

# Pharmacokinetic/Pharmacodynamic Modeling and Simulation for Concentration-Dependent Bactericidal Activity of a Bicyclolide, Modithromycin

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## Objective

- Modithromycin (also known as S-013420) is a bicyclolide (bridged bicyclic macrolide) that exhibits potent against various pathogens of respiratory tract infections [1]. The mechanism of the bactericidal activity of modithromycin involves inhibition of amplification by binding to the 50S subunit of the bacterial ribosome as observed with telithromycin and clarithromycin [1].
- The aim of this study was to develop PK/PD model of modithromycin to explain its concentration-dependent activity against *S. aureus*, *H. influenzae* and *S. pneumoniae* based on our drug-bacterium interaction model [2-5] and to simulate efficacy of modithromycin in patients using the PK/PD model.

## Method

### Modeling

- The PK/PD model reported for  $\beta$ -lactams [2-5] was used as a base model (Fig. 1).
- An effect compartment model and a turnover model were incorporated into the base model to explain PK/PD time lag and reduction of efficacy, respectively (Fig. 1).
- In vitro* time-kill data in 2 types of experiments [6, 7] were used for the modeling.
  - Static experiments, experiments using static concentration in medium
  - Dynamic experiments, experiments using mechanically simulated concentration in medium
  - Test drug: modithromycin, telithromycin and clarithromycin
  - Test strain: *S. aureus* SR20405, *H. influenzae* SR24159, SR24165 and SR24169, and *S. pneumoniae* SR26132
- The bacterial count data were fitted to the PK/PD model for the drug-bacteria combinations by the M3 method [8] using NONMEM (Version 7.1).

### Simulation

- The followings were considered to simulate time courses of bacterial counts for modithromycin in patients with pneumonia infected with *S. aureus*, *H. influenzae* and *S. pneumoniae*.
  - MIC distribution of clinical isolates collected at Japanese medical facilities in 2004 [6] (Fig. 2).
  - PD parameters ( $K_{max}/KC_{50}$  or Slope) based on the simulated MIC using the relationships shown in Fig. 4.
  - PK parameters estimated from the data in Ph1 studies [9, 10] as typical values in patients.
  - 20 of fraction in epithelial lining fluid (ELF) to plasma to simulate lung distribution [11].
  - Unbound fraction of 0.8 in ELF
  - 30% of inter-individual variability for parameters assuming a log-normal distribution.
  - Initial inoculum of  $10^4$  and  $10^7$  CFU/lung to simulate different severities.
- Three QD regimens with 2-fold dosage as an initial loading dose were simulated.
- 1000 simulations were performed for each scenario.
- Probability of bacterial eradication [ $\log(\text{CFU}/\text{lung}) < 0$ ] in simulated patients was calculated as efficacy index.

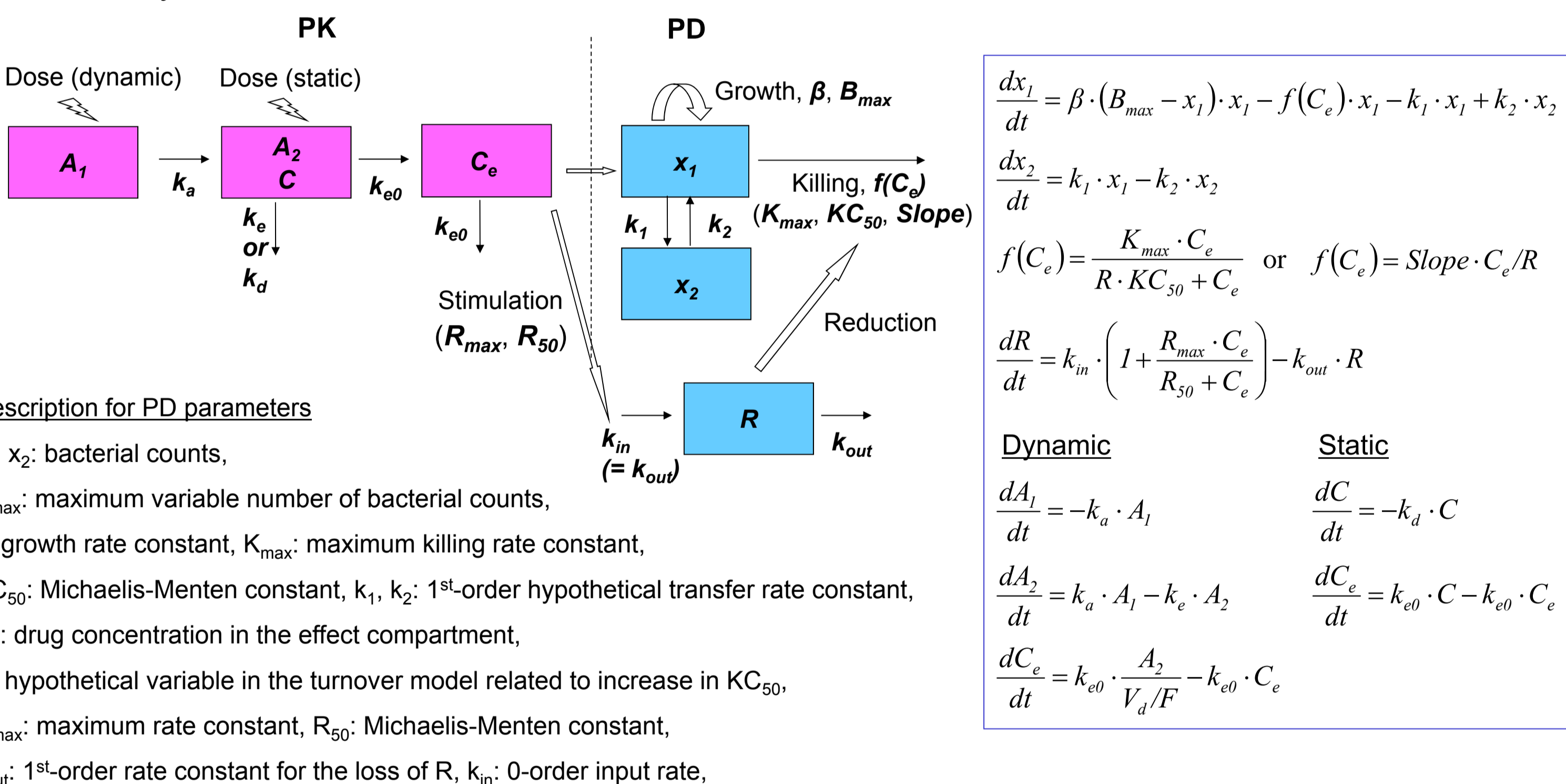


Fig. 1 Scheme of the PK/PD model for describing the bactericidal activity.

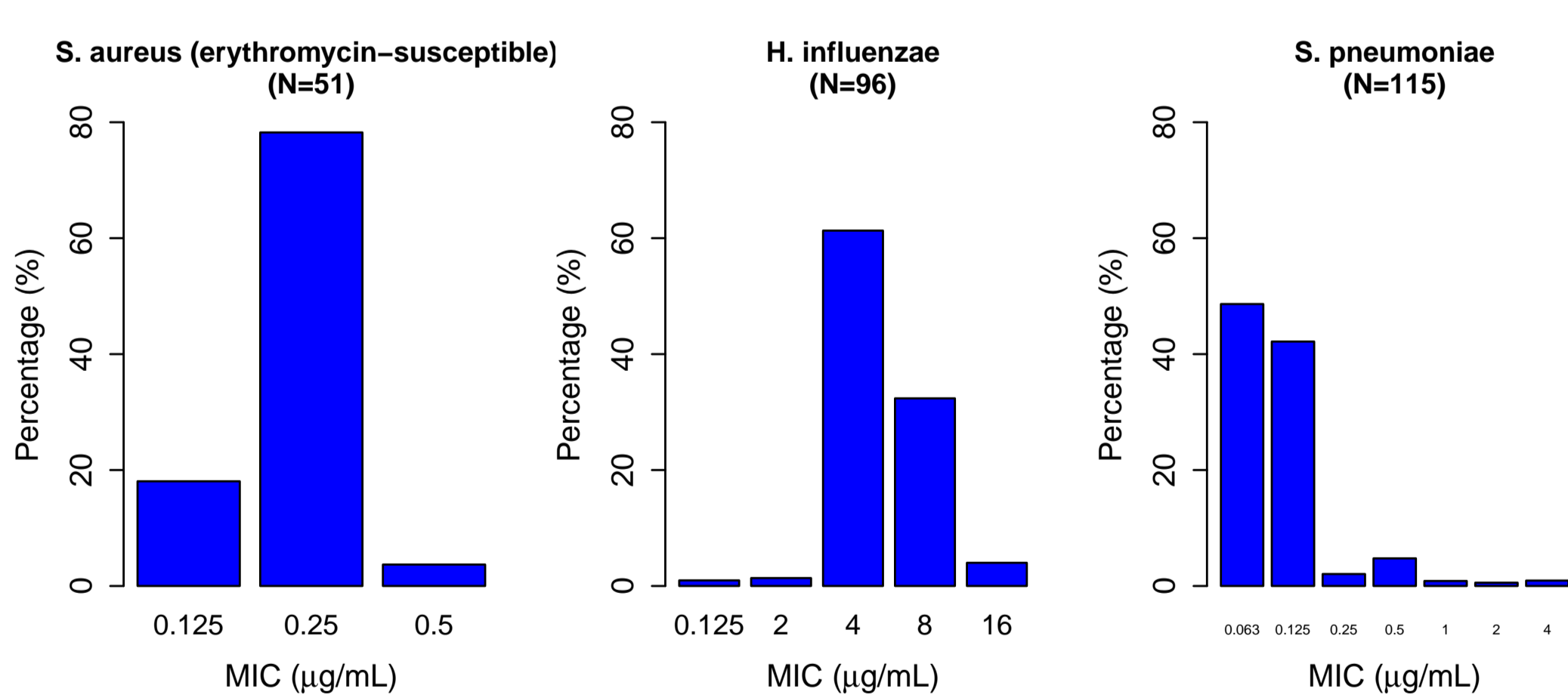


Fig. 2 MIC distribution of each bacterium used for the simulations.

## Summary and Conclusion

- The developed PK/PD model well described *in vitro* time-kill data of modithromycin against test strains.
- The initial loading dose followed by 200 mg QD, 400 mg QD and 100 mg QD of modithromycin would be potent against *S. aureus*, *H. influenzae* and *S. pneumoniae*, respectively.
- The 5-day dosing of modithromycin would be expected to exhibit efficacy regardless severity.

## Reference

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## Result - Modeling

- The developed PK/PD model well described *in vitro* time-kill data for all combinations of drugs and bacterium (Fig. 3 as typical cases).
- The PD parameters ( $K_{max}/KC_{50}$  and Slope) strongly correlated with MIC (Fig. 4).
- The simulated bactericidal activity of modithromycin strongly correlated to AUC/MIC (Fig. 5).

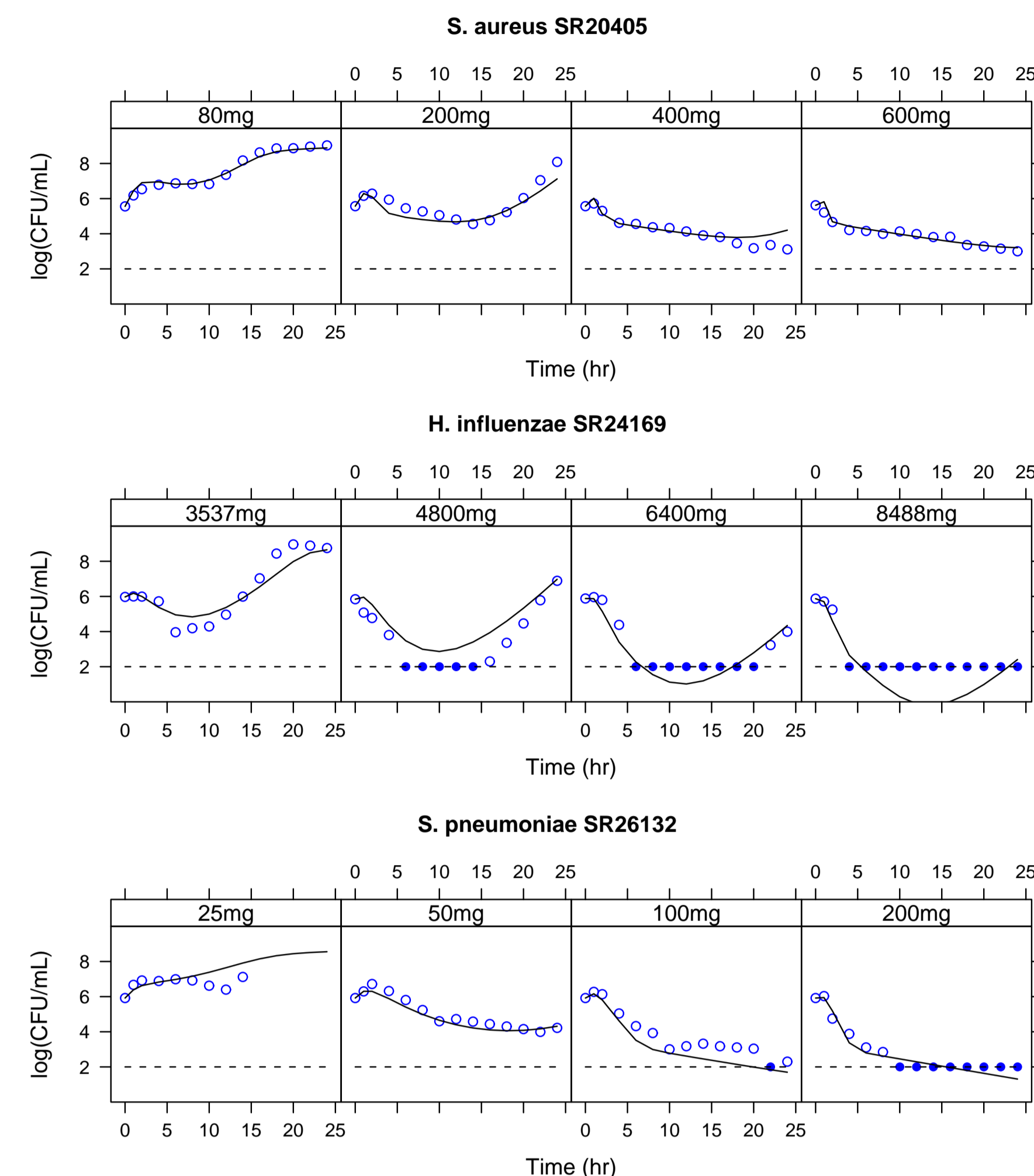


Fig. 3 Typical results of model fitting with *in vitro* bacterial count data of modithromycin against each strain. Dotted line: the lower limit of quantification. The data below the limit of quantification were plotted as 2 of  $\log(\text{CFU}/\text{mL})$  using closed circles.

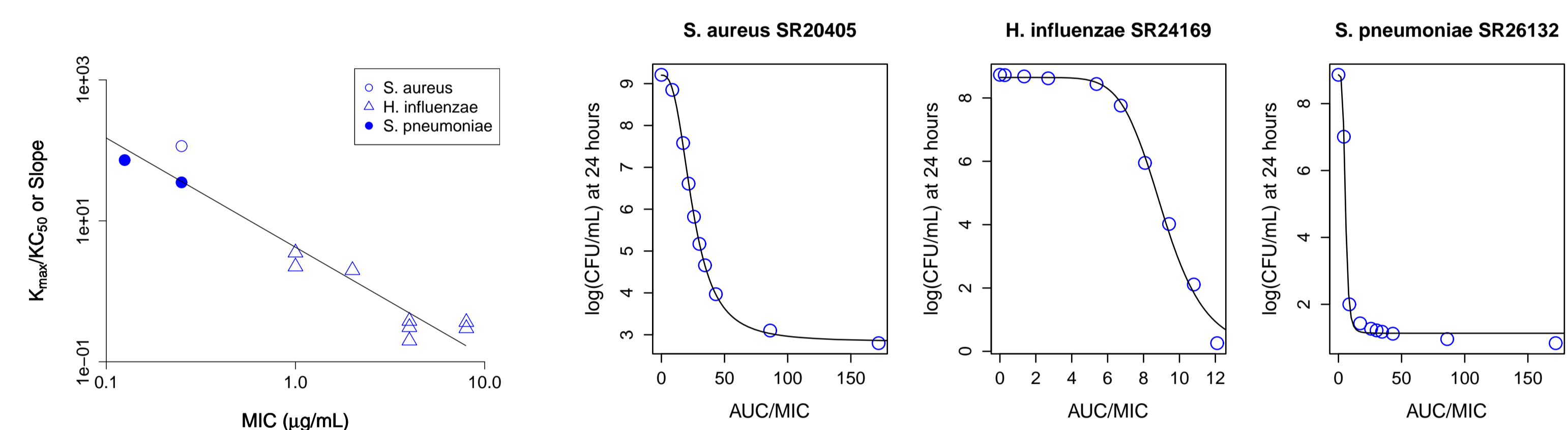


Fig. 4 Relationships between PD parameters and MIC.

Fig. 5 Relationships between simulated bacterial counts at 24 hours and AUC/MIC of modithromycin for each strain.

## Result - Simulation

- The parameters used in the simulations are shown in Table 1.
- Typically any dosage regimens exhibited bactericidal effect regardless the initial inoculums, except for the lowest regimen against *H. influenzae* (Fig. 6).
- The probability as efficacy index against *S. aureus*, *H. influenzae* and *S. pneumoniae* exceeded 80% at 200 mg QD, 400 mg QD and 100 mg QD, respectively, in both initial inoculums (Fig. 7).
- The probability in smaller and larger initial inoculums reached 80% within 3 days and 5 days from the start of effective dosage regimen, respectively (Fig. 7).

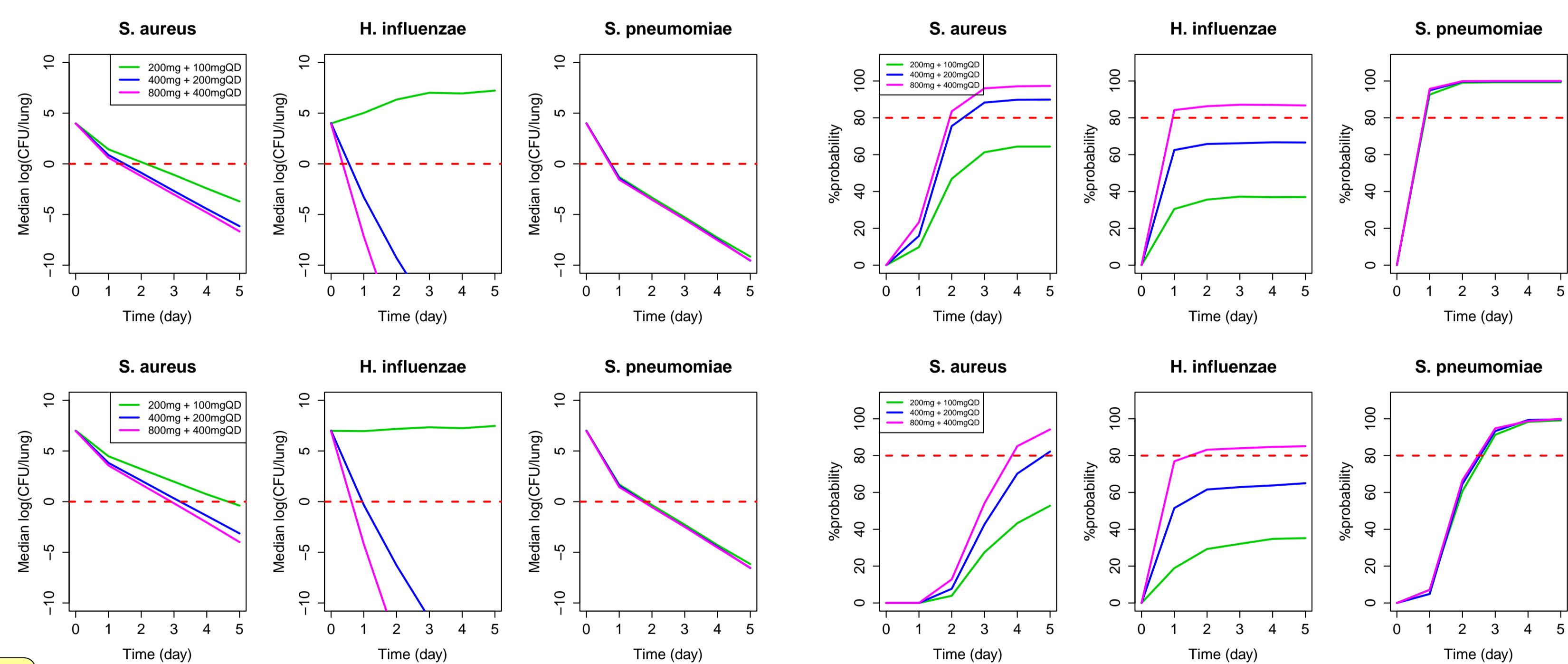


Fig. 6 Time courses of median simulated bacterial counts in 3 dosage regimens. Initial inoculum:  $10^4$  (upper) and  $10^7$  (lower) CFU/lung.

Fig. 7 Time courses of the probability [ $\log(\text{CFU}/\text{lung}) < 0$ ] as efficacy index in 3 dosage regimens. Initial inoculum:  $10^4$  (upper) and  $10^7$  (lower) CFU/lung.

Table 1 PK/PD parameters to simulate bactericidal activity of modithromycin

Bacterium	<i>S. aureus</i>	<i>H. influenzae</i>	<i>S. pneumoniae</i>
$\beta$ ( $10^{-10} \text{hr}^{-1} \cdot (\text{CFU}/\text{mL})$ )	18.4	21.2	18.1
$B_{max}$ ( $10^{10} \text{CFU}/\text{mL}$ )	0.129	0.0531	0.0716
$k_1$ ( $\text{hr}^{-1}$ )	0.0470	0.00852	0.000938
$k_2$ ( $\text{hr}^{-1}$ )	0.184	1.08	0.192
$K_{max}$ ( $\text{hr}^{-1}$ )	199	-	5.58
$KC_{50}$ ( $\mu\text{g}/\text{mL}$ )	$K_{max}[\text{exp}(1.44) \cdot \text{MIC}^{-1.55}]$	-	$K_{max}[\text{exp}(1.44) \cdot \text{MIC}^{-1.55}]$
Slope ( $\text{hr}^{-1} \cdot \mu\text{g}/\text{mL}$ )	-	$\text{exp}(1.44) \cdot \text{MIC}^{-1.55}$	-
$k_{e0}$ ( $\text{hr}^{-1}$ )	0.144	10.0	1.66
$R_{max}$ ( $\text{hr}^{-1}$ )	37.8	-	-
$R_{50}$ ( $\mu\text{g}/\text{mL}$ )	0.398	-	-
$k_{out}$ ( $\text{hr}^{-1}$ )	0.129	-	-
$V_d/F$ (L)	709	709	709
$k_a$ ( $\text{hr}^{-1}$ )	1.28	1.28	1.28
$k_e$ ( $\text{hr}^{-1}$ )	0.039	0.039	0.039