

Background and Objectives

Amodiaquine (AQ) is the partner drug of artesunate (AS) in the second most widely used combination therapy for malaria. Current dose recommendations in children are based on the assumption of a linear relationship between dose and body weight (BW) or body surface area ¹.

Dose regimens might be inappropriate in some subgroups of patients, such as young and malnourished children or pregnant women.

Objective: To describe the population pharmacokinetic-pharmacodynamics (PK/PD) of amodiaquine and its active metabolite from multi-study protocols and to identify covariates that explain differences between subpopulations

Methods

Five PK studies in 5 countries where AQ was given daily for 3 days, alone or in a combination with AS were used in this analysis

Data from 269 malaria patients (African and Asian) were available.

- 23.8% [67/269] under 5 years of age of which 53.7% [36/67] were under 2 years
- and 9.7% [26/269] pregnant women.

The dosage and sampling schedules varied between studies (Table 1) ^{2,3,4,5,6,7}.

Pooling of the data from the different studies and development of a combined model, was undertaken in a step-wise approach, as previously suggested ⁸.

Several structural PK models were investigated for AQ and its metabolite Desethyl-amodiaquine (DEAQ).

All clearance and volume of distribution parameters were scaled using body weight (BW) with allometric exponent fixed to 0.75 and 1, respectively.

To prevent flip-flop kinetics a prior on the absorption rate constant (K_a) was used

Age maturation (eq 1)¹⁰ and disease effect (eq 2) on CL was tested. Prior information on maturation was used ¹¹.

The M6 method ⁹ was used to handle BLQ values. Data modelled in NONMEM 7.3

Country	Study description and reference	Treatment	Study population	Number of patients	Number of samples per patient	Limit of quantification
Thailand	Effect of pregnancy on PK and PD of Amodiaquine and Desethyl amodiaquine (Tarning + Rijken)	AQ (10 mg/kg) daily for 3 days	Pregnant women (16 – 39 years) in their 2nd and 3rd trimester (with follow-up after delivery)	26 (7) ^a	14/22 (14/22)	1/2
Kenya	Efficacy of fixed vs non-fixed dose of AS/AQ (Jullien)	2 tablets of AS/AQ fixed dose (100/270 mg) or 4 tablets of AS (50 mg) + 4 tablets of AQ (153 mg) daily for 3 days	Adults (18 to 60 years)	54	4/8	1/1
Uganda	Determine PK parameters for AS/AQ in children (Mwesigwa)	AS (50 mg - tablets at 4 mg/kg twice a day for 3 days) + AQ (200mg - tablets at 10 mg/kg once a day on the first 2 days and 5 mg/kg on the third day)	Children (5 to 13 years)	20	2/6	5/5
Burkina Faso	Compare bioavailability of AS/AQ fixed vs AS/AQ separate (Stepniewska)	AS/AQ fixed dose (one dose of 25/67.5 mg/kg for children < 12 months or two doses for children 12 - 60 months) or AS (50 mg tablet, half tablet for children < 12 months and one tablet for children 12 - 60 months) + AQ (153 mg, half tablet for children < 12 months and one tablet for children 12 - 60 months) daily for 3 days	Children (6 months to 5 years)	70	2/3	1/1
Ghana	Compare the effect of AS on AQ (Comparison between AQ and AS/AQ-loose) (Adjei)	AQ (10 mg/kg single dose) or AS (4 mg/kg single dose) + AQ (10 mg/kg single dose) daily for 3 days	Children (6 months to 14 years)	102	1/2	10/10

^a Same women came with malaria 3 months post natal; All samples are venous plasma; AQ/DEAQ

Results

The final model was a two compartment disposition model for AQ, absorption through a chain of 6 transit absorption compartments, with a three compartment model for DEAQ.

Synthesis of DEAQ from central compartment of AQ, with complete transformation assumed.

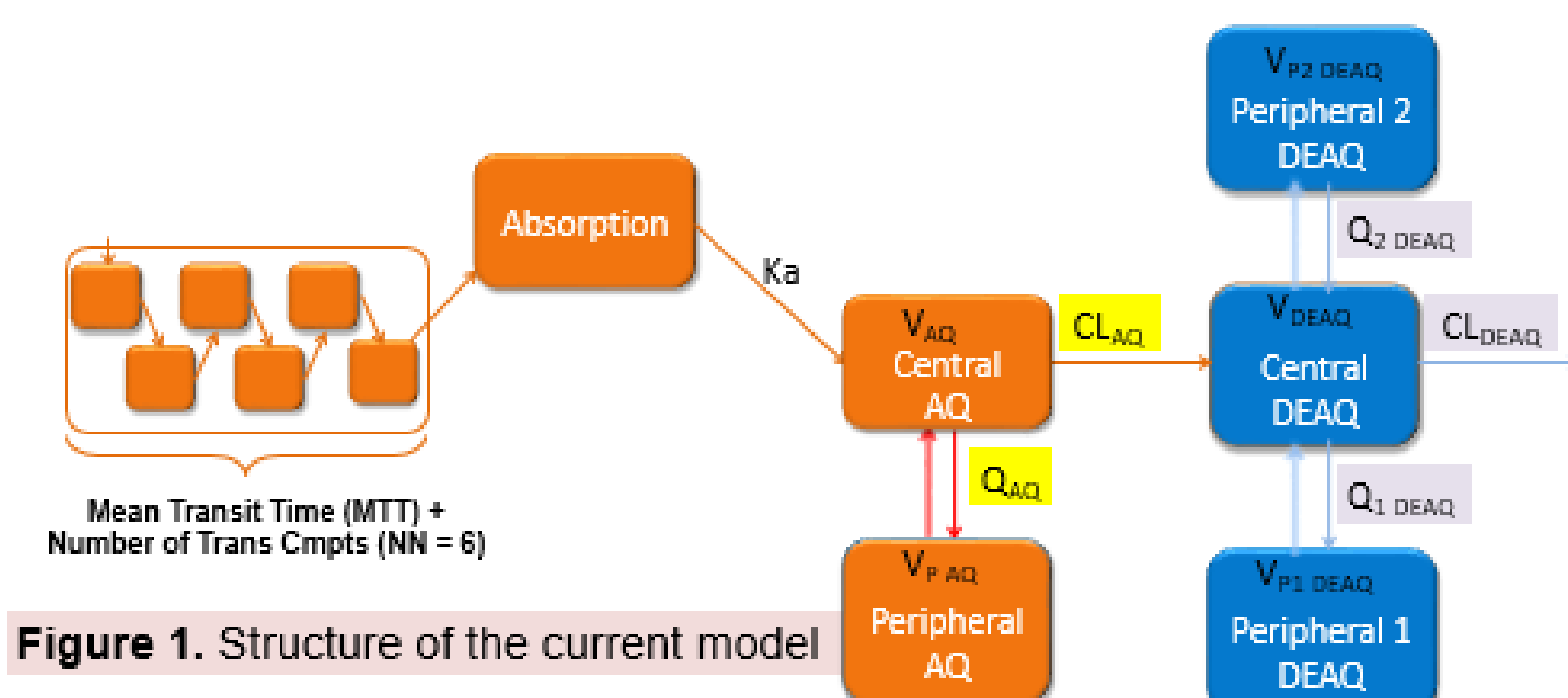


Figure 1. Structure of the current model

- A lognormal prior on K_a with typical value 2.81 1/h and 10 % uncertainty.
- The volume of distribution was lower in Thai patients (who where the only patients with Vivax infection) than in other patients.
- CL for both AQ and DEAQ was larger in patients with higher hemoglobin readings at baseline.

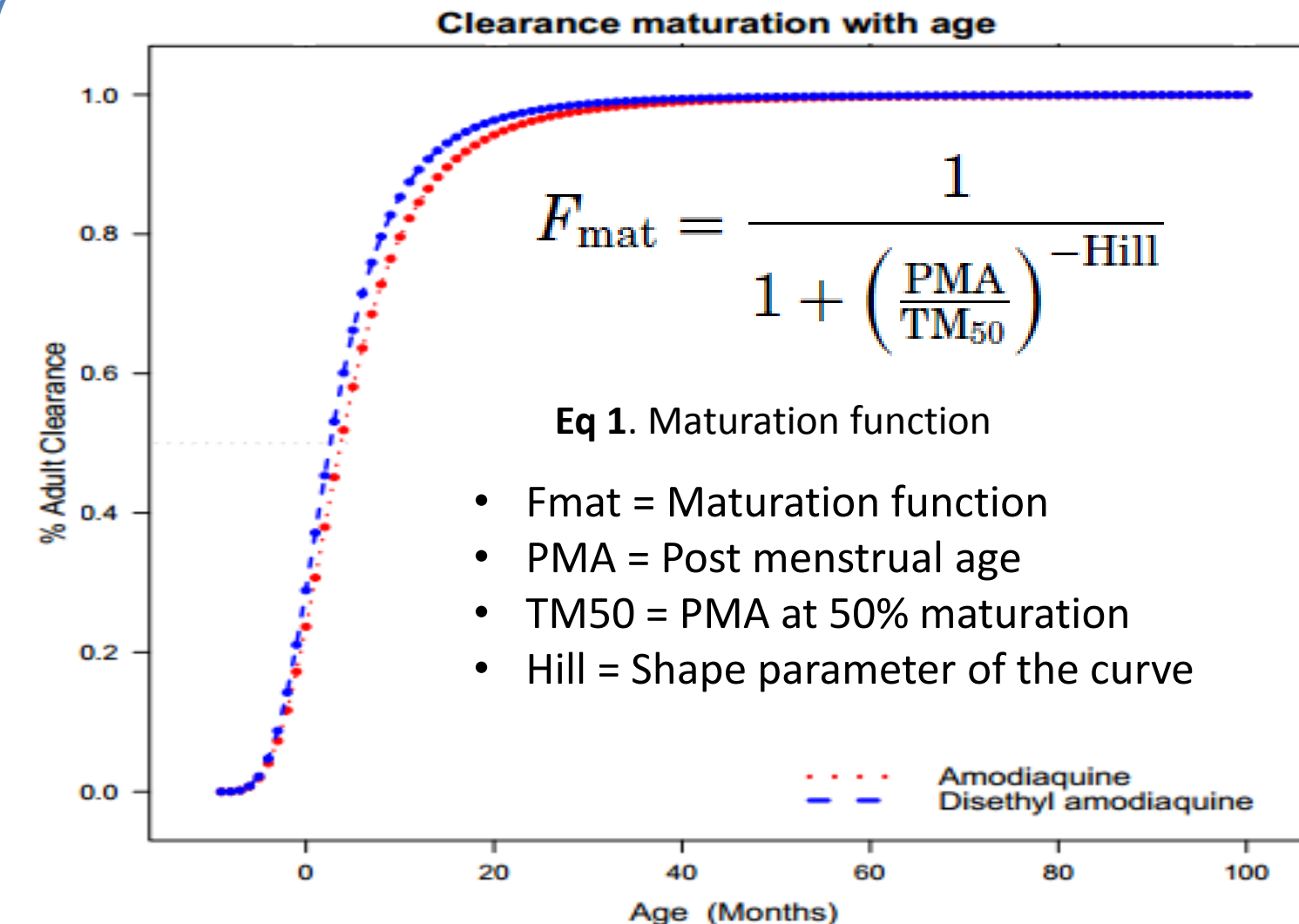


Figure 2. Clearance maturation

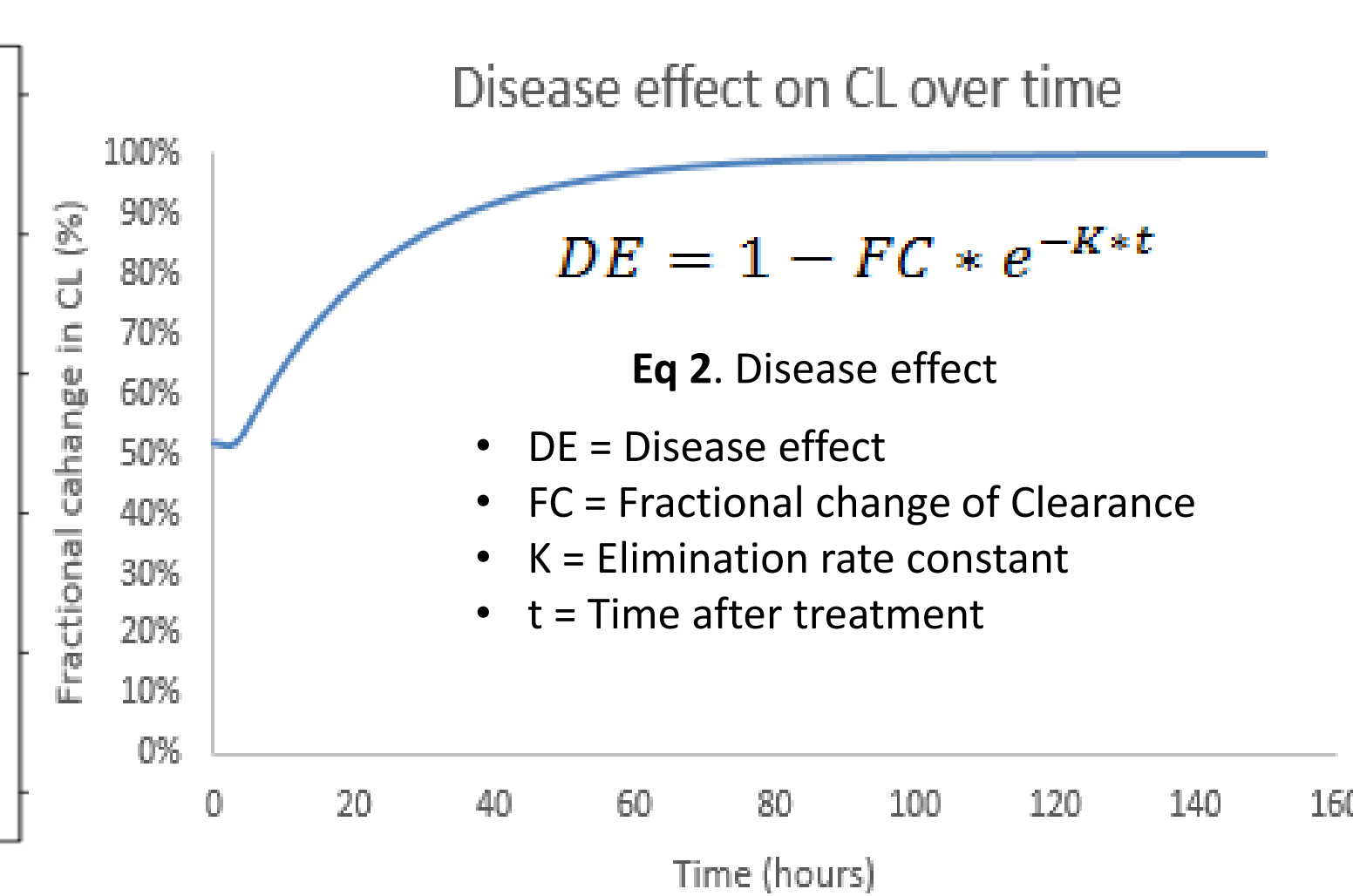
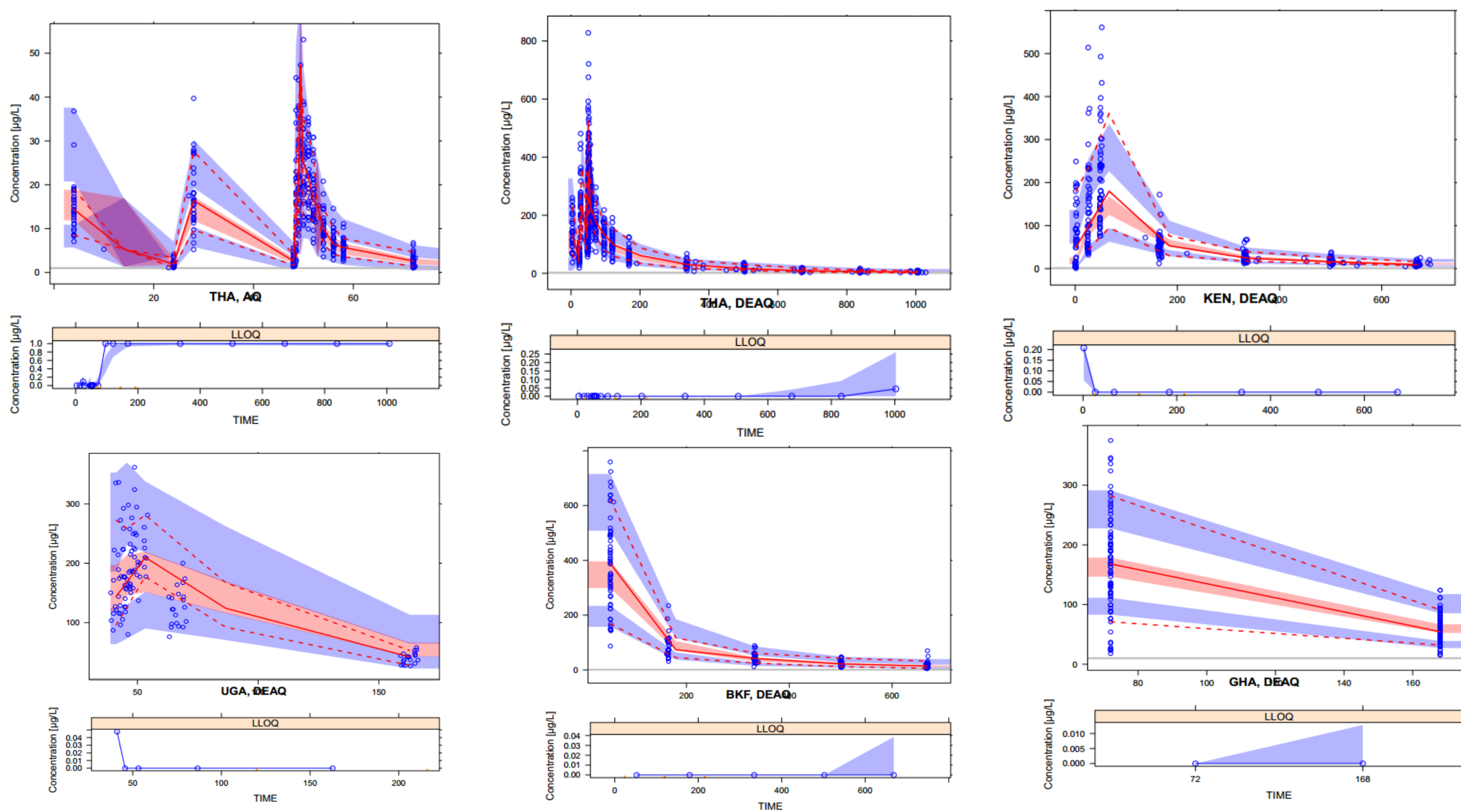


Figure 3. Disease effect on clearance

- Prior information on PMA age at 50 % maturation of 3 months after birth and a Hill coefficient of 3 with 10 % uncertainty around them were used.
- Clearance was found to mature with post-menstrual age, with children at birth having 24 % for AQ and 29 % for DEAQ of adult clearance, reaching about 85 % and 89 % by one year of age for AQ and DEAQ respectively.
- Clearance due to disease was found to be about 50 % of the final value at initiation of treatment.

Parameter	Amodiaquine		Desethyl amodiaquine	
	Estimates	BSV* ; BOV**	Estimates	BSV* ; BOV**
K_a [h^{-1}]	2.7	95.2%**	-	-
Mean absorption transit time [h]	0.36	97.2%**	-	-
CL^a [L/h]	2340	24.6%*	28.9	19.2%*
V_c [L]	32800	51.8%*	97	20.7%*
Q_1 [L/h]	1630	25.1%*	29.7	-
VP_1 [L]	40500	-	5920	29.9%*
Q_2 [L/h]	-	-	102	-
VP_2 [L]	-	-	1560	-
V_c for Thai [L]	10600	-	201	-
V_p for Thai [L]	22700	-	-	-
BIO []	1 FIX	29.5%**	-	-
$PMAGE_{50}$ [months]	12.7	-	11.6	-
Hill coefficient []	3.4	-	3.6	-
Disease effect half life [h]	14.2	-	-	-
Fractional change of CL due to disease effect [%]	0.48	1.8*	-	-
Delay in disease effect [h]	3.6	-	-	-
Additive error [mg/L]	0.2	-	0.1	-
Proportional error [%]	21.3	-	23.3	-

a CL at mature and at stead state *Standard deviation of ETAs in logit space



Conclusion

- ✓ Malaria disease severity affects the PK of AQ, and here we characterized an effect on CL
- ✓ Disease effects on AQ PK were previously reported, but further PK studies involving both healthy volunteers and malaria patients are warranted to test this result.
- ✓ Differences in AQ pharmacokinetics between adults and children can be largely accounted for by using allometric scaling, age-based maturation. Further factors are higher disease severity (here captured by HB), and possibly malnutrition.
- ✓ The type of plasmodium species may have different effect on PK parameter of AQ

References

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