

Mechanistic modelling of primaquine pharmacokinetics, gametocyte clearance, and mosquito infectivity

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Objectives & Methods :

Objectives: This study aimed to characterize the pharmacokinetic properties of primaquine and its metabolite, carboxyprimaquine. A mechanistic model of gametocyte clearance in the patients and the associated mosquito infectivity were modelled as pharmacodynamic outcomes.

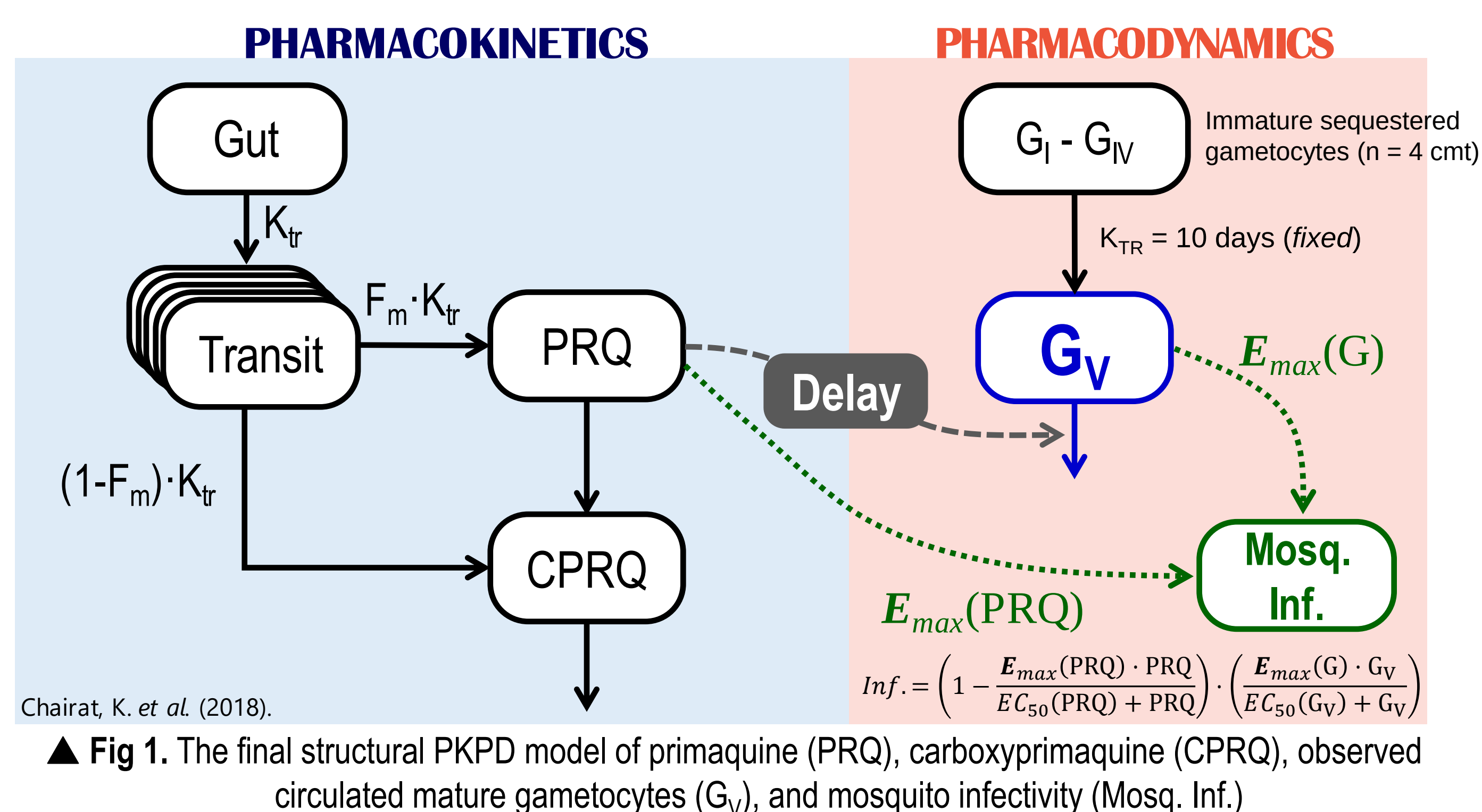
Methods: Eighty G6PD-normal males with uncomplicated *falciparum* malaria received a standard dose of dihydroartemisinin-piperaquine for treatment of the acute infection (2). Patients randomly received escalating primaquine doses (placebo, 0.0625, 0.125, 0.25, and 0.5 mg/kg). Primaquine and carboxyprimaquine concentrations were measured using LCMS/MS. Gametocyte density in the patients were measured using Pfs25 mRNA quantitative real-time (qRT) PCR. Venous blood was collected and fed to *Anopheles gambiae* mosquitoes. At the day 7 post-feeding, the proportion of dissected mosquito with *P. falciparum* oocysts was observed. Pharmacokinetic and pharmacodynamic properties of primaquine and carboxyprimaquine were investigated using nonlinear mixed-effects modelling (NONMEM v.7.4).

Conclusions :

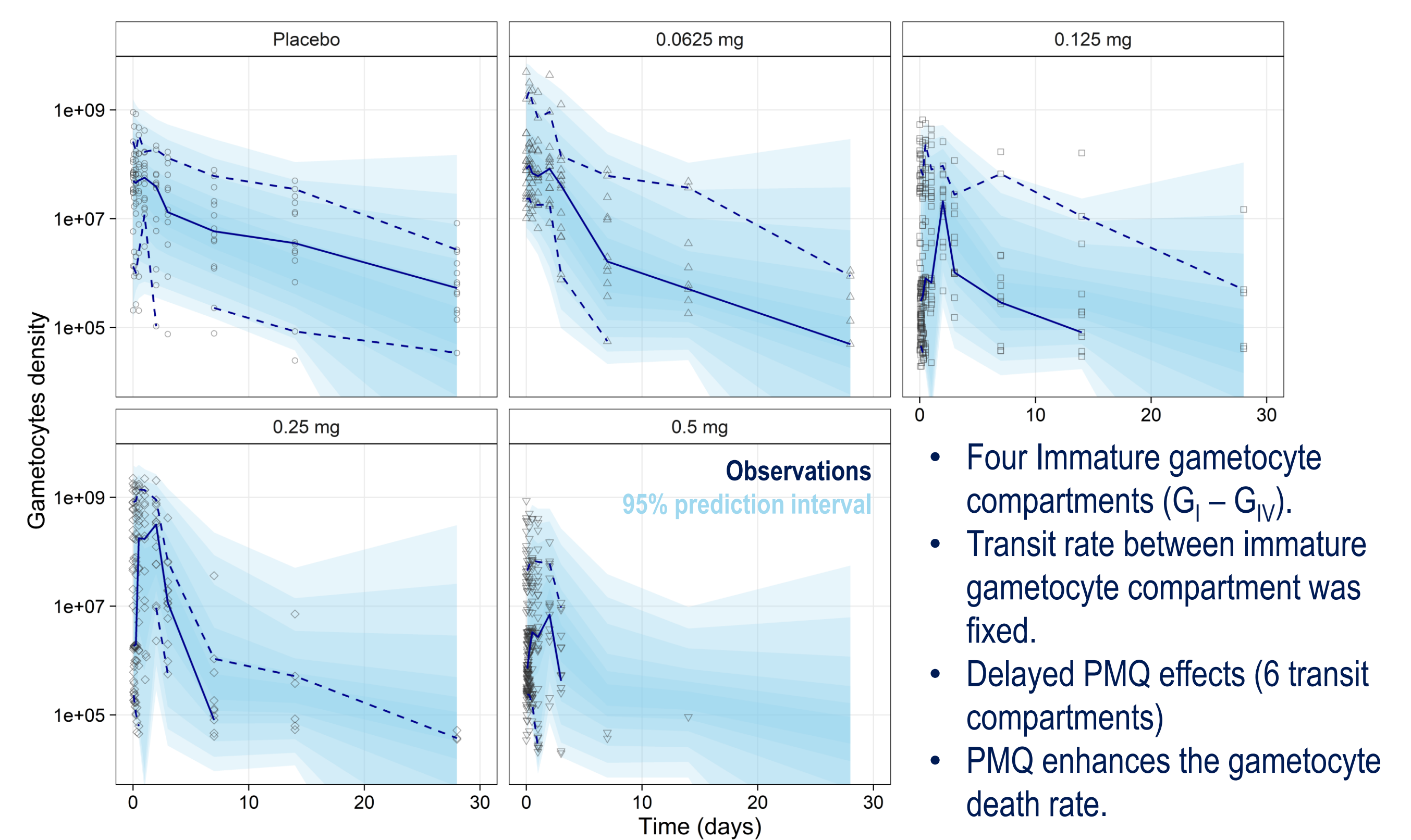
- A mechanistic PK-PD model of primaquine and its major metabolite, carboxyprimaquine, were characterised accurately.
 - PK model: Linear drug-metabolite model with first-pass mechanism.
 - Gametocyte PD model: Five-compartment model with a delayed primaquine effect on the gametocyte clearance.
 - Mosquito infectivity PD model: Both primaquine concentrations and gametocyte density had a significant impact on mosquito infectivity (double E_{MAX} direct-response model).
- Higher primaquine exposure was associated with increased gametocyte killing.
- Primaquine exposure and gametocyte density affected mosquito infectivity.
- Primaquine showed transmission-blocking effects by killing and sterilizing the sexual stage of malaria parasites.

Results & Discussions :

Structural model

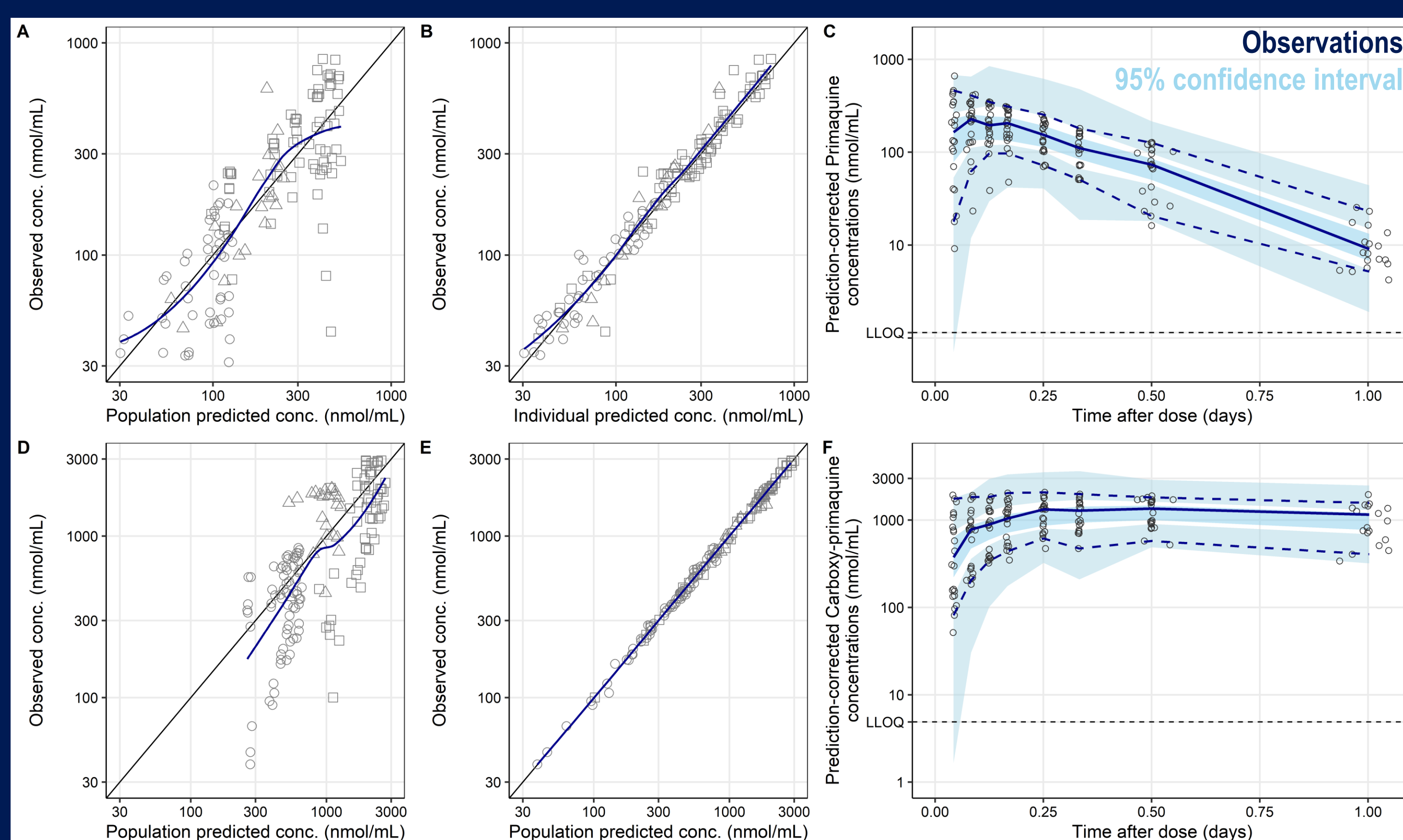


Gametocyte density



▲ Fig 3. The visual predictive plot of the gametocyte model (G_v) stratified by primaquine doses.

Primaquine and Carboxyprimaquine PK



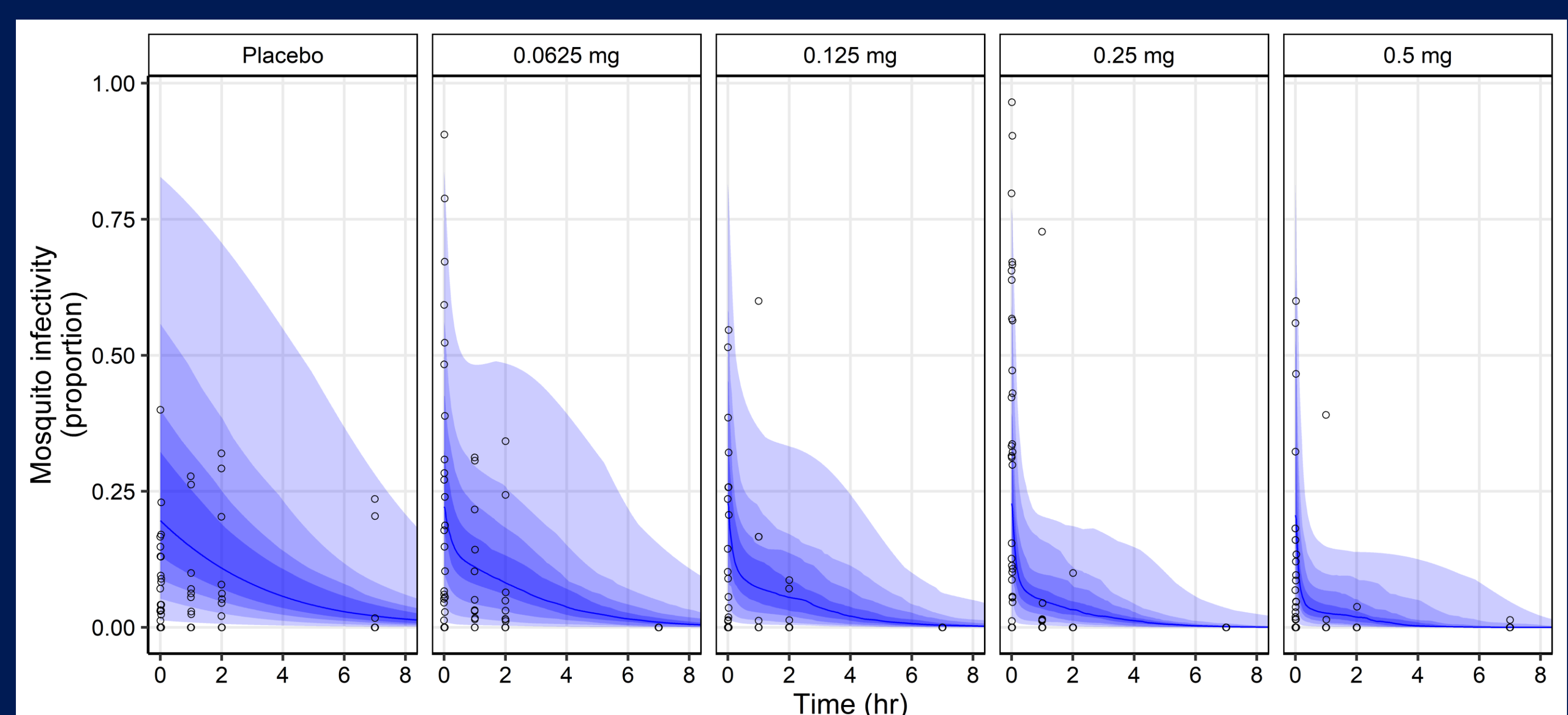
▲ Fig 2. Primaquine (A-C) and carboxyprimaquine (D-F) PK model diagnostics.

- This is the first study investigating the PK of primaquine and its effect on gametocytes and mosquito infectivity.
- Higher primaquine exposure showed a rapid gametocyte clearance. However, the effect was not immediate. Therefore, an unknown active metabolite of primaquine was assumed to be responsible for the elimination of gametocytes.
- Adding primaquine to the standard ACT therapy showed transmission blocking properties. Primaquine exposure and gametocyte density could accurately predict this mosquito infectivity, assuming sterilisation of parasites.

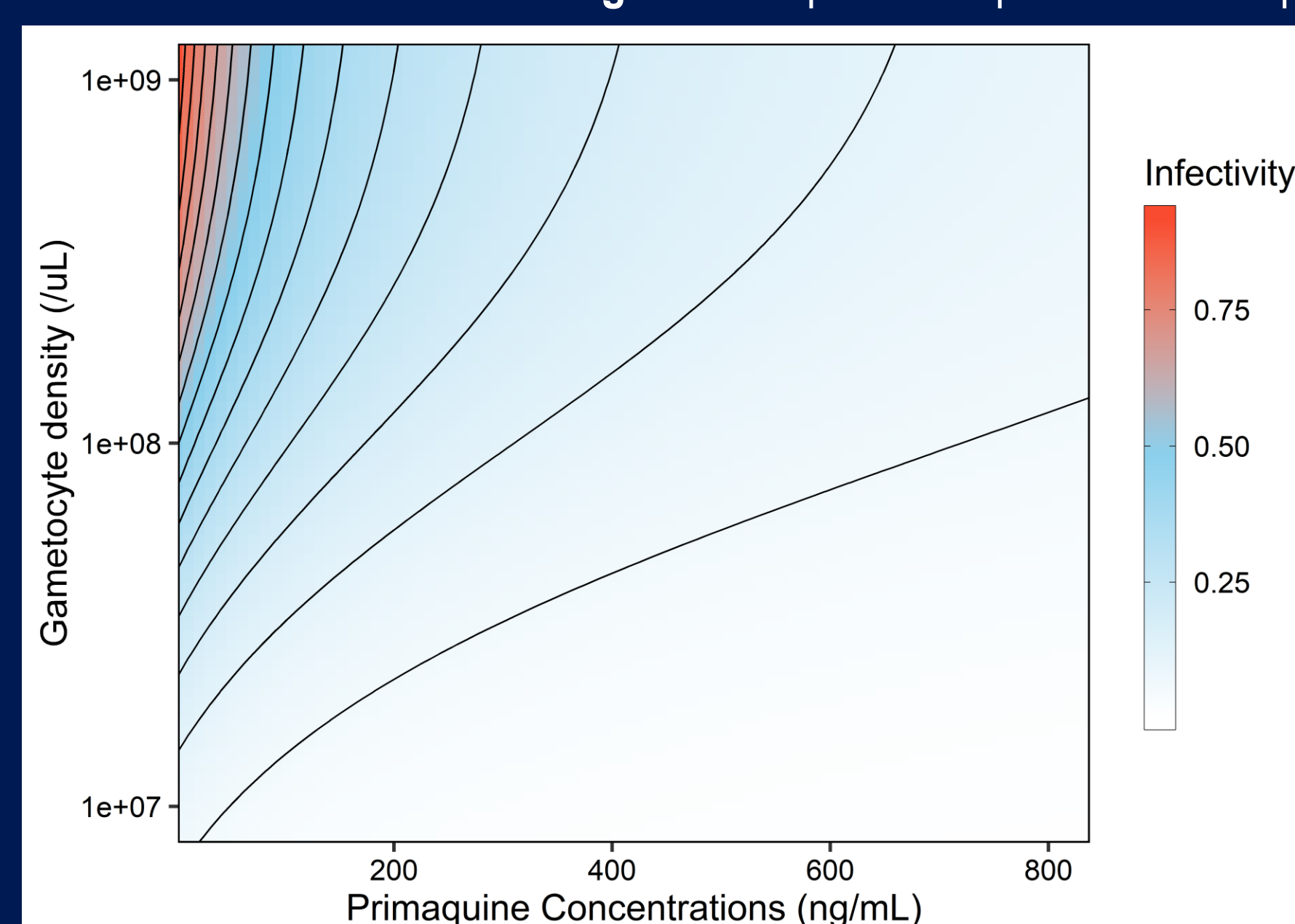
References :

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Mosquito infectivity



▲ Fig 4. Visual predictive plot of the Mosquito infectivity model.



- Mosquito infectivity is determined by the proportion of dissected mosquitoes which presented *P. falciparum* oocysts.
- The infectivity was described by a direct response model linking both primaquine concentrations and gametocyte density to the effect.
- ◀ Fig 4. Relationship between primaquine concentrations, gametocyte density, and mosquito infectivity.

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