

Predictive performance of a parasite growth dynamics model for the evaluation of anti-malarial drugs: a case study with mefloquine



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INTRODUCTION

- A semi-mechanistic pharmacokinetic-pharmacodynamic (PKPD) model was previously developed to help screen antimalarial compounds in the pre-clinical phase [1] (*Figure 2*)
- Assuming that the sensitivity of *Plasmodium falciparum* to mefloquine is comparable in both mice and humans, we attempted to scale drug- and disease-specific parameters from mice to humans as the basis for the prediction of parasitaemia in patients.
- The primary objective was to evaluate whether this model could make accurate quantitative parasite count predictions in humans based on humanised murine PKPD data
- The predictive performance was assessed over the acute phase of infection (72 hours) and the rate of recrudescence over 28 days.

GENERAL METHODOLOGY

- Modelling environment consisting of R v3.0.1, Pirana, Xpose v4, PsN and NONMEM V7.3 [2] (using FOCE-I estimation method)
- Model performance for murine data assessed using statistical criteria (RSE), goodness of fit (GOF), visual predictive checks (VPC)
- Extrapolation of murine model to humans was validated against individual level human clinical trial data from literature

Figure 1. Stages in our effort to predict recrudescence

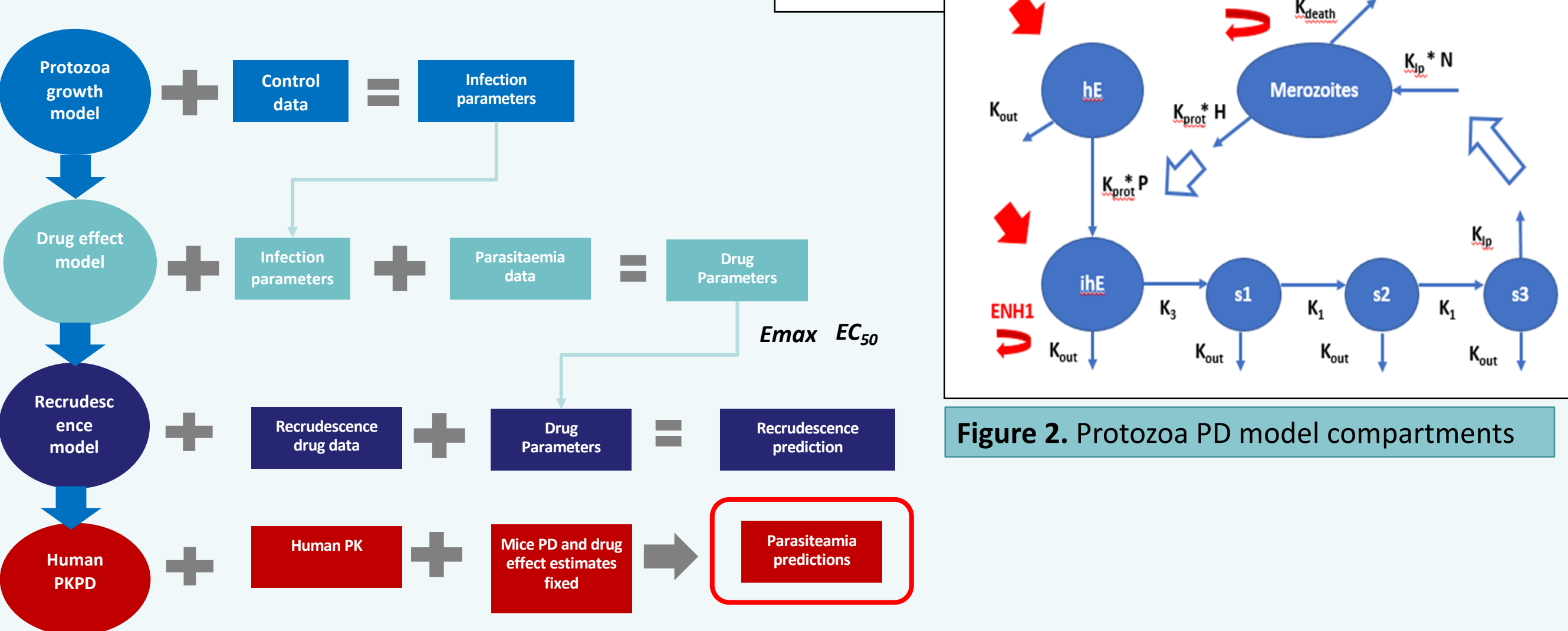


Figure 2. Protozoa PD model compartments

MODEL BUILDING in MICE

Murine data

- Parasite count collected from 10 mice (3 followed for 7 days, 7 followed for 34 days). Mice treated using five dose levels (0.025/0.125/0.25/0.625/1.25 mg/kg) for 4 consecutive days
- All animal studies ethically reviewed and carried out in accordance with European Directive 2010/63/EEC and the GSK Policy on the Care, Welfare and Treatment of Animals.

Murine PK model

- 2 CMT model with single transit absorption adequately described mice PK (*Figure 3*)
- Individual PK parameters were used to predict mefloquine concentrations at PD timepoints

Murine PD model

- Semi-mechanistic drug-disease model; erythrocytic cycle parameterised using six-compartment (*Figure 2*)
- Initial global parasitaemia was calculated in the model by the percentage of infected erythrocytes, divided by the total number of erythrocytes divided over the 4 parasite compartments
- The model allowed for natural regrowth after treatment cessation
- Mefloquine drug effect parameterised as potency (IC_{50}) and maximum effect (E_{MAX}) on the clearance of human erythrocytes (K_{out}) and degradation rate of merozoites (K_{death})
- Drug effect was estimated for acute phase data and extended follow up data

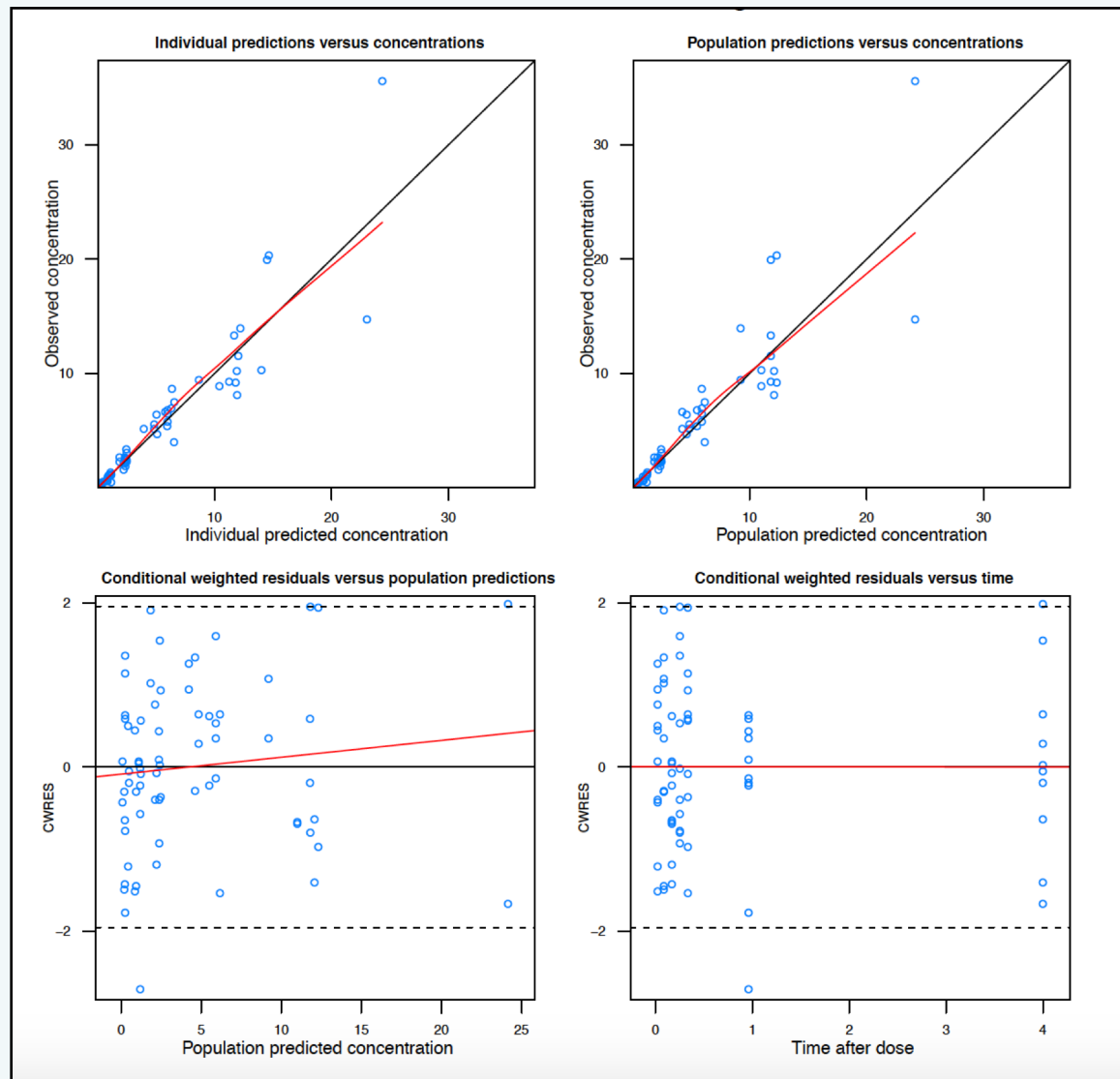


Figure 3: GOF for murine mefloquine PK after doses ranging from 0.025-1.25mg/kg

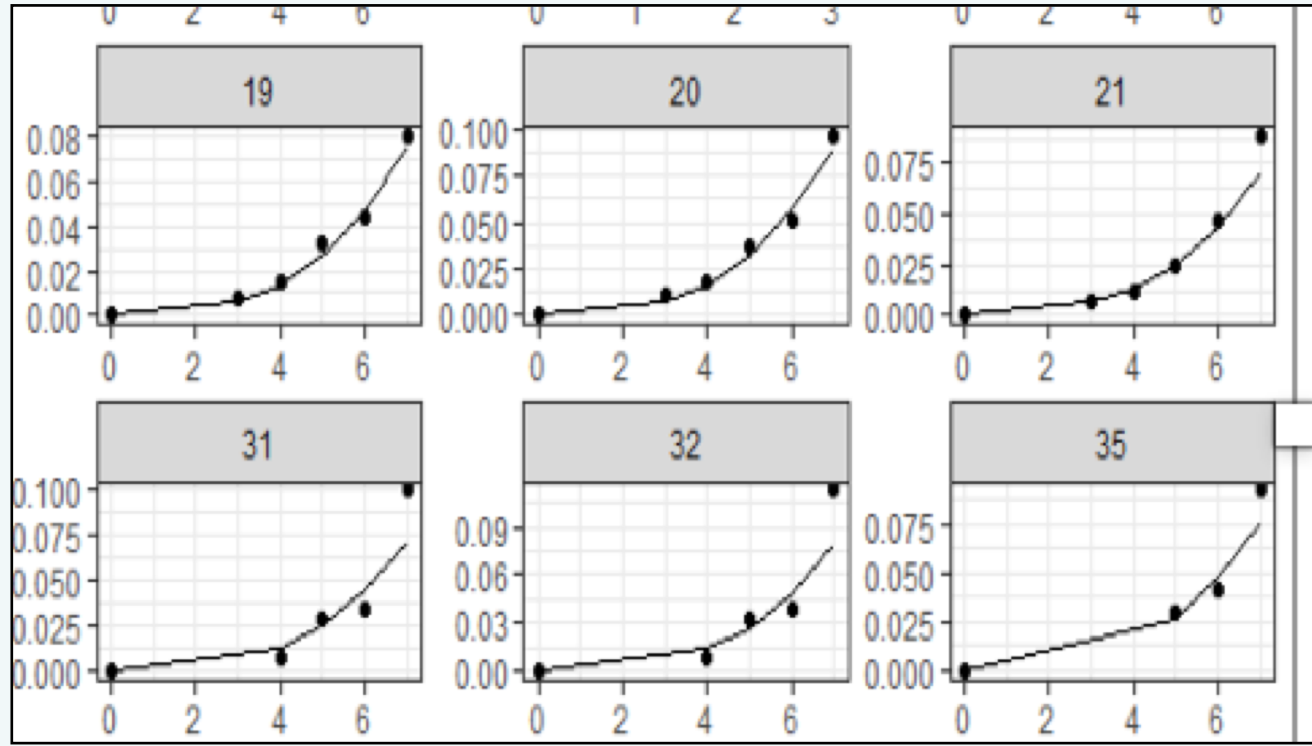


Figure 4: Protozoa growth in six of the mice – observations versus predicted

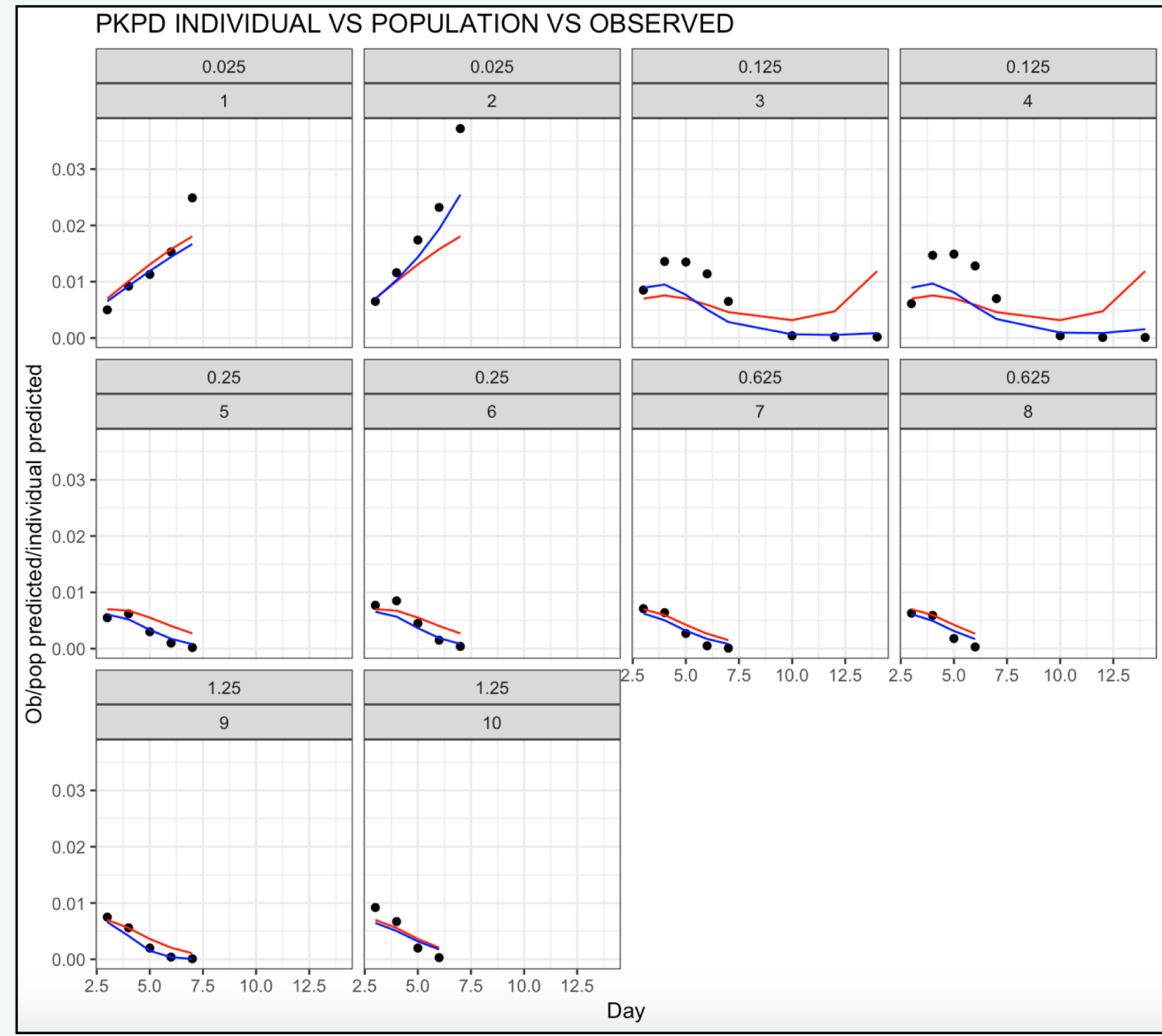


Figure 6: Mice PD – Individual predicted in blue vs. population predicted in red vs. observed

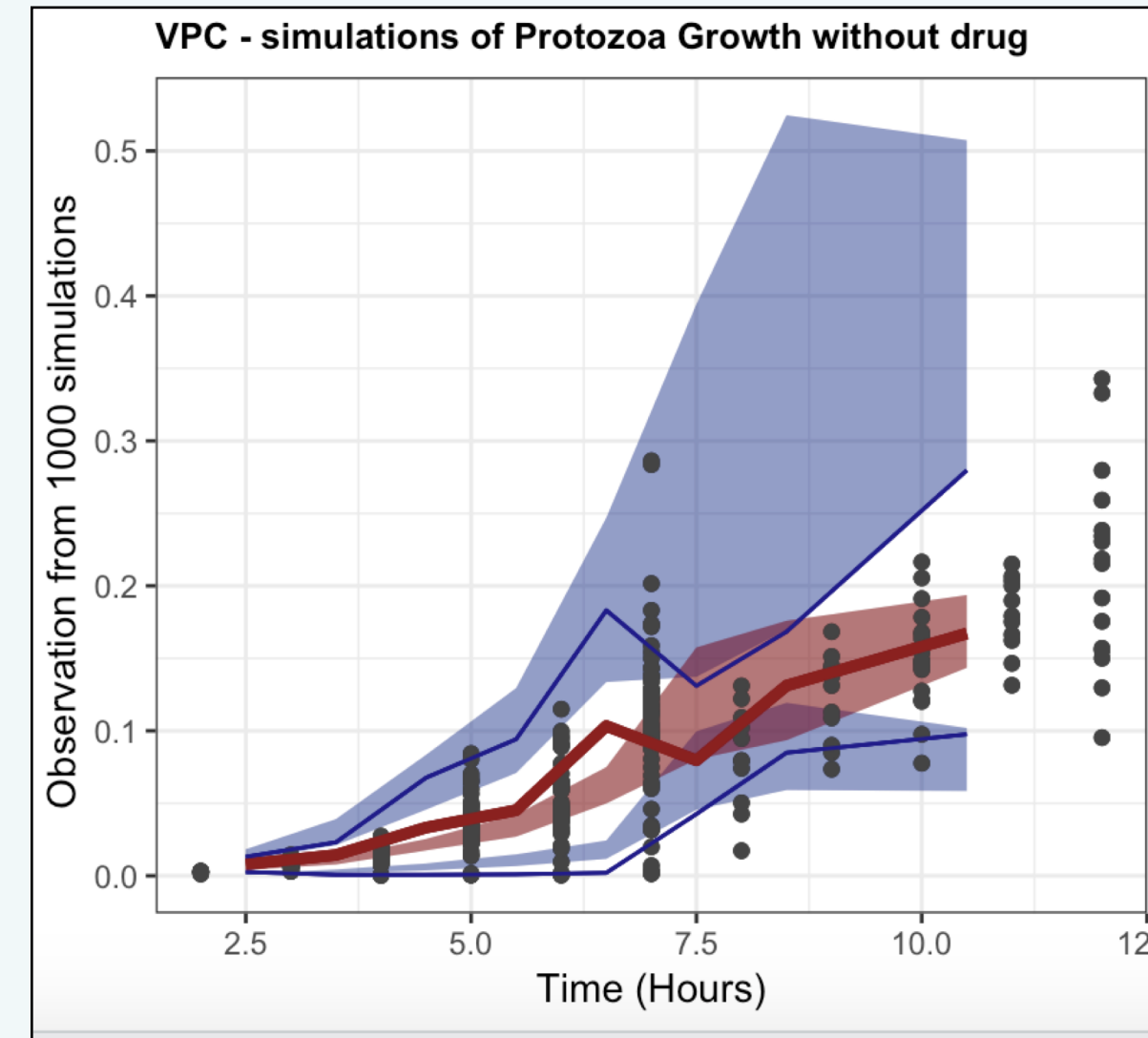


Figure 5: VPC of protozoa growth model – 1000 simulations

MODEL EXTRAPOLATION to HUMANS

Human data

- Data was retrieved from the publication by Looareesuwan et al (1999) [4] This clinical study included 90 patients, treated with mefloquine 750 mg STAT + 500mg 6 hours later
- These data were used to assess the predictive performance of the murine model
- The primary efficacy endpoint was 28-day cure rate.

Translational model building – human PK

- A two-compartment model, single transit compartment absorption and first order elimination [3] replaced the murine PK model
- Weight was a covariate on clearance and central volume of distribution

Translational model – human PD

- PD estimates from the final mice model were used to predict human parasite counts.
- Total human erythrocyte count was assumed to be at a steady state throughout the 3-day clinical trial simulation.
- Over 72 hours, it was assumed that the number of erythrocytes were constant, whereas over 28 days, parameters were adjusted under the assumption that 200 billion red blood cells are replenished per day.
- Parasitaemia for each individual in the clinical study was calculated based on their actual baseline parasite count (μ/L), used as a covariate in the model
- This model was able to predict short term response well (*Figure 8*)

	Number	Mean	Range
Baseline Parasite count (μ/L)	90	46,105	1,134–416,000
Baseline Haemoglobin (g/dl)	90	11.1	
Parasite clearance time (hr)	90	65.2	24–127
Recrudescence at 28 days	11		

Table 1. Demographics from literature clinical trial [4]

ACUTE STAGE (72 HOURS)

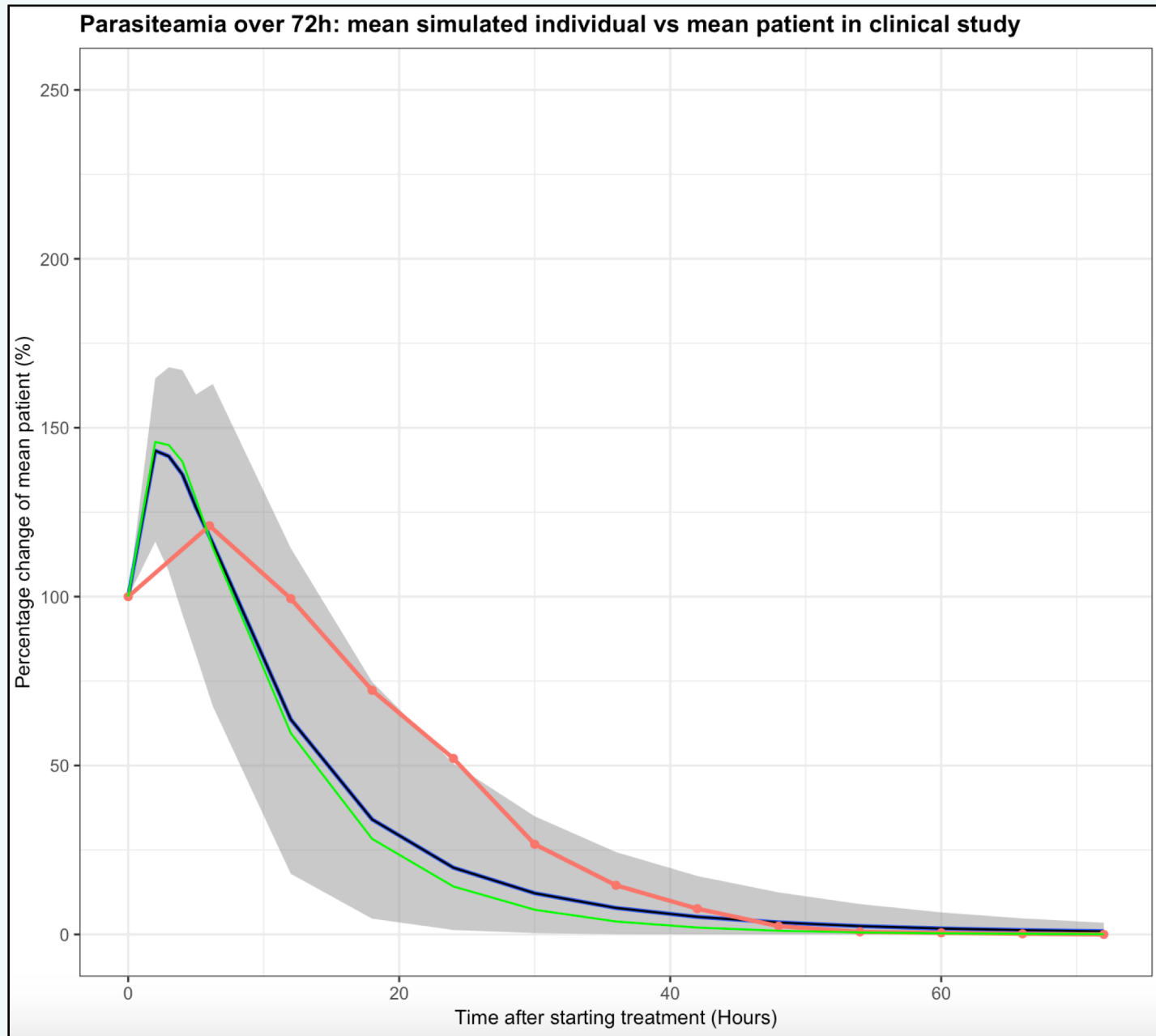


Figure 8: Simulated parasitaemia as change from baseline, using actual baseline parasite counts [4]
Mean patient profile as presented in Looareesuwan [4] in red
Mean patient profile of simulation and 95% confidence interval in blue

28 DAY RECRUDESCENCE RATES

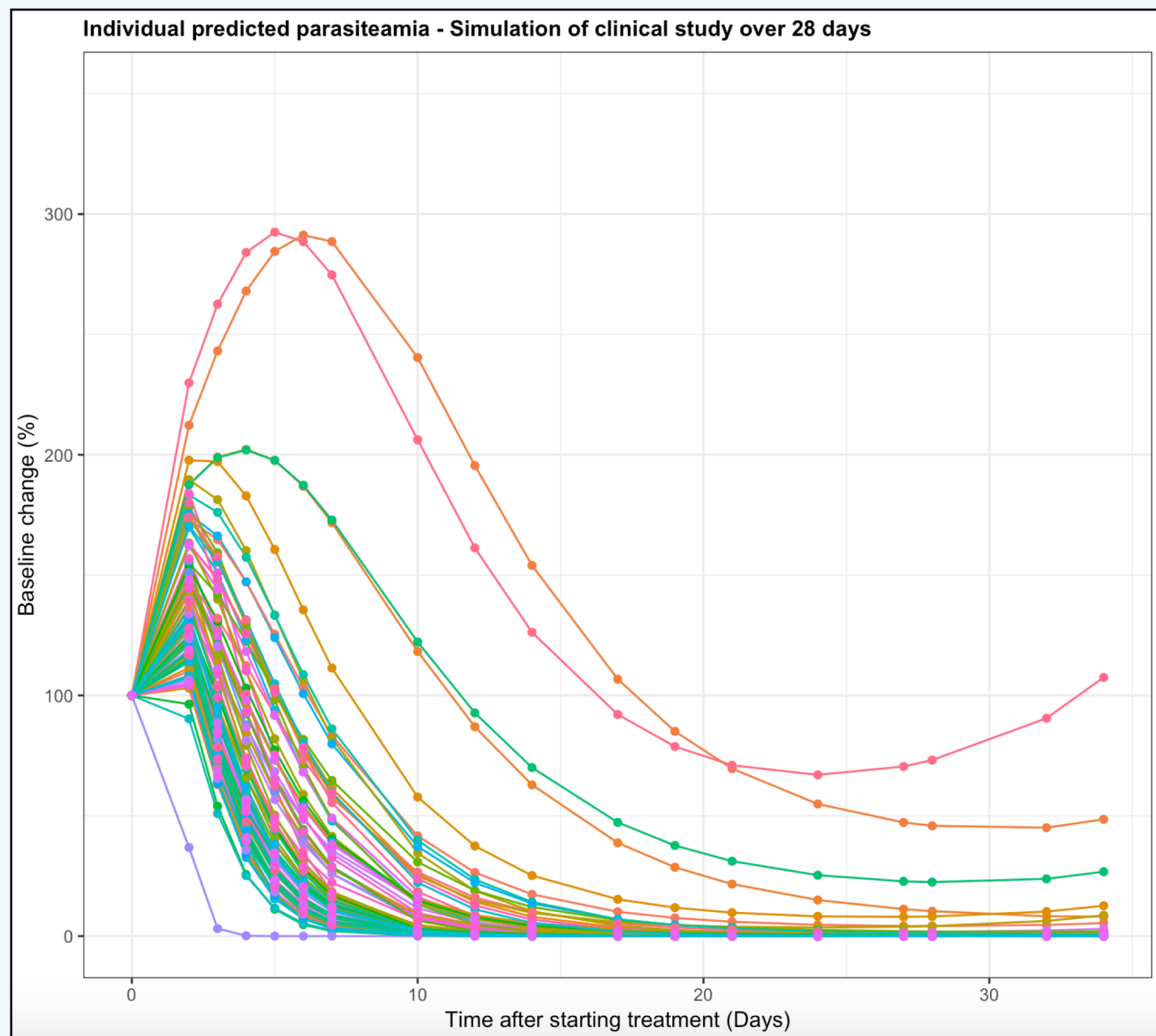


Figure 9: Simulations of individual parasite count change relative to baseline

Outcome	Predicted	Observed
Proportion cured at 72 hours	43 (47%)	57 (63%)
Number with recrudescence	7 (8%)	11 (12%)

Table 2. Model outcomes – cure threshold set at 20 parasites per (μ/L)

Parameters	Final estimates
IC_{50} Kdeath [ng/mL]	0.0074
EMAX KDeath	27.6
IC_{50} Kout [ng/mL]	0.0213
EMAX KOut	33.4

Table 3. Drug effect estimates – 3 days

Parameters	Final estimates
IC_{50} Kdeath [ng/mL]	13.6
EMAX KDeath	7.19
IC_{50} Kout [ng/mL]	2.53
EMAX KOut	49.5
γ [Kout]	0.363
γ [Kdeath]	0.627

Table 4. Drug effect estimates – 28 days

DISCUSSION

- Assuming a limit of detection for microscopy of 20 parasites per μL , the predicted parasitaemia/cure at 72 hours is similar to the observed data (47 vs. 63%)
- However, it cannot be excluded that this difference may represent underestimation of the maximal killing effect and potency of mefloquine
- Over 28 days, recrudescence was predicted in 7 cases vs. 11 observed cases in the original study
- Baseline parasite count alone is not sensitive enough to predict individual recrudescence, but the ratio of those predicted by the model was nevertheless comparable
- The ability of predicting a similar proportion of subjects cured and with recrudescence will aid in the screening and ranking of anti-malarial compounds pre-clinically
- The model does not account for 'resistant' parasites caused by stochastic mutation events, but this scenario can be reproduced mechanistically by increasing the in vivo IC_{50} to values associated with recrudescence

LIMITATIONS

- The infection rate (K_{Prot}) required empirical rescaling by 1000 to allow adequate predictions
- Immune response can have further effect on protozoa dynamics, which are assumed to have a minor impact on the overall treatment effect in mice

CONCLUSION

- The use of a semi-mechanistic model-based approach to scale pharmacodynamics from a murine model seems to enable the prediction of treatment response to mefloquine in patients
- Whilst these findings may not be generalisable, this exercise provides the groundwork for the translation of drug and disease characteristics from a humanised murine model to malaria infection in patients
- Possible other future use for the model would be a tool for personalised predictions of parasite counts

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- NONMEM v.7.3 (ICON Development Solutions, Ellicott City, MD).
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