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A Controlled Human Malaria Infection model comparing low-dose piperaquine and sulfadoxine-pyrimethamine to induce infectious male and female *P. falciparum* gametocytes

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Background

Efforts to reduce malaria transmission and eliminate malaria require a thorough understanding of malaria biology and transmission. A clinical model to induce gametocytes to understand their dynamics and evaluate transmission-blocking interventions (TBI) is currently unavailable. Here, we explore the use of the well-established Controlled Human Malaria Infection model (CHMI) to induce gametocyte carriage with different antimalarial drug regimens.

Primary objectives:
- Evaluate the safety of protocols.
- Determine the best protocol for induction of stable gametocytemia.

Secondary objectives:
- Determine the dynamics of gametocyte commitment, maturation and sex ratio.
- Determine the time-point of peak density of male and female gametocytes and the area under the curve of gametocyte density.

Exploratory Objectives:
- Gametocyte infectiousness through mosquito membrane feeding assay (DMFA).

Methods

In a single centre, open-label randomised trial, healthy malaria-naïve participants (aged 18-35 years) were infected with *Plasmodium falciparum* by bites of infected *Anopheles* mosquitoes. Subsequently, participants were randomly allocated to four different treatment arms (n=4 per arm) with low-dose (LD) of either piperaquine (PIP) or sulfadoxine-pyrimethamine (SP), followed by curative regimen of piperaquine or sulfadoxine-pyrimethamine upon recrudescence or day 21 post-challenge, whichever came first. Gametocyte density and sex-ratios were determined by molecular assays.

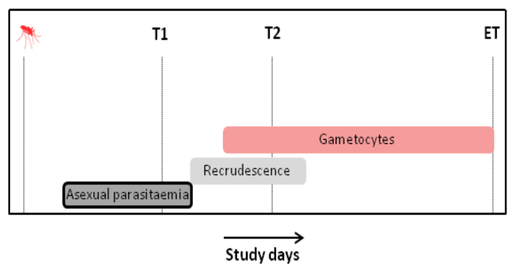

Figure 1: **Study design and main interventions**
Lines represent the expected parasitaemia curves.
T1=Treatment 1, T2=Treatment 2, ET=End-Treatment.

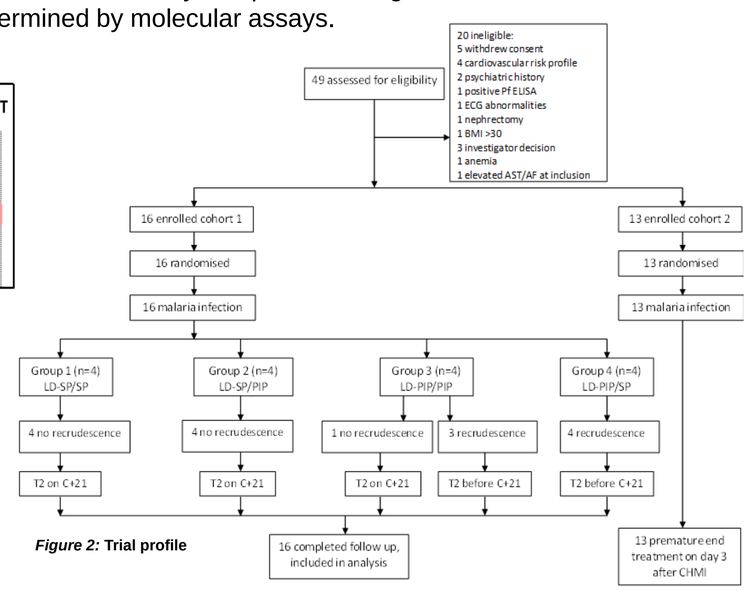

Figure 2: **Trial profile**

Results

Mature gametocytes were observed in all participants (16/16, 100%).

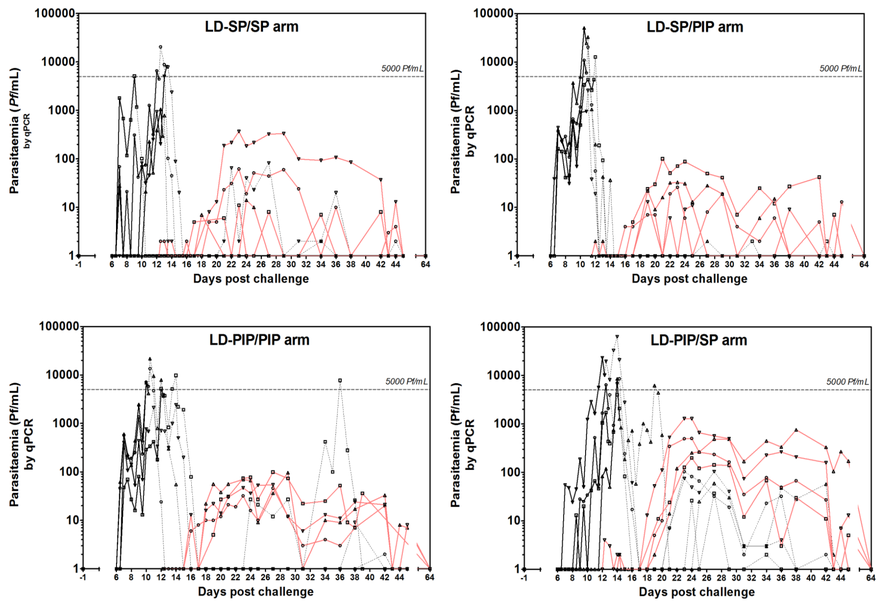

Figure 3: **Asexual parasitemia and gametocytemia.**
Black line represents 18S qPCR asexual parasitemia. Black dotted-line represents 18S qPCR after treatment 1. Red line represents Pfs25 qRT-PCR gametocytemia.

Male gametocytes had a mean estimated circulation time of 2.7 days (95%CI 1.5–3.9) compared to 5.1 days (95%CI 4.1–6.1) for female gametocytes.

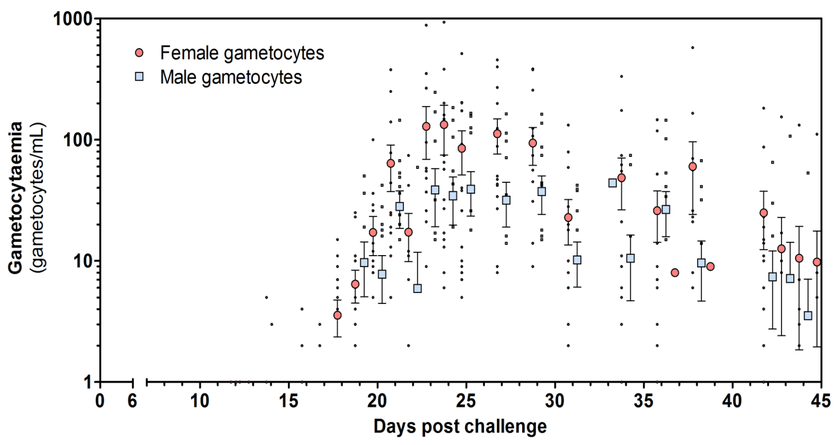

Figure 5: **Total female and male gametocyte density of all participants.**
Dots represent individual gametocyte data. Circles and squares represent mean and error (SEM) of gametocytes per timepoint.

Gametocytes appeared 8.5-12 days after the first detection of asexual parasites. Gametocyte burden was highest in the LD-PIP/SP arm, and associated with the preceding asexual parasite biomass (p=0.026).

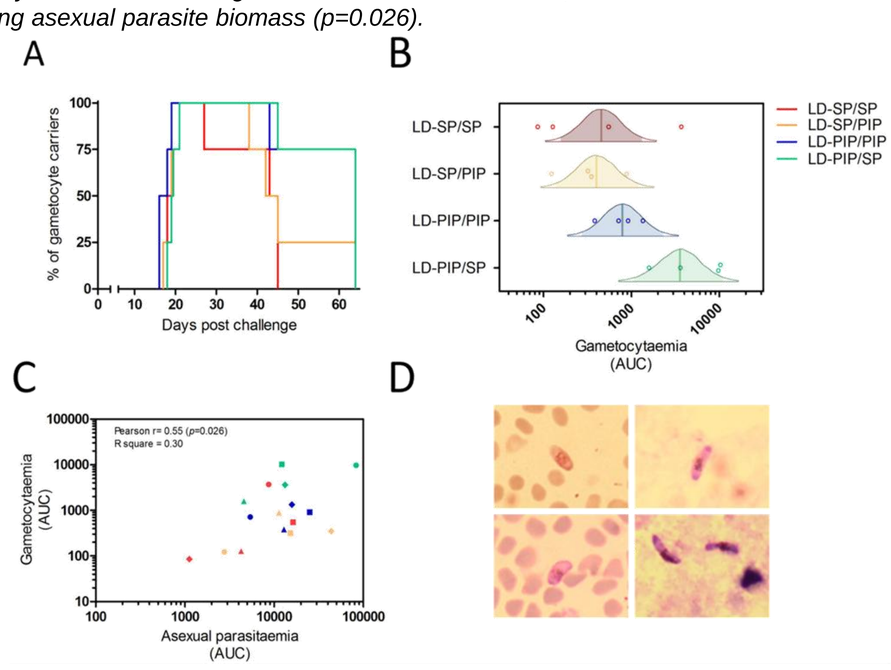

Figure 4: **Gametocyte kinetics between study arms.**

Exploratory mosquito feeding assays showed successful sporadic mosquito infections.

		LD-SP/SP	LD-SP/PIP	LD-PIP/PIP	LD-PIP/SP
Time to T1 (*days*)	Mean (SD)	11.6 (1.8)	10.8 (0.5)	10.5 (1.0)	12.8 (0.9)
Time between T1-T2 (*days*)	Mean (SD)	9.4 (1.8)	10.3 (0.3)	4.7 (4.1)	2.6 (1.6)
Area under the curve (AUC)*	Median (range)				
· Asexual		6490 (1120-16337)	13280 (2773-43777)	14347 (5408-24898)	12747 (4572-82973)
· Sexual		340 (86-3695)	335 (124-885)	816 (382-1348)	6666 (1582-10303)
Peak parasite density (*Pf*/mL)	Geo. mean (range)	6467 (1050-20261)	16376 (2590-50210)	11603 (2408-21565)	8491 (3976-63113)
Peak gametocyte density (gct/mL)	Geo. mean (range)	43 (11-368)	33 (13-101)	74 (46-99)	557 (199-1285)
Day of gametocyte detection after infection (days)	Mean (SD)	18.3 (1.0)	18.5 (1.0)	17.3 (1.5)	19.4 (1.3)
Time to gametocyte detection relative to first asexual parasites ** (days)	Mean (SD)	10.5 (1.3)	11.5 (1.0)	10.1 (1.3)	10.1 (1.2)
Duration gametocytemia*** (days)	Mean (SD)	10 (10.8)	7 (5.1)	17.8 (5.4)	22.8 (3.9)

*The area under the curve (AUC) is defined as the asexual- or sexual parasite density versus time.

**Time to gametocyte detection is calculated as the day of the detection of gametocytes (≥ 5 gct/mL) minus the day of first peak asexual parsitaemia.

***Maximum number of consecutive days of gametocytemia ≥ 5 gct/mL.

Table 1: **Group characteristics of the participants included in analysis.**

Conclusions

Here, we present a novel CHMI transmission model for *P. falciparum* that can be used to study gametocyte biology and dynamics providing novel insights and tools in malaria transmission and elimination efforts. The dynamics of gametocyte commitment, maturation, sex ratio, and sequestration found in our model reflect parasite dynamics found in naturally acquired infections although parasite densities are much lower than in many endemic settings. This model can be used to evaluate the effect of drugs and vaccines on gametocyte dynamics and sex ratios, and lays the foundation for fulfilling the critical unmet need to evaluate transmission-blocking interventions against *falciparum* malaria for downstream selection and clinical development.

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