

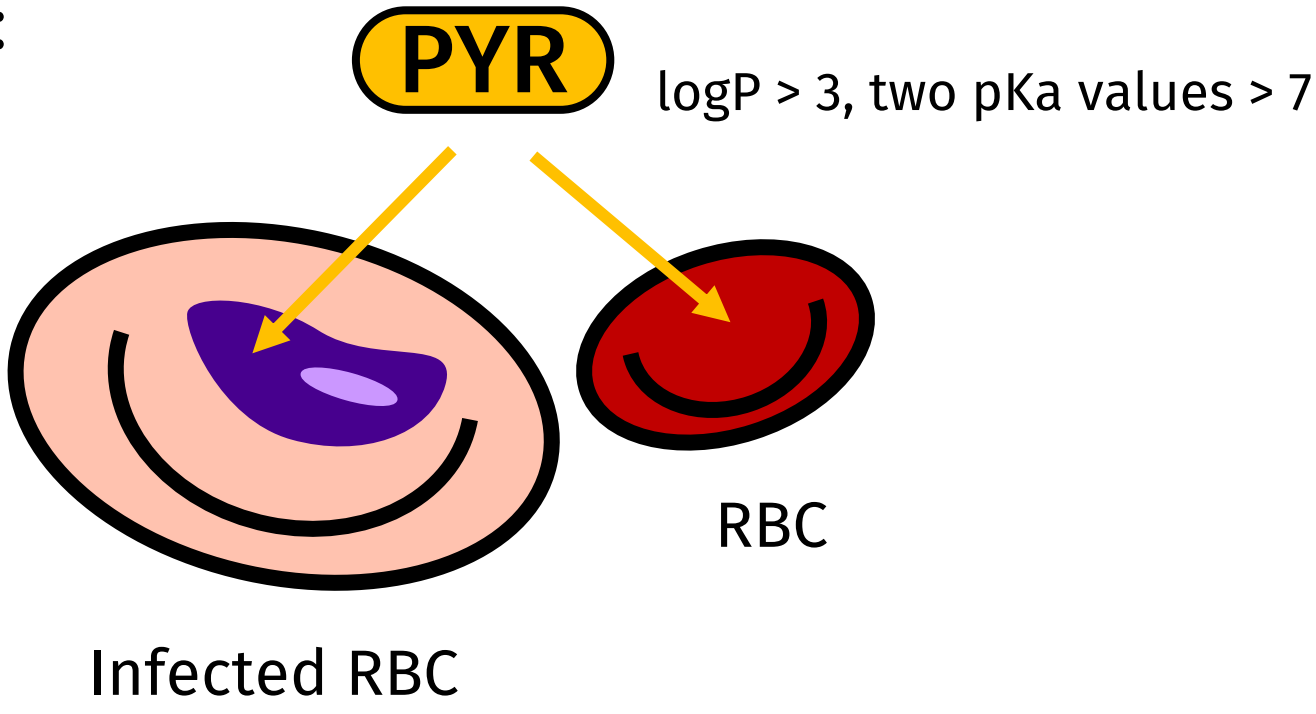
Pharmacokinetics of the antimalarial drug pyronaridine: impact of pregnancy, malaria infection and HIV co-infection

Wan-Yu Chu^{1,2}, Wietse M. Schouten², Hypolite Muhindo Mavoko³, Japhet Kabalu Tshiongo³, Esperanca Sevene^{4,5}, Anifa Vala⁴, Doudou Yobi³, Freddy-Arnold Kabasele³, Alwin D.R. Huitema^{2,6,7}, Umberto D'Alessandro⁸, Kassoum Kayentao⁹, Thomas P.C. Dorlo¹, on behalf of the PYRAPREG clinical trial consortium

1. Department of Pharmacy, Uppsala University, Uppsala, Sweden; 2. Department of Pharmacy and Pharmacology, Netherlands Cancer Institute, Amsterdam, the Netherlands; 3. Department of Tropical Medicine, Université de Kinshasa, Kinshasa, Democratic Republic of Congo; 4. Centro de Investigação em Saúde de Manhica, Manhica, Mozambique; 5. Universidade Eduardo Mondlane, Maputo, Mozambique; 6. Department of Pharmacology, Princess Máxima Center for Pediatric Oncology, Utrecht, the Netherlands; 7. Department of Clinical Pharmacy, University Medical Centre Utrecht, Utrecht University, Utrecht, the Netherlands; 8. Medical Research Council Unit, The Gambia at London School of Hygiene & Tropical Medicine, Banjul, The Gambia; 9. Malaria Research and Training Center, University of Sciences Techniques and Technologies of Bamako, Bamako, Mali.

1 INTRODUCTION

- The PYRAPREG study evaluated the efficacy and safety of pyronaridine-artesunate (Pyramax®) in pregnant women with malaria.¹
- 180 mg pyronaridine tetrphosphate (100 mg pyronaridine) + 60 mg artesunate.
- Substantial differences in pyronaridine PK between healthy individuals and patients suggest hematological changes may affect its volume of distribution in whole blood (V_{WB}).²
- Distribution properties:



OBJECTIVES

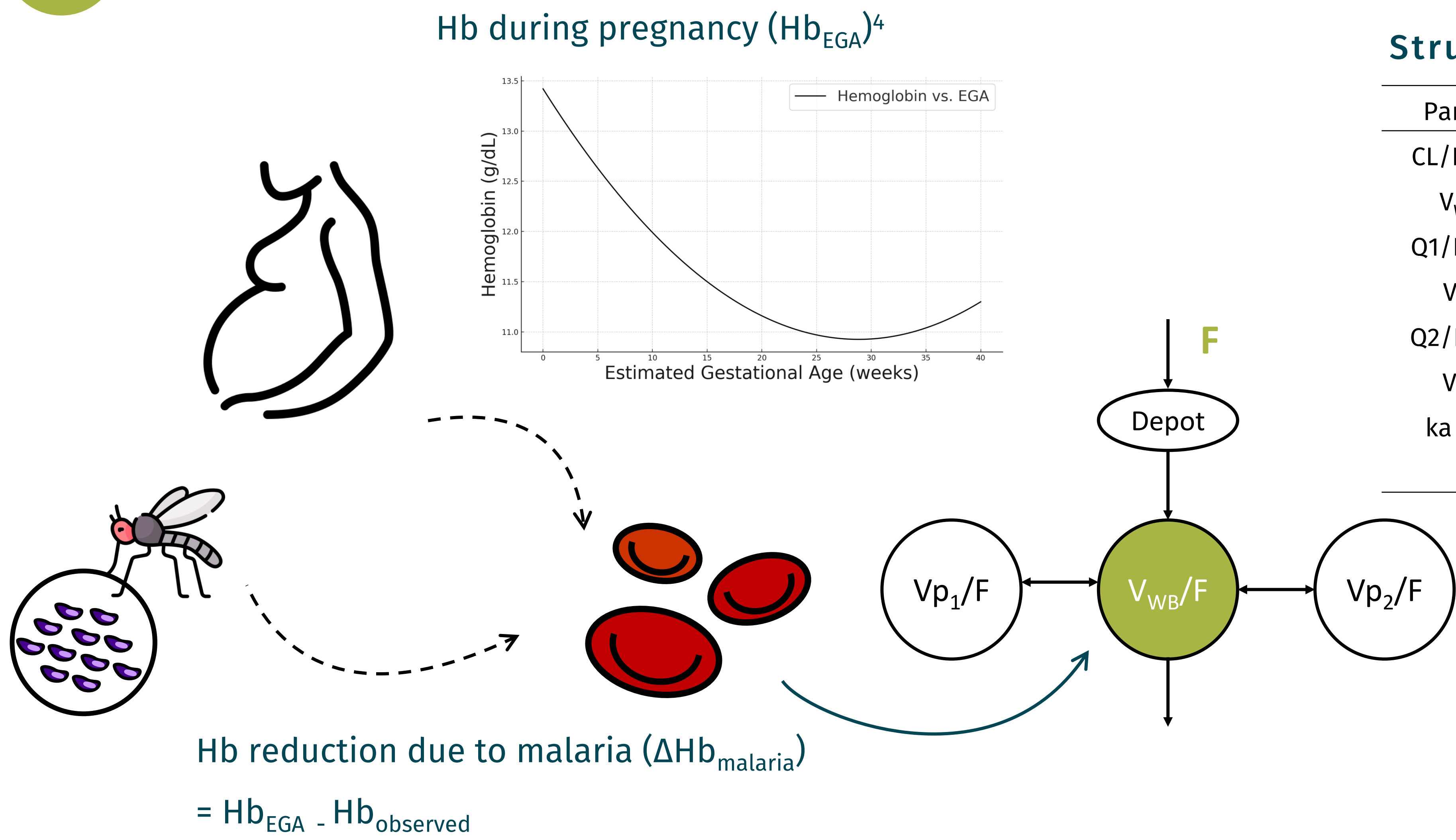
- To characterize the population whole blood PK of pyronaridine in pregnant and non-pregnant women (HIV+ and HIV-) with malaria.
- To evaluate the impact of pregnancy on PK of pyronaridine.
- To evaluate the need for dose adjustments in pregnant women.

2 METHODS

- PK data from Democratic Republic of the Congo and Mozambique.
- Pyramax® tablets once daily for 3 days based on body weight.
- Whole blood samples were analyzed using UPLC-MS/MS (range: 0.5-500 µg/L).³
- Number of patients:

	Non-pregnant	Pregnant (2nd & 3rd trimester)
HIV-	25	39
HIV+	32	26

3 RESULTS



Structural model

Parameters	Estimates	BSV	CV%
CL/F (L/hour)	43.5	V_{WB}/F	62.4
V_{WB}/F (L)	157	$V3/F$	23.3
Q1/F (L/hour)	147	F in non-pregnant, HIV-	18.9
V_{p1}/F (L)	6.39×10^3	F in pregnant, HIV+	57.2
Q2/F (L/hour)	13.2	F in non-pregnant, HIV+	35.6
V_{p2}/F (L)	5.32×10^3	F in pregnant, HIV-	31.4
ka (1/hour)	0.161		
F	1 (fixed)		

Covariate model

Parameters	Estimates	95%CI
% increase in F during third trimester	56.5	26.6-91.4
% increase in V_{WB}/F per $\Delta Hb_{malaria}$	32.6	13.8-60.8
% decrease in V_{WB}/F in HIV co-infection	30.6	7.80-51.0

Fig1. Effect of malarial anemia

Fig2. Effect of pregnancy

4 CONCLUSIONS

- F increases during pregnancy, particularly in the 3rd trimester.
- Malarial anemia is associated with an increased V_{WB} .
- Pyronaridine distribution is influenced by complex interactions between pregnancy, malaria infection, and Hb levels.
- Pyronaridine exposure (AUC_{0-1d}) was higher in pregnant women, but was not associated with signs of potential liver injury.
- Given the absence of exposure-response relationships, dose adjustment during pregnancy, including in HIV co-infected patients, may not be necessary.

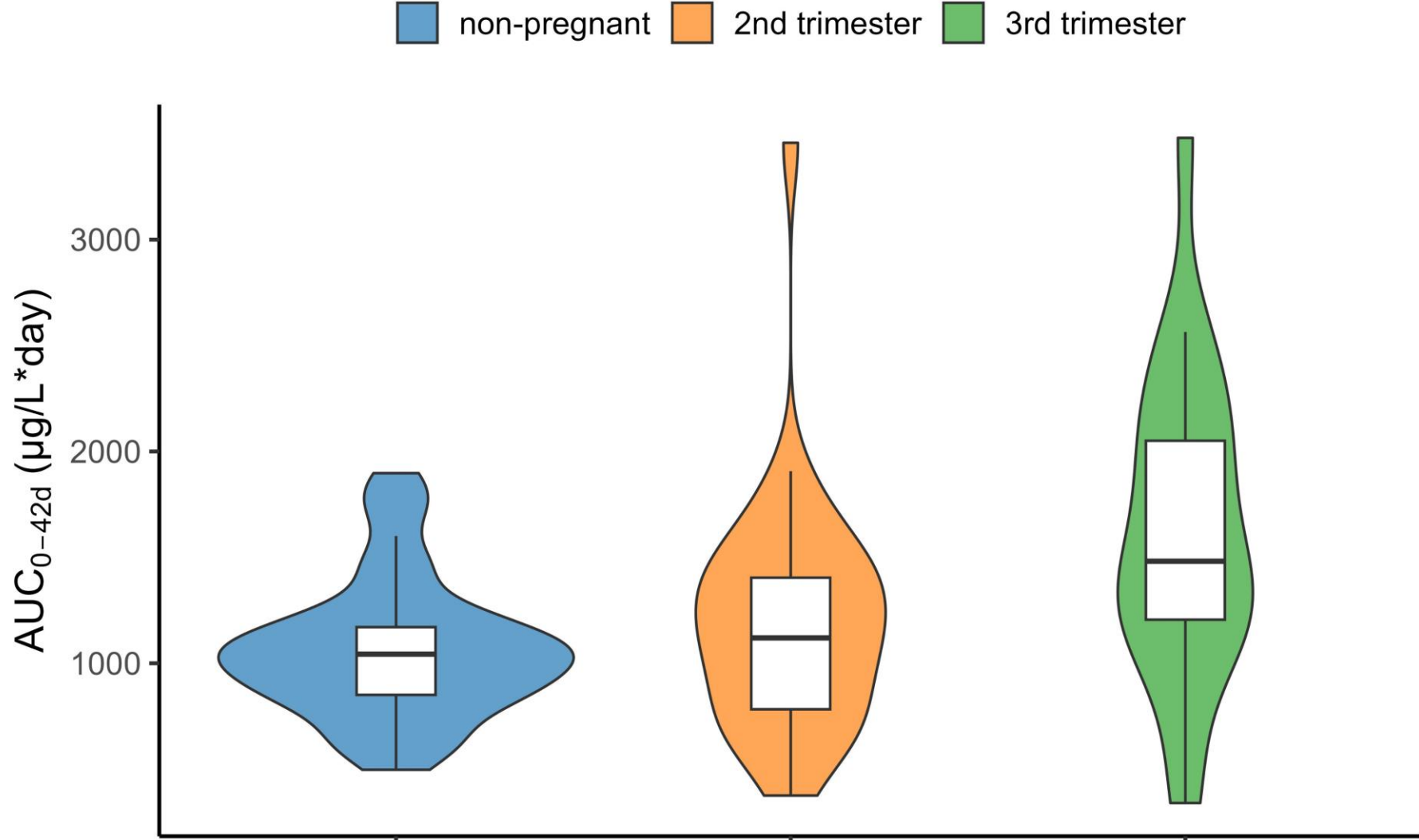
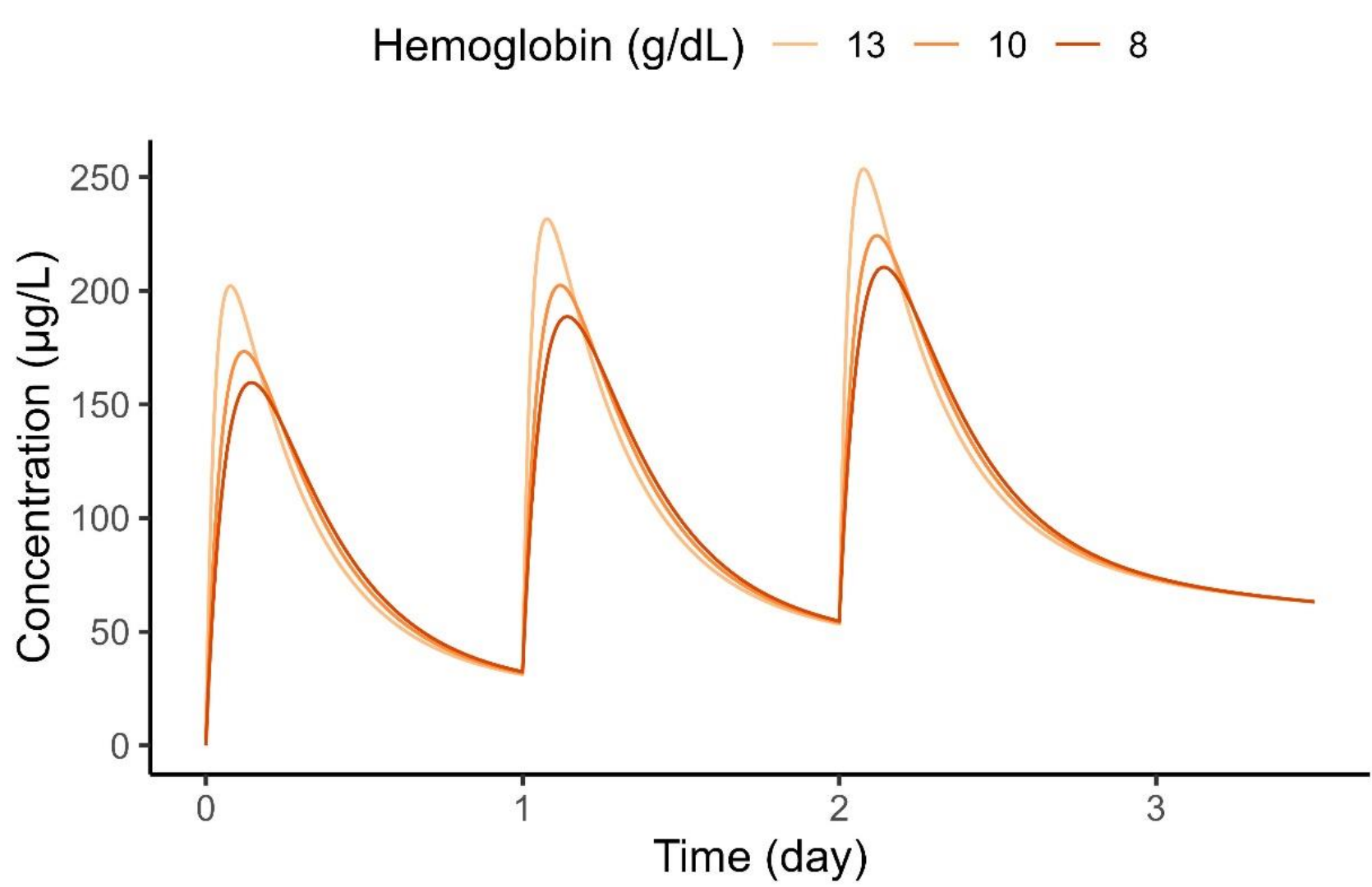
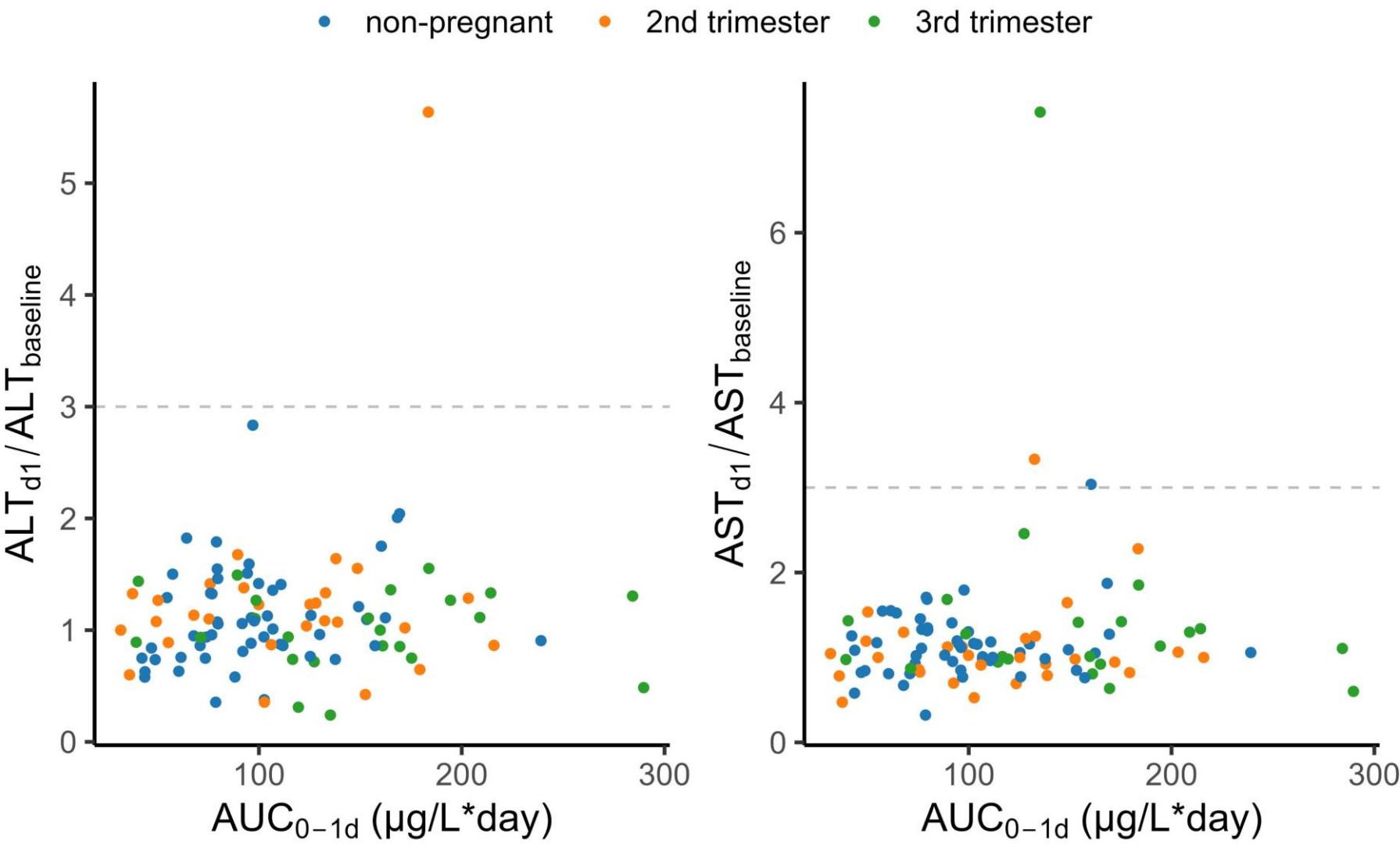
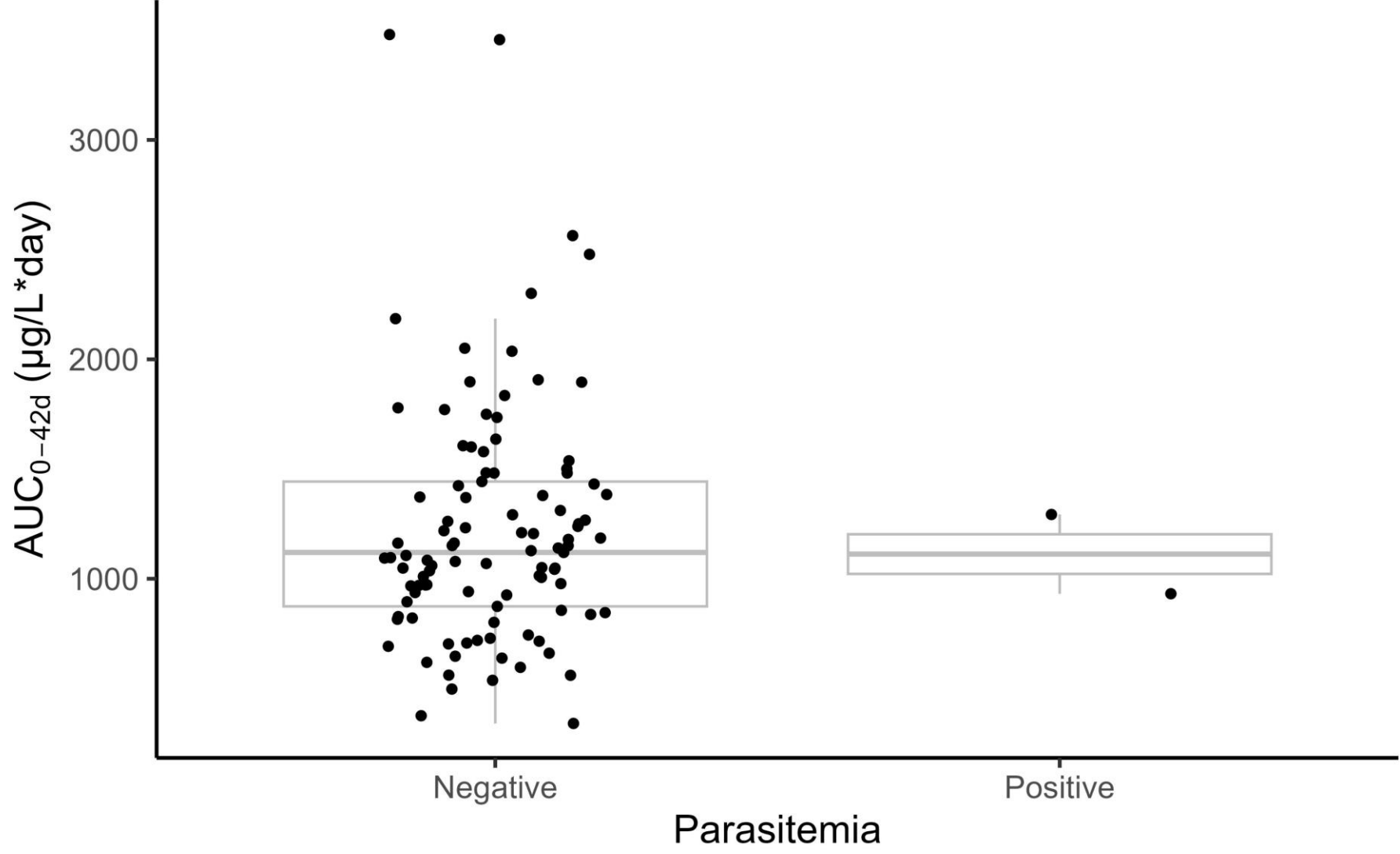


Fig3. Exposure-response

Fig4. Exposure-toxicity

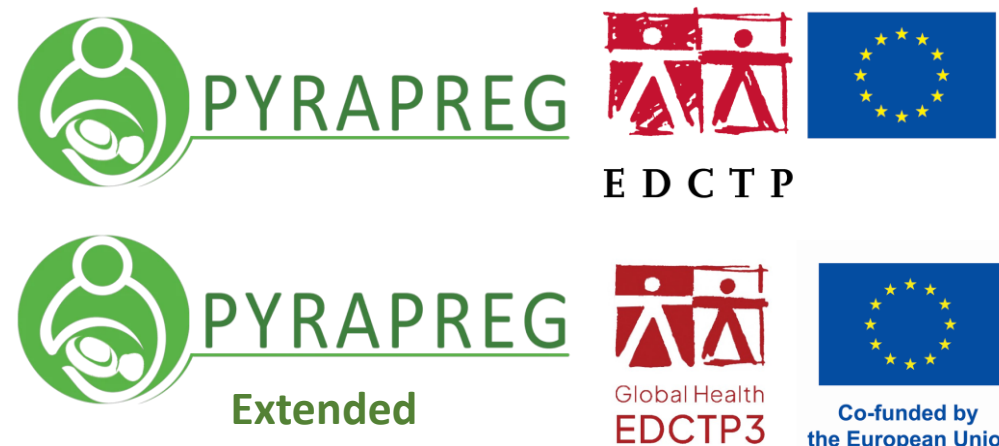


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Contact information

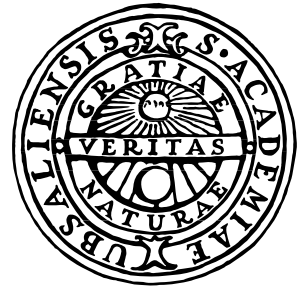
Wendy Chu
Tropical Pharmacology and Therapeutics,
Uppsala University
wendy.chu@uu.se



The PYRAPREG project is part of the EDCTP2 Programme supported by the European Union.



The PYRAPREG-extended project is part of the EDCTP3 Programme supported by the European Union.



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