Nonlinear mechanistic models for improving the treatment of malaria:
Balancing model complexity with statistical rigour

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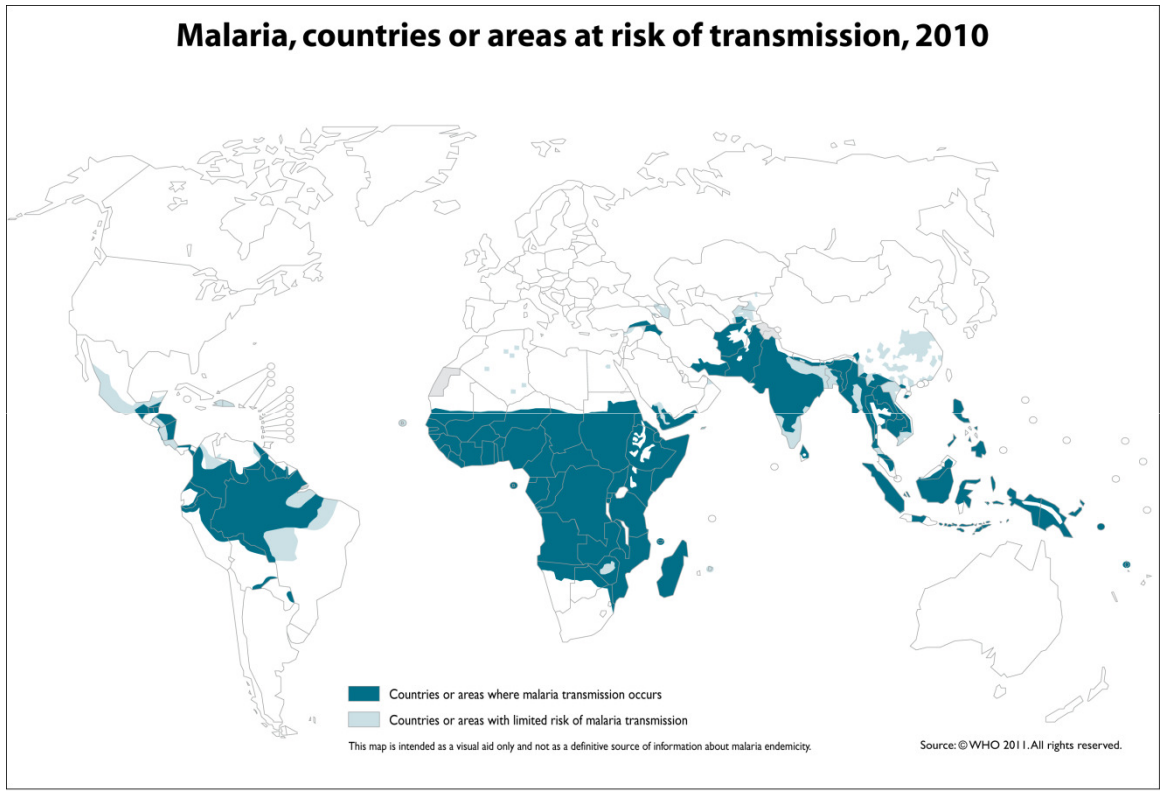
Overview of presentation

- Clinical research question
- Mechanistic pharmacokinetic models
  - Structural models
  - Statistical modelling
  - Design of future pharmacokinetic studies
- Mechanistic within-host pharmacokinetic-pharmacodynamic models for malaria
  - Parasite age-structured model
  - Statistical and data measurement challenges
- Translation to policy
- Future work

Clinical research question: Malaria current burden

216 million cases of malaria in 2010 - 655,000 deaths



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World Health Organization

Clinical research question: Malaria control

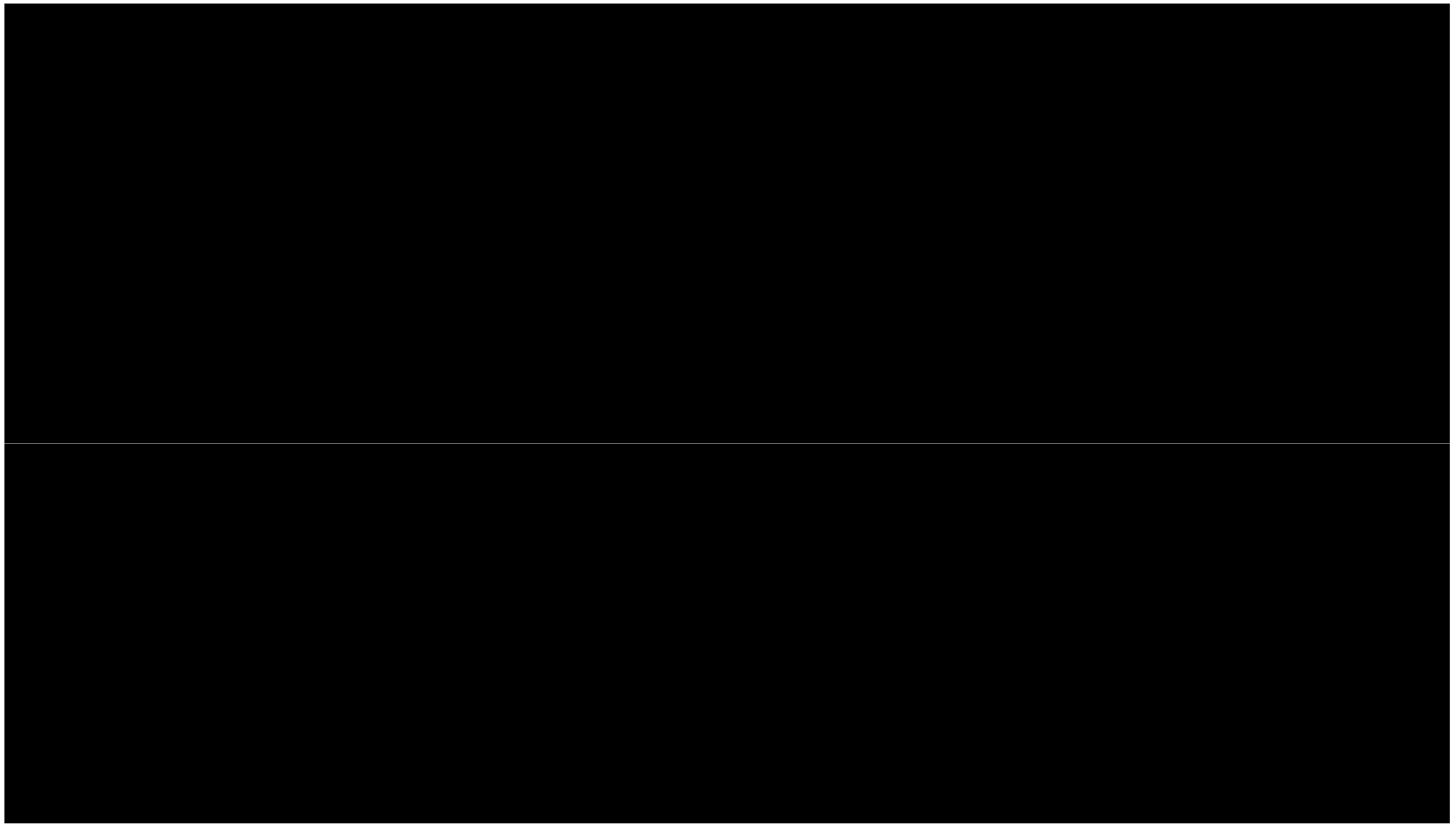
WHO recommendations

- Long lasting insecticidal nets
- Effective treatment

- Indoor residual spraying of insecticide
- Intermittent preventive treatment in pregnancy

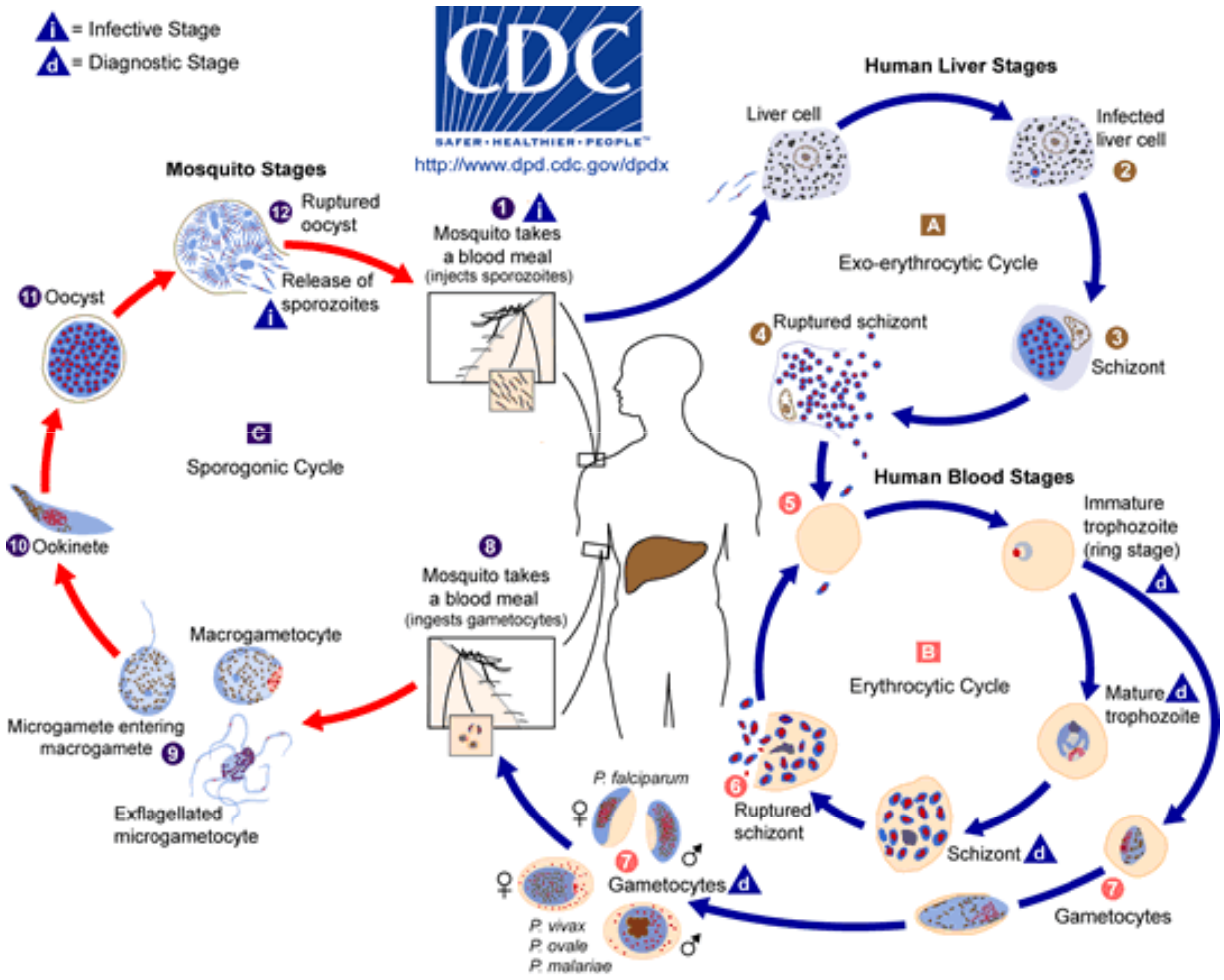
World Malaria Report 2011; WHO

Clinical research question: Malaria biology



http://www.wehi.edu.au/education/wehitv/malaria_lifecycle_part_1_human_host/

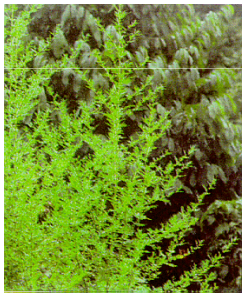
Clinical research question: Malaria biology



Clinical research question: Treatment of malaria

WHO recommends as first line treatment for uncomplicated and severe *falciparum* malaria

Artemisinin-based combination therapy (ACT)



Artemisinin derivative

+ partner drug(s)

Clinical research question: Treatment of malaria

WHO treatment guidelines 2010 – Uncomplicated malaria

	Artesunate (ARS) & Mefloquine (MQ)	Artemether (ART) & Lumefantrine (LF)	Dihydroartemisinin (DHA) & Piperaquine (PQ)
Dosing regimen (WHO)	ARS 4.0 mg/kg & MQ 8.3 mg/kg @ 0, 24, 48 h	ART 80.0 mg/kg & LF 480.0 mg/kg @ 0, 8, 24, 36, 48 & 60 h	DHA 4.0 mg/kg & PQ 18.0 mg/kg @ 0, 24 & 48 h

Pregnant women

1st trimester – Quinine + clindamycin

2nd & 3rd trimesters - ACT

Children

ACT – same weight adjusted dose recommend for infants, children & adults

Clinical research question: Treatment of malaria

WHO treatment guidelines 2010 –Severe malaria

(revision 1 – for children)

	IV or IM Artesunate
Dosing regimen (WHO)	2.4 mg/kg @ 0, 12, 24, 48, 72 h followed by oral ACT

Pregnant women

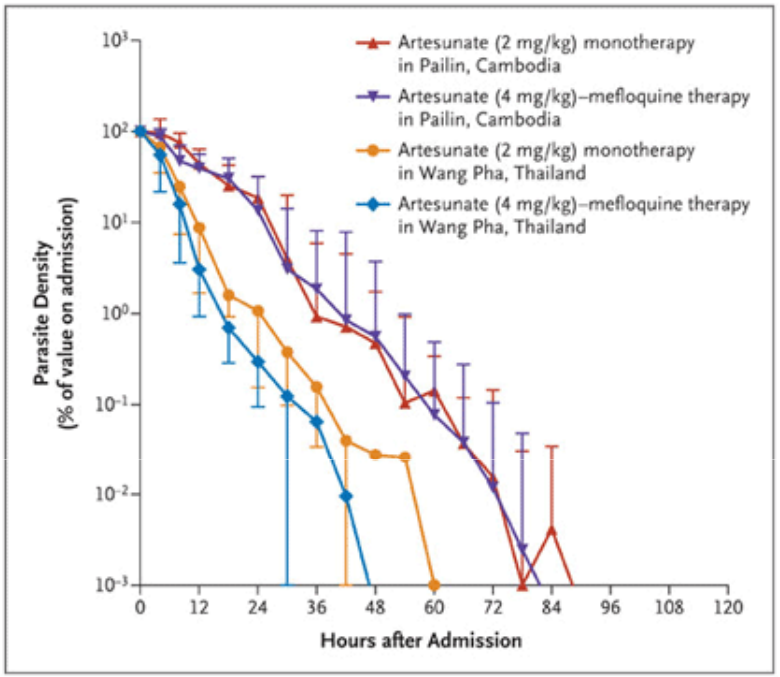
1st trimester – Both artesunate or quinine may be chosen

2nd & 3rd trimesters - Artesunate

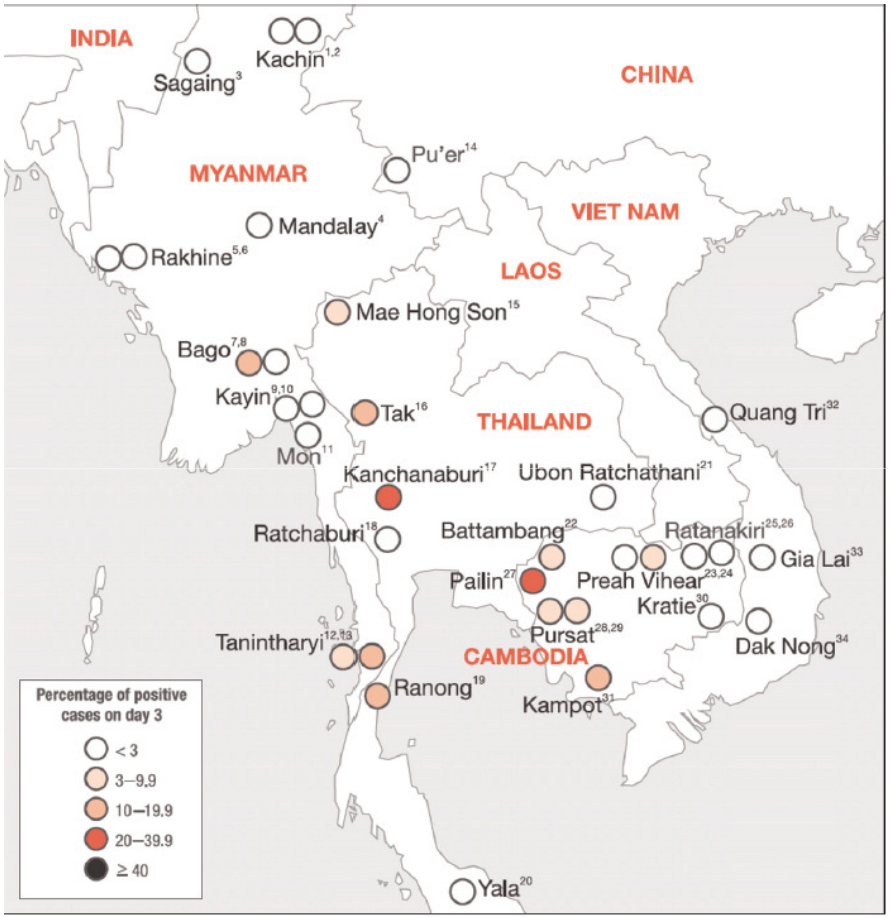
Children

IV or IM artesunate – same weight adjusted dose recommend for infants, children & adults

Clinical research question: Treatment of malaria



Dondorp A et al. *N Eng J Med* 2009



Fairhurst RM et al. *Am J Trop Med* 2012

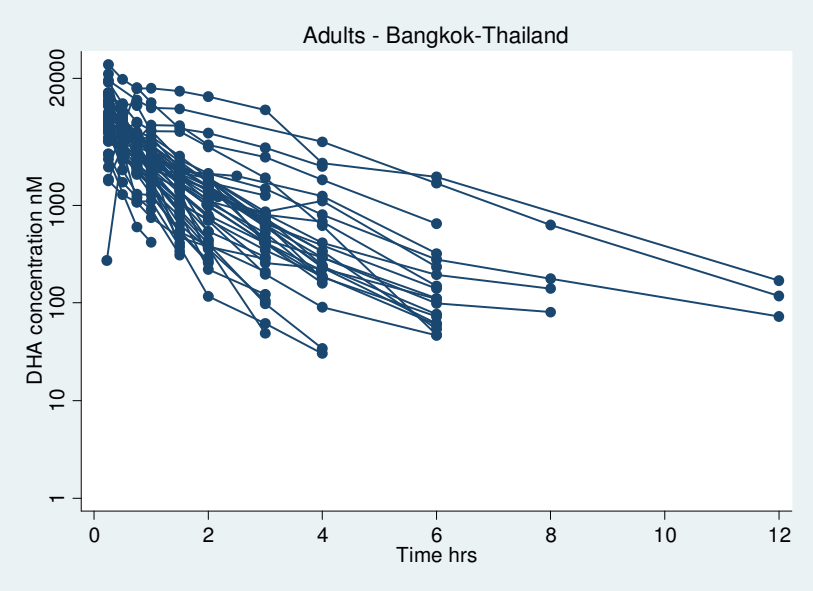
Clinical research question: Treatment of malaria

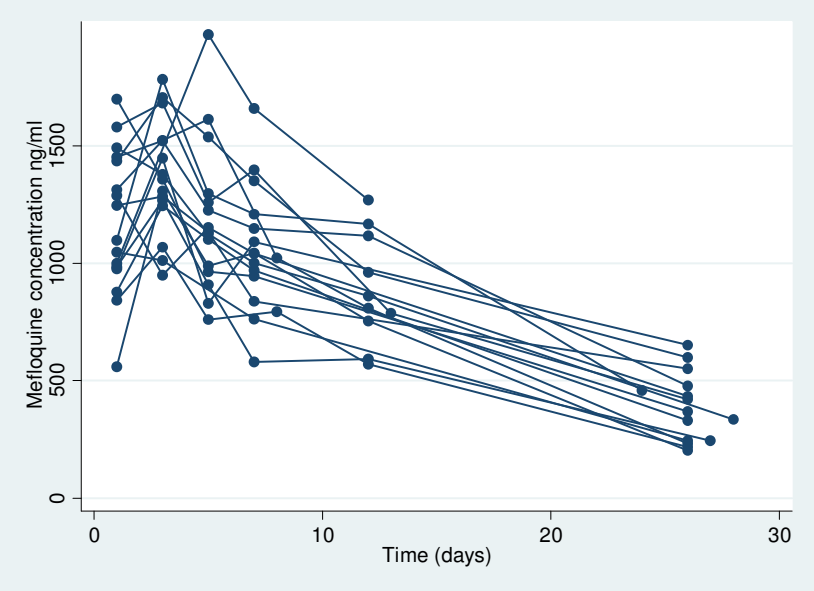
- Are the current WHO recommended dosing regimens of each anti-malarial optimal for all patients with malaria?

- With the emergence of resistance to the artemisinin derivatives, which anti-malarial combination therapies and alternative dosing regimens should be evaluated in clinical trials?

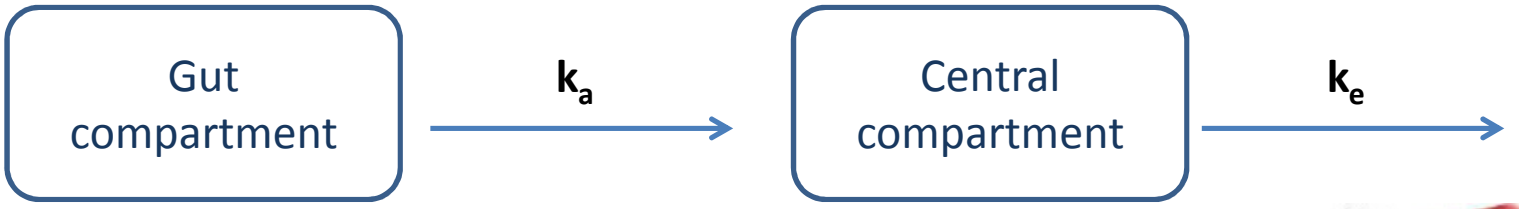
Mechanistic pharmacokinetic models

- Describes how the drug concentration changes over time using physiological parameters...
- Study design – repeated measures studies

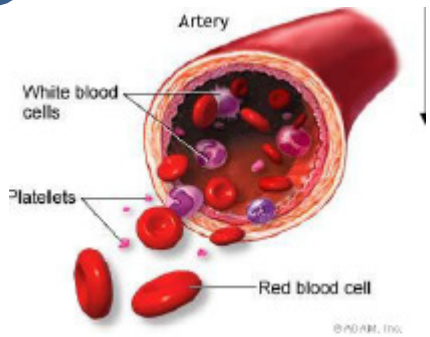




Mechanistic pharmacokinetic models

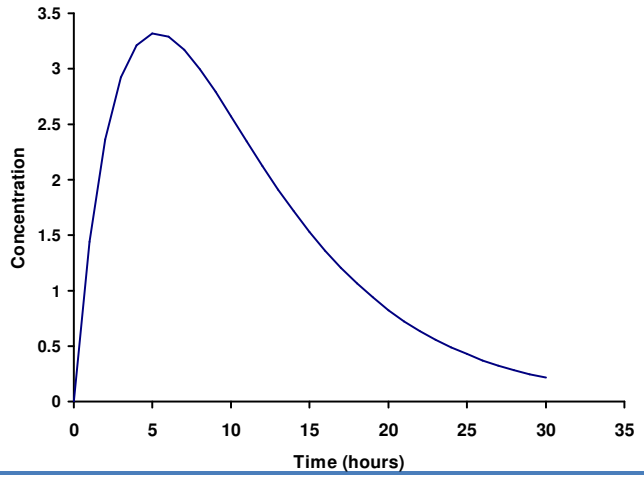


$$\frac{dA_G}{dt} = -k_a.A_G \qquad \frac{dA_C}{dt} = k_a.A_G - k_e.A_C$$



$$C(t) = \frac{dose.k_a}{V.k_a - CL}\left(e^{-\left(\frac{CL}{V}\right)t} - e^{-k_a t}\right)$$

$$C(t) = \frac{dose.\theta_1}{\theta_2.\theta_1 - \theta_3}\left(e^{-\left(\frac{\theta_3}{\theta_2}\right)t} - e^{-\theta_1 t}\right)$$



Mechanistic pharmacokinetic models – data collected

Anti-malarial population pharmacokinetic studies

- Often sparse & unbalanced designs for malaria patients (especially pregnant women and children)

  For example:-

Patient population	Sampling times for artesunate
Adults	0, 0.167, 0.25, 0.5, 0.75, 1, 1.5, 2, 4, 8 hrs
Children Group 1 Group 2 Group 3	 0, 0.25, 4 hrs 0, 0.5, 2 hrs 0, 0.25, 1 hr

Mechanistic pharmacokinetic models – statistical modelling

Nonlinear mixed-effects modelling

Need to provide:-

1) Structural pharmacokinetic model

2) Initial values (or prior dsns) for each parameter

3) Distribution of random effects (often use lognormal dsn for between-individual variability and combination of proportional and additive error terms for residual error)

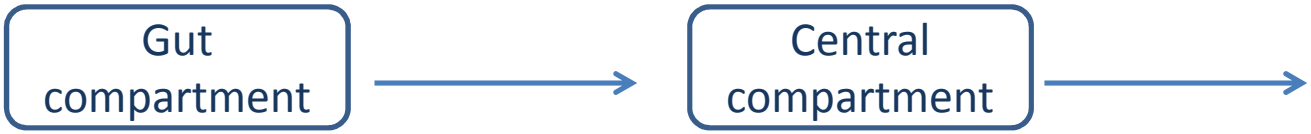
[Software packages used:- NONMEM, MONOLIX, PKBUGs]

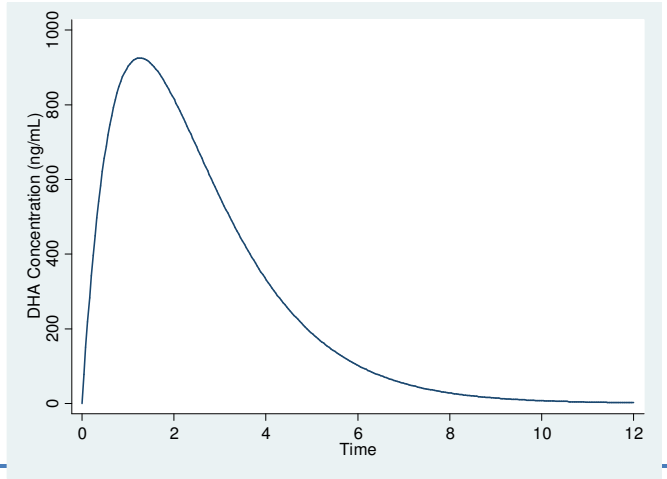
Mechanistic pharmacokinetic models – statistical modelling

Structural pharmacokinetic model

- Structural identifiability
  - Is there a unique set of parameter values?

Anti-malarial – Artesunate

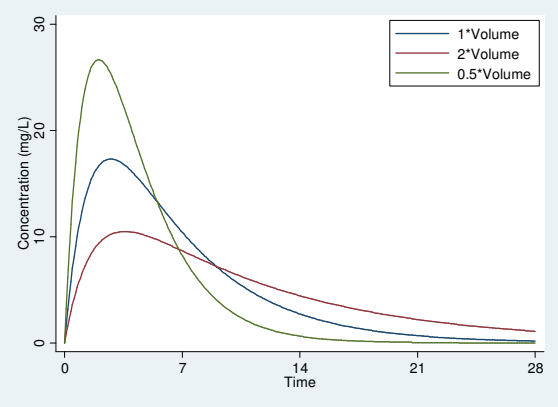


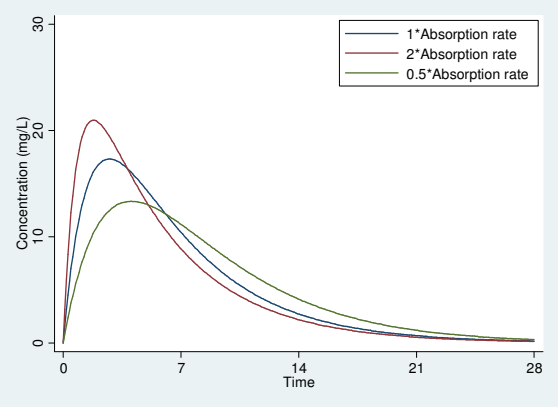


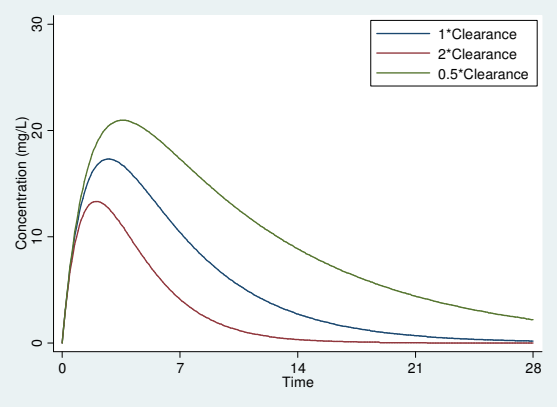
Mechanistic pharmacokinetic models – statistical modelling

Initial values for each parameter

$$C(t) = \frac{dose.k_a}{V.k_a - CL}\left(e^{-\left(\frac{CL}{V}\right)t} - e^{-k_a t}\right)$$







Mechanistic pharmacokinetic models – statistical modelling

- Deterministic identifiability
  - Is the study design sufficient to determine (or estimate precisely) the parameters of interest?

Mechanistic pharmacokinetic models – statistical modelling

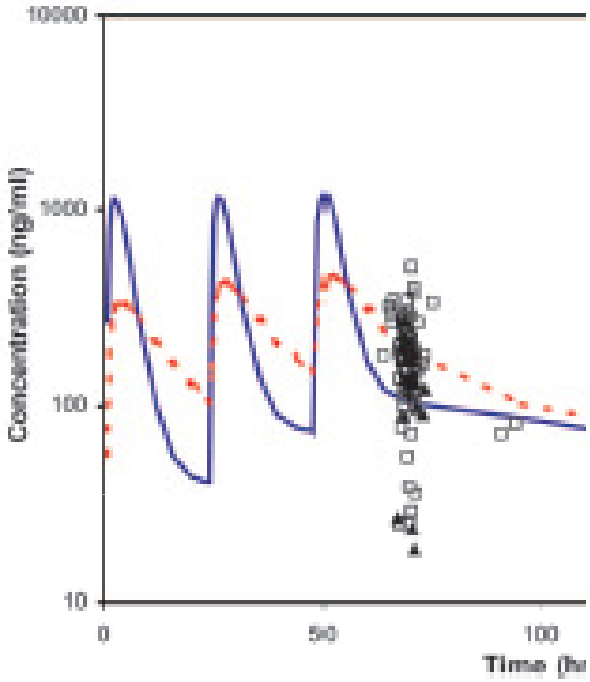
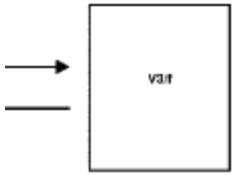


FIG. 5. Plasma concentration-versus-
on the final population model. The obser
following administration of AQ only (fil
(open squares) are shown. The lines rep
population estimates for a typical 6-yea
who was administered AQ only (solid lin
line).

TABLE 2. Parameter estimates of the final population pharmacokinetic model and results using the bootstrap validation procedure

Parameter	Estimate	RSE[a] (%)	Median (2.5–97.5% range) for 1,000 bootstrap replicates
K_a (h^{-1})	0.867 (fixed)		
T_{lag} (h)	0.84 (fixed)		
CL/f (liters/h)[b] (population mean)	15.5	32.0	
V_2/f (liters)[b] (population mean)	368	34.0	
Q/f (liters/h)	16.0	11.9	15.8 (11.8–19.3)
V_3/f (liters)	1,060	14	1,120 (854–2,433)
θ1[c]	29.9	24.7	32.5 (20.1–147)
θ2[c]	0.992	45.5	1.23 (0.44–10.4)
θ3[d]	85.4	37.2	84 (44.1–204)
θ4[d]	422	33.2	447 (236–884)
Interindividual variability (ω)			
$CV_{CL/f}$ (%)	31.9	41.6	31.6 (14.5–46.2)
$CV_{V2/f}$ (%)	40.9	64.7	44.3 (14.8–82.3)
Residual variability (σ) (proportional error [%])	31.9	18.3	30.8 (23.1–37.0)
$t_{1/2a}$ (h)[b] (population mean)	7.38	35.3	
$t_{1/2\beta}$ (h)[b] (population mean)	110	26.8	

[a] RSE, relative standard error.
[b] Means and SDs were calculated based on post hoc individual predicted parameters.
[c] Population oral clearance = θ1 · (BW/median)/[θ2 + (BW/median)], where BW is body weight. This works out to 29.9 · (BW/18)/[0.992 + (BW/18)].
[d] θ3 and θ4 represent the V_2/f of the typical individual in the population treated with AQ plus AS and with AQ alone, respectively. The population V_2/f is 85.4 liters without AS and 422 liters with AS.



model of a first-order absorp-
npresses information on the K_a
), and the clearance of DEAQ.

Design of population pharmacokinetic studies

1. How many patients should be included in the study?

2. How many samples need to be collected for each patient?

3. At what times should the samples be collected?

Design of population pharmacokinetic studies

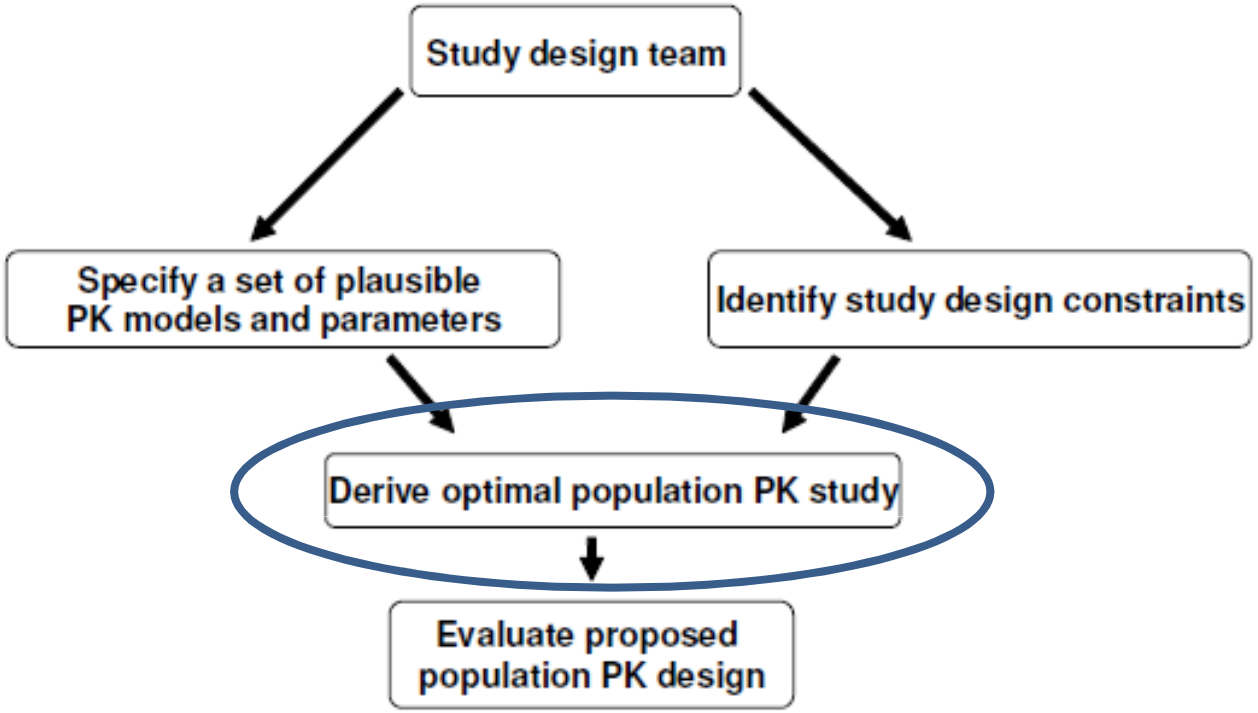


Figure 1
Flowchart for designing population pharmacokinetic studies using optimal design methods.

Design of population pharmacokinetic studies – Optimal design theory

Data independent approach using the Population Fisher information matrix (FIM), which is simply the sum of all individual(i=1,...,N) FIMs :-

$$M_F(A,D) = \sum_{i=1}^{N} M_F(A,d_i)$$

D represents the set of all individual designs (d_1, d_2,..., d_N)
where $d_1=(t_{i1},t_{i2},...,t_{in_i})$

A is the vector of population parameters (θ,Ω,σ)

Design of population pharmacokinetic studies – Optimal design theory

To find the optimal design, an optimisation algorithm is used to compare the determinant of the PFIM for several candidate designs:-

$$C(D) = \det\left(M_F(A,D)\right)^{1/\dim(A)}$$

Fortunately, software has been developed to do the above job efficiently.....

WinPOPT (or POPT; www.winpopt.com) – requires Matlab

PFIM (www.pfim.biostat.fr) – requires R

Design of population pharmacokinetic studies – Anti-malarials

Artesunate

Jamsen *et al. Malaria Journ*
http://www.malariajournal.

Table 2 Optimal samp

Design
Non-pregnant adults* (n = 60)
Non-pregnant adults and ch
<2 y (n = 10):
2-10 y (n = 10):
11-20 y (n = 10):
>20 y (n = 30):
Pregnant women*,†,‡ (n = 60)

Table 1 Optimal sampling times (h) and sampling windows for each drug

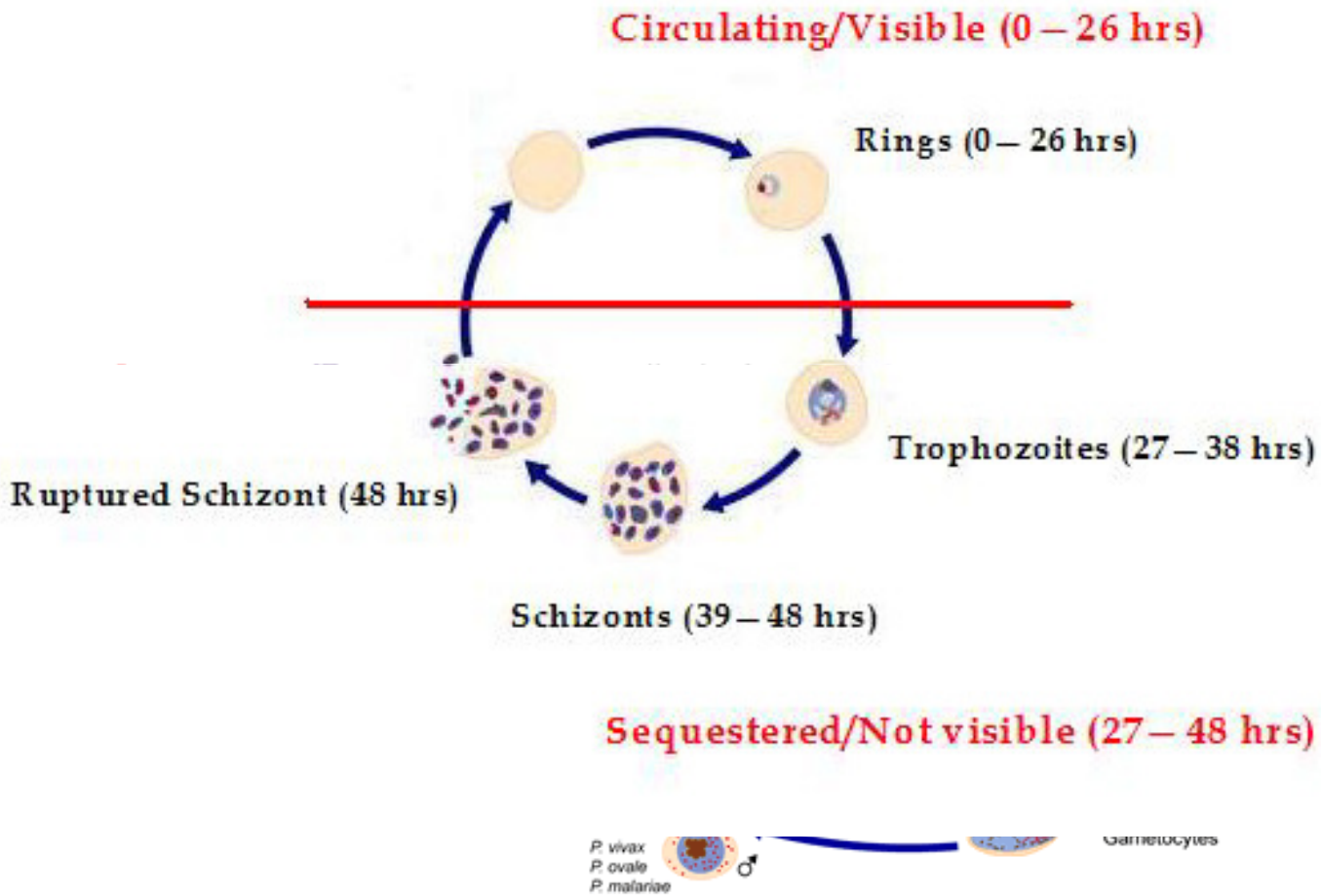
Drug		Optimal times (sampling windows)				
Mefloquine (8.3 mg/kg at 0, 24 and 48 h)	Group 1:	3.22	43.0	147*	496	1035
	(n = 50)	(2.35, 4.11)	(39.4, 47.6)	(139, 158)	(457, 546)	(988, 1058)
	Group 2:	2.02	28.0	67.8	147*	538
	(n = 50)	(1.49, 2.81)	(26.7, 29.6)	(62.7, 75.8)	(139, 158)	(456, 593)
Mefloquine (15 mg/kg at 24 h, 10 mg/kg at 48 h)	Group 1:	26.5	66.9	147*	544	1011
	(n = 50)	(25.8, 27.8)	(60.8, 71.7)	(134, 158)	(501, 593)	(971, 1058)
	Group 2:	26.5	66.3	66.5	147*	694
	(n = 50)	(25.8, 27.5)	(60.5, 71.6)	(60.5, 71.7)	(141, 158)	(650, 776)
Lumefantrine (12 mg/kg at 0, 8, 24, 36, 48 and 60 h)	Group 1:	2.28	30.3	100	147*	267
	(n = 50)	(1.78, 2.78)	(28.1, 31.7)	(86.9, 110)	(132, 159)	(231, 310)
	Group 2:	11.6	37.7	53.7	147*	218
	(n = 50)	(10.1, 13.4)	(37.7, 41.6)	(52.3, 56.6)	(130, 149)	(203, 261)
Piperaquine (18 mg/kg at 0, 24 and 48 h)	Group 1:	0.18	30.0	77.3	147*	705
	(n = 50)	(0.10, 0.61)	(29.1, 31.9)	(72.3, 84.9)	(138, 156)	(652, 747)
	Group 2:	2.54	24.0	147*	358	1291
	(n = 50)	(2.15, 3.95)	(24.0, 24.6)	(138, 155)	(259, 382)	(1204, 1322)
Desethylamodiaquine (10 mg/kg of amodiaquine at 0, 24 and 48 h)	Group 1:	9.67	24.0	147*	348	651
	(n = 50)	(7.03, 10.1)	(24.0, 24.1)	(129, 157)	(339, 398)	(599, 651)
	Group 2:	0.71	24.0	98.0	147*	348
	(n = 50)	(0.38, 1.36)	(24.0, 24.1)	(88.4, 106)	(129, 157)	(316, 397)

Mechanistic pharmacokinetic-pharmacodynamic models

Mechanistic model that links the drug concentrations to the effect (pharmacodynamic measure)

Mechanistic PK-PD models for falciparum malaria

Parasite-age structured model



Mechanistic PK-PD models for falciparum malaria

Number of parasites (*N*) in patient *k* at a particular stage (denoted by *a* = 1, 2, …, 48) at hourly time point *t*,

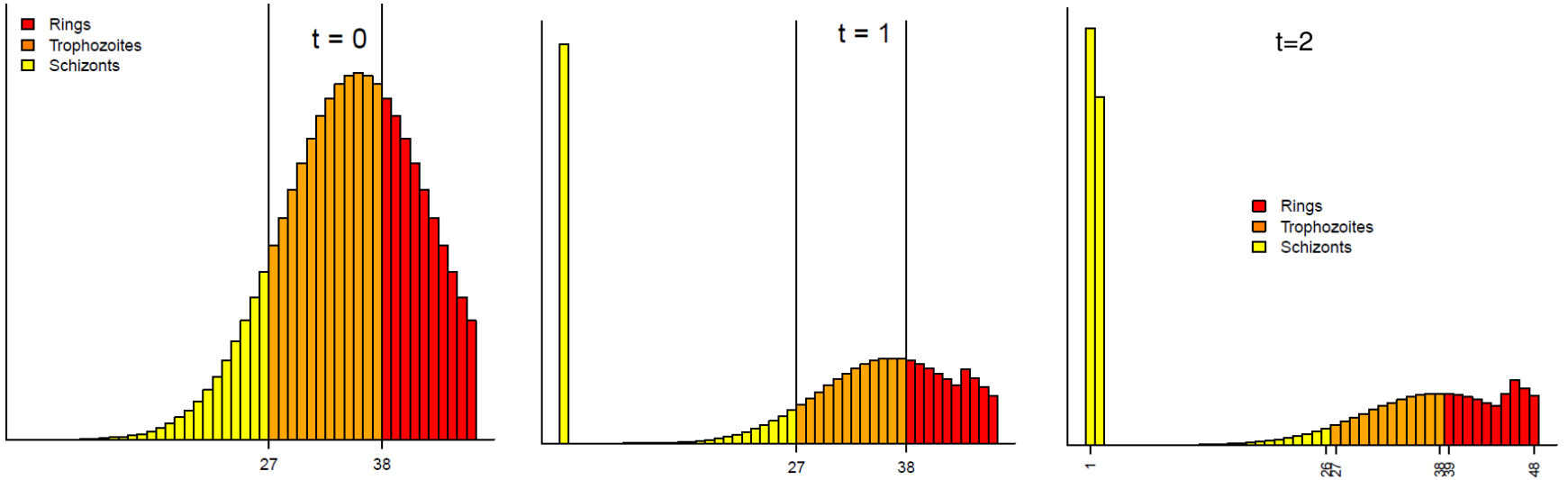
$$N_{k,1}(t+1) = PMF \times N_{k,48}(t)$$

$$N_{k,2}(t+1) = N_{k,1}(t)$$

$$\vdots$$

$$N_{k,48}(t+1) = N_{k,47}(t)$$

- **PMF – parasite multiplication factor**



Mechanistic PK-PD models for falciparum malaria

Number of parasites (*N*) in patient *k* at a particular stage (denoted by *a* = 1, 2, …, 48) at hourly time point *t* following drug administration,

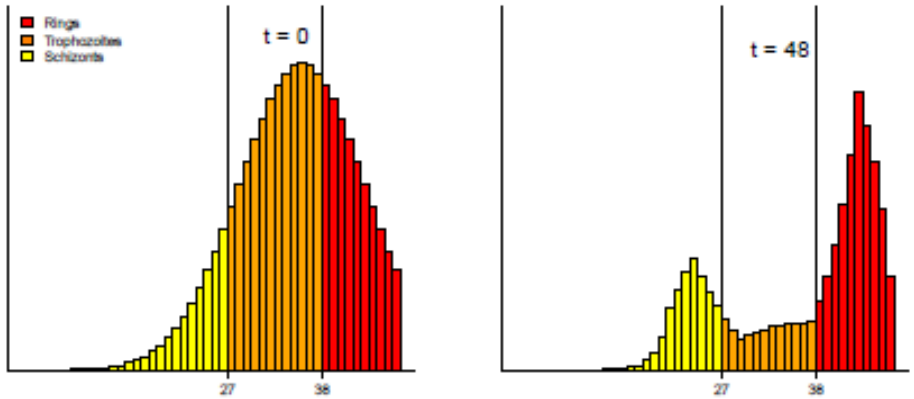
$$N_{k,1}(t+1) = PMF \times N_{k,48}(t) \times s_{k,48}(t)$$

$$N_{k,2}(t+1) = N_{k,1}(t) \times s_{k,1}(t)$$

$$\vdots$$

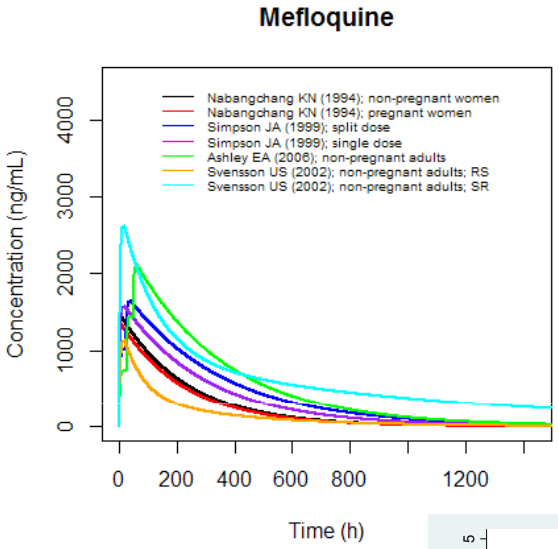
$$N_{k,48}(t+1) = N_{k,47}(t) \times s_{k,47}(t)$$

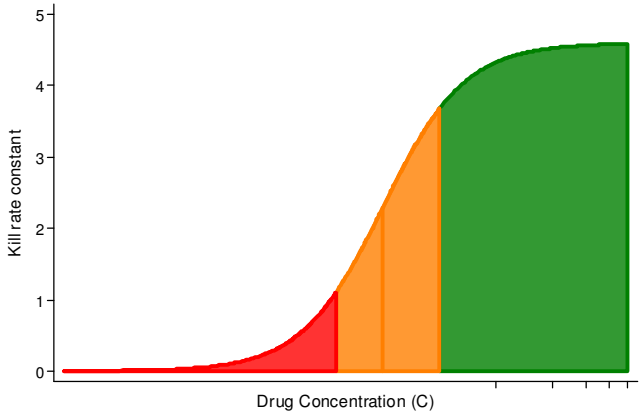
- **$s(t) = \exp(-k_{drug}.t)$ proportion of parasites that survive an hourly interval exposure to the antimalarial drug concentration**

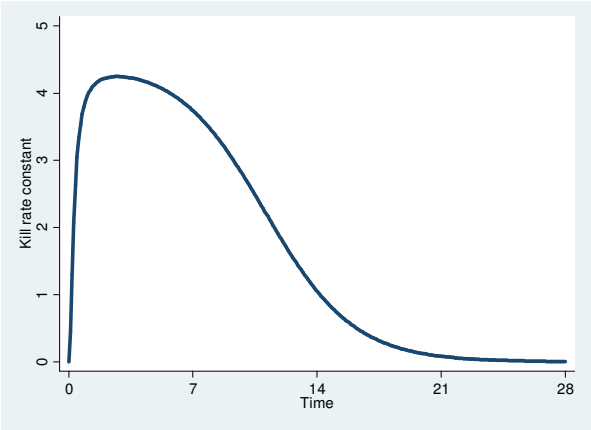


Mechanistic PK-PD models for falciparum malaria

k_{drua} – function, dependent on drug concentration and time







Mechanistic PK-PD models for falciparum malaria

Exploration of parameter space

Mechanistic PK-PD models for falciparum malaria-
Exploration of parameter space

Table 3 Parameter definitions for the within-host pharmacokinetic-pharmacodynamic model

Parameter	Description
μ_{IPL}	Mean of the age distribution of the initial parasite burden
σ_{IPL}	Standard deviation of the age distribution of the initial parasite burden
PMF	Parasite multiplication factor (/48 h cycle)
k_{max}	Maximal killing rate of the drug / h
γ	Slope of *in vivo* concentration-effect curve
EC_{50}	*In vivo* concentration when killing rate is 50% of the maximum

Mechanistic PK-PD models for falciparum malaria

Exploration of parameter space

1) Simulate 100 drug concentration-time profiles for each anti-malarial

2) Simulate 100 parasite-time profiles dependent on a single set of the 6 pharmacodynamic parameters and each of the drug concentration profiles for a particular anti-malarial combination therapy

3) Calculate from the100 parasite-time profiles the typical measures of clinical trials:-

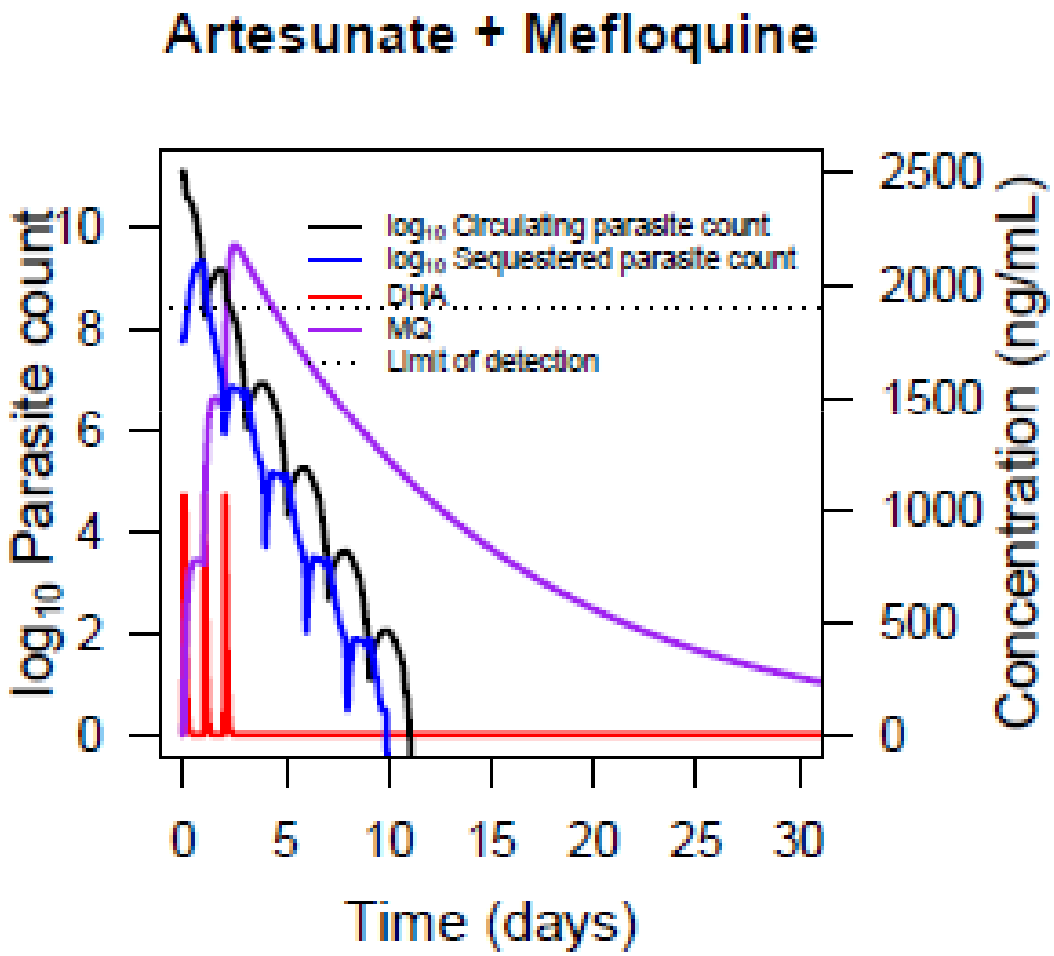
   PCT – parasite clearance time

   Cure – parasite infection cured within 28 days of follow-up

4) Repeat steps 2 and 3 for 5000 sets of the pharmacodynamic parameters that are sampled using Latin Hypercube Sampling

Mechanistic PK-PD models for falciparum malaria

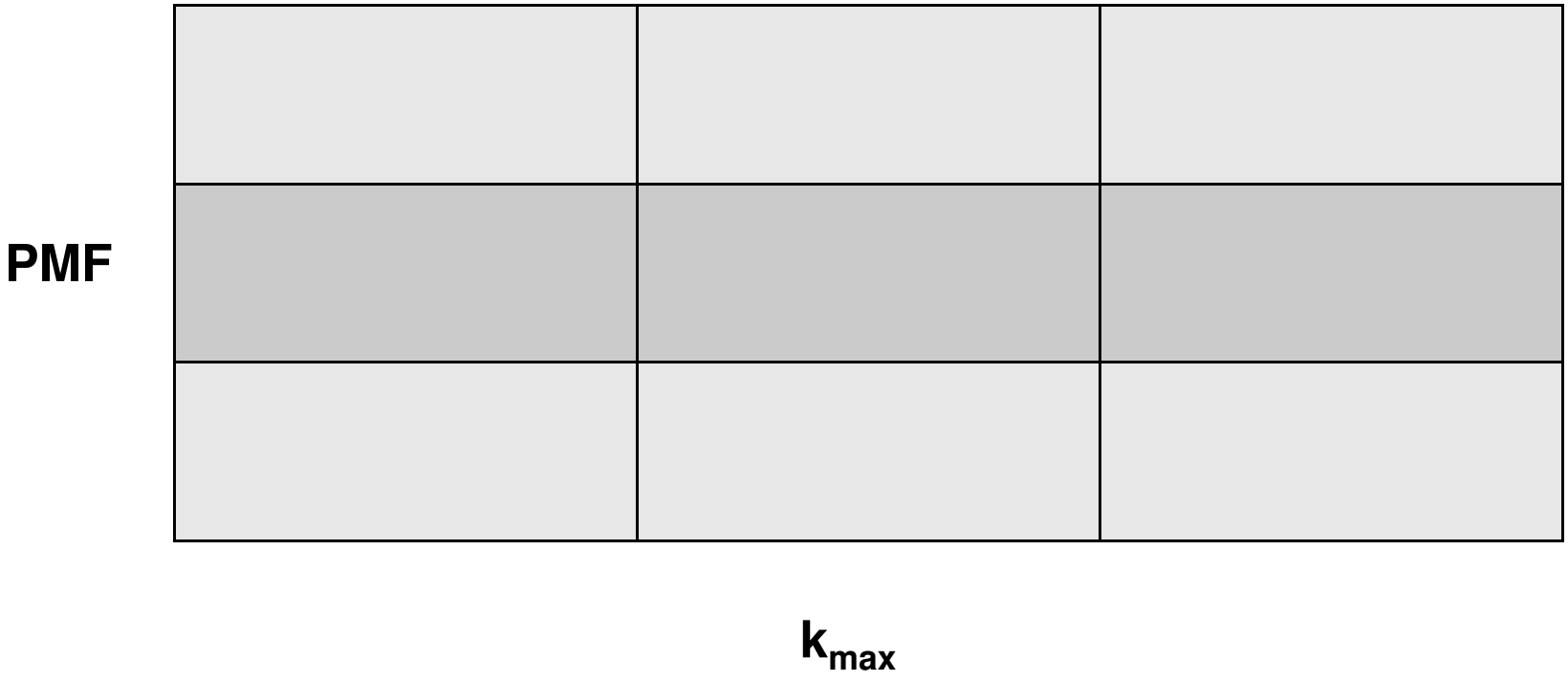
Exploration of parameter space



Zaloumis S, et. al. Malaria Journal 2012

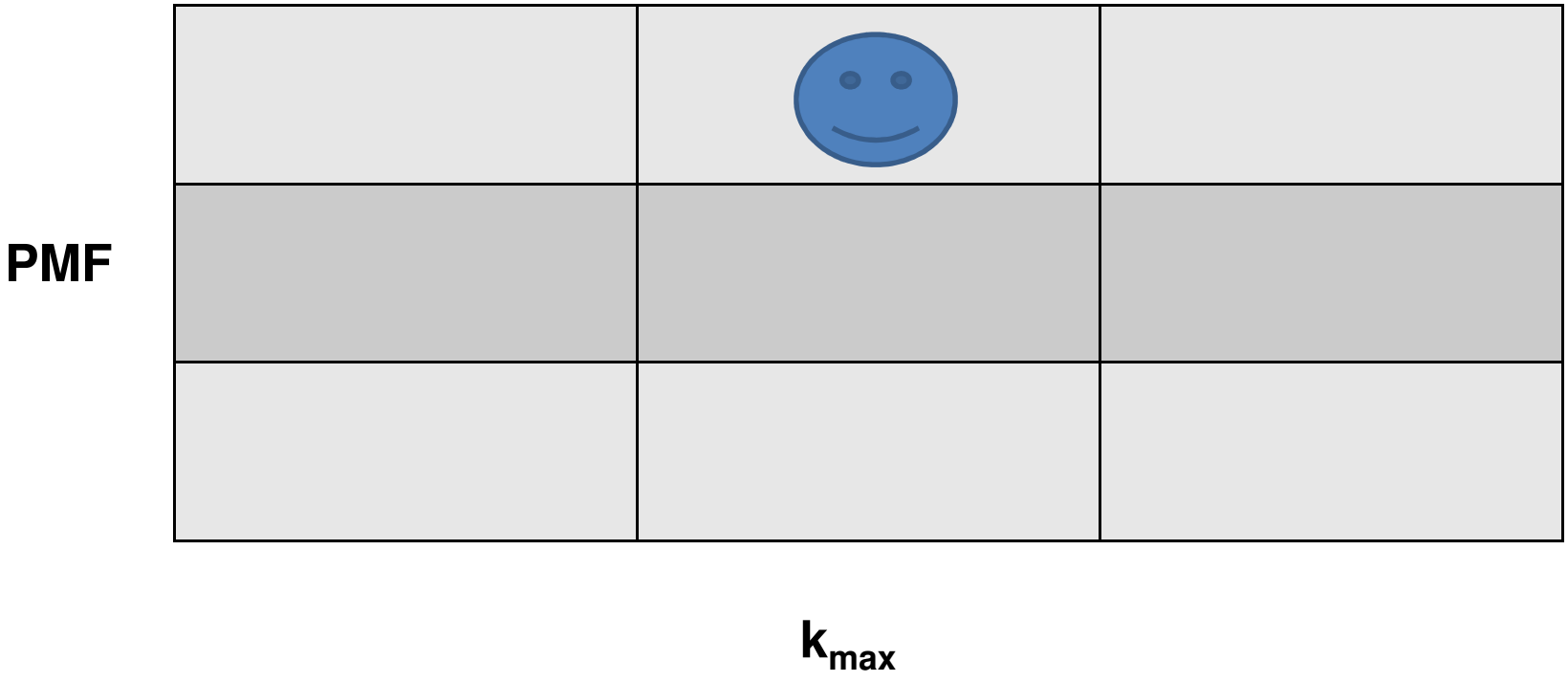
Mechanistic PK-PD models for falciparum malaria- Exploration of parameter space

- Latin Hypercube Sampling..



Mechanistic PK-PD models for falciparum malaria- Exploration of parameter space

- Latin Hypercube Sampling..



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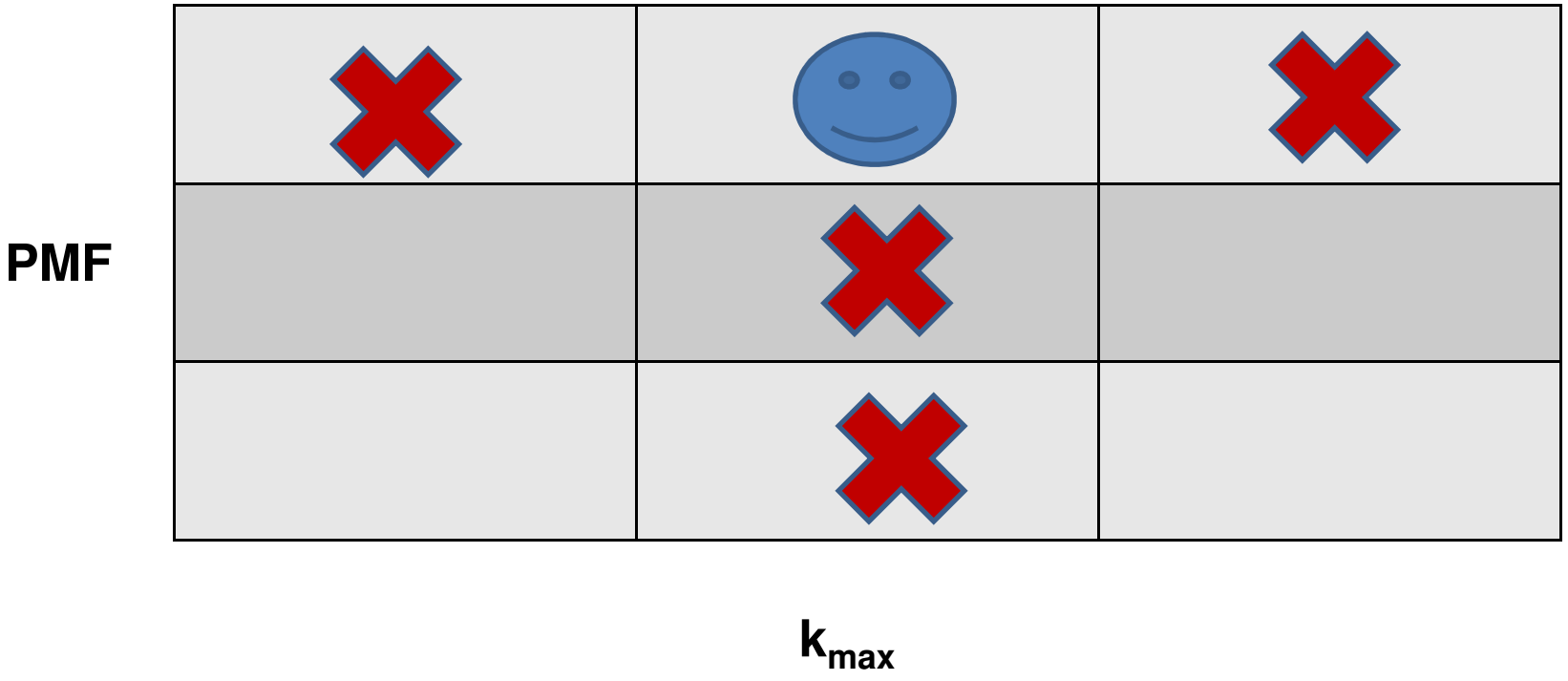

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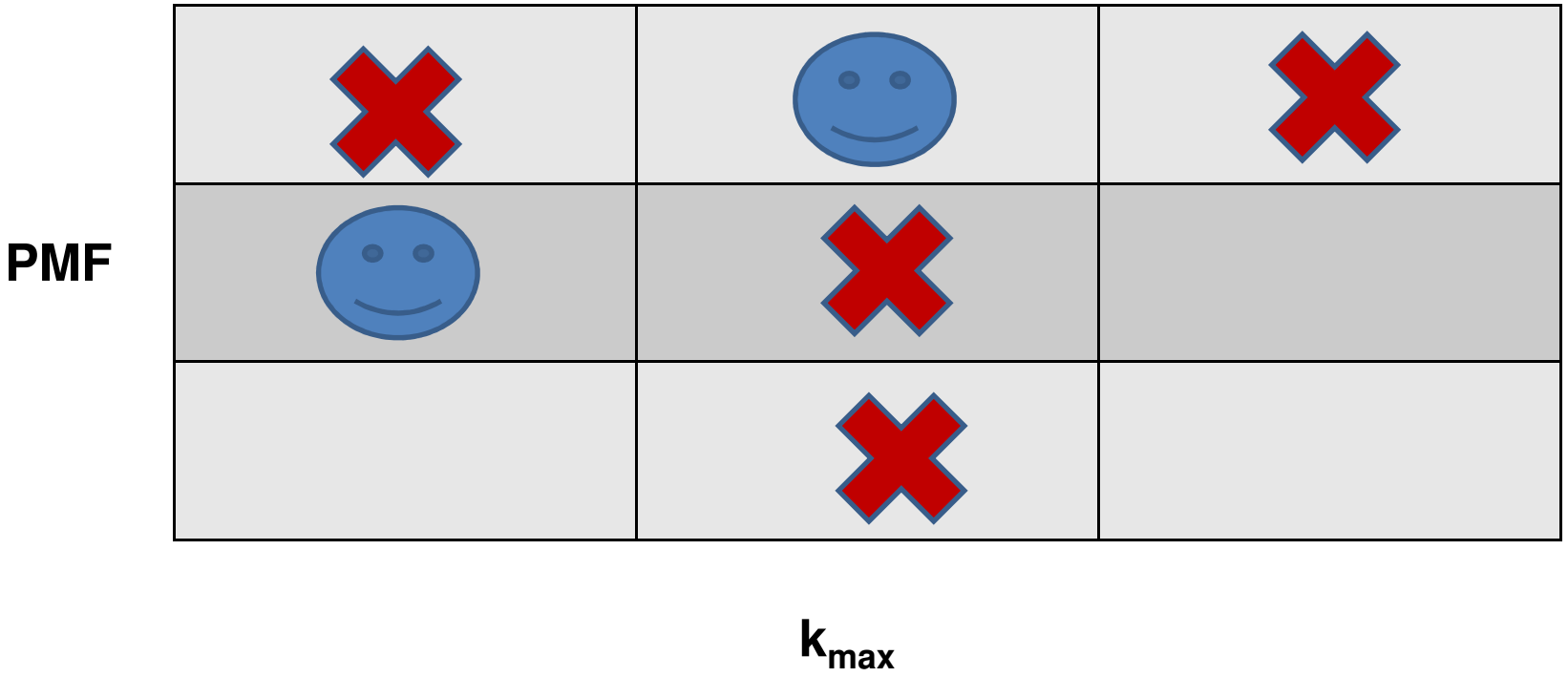

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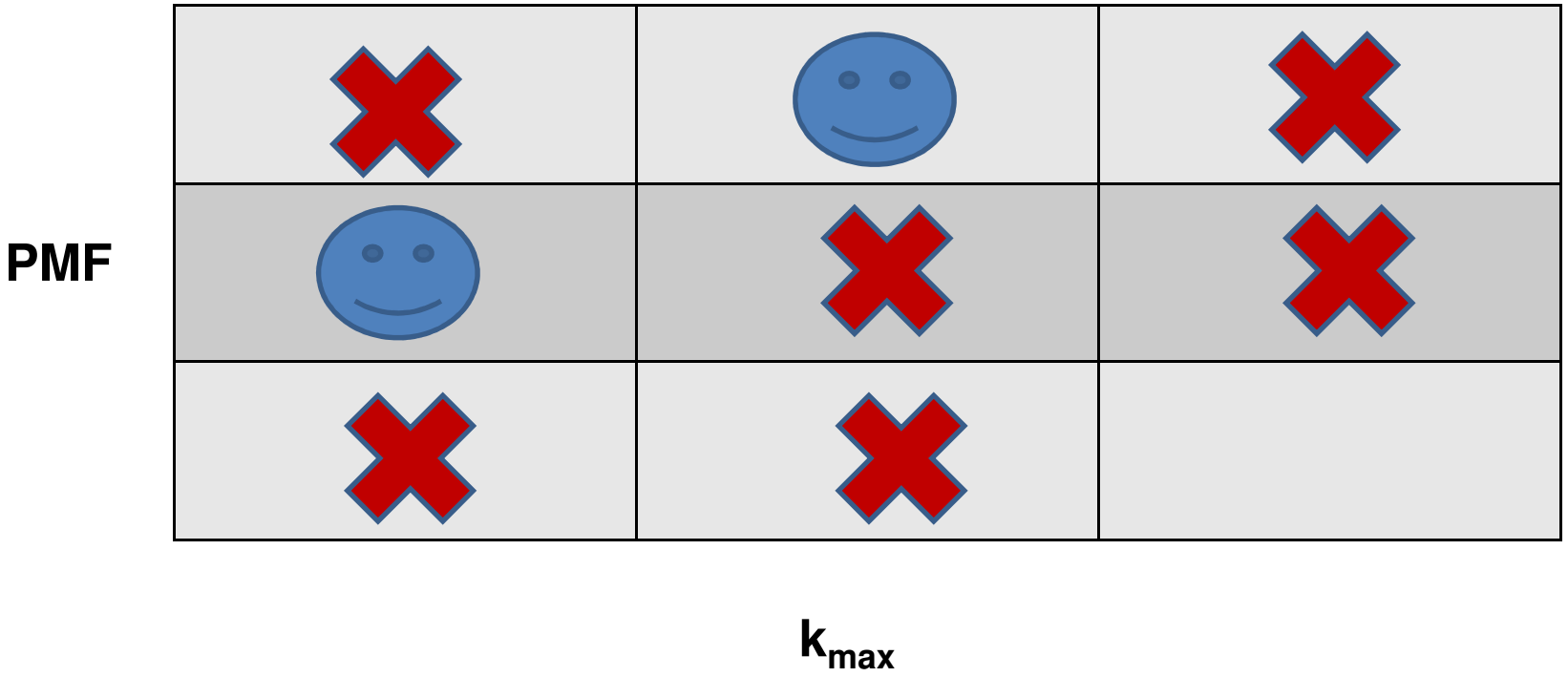

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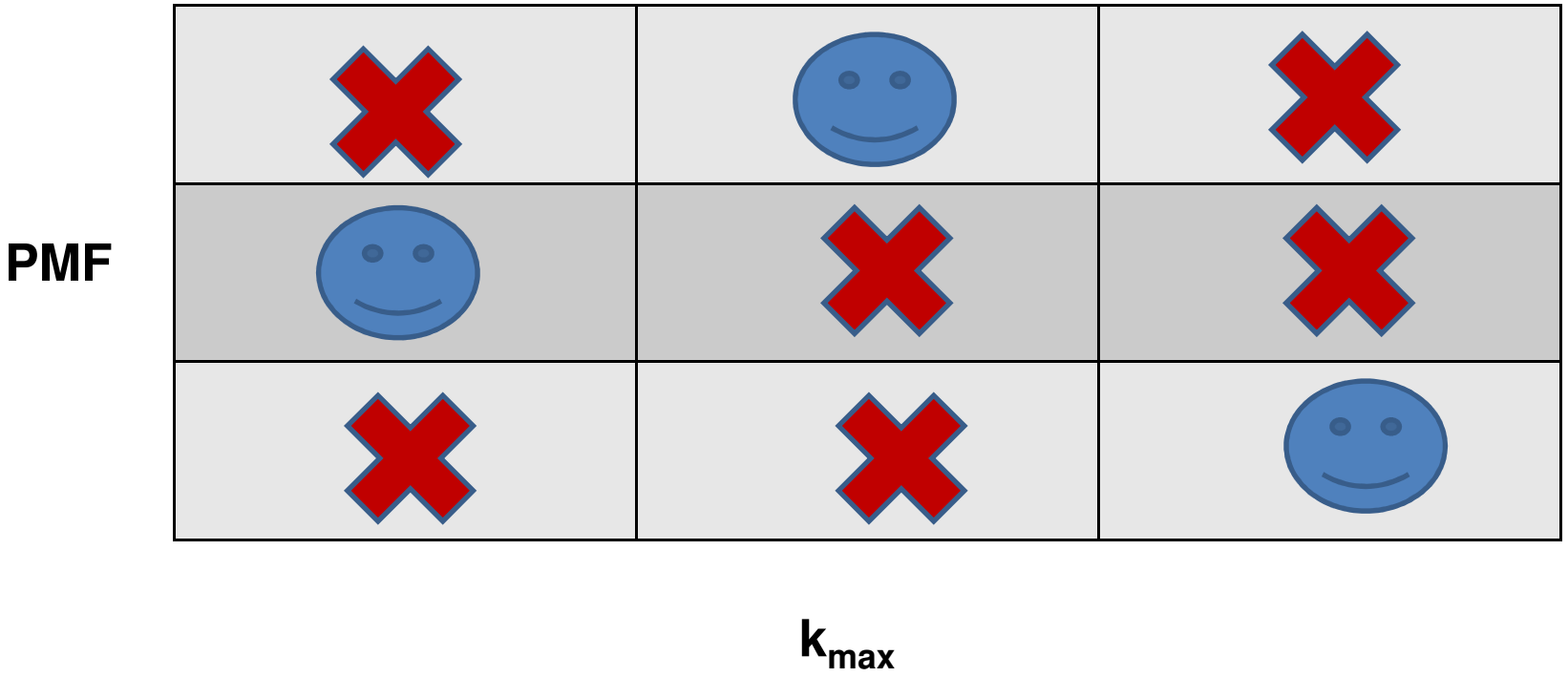
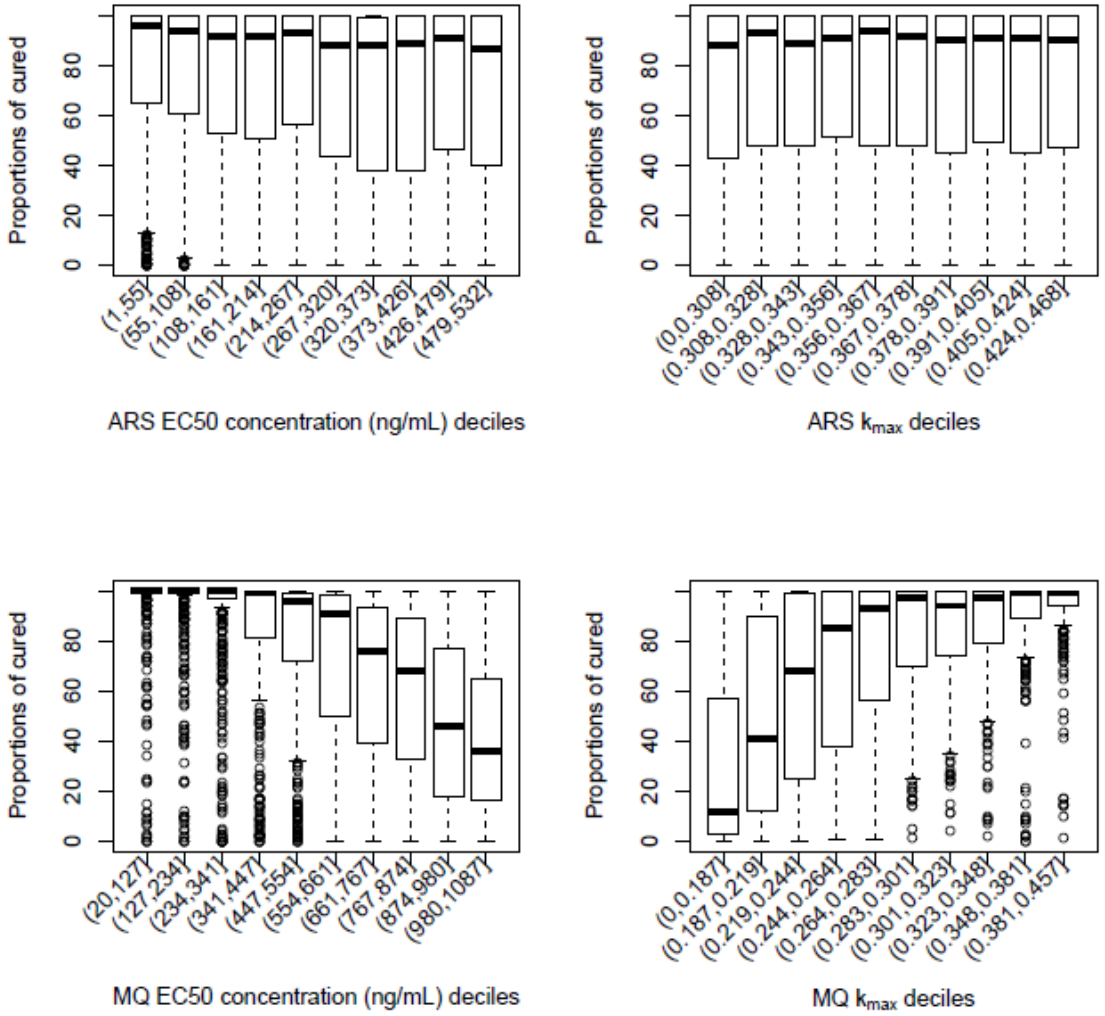


Mechanistic PK-PD models for falciparum malaria-

Exploration of parameter space



Mechanistic PK-PD models for falciparum malaria

Exploration of parameter space

Key findings.....

- k_{max}, EC_{50} of the anti-malarials are the key parameters that influence the outcome measure:- cure by day 28 & to a lesser extent, parasite clearance times.

- Current estimates of EC_{50} from *in vitro* (experimental) data did not accord well with the expected clinical outcomes.

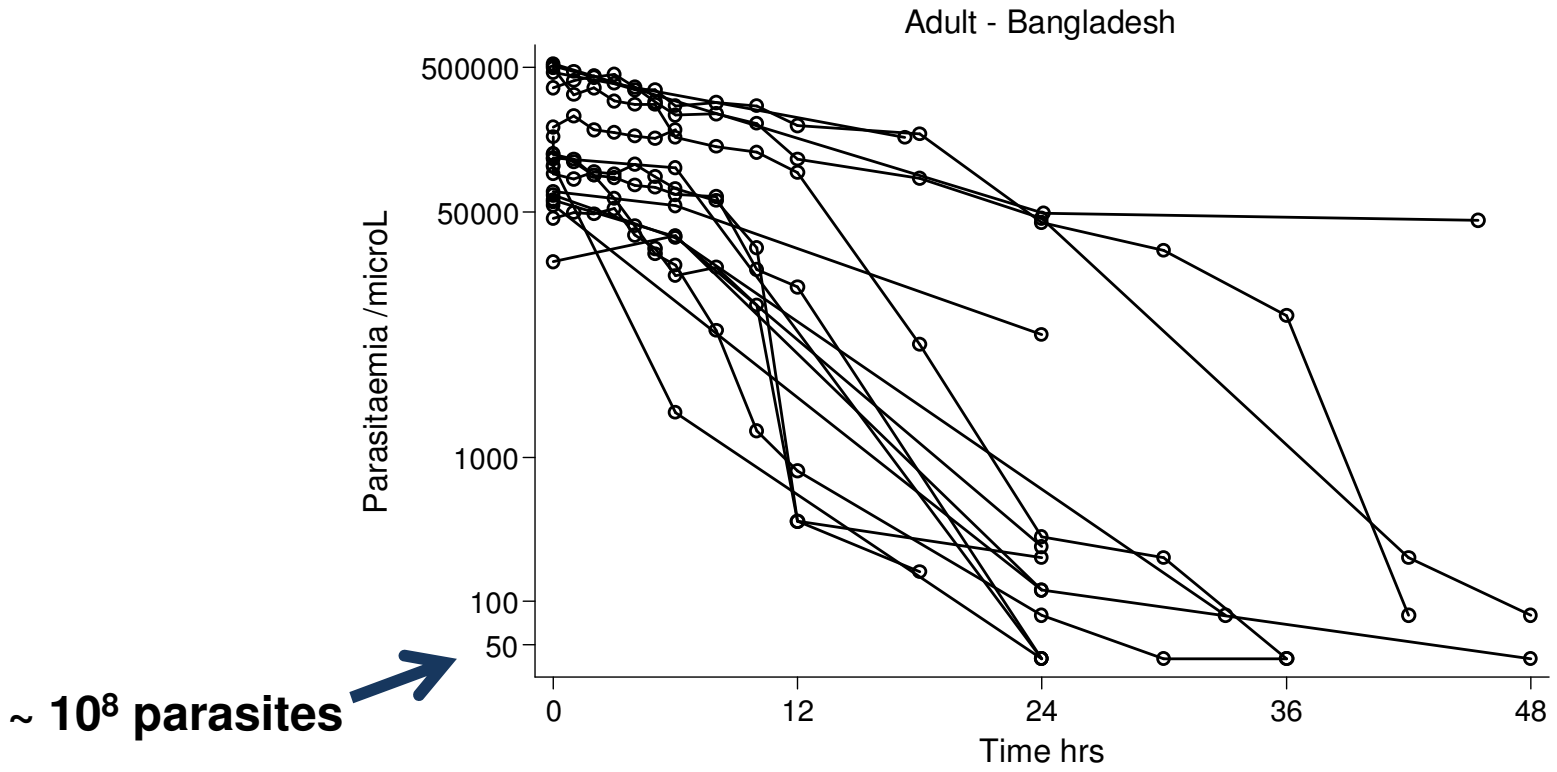
Mechanistic PK-PD models for falciparum malaria-

Statistical modelling

Challenges with measurement of parasite count data

Mechanistic PK-PD models for falciparum malaria-
Statistical modelling

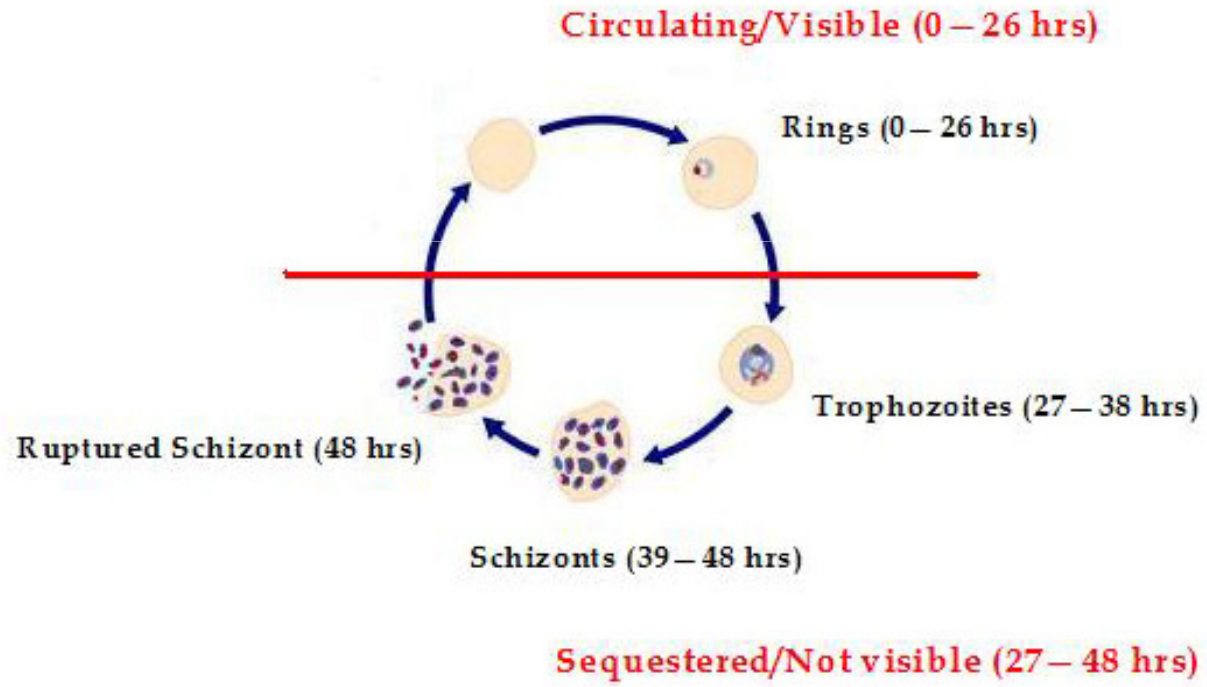
Challenges with measurement of parasite count data



~ 10^8 parasites

Mechanistic PK-PD models for falciparum malaria- Statistical modelling

- Challenges with measurement of parasite count data



Mechanistic PK-PD models for falciparum malaria-
Statistical modelling

Are all parameters (including the random effects) structurally and deterministically identifiabile?

- Back to the clinical research question....
- What have we achieved so far?

Translation.....

Translation to policy

Translation to policy – adopted by WHO

- Mefloquine - Recommend split dosing (Simpson JA et al CPT 1999 & AAC 2000)
- Lumefantrine - Co-administer with a fatty meal (Ezzet F et al. 2000)

Translation to policy – not yet in WHO guidelines

- Piperaquine - Higher doses suggested for young children (Tarning J et al 2012)
- Intra-muscular artesunate - Higher doses suggested for young children (Hendriksen ICE et al. 2013)

Translation to policy

Chapter 3. Optimizing sampling schemes for pharmacokinetics studies

3.1 CLINICAL INDICATIONS FOR MEASURING ANTIMALARIAL DRUG CONCENTRATIONS IN BLOOD

The profile of antimalarial drug concentrations must be characterized over time in order to optimize dosing, and thereby optimize cure rates, and to reduce the emergence of resistance, diminish gametocyte carriage and limit toxicity. Antimalarial PK often differs substantially between patients. The PK of antimalarial drugs must therefore be quantified precisely for all target populations, especially young children, pregnant women and patients with prevalent co-morbid conditions.

Future work

Optimising dosing of severe malaria patients

Future work – a collaborative approach

Principal Investigator	**Julie Simpson**
Postdoc biostatistician	**Sophie Zaloumis**
Collaborators	**Karen Barnes** **Arjen Dondorp** **Melba Gomes** **Tim Davis** **Lyle Gurrin** **Kris Jamsen** **Peter Kremsner** **Sanjeev Krishna** **Richard Maude** **James McCaw** **Paul Newton** **Piero Olliaro** **Ric Price** **Joel Tarning** **Nick White**

Funded by NHMRC Project Grant & ViCBiostat

Future work – Optimising dosing of severe malaria patients

Study descriptions

Study	Site	Population	Design	No. patients
Kremsner	Malawi	Children	RCT	163
Krishna	Ghana	Children	Cross-over	27 (10, 17)
Nealon	Gabon	Children	Cross-over	19 (11, 8)
Maude	Bangladesh	Adults	Clinical study	18
Newton	Thailand	Adults	RCT	17
WHO	Thailand	Adults	Cross-over	47 (23, 24)
Davis	Vietnam	Adults	RCT	7
Total	–	–	–	298*

* Children: 209; Adults: 89

DHA sampling

Study	No. samples	Mean (Min, Max) /patient
Kremsner	328	2.0 (2, 3)
Krishna	127 (43, 84)	4.7 (2, 7)
Nealon	131 (75, 56)	6.9 (4, 9)
Maude	95	5.3 (3, 7)
Newton	90	5.3 (4, 7)
WHO	354 (167, 188)	7.5 (3, 11)
Davis	81	11.6 (10, 13)
Total	1206	–

Summary(1)

- Current malaria treatment relies heavily on artemisinin derivatives.

- Clinical trials in Cambodia, Thailand and southern Myanmar have reported delayed clearance of the parasites following treatment of artesunate.

- Mechanistic population PK-PD modelling allow us to rationalise drug therapy, thereby, extending the life-span of current anti-malarials,

  BUT there are many challenges.....

Summary(2)

BUT there are many challenges.....

1) Does the mechanistic PK-PD model capture all the biology?

2) Can all the parameters be estimated precisely within a proper statistical framework? Model validation...

3) Current microscopic methods for determining parasite burden do not detect parasite burdens below 10^8 parasites nor parasites aged 26-48 hrs..

Epidemiology – empirical models....

- Most epidemiological studies assess relationships between exposures and outcomes using empirical models!

- We can learn from other areas, and think more about the mechanisms at play....

Causal Diagrams are a good starting point...