






Evidence Based Optimal Dosing of Intravenous Artesunate in Children with Severe Falciparum Malaria

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The majority of deaths from malaria are in young African children. Parenteral artesunate (ARS) is the first-line treatment for severe falciparum malaria. Since 2015, the World Health Organization has recommended individual doses of 3 mg/kg for children weighing <20 kg. Recently, the US Food and Drug Administration (FDA) has challenged this recommendation, based on a simulated pediatric population, and argued for a lower dose in younger children (2.4 mg/kg). In this study, we performed population pharmacokinetic (PK) modeling of plasma concentration data from 80 children with severe falciparum malaria in the Democratic Republic of Congo who were given 2.4 mg/kg of ARS intravenously. Bayesian hierarchical modeling and a two-compartment parent drug-metabolite PK model for ARS were used to describe the population PKs of ARS and its main biologically active metabolite dihydroartemisinin. We then generated a virtual population representative of the target population in which the drug is used and simulated the total first-dose exposures. Our study shows that the majority of younger children given the lower 2.4 mg/kg dose of intravenous ARS do not reach the same drug exposures as older children above 20 kg. This finding supports withdrawal of the FDA's recent lower ARS dose recommendation as parenteral ARS is an extremely safe and well-tolerated drug and there is potential for harm from underdosing in this rapidly lethal infection.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

✓ For the treatment of severe falciparum malaria, the World Health Organization (WHO) recommends a 3 mg/kg dose of parenteral artesunate (ARS) for children weighing <20 kg, whereas the US Food and Drug Administration (FDA) recommends the adult dose of 2.4 mg/kg. The FDA's recommendation is based on a simulated pediatric population that overlooks the established relationship between hemoglobin and age in severe malaria.

WHAT QUESTION DID THIS STUDY ADDRESS?

✓ We performed pharmacokinetic (PK) modeling of 80 African children with severe falciparum malaria administered ARS intravenously and used the largest available database of children with severe malaria to create a virtual population to generate a more accurate estimation of drug exposure.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

✓ Our findings confirm previous PK studies regarding the relationship among drug exposure, weight, and hemoglobin, and demonstrated that children weighing <20 kg have lower dihydroartemisinin exposures.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

✓ These findings validate the WHO's recommendation to administer a higher dose of intravenous ARS (3 mg/kg) to children weighing <20 kg, which is extremely safe and well tolerated. The FDA recommendation for children to receive the same dose as adults (2.4 mg/kg) is not supported and could result in increased mortality.

In 2021, there were an estimated 619,000 malaria deaths globally with 77% of these deaths in children under 5 years of age.¹ Parenteral artesunate (ARS) has been the treatment of choice for severe *Plasmodium falciparum* (*P. falciparum*) malaria because

it was shown to reduce mortality by 22–35% compared with the previously recommended quinine.^{2,3} ARS is active against a broad range of the developmental stages of asexual malaria parasites, notably the circulating ring stages (against which quinine

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has negligible activity).⁴ Rapid killing of ring stage *P. falciparum* parasites is critical for the life-saving benefit of ARS relative to quinine as it prevents cytoadherence to vascular endothelium of parasitized erythrocytes, which causes obstruction of the microcirculation in vital organs.^{5,6}

ARS is hydrolyzed rapidly *in vivo* to its active metabolite dihydroartemisinin (DHA).⁷ DHA contributes the majority of the antimalarial activity *in vivo*. Both are cleared very rapidly with plasma elimination half-lives of < 1 hour.⁸ Speed in attaining therapeutic antimalarial concentrations is critical to the outcome of severe malaria. Delay in achieving these levels probably explains why the slowly absorbed intramuscular artemether is inferior to parenteral ARS in the treatment of severe malaria.^{9,10} In children and adults with severe malaria, the majority of deaths occur within 48 hours of starting treatment (i.e., within one asexual parasite lifecycle).^{11,12} Most of the life-saving benefit of treatment is provided by the first dose, which reduces the parasite biomass by a factor of ~ 10,000.

Population pharmacokinetic (PK) studies in children with severe malaria, and an individual patient data meta-analysis of PK studies, indicated that young children have lower exposures to ARS and DHA relative to older children.^{13,14} Based on this evidence from PK modeling of data from over 300 children and adults with severe malaria, the World Health Organization (WHO) has recommended parenteral ARS treatment doses of 3 mg/kg for patients weighing < 20 kg (i.e., over 90% of African children with severe malaria) since 2015; a 25% higher dose compared with the 2.4 mg/kg recommended for children and adults that weigh > 20 kg.¹⁵ Recently, the US Food and Drug Administration (FDA), based on simulated data by Kitabi *et al.*,¹⁶ has challenged this recommendation and suggested that younger children have higher drug exposures, and should therefore not receive an increased dose. Using a population PK model developed by Zaloumis *et al.*,¹⁴ Kitabi *et al.*¹⁶ simulated a virtual pediatric population with severe malaria using US Centers for Disease Control and Prevention (CDC) growth charts,^{17,18} and predicted slower clearance and thus increased drug exposure (area under the concentration-time curve (AUC) over 0–12 hours) in children < 10 kg. Importantly their simulations assumed that weight (and age) are independent of another important covariate, hemoglobin, which is not the case in malaria endemic countries. Younger children with severe malaria are significantly more anemic than older children and adults,¹⁹ and lower hemoglobin levels are associated with reduced DHA exposures.^{13,14} There is no evidence that ARS is toxic at doses ≤ 4 mg/kg, so revising the dose downward only risks underdosing with no associated reduction in toxicity (i.e., it can only be suboptimal).²⁰ Underdosing therefore increases the risk of preventable death.

In order to resolve the therapeutic uncertainty created by the FDA report, we first performed population PK modeling of a recent PK study²¹ of 80 pediatric patients with severe *P. falciparum* malaria in the Democratic Republic of Congo who were given 2.4 mg/kg of ARS intravenously. This analysis was performed to generate a new set of PK parameter estimates in addition to the previously available estimates from Hendriksen *et al.*¹³ and Zaloumis *et al.*¹⁴ Second, we generated a virtual population representative of the target population in which the drug is given by utilizing the data from > 25,000 children enrolled in the Severe Malaria in

Africa Children (SMAC) network²² and then simulating the first-dose exposure levels (AUC from 0 to 12 hours ($_{0-12h}$)) for DHA. This evidence-based study provides an accurate estimation of drug exposure following intravenous ARS, which is applicable to the wide age range of children impacted by severe malaria.

METHODS

Study design and participants of the Rectal Artesunate in Children with severe falciparum malaria (REACH) study

Details of the study population, study design and noncompartmental PK analysis have been described previously.²¹ Briefly, REACH was a randomized sequence crossover study to evaluate the PKs of rectal ARS compared with intravenous ARS in pediatric patients with severe *P. falciparum* malaria. This trial was conducted by the Kinshasa School of Public Health–University of Oxford Medical Research Unit (KIMORU) team at Kingasani Hospital, Kinshasa, the Democratic Republic of Congo. Children were randomized to receive either one dose of rectal ARS (10 mg/kg) on admission (time zero) followed 12 hours later by intravenous ARS (2.4 mg/kg; intravenous artesunate (IVAS) at time 12 hour arm) or the same medicines in the reverse order (IVAS at time 0 hour arm). All children also received intravenous quinine. After 24 hours, all patients continued antimalarial therapy with parenteral ARS, followed by a full standard course of artemether-lumefantrine as soon they could take oral medication. Eleven blood samples were taken at fixed intervals: pretreatment, 5, 15, 30, and 45 minutes and 1, 2, 3, 4, 6, and 8 hours after the administration of the first dose of study drug. After 12 hours, 11 blood samples were taken again at the same sampling times following the administration of the second dose of the study drug. ARS and DHA were quantified using liquid chromatography-tandem mass spectrometry²³ with the lower limits of quantification set at 1.19 and 1.96 ng/mL, respectively.

Population PK modeling

Bayesian hierarchical modeling was used to analyze the ARS and DHA concentration profiles simultaneously over time for all 80 children following administration of intravenous ARS. A two-compartment parent drug-metabolite PK model from the intravenous administration to the central compartment for ARS was considered assuming complete *in vivo* conversion of ARS into DHA^{13,24} (see [Supplementary Information S1](#)). Drug concentration profiles were transformed into molar units and modeled as natural logarithms. The drug concentration data below the limit of quantification were modeled using the M3 method.²⁵

The prior distribution for the individual-specific PK parameters was assumed to be multivariate normal (MVN), $\theta_i \sim \text{MVN}(\theta, \Omega)$, where θ_i denotes the subject-specific PK parameters of the *i*th individual, and θ the population average PK parameters. The variance-covariance matrix (Ω) was decomposed into a vector of between-subject variances for the PK parameters and a correlation matrix. The hyperprior distributions for the elements of between-subject variance parameters, correlation matrix, and residual error were half-normal (0 and 1), Cholesky LKJ correlation distribution^{26,27} with shape parameter equal to 2, and half-Cauchy (0 and 5), respectively.

The analysis was performed in R²⁸ (version 4.1.1) and Stan²⁷ (RStan version 2.21.2) using the No-U-Turn Sampler to draw samples from the joint posterior distribution of the parameter values for the population average PK, subject-specific PK, and between-subject variability parameters. For each model parameter, four chains were initialized with different starting points. For each chain, 2,000 posterior samples were retained after a warm-up of 2,000 iterations (in total, 8,000 samples were drawn from the joint posterior distribution). The calculated posterior summary statistics were the median of the 8,000 samples for each parameter (posterior median) and 95% credible interval, which is calculated as the 2.5th and 97.5th percentiles of the 8,000 samples for each parameter.

Table 1 Baseline data for 82 children with severe falciparum malaria enrolled in the REACH study

Variable	IVAS at time 12 hour	IVAS at time 0 hour
No. of evaluated patients (n)	40 ^a	42 ^a
Median age (IQR), years	4.7 (2.8, 8.1)	4.0 (2.8, 8.8)
Median weight (IQR), kg	15.3 (12.0, 25.0)	14.3 (12.0, 24.5)
Median height (IQR), cm	102.0 (89.0, 129.0); n = 39	98.0 (88.0, 131.0)
No. male (%)	21 (52.5)	20 (47.6)
No. (%) with enlarged spleen	29 (72.5)	30 (71.4)
Mean hematocrit (SD), %	21.3 (7.6)	20.6 (7.1)
Mean hemoglobin (SD), g/dL	7.1 (2.5)	6.9 (2.3)
GM parasitemia at screening (95% CI), parasites/ μ L	33,733 (15,031–75,702); n = 37	46,067 (19,484–108,920); n = 39
Mean temperature (SD), °C	38.0 (1.1)	37.9 (1.1)
No. with blood transfusion (%)	26 (65.0)	27 (64.3)

CI, confidence interval; GM, geometric mean; IQR, interquartile range; IVAS, intravenous artesunate; SD, standard deviation.

^aUnless indicated otherwise.

Several diagnostic checks were performed, including trace plots (Figure S1) and calculation of the \hat{R} statistic to evaluate whether draws from each chain had converged to a common distribution, calculation of the number of independent draws of the parameter of interest from the posterior distribution (the effective sample size), and visual assessment of the joint posterior of the PK parameters (Figure S2). To visualize the extent to which the prior information was updated by the observed data, the prior distribution and marginal posterior distribution were plotted on the same axes for the population average PK parameters (Figure S3).

Study design and participants in the SMAC network

The SMAC network enrolled parasitemic children suspected of having severe malaria into a prospective multicenter network observational study.²² The participating hospitals of the SMAC network were located in five Sub-Saharan African countries: The Gambia, Malawi, Ghana, Kenya, and Gabon. Clinical and laboratory measures were documented, and children were followed during their hospital admission. Between December 2000 and May 2005, over 25,000 children between 1 month and 15 years of age were enrolled. This is the largest openly available dataset containing the age, weight, hemoglobin, and body temperature of children with severe malaria in a malaria endemic region. Full details have been published previously.²⁹

Simulation of virtual pediatric severe malaria population to explore optimal dosing schemes

The relationships among weight, hemoglobin concentration, and temperature, and the age of the child were quantified using the SMAC dataset described above. The LMS method³⁰ was used to capture the nonlinear and heteroscedastic relationship between weight and age and hemoglobin and age. The distribution of body temperature was constant across age intervals (Figure S5). The LMS method is applied widely in anthropometric measurements for children and captures the skewness/shape (L), center (M) and variation (S) of a distribution which changes with age.^{31,32} The procedure used to estimate the LMS parameters was the Generalized Additive Model for Location Scale and Shape (GAMLSS) package in R.³³ A virtual population of 9,000,000 children was simulated with age sampled from a uniform distribution and body temperature simulated from a normal distribution with mean 38.2°C and standard deviation 2.6°C, calculated from the SMAC dataset. Body weight and hemoglobin were simulated dependent on age using the LMS parameter estimates.

Monte Carlo simulations using the PK parameters from the current analysis of the REACH study as well as those derived from studies of Hendriksen *et al.*¹³ (70 Tanzanian children treated with intra-muscular ARS—2.4 mg/kg) and Zaloumis *et al.*¹⁴ (223 patients receiving ARS intravenously—2.4 mg/kg) were used to obtain representative population estimates of the exposure levels (area under the DHA concentration–time curve from time point 0 to 12 hours) at different body weights and under different dosing loads in the virtual population. More specifically, we ran 1,000 simulations at each 1 kg interval from 3 to 40 kg with different doses of ARS: the 2.4 mg/kg dose of ARS for all ages as currently endorsed by the FDA¹⁶ and the weight-based dose, 3 mg/kg for children < 20 kg, and 2.4 mg/kg for heavier patients, currently recommended by the WHO.¹⁵ We also considered an age-related enzyme-maturation effect which accounts for the reduced ability of younger children to metabolize DHA (see Supplementary Information S2). Because there is no drug exposure target defined for parenteral ARS, the exposure in children with a body weight of 20 kg was considered as the reference for the purpose of comparing drug exposures across the body weight range and selecting a practical parenteral dosing regimen for ARS.

The computer codes for the Bayesian hierarchical population PK modeling and the virtual population generation are fully publicly available at https://github.com/aliHaghiri/IV_ARS_PKModeling_VirtualPop_Codes.git.

RESULTS

Clinical details

The REACH study included 82 pediatric patients with severe *P. falciparum* malaria in the Democratic Republic of Congo. The most common severity signs at screening were prostration (65/82, 79.3%), respiratory distress (64/82, 78.0%), coma (14/82, 17.1%), and severe anemia (25/82, 30.5%). The geometric mean peripheral blood parasite density on admission was 33,733 parasites/ μ L (95% confidence interval: 15,031 to 75,702) in the IVAS at time 12-hour arm and 46,067 parasites/ μ L (19,484 to 108,920) in the IVAS at time 0-hour arm. The mean (standard deviation (SD)) hemoglobin on admission was 7.1 (2.5) g/dL in the IVAS at time 12-hour arm and 6.9 (2.3) g/dL in the IVAS at time 0-hour arm. Demographic, clinical, and laboratory characteristics of the study population are described in Table 1.

Population pharmacokinetics of ARS/DHA in children with severe falciparum malaria (REACH dataset)

For the Bayesian population PK modeling, we included data collected from the 80 pediatric patients (2 individuals were excluded from the analysis as there were no PK data following intravenous ARS) with 11 blood samples taken at fixed intervals up to 8 hours after the administration of intravenous ARS (2.4 mg/kg). A total of 543 ARS and 755 DHA concentrations were available for analysis.

The observed drug concentration-time data were best described by a two-compartment disposition model for both ARS and DHA (see the visual posterior predictive checks in Figure 1). We also examined a one-compartment disposition model and observed a significantly lower predictive performance (see Figure S4). Note that all models for both ARS and DHA included an allometric function of body weight on the population mean clearance (CL; power of 0.75), volume of the central compartment (V ; power of 1), intercompartmental clearance (power of 0.75), and volume of the peripheral compartment (power of 1) with an additional association between hemoglobin and the population mean CL for DHA (see Supplementary Information S1). We also investigated the effect of temperature and an age-related enzyme maturation function on the clearance of DHA in our PK modeling and observed minimal

changes to the estimated PK parameters (see Table S1). The parameter estimates of the PKs of ARS and DHA for the 2-compartment disposition model fitted to the data are presented in Table 2. DHA clearance increased 3.6% (95% Credible Interval: 0.25–6.90) per unit (g/dL) of decrease in hemoglobin levels.

Derived from the estimated model PK parameters, the median (2.5th–97.5th percentiles) half-life using the distribution phase ($t_{1/2\alpha}$) for DHA was 0.40 hours (0.24–0.67) compared with 0.05 hours (0.02–0.24) for ARS. The half-life during the elimination phase ($t_{1/2\beta}$) for DHA was 1.55 hours (0.83–4.09) compared with 0.27 hours (0.13–2.27) for ARS. For the one-compartment model the estimated terminal elimination half-life ($t_{1/2}$) for DHA was 0.50 hours (0.06–0.96) compared with 0.12 hours (0.08–1.22) for ARS, although this model was not used in the final analysis as the 2-compartment model had a better fit to the data.

Simulating DHA exposures following the first dose of parenteral ARS treatment in severe falciparum malaria

To obtain realistic simulations of drug exposure for children with different body weights, we generated a virtual population representing the target population of African children with severe *P. falciparum* malaria. The relationships between the variables weight, hemoglobin, and temperature as functions

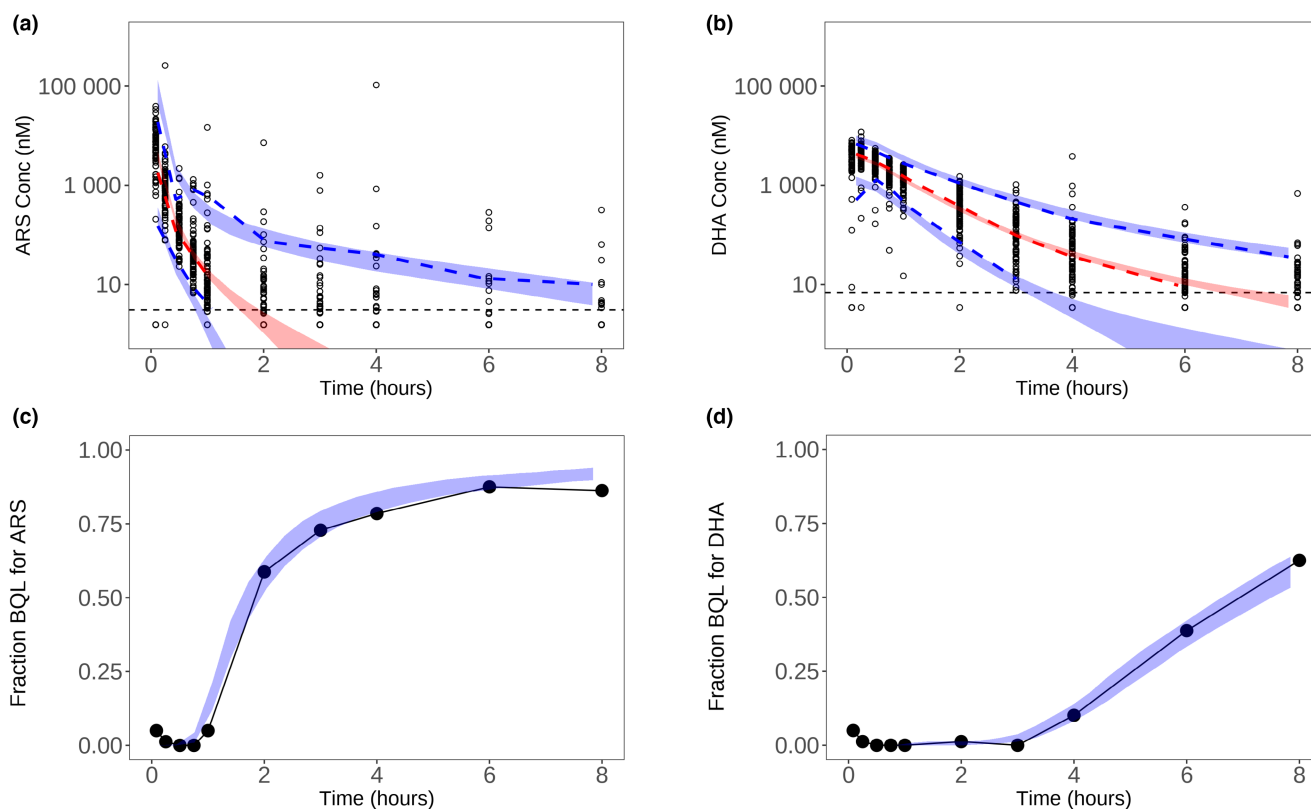


Figure 1 Visual posterior predictive checks for the two-compartment pharmacokinetic model describing the plasma concentrations of (a) artesunate (ARS) and (b) dihydroartemisinin (DHA) vs. time in African children with severe falciparum malaria. Open circles are the observed data points from REACH dataset. The dashed lines show the 5th, 95th (blue), and 50th (red) percentiles of the observations. The shaded areas are the simulated ($n=8,000$) 95% reference range of the 5th, 50th, and 95th percentiles of the predictions. Note that the black horizontal dashed line represents the drug's lower limit of quantification (BQL), and the blue region is the simulation-based 95% reference range for the predicted fraction of BQL ARS and DHA samples.

Table 2 Parameter estimates of the population PKs of ARS and DHA following intra-venous administration of artesunate in children ($n=80$) with severe falciparum malaria from the REACH dataset

	ARS	DHA
Variable	Population estimate ^a (95% CrI)	
Fixed effects		
CL (L/hour)	56.90 (43.52–73.14)	28.95 (26.09–32.03)
V (L)	4.41 (2.66–6.84)	18.26 (16.34–20.28)
Q (L/hour)	2.15 (1.36–3.53)	1.90 (0.96–3.69)
Vp (L)	1.13 (0.72–1.83)	3.97 (2.61–6.66)
– $\beta_{CL,DHA}$ (%)	n/a	3.56 (0.25–6.90)
Random effects		
ω_{CL}	0.61 (0.45–0.78)	0.43 (0.36–0.52)
ω_V	1.05 (0.79–1.36)	0.26 (0.17–0.35)
ω_Q	0.92 (0.37–1.44)	0.94 (0.15–1.68)
ω_{Vp}	0.82 (0.33–1.27)	0.69 (0.20–1.09)
$\rho_{CL,V}$	0.61 (0.39–0.71)	0.56 (0.34–0.65)
Post hoc estimates ^b		
CL (L/hour/kg)	3.33 (1.21–5.98)	1.62 (0.94–3.35)
V (L/kg)	0.25 (0.05–3.58)	0.98 (0.77–1.43)
Q (L/hour/kg)	0.13 (0.04–0.26)	0.11 (0.04–0.25)
Vp (L/kg)	0.05 (0.03–0.28)	0.22 (0.11–0.48)
$t_{1/2}\alpha$ (hour)	0.05 (0.02–0.24)	0.40 (0.24–0.67)
$t_{1/2}\beta$ (hour)	0.27 (0.13–2.27)	1.55 (0.83–4.09)
C_{max} (ng/mL)	9,518 (674–46,747)	1,288 (474–1700)
AUC _{0–12h} (hour×ng/mL)	737 (439–1997)	1,123 (567–1935)

ARS, artesunate; AUC_{0–12h}, area under the concentration–time curve from timepoint 0 to 12 hour; β_{CL-DHA} , fractional change in population mean CL for a unit (g/dL) increase in hemoglobin from the mean (7.9 g/dL); C_{max} , maximum concentration; DHA, dihydroartemisinin; CrI, credible interval; CL, clearance; $\rho_{CL,V}$, correlation between ω for CL and V; PK, pharmacokinetic; Q, inter-compartmental clearance; $t_{1/2\alpha}$, half-life during distribution phase; $t_{1/2\beta}$, half-life during terminal elimination phase; V, volume of the central compartment; Vp, Volume of the peripheral compartment; ω , the between-subject standard deviation.

^aThe reference body weight and hemoglobin value in the population PK modeling are 17.9 kg and 7.9 g/dL, respectively. ^bThe post hoc estimates (median (2.5th–97.5th percentiles)) were calculated using the PK estimates derived from our final population PK analysis.

of age were first investigated in the data of children from the SMAC network²² and compared with the associations in the CDC growth charts¹⁷ used by Kitabi *et al.*¹⁶ In our data, there was no meaningful difference in temperature by age (Figure S5) and therefore temperature was simulated independent of age from a normal distribution with mean of 38.2°C and SD of 2.6°C. It should be noted that Kitabi *et al.*¹⁶ used a normal distribution with the same mean but with an SD of 1.2°C based on data derived from 351 children aged 6 to 120 months with severe falciparum malaria in Africa in a study by Kremsner *et al.*,³⁴ see Figure S5. There is a clear relationship between hemoglobin and the age of the child in the SMAC data (Figure 2b),

unlike in Kitabi *et al.*,¹⁶ which simulated hemoglobin levels independent of age (Figure 2a). Further, the median hemoglobin for children under 50 months in the SMAC dataset (see Figure 2b—e.g., the lowest median from the LOESS curve is around 6.4 g/dL at about 10 months) is substantially lower than the assumed mean of 8.5 g/dL simulated by Kitabi *et al.* The SMAC dataset also shows that body weights are generally lower for African children with severe falciparum malaria than the weights in the CDC growth chart data¹⁷ used by Kitabi *et al.*¹⁶ (see Figure 3).

The *post hoc* estimates of the total drug exposure from 0 to 12 hours (AUC_{0–12h} (hour×ng/mL)) for DHA using the PK estimates derived from the REACH study under 2 dosing schemes (i.e., the standard 2.4 mg/kg dose of ARS endorsed by the FDA¹⁶ as well as the weight-based dose, 3 mg/kg for children < 20 kg, and 2.4 mg/kg otherwise, endorsed by the WHO¹⁵) and the summary statistics (median, interquartile range (IQR)) of the DHA exposure grouped by weight are shown in Figure 4 and Table 3, respectively.

When applied to the SMAC dataset, there is decreased DHA exposure in children weighing 8 to 18 kg compared with older children under the FDA endorsed dosing scheme (Figure 4, red dots). As an example, children given the 2.4 mg/kg dose of ARS with body weights of 6–10 and 11–15 kg showed mean reductions of 11.4% and 17%, respectively, in DHA exposures compared with children with body weights between 21 and 25 kg (see Table 3). This contrasts with results from the WHO-endorsed dosing scheme applied to the same data, which results in higher DHA exposures in children weighing 8–18 kg than in older children (Figure 4, black dots). It should be noted that over 90% of the children with severe falciparum malaria in the SMAC dataset weighed less than 20 kg (Figure 4), suggesting that most younger African children dosed with 2.4 mg/kg of ARS would not reach the same drug exposures as older children. In our model, higher DHA exposure levels are achieved by very young children (< 7 kg) under both dosing schemes due to the application of an assumed age-maturation function when simulating clearance (note that about 11% of children in SMAC weighed < 7 kg). The same findings were observed when DHA exposure was simulated using PK parameters estimated via population PK modeling of the AQUAMAT trial¹³ (70 Tanzanian children treated with intra-muscular ARS—2.4 mg/kg) and a large, pooled dataset from patients with severe malaria¹⁴ (223 patients receiving ARS intravenously—2.4 mg/kg). This was regardless of whether an exponential or a sigmoid functional form was specified for the age-related enzyme-maturation effect, which reduces the bio-transformation of DHA in younger children (see Figures S6, S7).

DISCUSSION

Parenteral ARS is the first-line treatment for adults and children with severe malaria, one of the major causes of preventable childhood deaths in tropical countries. The life-saving efficacy of ARS is dependent upon achieving parasitocidal concentrations in plasma as soon as possible after diagnosis. Our analysis of ARS and DHA drug concentrations in 80 African children with severe falciparum malaria who received intravenous ARS, confirmed previous findings from PK studies on the relationship between drug

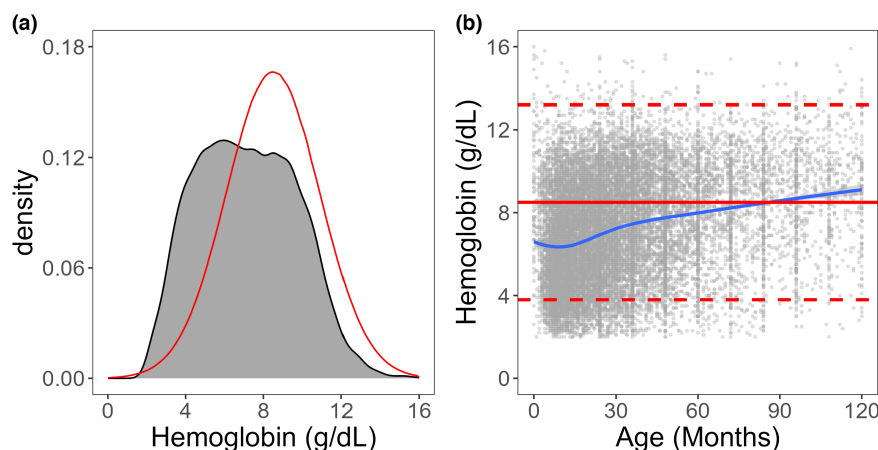


Figure 2 (a) Hemoglobin distribution in the SMAC dataset vs. the assumed distribution in the Kitabi *et al.* study.¹⁶ (a) The red curve indicates Kitabi *et al.*'s assumed normal distribution, the gray represents the SMAC dataset; (b) hemoglobin vs. age of the SMAC dataset with LOESS curve (blue), overlaid with the mean (red solid), and 95% reference range (red dashed) of Kitabi *et al.*'s assumed normal distribution. SMAC, Severe Malaria in Africa Children.

exposure and body weight and hemoglobin concentration. Using data from over 25,000 African children with severe malaria, we show that the relationship between body weight and age in the population receiving ARS is substantially different to that derived from CDC growth charts. Combining these findings to simulate drug exposure following intravenous ARS for children, we found that children weighing <20 kg have lower DHA exposures than children/adults above 20 kg, providing further support for the WHO-endorsed higher dose of 3 mg/kg in younger children.

The observed concentrations of ARS and DHA from the REACH dataset were described accurately by a two-compartment disposition model for both ARS and DHA. The *post hoc* estimates (median (2.5th–97.5th percentiles)) of CL, V, and AUC_{0-12h} for DHA using the PK estimates derived from our population PK analysis (1.62 L/hour/kg (0.94–3.35); 0.98 L/kg (0.77–1.43); and 1,123 hours \times ng/mL (567–1935), respectively) are consistent with those from a previously published 1-compartment PK model of intramuscular ARS in 70 Tanzanian children¹³ (2.01 L/h/kg (0.75–5.95); 1.24 L/kg (not

available); and 890 hours \times ng/mL (297–2,510)). The results of our one-compartment model fitting demonstrate DHA half-life estimates (median (2.5th–97.5th percentiles)) of 0.50 hours (0.06–0.96) comparable to the previously reported values of 0.43 hours (0.15–1.18).¹³ However, in this study, a biexponential (2-compartment model) fit was superior to the monoexponential (1-compartment model) fit in characterizing DHA elimination. As observed in other studies,^{13,14} there was a high correlation between the estimates of CL and V, suggesting there may be an unmeasured covariate that is related to both of these PK parameters. Of note, we observed a median 3.6% increase in the DHA clearance per unit (g/dL) decrease in hemoglobin in our study, which is lower than the reported 10.2% by Henriksen *et al.*¹³ for Tanzanian children with severe malaria. This may be because the AQUAMAT dataset had more anemic and younger children compared with the REACH dataset (median (IQR): 7.1 g/dL (4.9–9.2) vs. 8.3 g/dL (6.1–9.6)).

When simulating virtual populations to determine effective dosing, it is important that the relationships between relevant

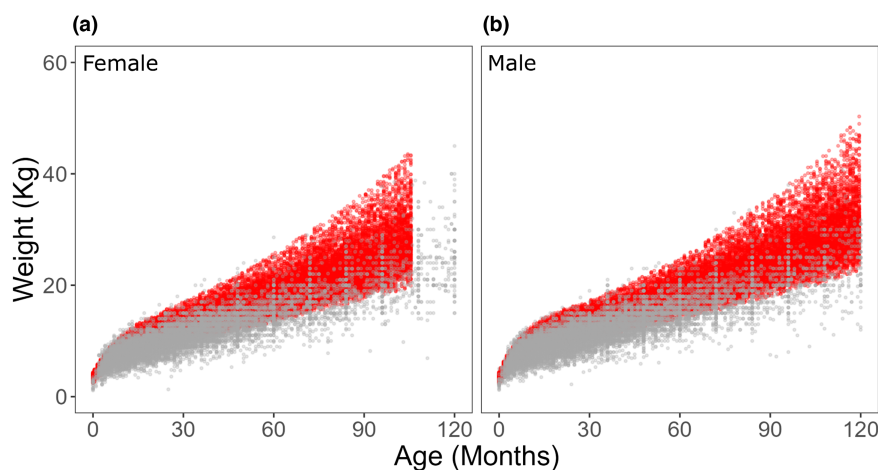


Figure 3 Weight vs. age for SMAC dataset (gray) and CDC dataset (red) for (a) female and (b) male individuals. CDC, Centers for Disease Control and Prevention; SMAC, Severe Malaria in Africa Children.

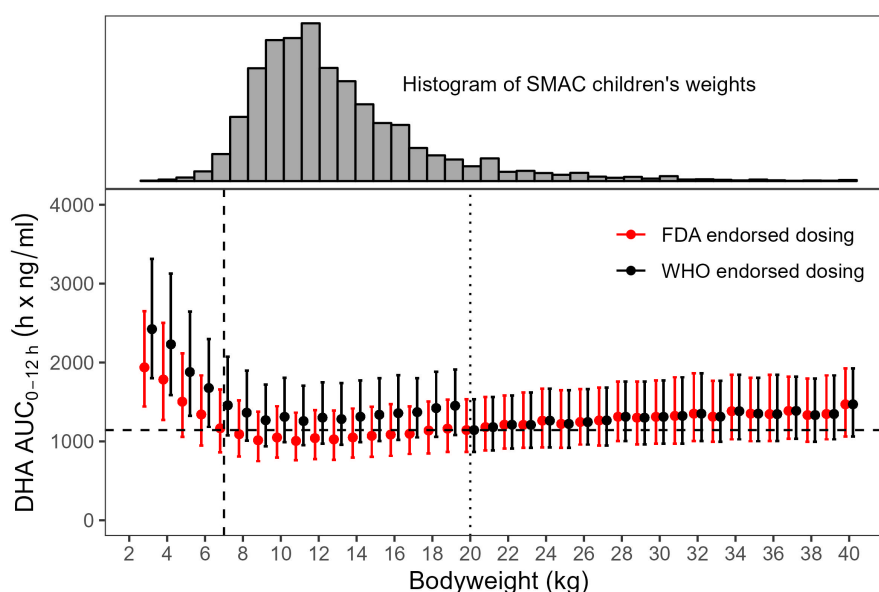


Figure 4 Simulated total first dose exposures of dihydroartemisinin (DHA) (bottom) after the FDA endorsed 2.4 mg/kg dosing of parenteral artesunate in children¹⁶ at different body weights (red) and weight-based dosing regimen endorsed by the WHO¹⁵ (black) using PK parameter estimates from population PK modeling of the REACH dataset and a virtual population based on the SMAC dataset. Circles represent the median and error bars display the 25th and 75th percentiles of the 1,000 simulations at each body weight. The horizontal dashed line is the median exposure for the 20 kg weight group after the standard 2.4 mg/kg dose. The vertical dashed line at 7 kg represents the minimum weight in the REACH dataset, indicating that the exposure levels for children below this weight were simulated by extrapolating the PK parameters for this weight group. In the large SMAC dataset 11% of children with severe falciparum malaria weighed less than 7 kg. The vertical dotted line indicates 20 kg body weight. The top histogram depicts the distribution of body weights in the SMAC dataset. AUC_{0-12h}, area under the concentration-time curve from 0 to 12 hours; FDA, US Food and Drug Administration; PK, pharmacokinetic; SMAC, Severe Malaria in Africa Children; WHO, World Health Organization.

covariates are derived from the target population in which the drug is to be used. The children in the SMAC dataset (the largest available dataset of childhood severe malaria) weighed substantially less than the children in the CDC dataset used by Kitabi *et al.*¹⁶ Thus, the virtual population generated in the current work (via the LMS method) better reflects the weight-for-age relationship of the target population than used by the FDA to derive recommendation. The relationship between hemoglobin and age was also described more accurately using the SMAC data and the LMS method. This is particularly relevant as hemoglobin is an important determinant of DHA exposure in malaria (and therefore severe malaria outcomes). There was a clear difference in the hemoglobin distributions between the SMAC data and the data

used by Kitabi *et al.*; a greater proportion of the SMAC children were anemic than data used by Kitabi *et al.*,¹⁶ which overestimates the hemoglobin concentrations for a large and important proportion of the population aged < 50 months. This is of particular importance as children of this age are at greater risk of severe malaria than older children. These differences between the distributions of hemoglobin and/or the relationship between hemoglobin and age may also explain why, on further investigation Kitabi *et al.*³⁵ did not observe any change in the AUC of DHA when accounting for the relationship between hemoglobin and age in their simulated virtual population.

The DHA exposure simulations with the 2.4 mg/kg dose of ARS endorsed by the FDA resulted in lower drug exposures in

Table 3 Median DHA exposure (hour × ng/mL), with 25th and 75th percentiles, for the two different dosing regimens by body weight groups

Body weight group	% of SMAC children in weight group (n = 25,779)	Median AUC _{0-12h,DHA} (hour × ng/mL) (25th–75th percentiles)	
		FDA-endorsed dosing	WHO-endorsed dosing
< 6 kg	4.6	1,722 (1,232–2,366)	2,153 (1,540–2,957)
≥ 6 to < 11 kg	50.3	1,088 (799–1,503)	1,360 (999–1,879)
≥ 11 to < 16 kg	30.4	1,019 (771–1,372)	1,273 (964–1,715)
≥ 16 to < 21 kg	9.1	1,135 (842–1,512)	1,321 (982–1,784)
≥ 21 to < 26 kg	3.3	1,228 (929–1,651)	
> 26 kg	2.4	1,345 (1,004–1,791)	

AUC_{0-12h}, area under the concentration-time curve from 0 to 12 hours; DHA, dihydroartemisinin; FDA, US Food and Drug Administration; SMAC, Severe Malaria in Africa Children; WHO, World Health Organization.

small children (around 8–18 kg) compared with those with higher body weights. As the majority of children (about 70%) with severe malaria weigh between 8 and 18 kg, according to the distribution of weights in the SMAC dataset, this shows that if most children with severe malaria were given the 2.4 mg/kg dose of ARS, they would not reach the same drug exposures as children weighing above 20 kg. This is consistent with the other population PK studies^{13,14} from over 300 children and adults with severe malaria. In contrast, the DHA exposure simulations under the WHO dosing regimen led to comparable drug exposures for young children (around 8–18 kg) and children above 20 kg.

Artesunate is an extremely safe drug. Individual parenteral doses up to 4 mg/kg have been very well-tolerated by children with falciparum malaria.^{34,36} The only dose-related toxicity reported for ARS is transient, mild, reversible reductions in neutrophil counts with oral doses of ≥ 6 mg/kg/day.³⁷ Although transient delayed reductions in neutrophil and reticulocyte counts have been reported, these have had no pathological consequences and cannot be compared with marked immediate benefits from parenteral ARS. Achieving therapeutic antimalarial concentrations rapidly in severe malaria is critical to save life. Underdosing children with severe malaria is therefore life-threatening. The risk–benefit trade-off between a hypothetical minimal increase in inconsequential toxicity vs. life-threatening subtherapeutic exposures to the drug is obviously in favor of a higher dose in young children. There is still uncertainty in the optimal dosing for very small children (<7 kg) where exposure may be increased, but this is a relatively small subgroup of children with severe malaria, and so there are very few observed data.

In conclusion, it is very important that therapeutic recommendations are based on observations in the appropriate populations. Given that parenteral ARS is an extremely safe and well-tolerated life-saving drug and there is potential for preventable mortality as a direct result of underdosing, these results do not support the FDA's recent ARS dose recommendation.¹⁶

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

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CONFLICT OF INTEREST

N.J.W. was a member of the WHO treatment guidelines committee that made the current antimalarial drug treatment recommendations and J.T. was a member of the WHO antimalarial dosing subgroup that advised

on artesunate dosing. All other authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

A.H., J.A.S., and N.J.W. wrote the manuscript. J.A.S., C.F., J.T., and N.J.W. designed the research. A.H., P.F., S.D., D.J.P., M.R. and J.A.W. performed the research and analyzed the data.

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