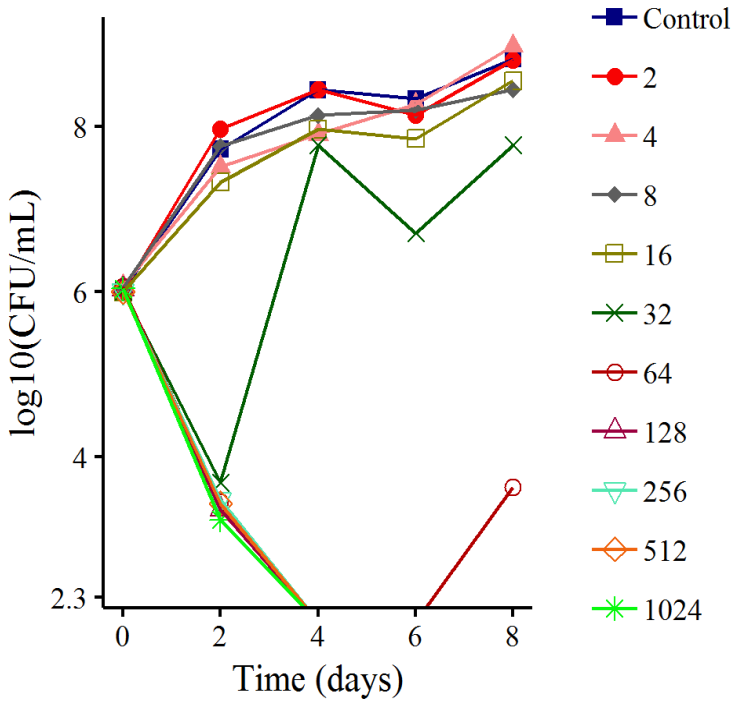
FOX time kill kinetics assay

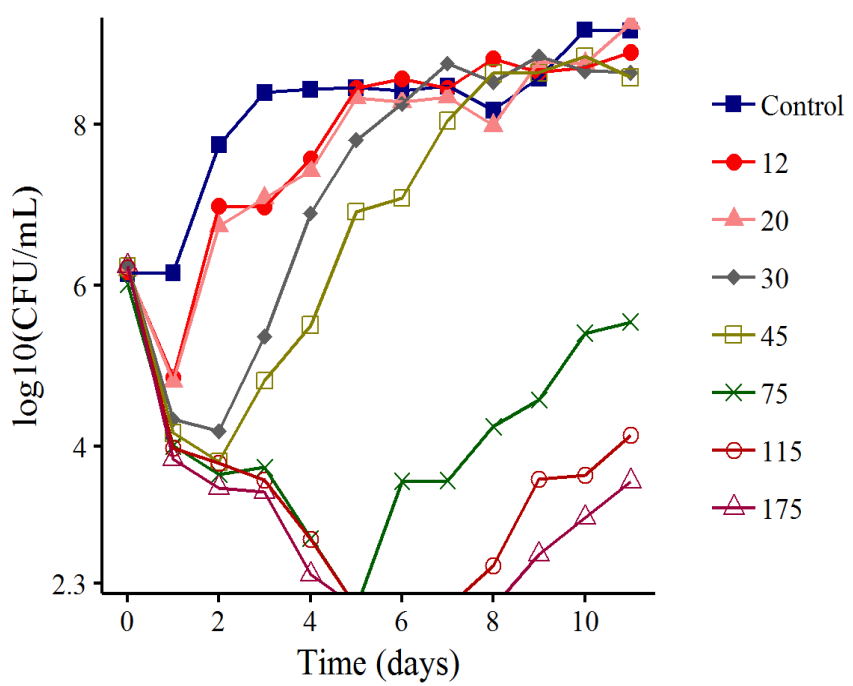


Concentrations: mg/L

FOX time kill kinetics assay

MIC: 8 mg/L





- ✓ No effect for initial FOX concentration < MIC
- ✓ An initial CFU decay followed by regrowth > MIC
- ✓ Regrowth depends on the increasing FOX initial concentration

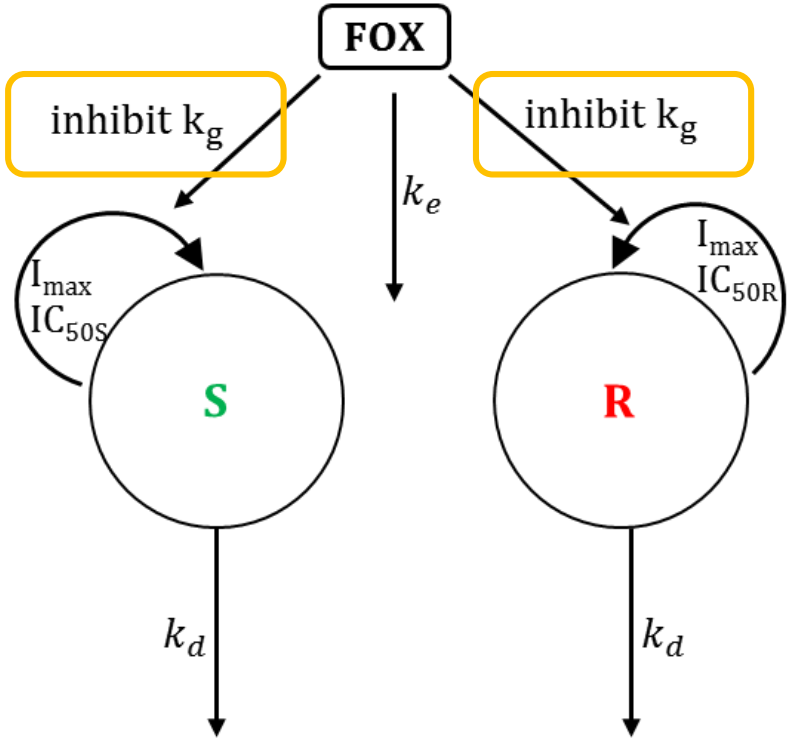
Concentrations: mg/L

Why Regrowth?

Experimental Design

Growth inhibition model with single homogeneous bacterial population (S)

FOX is bacteriostatic against *M. abscessus*



Schematic diagram of final PK/PD type model

Lefebvre *et al.* 2016
Ferro *et al.* 2016

Experimental Design

Ferro *et al.* identified a FOX resistant (R) subpopulation pre-existing at time 0

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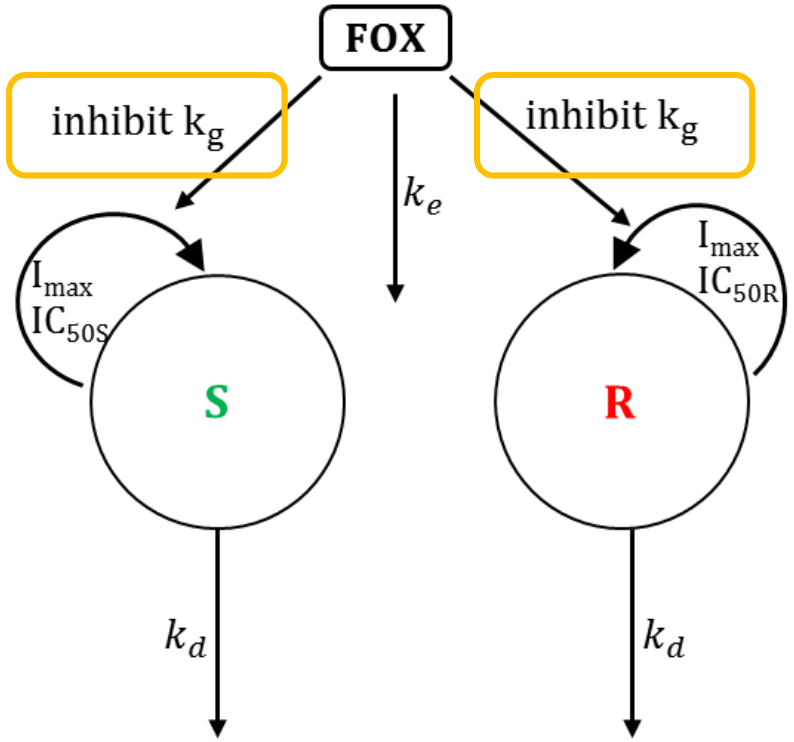

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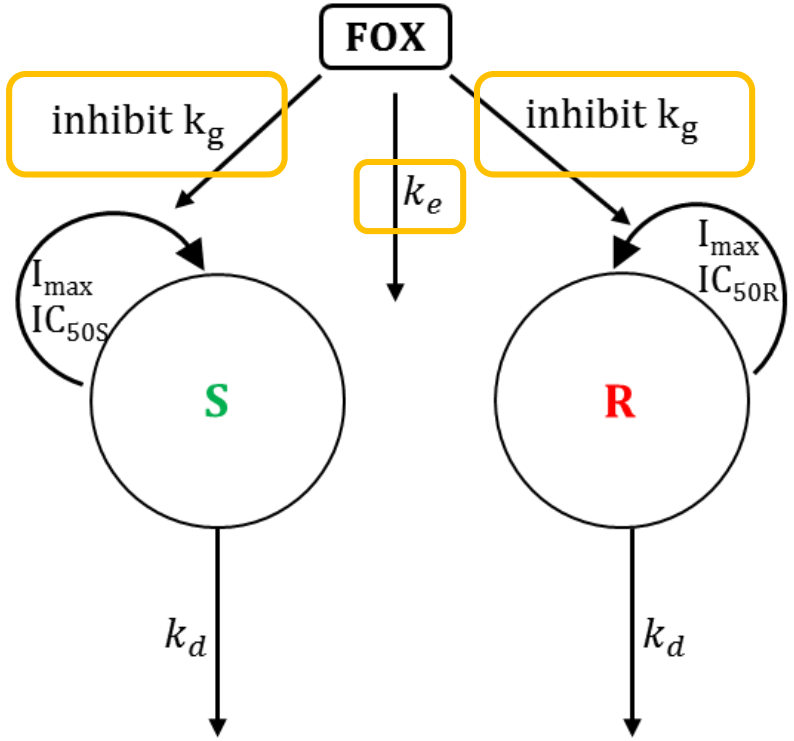
Growth inhibition model two subpopulation **S** & **R** and FOX degradation **(k_e)** PK/PD type modeling approach using NONMEM



Schematic diagram of final PK/PD type model

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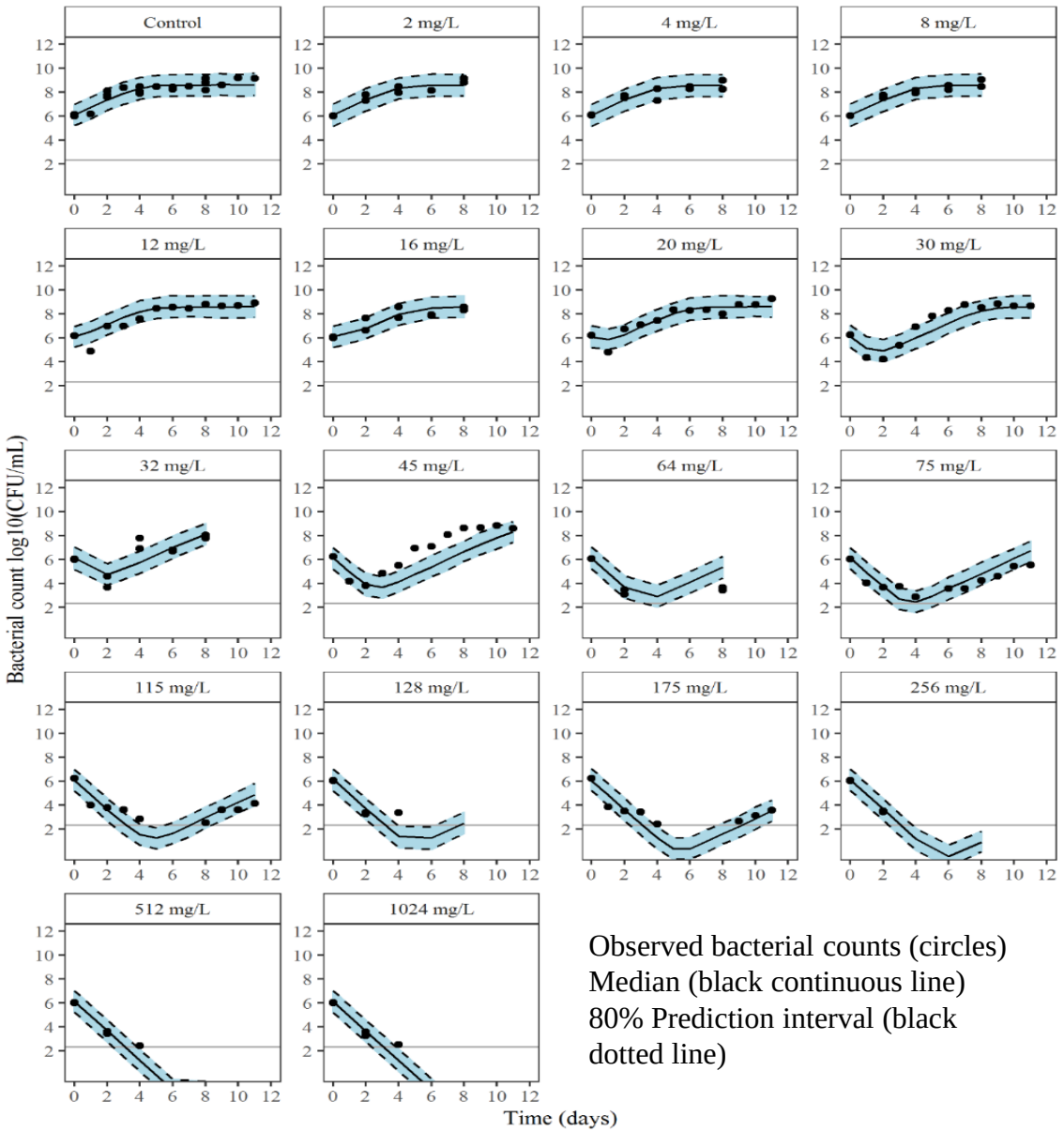
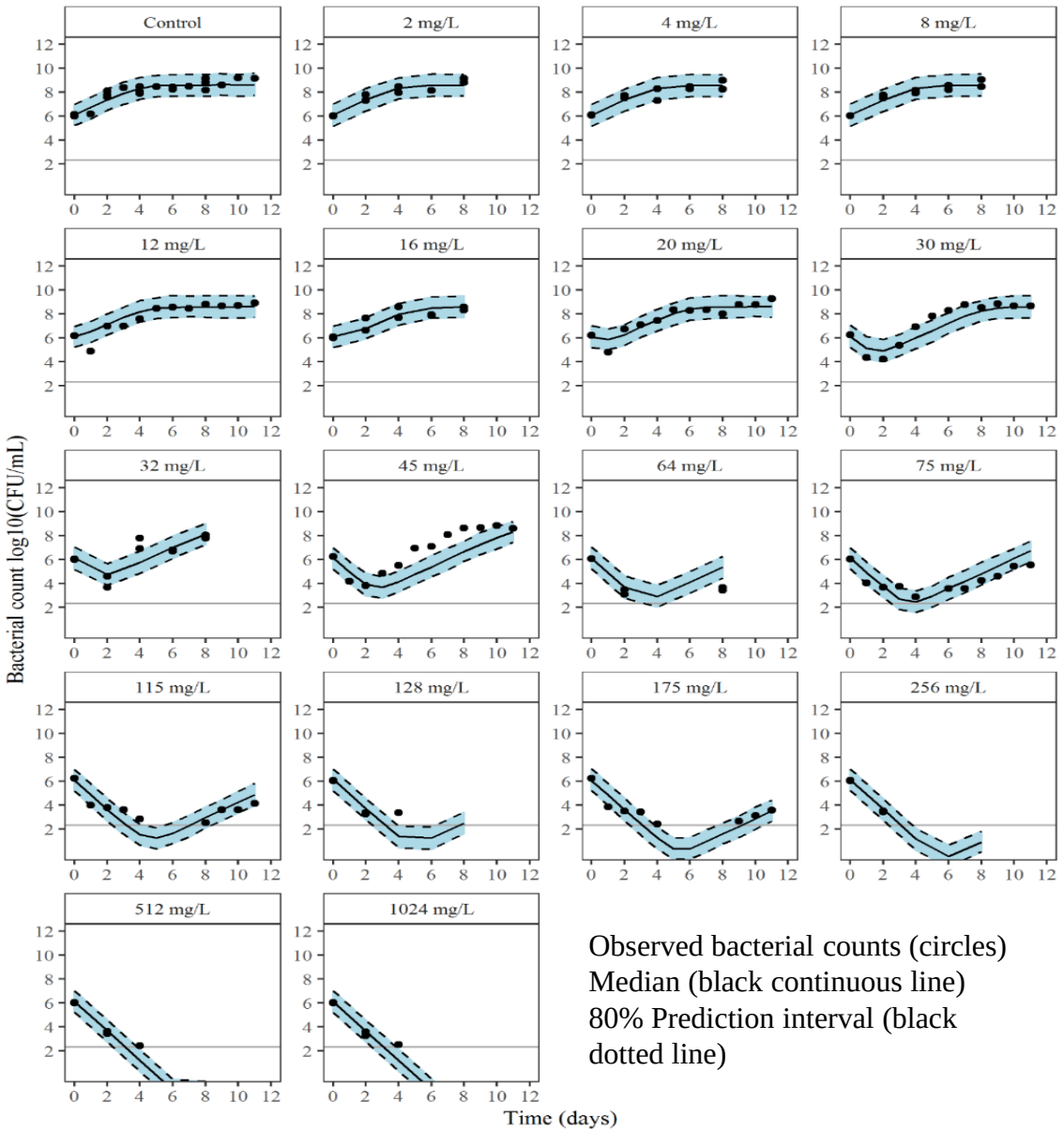
Results



Observed bacterial counts (circles)
Median (black continuous line)
80% Prediction interval (black dotted line)

Czaja *et al.* 2014

Results



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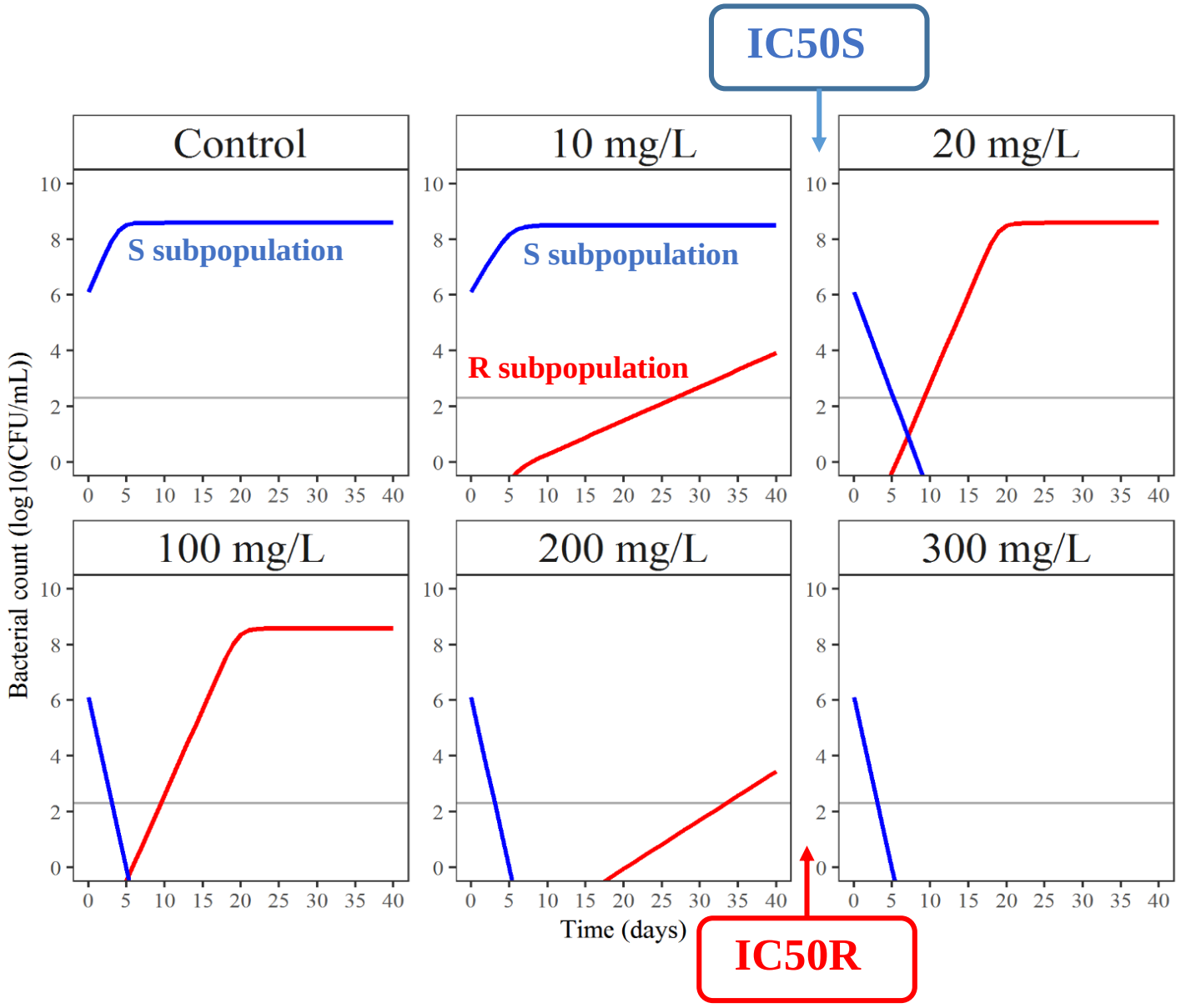
Parameter (units)	Estimation (%RSE)
LGINOC (Log_{10}CFU/mL)	6.1 (1%)
K_g (day^{-1})	4.3 (6%)
B_{max} (Log_{10}CFU/mL)	9.05 (1%)
K_d (day^{-1})	2.83 (7%)
I_{max}	1 (fixed)
IC_{50S} (mg/L)	16.2 (11%)
IC_{50R} (mg/L)	252 (20%)
K_e (day^{-1})	0.438 (fixed)
MUTF	-9.66 (6%)
γ	4.8 (39%)

Czaja *et al.* 2014

Results


IC50S
Control
10 mg/L
20 mg/L
100 mg/L
200 mg/L
300 mg/L
S subpopulation
S subpopulation
R subpopulation
Bacterial count (log10(CFU/mL))
Time (days)
IC50R

Conclusion

- ✓ A PK/PD type model: to predict the time-course of effects under different dosing regimens after correction for cefoxitin degradation

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