

Background and objectives

Meropenem is a broad-spectrum carbapenem antibiotic that is used off-label in the treatment of late-onset sepsis (LOS) and meningitis in infants.

We aimed to develop a population pharmacokinetic (PK) model for meropenem plasma and CSF concentrations, and use it for dosing recommendations in infants <3 months. We also aimed to investigate if the pharmacokinetic-pharmacodynamic (PKPD) target of 40% of time above the minimal inhibitory concentration (MIC) ($t > MIC$) [1] is sufficient for infants.

Methods

Meropenem was given at 20 mg/kg (LOS) or 40 mg/kg (meningitis) as a 30-min infusion; the dosing interval depended on the infant's gestational age (GA) and postnatal age (PNA) (Table 1). ED-optimal design (PopED) was used to define 3 plasma PK sampling times for a subset of patients, who provided >1 trough sample. CSF samples were taken during lumbar puncture for study-specific purposes at unspecified time after dose.

Table 1: Age groups and the corresponding dosing frequency

Age group	Dosing frequency
GA <32 weeks, PNA <2 weeks	Every 12 hours
GA <32 weeks, PNA ≥2 weeks	Every 8 hours
GA ≥32 weeks, PNA <2 weeks	Every 8 hours
GA ≥32 weeks, PNA ≥2 weeks	Every 8 hours

NONMEM 7.3 (first order conditional estimation with interaction) was used. Several different structural and residual error models were fitted to the plasma data. Allometric weight scaling and a function describing renal function maturation [2] were used *a priori*, and serum creatinine (SCr) and PNA were tested on clearance (CL). Then, a CSF compartment was added, and plasma-CSF clearance (Q_{CSF}), and the fraction of meropenem penetration from plasma to CSF (f_{CSF}) were estimated (Figure 1). The effect of markers of central nervous system inflammation on f_{CSF} was investigated. Monte-Carlo simulations ($n=1,000$) were used to generate the probability-of-target-attainment (PTA) curves. Finally, the PK model was combined with an *in vitro* PKPD model (Figure 2) [3], describing the effects of meropenem on the wild type *Pseudomonas aeruginosa* (ATCC27835).

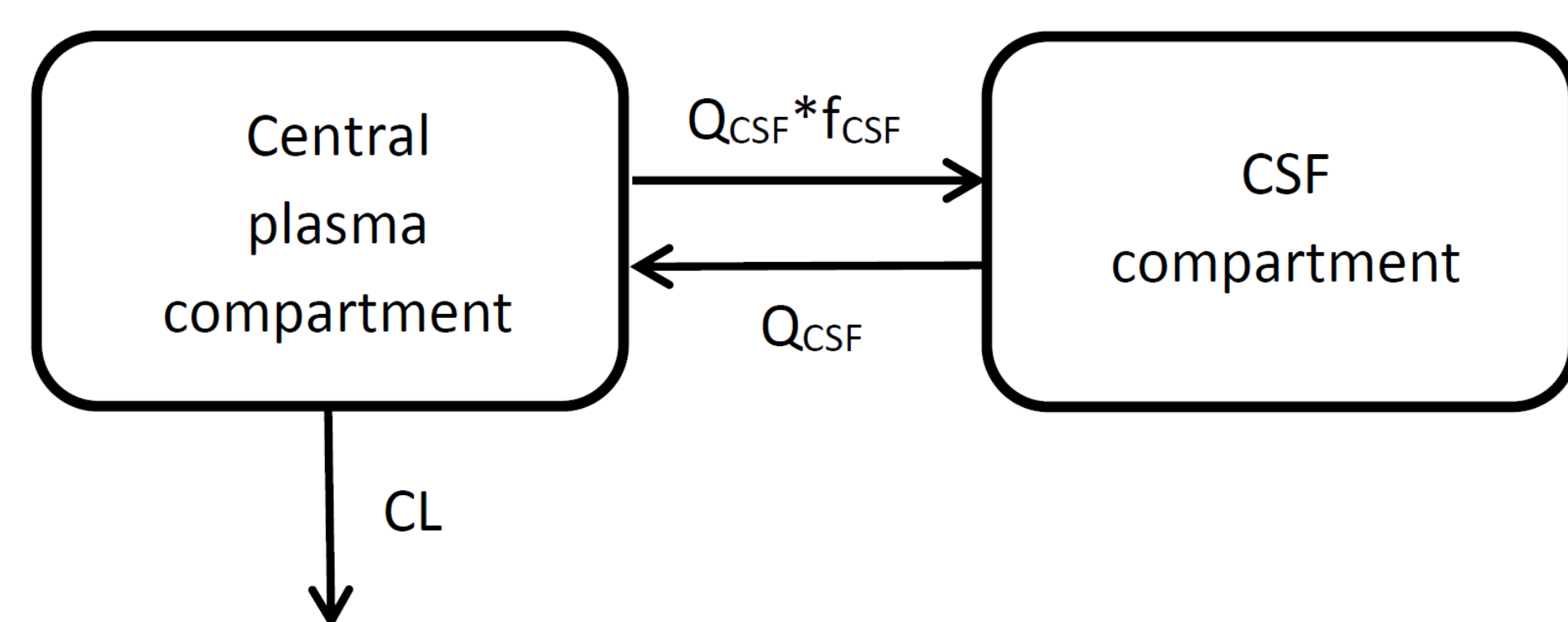


Figure 1: Schematic presentation of the PK model.

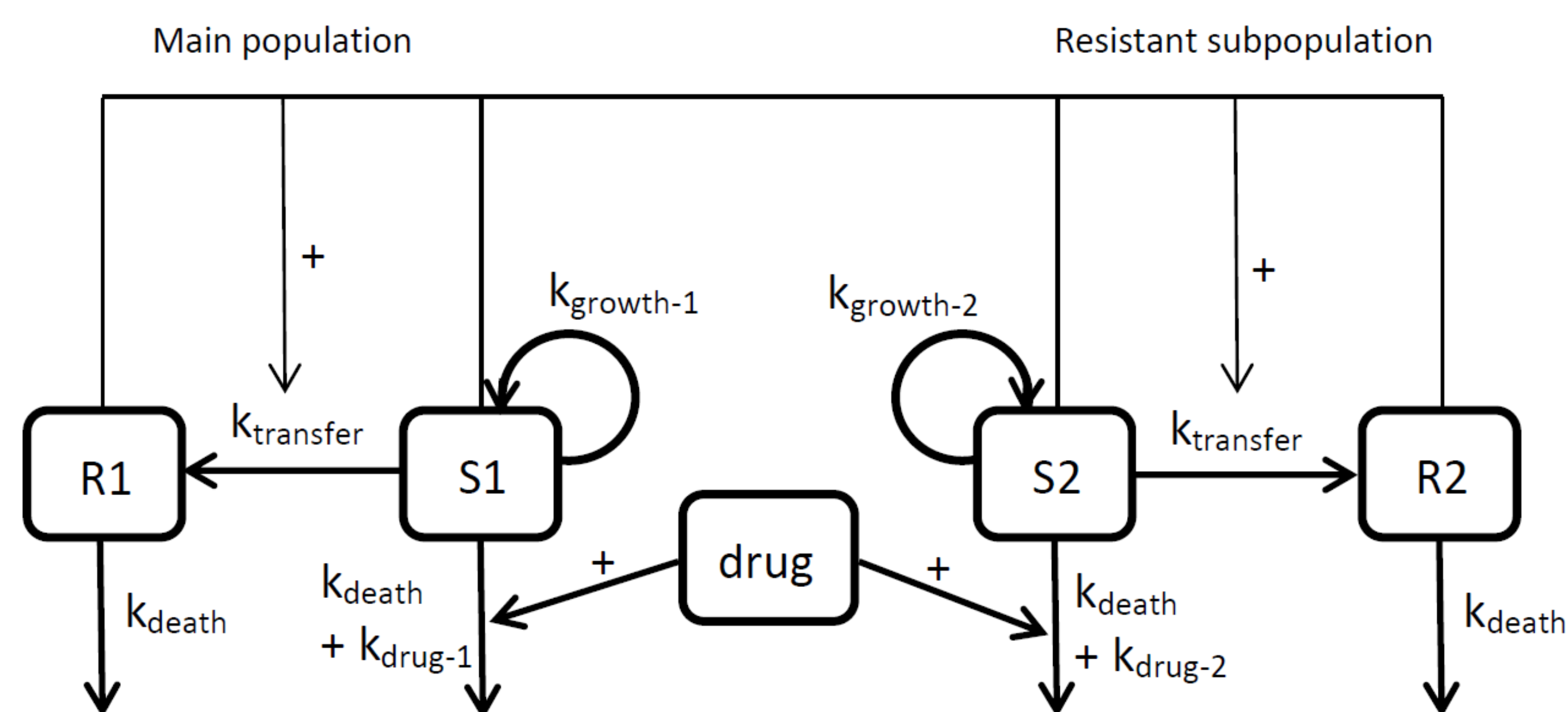


Figure 2: Schematic presentation of the PKPD model, adapted from [3]. The resistant subpopulation is pre-existent and represents 0.15% of the start inoculum. S are meropenem susceptible proliferating bacteria, and R are resting non-proliferating and non-susceptible bacteria. The drug effect (k_{drug}) was modelled as a power function: $k_{drug} = \text{slope} \cdot C^y$, where C is meropenem concentration.

Conclusions

A PK model for plasma and CSF meropenem data in young infants with LOS and/or meningitis was developed. The dosing regimen used in the study was shown appropriate for susceptible pathogens, but 40% $t > MIC$ appeared insufficient for severely immunocompromised infants.

Results

A total of 167 infants with median (range) GA 33.3 (22.6-41.9) weeks, and PNA 13 (1-90) days at enrolment provided 401 plasma and 78 CSF samples. The final PK model for plasma was a 1-compartment model, SCr proved significant on CL, and CSF total protein concentration on f_{CSF} . A Box-Cox power transformation [4] was used to address the non-normally distributed residuals. The parameter values (mean (relative standard error)) for a typical infant (weight=2.12 kg, postmenstrual age=37.4 weeks, SCr=32 $\mu\text{mol/L}$) were: CL=0.48 (5.2%) L/h, volume of distribution 1.18 (5.6%) L, Q_{CSF} =0.0012 (24.3%) L/h, f_{CSF} =0.085 (18.8%). Diagnostic plots showed adequate descriptive and simulation properties of the model (Figure 3). Dosing regimens used in the study were appropriate if MIC <4mg/L (LOS) or <1mg/L (meningitis) for a target of 40% $t > MIC$; however, this target overpredicted the meropenem effect, when compared to the *in vitro* target of 2log kill at 24h (Figure 4).

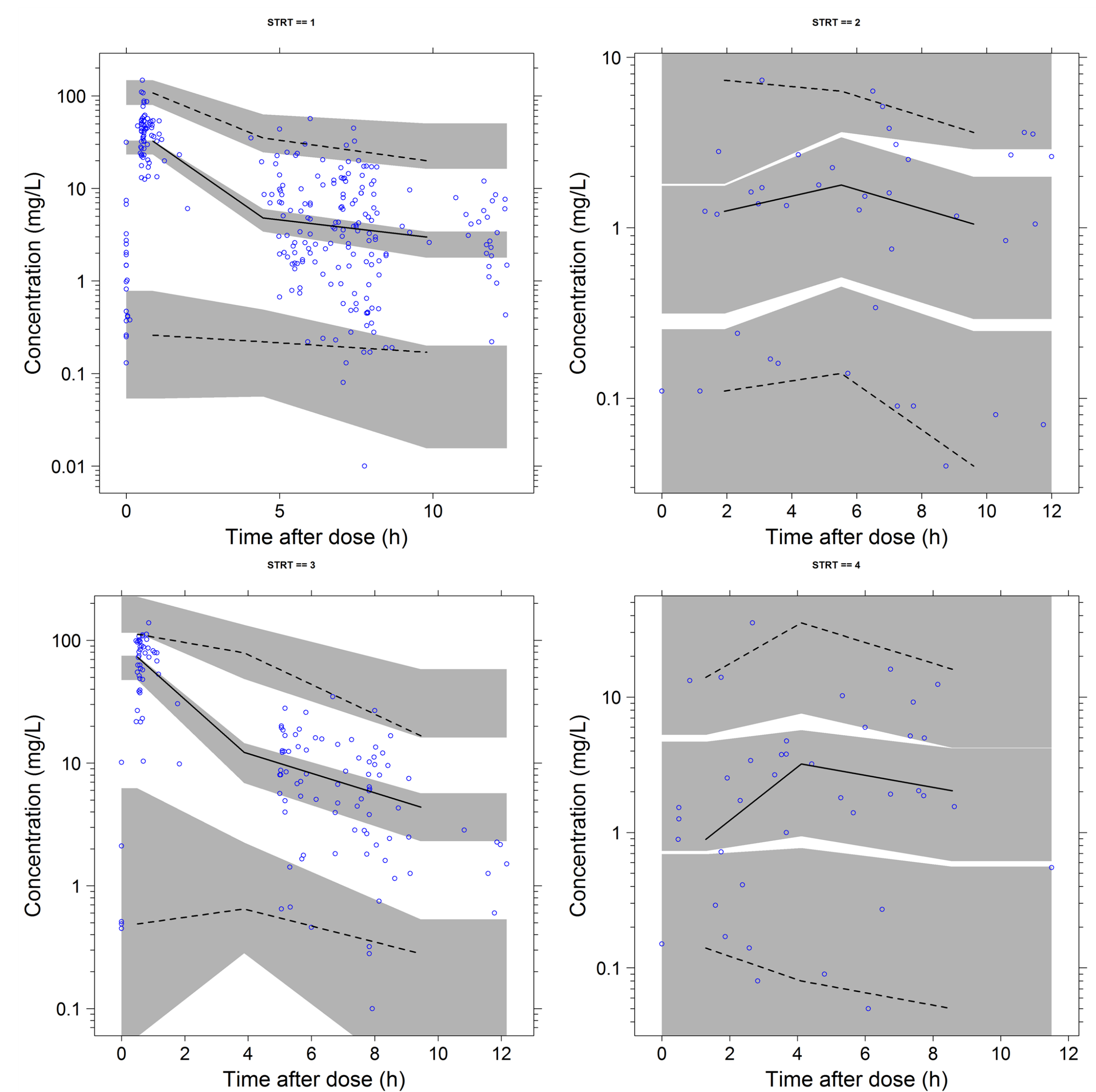


Figure 3: Visual predictive checks for plasma (right) and cerebrospinal fluid (left) for sepsis trial (top) and meningitis study (bottom). Blue dots are the observations, the lines are 2.5th, 50th, and 97.5th percentiles of the data, and the grey areas are 95% confidence intervals from 1,000 simulations using the final model parameter estimates.

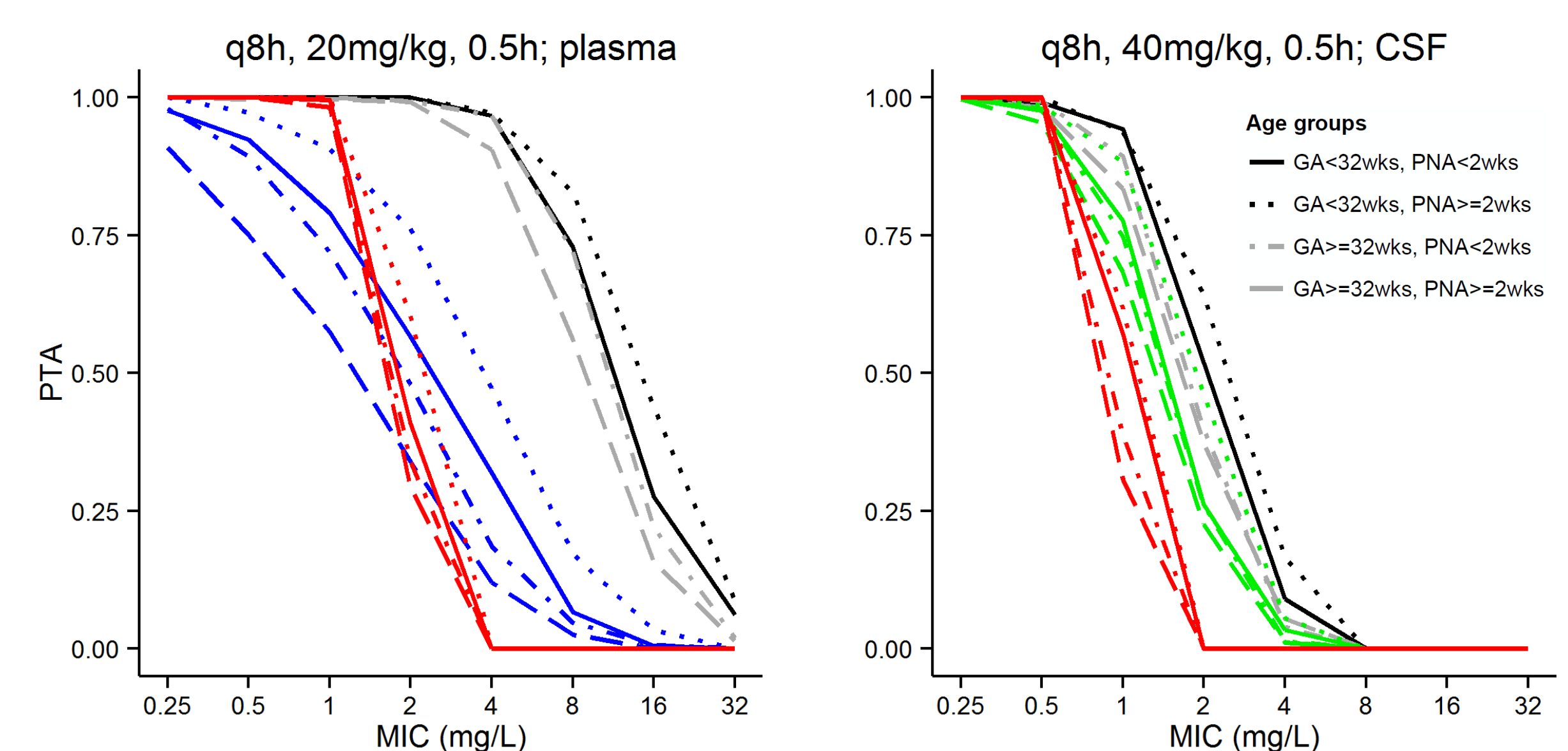


Figure 4: Probability of target attainment against minimal inhibitory concentration, where target was defined as: **Black** = 40% $t > MIC$, **Green** = 70% $t > MIC$, **Blue** = 100% $t > MIC$, **Red** = 2log kill.

References

- [1] Drusano, Antimicrobial pharmacodynamics: critical interactions of 'bug and drug'. Nat Rev Microbiol. 2004; 2(4):289-300.
- [2] Rhodin et al., Human renal function maturation: a quantitative description using weight and postmenstrual age. Pediatr Nephrol. 2009. 24(1):67-76.
- [3] Mohamed et al., Dynamic interaction of colistin and meropenem on a WT and a resistant strain of *Pseudomonas aeruginosa* as quantified in a PK/PD model. J Antimicrob Chemother. 2016; 1-12.
- [4] Dosne et al., A strategy for residual error modeling incorporating scedasticity of variance and distribution shape. J Pharmacokinet Pharmacodyn. 2015; 1-15.