



EFFECT OF PHARMACOKINETIC MODEL MISSPECIFICATION ON ANTIBIOTIC PROBABILITY OF TARGET ATTAINMENT PREDICTED BY MONTE CARLO SIMULATION

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Objectives

Many population pharmacokinetic (PK) models have been developed for an antibiotic, and the structures of such models are very diverse. We compared the predictability of efficacy by Monte Carlo simulation between one- and two-compartment models assuming sampling designs result in different numbers of compartments. We also explored the indicators used to identify the usefulness of one-compartment model by comparing PK/PD indices between three mis-specified one-compartment models and a true two-compartment model.

Materials & Methods

The reported population PK two-compartment model parameters of two doripenem studies (DRP1, DRP2) and one vancomycin study (VAN) were used to generate virtual observations of 200 concentration-time profiles for each study. The sampling times of the original reported designs were applied in each data simulation. The covariates included in the original model were generated within a range that was twice the standard deviations (2 SD) of the reported demographic data during PK parameter simulation. If the range of the covariates was reported, the covariates were not generated to exceed the range.

Sparse and dense sampling designs were selected to build one- and two-compartment models for a drug, respectively. For DRP1 and DRP2, the best sparse sampling design was used to build a good one-compartment model for each drug. For VAN, the original sampling times were used for the two-compartment model (V2) building. To investigate the effect of the model misspecification on the PK/PD indices, three mis-specified one-compartment models were built using three sparse sampling designs.

To explore the PDs of the antibiotics, 10,000-subject MCS was conducted with the newly estimated one- and two-compartment PK model parameter values developed in this study. The probability of target attainment (PTA) for PK/PD indices was compared in the one- and two-compartment PK models of the same drug by applying the clinical breakpoint distribution of MICs set by the European Committee on Antimicrobial Susceptibility Testing (EUCAST).

Results

The simulated concentration-time profiles well-reproduced the original data. For DRP1, the concentration-time profiles showed very little differences between the one- and two-compartment models. (Figure 1a). The doripenem CL was similar for both models (Table 1). For DRP2, the concentration-time profiles of two-compartment models were higher than those of the one-compartment models for all infusion times (Figure 1b). The CL of both models was also similar to the value used for data simulation, whereas the Vd of the one-compartment model was smaller than the sum of the V_c and V_p for the true model (Table 1). For VAN, we observed that the concentration-time profiles of three one-compartment models were lower than those of the two-compartment model. (Figure 2) There was a large difference in the estimated CL of the four models. Among the three one-compartment models, only the Vd for V1C was similar to the sum of the V_c and V_p for the two-compartment model (Table 2).

For DRP1, the PTAs were similar between the one- and two-compartment models when infusion time and MIC were the same. In addition, the maximum difference was 10.5% when infusion time was 1 h and MIC was 1 mg/L (Figure 1c). For DRP2, the maximum difference was 11.8% when the infusion time was 4 h and MIC was 4 mg/L (Figure 1d). The infusion times of 2 and 3 h were excluded from the Figure 1d due to similarities in the results of the four infusion times. For VAN, the maximum difference was 65.9% between V1A and V2 when MIC was 1 mg/L (Figure 2b). The PTA of the V1C was the closest to the V2, although the difference was 26.1% when MIC was 1 mg/L.

Results (cont'd)

Table 1. Table 1. Doirpenem population pharmacokinetic models for concentration-time profiles generation and Monte Carlo simulation ^a

	Model Structure	Parameter	Reported	1-comp	2-comp
DRP1					
CL (liter/h)	$= \theta_{TVCL} \times (BW/57)^{0.75} \times e^{\eta_{CL}}$	θ_{TVCL}	22.0	22.3	22.1
V _c (liter)	$= \theta_{TVVc} \times (BW/57) \times e^{\eta_{Vc}}$	θ_{TVVc}	16.0	18.3	16.3
Q (liter/h)	$= \theta_{TVQ} \times (BW/57)^{0.75}$	θ_{TVQ}	1.83	-	1.88
V _p (liter)	$= \theta_{TVVp} \times (BW/57)$	θ_{TVVp}	3.13	-	3.24
BSV					
		$\omega_{CL}(\%)$	31.6	36.3	29.6
		$\omega_{Vc}(\%)$	35.4	48.2	31.3
		corr _{CL-Vc}	0.871	0.944	0.926
RUV	$y_{ij} = \hat{y}_{ij} \times (1 + \varepsilon_{ij})$	$\sigma_{prop}(\%)$	30.1	36.3	27.9
DRP2					
CL (liter/h)	$= \theta_{TVCL} \times e^{\theta_{CLCR} \times (CL_{CR} - 82.5)} \times (BW/70)^{0.75} \times e^{\eta_{CL}}$	θ_{TVCL}	10.1	11.3	10.2
		θ_{CLCR}	0.0140	0.0163	0.0144
V _c (liter)	$= \theta_{TVVc} \times (BW/70) \times e^{\eta_{Vc}}$	θ_{TVVc}	15.5	44.1	14.8
Q (liter/h)	$= \theta_{TVQ} \times (BW/70)^{0.75}$	θ_{TVQ}	36.3	-	37.9
V _p (liter)	$= \theta_{TVVp} \times (BW/70) \times e^{\eta_{Vp}}$	θ_{TVVp}	17.7	-	17.4
BSV					
		$\omega_{CL}(\%)$	32.9	27.5	23.0
		$\omega_{Vc}(\%)$	56.7	55.9	54.6
		$\omega_{Vp}(\%)$	73.8	-	73.3
RUV	$y_{ij} = \hat{y}_{ij} \times (1 + \varepsilon_{ij})$	$\sigma_{prop}(\%)$	9.00	6.48	7.25

^a Abbreviations: 1-comp, one-compartment model; 2-comp, two-compartment model; CL, clearance, VC, central volume of concentration; Q, intercompartment clearance; VP, peripheral volume of concentration; TV, typical value; CLCR, creatinine clearance; BW, body weight; BSV, between subject variability; RUV, residual unexplained variability; corrCL-Vc, correlation coefficient between CL and VC
b volume of distribution of one-compartment model built using late sampling times

Table 2. Vancomycin population pharmacokinetic models for concentration-time profiles generation and Monte Carlo simulation ^a

	Model Structure	Parameter	Reported	V1A	V1B	V1C	V2
CL (liter/h)							
	$= \theta_{TVCL} \times (1 + \theta_{CLCR} \times (CL_{CR} - 83)) \times e^{\eta_{CL}}$	θ_{TVCL}	2.83	7.78	4.99	4.22	2.80
		θ_{CLCR}	0.0154	0.00698	0.00995	0.0123	0.0158
V_c (liter)							
	$= \theta_{TVVc}$	θ_{TVVc}	24.2	36.6	46.4	-	25.9
V_c (liter)^b							
	$= \theta_{TVV} \times (1 + \theta_{BW} \times (BW - 94.5)) \times e^{\eta_{Vc}}$	θ_{TVVc}	-	-	-	59.1	-
		θ_{BW}	-	-	-	0.00697	-
Q (liter/h)							
	$= \theta_{TVQ}$	θ_{TVQ}	11.2	-	-	-	11.7
V_p (liter)							
	$= \theta_{TVVp} \times (1 + \theta_{BW} \times (BW - 94.5)) \times e^{\eta_{Vp}}$	θ_{TVVp}	32.3	-	-	-	33.4
		θ_{BW}	0.0169	-	-	-	0.0186
BSV							
		$\omega_{CL}(\%)$	34.0	31.5	31.2	41.5	36.7
		$\omega_{Vc}(\%)$	77.0	43.9	36.3	31.5	68.4
RUV	$y_{ij} = \hat{y}_{ij} \times (1 + \varepsilon_{ij})$	$\sigma_{prop}(\%)$	8.19	7.03	12.2	6.39	7.32

^a Abbreviations: V1A, one-compartment model built with samples of 0, 2.5, 3, and 4 h; V1B, one-compartment model built with samples of 0, 2.5, 4 and 8 h; V1C, one-compartment model built with samples of 0, 4, 6, and 8 h; V2, two-compartment model built with samples of 0, 2.5, 3, 4, 6, and 8 h; CL, clearance, V_c, central volume of concentration; Q, intercompartment clearance; VP, peripheral volume of concentration; TV, typical value; BSV, CL_{CR}, creatinine clearance; BW, body weight; BSV, between subject variability; RUV, residual unexplained variability
^b volume of distribution of one-compartment model of V1C

Results (cont'd)

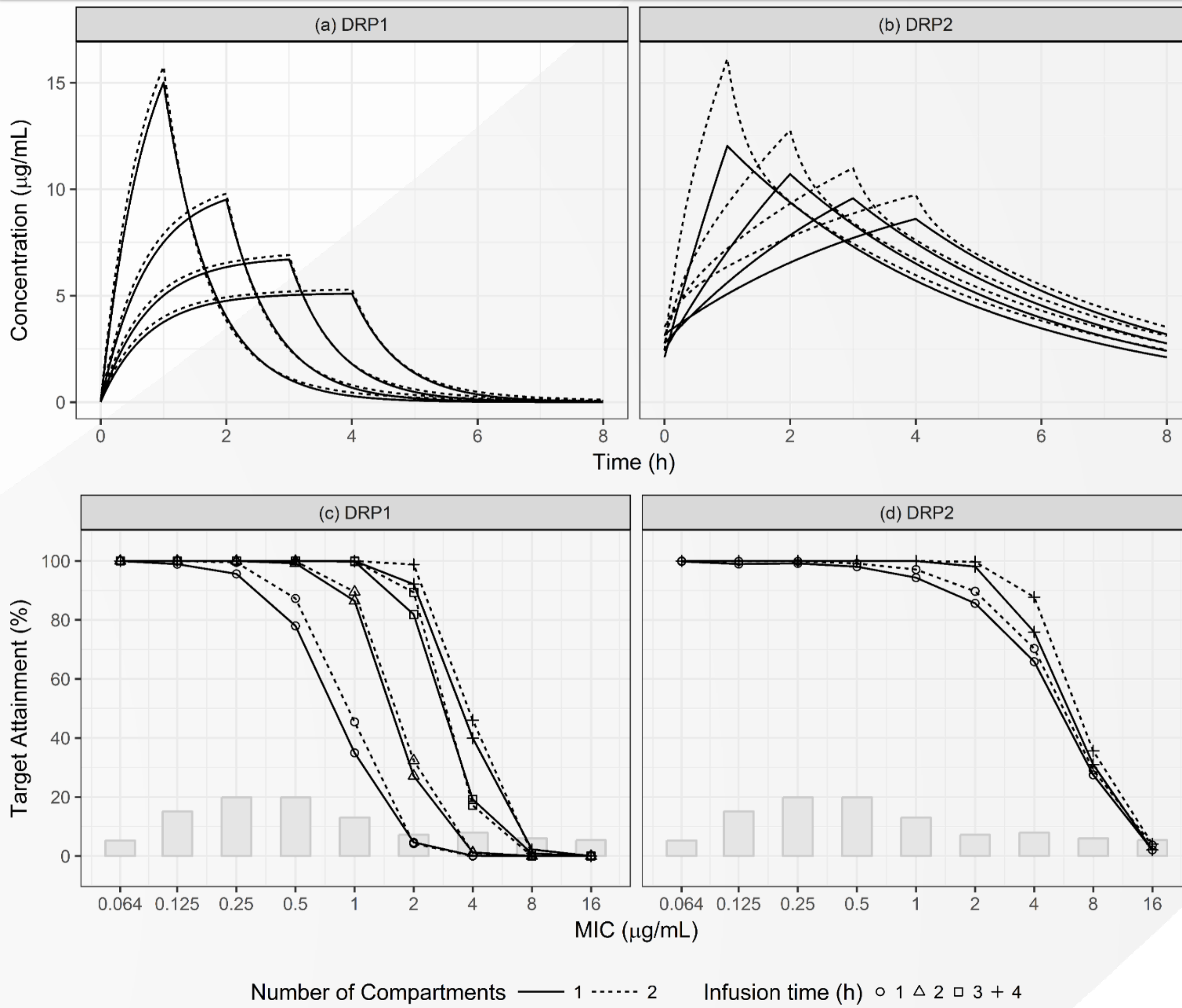


Figure 1. Population predicted concentration profiles (top) and probability of target attainment (bottom) for DRP1 and DRP2. Bars indicate the wild-type MIC distribution for Pseudomonas aeruginosa (bottom).

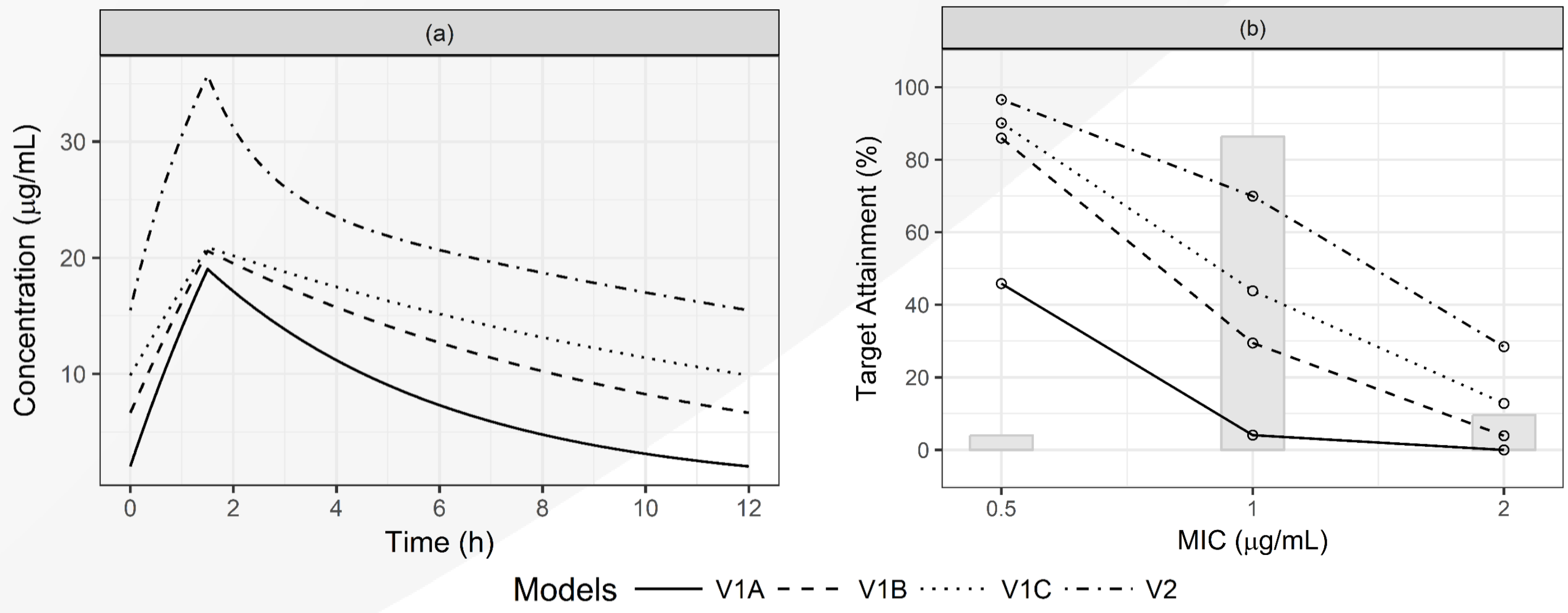


Figure 2. Population predicted concentration profiles (left) and probability of target attainment (bottom) for VAN. Bars indicate the wild-type MIC distribution for methicillin-resistant Staphylococcus aureus (right).

Conclusions

We explored the PK/PD indices of antibiotics using one- and two-compartment models built with same cohort and different sampling designs. When a mis-specified one-compartment model was established with sparse sampling data, the PTA was significantly different from that of the two-compartment model. Thus, a useful PK model must be verified through diagnostic plots and visual predictive checks and the range of sampling time should be sufficient to explain the PK of a drug.

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