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An optimal sampling schedule for neonates, infants & children receiving cefazolin +/- vancomycin for cardiopulmonary bypass

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Introduction

Dosing of prophylactic antibiotics in children during cardiopulmonary bypass (CPB) remains poorly defined. Pharmacokinetic (PK) studies can be improved using optimal design when sampling is limited or multiple factors influence PK. We aimed to optimise a sampling schedule designed to determine cefazolin and vancomycin PK in children undergoing CPB. We also aimed to determine the best age groups, and the minimum number of subjects, needed to estimate maturation parameters associated with clearance of cefazolin.

Methods

A one compartment distribution model for vancomycin(1) and a three compartment distribution model for cefazolin(2) were used with theory based allometric scaling and maturation to describe first-order elimination clearance. The CPB circuit was represented by an additional compartment. We assumed 60 subjects received cefazolin 50 mg/kg, with 50 of these subjects undergoing a procedure with CPB. We assumed 15 subjects also received 15 mg/kg vancomycin. The distribution of age was simulated using a mean of 5.0 y and CV of a log normal distribution of 0.8. Weight was predicted from age, assuming sex was female for all participants, using the model reported by Sumpter and Holford(3). Optimal times for up to 8 samples per patient were estimated for cefazolin, ignoring CPB effects, using WinPOPT (University of Otago, New Zealand). Optimal sampling times for determination of CPB related changes were considered separately. Designs were selected based on relative standard errors (RSEs) for model parameters and comparison of criterions summarising design efficiency. The final model was evaluated for vancomycin model parameters.

We also evaluated the number of subjects, and the group age (in postmenstrual age weeks, or pmaw), required to estimate maturation parameters associated with clearance (TM50 and hill). Minimum and maximum ages were set at 40 pmaw (full term neonate) and 976 pmaw (18 y). All optimal designs for maturation were done in PopED for R, version 0.3.0.

Results

The most efficient schedule design for Without CPB subjects (N=10, receiving two doses of cefazolin at 6 h intervals) had seven samples allocated to the first dose and an eighth to the second. For With CPB subjects (N=50, receiving two doses of cefazolin at 2.5 h intervals), the most efficient schedule design allocated six samples to the first dose and a further two to the second. RSEs for cefazolin parameters were <30% with the exception of V2, which had an estimated RSE of 49%. Evaluation of the cefazolin sampling schedule for vancomycin PKs resulted in RSEs of 19.6% for CL and 15.5% for V. Five samples directly taken from the CPB unit itself were required to estimate CPB related changes. Table 1 shows sample times for each group, plus RSEs for cefazolin parameters. RSEs < 20% could be obtained for both maturation parameters (TM50 and Hill) with 200 subjects split into three groups (of 50, 50 and 100 subjects). The optimised group ages were 40 pmaw (full term neonate), 80 pmaw (10 months post-natal age) and 976 pmaw (18 years). Model predictions overlaid with sample times are given in Figure 2.
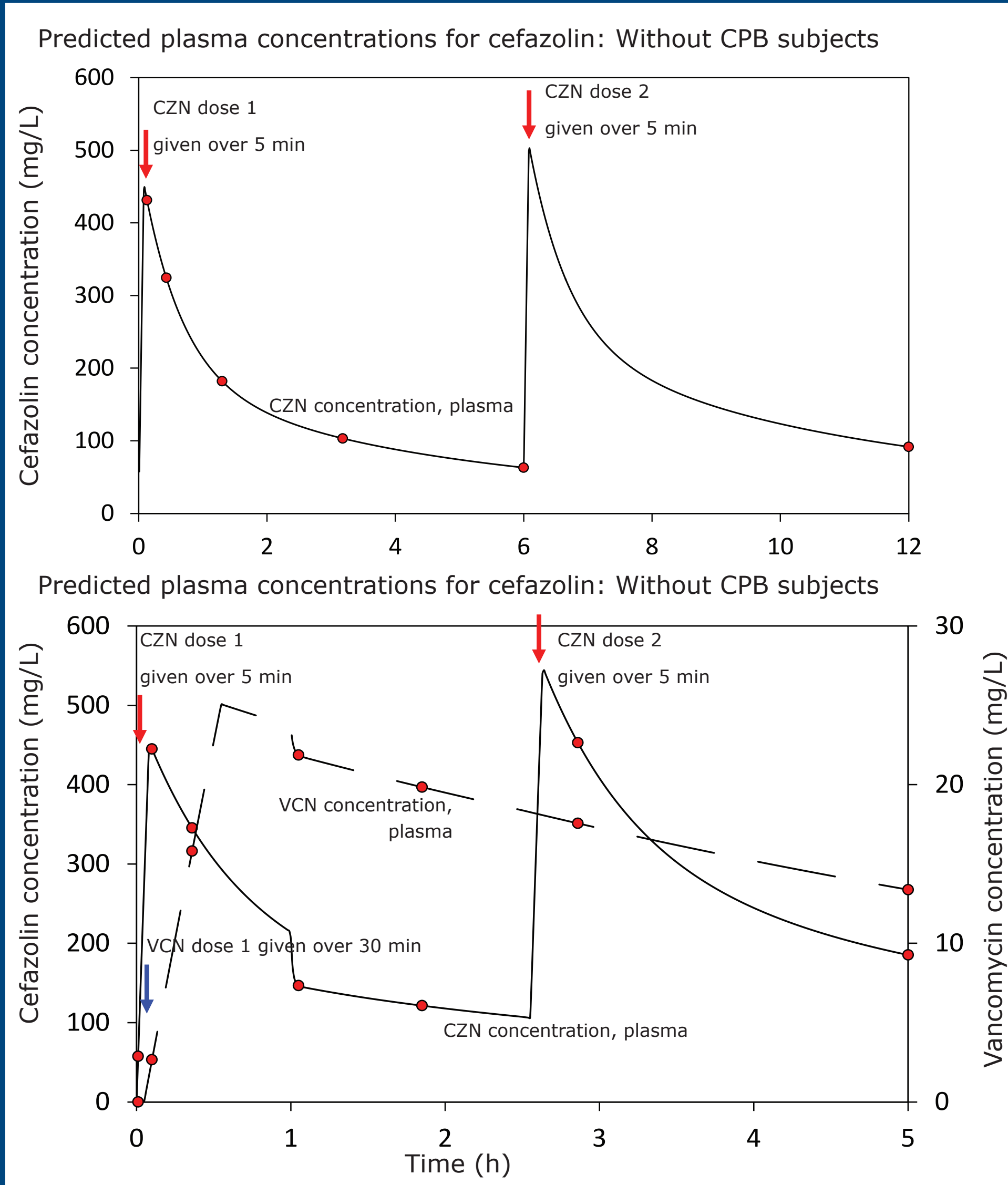
Figure 1. Summary of anticipated dosing schedule, simulated plasma concentrations and final sample times. Top panel: The Without CPB group is 10 patients receiving 50 mg/kg cefazolin at 6 h intervals. Bottom panel: The With CPB group is 50 patients receiving 50 mg/kg cefazolin at induction for a procedure involving CPB. A single dose of vancomycin (15 mg/kg over 30 min) is given to 15 of the With CPB patients immediately following the first dose of cefazolin. CPB is assumed to start 1 h after induction and take 1.5 h to complete, with a second dose of cefazolin given at the end of CPB (t=2.55 h). CZN=cefazolin; VCN=vancomycin. Samples are depicted as red circles and according to the sample times given in Table 1.
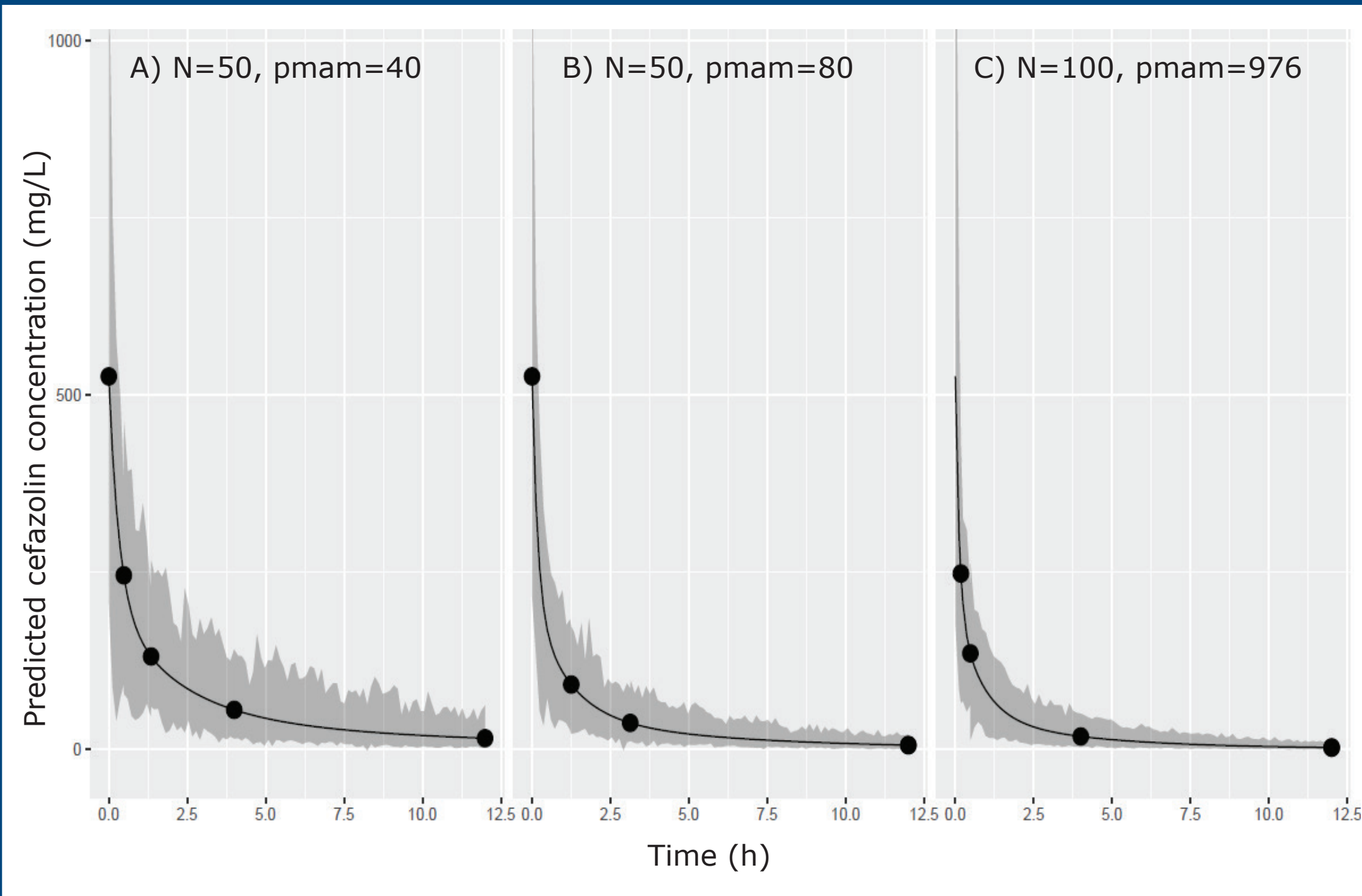
Figure 2. Predicted concentrations for groups of subjects (N=50, 50 and 100, total N=200) when sample times and group age are optimised for cefazolin PK and maturation parameters. The population mean is the solid black line and simulated observations are given in light grey.

Conclusion

We report a sampling schedule for determination of cefazolin and vancomycin PK in neonates, babies and children undergoing CPB. The schedule may be used in the planning of a clinical study in which developing PK models for these drugs to better inform dosing in this population will be our objective.

| Final sample times	(hours after dose)	
	Dose 1	Dose 2
No CPB subjects	0.127, 0.43, 0.43, 1.3, 3.18, 6, 6 h	6 h
With CPB subjects	0.001, 0.001, 0.108, 0.36, 1.05, 1.85 h	0.36, 2.5 h
CPB unit	0.001, 0.001, 0.001, 0.098, 0.098 h	
Parameter	**RSE (%) parameters**	**RSE (%) BSV**
CL1	10.18	47.48
CL2	21.29	176.65
CL3	10.56	72.97
V1	6.98	25.88
V2	49.05	542.77
V3	18.11	89.63
Proportional error	7.11	
Additive error	18.51	

Table 1. Final sample times for Without CPB, With CPB subects and the CPB unit. Estimated RSE associated with model parameters for cefazolin are given. CL=clearance, V=volume.

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