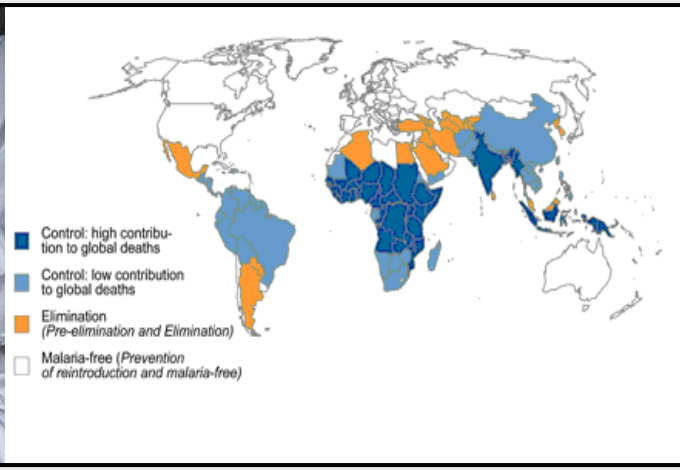
PK/PD modelling and simulation in Tropical Medicine



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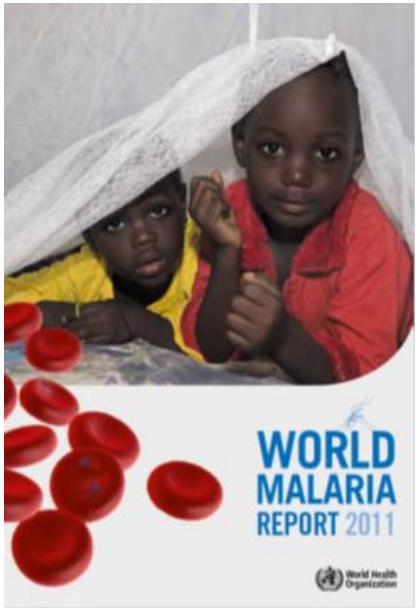
Background Malaria

Malaria statistics (estimates) according to WHO

- Half of the worlds population live in areas at risk of malaria transmission
- In 2010, an estimated 216 million clinical episodes and 655,000 deaths
- 86% of the malaria deaths in children under 5 years
- 125 million annual pregnancies in malaria endemic countries
- Malaria during pregnancy cause low birth weight and is associated with 100,000-200,000 new-born deaths annually in Africa



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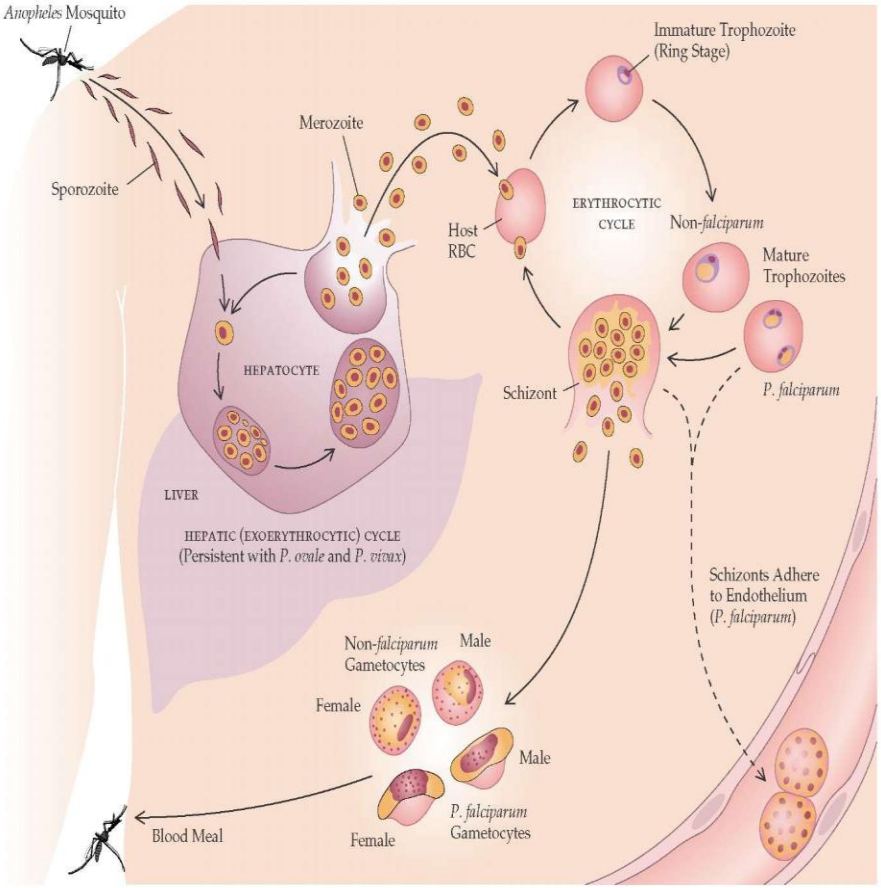
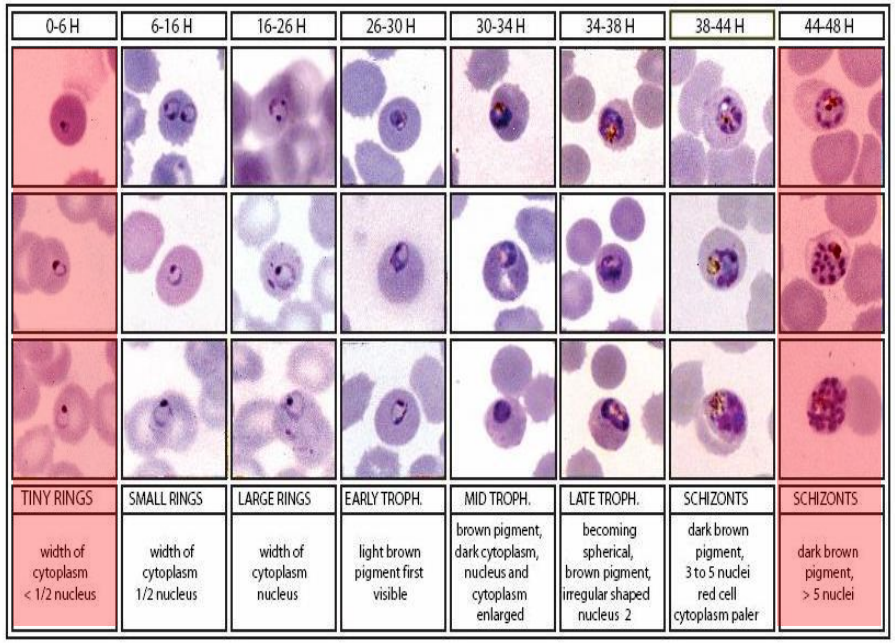
Background Malaria

Complicated life-cycle



Multiple stages with different characteristics and drug sensitivity

Circulating ⟷ Sequestered



Plasmodium falciparum staging (*in vitro* culture)

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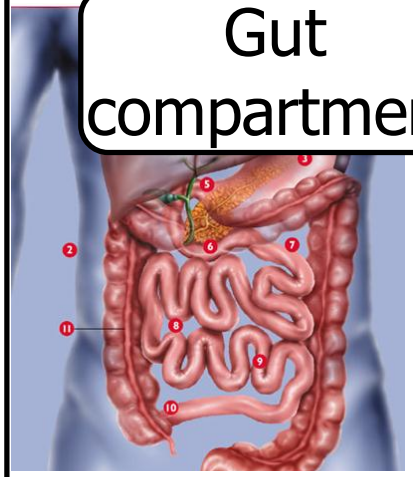
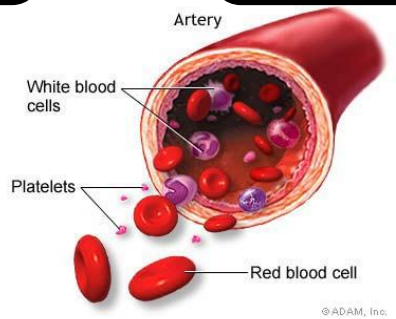
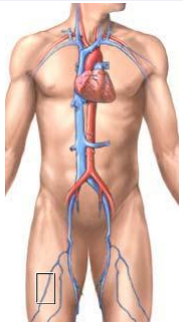
Background PK/PD modelling

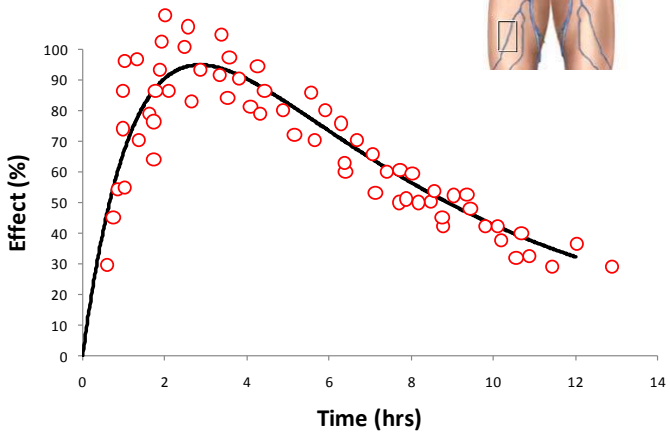
Gut compartment → *ka* → Central compartment → Effect compartment

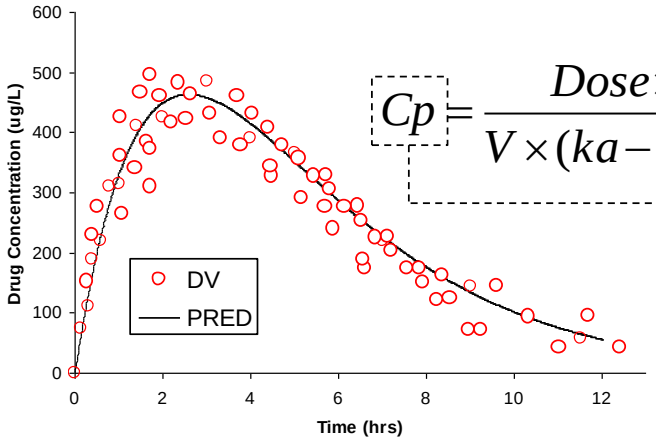




$\lambda = CL/V$







$$Cp = \frac{Dose \times ka}{V \times (ka - CL/V)} \times \left[e^{-\frac{CL}{V} \times t} - e^{-ka \times t} \right]$$

PK

PD

$$E = \frac{E_{max} \times C_P}{EC_{50} + C_P}$$

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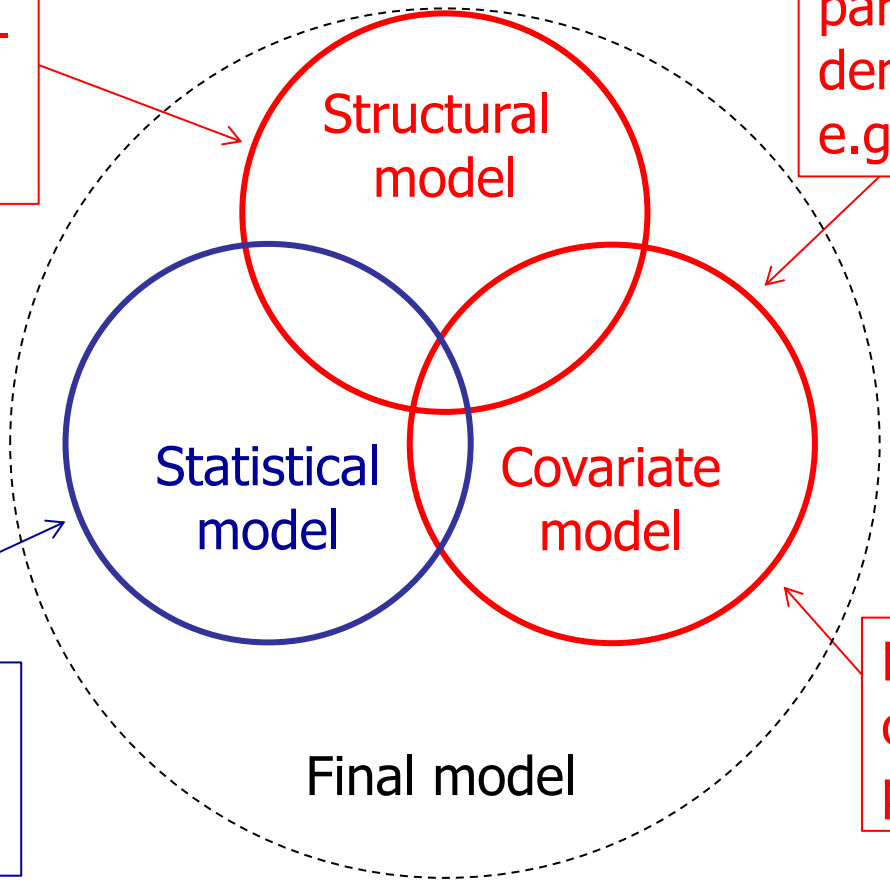
Background PK/PD modelling



E.g. one or two compartments, zero- or first-order absorption

Relationship between parameters & demographic factors e.g. age & body weight

Inter-individual, between-occasion & residual variability

Not always part of the modeling process

Background PK/PD modelling

2-compartment disposition model (PO administration)

$$A1(0) = Dose$$
$$A2(0) = 0$$
$$A3(0) = 0$$

$$\frac{dA3}{dT} = K23 \times A2 - K32 \times A3$$

Peripheral (3) Compartment (V_3/F)

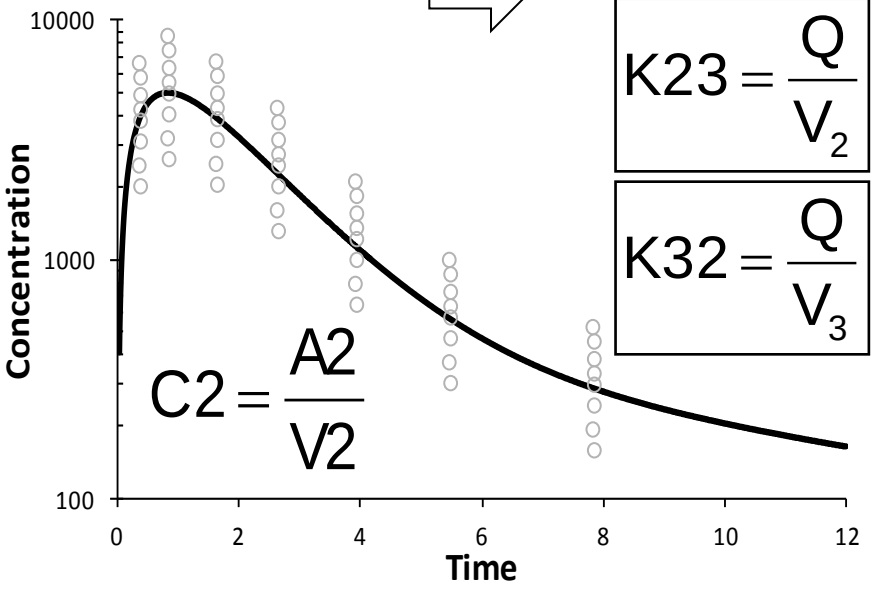
K32 *K23*

Gut (1) Compartment ($F \times dose$) *K12* Central (2) Compartment (V_2/F) *K20*

$$\frac{dA1}{dT} = -K12 \times A1$$

$$\frac{dA2}{dT} = K12 \times A1 - K23 \times A2 + K32 \times A3 - K20 \times A2$$

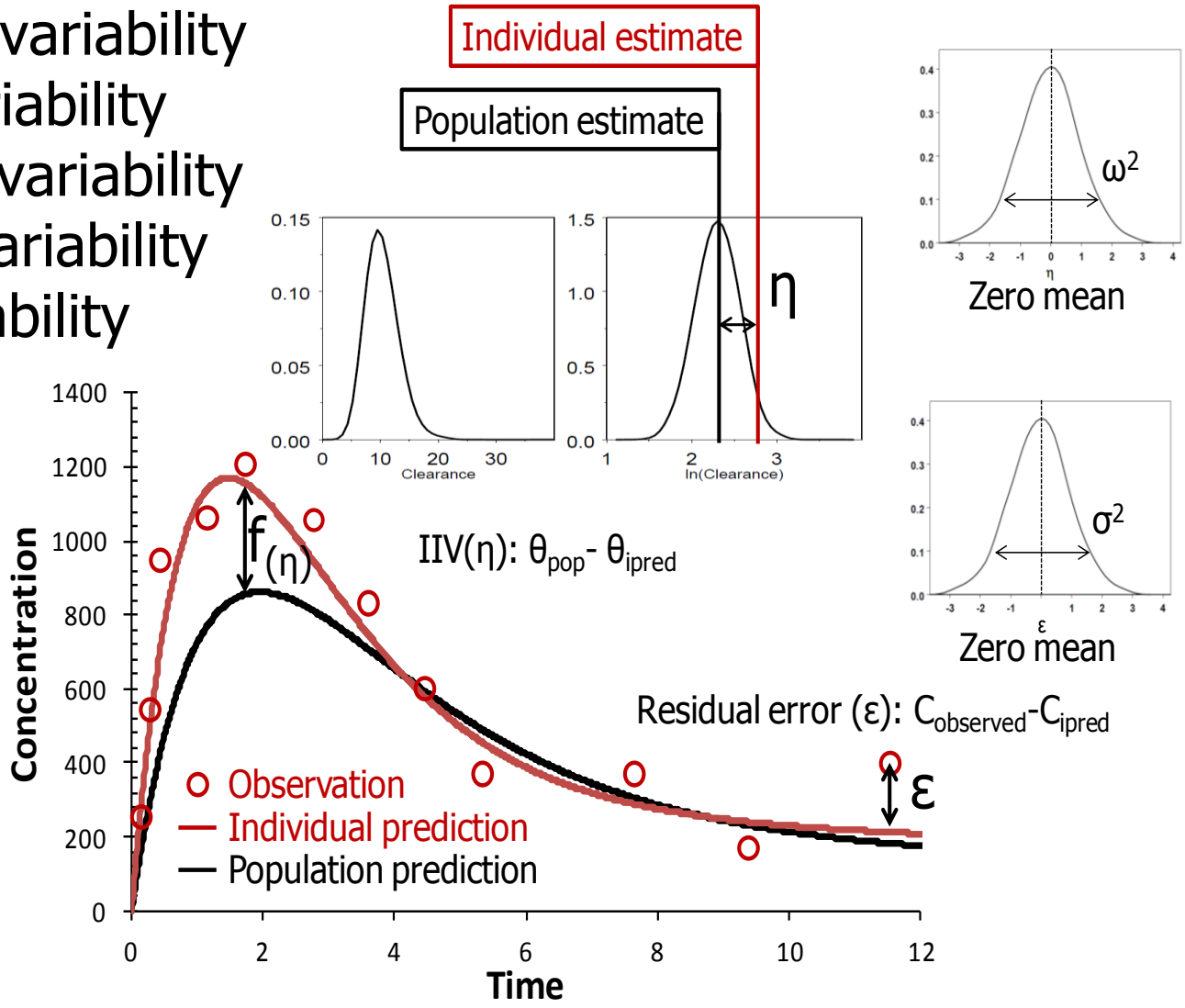
$$K12 = Ka$$
$$K20 = \frac{CL}{V_2}$$
$$K23 = \frac{Q}{V_2}$$
$$K32 = \frac{Q}{V_3}$$



Background PK/PD modelling

Two main sources of variability

- Inter-individual variability
  -between subject variability
- Residual random variability
  -unexplained variability



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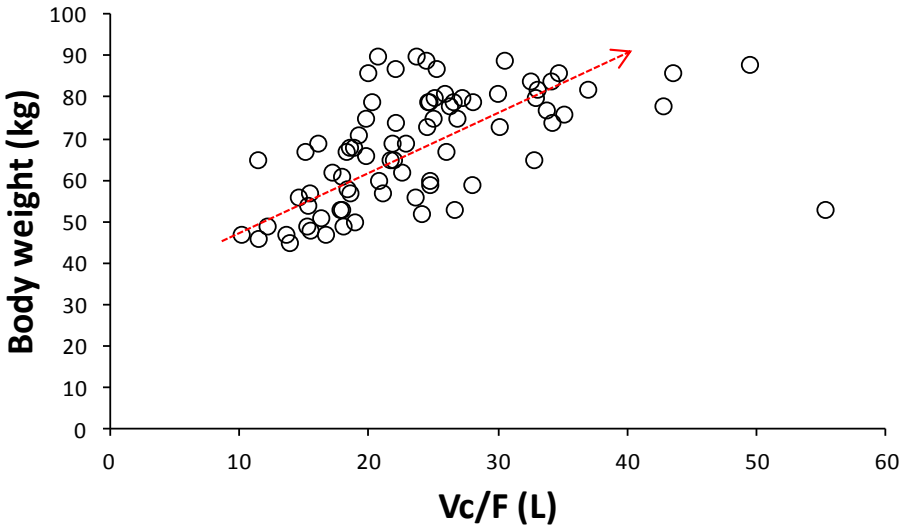
Background PK/PD modelling

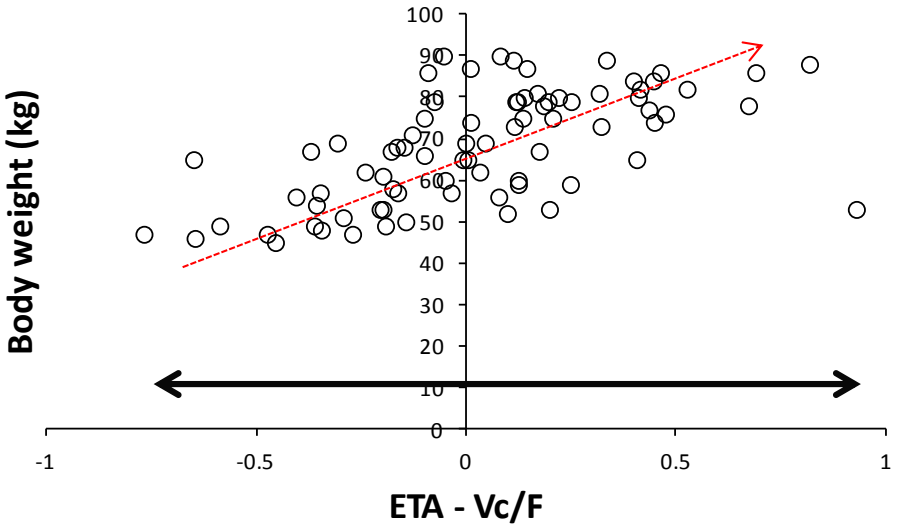
Covariate modelling

- Identify patient sub-groups at potential risk
- Increase the predictive performance of the model
- Increase the understanding of a studied system
- Increase the mechanistic interpretation of the model

Covariates

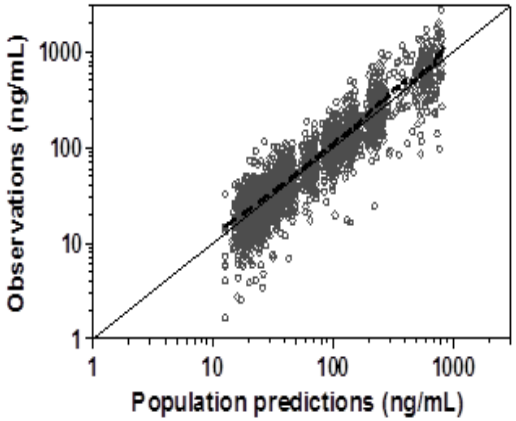
- Demographics (pregnancy, BMI)
- Lab values (bilirubin, AGP)
- Disease parameters (parasitemia)
- Therapy related (co-medication)
- Environmental (smoking)

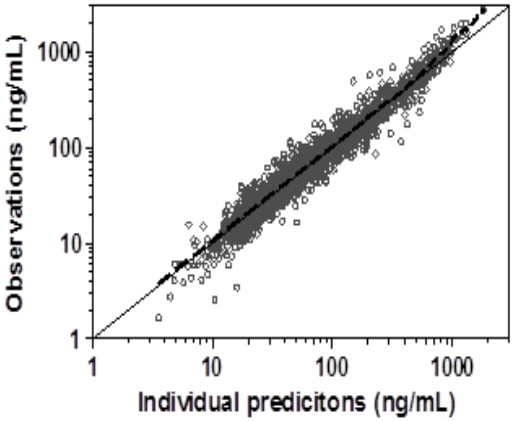


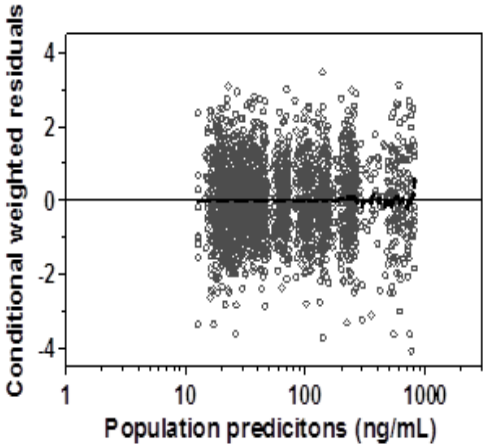


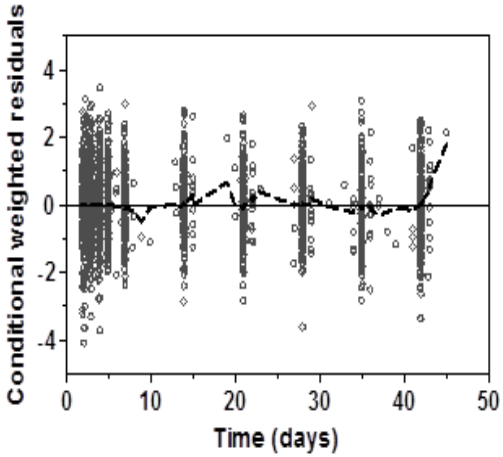
Background PK/PD modelling

Basic Goodness-of-fit diagnostics

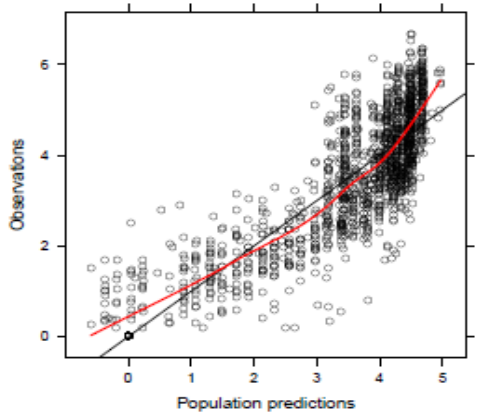


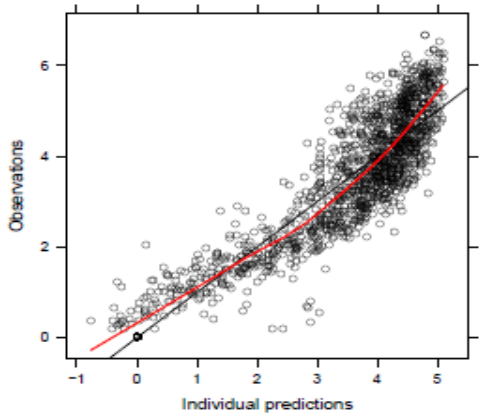






Substantial and systemic deviations/trends indicate model-misspecification





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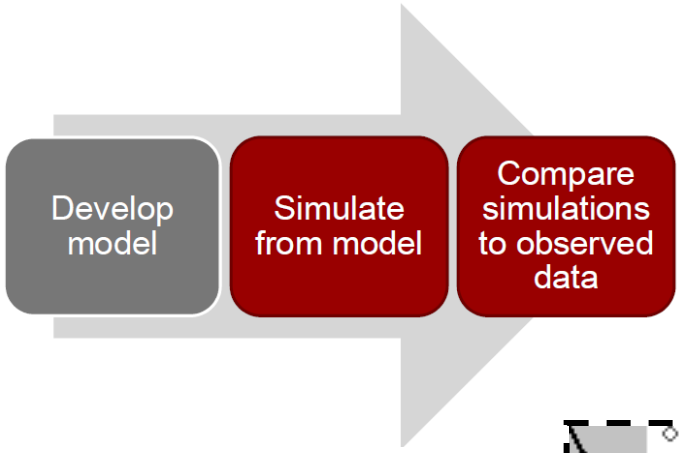
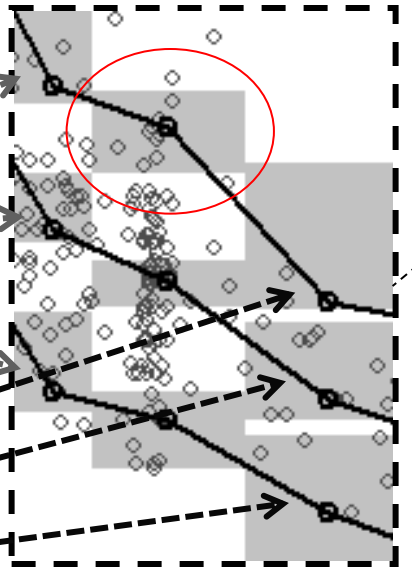
Background PK/PD modelling

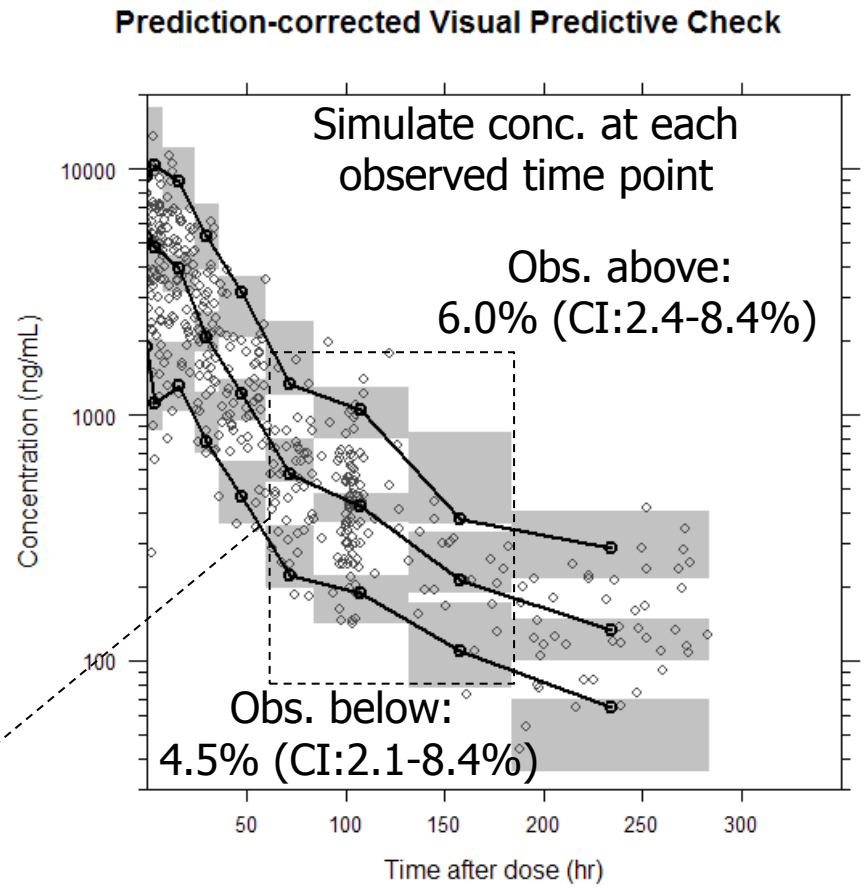
Simulation-based diagnostics



95% CI. of simulated
95th percentile
50th percentile
5th percentile

Observed
95th percentile
50th percentile
5th percentile





Predictive performance of the developed model

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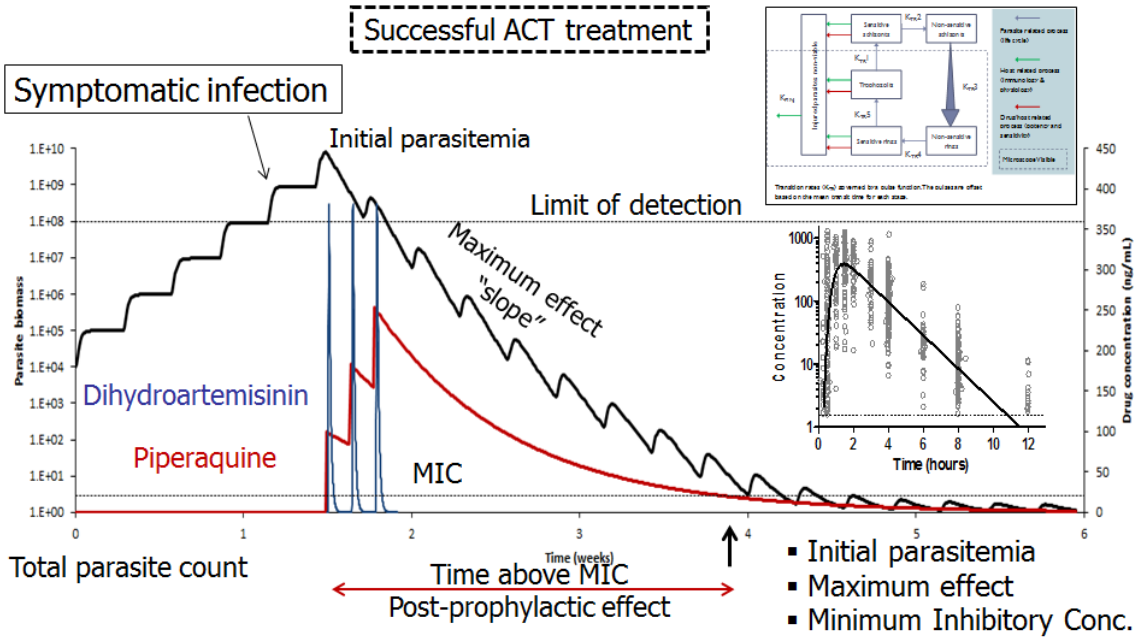
Background PK/PD modelling

- Mechanistic understanding
- Identify and quantify variability components
- Investigate/quantify the impact of covariates
- Dose-optimization
- Clinical trial design



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Thank you for your attention

Questions?

Department of Clinical Pharmacology

Pharmacometricians

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