Semi-Mechanistic Time-to-Event Modelling in Malaria

- a pharmacometric approach to tropical medicine research

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TROPICAL MEDICINE RESEARCH PROGRAMME

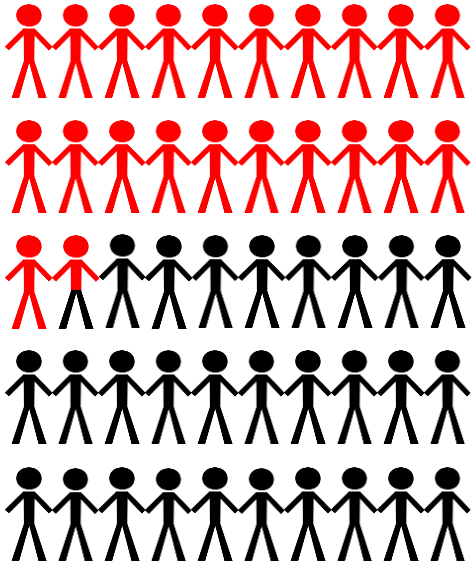
Mahidol-Oxford Tropical Research Unit

"MORU aims to fight infectious tropical diseases affecting rural communities in Asia and elsewhere in the developing world. We develop effective and practical means of diagnosing and treating Malaria and other neglected diseases such as Typhus, Melioidosis, and Leptospirosis"
(*http://www.tropmedres.ac*)

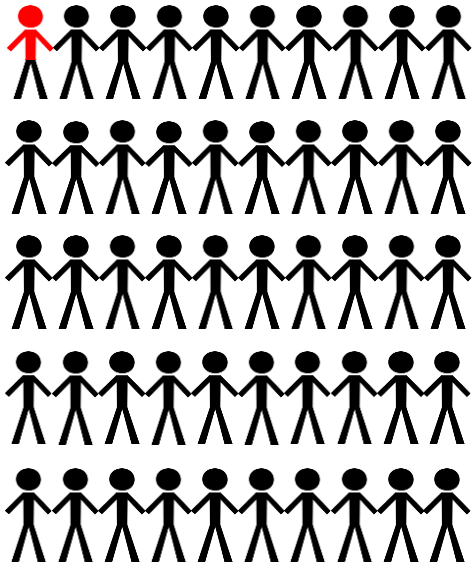
Neglected Tropical Diseases (NTDs)

- NTDs thrive mainly among the poorest populations
- NTDs are endemic in 149 countries and affect more than 1.4 billion people
- NTDs cost developing economies billions of dollars every year

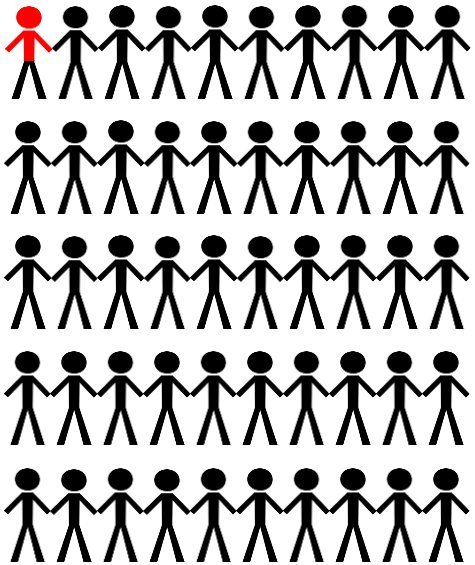
43% of the world's pop. at risk of NTDs



1% of new entities from the public market



1% of the global R&D goes toward NTDs

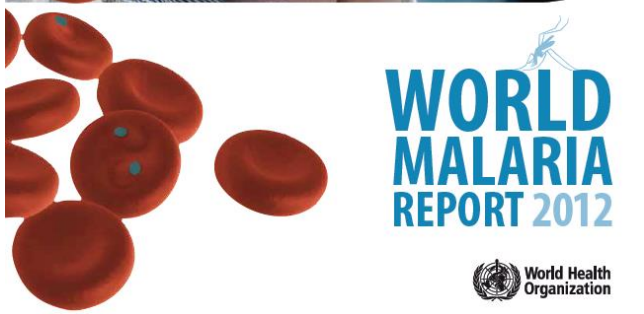


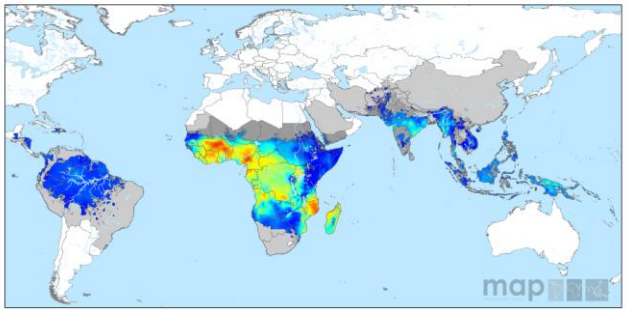
Slingsby, JITMM, 2014

Malaria

Malaria statistics (estimates) according to WHO

- **Half of the world's population live in areas at risk of malaria transmission**
- An estimated 207 million clinical episodes and 627,000 deaths annually (2012)
- **Approximately 1,700 people die each day from malaria**
- Children under the age of five and pregnant women are most severely affected
- Malaria is strongly associated with poverty
- **PK/PD properties are poorly understood for many of the current antimalarial drugs**
- Most antimalarial drugs were introduced at the wrong dose



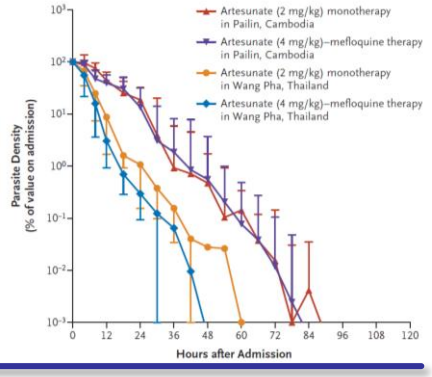


Malaria

Malaria control and elimination mechanisms

- **Vector control**
  - Indoor residual insecticide spraying
  - Long-lasting insecticide-treated bed nets
  - *Availability, price, resistance, usage*
- **Antimalarial drug therapy**
  - Artemisinin-based combination therapy (ACT); short acting drug + long acting drug
  - *Compliance, availability, price, resistance, drug quality*
- No available vaccines that can prevent malaria

Shrimp fishing with bed net (photo Moizo Bernard)



Artemisinin-resistant malaria is the single greatest threat to our ability to control and eliminate malaria

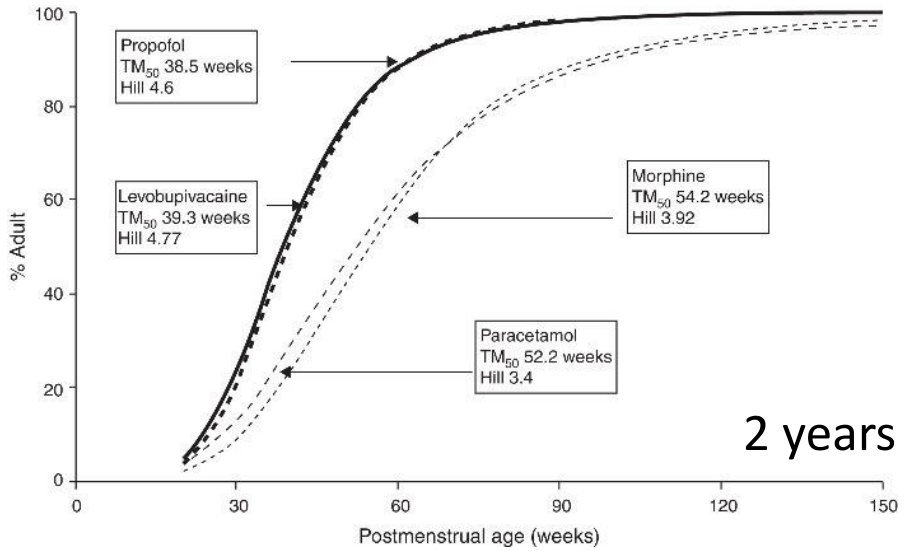
Dondorp et al, NEJM, 2009

PK/PD in children

Why a particular interest in paediatric patients?

- **85% of all malaria-related deaths occur in children under the age of 5**
- Children are not small adults!
- Nonlinear relationship between body weight (and age) and drug exposure

- Piperaquine: ↓ AUC [Tarning, 2012]
- Artesunate/DHA: ↓/↓ AUC [Tarning, 2013]
- Lumefantrine: ↓ AUC [Mwesigwa, 2010; Checchi, 2006]
- Amodiaquine: ↓ AUC [Mwesigwa, 2010]
- Chloroquine: ↓ AUC [Karunajeewa, 2008]
- Sulfadoxine: ↓ AUC [Barnes, 2006]
- Pyrimethamine: ↓ AUC [Barnes, 2006]
- Artemether/DHA: ↑/↑ AUC [Mwesigwa, 2010]
- Desethylamodiaquine: ↑ AUC [Mwesigwa, 2010]



Anderson, Rev. Colomb. Anestesiol. 2013

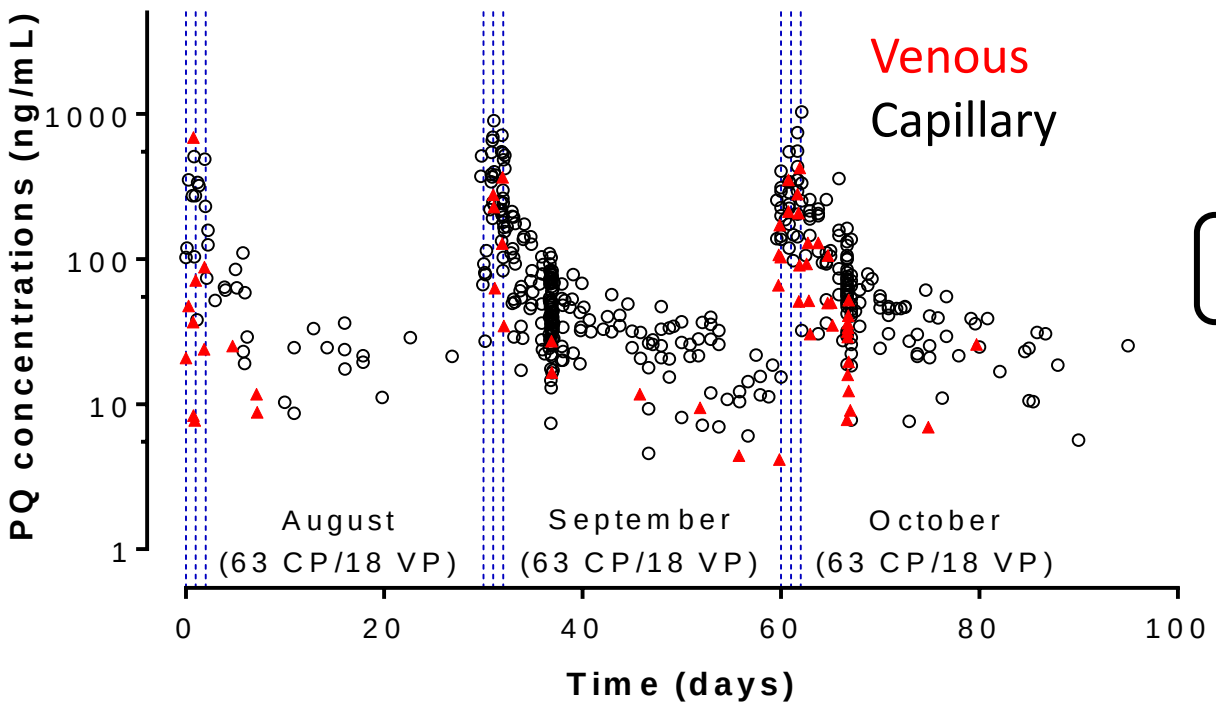
Piperaquine PK/PD in children

- Patients:
  - Intermittent seasonal preventive treatment in Burkina Faso
  - 183 children in PK/PD arm (0.2-5 years)
  - 562 children in PD arm (large efficacy trial)
  - High transmission season (August, September, October)
- Drug regimen:
  - WHO guided dosing (2 mg/kg/day DHA and 18 mg/kg/day PQ)
  - 3 day fixed oral dose, once a month for three months
- Sparse blood sampling:
  - Finger prick capillary sampling (~200 µl)
  - Pre-dose, 0-6 days, day 7, and 8-30 days
- Piperaquine assay:
  - LC-MS/MS
- NONMEM

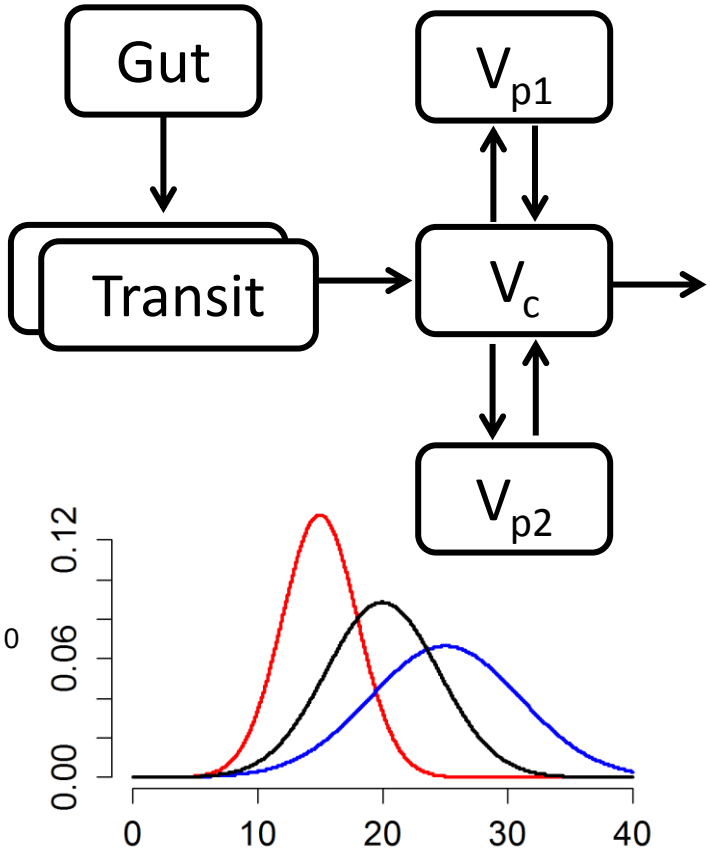
Chotsiri et al, unpublished

Piperaquine PK/PD in children

Observed piperaquine concentrations



Pharmacokinetic model



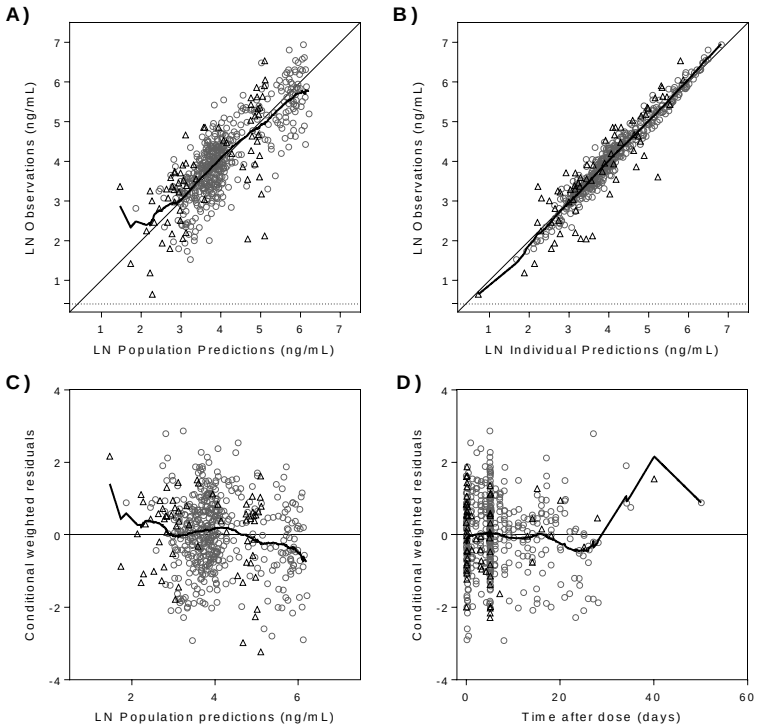
- Sparse sampling
- 2-4 samples/individual
- PRIOR approach (Tarning et al, CPT, 2012)
- Allometric scaling of PK parameters

$$P(\Theta|Data) = \frac{P(\Theta) \cdot P(Data|\Theta)}{P(Data)}$$

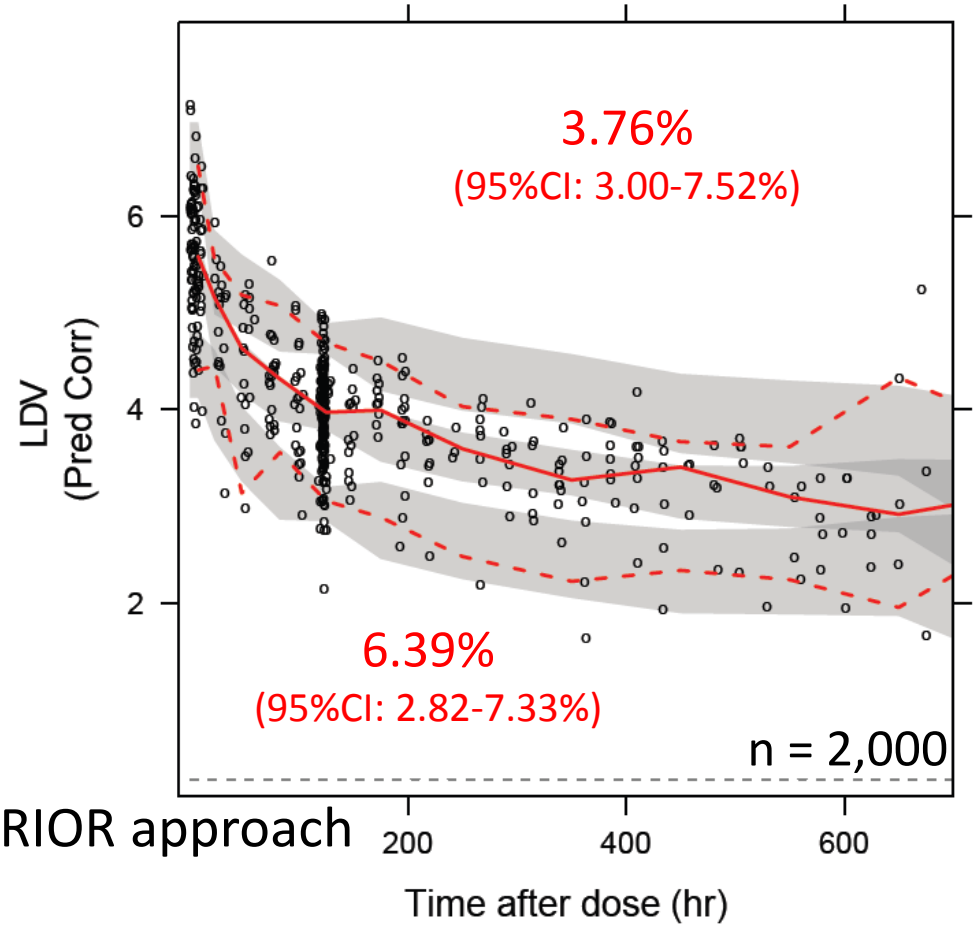
Chotsiri et al, unpublished

Piperaquine PK/PD in children

Basic Goodness-of-fit



Visual predictive check



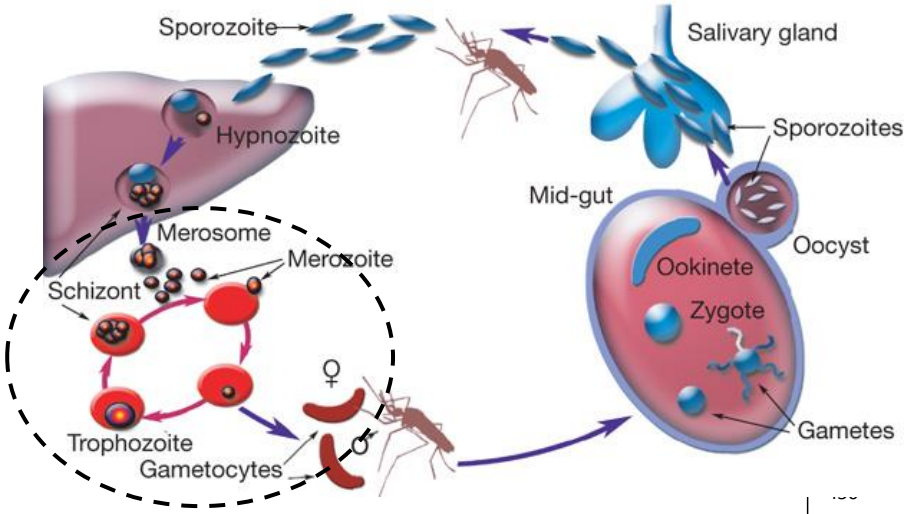
- Successfully stabilised PK with PRIOR approach
- High predictive performance

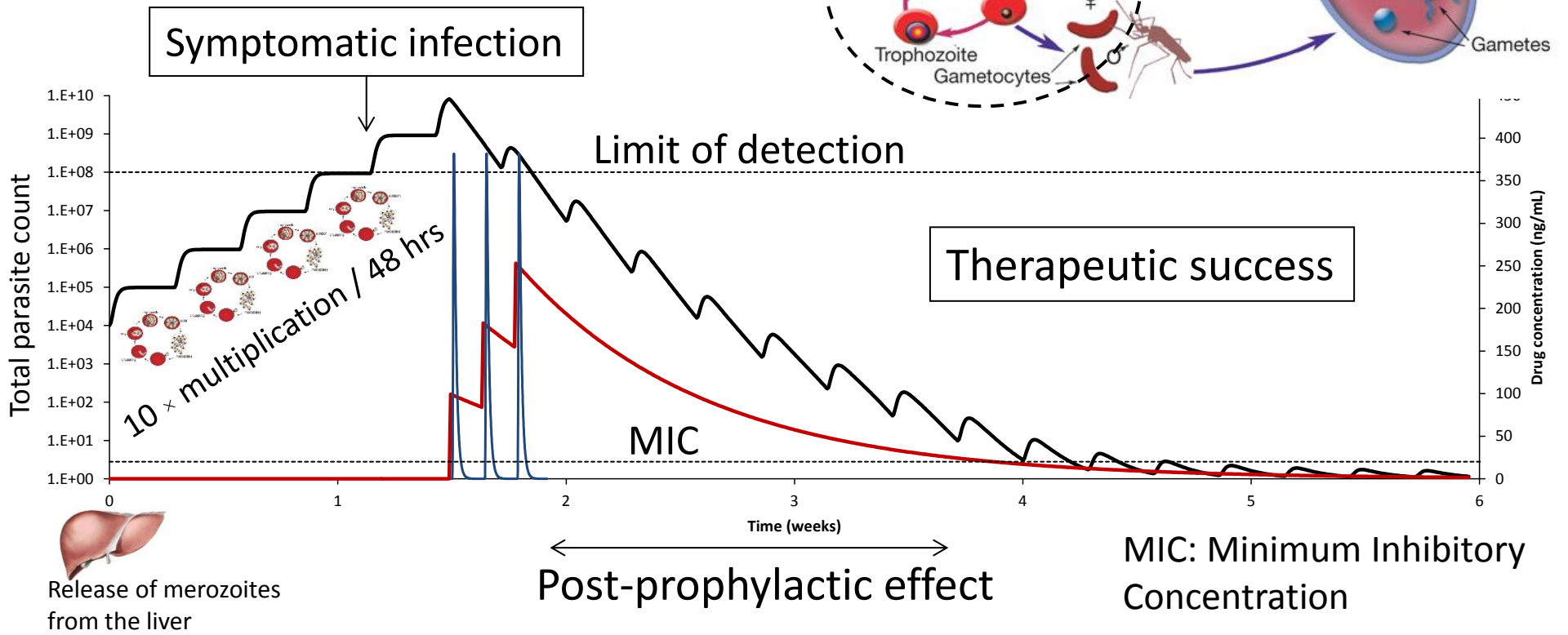
  => PD modelling (time to infection)

Chotsiri et al, unpublished

Malaria PK/PD

- PD modelling
- Treatment of malaria
- Sufficient drug concentrations to eliminate symptomatic infections?





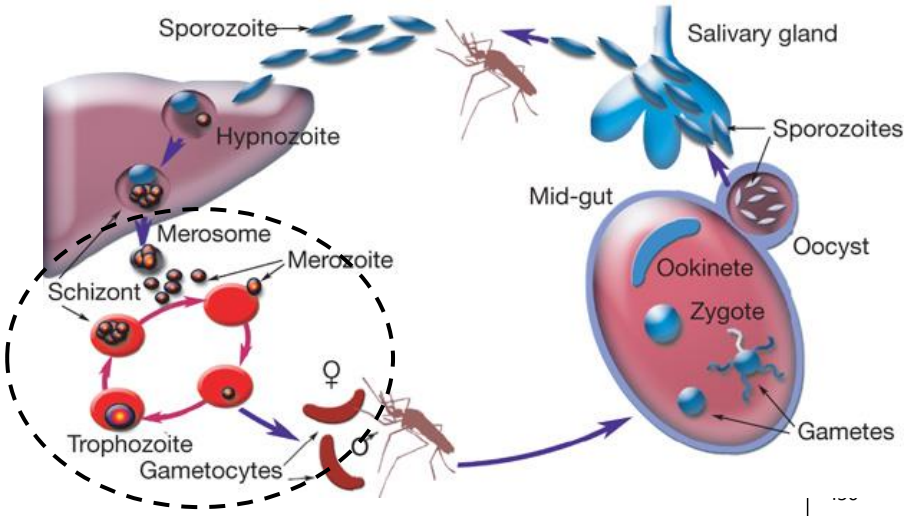
Release of merozoites from the liver

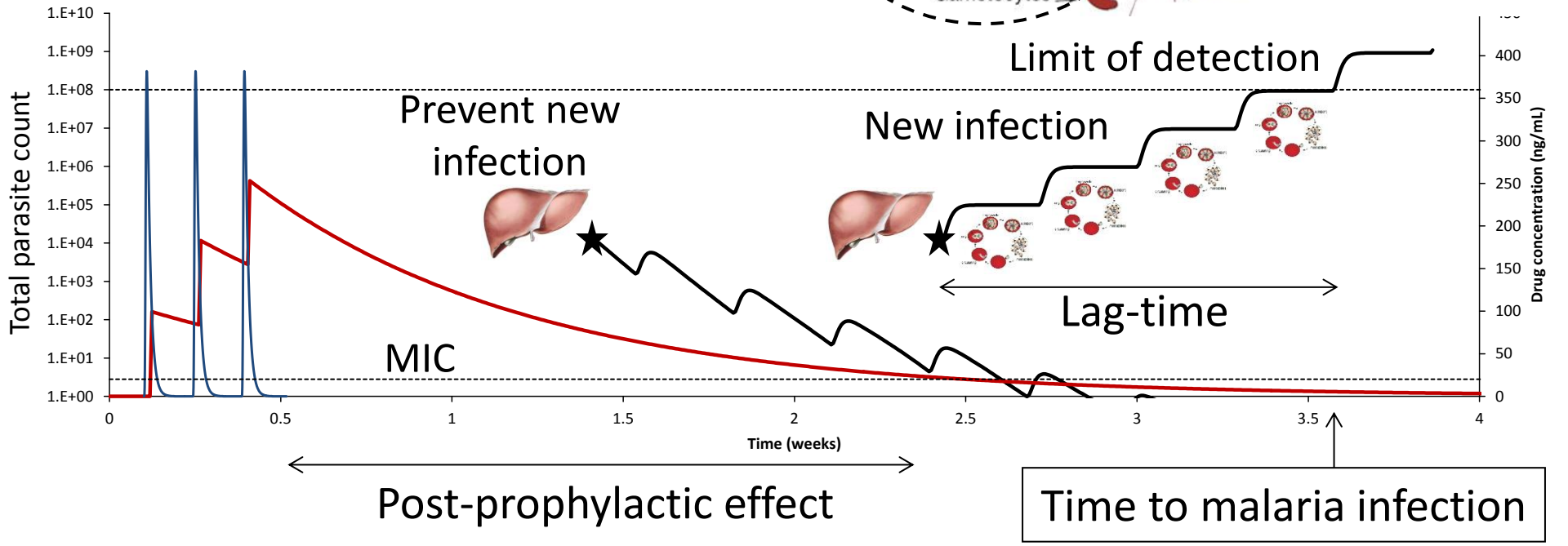
Post-prophylactic effect

MIC: Minimum Inhibitory Concentration

Malaria PK/PD

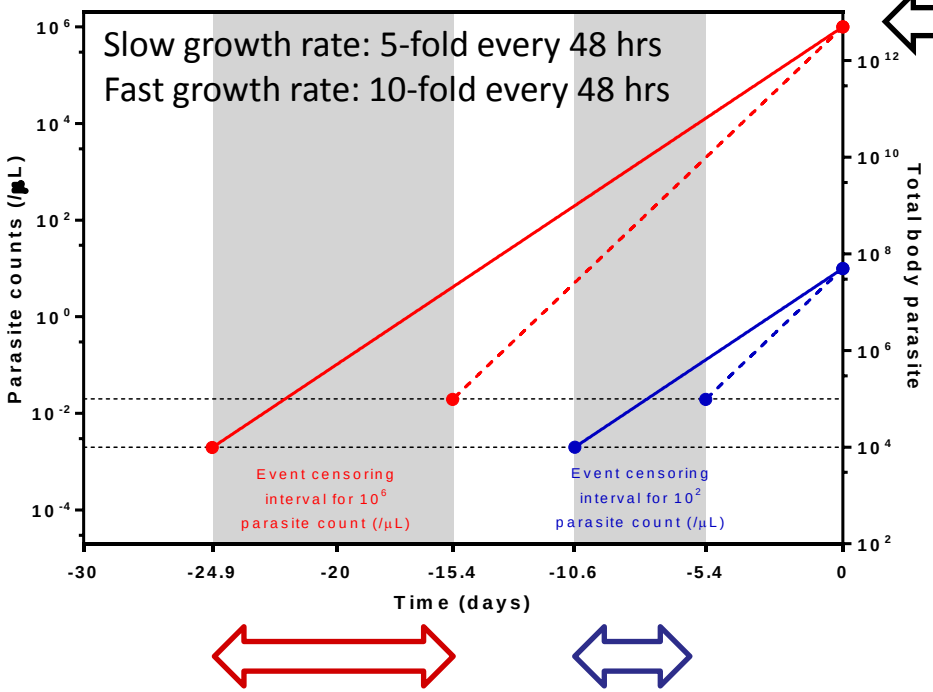
- Preventive treatment
- PD: Time to malaria infection
- Sufficient drug concentrations to eliminate new infections?
- Microscopic case detection / Lag-time





Piperaquine PK/PD in children

Parasitemia corrected censored interval (Bergstrand et al, Science Trans Med, 2014)



Observed high parasitemia

Starting interval of erythrocyte infection

Mechanistic interpretation of PK/PD estimates

Interval censoring TTE model

Hazard function:

$$Hz(t) = \Theta_{BASE} \times \left(1 - \frac{E_{MAX} \times CP(t)^{\gamma}}{EC_{50}^{\gamma} + CP(t)^{\gamma}}\right)$$

Survival function:

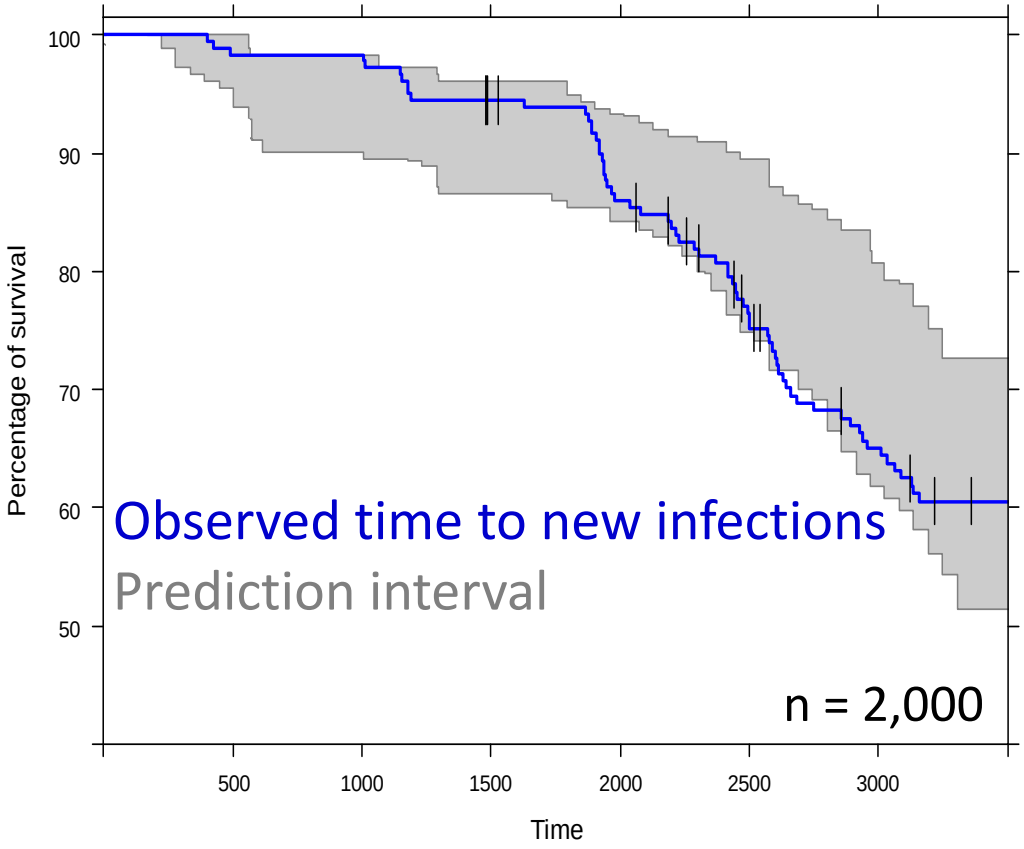
$$S(t) = \exp\left(-\int_0^t Hz(t)dt\right)$$

Probability of event occurring in the interval:

$$\Pr(a < t < b \mid \Theta) = 1 - [S(b) - S(a)]$$

Piperaquine PK/PD in children

Visual predictive check



Final PK/PD model

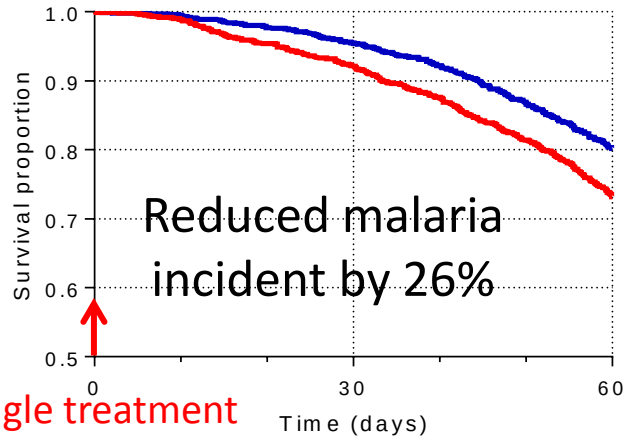
- PK: PRIOR – Allometry (BW)
- Parasite-based censoring provided a more mechanistic interpretation
- Constant hazard model with E_{MAX}-type drug effect
- Baseline hazard was 7.24 infections/year (CI: 4.61-11.5)
- EC_{50} of piperaquine was 6.08 ng/mL (CI: 5.04-14.3)
- Shape factor (γ) was 1.46 (CI: 1.23-2.78)

Developed PK/PD model is suitable for simulations

Chotsiri et al, unpublished

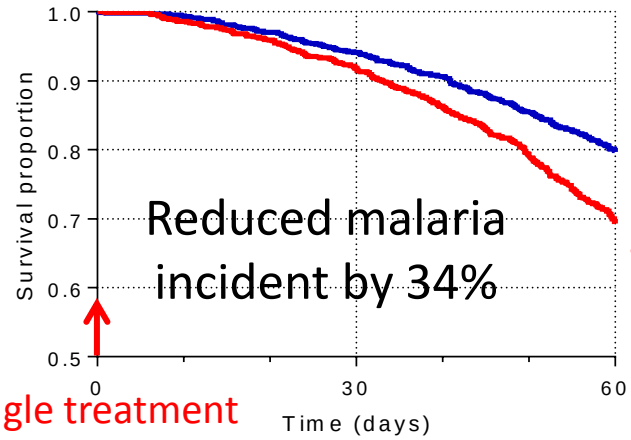
Piperaquine PK/PD in children

(A) 5-20 kg children



Single treatment

(B) 5-10 kg children

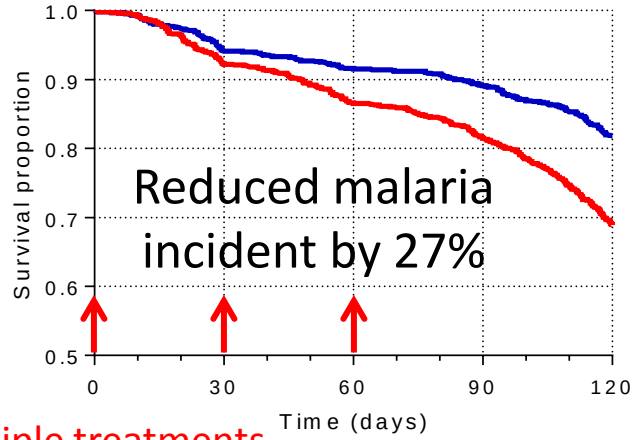


Single treatment

Increased dose (Tarning, CPT, 2012)

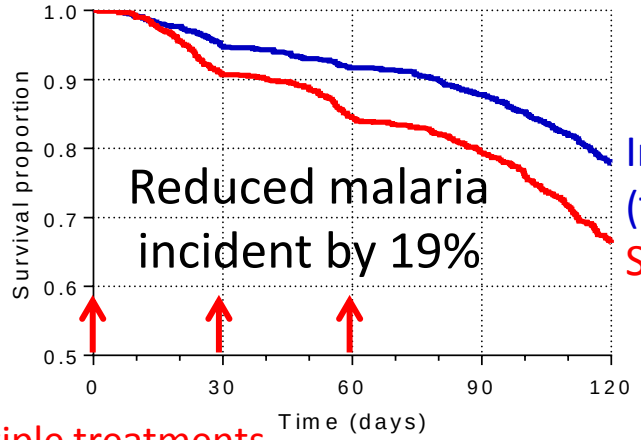
Standard dose

(C)



Multiple treatments

(D)



Multiple treatments

Increased dose (Tarning, CPT, 2012)

Standard dose

Chotsiri et al, unpublished

Piperaquine PK/PD in children & adults

Citation: CPT Pharmacometrics Syst. Pharmacol. (2014) 3, e132; doi:10.1038/psp.2014.29

www.nature.com/psp

ORIGINAL ARTICLE

Population Pharmacokinetics and Antimalarial Pharmacodynamics of Piperaquine in Patients With *Plasmodium vivax* Malaria in Thailand

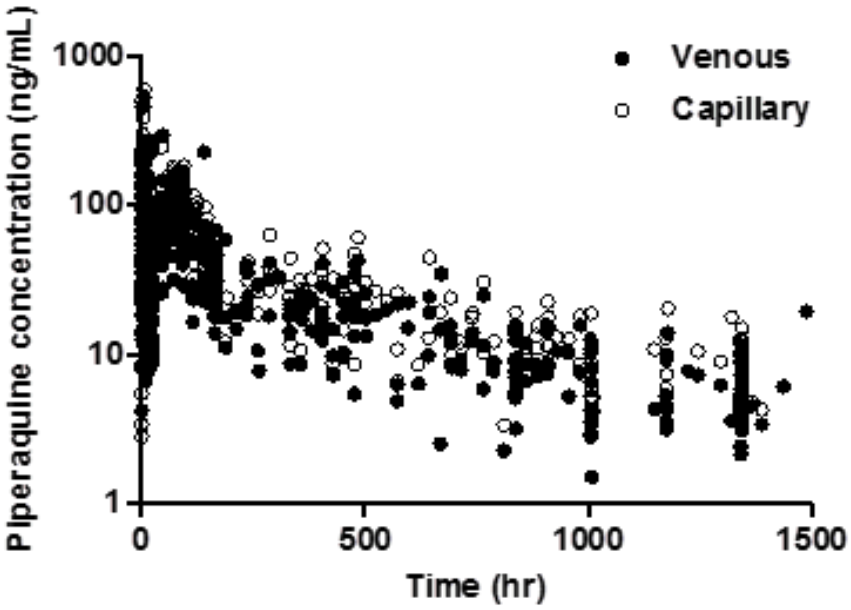
J Tarning[1,2], P Thana[1], AP Phyo[3], KM Lwin[3], W Hanpithakpong[1], EA Ashley[1,2,3], NPJ Day[1,2], F Nosten[1,2,3] and NJ White[1,2]

- 241 Karen and Burmese patients infected with *Plasmodium vivax* malaria
- Standard 3-day treatment with oral dihydroartemisinin and piperaquine
- Blood sampling from 116 patients at 6 random time points over 69 days and at relapsing malaria
- LC-MS/MS
- NONMEM

Tarning et al, CPT:PSP, 2014

Piperaquine PK/PD in children & adults

Concentration-time profile

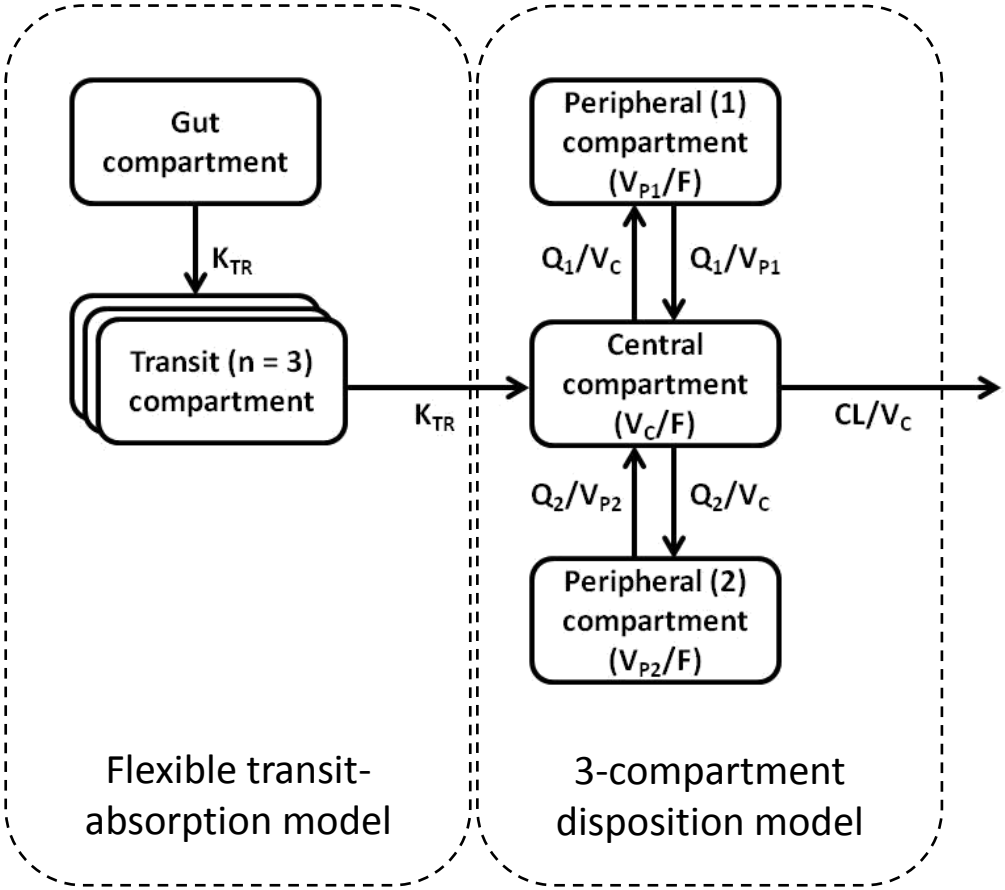


Sparse data (simultaneous fit)

- 435 venous plasma samples
- 356 capillary plasma samples

Tarning et al, CPT:PSP, 2014

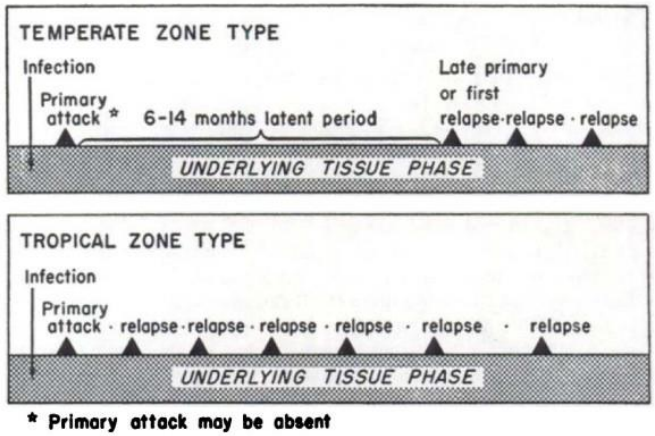
Structural model



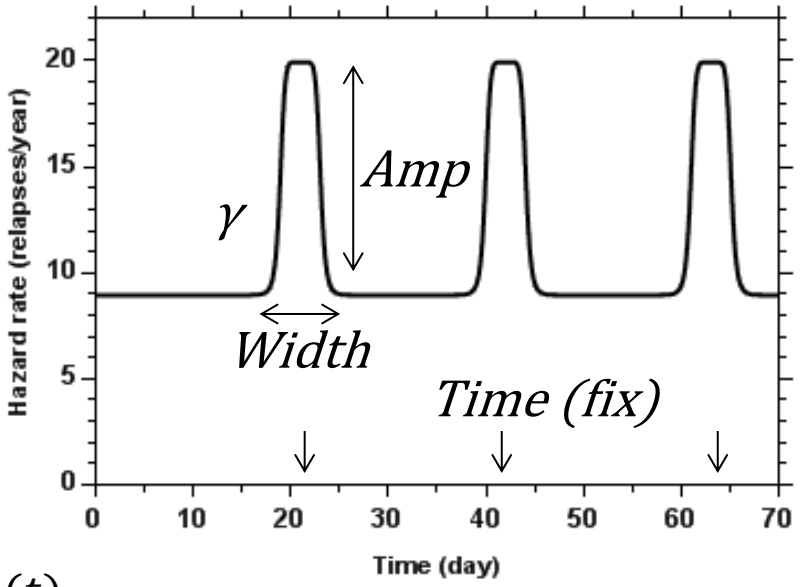
Body-weight – allometric function

Piperaquine PK/PD in children & adults

- *Vivax* malaria in tropical regions displays frequent relapses in 3 week intervals (White, 2011)
- Constant hazard function
- A multiple surge function was implemented to characterize the periodically increased risk of relapsing malaria



$$Surge(t) = 1 + \left\lfloor \frac{Amplitude}{\left(\frac{(t - Time)^2}{Width^2}\right)^{\gamma} + 1} \right\rfloor$$



$$Relapse(t) = Surge(t)_{3wk} \times Surge(t)_{6wk} \times Surge(t)_{9wk}$$

Tarning et al, CPT:PSP, 2014

Piperaquine PK/PD in children & adults

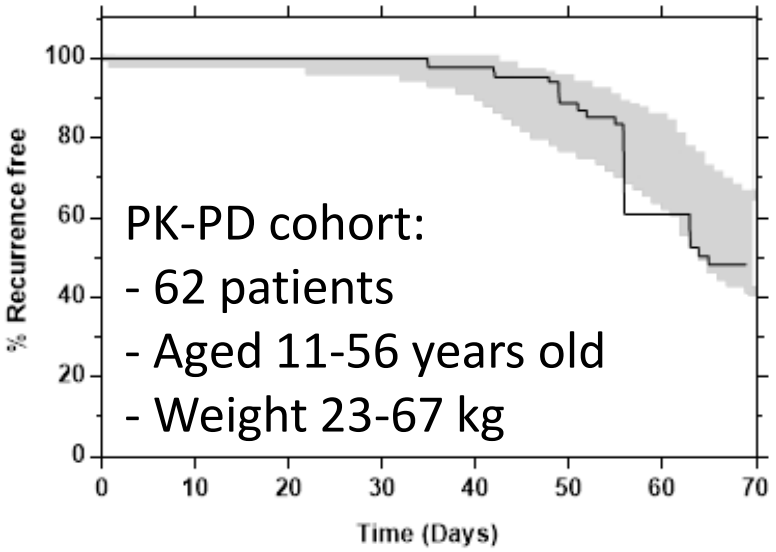
Drug effect and covariates were investigated

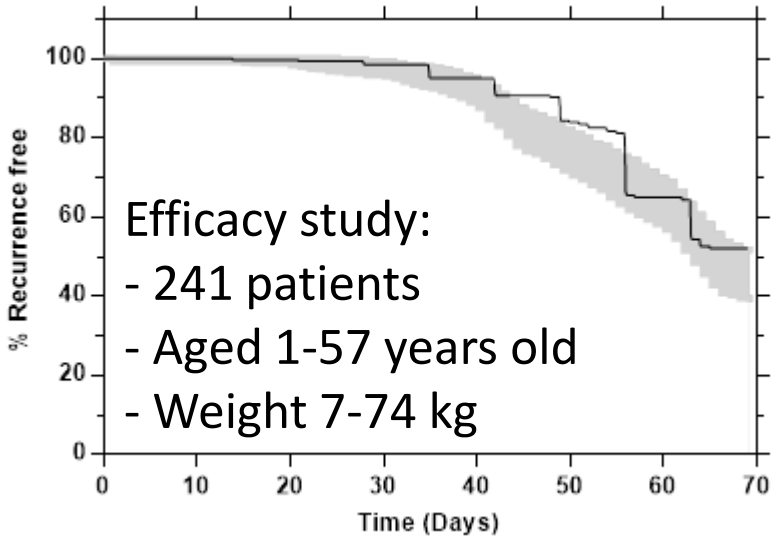
- Inhibitory maximum effect (E_{MAX}) function

$$h(t) = \theta_{BHZ} \times relapse(t) \times \left[1 - \frac{C(t)^{\gamma}}{C(t)^{\gamma} - IC50^{\gamma}}\right]$$

- Covariate free PD model

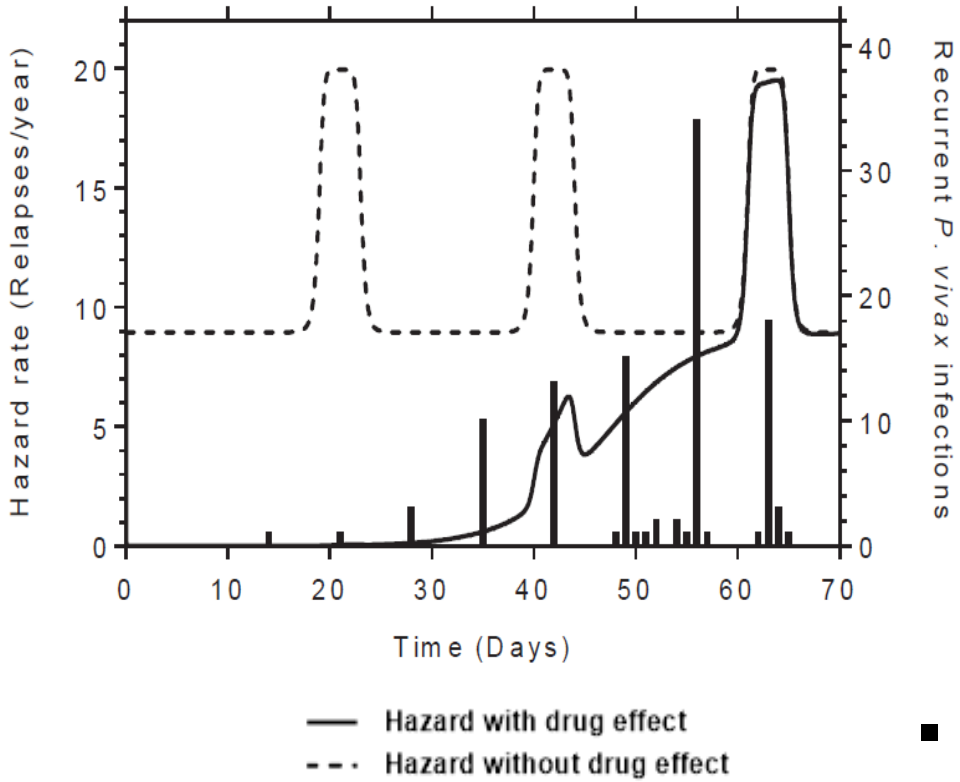
Pharmacodynamics parameters	Population estimates [%RSE]	95% CI for estimates
θ_{BHZ} (relapses/year)	8.94 [22.1]	4.80-11.7
θ_{SA} (%)	123 [23.7]	61.8-165
θ_{SW} (h)	49.5 [54.3]	35.7-80.4
θ_{SHP}	4 Fixed	-
PC_{50} (ng/ml)	6.92 [15.5]	6.15-11.3
γ	9.28 [25.6]	5.09-14.0

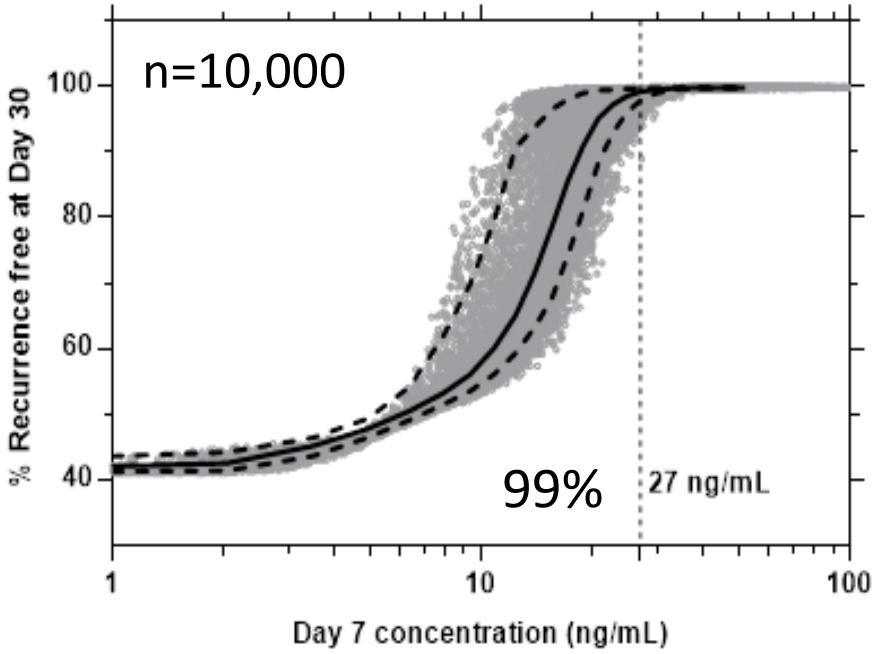




Tarning et al, CPT:PSP, 2014

Piperaquine PK/PD in children & adults





Piperaquine fully suppressed the first relapse 3 weeks after the initial infection

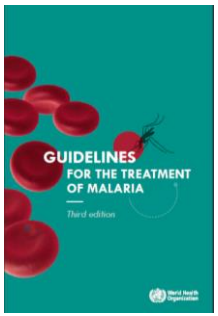
- Day 7 piperaquine concentration above 27 ng/mL can suppress the risk of relapse for 30 days
- Major implications on the disease burden (morbidity of relapses)

Tarning et al, CPT:PSP, 2014

Concluding remarks

- Half of the world's population live in areas at risk of malaria transmission
- Approximately 1,700 people die every day from malaria (mainly <5 year)
- Malaria is a preventable and curable disease
- We have used a pharmacometric approach to identify patient groups at particular risk of therapeutic failures (and resistance development)
- We have used a pharmacometric approach to optimise the dosing in these sub-groups of patients, up to 34% reduction of malaria in young children
- Dihydroartemisinin-piperaquine is a suitable treatment of *vivax* malaria, able to suppress fully the first relapse of malaria (morbidity impact)
- We have shown that a pharmacometric approach is a highly useful tool in tropical medicine research and can have a major impact on policy

Revised antimalarial treatment guidelines for young children



Acknowledgements

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- All colleagues at WWARN
- All colleagues at Oxford

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Poster # I 54

Thank you for your attention



Department of Clinical Pharmacology

Questions?



Pharmacometricians

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