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To cite this version:

Caroline Petit, Vincent Jullien, Adeline Samson, Jérémie Guedj, Jean-René Kiechel, et al.. Designing a paediatric study for an antimalarial drug including prior information from adults. Antimicrobial Agents and Chemotherapy, 2016, 60 (3), pp.1481-1491. 10.1128/AAC.01125-15 . hal-01255863

HAL Id: hal-01255863

https://univ-rennes.hal.science/hal-01255863

Submitted on 24 Mar 2016

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Designing a paediatric study for an antimalarial drug including prior information from adults

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Abstract

Objectives: To design a pharmacokinetic (PK) study using adult prior information and evaluate robustness of the recommended design, through a case-study on mefloquine.

Methods: PK data for adults and children were available from two different randomised studies for treatment of malaria with the same artesunate-mefloquine combination regimen. A recommended design for paediatric study on mefloquine was optimised based on an extrapolated model built from adult data through the following approach: (i) a PK model was built in adults, and parameters were estimated using the SAEM algorithm; (ii) paediatric PK parameters were then obtained by adding

allometry and maturation to the adult model; (iii) a D-optimal design in children was obtained with PFIM assuming the extrapolated design. Finally, the robustness of the recommended design was evaluated in terms of the relative bias and relative standard errors (RSE) of the parameters in a simulation study with four different models, and was compared to the empirical design actually performed in the paediatric study.

Results: Combining pharmacokinetic modelling, extrapolation and design optimisation led to a design for children with 5 sampling times. Pharmacokinetic parameters were well estimated with this design with low relative standard errors. Although the extrapolated model did not predict the observed mefloquine concentrations in children very accurately, it allowed precise and unbiased estimates across various model assumptions, contrary to the empirical design.

Conclusion: Using prior adult information combined with allometry and maturation can help provide robust designs for paediatrics studies.

1 Introduction

Paediatrics have long been poorly investigated in drug development for ethical, practical and methodological reasons [1]. Given these limitations, the dose given in children is often mostly derived from the adult dose by a linear body weight adjustment. However, a number of studies have shown that this crude approach could be misleading, prompting scientists and physicians to consider children less as small adults [2, 3], and more as a specific population with different drug metabolism and sensitivity. Recognising this challenge, the regulatory authorities have sought to bolster the efforts of the industry through the paediatric investigation plan (PIP) [4], and drug development in children has now become

an independent field, creating new challenges in medicine. Nowadays, an increasing number of clinical trials are performed to allow proper evaluation of the drug pharmacokinetics (PK) in children, holding the promise that a better balance between toxicity and efficacy may be found for drugs in paediatrics [5]. However, the precise characterisation of a drug PK is a difficult task that requires carefully choosing the dose regimen and the time to sample observations, which together form the design of the study. This is particularly problematic in paediatrics, where ethical constraints dramatically reduce the number of measurements possible, making PK parameter estimation a particularly difficult endeavour and the choice of an appropriate design a decision even more critical than in adults [6]. Contrary to the first-in-man trials, where no prior clinical information is available, the first-in-children study is often performed after studies in adults are available. When properly leveraged, the data from adults could be used to build an appropriate design for the paediatric study, and it is often the only source of information available at this early stage [7]. Within the PIP, incorporating prior knowledge from adults is also a way of streamlining paediatric drug development in the global development program [8].

In order to optimise the available information, PK are often analysed using non-linear mixed effect models, an approach which allows to handle sparse and heterogeneous designs [9]. In that framework, design optimisation based on the Fisher Information Matrix has become an increasingly popular tool to maximise the information collected in a study and determine the times for the sampling measurements which are most likely to provide a precise estimation of the PK parameters [10, 11].

In the present work, we investigate the process of designing a paediatric study using adult prior information. Mefloquine, an antimalarial drug, serves as a case-study, with data

from two clinical trials, in adults and children [12]. We use the adult data to obtain the PK model of mefloquine in adults, and leverage this information for children through allometric and maturation functions taking into account changes in body size and metabolic processes with age [13]. We then use the extrapolated model to design a study for a paediatric population with different age groups. We show that this approach provides a framework that may dramatically improve the design of a PK study in children, allowing for a precise estimation of PK parameters while limiting the number of sampling measurements.

2 Methods

In the present work, we considered the following methodological workflow, summarised in Figure 1. First, based on data collected in an adult population, we built a PK model. Extrapolation using allometry and maturation was then applied to the resulting model in order to derive the PK model and parameters in children. The extrapolated model was then used to optimise the design in children. The performance of the optimised design was evaluated by assessing its ability to estimate correctly the population parameters through a simulation study, under different model assumptions to assess its robustness. The evaluation process is illustrated separately in Figure 2. The optimised design was compared to the design of the paediatric database, called empirical design. Simulations were performed for 4 different models to ensure robustness. An external evaluation was also performed, by fitting the paediatric data with the different models used for simulations and comparing their predictive ability.

[Figure 1 about here.]

[Figure 2 about here.]

Data

The case-study involved two clinical trials.

- Adult data: the first study included data from adults taking part in a phase I-II clinical trial in India [8]. This multicentre, single-arm clinical trial was carried out to assess the safety, efficacy and population pharmacokinetics of a fixed-dose combination of artesunate-mefloquine in Indian adults infected with acute uncomplicated plasmodium falciparum. Seventy-seven (77) patients were included. Subjects received orally two tablets, containing 100 mg of artesunate and 200 mg of mefloquine, once daily for three consecutive days. Blood samples for the analysis of mefloquine pharmacokinetics and laboratory evaluation were collected before the first dose, within 72 hours of first dose, and on study day 7, 28, 35 or 42.

- Children data: the second study included children under 15 years old enrolled in a phase I-II clinical trial in Thailand [14]. This randomised trial was carried out to assess safety and efficacy of a new artesunate-mefloquine coformulation for the treatment of acute uncomplicated plasmodium falciparum malaria in children. A total of 101 children under 15 years old were included in this study. Paediatric patients were administered a weight-related dose, approximately 4 mg/kg/day of artesunate for 3 days of treatment, and 25 mg/kg of mefloquine split into 15 mg/kg on the second day and 10 mg/kg on the third day. The following PK samples were scheduled from the first day of administration and during follow-up: 3 to 4 samples randomly

selected from days 1, 2, 3 or 7-14 and 1 or 2 additional samples on days 21, 28, 35, 42, 49, 56 or 63.

Modelling the PK of mefloquine in adults

The PK of mefloquine in adults was analysed using non-linear mixed effect models (NLME). Denoting $y_i = (y_{i1}, y_{i2}, ..., y_{in_i})^T$ the n_i - vector of observations for individual i ($i = 1, ..., N$), collected at sampling times $t_i = (t_{i1}, t_{i2}, ..., t_{in_i})^T$, we have the following statistical model:

$$y_i = f(\phi_i, t_i) + \varepsilon_i \tag{1}$$

where f is a mathematical function representing the evolution of the concentration with time. The vector ϕ_i is the vector of individual parameters for i and ε_i a n_i-vector of random errors distributed as $\varepsilon_i \sim \mathcal{N}(0, \Sigma_i)$. We assume that the distribution of the parameters can be described through a log-normal distribution. For the kth component of ϕ, $k = 1...K$, we write the individual parameter $\phi_i^{(k)}$ as a function of a fixed effect $\mu^{(k)}$ and an individual random effect $b_i^{(k)}$:

$$\phi_i^{(k)} = \mu^{(k)} e^{b_i^{(k)}} \tag{2}$$

The distribution of the random effects was assumed to be multivariate normal, with a variance-covariance matrix denoted Ω^2.

The parameters of the NLME model were estimated using the stochastic approximation expectation-maximisation algorithm (SAEM) [15], implemented in the Monolix software (version 4.2.2) [16]. The likelihood was computed using importance sampling. Model building was based on the likelihood ratio test (LRT) for nested models, and the Bayesian

information criteria (BIC) for non-nested models. We investigated first the structural model, comparing different compartment models, then the interindividual variability, testing whether Ω^2 could be assumed to be diagonal or not, and finally the residual variability. Different residual error models were considered: a constant error model $\mathrm{Var}(\varepsilon_{ij}) = a^2$, a proportional error model $\mathrm{Var}(\varepsilon_{ij}) = b^2 \times f(\phi_i, t_{ij})^2$ and a combined error model $\mathrm{Var}(\varepsilon_{ij}) = (a + bf(\phi_i, t_{ij}))^2$. In order to evaluate the stability of the estimates, the run assessment feature in Monolix was used; this consists in performing the evaluation 5 times changing initial conditions and seed for the random number generators and comparing the estimates of the parameters and the log-likelihood across the 5 runs.

The final PK model in adult was called $(\mathcal{M}_{ad})$, and the adult population PK parameters μ_{adult}. It was evaluated through goodness-of-fit plots, including Visual Predictive Checks (VPC), predictions of individual concentration profiles, plots of observations versus predictions, and residual scatterplots involving normalised prediction distribution errors (NPDE) [17]. Empirical Bayesian Estimates (EBE) of the individual parameters were obtained for each subject as the conditional mean of the individual conditional distribution, and used for diagnostic plots. VPC and NPDE were obtained using 1000 datasets simulated under the tested model with the design of the original dataset [18]. Estimates of the standard errors and residual standard errors were obtained through a linear approximation of the Fisher information matrix. The predictive ability of $(\mathcal{M}_{ad})$ was evaluated by computing the bias and root mean square errors (RMSE) between predicted and observed concentrations:

$$Bias = \sum_{i=1}^{N} \frac{1}{n_i} \sum_{j=1}^{n_i} (y_{ij} - f(\hat{\mu}, t_{ij})) \quad (3)$$

$$RMSE = \sqrt{Bias^2 + Var(f(\hat{\mu}, t_{ij}))} \quad (4)$$

where $\hat{\mu}$ are the estimated population parameters and $Var(f(\hat{\mu},t_{ij})) = \sum_{i=1}^{N} \frac{1}{n_i-1} \sum_{j=1}^{n_i} (y_{ij} - f(\hat{\mu},t_{ij}))^2$ is the variance of the predicted concentrations.

Extrapolation from adults to children

$\mathcal{M}_{ad}$, the PK model developed in adults was then modified to adjust to the children population. The same structural model was left unchanged, but we scaled the values of the parameters using either allometry alone ($\mathcal{M}_{allo}$) or both allometry and maturation ($\mathcal{M}_{allo+mat}$), as detailed in the rest of this section.

Body size is a major determinant of metabolic rates, diffusion and transfer processes, as well as organ size, throughout the animal kingdom and beyond. Allometric theory models these processes throughout fractal geometry, and proposes a general scaling for many processes [19]. Denoting BW the body size, a parameter μ would vary as:

$$\mu = \alpha \times BW^{\beta} \tag{5}$$

where α is a constant characterising the type of organism, and β a scaling component. In particular, volumes of distribution tend to increase linearly with size ($\beta = 1$) while clearances, which are related to blood flow, increase non-linearly with a coefficient 3/4 ($\beta = 0.75$) derived from geometric considerations.

Model $\mathcal{M}_{allo}$ was derived from $\mathcal{M}_{ad}$ by introducing allometry in the population value of the parameters to account for size, through the relationship:

$$\mu_{child,allo} = \mu_{adult} \times \left(\frac{BW_{child}}{BW_{adult}}\right)^{\beta} \tag{6}$$

where BW_{adult} is the mean adult weight and BW_{child} is the mean body weight of a given child, β is 0.75 for clearances and 1 for volumes.

However, size differences do not explain all the variations between adults and children. Many physiological processes evolve slowly towards adult functionality during childhood. Model $\mathcal{M}_{allo+mat}$ was developed from the allometric model $\mathcal{M}_{allo}$, by introducing a maturation factor $K_{mat,child}$ in the previous equation:

$$\mu_{child,allo+mat} = \mu_{adult} \times \left(\frac{BW_{child}}{BW_{adult}}\right)^{\beta} \times K_{mat,child} \tag{7}$$

Maturation is highly correlated with age, and has been studied for many physiological processes, including absorption, first-pass effect, metabolism and transport. We derived maturation equations for mefloquine, and used them to adjust individual clearances and volumes in each child. These equations are described in the Appendix.

For both $\mathcal{M}_{allo}$ and $\mathcal{M}_{allo+mat}$, we assumed the same interindividual variability for all parameters, as well as the same residual errors, as those estimated in the adult populations.

Because in this work we had access to paediatric data, we used it as an external evaluation dataset to assess the extrapolation process for both $\mathcal{M}_{allo}$ and $\mathcal{M}_{allo+mat}$. The predictive capacity of these two models was evaluated by computing bias and RMSE on the paediatric data. We also evaluated the predictive capacity of the model without extrapolation, $\mathcal{M}_{ad}$. For comparison purposes, we also performed a population PK analysis of the paediatric data alone, using the same approach as for the adults. This led to model $\mathcal{M}_{ch}$.

Optimal design for a paediatric population

Design optimisation was performed for the model using both allometry and maturation $\mathcal{M}_{allo+mat}$. Design optimisation consists in selecting the best dose regimen and sampling times, given constraints such as the total number of samples or the times when samples can be taken, in order to allow precise estimation of the parameters. In this work we will focus on sampling times only because the doses were fixed in children. This is generally achieved through D-optimality, which consists in maximising the determinant of the Fisher information matrix (FIM) [6]. Although the FIM in NLME has no closed form solution, it can be approximated using a first order linearisation around the mean of the random effects. This method is implemented in PFIM, which we used here (PFIM version 4.0, running in R version 3.0) [20], and in most softwares performing design optimisation.

Because the design may be different depending on age, optimisation was performed in four different age-groups that were represented in the Thai study: an infant-toddler group (up to 3 years), which included only one infant in the actual study, a pre-school children group (4-5 years), a school-age group (6-11 years) and an adolescent group (12-15 years).

We therefore first performed optimisation on these 4 different groups, using the parameters $\mu_{child,allo+mat}$ with the average weight and age observed in the real paediatric study for each group. For each group the dose was set to the average dose in the group, yielding fixed parameters for $\mathcal{M}_{allo+mat}$ for each group. We used the Fedorov-Wynn algorithm [21], which optimises over a discrete set of times, using the sampling times from the original paediatric protocol (0.1, 0.5, 1, 2, 5, 10, 15, 25, 35, 55, 65) in a first step. We also set a constraint on the number of sampling points, performing several optimisations with 3 to 6 samples per subject. We refined this first design by running the Simplex

algorithm, adjusting the set of possible times to include more informative time points, and running the Fedorov-Wynn algorithm again. This led to an optimal design for each age-group, from which we derived the final optimal design by choosing the closest sample times across groups.

The resulting optimal design is exact, with fixed days, which may be difficult to implement. We can relax this assumption by using sampling windows, to add flexibility to the practical implementation. As this cannot be implemented prospectively in PFIM, we derived sensible windows for the optimised design assuming the patients can come in anytime during daytime, and for several days on later visits.

Evaluation of paediatric design

To illustrate the expected performance and the robustness of the optimal paediatric design, we evaluated its ability to estimate the PK parameters in children across a range of scenarios corresponding to different models and model parameters, through a simulation study. Figure 2 summarises the different stages of the evaluation.

We evaluated the design over the 4 different models previously introduced: (i) the extrapolated model with maturation ($\mathcal{M}_{allo+mat}$), which was used to optimise the design; (ii) the adult model ($\mathcal{M}_{ad}$) without extrapolation; (iii) a model derived from $\mathcal{M}_{ad}$, called ($\mathcal{M}_{ad,abs}$), with a rate constant of absorption modified to the value $k_a = 1$ to mimick a much slower absorption in children; (iv) the PK model obtained in the analysis of the paediatric data alone ($\mathcal{M}_{ch}$).

In each scenario, we simulated $L = 100$ data sets under the related model, for sampling times corresponding to the optimised design. The covariate distributions, the doses and the

number of subjects were kept identical to those of the real paediatric study. Therefore, the simulated population was identical to the paediatric population in the database. We then re-estimated model parameters using Monolix for each simulation. Finally, we computed the relative bias and empirical relative standard errors (RSE) for each estimated parameter compared to the theorical model value over the 100 simulations:

$$
\begin{aligned}
Bias(\theta_{k,th}) &= \frac{1}{L}\sum_{l=1}^{L}\frac{(\hat{\theta}_k^{(l)}-\theta_{k,th})}{\theta_{k,th}} \\
RSE(\theta_{k,th}) &= \frac{1}{L}\sum_{l=1}^{L}\sqrt{\left(\frac{\hat{\theta}_k^{(l)}-\theta_{k,th}}{\theta_{k,th}}\right)^2}
\end{aligned}
$$

where $\hat{\theta}_k^{(l)}$ is the estimate of the kth parameter in simulation $l = 1,...,L$ and $\theta_{k,th}$ the theoretical value.

The same simulations were also performed for the empirical design, to compare the performance of the optimal design with the design that was in fact implemented in the children study. The same parameters were used to simulate the concentrations in both designs (optimal and empirical).

We also evaluated the performance of the design when relaxing the fixed times through sampling windows. We again simulated 100 data sets, but this time the sampling times for each visit were drawn according to a uniform distribution from the chosen sampling windows. Evaluation was performed in a similar manner as for the optimal design.

3 Results

Characteristics of both populations

Table 1 shows the demographic characteristics and biological measurements in the adult (left) and paediatric (right) datasets used in the present analysis. The adult population was almost exclusively male (1 woman), while the recruitment was more balanced in the paediatric study (51 girls and 60 boys, 59% male).

[Table 1 about here.]

Figure 3 shows the evolution of mefloquine concentrations with time in the two populations. Most adults were sampled 4 to 5 times during the study. On average, the first sample was taken 4 hours after the first dose, and the next at days 2, 3, 11, 36 and 56, with a few concentrations measured up to 62 days after the first dose. Four patients had only one sample. Concentration profiles show accumulation over the first three days, when mefloquine is administered once daily, followed by a slow bi-phasic decline.

In children, the design was more sparse and variable (Figure 3b), and fewer samples were collected. Most children contributed three concentrations (51%) and 37% had only 2 concentrations taken. The first sample was usually taken at day 8, long after the end of the absorption phase. The second sample was around day 23, then at day 35 and 45.

[Figure 3 about here.]

Modelling the PK of mefloquine in adults

The final PK model was found to be a two compartment model with first-order absorption, due to significant tissular distribution. Absorption and elimination were found to be linear. The parameters in this model are the rate of absorption, the central and intercompartmental clearances, and the volumes of the two compartments, so that $\phi_i = (k_{ai}, Cl_i, V_{1i}, Q_i, V_{2i})$. The residual error was best described as a combined error model. We found that we could remove the variability in V_2 from the model. This may be due to either a low interindividual variability for that parameter, or more likely, a lack of information to estimate that parameter.

Table 2 shows the population parameters estimated for the adult model $\mathcal{M}_{ad}$. The residual variability was low, indicating that the model explained most of the variability. Estimates were well estimated, with low standard errors. Absorption k_a and inter-compartimental clearance Q had the highest interindividual variability.

There was no bias in predicting the adult concentrations (bias=0.06), showing no systematic model misspecification, and the RMSE was estimated to be 1.14.

[Table 2 about here.]

Extrapolation from adults to children

$\mathcal{M}_{ad}$ was then used as a basis for individual extrapolation to the paediatric population, yielding model $\mathcal{M}_{allo+mat}$.

Extrapolation was assessed using the paediatric data as an external evaluation dataset on models $\mathcal{M}_{allo+mat}$, $\mathcal{M}_{allo}$, $\mathcal{M}_{ad}$ and $\mathcal{M}_{ch}$. VPC are shown in Figure 4. $\mathcal{M}_{allo+mat}$ (Fig. 4a)

clearly overpredicts the observed concentrations in children during the first days of the trial, suggesting some discrepancy in absorption between the adult and the children population, either in the rate of absorption, in the bioavailability, or both. On the other hand, the elimination and distribution phases are not inconsistent with the prediction ranges, and the variability, shown by the breadth of the shaded areas, appears similar in children compared to adults.

To assess the impact of the different extrapolations involved in $\mathcal{M}_{allo+mat}$, we compared the predictive abilities of the other models. The model $\mathcal{M}_{ch}$ was obtained using a similar PK analysis as for the adults, and constitutes the best possible fit to the data. In our analysis, it served as a gold standard to assess the accuracy of model predictions, as it was the only model directly derived from the paediatric data. In children, we could not identify a distribution phase, therefore $\mathcal{M}_{ch}$ was a one-compartment model. The absorption phase was unidentifiable and the estimates of k_a were unstable. Therefore, the absorption rate constant k_a was fixed to the value obtained in the adult population, without interindividual variability. As expected, there was no bias for $\mathcal{M}_{ch}$ (0.06); the precision measured by RMSE was 0.89. The bias was significant for the three other models; the model with allometry $\mathcal{M}_{allo}$ has in fact a slightly lower bias (-0.15) than the model with maturation $\mathcal{M}_{allo+mat}$ (-0.27). Both these models tended to underpredict children concentrations, while the adult model $\mathcal{M}_{ad}$ systematically overpredicted concentrations in children (bias=0.34), as apparent in Figure 4. The RMSE for the two extrapolated models was quite high (respectively 1.2 and 1.1 with and without maturation). It was lower for $\mathcal{M}_{ad}$ (0.8) than for $\mathcal{M}_{ch}$ (0.9).

[Figure 4 about here.]

Optimal design for the paediatric population

$\mathcal{M}_{allo+mat}$ was then used to design a sampling schedule for the paediatric population. We first attempted to optimise designs with 3 or 4 sampling times, as this was close to the design in the paediatric database, which we call empirical design. But optimisation failed, indicating the model was not identifiable with so few samples. We therefore increased the number of samples to 5 or 6. Table 3 shows the optimal times found for each group for designs with 5 sampling points; several sampling times were found to be quite similar across designs, with three samples in the first 4 days and two after 65 days. The parameters were well estimated in each group, according to the RSE predicted by PFIM, with RSE around 5% for Cl, V_1 and V_2, and around 10% for k_a and Q. Inter-subject random effects should have somewhat higher RSE, between 20% and 30%, but the designs would still allow proper estimation of the variabilities. Designs with 6 sampling times gave similar results in terms of RSE, suggesting that 5 sampling times were sufficient in our case.

The optimal design merged the 4 designs, and the corresponding times are given in the last row of Table 3.

[Table 3 about here.]

Design evaluation

In order to assess robustness, we performed a set of simulations under different model assumptions.

Table 4 summarises the results of the evaluation for each combination of model (rows) and design (columns). For each model, we recall the values of the parameters used in

the simulation, and for each design we give the relative bias and the empirical relative standard errors (RSE), expressed in percentages. Simulated patients had the same covariate distribution than in the real study. For the datasets simulated with the optimal design, parameter estimation was successful for all 100 datasets. The design in the paediatric database, or empirical design, on the other hand, generated a few simulations for which we were unable to estimate all the standard errors, mostly for absorption, inter-compartmental clearance and their respective random effects. Because only the estimated values, not their RSE, were used to compute the relative bias and empirical RSE, all the figures in Table 4 were computed over all the corresponding runs. As seen in the table, there was no bias in the parameter estimates when the data was simulated according to the optimal design, regardless of the actual model. For the first model, $\mathcal{M}_{allo+mat}$, this only shows that the estimation algorithm provides unbiased estimates, as expected. For the other models, it reflects that there is enough information in this design to estimate the parameters under different model misspecifications. The empirical RSE were also in line with predictions from PFIM, ranging from 3 to 15% for model $\mathcal{M}_{allo+mat}$, the model used to establish the optimal design. More interestingly, precision of parameters was also similar for the other models, showing that the optimal design allows unbiased and precise estimates to be obtained over a range of model changes.

We can contrast this behaviour with the performance of the empirical design. Across all four models, we found that this design had relatively high bias for either k_a or its variability ω_{k_a} or both, even when the true model was the much simpler one-compartment model that was estimated to best describe the real data collected in children. In addition, this design was less robust to changes in the model assumptions, as other parameters such as ω_Q and

ω_{V_1} proved difficult to estimate, yielding very large and implausible values or very large RSE.

[Table 4 about here.]

Although the optimal design gives good results, actually respecting the exact sampling times may be difficult to implement in practice. We therefore also evaluated a design with the following sampling windows, which relaxes the exact optimised design: the first sample time was taken between 1 and 5 hours after the first dose, the second between 1 hour before and 12 hours after the second dose. For the third to fifth sampling time, we allowed for 12 hours sampling windows over several days, as the concentrations changed more slowly over this period: the third time was assumed to be in daytime during days 4 or 5, the fourth during days 13 to 16, and the final sampling window was from day 55 to 60. The evaluation over 100 simulated datasets of this design gave similar results for every model compared to the optimal design, in terms of empirical RSE and relative bias. Full numerical results for simulations on the sampling windows design can be found in Appendix, Table 5.

4 Discussion

The objective of the present work was to design a pharmacokinetic paediatric study using adult information in malaria. To this end, we investigated the impact of design on the information gained from the children study, exploring models taking into account prior adult information through extrapolation by allometry and maturation. We used the paediatric data both as an external evaluation dataset and to suggest alternative models to test the

robustness of both the empirical design actually performed in children and the optimised design. We assessed their performance with regard to changes in parameter assumptions.

In the pharmacokinetic analysis in adults, a two-compartment model was found to best describe the pharmacokinetics of mefloquine. In previous studies [22, 23, 24, 25], both one and two-compartment models have been used to describe its pharmacokinetics. However, a more appropriate sampling schedule shows evidence of tissular distribution [26, 27], both in patients [28] and in a large population of healthy military personnel administered with mefloquine for malaria prophylaxis [29]. The parameter estimates we obtained in the present analysis were consistent with the estimates from these two studies. In particular, we found a slow elimination for mefloquine, with a terminal half-life of 17 days, in line with previous estimates of 14 to 16 days.

In our study, we derived the PK parameters in children from the parameters in adults by using simple methods combining allometry and maturation functions. Allometric scaling to predict structural and functional properties of vertebrate cardiovascular and respiratory system was formally introduced by West *et al.* in 1997 [19]. As the etymology underlines, the purpose of allometry was initially to find measurements working across and within species. The allometric coefficients (e.g. 0.75 for clearances or 1 for volumes [19]) have been estimated in human populations and found to be compatible with the theory [30]. Allometric coefficients can also be estimated in specific PK studies, although conclusive evidence that they differ from the theoretical values is questionable and may in fact reflect model misspecification. On the other hand, there is mounting evidence that allometric relationships may need to be adjusted in early childhood. For example, Peeters *et al.* found differences of clearance exponents in a study including 98 subjects from neonates

to adults, and suggested to use an exponent varying with weight [3]. This discrepancy between size-based scaling and effective changes in model parameters in neonates and very young children can partially be explained by additional maturational changes in physiological processes during this period. Maturation functions have been proposed for several drugs [31, 32], and we adapted them to the characteristics of mefloquine, such as binding properties and first-pass metabolism. A similar approach was used by Anderson and Holford in several studies [33, 34, 30, 35]. In particular, their work on paracetamol involved different physiological processes such as renal and hepatic clearance [13]. In the present work, we applied their methods with formulae specific to mefloquine by considering the maturation of the cytochromes and of albumin concentrations.

The extrapolated models were evaluated using the data collected in the paediatric study as an external evaluation dataset, to assess how well the children data could be predicted considering only prior information in adults. The results were not particularly good, as the model was found to systematically underpredict the early concentrations in children. Using the adult parameters directly was of course also not appropriate, as not taking into account the body size factor led to a systematic overprediction. Compared to the impact of allometry, the contribution of maturational changes here was small and even slightly increased the prediction bias. This may be due to the fact that the major impact of maturation for mefloquine occurs in neonatal and infants, and our population included only 6 very young children (less than 2 years old).

Other methods could be used to extrapolate from adults to children. A physiological approach, describing the intricacies of biological processes, is provided by the physiologically based pharmacokinetic models (PBPK). The model equations rely on principles of mass

transport, fluid dynamics and require knowing the exact drug process. Although very rich, the PBPK models often contain a large number of unknown parameters, the determination of which requires many specific studies. PBPK models have not yet been established for mefloquine. Knibbe *et al.* [36] proposed an alternative model combining both PBPK models and maturation with the development of semi-physiological functions for specific processes. They applied this method on glomerular filtration rate in a study of gentamicin, tobramycin and vancomycin including 1,760 patients from preterm to adults. The present work could benefit from such an approach, using biological system-specific rather than drug specific informations. Approaching a physiological process such as maturation of cytochrome, in particular CYP3A, in childhood would give more precise results. However, it would require more covariates which were not available in our paediatric study.

Despite the lacklustre performance of the maturation model in terms of predictive ability, in the present work, we used the full extrapolated model, including both maturation and allometry, to produce the optimal design. We wanted to reproduce the actual clinical process, where the children data would not be available to assess which model performs best, and to take into account all the prior knowledge on the drug. The recommended design, blending the 4 age-group specific optimal designs, performed very well in our simulations, yielding low RSE for all parameters, confirming that the blended recommended design is appropriate for the entire paediatric dataset. Even in this complex study with a distribution of ages and weights, PFIM predicted quite well the range of standard errors found in the simulation study. Optimising the design of a clinical trial for mefloquine has already been addressed in adults [37, 24], and our results here are in agreement with these previous studies. In particular, Jamsen *et al.* [24] considered optimal designs for various

combinations of mefloquine and another malaria drug, but for a mixed population including adults, pregnant women and children. The optimal designs consisted of two groups of subjects with 5 samples each, including an early sample (2 or 3 hours after dosing), a sample at day 2 and day 7, and 2 additional samples different among the two groups. In our own work, we focused only on the paediatric population, but the results over the different age-groups in the study, including adolescents, suggested that there is not much difference in the sampling schedule recommended over a large span of ages. Indeed, the similar RSE found in study [24] suggest that their design would also be quite robust.

We assessed the performance of the optimal design in a simulation study including four different sets of model assumptions, designed to test model departures from the predicted PK in children. Of course, we cannot expect a design to perform well when the PK changes completely, but the range of scenarios we simulated reflected changes that could be expected when moving from adults to children. Overall, the optimal design performed much better than the empirical design from the real paediatric study in all scenarios. With the empirical design, absorption parameters were always poorly estimated, because of the lack of early time points, and this seemed to have an impact also on the distribution parameters. If we were then performing a real analysis of the paediatric data, we would need to simplify the model, to fix some parameters to the adult value, or to perform a joint analysis of adult and children data together, risking biased estimates if populations are in fact different. Here, in the analysis of the paediatric data alone, we had to use a simplified one-compartment model with fixed absorption ($\mathcal{M}_{ch}$), illustrating the choices that poor designs will lead to.

In this particular case, the empirical design also reflected logistic and practical constraints. Indeed, most children did not have as many measurements as was originally

planned per protocol, which specified that 3 or 4 samples were supposed to be randomly collected during the first three days and during the second week, with an additional 1 or 2 samples taken on different days between the 21st and the 63rd. In the empirical design, most patients only had 3 samples and the first sample was usually after 5 days, yielding no information about the absorption phase. Because mefloquine has a long half-life, late follow-up requires additional visits to the treating centres which may not be convenient or cheap enough for the families to afford. However these late time-points are crucial for a good estimation of the distribution and terminal phases.

A few studies on the PK of mefloquine included children [22], but there has been no specific paediatric study of mefloquine with an informative design. Here, when we analysed separately the paediatric data, we could not identify a two-compartment model. But the poor performance of the empirical design in the simulations also suggested that a more informative design could have been obtained if the available adult information had been taken into account, even if the paediatric PK differed substantially from the adult PK.

In order to get around some of the logistic and practical constraints of a fixed design, a solution is to propose time windows around the sampling times found for the optimal design. In the present study, we evaluated a relaxed design with the same simulation setting as for the optimal and empirical designs, and found similar performances. The windows were chosen empirically, with sensible assumptions, and a similar approach could be implemented in practice with the physicians of the trial, who are generally aware of the logistic constraints they need to respect. Evaluating relaxed designs through simulations like we did in the present study is possible for a limited number of designs, but this approach can also be implemented prospectively. Sampling windows can be specified for instance in

the software PopED, which could be used instead of PFIM to further develop the presented method [38]. Here however, we found good results with sensible sampling windows derived from the optimal design.

An interesting finding of our work is the message that the design need not be perfect, as long as it is robust enough. As is always the case in optimal design, the model we are trying to estimate is unknown prior to performing the study, but needs to be specified to design that study, and the design will only be appropriate if the model is correct. A way to enhance robustness is to ensure that the design performs well across different model and parameter assumptions. Here, we show how a cycle of simulation-evaluation can be integrated in the decision process to safeguard against reasonable departures from candidate model assumptions, by comparing the performance of the optimised design for different models. In the case of mefloquine, the optimised design performed well both for the extrapolated model $\mathcal{M}_{allo+mat}$ and for the real model derived from children data ($\mathcal{M}_{ch}$). Here, we used D-optimality, which relies on prior knowledge of the parameters, but we could enhance robustness through ED-optimality, which allows to incorporate uncertainty in the prior parameter specifications [39]. These methods could be investigated in order to obtain more robust design in paediatrics studies, where parameters are usually unknown and the inter-individual variability very high.

In our study, we used data from an adult population and extrapolated the estimated parameters to the children through allometric and maturation considerations. A similar method could be applied to estimates obtained from the literature. Another interesting approach in this context is adaptive designs, where the initial design is refined through one or several intermediate analysis. Dumont *et al.* [7] applied optimal two-stage designs in a

paediatric context and showed that such designs can correct initial model misspecifications. In their work, the prior information on children was obtained by extrapolating to a children population a PBPK model developed in adults and performing a population PK analysis on simulated data from a virtual paediatric population, an alternative to extrapolation models.

In the present study we use repeated optimisation and simulation to evaluate the optimised and alternative designs before implementation, chalking them across different model assumptions. The framework presented in Figure 2 can therefore be implemented in the clinical development process as a way of qualifying prospective designs to gauge the probability of success of a future trial, as well as convey to clinical teams the importance of implementing the designs in a rigorous way. Because logistic constraints can be elicited prior to the study to be taken into account both at the design stage and at the implementation stage, it is a powerful way of ensuring that the constraints are well accepted and that the design is applicable in practice.

In conclusion, the present work supports using adult prior information for design optimisation in paediatrics. Optimal design methodology combined with allometry and maturation allowed determination of sampling schedules appropriate for children. The optimal design was more robust and provided better estimates for pharmacokinetic parameters for paediatrics, taking into account age specificities.

Acknowledgment

Caroline Petit was supported during this work by a grant IDEX from the university Sorbonne Paris Cité (2013, project 24).

Sarah Zohar and Emmanuelle Comets were funded by the InSPiRe (Innovative methodology for small populations research) project received by the European Union's Seventh Framework Programme for research, technological development and demonstration under grant agreement number FP HEALTH 2013-602144.

We thank the Drugs for Neglected Diseases initiative (DNDi) for making their datasets available for this project.

A Appendix - Maturation and Allometry

Mechanisms of absorption, distribution and elimination of mefloquine during treatment involve different physiological processes. Mefloquine is well absorbed, with a bioavailability estimated around 85% [40], but little is known about the exact mechanism of absorption. Molecules of mefloquine bind strongly with albumin (98% in adults), resulting in a slow diffusion. The unbound molecules of mefloquine are metabolised by cytochrome CYP3A4. Afterwards, mefloquine is eliminated through renal clearance.

These processes are slightly modified for children, due to ongoing maturation. Indeed, in parallel of the size differences warranting a first adjustment from adults, metabolism functions are not fully developed until a certain age. Therefore, drug metabolism has a distinct evolution which is characterised by differences of value for pharmacokinetic parameters. Analysing metabolism processes makes it possible to identify those which

induce a difference with adults values and to adjust pharmacokinetic parameters with a maturation factor.

During absorption, bioavailability is the first process susceptible of maturation. As a substrate of CYP3A, mefloquine bioavailability will decrease with the available quantity of CYP3A during intestinal and hepatic first-pass effects. Each first-pass is characterised by its own extraction coefficient, E_{gut} for intestinal and E_{hepa} for hepatic. Consequently, the overall bioavailability F represents the amount of mefloquine that, once absorbed, is not metabolised during intestinal and hepatic first-passes and reaches the systematic circulation. Adult bioavailability is $F_{ad} = (1 - E_{gut})(1 - E_{hepa})$. However, in children both processes are modulated by the quantity of CYP3A. Indeed, depending on age, CYP3A are not produced in the same amount in children compared to adults. Gut and hepatic CYP3A abundance are characterised by their own maturation function [32]. Denoting K_{CYP3A} the maturation of CYP3A and $K_{CYP3A4/5}$ the maturation of CYP3A4/5, the bioavailability for children can be written:

$$F_{ch} = (1 - E_{gut}K_{CYP3A})(1 - E_{hepa}K_{CYP3A4/5}) \tag{8}$$

With oral drugs, bioavailability is a key value in estimation of pharmacokinetic parameters, which are estimated as apparent, that is relative to the bioavailability. Therefore, it has an impact on all clearance and volume parameters. Let Cl_{ad} the apparent adult clearance related to the real clearance $Cl_{ad,real}$ through $Cl_{ad} = Cl_{ad,real}/F_{ad}$ where F_{ad} is the adult bioavailability. Likewise, we express the apparent clearance for children $Cl_{ch} = Cl_{ch,real}/F_{ch}$.

As for volume, we have $V_{ad} = V_{ad,real}/F_{ad}$ with V_{ad} the apparent volume, $V_{ad,real}$ the real

volume. Likewise, for children, we have $V_{ch} = V_{ch,real}/F_{ch}$.

In the blood stream, mefloquine binds strongly to albumin, leaving only a small fraction of mefloquine unbound. Let $f_{u,ch}$ this fraction in children. While bound to albumin, mefloquine can not be eliminated from the blood stream and only the unbound fraction can be eliminated. Let $Cl_{ch,u}$ the clearance of the unbound fraction of mefloquine in the blood. Therefore, we have:

$$Cl_{ch,real} = Cl_{ch,u} \times f_{u,ch} \tag{9}$$

leading to:

$$Cl_{ch} = \frac{f_{u,ch} Cl_{ch,u}}{F_{ch}} \tag{10}$$

In adults, 98% of mefloquine is bound to albumin, such that the adult unbound fraction is $f_{u,ad} = 0.02$. In children, the fraction of unbound mefloquine can be related to adult unbound fraction of mefloquine $f_{u,ad}$ and to albumin concentration, which varies from C_{ad} (40 g/L on average) and the corresponding value in children, C_{ch}, respectively [32]. The following relationship links the unbound fraction of mefloquine in children to the albumin concentration:

$$f_{u,ch} = \frac{1}{1 + \frac{1-f_{u,ad}}{f_{u,ad}} \frac{C_{ch}}{C_{ad}}} \tag{11}$$

Moreover, albumin concentration in children can be expressed as a function of age [32]:

$$C_{ch} = 1.1287 \ln(age) + 33.746 \tag{12}$$

Therefore, we have:

$$Cl_{ch} = \frac{Cl_{ch,u}}{F_{ch}(1.383 \ln(age) + 42.339)} \tag{13}$$

Unbound mefloquine is metabolised by CYP3A4/5. Again, the quantity of CYP3A4/5 influences the extent of metabolism and its lower value in children needs to be taken into account. Moreover, clearance is also related to weight and an allometric factor needs to be introduced. Therefore, clearance of children unbound fraction of mefloquine is related to the adult value $Cl_{ad,u}$ according to

$$Cl_{ch,u} = Cl_{ad,u} \times K_{CYP3A4/5} \times \left(\frac{W}{70}\right)^{0.75} \tag{14}$$

As previously stated, we deduce from equation 9 that clearance of unbound fraction in adults is $Cl_{ad,u} = Cl_{ad,real}/0.02 = Cl_{ad} \times F_{ad}/0.02$. Therefore:

$$Cl_{ch} = \frac{Cl_{ad}}{0.02(1.383 \ln(age) + 42.339)} \times \frac{F_{ad}}{F_{ch}} \times K_{CYP3A4/5} \times \left(\frac{W}{70}\right)^{0.75} \tag{15}$$

with

$$\frac{F_{ad}}{F_{ch}} = \frac{(1 - E_{gut})(1 - E_{hepa})}{(1 - E_{gut} K_{CYP3A})(1 - E_{hepa} K_{CYP3A4/5})} \tag{16}$$

As extraction coefficient are unknown for mefloquine, we arbitrary chose $E_{gut} = E_{hepa} = 0.5$.

We then need to evaluate maturation of the cytochrome. Their maturation have been characterised by T. Johnson *et al* [32] with:

$$K_{CYP3A4/5} = \frac{age^{0.83}}{0.31 + age^{0.83}} \tag{17}$$

$$K_{CYP3A} = 0.42 + \frac{0.639\ age}{2.35 + age} \tag{18}$$

Contrary to clearance, no maturation process interferes with volume in the blood. However, as previously stated, estimated volumes are apparent volumes. Therefore, adjustment with bioavailability is appropriate. Although there is no maturation, size adjustment is still warranted and we have $V_{ch,real} = V_{ad,real} \times (W/70)$. Therefore:

$$V_{ch} = V_{ad} \times \frac{F_{ad}}{F_{ch}} \times \left(\frac{W}{70}\right) \tag{19}$$

where F_{ad}/F_{ch} is given by in Equation 16.

B Appendix - Evaluation of the sampling windows design

Table 4 presents the results of the evaluation for the design with sampling windows that were derived empirically from the optimised design. It shows the same evaluation metrics presented in the main text for the optimised and empirical designs.

[Table 5 about here.]

References

[1] Roberts R., Rodriguez W., Murphy D., and Crescenzi T. Pediatric drug labeling : Improving the safety and efficacy of pediatric therapies. *JAMA*, 290:905–911, 2003.

[2] Anderson B.J., Woollard G.A., and Holford N.H. A model for size and age changes in the pharmacokinetics of paracetamol in neoates, infants and children. *Br. J. Clin. Pharmacol.*, 50:125–134, 2000.

[3] Peeters M.Y.M., Allegaert K., Blussé van Oud-Albas H.J., Cella M., Tibboel D., Danhof M., and Knibbe C.A.J. Prediction of propofol clearance in children from an allometric model developed in rats, children and adults versus a 0.75 fixed-exponent allometric model. *Clin. Pharmacokinet.*, 49:269–275, 2010.

[4] European Medecines Agency (EMA). Policy on the determination of the condition(s) for a Paediatric Investigation Plan/Waiver (scope of the PIP/Waiver). *Available at* `http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/09/WC500133065.pdf`, September 2012. EMA/272931/2011.

[5] Institute of Medicine (US) Forum on Drug Discovery Development and Translation. *Addressing the Barriers to Pediatric Drug Development*. National Academies Press (US), 2008.

[6] Mentré F., Baccar D., and Mallet A. Optimal design in random-effects regression models. *Biometrika*, 84:429–442, 1997.

[7] Dumont C., Chenel M., and Mentré F. Two-stage adaptive designs in nonlinear mixed effects models: application to pharmacokinetics in children. *Commun. Stat. - Simul. C.*, 2014.

[8] Clinical path initiative - reports on projects receiving critical path support. *Available at* `http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/CriticalPathInitiative/UCM249262.pdf`, September 2010. Protocol: DND-ASM-07.

[9] Ette E. and Williams P.J. *Pharmacometrics: the science of quantitative pharmacology*. Wiley-Interscience, Hoboken, New Jersey, 2007.

[10] Mentré F., Dubruc C., and Thénot J.P. Population pharmacokinetic analysis and optimization of the experimental design for mizolastine solution in children. *J. Pharmacokinet. Pharmacodyn.*, 28:299–319, 2001.

[11] Mentré F., Chenel M., Comets E., Grevel J., Hooker A., Karlsson M.O., Lavielle M., and Gueorguieva I. Current use and developments needed for optimal design in pharmacometrics: A study performed among DDMoRe's European federation of pharmaceutical industries and associations members. *CPT Pharmacometrics Syst. Pharmacol.*, 2:e46, 2013.

[12] Jullien V., Valecha N., Srivastava B., Sharma B., and Kiechel J-R. Population pharmacokinetics of mefloquine, administered as a fixed-dose combination of artesunate-mefloquine in indian patients for the treatment of acute uncomplicated plasmodium falciparum malaria. *Malar. J.*, 13, 2014.

[13] Anderson B.J. and Holford N.H.G. Mechanistic basis of using body size and maturation to predict clearance in humans. *Drug. Metab. Pharmacokinet.*, 24:25–36, 2009.

[14] A single dose two-phase crossover study to assess the tolerability and pharmacokinetic parameters of a fixed dose formulation of artesunate-mefloquine and standard dose artesunate and mefloquine as loose tablets in healthy normal volunteers (Thailand). *Available at* `http://www.isrctn.com/ISRCTN22508774`, November 2008. Protocol: ICA4-2001-10193.

[15] Kuhn E. and Lavielle M. Maximum likelihood estimation in nonlinear mixed effects models. *Comput. Statist. Data Anal.*, 49:1020–1038, 2005.

[16] Lixoft. Monolix methodology. *Available at* `http://www.lixoft.com/wp-content/resources/docs/monolixMethodology.pdf`, March 2013. Version 4.2.2.

[17] Brendel K., Comets E., Laffont C., Laveille C., and Mentré F. Metrics for external model evaluation with an application to the population pharmacokinetics of gliclazide. *Pharm. Res.*, 23:2036–49, 2006.

[18] Bergstrand M., Hooker A.C., Wallin J.E., and Karlsson M.O. Prediction-corrected visual predictive checks for diagnosing nonlinear mixed-effects models. *AAPS J*, 13:143–51, 2011.

[19] West G.B., Brown J.H., and Enquist B.J. A general model for the origin of allometric scaling laws in biology. *Science*, 276:122–126, April 1997.

[20] PFIM group - IAME UMR1137, INSERM, and Université Paris Diderot in Paris France. Pfim user guide. *Documentation available at* `http://www.pfim.biostat.fr/`, August 2014. Version 4.0.

[21] Retout S., Comets E., Samson A., and Mentré F. Design in nonlinear mixed effects models: Optimization using the Fedorov-Wynn algorithm and power of the Wald test for binary covariates. *Stat. Med.*, 26:5162–79, 2007.

[22] Hodel E., Guidi M., Zanolari B., Mercier T., Duong S., Kabanywanyi A., Ariey F., Buclin T., Beck H-P., Decosterd L., Olliaro P., Genton B., and Csajka C. Population pharmacokinetics of mefloquine, piperaquine and artemether-lumefantrine in cambodian and tanzanian malaria patients. *Malar. J.*, 12:235, July 2013.

[23] Simpson J.A., Watkins E.R., Price R.N., Aarons L., Kyle D.E., and White N.J. Mefloquine pharmacokinetics-pharmacodynamic models : Implications for dosing and resistance. *Antimicrob. Agents Chemother.*, 44:3414–3424, December 2000.

[24] Jamsen K., Duffull S., Tarning J., Lindegarth N., White N., and Simpson J. Optimal designs for population pharmacokinetic studies of the partner drugs co-administered with artemisinin derivatives ni patients with uncomplicated falciparum malaria. *Malar. J.*, 11:143–152, 2012.

[25] Na Bangchang K., Davis T., Looareesuwan S., White N., Bunnag D., and Karbwang J. Mefloquine pharmacokinetics in pregnant women with acute falciparum malaria. *Trans R Soc Trop Med Hyg*, 88:321–323, 1994.

[26] Hung L.Q., De Vries P.J., Binh T.Q., Giao P.T., Nam N.V., Holman R., and Kager P.A. Artesunate with mefloquine at various inervals for non-severe plasmodium falciparum malaria. *Am. J. Trop. Med. Hyg.*, 71:160–166, 2004.

[27] Svensson US., Alin MH, Karisson MO., Bergqvist Y., and Ashton M. Population pharmacokinetic and pharmacodynamic modelling of artemisinin and mefloquine enantiomers in patients with falciparum malaria. *Eur J Cli Pharm*, 58:339–351, 2002.

[28] Reuter S., Upton R., Evans A., Navaratnam V., and Olliaro P. Population pharmacokinetics of orally administered mefloquine in healthy volunteers and patients with uncomplicated plasmodium falciparum malaria, 2014. To be published.

[29] Charles B., Blomgren A., Nasveld P., Kitchener S., Jensen A., Gregory R., Robertson B., Harris I., Reid M., and Edstein M. Population pharmacokinetics of mefloquine in military personnel for prophylaxis against malaria infection during field deployment. *Eur J Clin Pharmacol*, 63:271–278, 2007.

[30] Anderson B.J. and Holford N.H.G. Mechanism-based concepts of size and maturity in pharmacokinetics. *Annu. Rev. Pharmacol. Toxicol.*, 48:303–332, 2008.

[31] Edginton A.N., Schmitt W., Voith B., and Willmann S. A mechanistic approach for the scaling of clearance in children. *Clin. Pharmacokinet.*, 45:683–704, 2006.

[32] Johnson T.N., Rostami-Hodjegan A., and Tucker G.T. Prediction of the clearance of eleven drugs and associated variability in neonates, infants and children. *Clin. Pharmacokinet.*, 45:931–956, 2006.

[33] Anderson B.J., Allegaert K., and Holford N.H.G. Population clinical pharmacology of children: Modelling covariate effects. *Eur. J. Pediatr.*, 165:819–829, 2006.

[34] Anderson B.J., Allegaert K., Van den Anker J.N., Cossey V., and Holford N.H.G. Vancomycin pharmacokinetics in preterm neonates and the prediction of adult clearance. *Br. J. Clin. Pharmacol.*, 63:75–84, 2007.

[35] Anderson B.J. and Holford N.H.G. Tips and traps analyzing pediatric PK data. *Paediatr. Anaesth.*, 21:222–237, March 2011.

[36] De Cock R., Allegaert K., Sherwin C., Nielsen E., de Hoog M., van den Anker J., Danhof M., and Knibbe C. A neonatal amikacin covariate model can be used to predict ontogeny of other drugs eliminated through glomerular filtration in neonates. *Pharm. Res.*, 31:754–767, 2014.

[37] Simpson J., Jamsen K., Price R., White N., Lindegardh N., Tarning J., and Duffull S. Towards optimal design of anti-malarial pharmacokinetic studies. *Malar. J.*, 8:189–196, 2009.

[38] The PopED development team. PopED manual. *Documentation available at* `http://poped.sourceforge.net/docs.php`, March 2015. Version 2.13.

[39] Dodds M., Hooker A., and Vicini P. Robust population pharmacokinetic experiment design. *J. Pharmacokinet. Pharmacodyn.*, 32:33–63, 2005.

[40] Roche Laboratories. Lariam brand of mefloquine hydrochloride. `http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/019591s023lbl.pdf`, 2008. [Online; accessed 03-March-2015].

	Adults (N=77)	Children (N=101)
Weight (kg)	53.2 (7.3) - 52.0 [48.0; 58.0]	24.6 (10.8) - 23.0 [15.0; 35.0]
Age (year)	28.2 (8.8) - 25.0 [21.0; 35.0]	8.8 (4.2) - 10.0 [5.0; 13.0]
Haemoglobin (g/dL)	13.1 (2.14) - 13.3 [11.7; 14.9]	10.9 (1.9) - 11.0 [9.7; 12.4]
ASAT (UI/L)	34.4 (14.1) - 21.0 [25.0; 41.0]	34.9 (38.6) - 22.0 [18.0; 29.0]
ALAT (UI/L)	26.2 (17.1) - 21.0 [15.0; 31.0]	17.3 (27.0) - 8.0 [6.0 ;12.8]

Table 1 – Summary of demographic and covariate data. The values are the mean of the variables, with standard deviation in parentheses, followed by the median and the interquartile interval ([Q_1; Q_3]).

Parameters	Population values (RSE %)	Variability % (RSE %)
k_a (Day^{-1})	4.2 (12)	81 (12)
Cl (L/Day^{-1})	26.0 (5)	34 (11)
V_1 (L)	248.0 (5)	25 (17)
Q (L.Day^{-1})	41.6 (15)	70 (18)
V_2 (L)	282.0 (7)	-
a	0.07 (24)	-
b	0.14 (11)	-

Table 2 – Estimates of the parameters in model $\mathcal{M}_{ad}$ along with the relative standard errors of estimation (RSE) given in brackets. The first column shows the value of the fixed effect, while the second column gives the variabilities expressed as %.

Group	Age	Dose (ml/day)	Optimised times (days)
Infants-Toddlers	$<$ 3 y.o.	87	0.1, 0.9, 4.5, 12, 57
Pre-School	4 - 5 y.o.	113	0.1, 0.9, 4.5, 13, 55
School age	5 - 11 y.o.	178	0.1, 2, 5, 14, 57
Adolescent	12 - 15 y.o.	342	0.2, 2, 6, 16, 66
Overall (optimal design)			0.1, 1, 5, 14, 57

Table 3 – Optimal sampling times for each age-group (first four rows), and for the optimal design across groups (last row). The four age groups correspond to an infant-toddler group including only one infant (13%), a pre-school children group (17%), a school-age group (37%) and an adolescent group (33%). Dose indicates the average quantity of mefloquine given per day.

Model	Parameter	Value	Optimal design		Empirical design	
			Relative bias (%)	Empiric RSE (%)	Relative bias (%)	Empiric RSE (%)
$\mathcal{M}_{allo+mat}$	k_a (Day^{-1})	4.16	-1.29	7.90	469.43	486.60
	Cl (L.Day^{-1})	26.00	0.58	2.67	-0.73	3.72
	V_1 (L)	248.00	-2.33	4.39	-6.85	10.82
	Q (L.Day^{-1})	41.60	4.21	9.86	6.56	21.78
	V_2 (L)	282.00	2.30	4.98	0.91	7.13
	ω_{k_a} (-)	0.81	-2.22	8.10	16.11	34.97
	ω_{Cl} (-)	0.34	-0.31	5.66	-2.37	8.11
	ω_{V_1} (-)	0.25	-1.71	11.45	18.02	29.94
	ω_Q (-)	0.70	-0.03	15.37	-1.24	20.71
	a (mg.kg^{-1})	0.07	-1.32	7.47	1.16	11.16
	b (-)	0.14	-2.07	9.48	-8.63	14.01
$\mathcal{M}_{ad}$	k_a (Day^{-1})	4.16	-2.75	8.33	219.15	240.32
	Cl (L.Day^{-1})	26.00	-0.52	3.73	-1.69	3.98
	V_1 (L)	248.00	-1.46	4.08	-11.27	13.39
	Q (L.Day^{-1})	41.60	5.54	14.08	22.60	31.75
	V_2 (L)	282.00	2.78	5.34	5.79	9.30
	ω_{k_a} (-)	0.81	-2.61	8.38	15.17	33.64
	ω_{Cl} (-)	0.34	-1.12	7.89	-2.43	8.93
	ω_{V_1} (-)	0.25	0.59	14.18	14.58	30.73
	ω_Q (-)	0.70	3.74	17.12	5.95	23.87
	a (mg.kg^{-1})	0.07	-1.73	6.10	0.14	7.38
	b (-)	0.14	-4.15	12.62	-15.82	23.08
$\mathcal{M}_{ad,abs}$	k_a (Day^{-1})	1.00	-1.67	12.11	319.11	337.19
	Cl (L.Day^{-1})	26.00	-0.28	3.58	-1.60	4.15
	V_1 (L)	248.00	-2.35	8.70	-3.54	14.92
	Q (L.Day^{-1})	41.60	2.45	15.95	40.62	53.55
	V_2 (L)	282.00	3.03	7.08	2.44	11.33
	ω_{k_a} (-)	0.81	-2.93	9.09	1.63	32.17
	ω_{Cl} (-)	0.34	0.17	8.68	-1.65	10.18
	ω_{V_1} (-)	0.25	4.68	19.47	31.07	39.23
	ω_Q (-)	0.70	0.72	21.54	30.07	42.85
	a (mg.kg^{-1})	0.07	-0.53	4.55	-0.88	7.99
	b (-)	0.14	-8.68	15.15	-13.45	26.38
$\mathcal{M}_{ch}$	k_a (Day^{-1})	4.16	3.77	10.23	13.51	50.28
	Cl (L.Day^{-1})	14.30	1.82	5.54	1.92	7.32
	V (L)	263.00	0.64	5.43	-0.62	7.81
	ω_{k_a} (-)	0.81	-1.74	14.36	52.26	53.87
	ω_{Cl} (-)	0.63	-2.33	8.69	-0.41	8.80
	ω_V (-)	0.66	0.18	6.93	-4.48	10.43
	a (mg.kg^{-1})	0.08	-0.84	7.66	3.05	11.80
	b (-)	0.35	-0.04	5.32	-4.18	9.98

Table 4 – Validation of optimal design on different models. Models are $\mathcal{M}_{allo+mat}$ based the adult model $\mathcal{M}_{ad}$ with allometry and maturation; $\mathcal{M}_{ad}$ the adult model; $\mathcal{M}_{ad,abs}$ the adult model with a different absorption; $\mathcal{M}_{ch}$ the model built from the children data. Relative bias and empiric RSE are expressed in pourcentages.

Model	Parameter	Value	sampling windows	
			Relative bias	Empiric RSE
$\mathcal{M}_{allo+mat}$	k_a (Day^{-1})	4.16	-1.23	9.12
	Cl (L.Day^{-1})	26.00	-0.39	3.08
	V_1 (L)	248.00	-1.61	3.93
	Q (L.Day^{-1})	41.60	4.28	11.19
	V_2 (L)	282.00	1.28	4.12
	ω_{k_a} (-)	0.81	0.51	7.81
	ω_{Cl} (-)	0.34	-0.08	6.66
	ω_{V_1} (-)	0.25	-1.79	10.39
	ω_Q (-)	0.70	-0.71	14.87
	a (mg.kg^{-1})	0.07	-2.45	8.81
	b (-)	0.14	-2.08	7.75
$\mathcal{M}_{ad}$	k_a (Day^{-1})	4.16	-3.01	9.26
	Cl (L.Day^{-1})	26.00	0.67	3.57
	V_1 (L)	248.00	-1.34	4.37
	Q (L.Day^{-1})	41.60	2.27	12.50
	V_2 (L)	282.00	1.36	5.62
	ω_{k_a} (-)	0.81	-2.58	7.25
	ω_{Cl} (-)	0.34	-0.48	7.12
	ω_{V_1} (-)	0.25	0.09	15.32
	ω_Q (-)	0.70	0.69	17.64
	a (mg.kg^{-1})	0.07	-1.94	6.30
	b (-)	0.14	-3.05	10.99
$\mathcal{M}_{ad,abs}$	k_a (Day^{-1})	1.00	-0.72	11.57
	Cl (L.Day^{-1})	26.00	-0.48	3.78
	V_1 (L)	248.00	-1.28	7.92
	Q (L.Day^{-1})	41.60	1.21	16.88
	V_2 (L)	282.00	2.71	7.95
	ω_{k_a} (-)	0.81	-1.17	8.01
	ω_{Cl} (-)	0.34	0.36	8.19
	ω_{V_1} (-)	0.25	1.69	20.19
	ω_Q (-)	0.70	-0.15	21.64
	a (mg.kg^{-1})	0.07	-0.83	4.88
	b (-)	0.14	-5.86	13.53
$\mathcal{M}_{ch}$	k_a (Day^{-1})	4.16	0.48	9.45
	Cl (L.Day^{-1})	14.30	0.53	5.60
	V (L)	263.00	1.43	5.15
	ω_{k_a} (-)	0.81	-0.29	12.86
	ω_{Cl} (-)	0.63	-0.91	6.75
	ω_V (-)	0.66	-1.13	6.98
	a (mg.kg^{-1})	0.08	-0.84	8.31
	b (-)	0.35	-0.10	5.10

Table 5 – Evaluation of the design with sampling windows derived from the optimised design. Models are $\mathcal{M}_{allo+mat}$ based the adult model $\mathcal{M}_{ad}$ with allometry and maturation; $\mathcal{M}_{ad}$ the adult model; $\mathcal{M}_{ad,abs}$ the adult model with a different absorption; $\mathcal{M}_{ch}$ the model built from the children data.

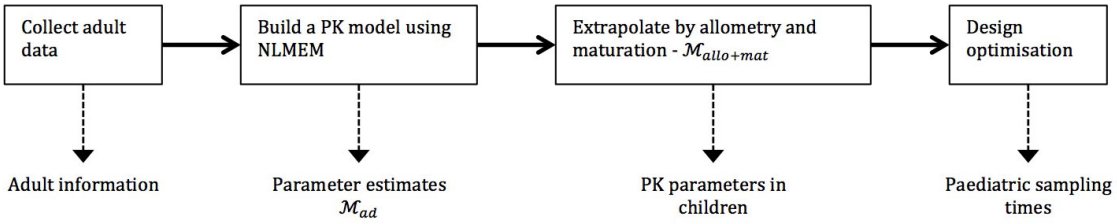


Figure 1 – Framework used to design the paediatric study using adult information.

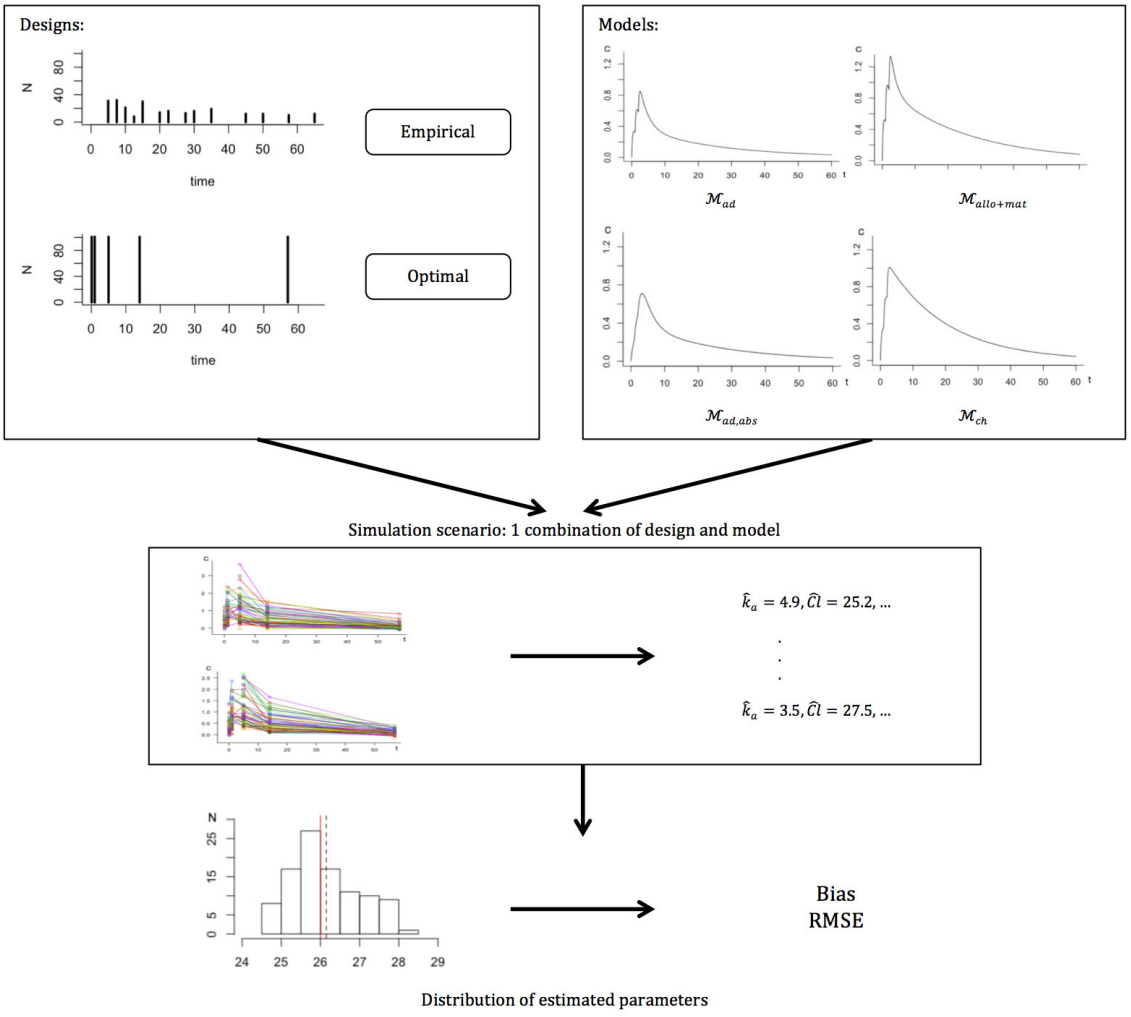
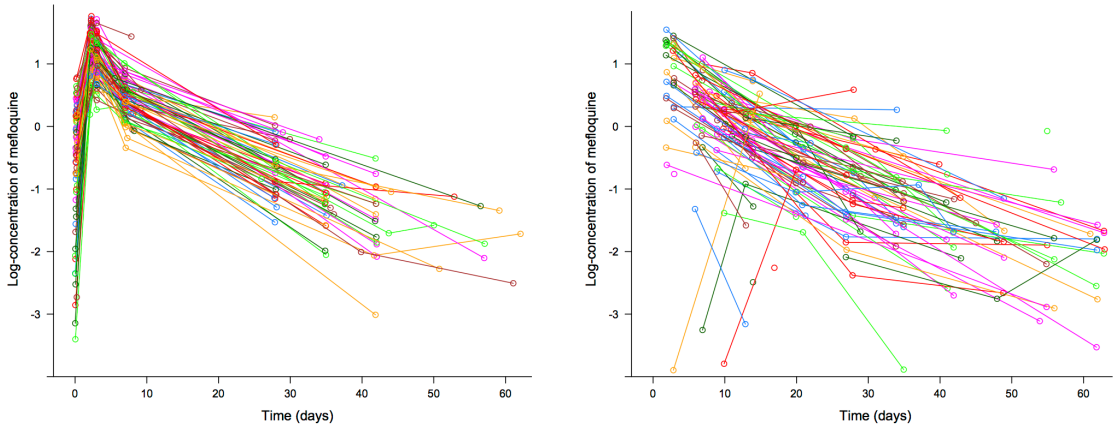
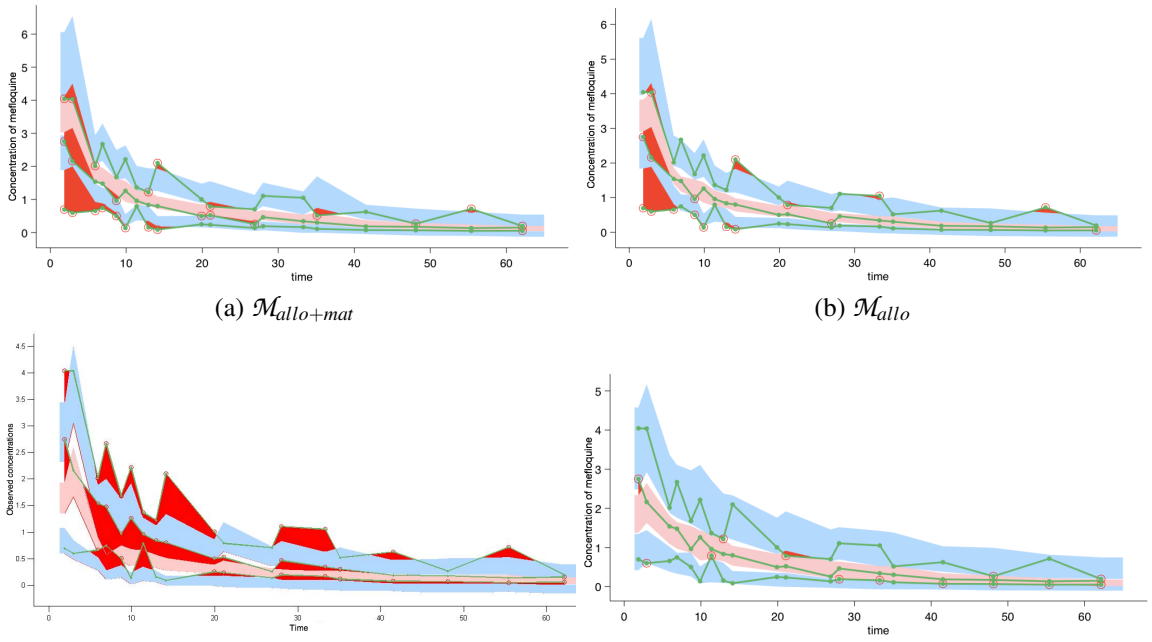


Figure 2 – Schema of simulation study. For both the optimal design and the empirical design from the paediatric database, and for each model tested, 100 datasets are simulated. For each dataset, PK parameters are estimated and then compared to the theoretical value of the original model with bias and RMSE. Models are $\mathcal{M}_{ad}$ the adult model; $\mathcal{M}_{allo+mat}$ the maturation model using the adult model with allometry and maturation; $\mathcal{M}_{ad,abs}$ the adult model with a modified absorption at 1; $\mathcal{M}_{ch}$ model resulting of the pharmacokinetic of the paediatric data



(a) (b)

Figure 3 – Concentrations of mefloquine in blood (in mg/L), shown in log-scale: (a) adults; (b) children.



(a) $\mathcal{M}_{allo+mat}$ (b) $\mathcal{M}_{allo}$

(c) $\mathcal{M}_{ad}$ (d) $\mathcal{M}_{ch}$

Figure 4 – Visual predictive check for extrapolation models on paediatric data

The 95% confidence interval for the median of the model is in pink, the blue area correspond to the 95% prediction band for the upper and lower limit of the 80% predictive interval, the red area characterize outliners data points. (a) extrapolation $\mathcal{M}_{allo+mat}$ from the adult model with allometry and maturation; (b) extrapolation $\mathcal{M}_{allo}$ from the adult model with allometry; (c) extrapolation from the adult model $\mathcal{M}_{ad}$; (d) model $\mathcal{M}_{ch}$ constructed from the children database.