UPPSALA UNIVERSITET

Modeling of the concentration-effect relationship for piperaquine in preventive treatment of malaria

Martin Bergstrand[1], François Nosten[2,3,4], Khin Maung Lwin[4], Mats O. Karlsson[1], Nicholas White[2,3], Joel Tarning[2,3]

1 Department of Pharmaceutical Biosciences, Uppsala University

2 Mahidol-Oxford Tropical Medicine Research Unit, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand

3 Centre for Tropical Medicine, Nuffield Department of Clinical Medicine, University of Oxford, Oxford, UK

4 Shoklo Malaria Research Unit (SMRU), Mae Sod, Thailand

Mahidol Oxford

WELLCOME TRUST - MAHIDOL UNIVERSITY-OXFORD TROPICAL MEDICINE RESEARCH PROGRAMME

UPPSALA UNIVERSITET

Background

Malaria statistics (estimates) according to WHO

- Half of the worlds population live in areas at risk of malaria transmission
- In 2010, an 216 million clinical episodes, and 655 000 deaths
- 86% of the malaria deaths in children under 5 years

Chemoprevention

- Primarily in Children and Pregnant (Intermittent Preventive Treatment (IPT))
- Commonly used treatment alternatives has in many places been rendered ineffective by the development of resistance (i.e. sulfadoxine-pyrimethamine “SP” and chloroquine)

UPPSALA UNIVERSITET

AAC Journals.ASM.org

Randomized, Double-Blind, Placebo-Controlled Trial of Monthly versus Bimonthly Dihydroartemisinin-Piperaquine Chemoprevention in Adults at High Risk of Malaria

Khin Maung Lwin,[a] Aung Pyae Phyo,[a] Joel Tarning,[b,c] Warunee Hanpithakpong,[b] Elizabeth A. Ashley,[a,b,c] Sue J. Lee,[b,c] Phaikyeong Cheah,[b,c] Pratap Singhasivanon,[d] Nicholas J. White,[b,c] Niklas Lindegårdh,[b,c] and François Nosten[a,b,c]

Shoklo Malaria Research Unit, Mae Sod, Thailand[a]; Mahidol Oxford Research Unit, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand[b]; Centre for Tropical Medicine, Nuffield Department of Clinical Medicine, University of Oxford, Churchill Hospital, Oxford, United Kingdom[c]; and Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand[d]

- Randomized, placebo controlled trial
- Northwest border of Thailand
- Treatment regimens:
  - 3 tablets (120 mg DHA and 960 mg PQ) dosing on three consecutive days
  - Repeated every monthly or every second month (bimonthly)
- 1000 healthy adult male subjects
  400+400+200 (placebo)
- Follow-up weekly for 9 months of treatment
  - PQ plasma concentration
  - Blood smears for parasite detection

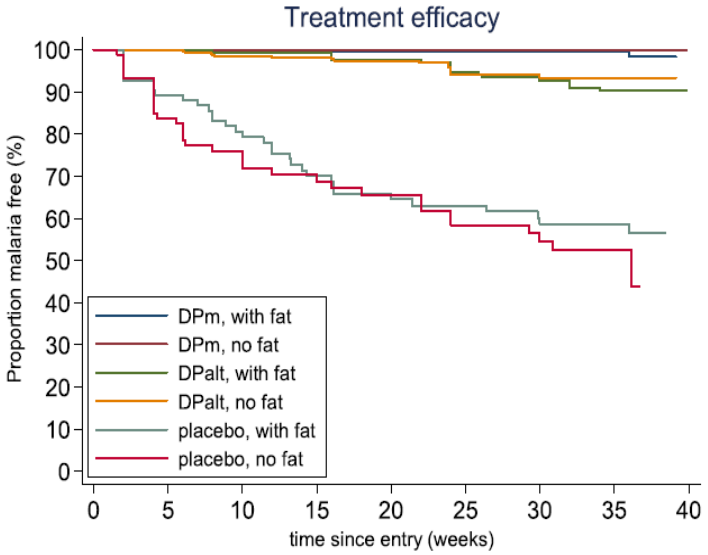


FIG 1 Kaplan-Meier survival curves for malaria-preventive efficacy in the three groups. Dihydroartemisinin-piperaquine treatment doses (over 3 days) monthly (DPm) or every 2 months (DPalt) or an identical placebo were given with or without 6.4 g of fat for each dose administered.

DHA = Dihydroartemisinin
PQ = Piperaquine

UPPSALA UNIVERSITET

Objectives

1. Characterize the concentration-effect relationship for the malaria preventive effect of piperaquine
2. Utilize the developed model and literature information on PK to simulate expected outcome in IPT populations:
   - Children
   - Pregnant
3. Use simulations to investigate the expected consequence of potential piperaquine resistance
4. Identify target observed PQ plasma concentration to guide treatment
5. Explore alternative dosing regimens for chemoprophylaxis with DHA-PQ [1]

[1] Poster III-20:
Jesmin Lohy Das et al. Simulations to investigate new Intermittent Preventive Therapy Dosing Regimens for Dihydroartemisinin-Piperaquine.
PAGE 22 (2013) Abstr 2923 [www.page-meeting.org/?abstract=2923]

UPPSALA UNIVERSITET

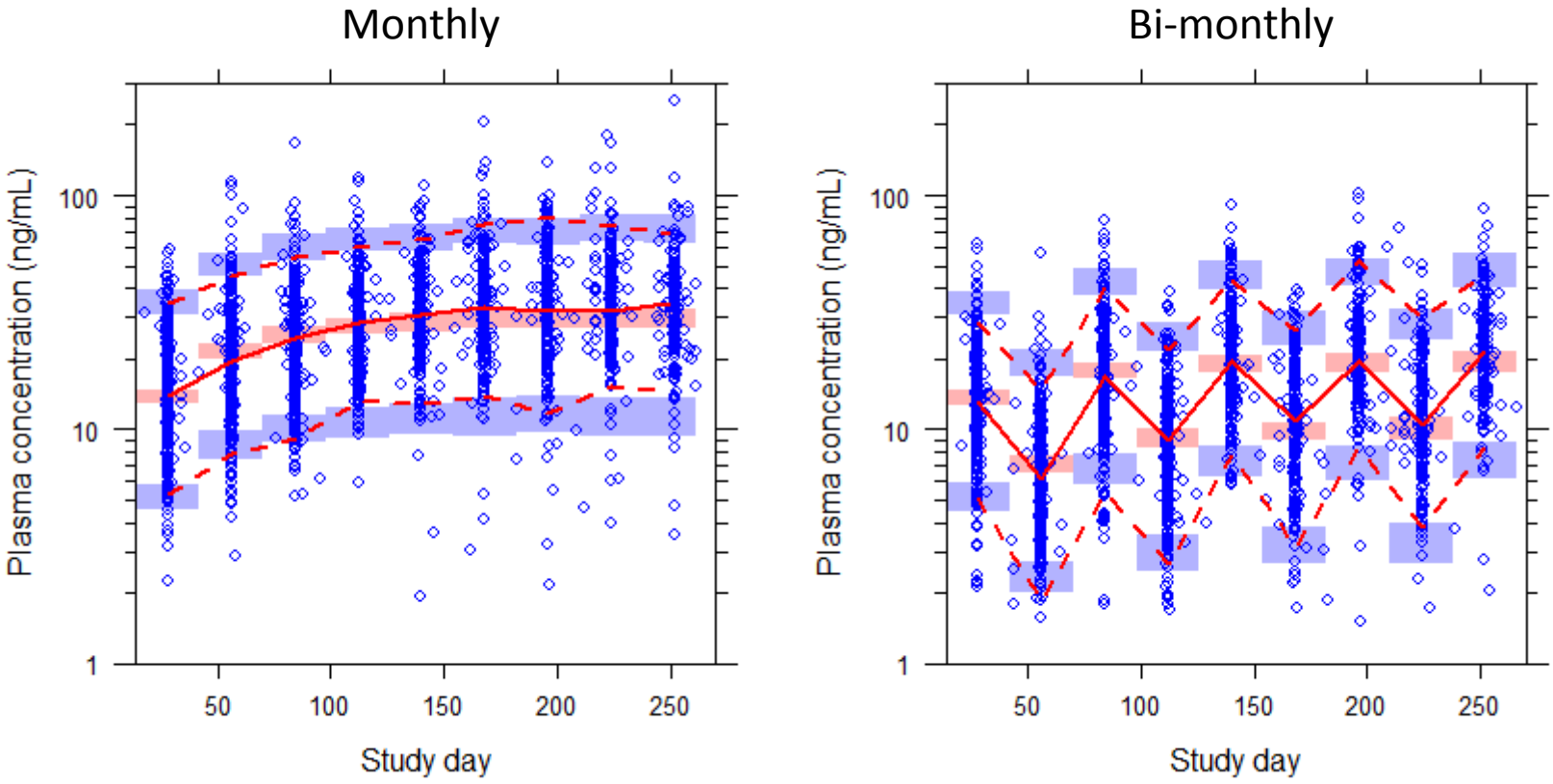
Model building procedure

1. **Model piperaquine PK**
   - Monthly PK observations
   - Analyzed with a frequentist prior based on a previously developed PK model [2, 3]
2. **Establish baseline time-to-event model**
   (i.e. natural hazard of malaria infection in study)
   - Subset only placebo cohort
   - Explored potential predictors of baseline hazard (seasonal variations and demographics etc.)
3. **Establish PKPD model**
   - Explored concentration-effect relationship
   - Account for DHA effect and biological lag-time

[2] Tarning, J., et al., Population pharmacokinetics of dihydroartemisinin and piperaquine in pregnant and nonpregnant women with uncomplicated malaria. Antimicrobial Agents and Chemotherapy, 2012. 56(4)
[3] Gisleskog PO, Karlsson MO, Beal SL. Use of prior information to stabilize a population data analysis. J Pharmacokinet Pharmacodyn. 2002;29(5-6):473-505.

UPPSALA UNIVERSITET

Visual Predictive Check: PQ PK model



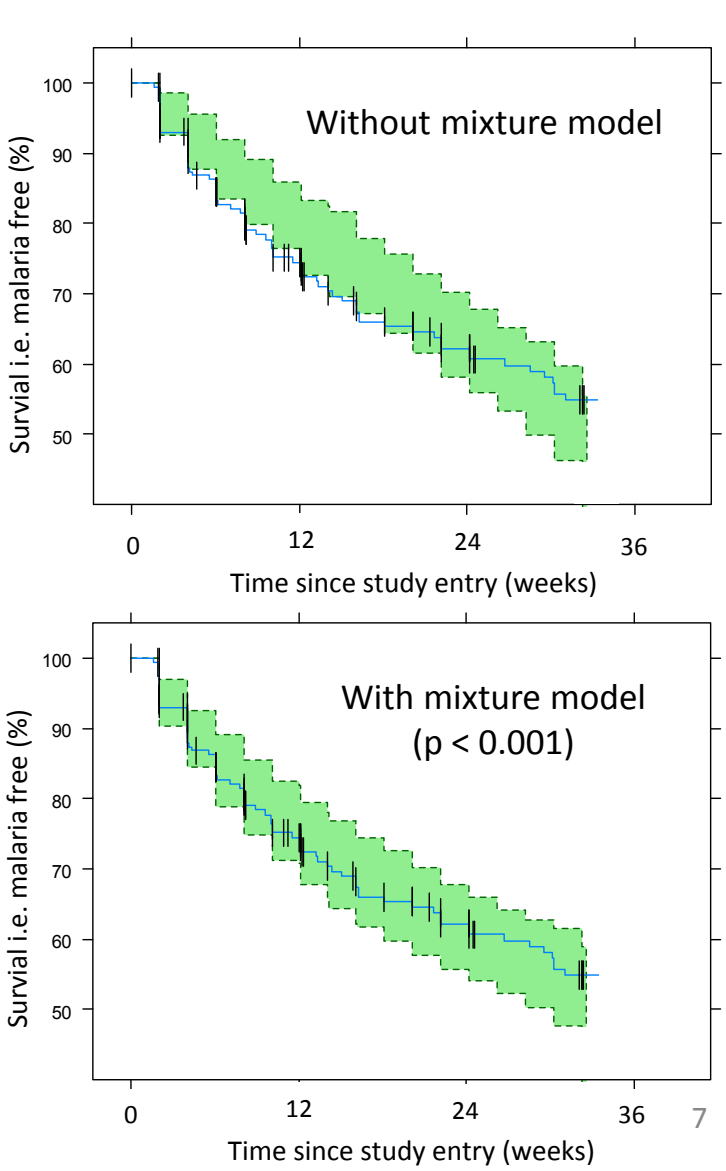
- Solid red line => Observed median
  red field => corresponding 95% confidence interval based on model simulations
- Dashed red lines => Observed 90% prediction interval
  blue fields => corresponding 95% confidence interval based on model simulations

UPPSALA UNIVERSITET

Baseline time-to-event model

Constant hazard model with:

- A seasonal peak in malaria transmission rate from May throughout June
  $\Rightarrow$ hazard $\uparrow$ 217%
- Mixture model for baseline hazard
  - Probability of belonging to a low hazard population estimated to 0.7
  - The low hazard population: 0.25 infections/year
  - High hazard population: 3.77 infections/year
- Covariate relationship:
  - Age on mixture probability
    $\Rightarrow$ generally higher hazard for younger subjects



UPPSALA UNIVERSITET

PKPD model

- The inclusion of categorical treatment effects were statistically significant (p<<0.001) (i.e. separate hazard for placebo, monthly and bi-monthly dosing)
- A continuous PQ concentration effect relationship with a single estimated parameter, IC_{50}, clearly outperformed the categorical effect model with two parameters.
- Model fit was improved further (p<0.001) by assuming a sigmoidal concentration-effect relationship (i.e. estimated Hill factor, γ)

$$Def\left(t\right) = 1 - \frac{C(t)^{\theta_\gamma}}{\theta_{IC_{50}}{}^{\theta_\gamma} + C(t)^{\theta_\gamma}}$$

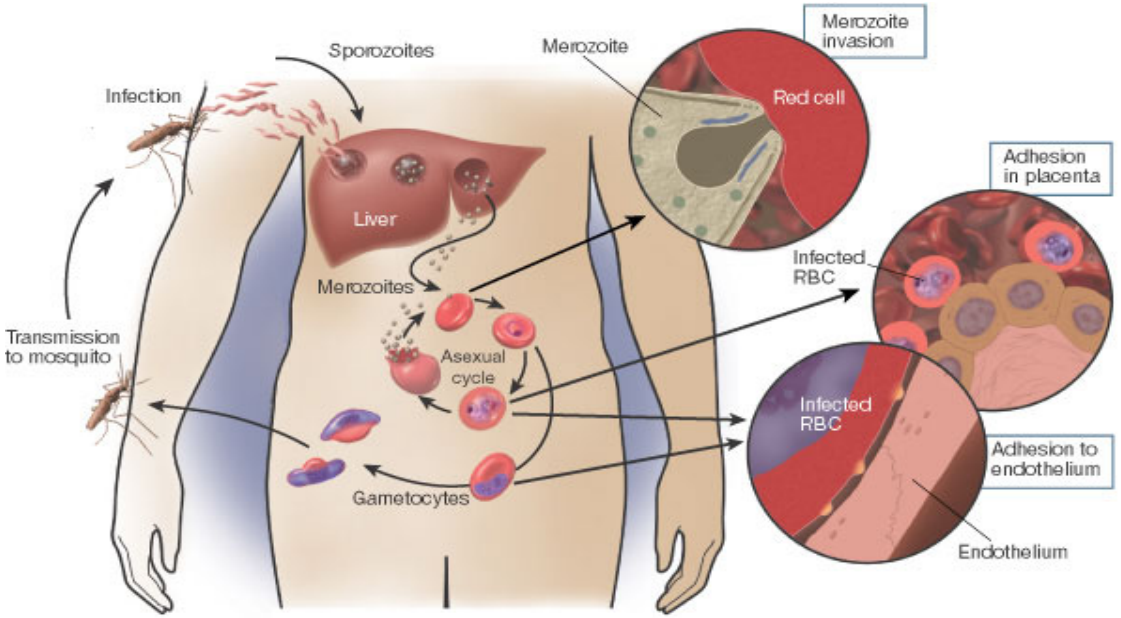
$$h\left(t \mid MIX_i = 1\right) = \theta_{BHz_1} \cdot Season\left(t\right) \cdot Def\left(t\right)$$

$$h\left(t \mid MIX_i = 2\right) = \theta_{BHz_2} \cdot Season\left(t\right) \cdot Def\left(t\right)$$

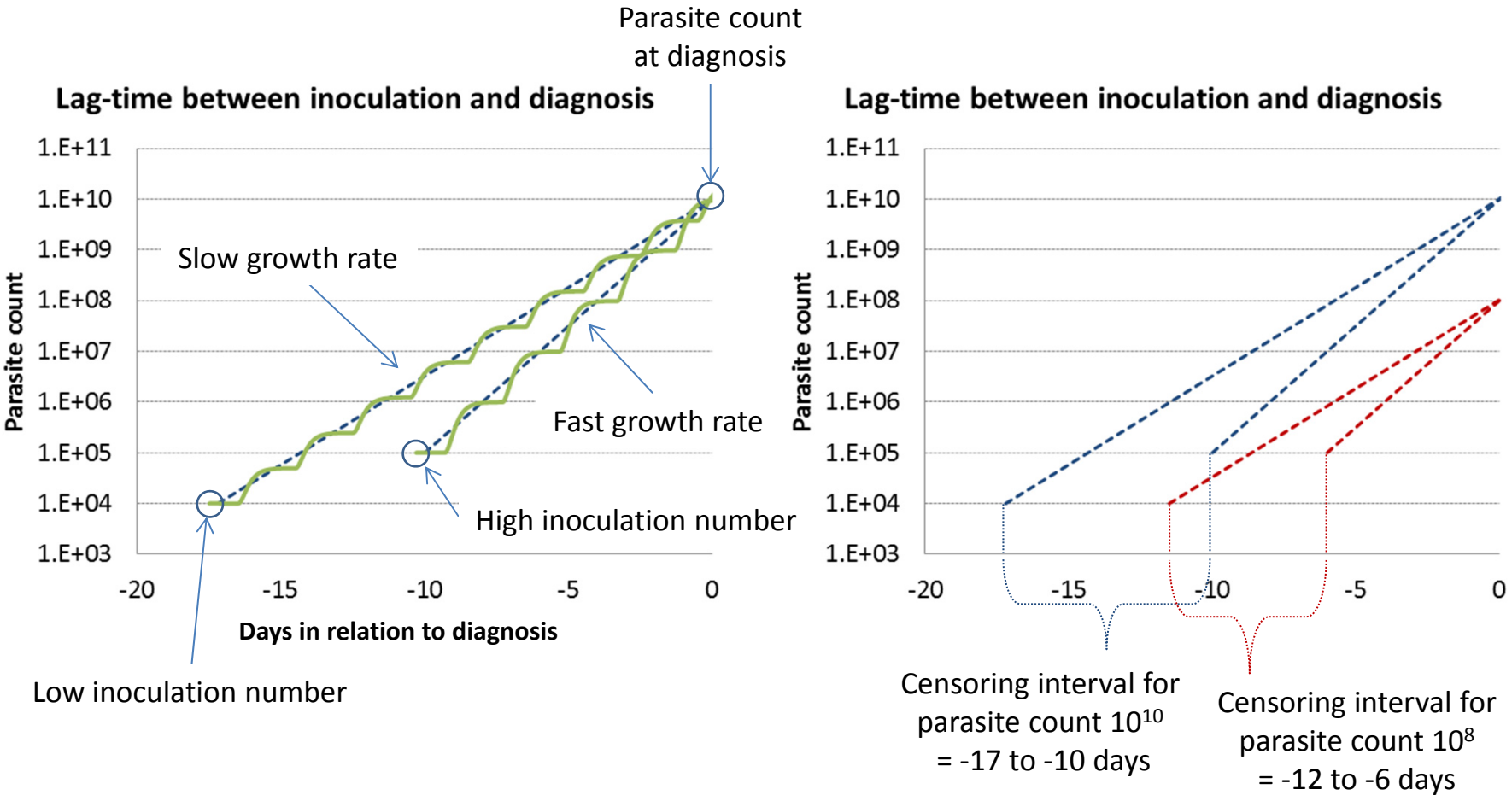
UPPSALA UNIVERSITET

A potential issue for PKPD

- The concentrations at time of diagnosed malaria is not the most relevant
- The critical point is at the start of the parasite blood stage (parasite release from liver)
- If PQ plasma concentrations are sufficient at this stage there will be no symptomatic infection



The solution:
Event time censoring interval



$$\text{Lag-time} = \text{Ln}(PAR_{observed}/PAR_{inoculation}) / K_{growth}$$

UPPSALA UNIVERSITET

Account for DHA effect

- Piperaquine is given in combination with DHA which has a very potent effect but also a very short half-life (1-2 hr)
- Ongoing infections that is not visible on a microscope slide (approx. $<10^7$) will be censored due to the curative effect of DHA (and PQ)
- Assumption: rapid growth (x10 every 48 h) and high inoculation (10^5) $\Rightarrow$ hazard assumed to be zero during 4 days prior to DHA dosing
  - ! Improved model fit
  - ! Important assumption for extrapolations into more frequent dosing

UPPSALA UNIVERSITET

Accounting for lag-time and DHA effect

⇒ Small increase in estimated IC_{50} value
6.3 -> 7.0 ng/mL

⇒ Decreased hill-factor (γ):
3.6 -> 2.8
(i.e. slightly less steep concentration-effect relationship)

⇒ Generally better precision for all model parameters

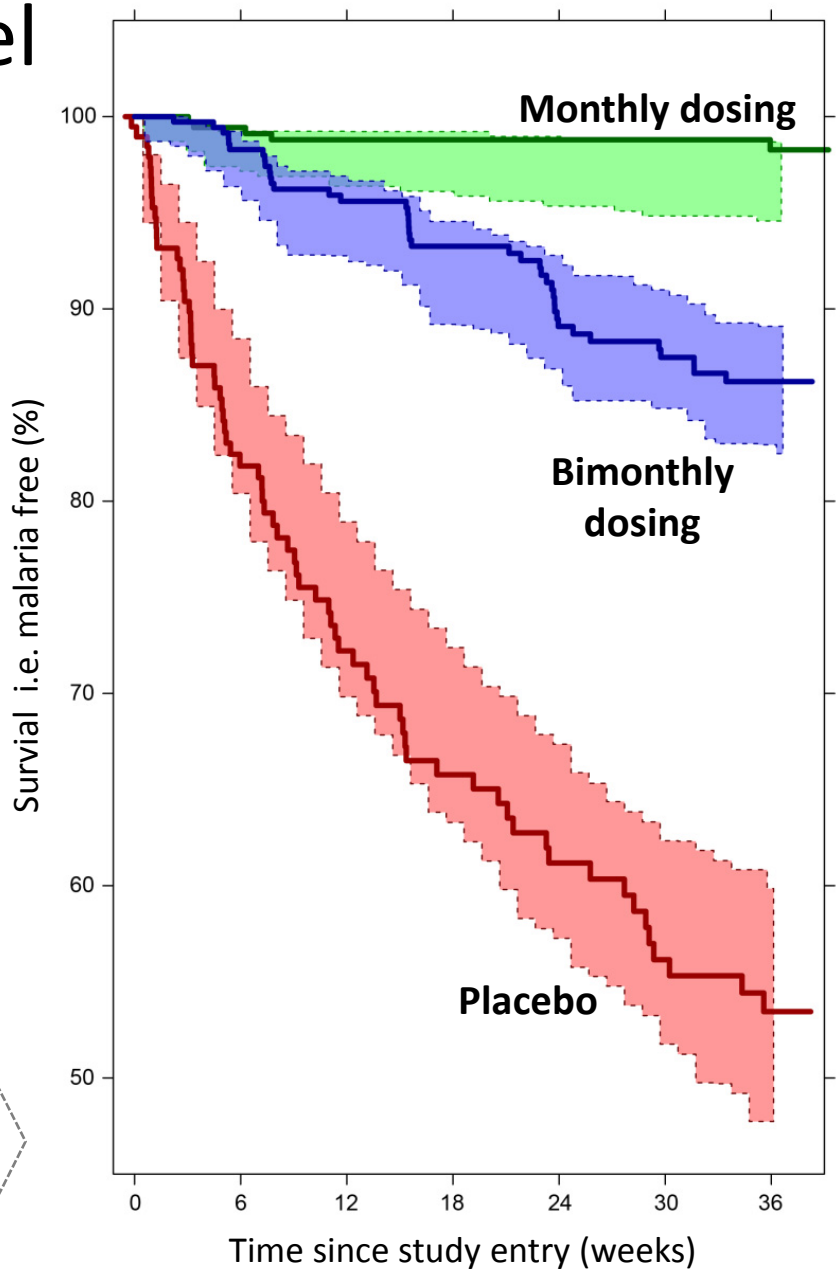
- The impact was modest due to the long terminal $t_{½}$ of PQ

UPPSALA UNIVERSITET

Final PKPD model

Parameter	Estimate (RSE, %)
Pharmacodynamics	
Baseline hazard mixture 1, BHz_1 ($year^{-1}$)	3.77 (10)
Baseline hazard mixture 2, BHz_2 ($year^{-1}$)	0.25 (10)
Probability of mixture 2, PMIX-2	0.70 (6)
Amplitude of seasonal peak, AMP	2.17 (27)
Center of seasonal peak, PT (months)	4.93 (3)
Duration of seasonal peak, WD (months)	2.59 (9)
Age on mixture 2 probability, AGE-PMIX-2	1.64 (36)
Pharmacokinetic – Pharmacodynamic interaction	
PQ IC_{50} (ng/mL)	6.96 (13)
Hill-factor, γ	2.79 (15)

Solid lines => Kaplan–Meier survival curve
Corresponding fields => simulation based 95% confidence interval



UPPSALA UNIVERSITET

Translational simulations

IPT in children

- What is the clinical relevance of the previously established lower exposure in children (with recommended dosing)?
- Translate to IPT treatment

nature publishing group
ARTICLES
Open

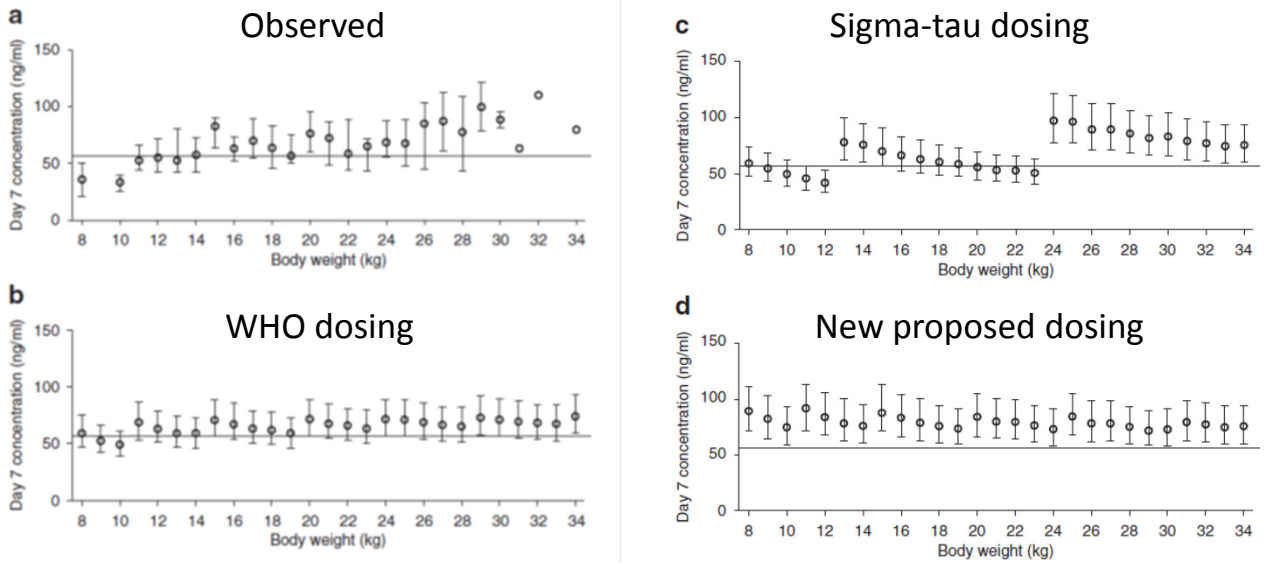
Population Pharmacokinetics and Pharmacodynamics of Piperaquine in Children With Uncomplicated Falciparum Malaria

J Tarning[1,2], I Zongo[3], FA Somé[3], N Rouamba[3], S Parikh[4], PJ Rosenthal[4], W Hanpithakpong[1], N Jongrak[1], NPJ Day[1,2], NJ White[1,2], F Nosten[1,2,5], J-B Ouedraogo[3] and N Lindegardh[1,2]

[1]Mahidol-Oxford Tropical Medicine Research Unit, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand; [2]Centre for Tropical Medicine, Nuffield Department of Clinical Medicine, University of Oxford, Oxford, UK; [3]Institut de Recherche en Sciences de la Santé, Bobo-Dioulasso, Burkina Faso; [4]Department of Medicine, University of California, San Francisco, San Francisco, California, USA; [5]Shoklo Malaria Research Unit, Mae Sot, Thailand. Correspondence: J Tarning (joel@tropmedres.ac)

Received 20 June 2011; accepted 6 September 2011; advance online publication 18 January 2012. doi:10.1038/clpt.2011.254

CLINICAL PHARMACOLOGY & THERAPEUTICS



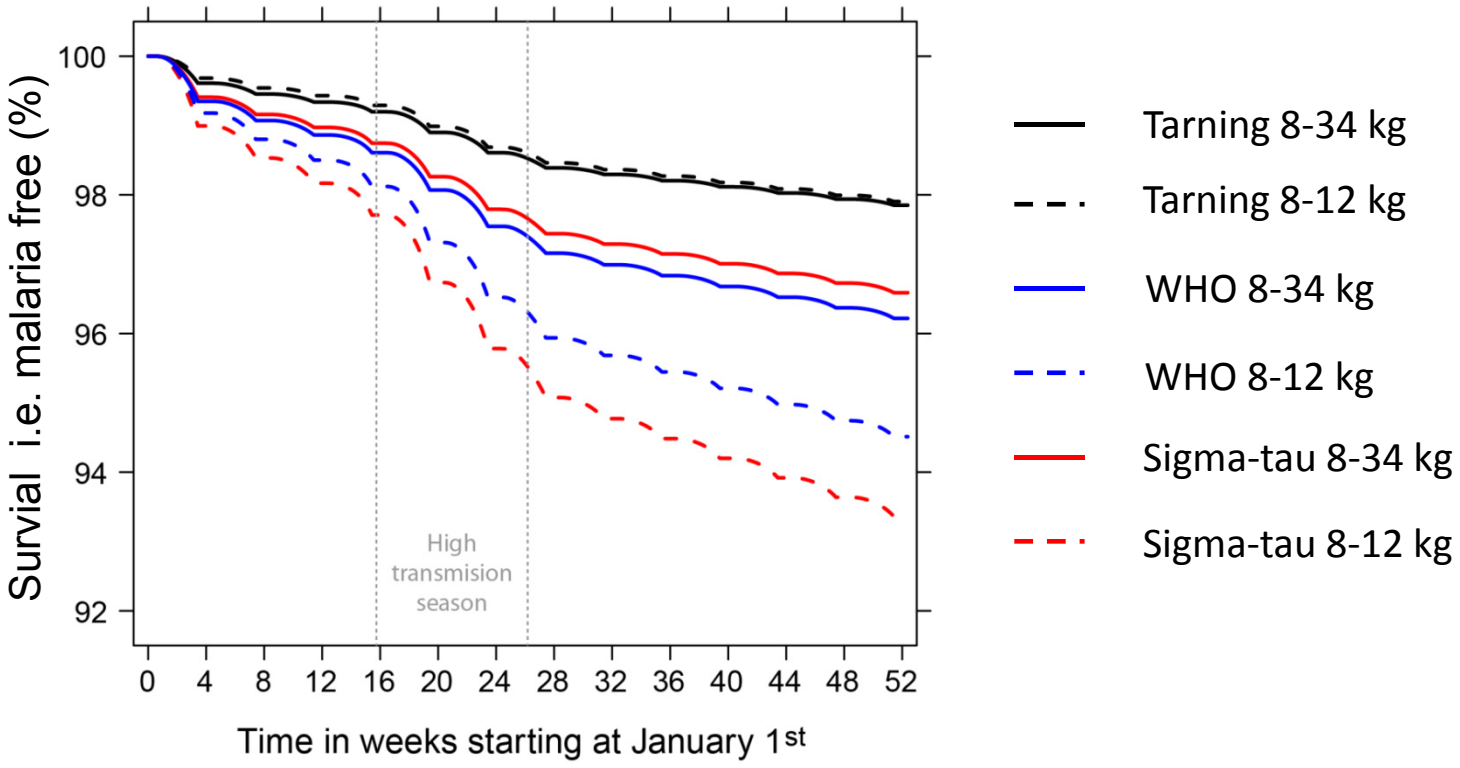
Note:
Capillary piperaquine concentrations in graph (≈ 1.4 × plasma concentrations)

UPPSALA UNIVERSITET

Translational simulations

IPT in children

- PK model and dosing algorithms according to Tarning et al. 2012
- PD and PKPD parameters according to presented model
- Monthly dosing (all subjects start 1st of January)



UPPSALA UNIVERSITET

Translational simulations

PQ resistance

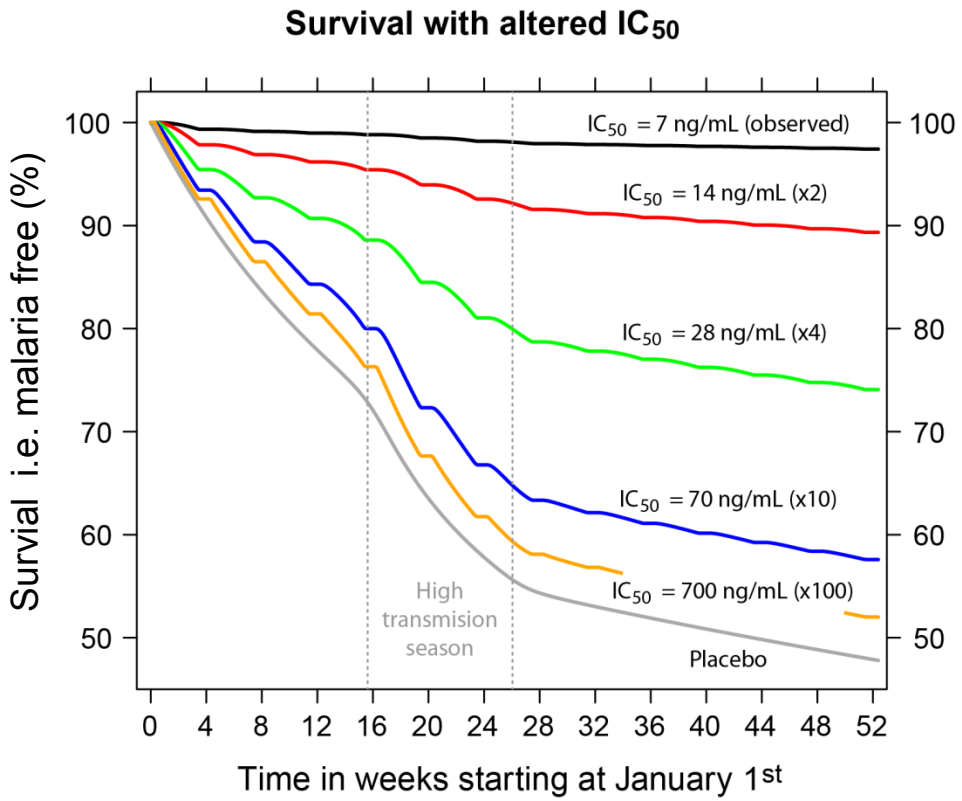
- The estimated IC_{50} value corresponds well with reported values on *in vitro* IC_{50} values on parasite growth
  - Estimated *in vivo* IC_{50} (on hazard) = 7 ng/mL
  - Reported *in vitro* IC_{50} (parasite growth) = 4.2 - 42 ng/mL (most recent reported value 9 ng/mL [4])
- Piperaquine resistance have been reported to increase the *in vitro* IC_{50} value up to 100 fold both when resistance was induced *in vitro* and observed in field isolates [4]
- Based on a proportionality between *in vitro* and *in vivo* IC_{50}, simulations was performed to predict the consequence of different degrees of PQ resistance

[4] Richard T. Eastman etal. Piperaquine Resistance Is Associated with a Copy Number Variation on Chromosome 5 in Drug-Pressured Plasmodium falciparum Parasites. Antimicrob Agents Chemother. 2011 August; 55(8): 3908–3916

UPPSALA UNIVERSITET

Translational simulations

PQ resistance



- Simulation of monthly dosing in the study population with altered IC_{50}
- A modest resistance (2-4 x IC_{50}) drastically alter the expected outcome
- A 10-fold increase or more makes the treatment virtually ineffective

UPPSALA UNIVERSITET

Conclusions

- A *in vivo* concentration-effect relationship for the malaria preventive effect of PQ has been established
- The established model was useful in translating observed results from a healthy male population to that expected in target populations and under other circumstances
  - A new dosing recommendation for PQ in children has the potential to lower the yearly malaria incidence with 50% for children in general and by 70% for the 8 to 12 kg weight strata

Thanks to colleagues at:

UPPSALA UNIVERSITET

Mahidol Oxford MORU
WELLCOME TRUST - MAHIDOL UNIVERSITY-OXFORD TROPICAL MEDICINE RESEARCH PROGRAMME

and the Clinical Pharmacology Department in particular

The Pharmacometrics research group at

UPPSALA UNIVERSITET

Pharmetheus
Pharmacometrics Consulting Services