Received: 21 September 2020 | Revised: 2 February 2021 | Accepted: 17 February 2021

DOI: 10.1111/cts.13018

ARTICLE

Model-based approach to sampling optimization in studies of antibacterial drugs for infants and young children

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Funding information
No funding was received for this work.

Abstract

Clinical trials for pediatric indications and new pediatric drugs face challenges, including the limited blood volume due to the patients' small bodies. In Japan, the Evaluation Committee on Unapproved or Off-labeled Drugs with High Medical Needs has discussed the necessity of pediatric indications against the background of a lack of Japanese pediatric data. The limited treatment options regarding antibiotics for pediatric patients are associated with the emergence of antibiotic-resistant bacteria. Regulatory guidelines promote the use of model-based drug development to reduce practical and ethical constraints for pediatric patients. Sampling optimization is one of the key study designs for pediatric drug development. In this simulation study, we evaluated the precision of the empirical Bayes estimates of pharmacokinetic (PK) parameters based on the sampling times optimized by published pediatric population PK models. We selected three previous PK studies of cefepime and ciprofloxacin in infants and young children as paradigms. The number of sampling times was reduced from original full sampling times to two to four sampling times based on the Fisher information matrix. We observed that the precision of empirical Bayes estimates of the key PK parameters and the predicted efficacy based on the reduced sampling times were generally comparable to those based on the original full sampling times. The model-based approach to sampling optimization provided a maximization of PK information with a minimum burden on infants and young children for the future development of pediatric drugs.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

The clinical trials in vulnerable populations, such as infants, face challenges, including the limited blood volume due to the small bodies. In Japan, the necessity of pediatric indications has been discussed against the background of a lack of Japanese pediatric data.

WHAT QUESTION DID THIS STUDY ADDRESS?

This simulation study aimed to apply a model-based approach to the development of antibiotics for pediatric patients to reduce practical and ethical constraints.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

The model-based approach to sampling optimization provided a maximization of pharmacokinetic information with a minimum burden on infants and young children.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

The approach will support future pediatric clinical trials and investigator-initiated trials, as well as provide the valuable information for therapeutic drug monitoring and the administration plans for antibiotics in clinical settings.

INTRODUCTION

In Japan, many drugs that are used in pediatric clinical settings are either unlicensed or used in an off-label manner. It was estimated that ~60%–70% of the package inserts of drugs prescribed in pediatric clinical settings in Japan did not provide a sufficient description of the dosage and administration for pediatric patients.[1] The prescription of unlicensed or off-label drugs can result in an increased risk of adverse events and treatment failure. In general, when the indication(s) and the dosage for pediatric patients are specified in a drug's package insert, the efficacy and safety data should be submitted to the regulatory agency. Japan's Ministry of Health, Labour and Welfare (MHLW) has provided premiums to pharmaceutical companies to encourage the development of drugs for pediatric patients, and this has resulted in great progress in the access to already approved drug and the clinical trial environment.[2] However, the rate of clinical trials for new drugs for pediatric patients was still ~20% of the rate for the total approved new drugs.[2] Globally, clinical trials in pediatric patients are more challenging compared with those in adult patients because of the small number of eligible patients entering clinical trials, the difficulty in gaining consent from the patients' parents, the limited blood volume of children, and the challenge of dose adjustments in accord with the physiological growth and organ maturation of children.[3–5] Data for infants and young children with either acute or chronic disease in clinical trials are even more limited due to specific blood volume constraints under their regular clinical blood sampling.[4,6]

In 2017, the World Health Organization (WHO) published a global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics, and a WHO advisory panel stressed the importance of new antibiotics for pediatric populations.[7] Since the WHO's first analysis of the clinical antibacterial pipeline in 2017, eight new antibiotics have been approved by the US Food and Drug Administration (FDA) and/or the European Medicines Agency (EMA),[8] but the safety and effectiveness of these antibiotics for pediatric patients have not been established. The limited treatment options regarding antibiotics for pediatric patients are associated with the emergence of antibiotic-resistant bacteria.[9,10]

The development of antibiotics for pediatric patients in Japan has often been initiated after pediatric indications for the antibiotics were approved in other countries and a sufficient amount of evidence from frequent-sampling pharmacokinetic (PK) studies and pediatric population PK models were already available. The E11 guideline of the International Conference on Harmonization (ICH; R1) describes the use of a population PK analysis, sparse sampling based on sampling optimization, and modeling and simulation in pediatric drug development in order to facilitate the design of protocols and to reduce practical and ethical constraints.[11,12]

Our objective in the present study was to apply a model-based approach to pediatric drug development so that optimizing the sampling times by published population PK models would enable the maximization of PK information with a minimum burden on infants and young children. In addition, the predicted efficacy based on the optimized sampling times was evaluated. We focused on antibacterial drugs examined in PK studies of pediatric patients conducted in other countries and the pediatric population PK models.

METHODS

Drugs investigated

We selected cefepime (CFPM) and ciprofloxacin (CPFX) as model drugs with limited Japanese pediatric data.[13,14]

There are no ethnicity-related differences in the PK or dose setting for adults for these two drugs.[13,14] CFPM is a fourth-generation cephalosporin that is widely used to treat infections caused by Gram-negative bacteria.[15] Although no pediatric indication for CFPM is approved at this time in Japan, CFPM is used in an off-label manner. CPFX is one of the fluoroquinolones, the spectrum of which covers several clinically important pathogens—especially Gram-negative bacteria, including *Pseudomonas aeruginosa*.[16] The pediatric indication for CPFX in Japan was approved as a public knowledge-based application based on both foreign data and the results of a survey of the use of CPFX in Japan reviewed by The Evaluation Committee on Unapproved or Off-labeled

Drugs with High Medical Needs, and no clinical trial had been conducted in Japanese pediatric patients.

Population PK models

Pediatric population PK models for CFPM and CPFX were reported based on pediatric clinical trials that used the traditional frequent sampling approach.[15,17]

The pediatric population PK model for CFPM was developed based on PK data from 91 pediatric patients, including preterm infants who received CFPM by the i.v. route in two pediatric clinical trials.[15,18,19] In those trials, the median gestational age of the patients was 29 weeks, their median age was 1.0 month, and their median body weight was 3.1 kg.

The pediatric population PK model for CFPM was summarized as follows:

$$\mathrm{CL(clearance)(L/h)} = \mathrm{WT}^{0.75} \times 0.395 \times \{-0.09 + 1.09 \times [1 - \exp(-0.00958 \times \mathrm{PMA})]\} \times (\mathrm{SCR}/0.6)^{-0.392}$$

$$V_{SS}\text{(volume distribution at steady state)(L)} = 0.406 \times \mathrm{WT} \times (\mathrm{GA}/30)^{-0.548}$$

where WT is the patient's body weight (kg), PMA is the postmenstrual age (weeks), SCR is the serum creatinine (mg/dl), and GA is the gestational age (weeks). The interindividual variabilities (percentage coefficient of variation [%CV]) in CL and V_{SS} in the pediatric population PK model for CFPM were 31.8% and 22.2%, respectively. The residual variability (%CV) was 66.3%.

The pediatric population PK model for CPFX was developed based on PK data from 150 pediatric patients, including 28 patients with cystic fibrosis (CF) who received CPFX by the p.o. and/or i.v. routes in 5 pediatric clinical trials.[16,17,20–22] The patients' median age was 2.5 years, and their median body weight was 13.5 kg. The pediatric population PK model for CPFX was summarized as follows:

$$\mathrm{CL(L/h)} = 30.3 \times (\mathrm{WT}/70)^{0.75} \times [1 + 0.045 \times (\mathrm{AGE} - 2.5)]$$

$$V_C\text{(volume of distribution for central compartment)(L)} = 56.7 \times (\mathrm{WT}/70)^{1.0}$$

$$V_P\text{(volume of distribution for peripheral compartment)(L)} = 89.8 \times (\mathrm{WT}/70)^{1.0}$$

$$Q\text{(intercompartmental clearance)(L/h)} = 37.5 \times (\mathrm{WT}/70)^{0.75}$$

$$K_a\text{(absorption rate constant)(1/h)} = 1.27 \times [1 + (-0.611 \times \mathrm{CF})]$$

$$\mathrm{ALAG1(absorption\ lag\ time)} = 0.353\ \mathrm{h}$$

$$F1\text{(oral bioavailability fraction)} = 61.1\,\%$$

where WT and AGE are the patient's body weight (kg) and age (years), respectively, and the variable CF = 1 for patients with CF and 0 for non-CF patients. The interindividual variabilities (%CV) were as follows: CL, 30.0%; V_C, 34.6%; V_P, 31.0%; Q, 40.6%; F1, 22.6%; and Ka, 49.8%. The residual variabilities (%CV) for the oral and i.v. data were 40.7% and 26.7%, respectively. The shared additive residual variance component was 0.00169 (SD =0.0411 mg/L).

Optimal sampling scenario

For the sampling optimization in the present study, we selected three studies conducted outside Japan. CFPM study 1, CPFX study 1, and CPFX study 2 enrolled infants and young children with traditional frequent sampling times,[16,18,20] and these were used in developing the pediatric population PK models for CFPM or CPFX.[15,17] Table 1 shows the brief study design and characteristics in each study. We selected two specific infant groups (2 to <6 months and 6 to <24 months) in the CFPM study 1 for the present study. We used the model-based approach to determine optimal sampling scenarios. This approach relies on the Fisher information matrix for a nonlinear mixed effect model. We selected Population Fisher Information Matrix (PFIM) version 4.0 from among the several software tools that are available for population design evaluations,[23–25] as the PFIM is the only tool that uses the free software R. We

TABLE 1 Summary of published pharmacokinetic studies

Study	References	Dosing regimen	Number	Age mean (SD)	Body weight mean (SD)	Serum creatinine mean (SD)
CFPM study 1[a]	Reed et al.[18]	50 mg/kg i.v. infusion for 0.5 h q8 h	8 13	3.6 (1.3) months 11 (4.1) months	NR	0.4 (0.2) mg/dl
CPFX study 1	Peltola et al.[16]	10 mg/kg p.o. q8 h	16	3.1 (2.3) years	14 (5.6) kg	NR
CPFX study 2	Lipman et al.[20]	10 mg/kg i.v. infusion for 1 h q12 h	20	1.3 (1.3) years	6.9 (2.1) kg	NR

Abbreviations: CFPM, cefepime; CPFX, ciprofloxacin; NR, not reported.

[a]Two specific infant groups (2 to <6 months and 6 to <24 months) were selected.

used the Fedorov-Wynn algorithm,[26] which optimizes over a discrete set of times, by using the sampling times from the original design, avoiding clinically unfeasible sampling times. The ICH E11 (R1) guideline recommends sparse sampling approaches in which each patient contributes as few as two to four observations at predetermined times to an overall "population area under the curve,"[11] and we therefore determined the optimal sampling scenarios with two (S2), three (S3), and four (S4) sampling times from the original design by PFIM. The number of sampling times must be as limited as possible for a vulnerable population, such as infants, and we therefore evaluated an extended scenario (S1G3) with one sampling time per patient. For this extended scenario (S1G3), one sample in each patient was randomly collected from the optimized three sampling times (S3).

Simulation of drug concentrations

We generated virtual pediatric populations from CFPM study 1, CPFX study 1, and CPFX study 2 for the simulation of the time-concentration profiles. The age (or PMA), body WT, and SCR for the virtual pediatric populations were generated by log normal distribution based on the patients' characteristics in Table 1. In CFPM study 1, the body WT and the GA in both of the infant groups were not reported. For these groups, the body WT was generated by the distribution by using the standard age versus body WT growth charts,[27] and the GA was 36 weeks by a fixed value. Drug concentrations were simulated 1000 times in each study based on the population PK models by the software NONMEM version 7.4 (ICON Development Solutions, Ellicott City, MD). Data processing was performed with R version 3.5.0.

Assessment of the precision of PK parameters

Using the simulated drug concentrations, individual Bayes PK parameters (e.g., CL, V_{SS}, Ka, V_C, V_P, Q, and F1) were estimated based on the population PK models in original design and optimal sampling scenarios (i.e., S4, S3, S2, and S1G3). The area under the drug concentration-time curve (AUC) is one of the key PK parameters associated with the efficacy and/or safety of antibacterial drugs,[28] that we assessed for the appropriateness of optimal sampling scenarios. Each individual AUC is calculated from CL (or CL/F) and dosage. The relative bias for each individual AUC in each optimal sampling scenario compared with those in original design was calculated as follows:

$$\%\,\mathrm{Bias(AUC)} = \left[\frac{1}{N}\sum_{i=1}^{N}\left(\frac{\mathrm{AUC}_{i,\mathrm{optimal}} - \mathrm{AUC}_{i,\mathrm{original}}}{\mathrm{AUC}_{i,\mathrm{original}}}\right)\right] \times 100\,\%$$

where $\mathrm{AUC}_{i,\mathrm{optimal}}$ and $\mathrm{AUC}_{i,\mathrm{original}}$ are the individual AUCs of the ith patient in each optimal sampling scenario and the original design, respectively. N is the number of patients in each study. A box plot represents 1000 simulated %Bias (AUC) in each scenario for the assessment of the precision of the AUC.

Furthermore, the precision of the individual Bayes estimates in each optimal sampling scenario was also assessed. The relative bias for the individual Bayes PK parameters in each optimal sampling scenario compared with those in the original design was calculated as follows:

$$\%\,\mathrm{Bias}(\theta_k) = \frac{\theta_{k,\mathrm{optimal}} - \theta_{k,\mathrm{original}}}{\theta_{k,\mathrm{original}}} \times 100\,\%$$

where $\theta_{k,\mathrm{optimal}}$ and $\theta_{k,\mathrm{original}}$ are the empirical Bayes estimates of the PK parameter k (e.g., CL, V_{SS}, K_a, V_C, V_P, Q, and $F1$) of individuals based on each optimal sampling scenario and the original design, respectively. We calculated the median and 10th and 90th percentiles from %Bias (θ_k) in each simulation. A table summarizes the median of 1000 simulated medians and 10th to 90th percentiles, respectively.

PK/pharmacodynamic target attainment analyses

The PK/pharmacodynamic (PD) target that best correlates with the efficacy of CFPM is the percentage of time that the free plasma concentrations are above a minimum inhibitory concentration (%fT>MIC).[28] Because several recent articles used the optimized 60% target attainment of CFPM,[29,30] we used a %fT>MIC of 60% as the target value for the efficacy. Using the estimated individual Bayes PK parameters for CFPM study 1, fT>MIC in the original design and each optimal sampling scenario was calculated assuming an unbound free fraction of 80%[31] as follows:

$$f\mathrm{T} > \mathrm{MIC} = \frac{\mathrm{lnDose}/(V_\beta/f) - \mathrm{lnMIC}}{\mathrm{CL}/V_\beta}$$

where V_β is the volume of distribution at the terminal phase, and f is the unbound free fraction.

The individual Bayes PK parameters were used to calculate the %fT>MIC. The probability of target attainment (PTA) of the %fT>MIC of greater than 60% was calculated for various MICs (1, 2, 4, 8, 16, and 32 μg/ml) in each simulation. A table summarizes the mean and the SD of the PTA values of 1000 simulations, respectively.

The PK/PD target that best correlates with the efficacy of CPFX is the ratio of the area under the unbound concentration–time curve to the MIC (fAUC/MIC).[28] Since the PD model for the probability of cure was established,[32] we used the fAUC/MIC of 86 as the target value for the

efficacy. Using the estimated individual Bayes PK parameters in CPFX study 1 and CPFX study 2, the *f*AUC/MIC in the original design and each optimal sampling scenario was calculated assuming an unbound free fraction of 70%[33] as follows:

$$f\text{AUC} = f \times \frac{\text{Dose}}{\text{CL(or CL}/F)}$$

The individual Bayes PK parameters were used to calculate the *f*AUC/MIC. The PTA of the *f*AUC/MIC of greater than 86 was calculated for various MICs (0.125, 0.25, and 0.5 μg/ml) in each simulation. A table summarizes the mean and the SD of the PTA values of 1000 simulations, respectively.

RESULTS

Optimal sampling scenario

We observed that the sampling times were optimized by PFIM and the optimal sampling times were different among studies. The optimization of the design for 3 studies with 16 or 18 sampling times was performed by PFIM in 4 (S4), 3 (S3), and 2 (S2) sampling times (Table 2). There were several overlapped sampling times between S2 and S4 in each study. For S1G3, the patients were allocated randomly to 3 groups that follow 1 of 3 sampling times based on S3 (Table 2).

For CFPM study 1 (i.v. infusion for 0.5 h), sampling times between 0.5 and 2 h were selected in the initial distribution phase, and sampling times between 2 and 8 h (predose at the steady-state) were selected in the terminal elimination phase. For CPFX study 1 (oral administration), sampling times between 0.5 and 4 h were selected in the absorption phase and the initial distribution phase, and sampling times between 4 and 6 h were selected in the terminal elimination phase. For CPFX study 2 (i.v. infusion for 1 h), sampling times between 0.5 and 2 h were selected in the initial distribution phase, and sampling times between 2 and 12 h were selected in the terminal elimination phase.

Assessment of the precision of PK parameters

As shown by the box plots of %Bias (AUC) for CFPM study 1, CPFX study 1, and CPFX study 2 from each set of 1000 simulations (Figure 1), the median of %Bias (AUC) was generally comparable among S4, S3, and S2 in each study. There was no significant variability of %Bias (AUC) at S4, S3, or S2 (within the range of ~±20%), but large variability was observed at S1G3 (within the range of ~±30%) despite the use of the same sampling times as S3 because of one sampling time in each patient.

The median and 10th and 90th percentiles of %Bias (CL) for the AUC calculation are presented in Table 3. For CFPM study 1 and CPFX study 1, the median of %Bias (CL) shows the slightly overestimated CL values (2.36%–3.29%) at S4, S3, and S2. The median of %Bias (CL) at S1G3 were −0.712% and 1.89%, respectively. For CPFX study 2, the median of %Bias (CL) at S4, S3, S2, and S1G3 were between −0.115% and 1.28%.

The other PK parameters (i.e., V_{SS}, K_a, V_C, V_P, Q, and $F1$) were calculated as a reference in this simulation study. Larger variabilities of %Bias were observed for several PK parameters at fewer sampling times.

PK/PD target attainment

For the original design and optimal sampling scenarios in CFPM study 1 (50 mg/kg i.v. every 8 h), the PTA of greater than 60% for the various MICs are presented in Table 4. The PTA of CFPM for various MICs was generally comparable

TABLE 2 Sampling times of original design and optimal sampling scenarios

			Optimal sampling scenarios			
Study	**Sampling day**	**Original design**	**Four sampling times (S4)**	**Three sampling times (S3)**	**Two sampling times (S2)**	**One sampling time[a] (S1G3)**
CFPM study 1	Day1	0, 0.5, 0.75, 1, 2, 4, 6, 8 h	0.5, 0.75, 2, 8 h	0.5, 2 h	2, 8 h	Day 1 0.5 h, 2 h or
	Steady-state	0, 0.5, 0.75, 1, 2, 4, 6, 8 h	–	0 h	–	Steady-state 0 h
CPFX study 1	Day1	0, 0.5, 1, 2, 4, 6, 8 h	0.5 h	0.5, 4 h	0.5, 4 h	Day 1 0.5 h, 4 h or
	Steady-state	0, 0.5, 1, 2, 4, 6, 8, 12, 24 h	0.5, 4, 6 h	4 h	–	Steady-state 4 h
CPFX study 2	Day1	0, 0.5, 1, 2, 3, 4, 6, 8, 12 h	0.5, 2, 4, 12 h	1, 3, 12 h	4, 12 h	Day 1 1 h, 3 h or
	Steady-state	0, 0.5, 1, 2, 3, 4, 6, 8, 12 h	–	–	–	12 h

Abbreviations: CFPM, cefepime; CPFX, ciprofloxacin.

[a]The patients were allocated randomly to three groups that follow one of three sampling times based on S3.

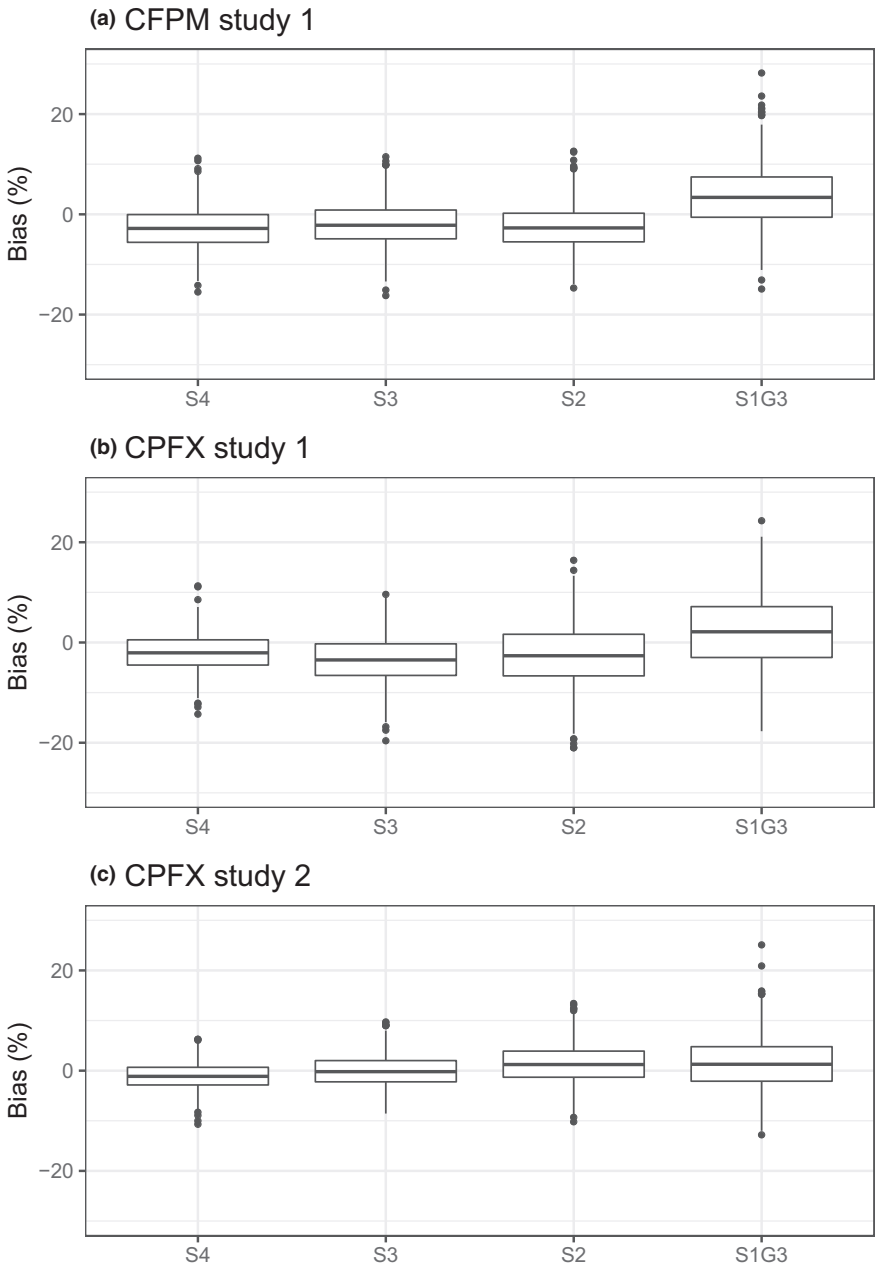

FIGURE 1 Comparison of AUC relative bias to original design from 1000 simulations among four sampling times (S4), three sampling times (S3), two sampling times (S2), and one sampling time with three groups (S1G3) following i.v. administration of CFPM 50 mg/kg every 8 h (a), oral administration of CPFX 10 mg/kg every 8 h (b), and i.v. administration of CPFX 10 mg/kg every 12 h (c). The boundaries of the box indicate the 25th and 75th percentile with the line representing the median. AUC, area under the drug concentration-time curve; CFPM, cefepime; CPFX, ciprofloxacin

among the original design and all four optimal sampling scenarios. All mean PTA values approached 1.00 when the MICs were between 1 and 4 μg/ml. All mean PTA values in CFPM study 1 at the MIC of 8, 16, and 32 μg/ml were 0.91–0.97, 0.65–0.78, and 0.09–0.19, respectively.

For the original design and optimal sampling scenarios in CPFX study 1 (10 mg/kg p.o. every 8 h) and CPFX study 2 (10 mg/kg i.v. every 12 h), the PTA of greater than 86 for various MICs are presented in Table 5. As an additional analysis, the PTA at the recommended regimen (15 mg/kg p.o. every 8 h and 10 mg/kg i.v. every 8 h) in the pediatric dosage guideline was calculated. The PTA of CPFX for various MICs was generally comparable among the original design and all four optimal sampling scenarios in both CPFX study 1 and CPFX study 2. All mean PTA values approached 1.00 when the MICs were at 0.125 μg/ml. All mean PTA values for the study regimen in CPFX study 1 and CPFX study 2 at the MIC of 0.25 μg/ml were 0.22–0.35 and 0.33–0.42, respectively. All mean PTA values for the recommended regimens (15 mg/kg p.o. every 8 h and 10 mg/kg i.v. every 8 h) at the MIC of 0.25 μg/ml were 0.74–0.89 and 0.87–0.97, respectively.

DISCUSSION

Our results indicated that it was possible to estimate the AUC, which is one of the key PK parameters associated with the efficacy and/or safety of antibacterial drugs with a reduction to fewer sampling times. It was possible to

TABLE 3 PK parameter relative bias to original design in each optimal sampling scenario

		Four sampling times (S4)			Three sampling times (S3)			Two sampling times (S2)			One sampling time (S1G3)		
		Bias (%)			Bias (%)			Bias (%)			Bias (%)		
Study	**Parameter**	**Median**	**P10**	**P90**	**Median**	**P10**	**P90**	**Median**	**P10**	**P90**	**Median**	**P10**	**P90**
CFPM study 1	CL	3.20	−14.0	29.8	2.53	−14.0	27.8	3.22	−14.5	31.0	−0.712	−24.8	32.9
	V_{SS}	−1.94	−14.0	12.5	−1.96	−13.3	14.0	−2.13	−14.4	14.4	−0.456	−14.4	20.0
CPFX study 1	CL	2.36	−8.68	18.2	3.29	−12.3	24.9	3.05	−15.8	30.7	1.89	−18.9	29.6
	K_a	−1.33	−18.8	20.4	−1.48	−22.3	20.4	−1.78	−23.4	23.8	1.06	−31.1	49.8
	V_C	−0.275	−11.6	13.1	0.678	−10.4	16.8	1.35	−11.2	19.0	−0.780	−18.5	22.9
	V_P	−3.28	−21.9	17.4	−2.00	−22.2	21.9	−1.30	−22.3	23.3	−2.52	−23.8	24.2
	Q	−2.33	−20.5	19.9	−1.19	−19.4	23.2	−0.560	−18.7	24.1	−2.73	−23.4	26.8
	F1	0.550	−8.73	10.2	−0.602	−9.07	7.42	−0.688	−11.2	9.11	0.788	−12.1	13.6
CPFX study 2	CL	1.28	−10.8	16.7	0.811	−13.2	17.9	−0.115	−17.3	21.8	0.810	−21.6	31.7
	V_C	0.681	−15.5	25.5	0.777	−17.9	28.2	−1.52	−30.1	38.9	−0.238	−26.5	37.2
	V_P	0.207	−16.7	22.2	0.599	−17.3	25.8	−1.84	−25.5	29.6	−0.937	−26.9	33.0
	Q	0.843	−19.9	32.9	1.61	−20.8	36.3	−2.12	−34.6	47.8	−0.671	−31.0	45.9

Abbreviations: CFPM, cefepime; CL, clearance; CPFX, ciprofloxacin; F1, oral bioavailability fraction; P10, 10th percentile; P90, 90th percentile; K_a, absorption rate constant; PK, pharmacokinetic; Q, intercompartmental clearance; V_C, volume of distribution for central compartment; V_P, volume of distribution for peripheral compartment; V_{SS}, distribution at steady state.

TABLE 4 PTA of original design and optimal sampling scenarios for CFPM study 1

		Mean PTA (SD) with MIC (μg/ml) of:					
		1	**2**	**4**	**8**	**16**	**32**
CFPM study 1 (50 mg/kg i.v. q8 h)							
Original design		1.00 (0.01)	0.99 (0.02)	0.98 (0.03)	0.91 (0.06)	0.69 (0.10)	0.19 (0.08)
Optimal sampling scenarios	S4	1.00 (0.00)	1.00 (0.00)	1.00 (0.01)	0.97 (0.04)	0.78 (0.06)	0.09 (0.05)
	S3	1.00 (0.00)	1.00 (0.00)	0.99 (0.02)	0.92 (0.06)	0.66 (0.09)	0.12 (0.07)
	S2	1.00 (0.00)	1.00 (0.00)	0.99 (0.02)	0.92 (0.06)	0.65 (0.09)	0.13 (0.07)
	S1G3	1.00 (0.00)	1.00 (0.00)	0.99 (0.02)	0.92 (0.06)	0.65 (0.09)	0.13 (0.07)

Abbreviations: CFPM, cefepime; MIC, minimum inhibitory concentration; PK, pharmacokinetic; PTA, probability of target attainment; S1G3, 1 sampling time per patients with patients allocated randomly to 1 of 3 groups; S2, 2 sampling times; S3, 3 sampling times; S4, 4 sampling times.

TABLE 5 PTA of original design and optimal sampling scenarios for study regimen (CPFX study 1 and study 2) and recommended regimen

		Mean PTA (SD) with MIC (μg/ml) of:		
		0.125	**0.25**	**0.5**
Study regimen				
CPFX study 1 (10 mg/kg p.o. q8 h)				
Original design		0.94 (0.06)	0.35 (0.12)	0.01 (0.03)
Optimal sampling scenarios	S4	1.00 (0.00)	0.22 (0.10)	0 (0.01)
	S3	0.99 (0.03)	0.23 (0.11)	0 (0.01)
	S2	0.94 (0.06)	0.28 (0.11)	0.01 (0.02)
	S1G3	0.94 (0.06)	0.31 (0.11)	0.01 (0.02)
CPFX study 2 (10 mg/kg i.v. q12 h)				
Original design		0.98 (0.03)	0.42 (0.11)	0.01 (0.02)
Optimal sampling scenarios	S4	1.00 (0.00)	0.33 (0.10)	0 (0.01)
	S3	1.00 (0.01)	0.37 (0.11)	0 (0.01)
	S2	1.00 (0.01)	0.37 (0.10)	0 (0.01)
	S1G3	0.99 (0.02)	0.38 (0.10)	0 (0.01)
Recommended regimen				
15 mg/kg p.o. q8 h				
Original design		1.00 (0.01)	0.77 (0.11)	0.12 (0.08)
Optimal sampling scenarios	S4	1.00 (0.00)	0.89 (0.07)	0.04 (0.05)
	S3	1.00 (0.00)	0.77 (0.11)	0.05 (0.05)
	S2	1.00 (0.00)	0.74 (0.11)	0.07 (0.06)
	S1G3	1.00 (0.01)	0.75 (0.11)	0.09 (0.08)
10 mg/kg i.v. q8 h				
Original design		1.00 (0.00)	0.87 (0.07)	0.12 (0.07)
Optimal sampling scenarios	S4	1.00 (0.00)	0.97 (0.04)	0.04 (0.05)
	S3	1.00 (0.00)	0.93 (0.05)	0.08 (0.06)
	S2	1.00 (0.00)	0.90 (0.06)	0.09 (0.06)
	S1G3	1.00 (0.00)	0.88 (0.07)	0.09 (0.06)

Abbreviations: CPFX, ciprofloxacin; MIC, minimum inhibitory concentration; PTA, probability of target attainment; S1G3, 1 sampling time per patients with patients allocated randomly to one of three groups; S2, 2 sampling times; S3, 3 sampling times; S4, 4 sampling times.

estimate the AUC even with a single sampling time per patient (S1G3), but the interpretation of individual estimated AUC values requires caution. Our present findings demonstrated that the precision of the individual CL (used for AUC calculation) estimated by the reduced optimal sampling times, even with only two sampling times, was

generally comparable to that estimated by the original full sampling times. For CFPM study 1 and CPFX study 1, the slightly overestimated CL values at S4, S3, and S2 were observed due to the few sampling points at the terminal elimination phase.

The predicted efficacy for CFPM and CPFX in our analysis were generally comparable among the original design and all four optimal sampling scenarios. CFPM at doses of 50 mg/kg i.v. every 8 h in our analysis achieved a greater than 0.90 PTA at the MIC of 8 μg/ml, which was consistent with 0.69 PTA at the same dose in patients greater than or equal to 30 days old.[15] CPFX at the recommended regimens (15 mg/kg p.o. every 8 h and 10 mg/kg i.v. every 8 h) in our analysis achieved a greater than 0.70 PTA at the MIC of 0.25 μg/ml, which was similar to 0.69 PTA at the standard dose (400 mg i.v. every 12 h) in adults.[32]

Because most optimal sampling times overlap in S4 and S2 (Table 2), our results indicated that the effect on the empirical Bayes estimates of the key PK parameters and the predicted efficacy was limited even when the number of sampling points was reduced to two sampling points. In addition, reducing the number of three sampling times (S3) to one sampling time per patient (S1G3) did not significantly affect the PTA, although large variability of %Bias (AUC) was observed. Based on our finding, we recommend planning three or four optimized sampling times for PK studies of CFPM and CPFX, and it is good to consider one or two optimized sampling times as the priority in cases in which blood samples cannot be collected at the specified points in a clinical trial. If the PK and PK/PD parameters of interest are related to C_{max} and/or C_{max}/MIC, an increased number of sampling times in absorption phase should also be considered.

In Japan, the Evaluation Committee on Unapproved or Off-labeled Drugs with High Medical Needs has discussed the necessity of determining pediatric indications and off-label uses against the background of a lack of Japanese pediatric data. In the future, pediatric clinical trials by collaborations among academia, industry, and governmental agencies and as investigator-initiated trials are likely to proceed to achieve the necessary progress in the development of pediatric drugs.[34] The model-based approach to sampling optimization described herein will help reduce the burden of blood sampling in these studies. We investigated the sampling optimization from pediatric studies conducted outside Japan, but it may also be possible to investigate the optimization by using adult or other pediatric population studies. A study of an antimalarial drug for pediatric patients optimized the sampling times by using data obtained from adults.[35] In a similar case of pediatric study design, the number of sampling times for 2–5-year-old patients was optimized by using a population PK model developed with data from patients who were 6–11 years old.[36]

The two drugs (CFPM and CPFX) investigated in this study are eliminated primarily by renal excretion; although the approach used in this study may not be applied to all types of antibacterial drugs, most antibacterial drugs, including several new antibiotics approved by the FDA and/or EMA, are renal excretion-type drugs.[8] We did not investigate optimal sampling times in a more vulnerable population, such as neonates and pre-term infants. These populations often become anemic either due to their concurrent illness(es) or also because of regular clinical blood sampling.[4,6] Clearance in neonates and pre-term infants is highly variable due to their underdeveloped renal function. In these populations, renal excretion-type drugs often result in an overdose or delayed elimination. In addition, there was a sparse-sampling design for CFPM with some neonate or pre-term groups instead of the frequent sampling design.[19] The model-based approach that we used herein will support the further optimization of the sparse-sampling design.

Opportunistic samples collected from blood remaining after routine laboratory tests as part of clinical care is one of the novel proposed methods.[37,38] However, the opportunistic-sampling approach also poses issues, such as variability in available sample numbers among patients. The optimal-sampling approach used in the present study will help guide which blood sampling times' data should be noted. These two approaches can be combined for the vulnerable population.

This simulation has a limitation to address. We generated the body WT and SCR for the virtual patient characteristics independently. We confirmed that there were no clinically significant values above the body WT and SCR ranges for age.

In conclusion, our study demonstrated that the model-based approach to sampling optimization could provide the maximum informative data while minimizing the burden to infants and young children. Because the development of antibiotics is expected to continue in the future with the need for pediatrics, we expect that the approach described herein will enable the efficient development of pediatric drugs, as well as provide the valuable information for therapeutic drug monitoring and the administration plans for antibiotics in clinical settings. We foresee that the accumulation of pediatric data will enrich physiologically based PK models, including those accounting for patients' growth, and discussions regarding the use and extrapolations of data from foreign sources will continue to be fruitful.

ACKNOWLEDGMENTS

The authors would like to thank to Hiroyuki Yoshitsugu (MSD K.K.) and Mari Shiomi (MSD K.K.) whose comments and suggestions were of inestimable value for this study.

CONFLICT OF INTEREST

Y.O. and M.K. are current employees of MSD K.K., and may hold stock and/or stock options in the company. MSD K.K.

was not involved in this study. All other authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

Y.O., M.K., A.O., and N.N. wrote the manuscript. Y.O., M.K., A.O., and N.N. designed the research. Y.O. performed the research. Y.O. and M.K. analyzed the data. Y.O. and M.K. contributed new reagents/analytical tools.

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How to cite this article: Orito Y, Kakara M, Okada A, Nagai N. Model-based approach to sampling optimization in studies of antibacterial drugs for infants and young children. *Clin Transl Sci*. 2021;14:1543–1553. https://doi.org/10.1111/cts.13018