Development of a paediatric physiologically based pharmacokinetic model to assess the impact of drug-drug interactions in tuberculosis co-infected malaria subjects: a case study with artemether-lumefantrine and the CYP3A4-inducer rifampicin

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ABSTRACT

The fixed dosed combination of artemether and lumefantrine (AL) is widely used for the treatment of malaria in adults and children in sub-Sahara Africa, with lumefantrine day 7 concentrations being widely used as a marker for clinical efficacy. Both are substrates for CYP3A4 and susceptible to drug-drug interactions (DDIs); indeed, knowledge of the impact of these factors is currently sparse in paediatric population groups. Confounding malaria treatment is the co-infection of patients with tuberculosis. The concomitant treatment of AL with tuberculosis chemotherapy, which includes the CYP3A4 inducer rifampicin, increases the risk of parasite recrudescence and malaria treatment failure. This study developed a population-based PBPK model for AL in adults capable of predicting the pharmacokinetics of AL under non-DDI and DDI conditions, as well as predicting AL pharmacokinetics in paediatrics of 2-12 years of age. The validated model was utilised to assess the concomitant treatment of rifampicin and lumefantrine under standard body-weight based treatment regimens for 2-5 year olds, and demonstrated that no subjects attained the target day 7 concentration (C_{d7}) of 280 ng/mL, highlighting the importance of this DDI and the potential risk of malaria-TB based DDIs. An adapted 7-day treatment regimen was simulated and resulted in 63 % and 74.5 % of subjects attaining the target C_{d7} for 1-tablet and 2-tablet regimens respectively.

KEYWORDS

Physiologically-based pharmacokinetics; malaria; tuberculosis; paediatrics; pharmacokinetics.

1. INTRODUCTION

Malaria is a deadly parasitic disease spread by female *anopheles* mosquitoes infected with *Plasmodium falciparum* [1, 2]. The World Health Organisation's (WHO) target is to eliminate malaria in 35 countries by 2030 and this has led to several measures being taken over the past few decades directed towards malaria prevention and treatment in order to reduce its prevalence and mortality rates [2]. At the turn of the millennium, the global estimate of malaria cases averaged 262 million which, by 2015, had fallen to 214 million, reflecting a decrease of 18 % [3]. Furthermore, 88 % of these malaria cases were reported in the sub-Saharan African region. Alarmingly however, within the paediatric population group 70% of the total malaria related deaths were attributed to children under five years of age [2].

In 2006, artemisinin or artemisinin derivatives were recommended by the WHO for the first line treatment of malaria in endemic areas. During every 48 hour *P. falciparum* replication period, artemether and its active metabolite dihydroartemisinin (DHA) decreases parasite load by approximately 10,000 fold [4, 5]. Artemether's oral absorption and onset of action are both rapid, with an approximate t_{max} following oral administration of two hours [6, 7]. Furthermore, oral absorption is improved following a fat-rich meal [8], with bioavailability increasing by 2-fold compared to a fasted-state in healthy volunteers [9]. Hepatic metabolism of artemether is rapid and predominantly mediated by CYP3A4, as well as CYP2B6 [5, 10, 11]. Lumefantrine is a racemic fluorine mixture possessing a chemical structure related to the arylaminoalcohol group of antimalarials such as quinine, halofantrine and mefloquine [12]. Lumefantrine is well orally absorbed but, as with artemether, demonstrates absorption pharmacokinetics which are highly variable in malaria patients [9]. As with artemether, the administration of food increases the bioavailability by 16-fold when compared to the fasted state in healthy volunteers [9]. CYP3A4 is primarily responsible for the metabolism of lumefantrine. As a result of low hepatic intrinsic clearance and negligible renal excretion, lumefantrine possess a prolonged half-life [8] of up to six days in healthy volunteers [13] [14]. Artemether is recommend for dosing in conjunction with lumefantrine (AL) as a fixed dose combination (FDC) of 20mg/120mg respectively, in six doses usually over three days (commonly at 0, 8, 24, 26, 48 and 60 hours). Typical treatment regimens for children include a similar 3 day six-dose regimen stratified based on body weight: 5-15 kg 1 tablet per dose; 15-25 kg 2 tablets per dose; 25-35 kg 3 tablets per dose and >35 kg 4 tablets per dose [15], with the latter dose primarily being the default adult dose.

Contrary to adults who possess naturally acquired immunity, children often do not, this puts them at risk of succumbing to the infection [16] and this is further complicated by possible trans-placental transmission in pregnant women leading to congenital malaria [2]. Whilst malaria is endemic to many areas of sub-Sahara Africa, other communicable diseases such as tuberculosis are also commonplace, and particularly impacts upon paediatric population groups. In 2015, there were an estimated 10 million new TB cases worldwide of which 10 % were children [17]. Worryingly, the mainstay treatments for tuberculosis, namely a FDC of rifampicin (10-20 mg/kg), isoniazid (10-15 mg/kg), pyrazinamide (30-40 mg/kg) and ethambutol (15-25 mg/kg), can directly affect CYP3A4 activity through primarily rifampicin being a strong inducer [18, 19] or isoniazid being a modrate inhibitor [19, 20]. Thus, drug-drug interactions are commonplace in patients who are likely to present with both malaria and tuberculosis making dosing strategies in paediatrics complex. Although data is sparse and the connection between malaria and tuberculosis co-infection has not been widely investigated (in contrast to HIV and tuberculosis coinfection), one study in Angola reported that the presence of malaria in patients admitted for tuberculosis as 37.5 % [21]. Furthermore, the risk of rifampicin-mediated induction in CYP3A4 expression/activity would have the potential to significantly increase the clearance of AL, as has been demonstrated in adult populations [22] and has further been contraindicated when used with strong inducers such as rifampicin [23].

However, the magnitude of this induction effect on AL pharmacokinetics has not been investigated. DDIs between antimalarials and other drugs in paediatrics are not well studied and this may impact on the clinical efficacy, and safety of antimalarial drug therapy. *In-lieu* of complex clinical studies, physiologically-based pharmacokinetic (PBPK) modelling has been used to explore the potential risk of DDIs in adults [24, 25] and paediatric populations [26-28].

The objective of the current study was to demonstrate the application of PBPK modelling to the prediction of DDI risks in malaria-tuberculosis co-infection paediatric population groups. Specifically, the potential for a DDI between the CYP3A4 inducer rifampicin and AL will be explored over 2-5 year old population groups.

2. METHODS

All population based PBPK modelling was conducted using the virtual clinical trials simulator Simcyp® (Simcyp® Ltd, a Certara company, Sheffield, UK, Version 16) using either the pre-validated in-built 'Healthy Volunteer' or 'Paediatric' population groups. The latter population group accounts for age-related changes in systems-parameters such as organ volumes, organ perfusion and ontogeny of drug metabolising enzymes[29] [30] [31] and allows for the prediction of drug behaviour in paediatric population groups . In the case of both models, population variability is accounted for by the inclusion of a variability metric (% coefficient variability) having been established from public health data bases such as the US National health and Nutrition Examination Survey (https://www.cdc.gov/nchs/nhanes/).

2.1 Study design

A four stage strategy was employed for model development and validation (Figure 1).

Step 1: this step focussed on the development of Simcyp® compound files and validation of simulations with published clinical studies. For artemether and lumefantrine, these included a study conducted in 120 adult subjects who were orally dosed the branded combination Coartem® [69], and studies conducted in 16 subjects who were orally dosed the branded combiantion Riamet® [32]. For lumefantrine an additional study included a 6-dose study conducted in 17 subjects [33].

Step 2: this step focussed on the validation of the adult DDI predictions. CYP3A4 inhibition and induction mechanisms were simulated using ketoconazole and rifampicin respectively. Clinical studies demonstrating such a DDI were obtained from Lefèvre *et al* who studied AL with ketoconazole [32] (single dose of 80/480 mg of AL and 5 day treatment with ketoconazole) and Lamorde *et al* [34], who studied AL DDI with rifampicin where rifampicin was dosed at 10 mg/kg for the duration of the study with AL dosed as six 80/480 mg doses (12 hourly) on days 8, 9 and 10.

Step 3: this step focussed on the validation of artemether and lumefantrine model predictions in paediatrics. In these studies, weight bandings were simulated based on dosing strategies for AL if the clinical study did not use a weight normalised dosing method. Dosing boundaries were set at 1 tablet for 5-14.9 kg, 2 tablets for 15-24.9 kg and 3 tablets for 25-34.9 kg and trials were run to ensure, where possible, an equal proportion of subjects were included into each distribution banding based on the total number of subjects recruited within each reported trial.

Simulated profiles were body weight stratified and analysed accordingly. Clinical studies used are detailed the results section 3.3 and 3.4.

Step 4: this step focussed on simulations to predict the impact of rifampicin-mediated DDIs on artemether and lumefantrine pharmacokinetics in children of 2-5 years of age over a weight boundary of 5-14.9 kg or 15-24.9 kg. In these simulations, trials of 100 subjects were simulated and analysed with appropriate weight-based dosing (see above) and under treatment of rifampicin with AL.

For all validation steps, unless otherwise stated, all observed data sets were obtained from 'supervised' administration groups in reported clinical studies and simulated under 'fed' conditions. Furthermore, unless otherwise stated all simulations included subjects of ≥ 5 years

2.2 Artemether-lumefantrine model development

The physicochemical and pharmacokinetic parameters required to describe the pharmacokinetic properties of artemether, lumefantrine and isoniazid are detailed in table 1. For artemether, literature- reported isozyme specific hepatic intrinsic clearances were utilised for the description of drug metabolism (Table 1). For lumefantrine, the isozyme specific hepatic intrinsic clearance (CL_{int}) was back-calculated using the Simcyp® retrograde calculator from the oral clearance and assuming CYP3A4 was the predominant isozyme for lumefantrine metabolism[6]. This approach is essential in order to mechanistically model DDIs.

Where necessary, the human jejunal effective permeability (P_{eff}) and Kp scalar were further optimised for AL using a parameter estimate method within Simcyp® to yield optimal estimates for the absorption (P_{eff}) and tissue distribution/Vss prediction (Kp scaler). Furthermore, for artemether, where necessary, the *in-vitro* metabolic clearance was optimised through the parameter estimation of the Inter System Extrapolation Factor (ISEF) (Table 1).

Rifampicin and ketoconazole compounds were used in simulations without modification from the library of pre-validated drug molecules within the Simcyp® simulator, using a 1st-order absorption model and assuming dosing in solution form. Where Simcyp® ADAM (Advanced Dissolution Absorption Model) was used, an immediate release formulation with an applied diffusion layer model was utilised for modelling with literature-reported solubility parameters included. Where simulations were performed in paediatrics, all APIs were assumed to be dosed in solution form, mimicking the dispersible/crushed application of AL in paediatric subjects [15].

2.2.1 Artemether-lumefantrine DDI model development

The successful development and validation of AL compounds within Simcyp® was followed by assessing the ability to predict DDIs in adults and paediatrics. All adult DDI simulations were, where possible, run identically to the reported clinical study with which the validation was conducted against, and primarily included matching age ranges, male-to-female ratios and identical dose/dosing intervals. In order to validate the capability of the model to predict a broad range of DDIs, the prevalidated Simcyp® in-built compounds ketoconazole and rifampicin were directly utilised in simulations as candidates to simulate CYP3A4 inhibition DDIs (ketoconazole) and CYP3A4 induction DDIs (rifampicin).

A previously validated isoniazid compound file [35] was used for all rifampicin DDI simulations to account for the impact of isoniazid mediated CYP3A4-inhibition associated with TB chemotherapy. All simulations included both rifampicin (as the primary perpetrator) and isoniazid (as the secondary perpetrators), however results are presented for the key interactions between AL and rifampicin only, and reflects the clinical net effect of CYP3A4 induction with the clinical use of the combination of rifampicin and isoniazid in DDI-focussed studies [36-38].

For paediatric DDI simulations (Step 4), a 100 subject simulation was run in a 10x10 trial (10 subjects per trial with 10 trials) to ensure that reasonable inter-/intra individual variability is captured within the model simulations. However, as simulations are not possible with defined age and weight ranges, pooling and post-processing of output data was conducted to match individuals to the required age-weight boundary conditions for the study.

Table 1. Input parameter values and predicted PBPK values for use in the simulation of artemether, lumefantrine and isoniazid.

Parameters	Artemether	Lumefantrine	Isoniazid[d]
Compound type	Monoprotic base	Diprotic base	Monoprotic base
Molecular weight (g/mol)	298.4[39]	528.94[39]	137.1
Log P	3.53[40]	8.70[41]	-0.7
fu	0.05[42]	0.003 [42]	0.95
pKa 1	3.9[39]	14.1[39]	1.82
pKa 2	-	9.80[39]	-
B/P	0.55[a]	0.80[43]	0.825
Vss (L/kg)	1.77[b]	0.70[b]	0.63[a]
P_{eff} (10^{-4} cm/s)	3.67[a]	0.97[a]	10.23[a]
Kp scalar	0.21[a]	0.10[a]	-
Solubility (mg/mL)	0.012[44]	0.002[45]	-
CL_{po} (L/min)	-	0.25[7]	12
$CLint_{3A4}$ (µL/min/pmol)	1.47[11]	2.61[a,c]	-
$CLint_{2B6}$ (µL/min/pmol)	9.31[11]	-	-
ISEF CYP 3A4	2.424[a]	-	-
ISEF CYP 2B6	1.697[a]	-	-
Ki (µM)	-	-	36[20]
K_{inact} (min^{-1})	-	-	0.08[20]
Kapp (µM)	-	-	228[20]
Absorption model	ADAM	ADAM	1st order
Distribution model	Full	Full	Minimal

[a] Parameter estimated; [b] Simcyp® mechanistic prediction; [c] Simcyp® retrograde calculation from population estimates of CL_{po} followed by parameter estimation (final optimised value: 0.85 µL/min/pmol for CYP3A4); [d] Unless otherwise detailed data was obtained from Gaohua *et al* (2015) [46]. MW: Molecular weight; P_{eff}: human effective permeability; B/P: blood-to-plasma ratio; CLint: *in vitro* intrinsic clearance; Vss: Steady state volume of distribution; ISEF: Intersystem extrapolation factor for scaling CYP *in-vitro* kinetic data; Ki: concentration of inhibitor supporting half-maximal inhibition; K_{inact}: inactivation rate of the enzyme; K_{app}: concentration of mechanism based inhibitor associated with half-maximal inactivation rate.

2.3 Predictive performance

Whilst no agreed criterion has been suggested for an 'optimal' predictive performance range, it is generally considered that a prediction to within 2-fold of the observed data is acceptable [47]. Given the wide inter-subject variability in artemether pharmacokinetics, we selected this 2-fold range (0.5-2.0) as our criterion for comparing C_{max} and AUC parameters between model predictions and those clinically reported. Where a DDI was simulated, the model performance was primarily dictated by a comparison of the AUC ratio (ratio of AUC in the absence and presence of the perpetrator agent) (AUC_r), with a prediction of AUC_r to within 2-fold of the reported AUC_r being considered as acceptable, with an AUC_r greater than 1.25 being indicative of an inhibition reaction whereas an AUC_r less than 0.8 indicating an induction reaction whilst an AUC ratio of between 0.8 – 1.25 indicating no interaction.

2.4 Data analysis

Unless otherwise stated, all simulations of plasma concentration-time profiles were presented as arithmetic mean and 5-95th percentiles. In circumstances where reported concentration-time profiles did not provide corresponding tabulated summary data, the observed data points were retrieved using the WebPlotDigitizer v3.10 [48] and superimposed onto simulated profiles for visual predictive checks.

3. RESULTS

3.1 Step 1: Predictive performance for artemether-lumefantrine models for adults

Following optimisation of parameter estimates (Table 1) the predicted population plasma concentration profile for both artemether and lumefantrine were within the observed trial means for plasma concentration profiles. The model predicted C_{max} values were within 2-fold of the reported C_{max} for each clinical study for both artemether (139.1 ± 116.2 ng/mL; table 2; figure 2A) and lumefantrine (single dose: 6.31 ± 3.72 µg/mL; six dose: 9.56 µg/mL; range: 5.67-16.78 µg/mL; table 2; figure 2B and 2C). The 24 h, 48 h, 72 h and day 7 lumefantrine concentrations were also predicted to within 2-fold of those reported by Ashley *et al* [33].

Similarly, the model predicted AUC_{last} for artemether (521.2 ± 254.1 ng/mL.h) (Table 2) and lumefantrine (single dose: 251.4 ± 1.45 µg/mL; six dose $AUC_{0-\infty}$: 387.4 µg/mL.h (98-1157 µg/mL.h) (Table 2) were within 2-fold of the reported AUC_{last}.

Table 2: Summary of predicted and observed pharmacokinetic parameters of artemether and lumefantrine in healthy adults

		Prediction	Lefevre et al 2013[49]	Lefevre et al 2002[32]	Ashley et al 2007[33]
Artemether	**Dose (mg)**	80	80	80	
	Population size (n)	100	58	16	
	C_{max} (ng/ml)	139.1 ± 116.2	113 ± 69.5	104 ± 40	
	AUC_{last} (ng/ml.h)	521.2 ± 254.1	408 ± 209	302 ± 135	
Lumefantrine	**Dose (mg)**	480	480	480	
	Population size (n)	100	58	16	
	C_{max} (µg/ml)	6.31 ± 3.72	8.92 ± 3.18	7.91 ± 3.49	
	AUC_{last} (µg/ml.h)	251.4 ± 112.3	236 ± 93	195 ± 119	
Lumefantrine[a]	**Dose (mg)**	6 dose regimen			6 dose regimen
	Population size (n)	100			17
	C_{max} (µg/ml)	9.56 (5.67-16.78)			6.89 (3.69-13.19)
	C_{24h} (pre-dose)	3.39 (1.98-9.28)			2.53 (0.68-9.8)
	C_{48h} (pre-dose)	5.81 (1.48-13.14)			3.84 (1.91-6.80)
	C_{72h} (pre-dose)	5.84 (1.12-12.75)			3.91 (2.15-9.64)
	C_{d7}	0.32 (0.11-0.78)			0.35 (0.20-0.87)
	$AUC_{0-\infty}$ (µg/ml.h)	387.4 (98-1157)			432 (308-991)

Data represent mean ± SD or mean (range).

[a] Concentrations measured at 24, 48 and 72 hour immediately pre-dose are labelled by the subscript time (hour) nominals, with all concentrations units express as µg/ml. C_{d7} indicates the 7th day concentration.

3.2 Step 2: Simulation of the AL DDIs following exposure to ketoconazole and rifampicin

The artemether and lumefantrine compound files were further assessed for the ability to recapitulate the literature reported extent of DDIs on plasma concentration profiles in adults.

Predictions for inhibition-based DDIs with artemether and ketoconazole resulted in predicted plasma-concentration profiles for the simulated population within the observed range reported by Lefevre *et al* 2002 [13] (Figure 3A). The predicted C_{max} ratio was 2.49 ± 0.51 compared with a reported ratio of 2.24 and predicted AUC_r was 2.96 ± 0.80 compared to a reported ratio of 2.51 (Table 3).

Predictions for inhibition-based DDIs with lumefantrine and ketoconazole, resulted in plasma-concentration profiles for the simulated population within the observed range reported by Lefevre *et al* 2002 [13] (Figure 3B). The predicted C_{max} ratio was 1.16 ± 0.89 compared with a reported ratio of 1.26 and predicted AUC_r was 2.10 ± 0.54 compared to a reported ratio of 1.65 (Table 3).

Table 3: Summary of predicted and observed pharmacokinetic parameters of artemether and lumefantrine in the absence and presence of ketoconazole in healthy adults

		-Ketoconazole		+Ketoconazole		Ratio	
		C_{max} (ng/mL)	AUC[a] (ng/mL.h)	C_{max} (ng/mL)	AUC[a] (ng/mL.h)	C_{max}	AUC
Artemether	**Predicted**	71.2 ± 62.7	316.2 ± 96.05	171.39 ± 115.21	911.24 ± 324.60	2.49 ± 0.51	2.96 ± 0.80
	Observed	104 ± 40	302 ± 135	225 ± 77	718 ± 279	2.24	2.51
Lumefantrine	**Predicted**	5476 ± 2168	118211 ± 57079	6305 ± 2432	235041 ± 97260	1.16 ± 0.89	2.10 ± 0.5
	Observed	7910 ± 3490	195000 ± 119000	10100 ± 4740	312000 ± 181000	1.26	1.65

[a] Artemether: $AUC_{(0-\infty)}$; lumefantrine: $AUC_{(0-last)}$

Data represent mean ± SD.

For induction based DDI studies, only one clinical study was identified with rifampicin mediated DDIs reporting the impact on both artemether and lumefantrine in the same subjects [22]. However, due to the small clinical study size (6 subjects) and narrow age and weight range used in the study, we simulated a virtual clinical trial of 10 trials consisting of 10 subject per trial within the weight and age boundaries reported by Lamorde *et al* [22]. As there was no direct way to specify an age boundary, the trials containing at least 6 subjects within the correct weight boundaries were selected for study and subsequent analysis.

Predictions for induction-based DDIs with artemether and rifampicin were validated against a single study reporting a single time point artemether concentration at 12-hours (C_{12h}) post final dose [22] in six subjects in the absence and presence to subjects taking a FDC for tuberculosis which included rifampicin [22]. Predicted C_{12h} was 3.56 ± 3.13 ng/mL which reduced to 0.77 ± 1.14 ng/mL in the presence of rifampicin, and was within 2-fold of the reported C_{12h} of 0.5 ± 1 ng/mL (Figure 4A).

Predictions for induction-based DDIs with lumefantrine and rifampicin were validated against a single study reporting a single time point lumefantrine concentration on the 8th day after initiating lumefantrine dosing (C_{d8}) (7.3 days' post first dose). Using this approach, the predicted C_{d8}, 59.83 ± 24.86 ng/mL, was within 2-fold of the observed reported C_{d8} of 107.75 ± 19.58 ng/mL [22] (Figure 4B).

3.3 Step 3: Predictive performance for artemether in children

The majority of clinical studies assessing AL pharmacokinetics in children often focus on the longer-half life drug lumefantrine. Existing arthemeter clinical studies are sparse and include either sampling around the expected C_{max} (1-2 hours) [50, 51] or limited large population based sampling approaches [10], with dosing based on the body weight stratification.

The model predicted mean artemether plasma concentration for the lower doses (221.25 µg/mL ± 104.51 µg/mL) and higher doses (293.51 ± 98.62 µg/mL) were within the 2-fold of the literature reported plasma concentrations for both lower (150 ± 206 µg/mL) and higher doses (196 ± 204 µg/mL) (Figure 5A) [50].

Similarly when using a single lower dose and stratifying further for weight into 5 < 10kg and 10 to < 15 kg, the reported concentrations for the lower and higher weight banding, 295 ± 214 µg/mL and 137 ± 111 µg/mL, were within the 5th and 95th percentiles of the mean prediction profiles (Figure 5B), with a predicted mean concentration (mean of 1 and 2 hour time points)

of 225.59 ± 187.27 µg/mL for the lower weight boundary and 238.84 ± 187.12 µg/mL for the higher weight boundary [51] (Figure 5B).

To confirm a successful model prediction of the distribution and elimination phases of artemether pharmacokinetics, Figure 5C illustrates model predicted concentration-time profiles for artemether dosing at the lowest (5-14 kg) and highest (25-34 kg) doses, where observed sampling points were obtained from a population study reported by Hietala *et al* (2010) [10] at 2, 4, 8, 16, 24, 36, 48 and 60 hours. The predicted profile for each dosing band fell within the range reported by Hietala *et al* [10]. However, due to the well documented variability in the absorption phase of artemether, the predicted concentrations during the absorption phases (0-4 hours) were slightly over-predicted.

3.4 Step 3: Predictive performance for lumefantrine in children

Lumefantrine is often studied, in preference to artemether, in clinical trials due its longer half-life [13] [14], and a range of clinical studies are available to support PBPK-based model development where 7-day post-dosing concentration (~280 ng/mL [7]) is used as a marker of successful 'target' concentration to obtain parasite clearance.

To validate the lumefantrine compound we first assessed the predictive performance against two studies reporting mean plasma concentration through the study duration period. Based on a study by Borrman *et al* (2010) [8] where mean ± SD plasma concentration data was available for 30, 54, 66, 84 and 168 hours post first dose, the $CL_{int,3A4}$ was optimsied to 0.71 and Kp scaler optimised to 0.05 (Vss: 0.53 L/kg). Using this revised lumefantrine compound file, we are able to capture the 4 time-points reported by Borrmann *et al* over the 3 doses stratification used (Figure 6A).

This optimised compound file was then applied to all subsequent simulations, and was confirmed with a second study reported by Piola *et al* [52] where 5-14 year olds were simulated with appropriate weight-based dosing, and where observed mean ± SD plasma concentration data was available for day 3 and day 7 (Figure 6B). Day 3 predicted concentration was 7958 ± 2381 ng/mL and 8246 ± 5478 ng/mL for the 5-15 kg and 15-25 kg doses, and day 7 predicted concentrations of 658.5 ± 289 ng/mL and 718.9 ± 554 ng/mL for the 5-15 kg and 15-25 kg doses. The observed day 3 (7050 ± 3560 ng/mL) and day 7 (376 ± 217 ng/mL) mean plasma concentration were within 2-fold of the predicted mean concentrations, in addition to being within the 5^{th} and 95^{th} percentiles of the mean lumefantrine predicted plasma concentration for the two weight-based doses (Figure 6B).

This optimised compound file was further utilised to assess the predictive performance for median day 3 and day 7 (predominantley) concentrations (Table 5), and was able to capture day 3 and day 7 concentrations to within 2-fold of those reported in clinical studies.

Table 4: Summary of simulated and observed median day 3 or day 7 lumefantrine concentrations in children

Study	Notes	Observed		Simulated	
		Median Concentration [Range] (ng/mL)			
		Day 3	Day 7	Day 3	Day 7[a]
Mayxay *et al* (2004) [53]	n=77; 95% CI reported	-	520 [390–650]	-	1 dose: 374.12 [0.1-2341] 2 doses: 392.32 [0.1-4719] 3 doses: 411.12 [0.3-4853]
Schramm *et al* (2013) [54]	n=139; IQR reported; ACRP results	-	356 [211-547]	-	1 dose [b]: 368.43 [37-885]
Ngasala *et al* (2011) [55]	n=177; Range reported	-	205 [0-1887]	-	1 dose: 392.15 [0.12-6785] 2 doses: 408.29 [0.13-7511]
Borrmann *et al* (2011) [56]	n=15; Range reported from 2005-2006 study	-	536 [178-3270]	-	369.89 [c] [0.1-5028]
Checchi *et al* (2006) [57]	n=70; Range reported in supervised group in under 5 years	7050 [1876-14985]	367 [0.12-768]	4877 [1678-25285]	1 dose: 389.752 [0.1-7544] 2 doses: 347.93 [0.3-8641]

[a] Simulated day 7 median concentrations were predicted following dosing based on body-weight stratification as a result of the lack of clear age-weight dosing strategies detailed in the observed studies.

[b] Observed study demographics required single dose of AL based on weight

[c] Dosed as 12mg/kg

3.5 Step 4: Simulating the impact of rifampicin-mediated CYP3A4 induction on artemether and lumefantrine pharmacokinetics in children

The presence of tuberculosis is thought to occur in at least 37.5 % of subjects infected with malaria [21], and given the potential for TB treatments to attenuate CYP-mediated drug metabolism (rifampicin being a CYP3A4 inducer and isoniazid a CYP3A4 inhibitor), the potential risk in paediatrics patients is important to assess considering the ontogeny CYP3A4 expression during the first 5 years of life [26-28]. Simulations to predict the potential impact of TB treatment on subjects established on anti-malarial treatment was assessed to quantify the change in AL plasma concentrations in the absence and presence of dosing with rifampicin (and isoniazid) for subjects of 2-5 years of age with weight-based dosing (1 tablet: 5-14.9 kg and 2 tablets 15-24.5 kg) where rifampicin (and isoniazid) was dosed daily for 7 days prior to the initiation of AL.

3.5.1 Artemether

A DDI initiated with a combination of rifampicin and isoniazid significantly reduces the C_{max} for both one and two table regimens by approximately 80 %, with a calculated C_{max} ratio of 0.21 (Table 5) (Figure 7). Similarly a significant reduction in the AUC following the DDI resulting an AUC_r of 0.22 (Table 5) (Figure 7). No differences in the overall impact of the DDI between the two dosing groups was reported suggesting the magnitude of the DDI is similar across the 2-5 years' age range.

Table 5: Summary of predicted artemether pharmacokinetics in the absence and presence of a DDI in children aged 2-5 year.

	No Rifampicin		Rifampicin		Ratio	
	C_{max} (ng/mL)	**AUC (ng/mL.h)**	**C_{max} (ng/mL)**	**AUC (ng/mL.h)**	**C_{max}**	**AUC**
One	89.12 ± 78.93	563.60 ± 316.64	18.47 ± 31.18	121.53 ± 143.43	0.21	0.22
Two	210.95 ± 179.81	1127.21 ± 633.27	39.12 ± 136.37	243.06 ± 290.1	0.18	0.21

C_{max} data is from the final dose; AUC calculated from final dose to end of study period.

3.5.2 Lumefantrine

In the absence of a DDI (i.e. malaria only patients), the predicted mean day 7 concentration was above the minimum therapeutic target of 280 ng/mL (Figure 8) for both the single tablet per dose (5-14.9 kg) and two tablets per dose (15-24.9 kg) strategies, 300.49 ng/mL (range: 0.1-4442 ng/mL) and 614.37 ng/mL (range: 0.14-6485 ng/mL) respectively (Table 6).

However, in TB co-infected patients, the predicted day 7 concentration fell significantly below the therapeutic target of 280 ng/mL (Table 6) for both the single and two tablet regimens, with a resultant AUC_r of 0.41 and AUC_r 0.40 respectively (Figure 8) and no subjects presenting with a simulated day 7 concentration of > 280 ng/mL (Table 6). The potential risk for failure of AMT is therefore of significant concern in TB co-infected paediatric patients, particularly those falling into the lower body-weight stratification who would typically be younger in age and therefore more prone to treatment failure.

Given that orally administrated AL often shows absorption saturation kinetics, to overcome the risk of significant treatment failure increasing the dose of AMT administrated in each FDC would not be appropriate. We assessed the impact of increasing the duration of treatment from 3 days to 5 or 7 days on the potential impact on day 7 lumefantrine concentrations (Figure 9).

Increasing the duration of treatment to 5 days had a minimal impact on day 7 mean concentrations, with a modest increase for the single tablet to 63.63 ng/mL leading to a 11.1 % (n=5/46) increase in the subjects with day 7 target > 280 ng (Table 6) (Figure 9A). Similarly, for the two tablet treatment an increase in the mean day 7 concentration was simulated 76.93 ng/mL which resulted in an overall increase in subjects with a target concentration > 280 ng of 11.3 % (n=6/53) (Table 6) (Figure 9B).

However, for a 7-day treatment 63 % (one tablet) and 74.5 % (two tablets) of subjects demonstrated day 7 concentration in excess of 280 ng/mL (Table 6) (Figure 9A and B: lower panels).

Table 6: Summary of predicted mean day 7 lumefantrine concentrations during a 3, 5 and 7-day treatment schedule in children

Dosing	Mean C_{d7} (Range) (ng/mL) Regimen			Lumefantrine ≥ 280ng/mL[a] Regimen		
	3 day	5 day	7 day	3 day	5 day	7 day
1 tablet/NI	300.49 (0.1-4442)	1451.01 (15.2-8367)	7509.77 (79.67-12438.06)	47.8 (n=22)	86.7 (n=39)	95.6 (n=44)
1 tablet/I	18.12 (0.01-88.91)	63.63 (0.01-578.12)	329.71 (0.12-4385.12)	0	11.1 (n=5)	63 (n=29)
2 tablets/NI	614.37 (0.14-6485)	1516.07 (14.9-9656)	9748.96 (28.55-14375.5)	46.6 (n=21)	60.3 (n=32)	85 (n=40)
2 tablets/I	42.69 (0.01-154.3)	76.93 (0.02-1087.99)	704.25 (0.08-7895.21)	0	11.3 (n=6)	74.5 (n=35)

[a] Percentage (number) of subjects with $C_{d7} \geq 280$ng/mL.
3 days: 1 tablet (n=53), 2 tablets (n=45); 5 days: 1 tablet (n=46), 2 tablets (n=53); 7 days: 1 tablet (n=46), 2 tablets (n=47).
NI: no interaction; I: interaction. C_{d7}: mean day 7 concentration.

4. DISCUSSION

The study of pharmacokinetics in paediatric population groups is often neglected for many therapeutic agents because of complexities in ethical/legal and recruitment strategies coupled with the requirement for limited sample collection and often diverse population based data analysis.

Although allometric scaling remains a useful tool for first predictions of primary pharmacokinetics parameters such as Vss or clearance [58, 59] it can often fail for example in the prediction of clearance [60-63]; when assessing dosing-optimisation strategies in paediatrics [30]; in situations where body weight may be significantly variable based on geographical locations [64]. Further allometry often does not address the impact of maturation at early ages of childhood and can often over-predict clearance during the maturation of metabolic elimination pathways [65]. However PBPK modelling can often be used to support population modelling approaches with deviations in covariate models can be build and based upon the mechanistic knowledge for the population to study allowing the rational extrapolation of a drug pharmacokinetics across age groups. In light of these facts, PBPK is now gaining regulatory acceptance [66-70] as one approach to assess pharmacokinetics in paediatric patients [71] and complex scenarios such DDIs [72, 73].

Although standard regimens for malaria treatment have shown positive treatment benefits with a reduction in mortality rates [2], in many developing countries with a high burden of communicable disease such as HIV/AIDS and tuberculosis, the risk potential of DDIs with co-infected malaria patients is high [21]. Such DDI issues are more apparent in children where the recruitment and inclusion of children onto antimalarial clinical trials is limited. Pragmatically assessing the risk of a DDIs in paediatrics is difficult due to CYP-ontogeny observed in key drug metabolic pathways associated the AMT metabolism, mainly CYP3A4, during the first 5 years of life [26-28], where maturation of CYP3A4 expression will lead to both altered plasma concentrations of CYP3A4-subtrates (such as AL) whilst also dynamically altering the magnitude of any CYP3A4-induction process.

Furthermore, rifampicin is a known potent CYP3A4 inducer, and therefore has the potential to lead to AMT treatment failure if the AMT metabolic pathway favours CYP3A4-mediated transformation.

The ultimate goal of this study was to address the potential risk associated with DDIs related to tuberculosis therapy in children between 2-5 years of age, which accommodate the lowest

dosing range (age based) for use of both AMT and rifampicin. Our modelling strategy included a 4-step approach commencing in prediction AL pharmacokinetics in adult population groups to develop and optimise compound files (Step 1 and 2) before scaling to paediatrics and conducting validation with published non-DDI clinical studies (Step 3) before finally making predictions for potential DDI risks in co-infected malaria-tuberculosis children (Step 4).

In adults, successful AL compound development (Step 1) was achieved through comparison to 3 key clinical studies quantifying both artemether and lumefantrine in each study and all predictions were within 2-fold of the reported C_{max} and AUC from clinical studies (Table 2). The large variability in the absorption phase of artemether and lumefantrine (Figure 2) was evident in the observed clinical data and the slight model over prediction may be a result of the lower limit of detection for artemether in the studies reported by Lefevre et al [49] [32] compared to that reported by Bindschedler *et al* 2002[74].

Following successful compound development, the ability of each compound file to mechanistic predict a DDI was then assessed through the use of two inbuilt Simcyp® inhibitors, namely ketoconazole (CYP3A4 inhibitor) and rifampicin (CYP3A4 inducer) (Step 2). For CYP3A4 inhibition, the model was able to recapitulate the extent of DDIs with reported plasma concentration within the predicted 5^{th}-95^{th} percentiles for the simulation for artemether and lumefantrine (Figure 3 and Table 3).

For the induction based interactions of CYP3A4 with AL, very few reports have characterised rifampicin mediated DDIs and we utilised a study reported AL concentration within the same subjects [22]. Under these circumstances, the model predicted 12-hour post final dose concentration (artemether) and day 8 concentration (lumefantrine) was similar (within 2-fold) to that reported by Lamorde *et al* [22]. Steps 1 and 2 demonstrate the ability of the development AL model compounds to capitulate pharmacokinetic parameters reported from a range of non-DDI and DDI studies, confirming successful model development.

To consider the potential impact of DDI on AL pharmacokinetic in 2-5 year olds, it was important to demonstrate the capability of the developed model to predict AL pharmacokinetics in children. To this end step 3 focussed on validation of artemether and lumefantrine in children. Artemether model predictions in children were able to capture the difference in weight based dosing strategies on the outcome pharmacokinetic profiles, both in 'single' point concentrations centred around the C_{max} (Figure 5A and B) and population based sampling over a dosing period (Figure 5C). Lumefantrine model predictions required an optimisation step and

following this optimisation procedure, observed time-point data for 30, 54, 66, 84 and 168 hours [8] and model predictions and day 3 and day 7 points [52] were within 2-fold of the simulated profiles and within the 5^{th} and 95^{th} percentiles of the mean predicted profiles (Figure 6). Lumefantrine model predictions were finally further validated using median concentration data at day 3 or day 7 (Table 4), which were found to be well predicted and within 2-fold of the reported concentrations. The approach described in Step 3 resulted in appropriate model predictions based on existing published literature detailing either single-time point or multiple-time point concentration data of AL in children.

Having established a working model for AL pharmacokinetics in adults and children, along with a working model for quantifying AL DDIs in adults, we addressed the major focus of this study, the prediction of potential AL based DDIs in children between the ages of 2-5 years of age. As expected the impact of rifampicin on the pharmacokinetics of artemether was significant, reducing both the final dose C_{max} for both one and two tablet regimens by approximately 80 % (C_{max} ratio: 0.18-0.21) (Table 5) along with an AUC_r of 0.21-0.22 for both dosing regimens.

To infer a clinical consequence of this is difficult, given the shorter half-life of artemether compared to lumefantrine. AL is a very efficacious therapy in uncomplicated malaria patients with the recommend 6-dose treatment show efficacy of 97·6% on day 28 and 96·0% on day 42 [75], however the efficacy of treatment reduces with patients receiving lower doses (an 8% decrease in patients for every 1 mg/kg decrease in dose received). However, the overall determinant of artemether–lumefantrine clinical efficacy is the area under the curve of lumefantrine [6], with day 7 concentration (~280 ng/mL) being the primary marker for successful therapy under dosing with 3-day dosing regimen.

The DDI has a detrimental effect on lumefantrine C_{d7}, significantly reducing this below the target concentration for both one and two dose treatment (Figure 8). Although data on such interactions in paediatric is lacking, Lamorde *et al* [22] have demonstrated a similar effect in adults with a significant decrease (3-10 fold) in lumefantrine concentrations during TB treatment [22].

Artemether and lumefantrine have been reported to show saturation in the absorption pharmacokinetics and it would be expected that dose increases would have a limited impact on resultant pharmacokinetics lumefantrine [33] [76]. Therefore, to overcome the DDI-based decrease in C_{d7}, an increase in the dose administrated would not be viable for increasing C_{d7}.

We then simulated the impact of a change in dosing frequency would influence the plasma concentration of AL, and whether an increase in C_{d7} would be evident.

Whilst a 3-day treatment is viable for patient compliance, day 7 concentration in malaria-TB co-infected children are significantly lower than this target concentration. An increase in dosing frequency was investigated to assess the impact on the predicted target concentration. Whilst a 5-day course resulted in some modest increase in the percentage of subjects with a C_{d7} > 280ng/mL (~11% increase), this increase was far greater for a 7-day treatment regimen with ~63-75% of subjects demonstrated C_{d7} > 280ng/mL across both dosing bandings (Table 6). A recent population pharmacokinetic study by Hoglung *et al* (2015) [77] assessed the potential for DDI with malaria-HIV co-infected adult patients. In prospective simulations they demonstrated a similar beneficial effect of an increase in dosing frequency to counteract the induction effect of antiretroviral on malaria (AL) treatment regimens.

Whilst the impact of this will require prospective clinical analysis, it is suggested that an increase in the dosing frequency for children who are co-infected with malaria and TB and subjected to TB chemotherapy, including rifampicin, may benefit from an increase in treatment duration to 7 days to full ensure parasite clearance. Our results have demonstrated that children aged 2-5 years of age are susceptible to significant DDI when being co-treated with TB chemotherapy, which directly impacts upon the potential for AL therapy failure.

Challenges remain however, the impact of non-adherence to designated treatment regimens would render the impact of the induction effect as variable and unpredictable [78]. However, given the erratic absorption of lumefantrine (and artemether) [79], the extension of a dosing regimen from 3 to 5 days would not alter the peak concentrations significantly (Figure 9) and would be within this erratic absorption range absorption range (Figure 6).

Furthermore, it should be noted that simulations were performed in healthy subjects in our simulations, and therefore we have assumed that any physiological changes associated with malaria are negligible and does not impact upon the extent of the DDI in our simulation trials.

Malaria patients are susceptible to reduced albumin and α1-acidic glycoprotein, which can directly impact upon the extent of plasma protein binding and therefore exposure of AL to metabolic extraction with reports demonstrating a decrease of ≥ 30 % of serum albumin, (≤ 35 g/L) [80-82]. For highly protein bound drugs, such as lumefantrine, any change subsequent changes in the extent of protein binding (e.g. reduce binding due to reduced serum protein) will

inevitably increase the unbound drug fraction and potentially enhance both drug tissue distribution along with metabolic clearance.

The potential impact of such a change was assessed in 2-5 year olds (1 tablet per dose over the 7 day optimised regimen) (Figure 10) and demonstrated that a modest increase in $fu_{,plasma}$ from 0.003 to 0.005, results in all subjects possessing a C_{d7} of just below the target < 280 ng/mL subjects (when considering the range of simulated values). Furthermore a 10-fold increase in $fu_{,plasma}$ (0.003 to 0.03) yields C_{d7} which would be irreconcilable by dosing adjustments.

In adults, it has been noted that changes in body weight (malnutrition) and potentially changes which can impact upon absorption, distribution, metabolism and excretion. Nevertheless, our dosing range for the age selection (5-15kg and 15-25kg) is broad enough to simulate the impact on potential underweight children who are within the simulated age range (2-5 years).

Interesting, a clinical trial is on-going [83] to assess the impact of an increased treatment frequency to 5 days for AL, the outcomes of which may support the requirement for an increase in dosing frequency for patients subjected to induction-based DDIs.

5. CONCLUSION

The WHO have highlighted the increased risks of mortality children face with malaria infection [2, 3] and coupled with the innate complications of co-infection with tuberculosis, children are at significant risk of potential drug-drug interactions in many areas of sub-Sahara Africa which may inadvertently impact upon parasite clearance. Whilst clinical studies exploring this risk of DDI in co-infected paediatric population groups are sparse, mechanistic population-based PBPK modelling provides a potential approach to assess this risk-potential. The pharmacokinetics of artemether and lumefantrine has been simulated for two-body weights in children ages 2-5 years old, who would be a greater risk of mortality associated with both malaria and tuberculosis. We demonstrated that an extension of the current recommend dosing range for AL, from 3 to 7 days, would counteract the potential rifampicin-mediated induction on lumefantrine (and artemether) metabolic clearance and yields a significantly greater proportion of subjects attaining a target lumefantrine concertation thereby preventing recrudescence and potential mortality.

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List of Figures

Figure 1

Model development strategy.

Figure 2

The simulated plasma concentration-time profile of artemether and lumefantrine.

Simulation of (A) artemether and (B and C) lumefantrine plasma concentration-time profile following a single oral dose of 80mg (artemether) (A), a single oral dose of 480 mg (lumefantrine) (B) and a six-dose three-day regimen (lumefantrine) (C) [29]. For all simulations a standard population size of 100 individuals was used. Solid line represents population mean prediction with dashed lines representing the 5^{th} and 95^{th} percentiles of prediction. Mean observed plasma concentrations represented by the solid circles [28] and diamonds [42].

Figure 3

The simulated plasma concentration-time profile of artemether and lumefantrine in the absence and presence of ketoconazole

(A) Artemether was dosed as a single 80 mg oral dose in the absence and presence of ketoconazole, dosed as a single 400 mg oral dose over a 24-hour period under fed-conditions. Open circles represent observed mean data points [13]. (B) Lumefantrine was dosed as a single 480 mg oral dose in the absence and presence of ketoconazole, dosed as a single 400 mg oral dose over a 24-hour period under fed-conditions. Open circles represent observed mean data points [13]. Solid line represents population mean prediction with shaded regions representing the 5^{th} and 95^{th} percentiles of prediction (grey: no interaction; red: interaction).

Figure 4

The simulated plasma concentration-time profile of artemether and lumefantrine in the absence and presence of rifampicin.

(A) Artemether was dosed as 6 doses (80 mg per dose) over 3 days (on days 8-10) of a 14-day trial with rifampicin dosed at 10 mg/kg once daily during the duration of the trial. Isoniazid was also dosed at 10 mg/kg and used as a secondary perpetrator in light of its inclusion in anti-Tb therapy. Open circle represents observed mean 12-hour post final dose concentration ± SD [22]. Solid line represents population mean prediction with shaded regions representing the 5^{th} and 95^{th} percentiles of prediction (grey: no interaction; red: interaction). (B) Lumefantrine was dosed as 6 doses (480 mg per dose) over 3 days (on days 8-10) of a 14-day trial with rifampicin dosed at a dose of 10mg/kg once daily and isoniazid (secondary perpetrator) administered at a dose of 5mg/kg during the duration of the trial. Open circles represent observed mean day 8

concentration (7.3 hours after final dose) ± SD [22]. Solid line represents population mean prediction with shaded regions representing the 5th and 95th percentiles of prediction (grey: no interaction; red: interaction). Dashed line represents minimum effective parasite clearance plasma concentration for lumefantrine (280 ng/mL).

Figure 5

The simulated plasma concentration-time profile of artemether in paediatrics.

Six doses of artemether were administered at 0, 8, 24, 36, 48 and 60 hours based on patient weight (20 mg: 5-15 kg or 40 mg: 15-25kg). Shaded regions between 1-2 hours indicates observed sampling times (1-2 hours). (A) Red circle and black square are observed data from subjects receiving the lower dose and higher doses respectively [45] with red and black solid lines indicating mean profiles with 5th and 95th percentiles illustrates by dashed coloured lines. (B) Circle and triangle symbols are observed data from subjects receiving the lower dose but stratified for body weight [44] with red solid line indicating mean profile for the lower weight range and black solid line indicating mean profile for the higher dose range. Dashed lines indicate 5th and 95th percentiles. (C) Black line represents simulated lower doses (5-14 kg) and red line represents simulated highest dose (25-34 kg). Observed data points are represented by solid red circles [10] with red and black solid lines indicating mean profiles with 5th and 95th percentiles illustrated by dashed coloured lines.

Shaded regions representing the 5th and 95th percentiles range of the prediction

Figure 6

The simulated plasma concentration-time profile of lumefantrine in children.

(A) Blue, green and black solid lines indicate 1 (5-14.9 kg), 2 (15-24.9 kg) or 3 (25-34.9 kg) tablet dosing regimens respectively. Upper and lower dashed lines represent the 95th percentile for the 360 mg (3 tablet) dose and 5th percentile for the 120 mg (1 tablet) dose, respectively. Red circles represent mean population observed concentrations reported in Borrmann *et a*l (2010) [8]. (B) Black and green solid lines indicate increasing doses of lumefantrine (1 tablet: 5-14.9 kg); 2 tablets 15-24.9 kg). Upper and lower dashed lines represent the 95th percentile for the 240 mg dose and 5th percentile for the 120 mg dose, respectively. Red circles represented mean population observed concentration reported in reported by Piola *et al* (2005) [46].

Figure 7

The simulated mean plasma concentration-time profile of artemether in paediatrics in the absence and presence of a DDI.

Artemether plasma concentrations following dosing with 1 tablet (5-14.9kg) or 2 tablets (15-24.5kg) to children (2-5 years). Solid lines represent clinical trials with artemether alone. Dashed lines represented artemether dosing with rifampicin (10mg/kg). One tablet doses are indicated in black and two tablet doses in blue. Isoniazid was also dosed at 10 mg/kg and used as a secondary perpetrator in light of its inclusion in anti-Tb therapy

Figure 8

The simulated mean plasma concentration-time profile of lumefantrine in paediatrics in the absence and presence of a DDI for a standard 3 day regimen.

Lumefantrine plasma concentrations following dosing with 1 tablet (5-14.9 kg) or 2 tablets (15-24.5 kg) to children (2-5 years). Solid lines represent clinical trials with lumefantrine alone. Dashed lines represented lumefantrine dosing with rifampicin (10 mg/kg). Isoniazid was also dosed at 10 mg/kg and used as a secondary perpetrator in light of its inclusion in anti-Tb therapy.

Figure 9

The simulated mean plasma concentration-time profile of lumefantrine in paediatrics in the presence of a DDI for an adapted 5 and 7-day regimen.

Lumefantrine plasma concentrations following dosing with (A) 1 tablet (5-14.9 kg) or (B) 2 tablets (15-24.5 kg) to children (2-5 years) in the presence of rifampicin (10 mg/kg) when dosed for 5 days (upper panels) or 7 days (lower panels). Solid lines represent mean and dashed line represents upper and lower ranges of predicted concentrations with shaded regions representing the range of predictions concentrations. Isoniazid was also dosed at 10 mg/kg and used as a secondary perpetrator in light of its inclusion in anti-Tb therapy

Figure 10

The impact of alterations in lumefantrine plasma unbound fraction on simulated C_{d7} in paediatrics in the presence of a rifampicin-mediated DDI for a 7-day regimen (one table/dose)

Day 7 lumefantrine plasma concentrations (C_{d7}) were simulated for 56 subjects within a weight range of 5-15 kg (1 tablet/dose) in the presence of rifampicin (10mg/kg) following a treatment regimen described in section 3.5.2. Solid line represents 280 ng/mL lumefantrine 'target' concentration. Dashed lines represented simulated range (upper and lower) and C_{d7} target concentration when $fu_{,plasma}$ = 0.003. Dotted lines represented simulated range (upper and lower) concentrations when $fu_{,plasma}$ = 0.005. Isoniazid was also dosed at 10 mg/kg and used as a secondary perpetrator in light of its inclusion in anti-Tb therapy