



HAL
open science

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

Caroline Petit, Vincent Jullien, Adeline Samson, Jérémie Guedj, Jean-René Kiechel, Sarah Zohar, Emmanuelle Comets

► **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

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

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

3 Caroline PETIT¹, Vincent JULLIEN², Adeline SAMSON³, Jérémie GUEDJ⁴, Jean-René
4 KIECHEL⁵, Sarah ZOHAR¹, and Emmanuelle COMETS^{4,6}

5 ¹INSERM, UMRS 1138, CRC, Team 22, Univ. Paris 5, Univ. Paris 6, Paris, France

6 ²Pharmacology Department, Univ. Paris 5, Sorbonne Paris Cité, Inserm U1129, HEGP,
7 Paris, France

8 ³LJK, UMR CNRS 5224, Univ. J. Fourier, Grenoble, France

9 ⁴INSERM, IAME, UMR 1137, F-75018 Paris, France; Univ Paris Diderot, Sorbonne Paris
10 Cité, F-75018 Paris, France

11 ⁵Drugs for Neglected Diseases initiative, 15 chemin Louis-Dunant, 1202 Geneva,
12 Switzerland

13 ⁶INSERM, CIC 1414, Univ. Rennes 1, Rennes, France

14 **Abstract**

15 **Objectives:** To design a pharmacokinetic (PK) study using adult prior informa-
16 tion and evaluate robustness of the recommended design, through a case-study on
17 mefloquine.

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

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

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

35 **Conclusion:** Using prior adult information combined with allometry and matura-
36 tion can help provide robust designs for paediatrics studies.

37 **1 Introduction**

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

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

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

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

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

76 **2 Methods**

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

89 [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

111 selected from days 1, 2, 3 or 7-14 and 1 or 2 additional samples on days 21, 28, 35,
112 42, 49, 56 or 63.

113 **Modelling the PK of mefloquine in adults**

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

$$y_i = f(\phi_i, t_i) + \varepsilon_i \quad (1)$$

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

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

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

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

129 information criteria (BIC) for non-nested models. We investigated first the structural
 130 model, comparing different compartment models, then the interindividual variability, testing
 131 whether Ω^2 could be assumed to be diagonal or not, and finally the residual variability.
 132 Different residual error models were considered: a constant error model $\text{Var}(\epsilon_{ij}) = a^2$, a
 133 proportional error model $\text{Var}(\epsilon_{ij}) = b^2 \times f(\phi_i, t_{ij})^2$ and a combined error model $\text{Var}(\epsilon_{ij}) =$
 134 $(a + bf(\phi_i, t_{ij}))^2$. In order to evaluate the stability of the estimates, the run assessment
 135 feature in Monolix was used; this consists in performing the evaluation 5 times changing
 136 initial conditions and seed for the random number generators and comparing the estimates
 137 of the parameters and the log-likelihood across the 5 runs.

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

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

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

149 where $\hat{\mu}$ are the estimated population parameters and $Var(f(\hat{\mu}, t_{ij})) = \sum_{i=1}^N \frac{1}{n_i-1} \sum_{j=1}^{n_i} (y_{ij} -$
 150 $f(\hat{\mu}, t_{ij}))^2$ is the variance of the predicted concentrations.

151 **Extrapolation from adults to children**

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

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

$$\mu = \alpha \times BW^\beta \quad (5)$$

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

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

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

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

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

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

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

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

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

185 **Optimal design for a paediatric population**

186 Design optimisation was performed for the model using both allometry and maturation
187 $\mathcal{M}_{allo+mat}$. Design optimisation consists in selecting the best dose regimen and sampling
188 times, given constraints such as the total number of samples or the times when samples
189 can be taken, in order to allow precise estimation of the parameters. In this work we will
190 focus on sampling times only because the doses were fixed in children. This is generally
191 achieved through D-optimality, which consists in maximising the determinant of the Fisher
192 information matrix (FIM) [6]. Although the FIM in NLME has no closed form solution, it
193 can be approximated using a first order linearisation around the mean of the random effects.
194 This method is implemented in PFIM, which we used here (PFIM version 4.0, running in R
195 version 3.0) [20], and in most softwares performing design optimisation.

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

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

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

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

217 **Evaluation of paediatric design**

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

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

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

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

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

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

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

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

245 **3 Results**

246 **Characteristics of both populations**

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

251 [Table 1 about here.]

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

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

262 [Figure 3 about here.]

263 **Modelling the PK of mefloquine in adults**

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

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

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

278 [Table 2 about here.]

279 **Extrapolation from adults to children**

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

282 Extrapolation was assessed using the paediatric data as an external evaluation dataset
283 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)

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

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

305 [Figure 4 about here.]

306 **Optimal design for the paediatric population**

307 $\mathcal{M}_{allo+mat}$ was then used to design a sampling schedule for the paediatric population.
308 We first attempted to optimise designs with 3 or 4 sampling times, as this was close to the
309 design in the paediatric database, which we call empirical design. But optimisation failed,
310 indicating the model was not identifiable with so few samples. We therefore increased
311 the number of samples to 5 or 6. Table 3 shows the optimal times found for each group
312 for designs with 5 sampling points; several sampling times were found to be quite similar
313 across designs, with three samples in the first 4 days and two after 65 days. The parameters
314 were well estimated in each group, according to the RSE predicted by PFIM, with RSE
315 around 5% for Cl , V_1 and V_2 , and around 10% for k_a and Q . Inter-subject random effects
316 should have somewhat higher RSE, between 20% and 30%, but the designs would still
317 allow proper estimation of the variabilities. Designs with 6 sampling times gave similar
318 results in terms of RSE, suggesting that 5 sampling times were sufficient in our case.

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

321 [Table 3 about here.]

322 **Design evaluation**

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

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

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

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

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

352 [Table 4 about here.]

353 Although the optimal design gives good results, actually respecting the exact sampling
354 times may be difficult to implement in practice. We therefore also evaluated a design with
355 the following sampling windows, which relaxes the exact optimised design: the first sample
356 time was taken between 1 and 5 hours after the first dose, the second between 1 hour before
357 and 12 hours after the second dose. For the third to fifth sampling time, we allowed for
358 12 hours sampling windows over several days, as the concentrations changed more slowly
359 over this period: the third time was assumed to be in daytime during days 4 or 5, the fourth
360 during days 13 to 16, and the final sampling window was from day 55 to 60. The evaluation
361 over 100 simulated datasets of this design gave similar results for every model compared to
362 the optimal design, in terms of empirical RSE and relative bias. Full numerical results for
363 simulations on the sampling windows design can be found in Appendix, Table 5.

364 **4 Discussion**

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

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

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

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

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

403 The extrapolated models were evaluated using the data collected in the paediatric
404 study as an external evaluation dataset, to assess how well the children data could be
405 predicted considering only prior information in adults. The results were not particularly
406 good, as the model was found to systematically underpredict the early concentrations in
407 children. Using the adult parameters directly was of course also not appropriate, as not
408 taking into account the body size factor led to a systematic overprediction. Compared to
409 the impact of allometry, the contribution of maturational changes here was small and even
410 slightly increased the prediction bias. This may be due to the fact that the major impact of
411 maturation for mefloquine occurs in neonatal and infants, and our population included only
412 6 very young children (less than 2 years old).

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

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

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

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

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

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

462 planned per protocol, which specified that 3 or 4 samples were supposed to be randomly
463 collected during the first three days and during the second week, with an additional 1 or
464 2 samples taken on different days between the 21st and the 63rd. In the empirical design,
465 most patients only had 3 samples and the first sample was usually after 5 days, yielding
466 no information about the absorption phase. Because mefloquine has a long half-life, late
467 follow-up requires additional visits to the treating centres which may not be convenient or
468 cheap enough for the families to afford. However these late time-points are crucial for a
469 good estimation of the distribution and terminal phases.

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

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

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

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

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

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

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

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

526

527 **Acknowledgment**

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

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

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

536 **A Appendix - Maturation and Allometry**

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

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

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

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

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

562 With oral drugs, bioavailability is a key value in estimation of pharmacokinetic pa-
 563 rameters, which are estimated as apparent, that is relative to the bioavailability. Therefore,
 564 it has an impact on all clearance and volume parameters. Let Cl_{ad} the apparent adult
 565 clearance related to the real clearance $Cl_{ad,real}$ through $Cl_{ad} = Cl_{ad,real}/F_{ad}$ where F_{ad}
 566 is the adult bioavailability. Likewise, we express the apparent clearance for children
 567 $Cl_{ch} = Cl_{ch,real}/F_{ch}$.

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

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

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

$$Cl_{ch,real} = Cl_{ch,u} \times f_{u,ch} \quad (9)$$

575 leading to:

$$Cl_{ch} = \frac{f_{u,ch} Cl_{ch,u}}{F_{ch}} \quad (10)$$

576 In adults, 98% of mefloquine is bound to albumin, such that the adult unbound fraction
577 is $f_{u,ad} = 0.02$. In children, the fraction of unbound mefloquine can be related to adult
578 unbound fraction of mefloquine $f_{u,ad}$ and to albumin concentration, which varies from C_{ad}
579 (40 g/L on average) and the corresponding value in children, C_{ch} , respectively [32]. The
580 following relationship links the unbound fraction of mefloquine in children to the albumin
581 concentration:

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

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

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

583 Therefore, we have:

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

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

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

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

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

591 with

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

592 As extraction coefficient are unknown for mefloquine, we arbitrary chose $E_{gut} =$
593 $E_{hepa} = 0.5$.

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

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

$$K_{CYP3A} = 0.42 + \frac{0.639 \, age}{2.35 + age} \quad (18)$$

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

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

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

601 **B Appendix - Evaluation of the sampling windows design**

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

605 [Table 5 about here.]

606 **References**

- 607 [1] Roberts R., Rodriguez W., Murphy D., and Crescenzi T. Pediatric drug labeling :
608 Improving the safety and efficacy of pediatric therapies. *JAMA*, 290:905–911, 2003.
- 609 [2] Anderson B.J., Woollard G.A., and Holford N.H. A model for size and age changes
610 in the pharmacokinetics of paracetamol in neonates, infants and children. *Br. J. Clin.*
611 *Pharmacol.*, 50:125–134, 2000.
- 612 [3] Peeters M.Y.M., Allegaert K., Blussé van Oud-Albas H.J., Cella M., Tibboel D.,
613 Danhof M., and Knibbe C.A.J. Prediction of propofol clearance in children from an
614 allometric model developed in rats, children and adults versus a 0.75 fixed-exponent
615 allometric model. *Clin. Pharmacokinet.*, 49:269–275, 2010.
- 616 [4] European Medicines Agency (EMA). Policy on the determination of
617 the condition(s) for a Paediatric Investigation Plan/Waiver (scope of the
618 PIP/Waiver). Available at [http://www.ema.europa.eu/docs/en_](http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/09/WC500133065.pdf)
619 [GB/document_library/Other/2012/09/WC500133065.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/09/WC500133065.pdf), Septem-
620 ber 2012. EMA/272931/2011.
- 621 [5] Institute of Medicine (US) Forum on Drug Discovery Development and Translation.
622 *Addressing the Barriers to Pediatric Drug Development*. National Academies Press
623 (US), 2008.
- 624 [6] Mentré F., Baccar D., and Mallet A. Optimal design in random-effects regression
625 models. *Biometrika*, 84:429–442, 1997.

- 626 [7] Dumont C., Chenel M., and Mentré F. Two-stage adaptive designs in nonlinear mixed
627 effects models: application to pharmacokinetics in children. *Commun. Stat. - Simul.*
628 C., 2014.
- 629 [8] Clinical path initiative - reports on projects receiving critical path support.
630 Available at [http://www.fda.gov/downloads/ScienceResearch/
631 SpecialTopics/CriticalPathInitiative/UCM249262.pdf](http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/CriticalPathInitiative/UCM249262.pdf), September
632 2010. Protocol: DND-ASM-07.
- 633 [9] Ette E. and Williams P.J. *Pharmacometrics: the science of quantitative pharmacology*.
634 Wiley-Interscience, Hoboken, New Jersey, 2007.
- 635 [10] Mentré F., Dubruc C., and Thénot J.P. Population pharmacokinetic analysis and
636 optimization of the experimental design for mizolastine solution in children. *J.*
637 *Pharmacokinet. Pharmacodyn.*, 28:299–319, 2001.
- 638 [11] Mentré F., Chenel M., Comets E., Grevel J., Hooker A., Karlsson M.O., Lavielle
639 M., and Gueorguieva I. Current use and developments needed for optimal design
640 in pharmacometrics: A study performed among DDMoRe’s European federation of
641 pharmaceutical industries and associations members. *CPT Pharmacometrics Syst.*
642 *Pharmacol.*, 2:e46, 2013.
- 643 [12] Jullien V., Valecha N., Srivastava B., Sharma B., and Kiechel J-R. Population phar-
644 macokinetics of mefloquine, administered as a fixed-dose combination of artesunate-
645 mefloquine in indian patients for the treatment of acute uncomplicated plasmodium
646 falciparum malaria. *Malar. J.*, 13, 2014.

- 647 [13] Anderson B.J. and Holford N.H.G. Mechanistic basis of using body size and mat-
648 uration to predict clearance in humans. *Drug. Metab. Pharmacokinet.*, 24:25–36,
649 2009.
- 650 [14] A single dose two-phase crossover study to assess the tolerability and pharmacokinetic
651 parameters of a fixed dose formulation of artesunate-mefloquine and standard dose
652 artesunate and mefloquine as loose tablets in healthy normal volunteers (Thailand).
653 Available at <http://www.isrctn.com/ISRCTN22508774>, November 2008.
654 Protocol: ICA4-2001-10193.
- 655 [15] Kuhn E. and Lavielle M. Maximum likelihood estimation in nonlinear mixed effects
656 models. *Comput. Statist. Data Anal.*, 49:1020–1038, 2005.
- 657 [16] Lixoft. Monolix methodology. Available at [http://www.lixoft.com/
658 wp-content/resources/docs/monolixMethodology.pdf](http://www.lixoft.com/wp-content/resources/docs/monolixMethodology.pdf), March
659 2013. Version 4.2.2.
- 660 [17] Brendel K., Comets E., Laffont C., Laveille C., and Mentré F. Metrics for external
661 model evaluation with an application to the population pharmacokinetics of gliclazide.
662 *Pharm. Res.*, 23:2036–49, 2006.
- 663 [18] Bergstrand M., Hooker A.C., Wallin J.E., and Karlsson M.O. Prediction-corrected
664 visual predictive checks for diagnosing nonlinear mixed-effects models. *AAPS J.*,
665 13:143–51, 2011.
- 666 [19] West G.B., Brown J.H., and Enquist B.J. A general model for the origin of allometric
667 scaling laws in biology. *Science*, 276:122–126, April 1997.

- 668 [20] PFIM group - IAME UMR1137, INSERM, and Université Paris Diderot
669 in Paris France. Pfim user guide. *Documentation available at [http://www.pfim.](http://www.pfim.biostat.fr/)*
670 *biostat.fr/*, August 2014. Version 4.0.
- 671 [21] Retout S., Comets E., Samson A., and Mentré F. Design in nonlinear mixed effects
672 models: Optimization using the Fedorov-Wynn algorithm and power of the Wald test
673 for binary covariates. *Stat. Med.*, 26:5162–79, 2007.
- 674 [22] Hodel E., Guidi M., Zanolari B., Mercier T., Duong S., Kabanyanyi A., Arieu F.,
675 Buclin T., Beck H-P., Decosterd L., Olliaro P., Genton B., and Csajka C. Popula-
676 tion pharmacokinetics of mefloquine, piperaquine and artemether-lumefantrine in
677 cambodian and tanzanian malaria patients. *Malar. J.*, 12:235, July 2013.
- 678 [23] Simpson J.A., Watkins E.R., Price R.N., Aarons L., Kyle D.E., and White N.J.
679 Mefloquine pharmacokinetics-pharmacodynamic models : Implications for dosing
680 and resistance. *Antimicrob. Agents Chemother.*, 44:3414–3424, December 2000.
- 681 [24] Jansen K., Duffull S., Tarning J., Lindgarth N., White N., and Simpson J. Optimal
682 designs for population pharmacokinetic studies of the partner drugs co-administered
683 with artemisinin derivatives in patients with uncomplicated falciparum malaria. *Malar.*
684 *J.*, 11:143–152, 2012.
- 685 [25] Na Bangchang K., Davis T., Looareesuwan S., White N., Bunnag D., and Karbwang
686 J. Mefloquine pharmacokinetics in pregnant women with acute falciparum malaria.
687 *Trans R Soc Trop Med Hyg*, 88:321–323, 1994.

- 688 [26] Hung L.Q., De Vries P.J., Binh T.Q., Giao P.T., Nam N.V., Holman R., and Kager P.A.
689 Artesunate with mefloquine at various intervals for non-severe plasmodium falciparum
690 malaria. *Am. J. Trop. Med. Hyg.*, 71:160–166, 2004.
- 691 [27] Svensson US., Alin MH, Karisson MO., Bergqvist Y., and Ashton M. Population
692 pharmacokinetic and pharmacodynamic modelling of artemisinin and mefloquine
693 enantiomers in patients with falciparum malaria. *Eur J Clin Pharm*, 58:339–351, 2002.
- 694 [28] Reuter S., Upton R., Evans A., Navaratnam V., and Olliaro P. Population pharma-
695 cokinetics of orally administered mefloquine in healthy volunteers and patients with
696 uncomplicated plasmodium falciparum malaria, 2014. To be published.
- 697 [29] Charles B., Blomgren A., Nasveld P., Kitchener S., Jensen A., Gregory R., Robertson
698 B., Harris I., Reid M., and Edstein M. Population pharmacokinetics of mefloquine in
699 military personnel for prophylaxis against malaria infection during field deployment.
700 *Eur J Clin Pharmacol*, 63:271–278, 2007.
- 701 [30] Anderson B.J. and Holford N.H.G. Mechanism-based concepts of size and maturity
702 in pharmacokinetics. *Annu. Rev. Pharmacol. Toxicol.*, 48:303–332, 2008.
- 703 [31] Edginton A.N., Schmitt W., Voith B., and Willmann S. A mechanistic approach for
704 the scaling of clearance in children. *Clin. Pharmacokinet.*, 45:683–704, 2006.
- 705 [32] Johnson T.N., Rostami-Hodjegan A., and Tucker G.T. Prediction of the clearance
706 of eleven drugs and associated variability in neonates, infants and children. *Clin.*
707 *Pharmacokinet.*, 45:931–956, 2006.

- 708 [33] Anderson B.J., Allegaert K., and Holford N.H.G. Population clinical pharmacology
709 of children: Modelling covariate effects. *Eur. J. Pediatr.*, 165:819–829, 2006.
- 710 [34] Anderson B.J., Allegaert K., Van den Anker J.N., Cossey V., and Holford N.H.G. Van-
711 comycin pharmacokinetics in preterm neonates and the prediction of adult clearance.
712 *Br. J. Clin. Pharmacol.*, 63:75–84, 2007.
- 713 [35] Anderson B.J. and Holford N.H.G. Tips and traps analyzing pediatric PK data.
714 *Paediatr. Anaesth.*, 21:222–237, March 2011.
- 715 [36] De Cock R., Allegaert K., Sherwin C., Nielsen E., de Hoog M., van den Anker J.,
716 Danhof M., and Knibbe C. A neonatal amikacin covariate model can be used to
717 predict ontogeny of other drugs eliminated through glomerular filtration in neonates.
718 *Pharm. Res.*, 31:754–767, 2014.
- 719 [37] Simpson J., Jansen K., Price R., White N., Lindegardh N., Tarning J., and Duffull
720 S. Towards optimal design of anti-malarial pharmacokinetic studies. *Malar. J.*,
721 8:189–196, 2009.
- 722 [38] The PopED development team. PopED manual. *Documentation available at <http://poped.sourceforge.net/docs.php>*, March 2015. Version 2.13.
723
- 724 [39] Dodds M., Hooker A., and Vicini P. Robust population pharmacokinetic experiment
725 design. *J. Pharmacokinet. Pharmacodyn.*, 32:33–63, 2005.
- 726 [40] Roche Laboratories. Lariam brand of mefloquine hydrochloride. [http://www.
727 accessdata.fda.gov/drugsatfda_docs/label/2008/019591s0231bl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/019591s0231bl.pdf),
728 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.

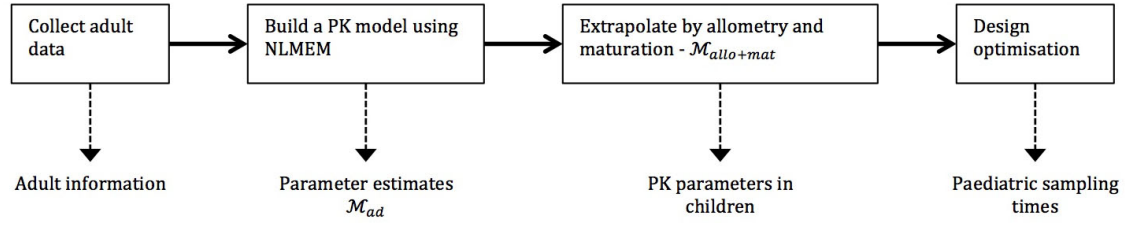


Figure 1 – Framework used to design the paediatric study using adult information.

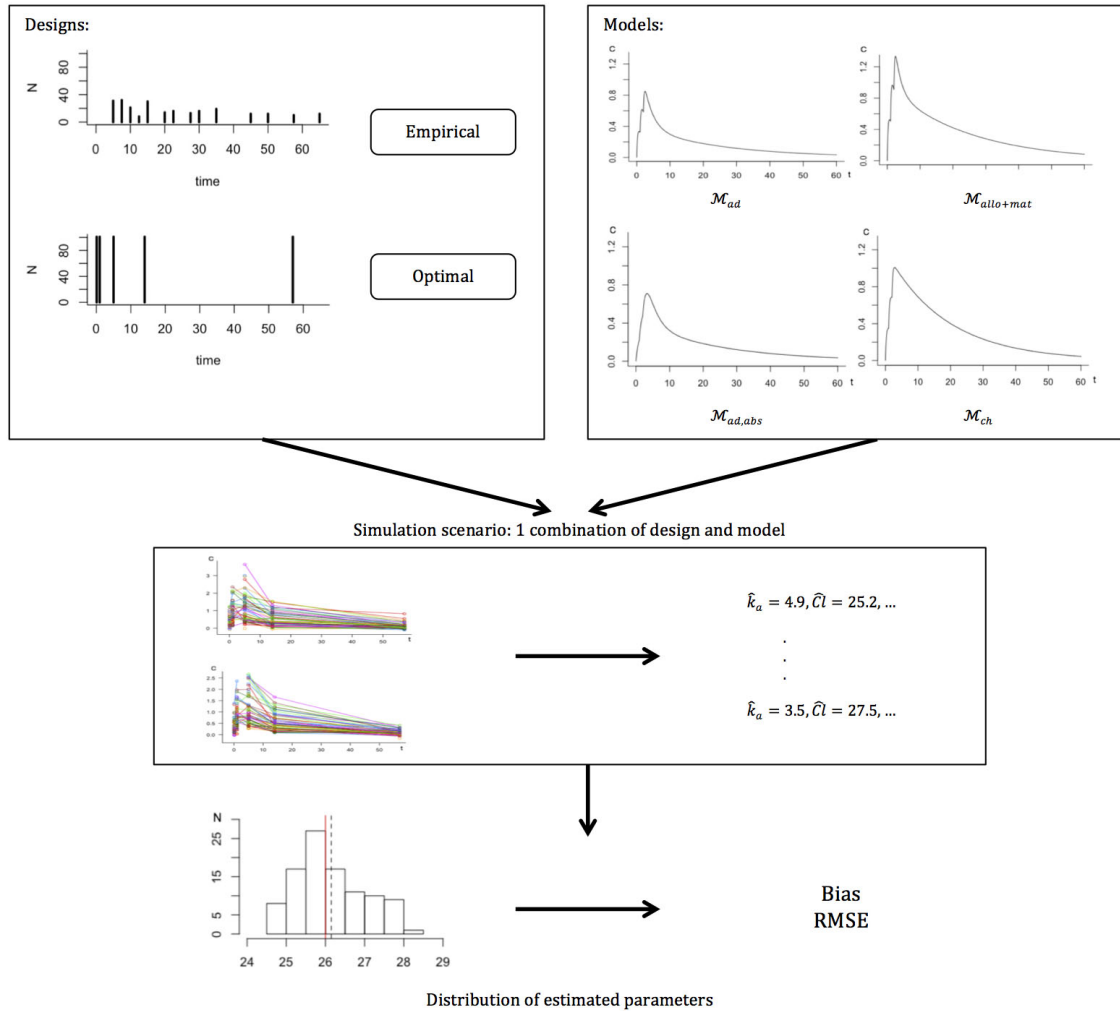
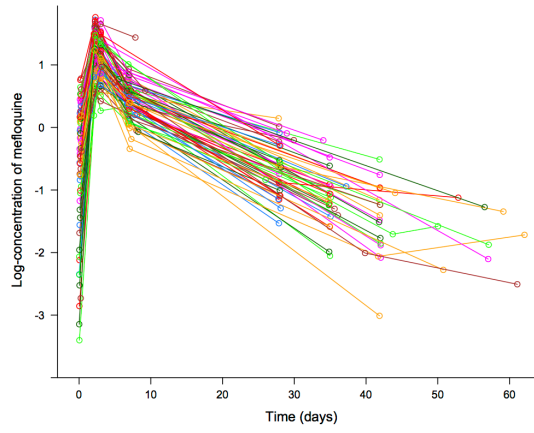
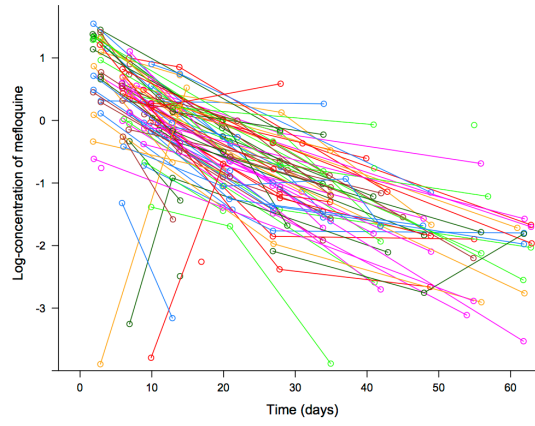


Figure 2 – Schema of simulation study. For both the optimal design and the empirical design from the paediatric database, and for each model tested, 100 datasets are simulated. For each dataset, PK parameters are estimated and then compared to the theoretical value of the original model with bias and 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.

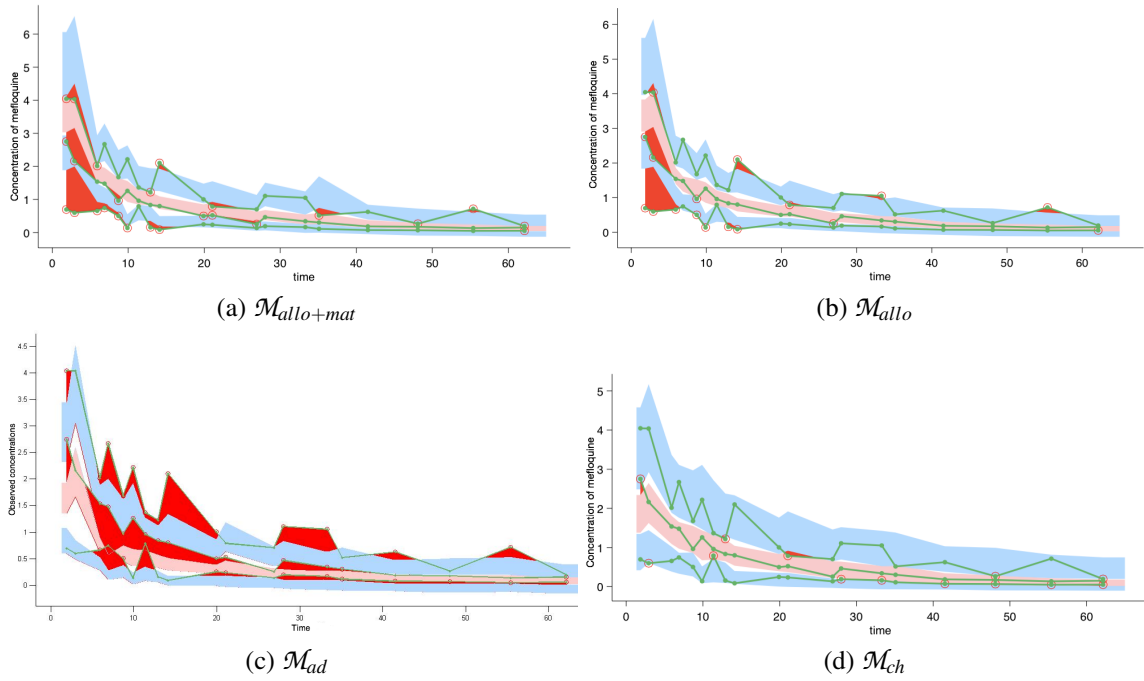


Figure 4 – Visual predictive check for extrapolation models on paediatric data

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 outliers 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.