Ivermectin for Malaria Elimination - Clinical Trials

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Principal Investigator, The Geneva Foundation

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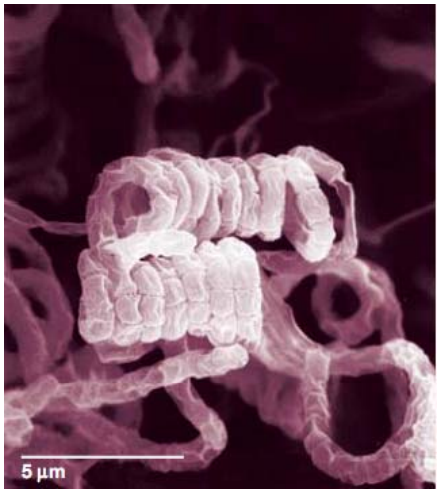
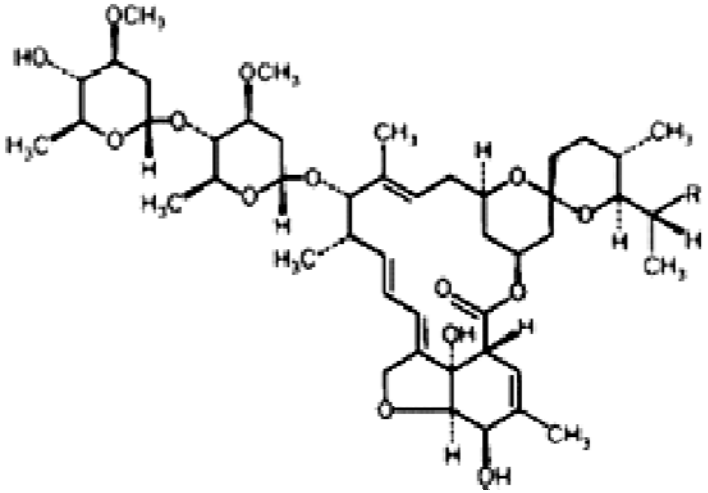
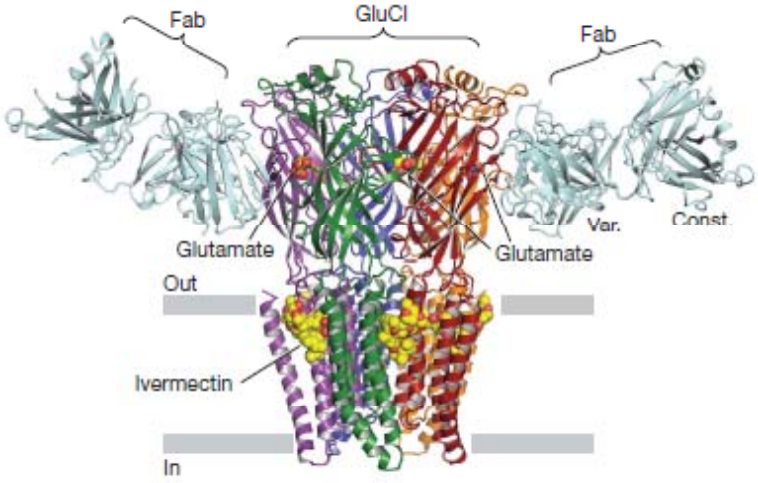
JITMM

Ivermectin - background

- Endectocide – activity against internal and external parasites
- Macrocyclic lactone isolated from the bacteria *Streptomyces avermitilis*
- Mode of action – binds at subunit interfaces of the glutamate-gated chloride (GluCl) ion channel, which distorts the channel from closed to open, hyperpolarizing the cell (Hibbs and Gouaux 2011) which leads to the paralysis of the nematode or ectoparasite musculature (Cully et al. 1994, 1996, Kane et al. 2000)
- Lethal against *Anopheles* mosquitoes!
- Different class of insecticides than those used for ITNs or IRS







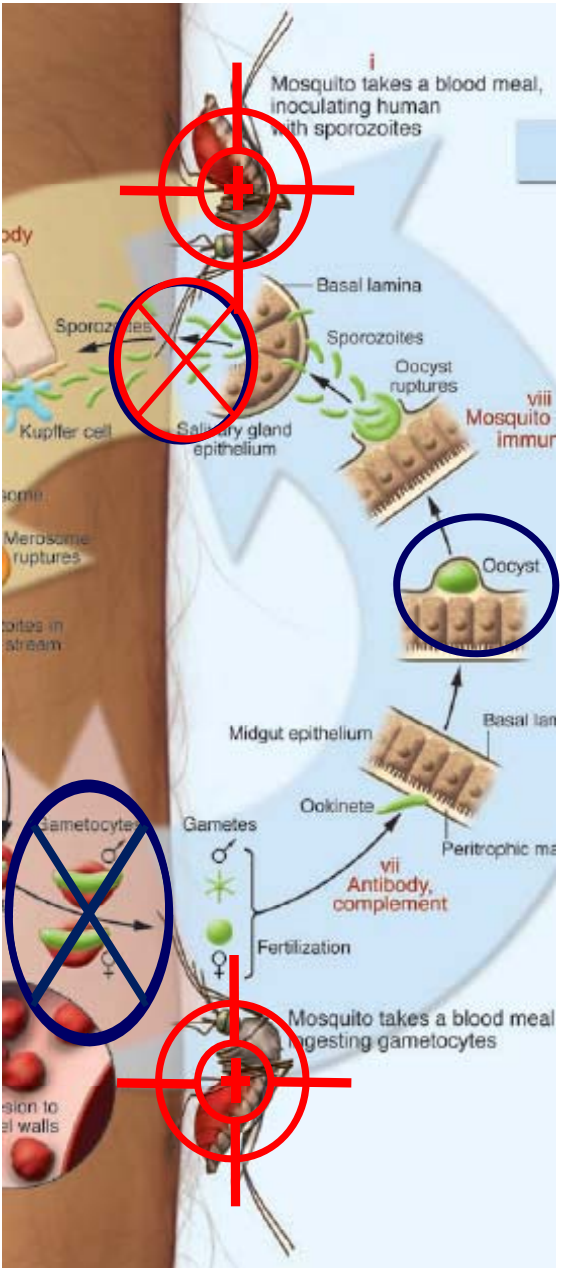
Ivermectin - Neglected Tropical Diseases

- Onchocerciasis – *Onchocerca volvulus*
- Lymphatic filariasis – *Wuchereria bancrofti, Brugia malayi,* and *Brugia timori*
  - >300 million people given ivermectin mass drug administration (MDA) annually
  - 11/13 onchocerciasis foci in Latin America eliminated (x1-4 MDAs/year)
  - Ivermectin/Albendazole/Diethylcarbamazine MDAs will be implemented for LF in 100 million people starting 2019 (Richards, personal communication)
- Ascariasis – *Ascaris lumbricoides*
- Trichuriasis – *Trichuris trichiura*
- Strongyloidiasis – *Strongyloides stercoralis*
  - Currently approved treatment in Thailand (oral 200 µg/kg)
- Pediculosis – *Pediculus humanus humanus* and *P. h. capitus*
- Scabies – *Sarcoptes scabei*
  - One person treated 150 times in 13 years, 12 times in 1 month (Mounsey et al. 2008)
  - Safe in healthy volunteers up to 2,000 µg/kg (Guzzo et al. 2002)

MDA by Community Directed Treatment with Ivermectin

Ivermectin MDA as a possible malaria vector control tool

- Small scale field trials in West Africa demonstrate that ivermectin MDA can kill wild *An. gambiae*, shifts population age structure, reduces proportion of infectious *An. gambiae* (Sylla et al. 2010, Kobylinski et al. 2011, Alout et al. 2014) and reduces clinical falciparum incidence in <5yo (Foy et al. in press)
- Targets residual malaria transmission, (ie. outdoor or early feeding mosquitoes)
- Will complement other vector control tools, bednets and indoor residual spraying
- Can integrate with antimalarial MDAs



MDAs for *Plasmodium falciparum* control

- MDAs with dihydroartemisinin-piperaquine and single low-dose primaquine have been performed in Myanmar, Laos, Vietnam, and Cambodia
- Target to reduce infectious human reservoir, inhibit new blood-stage infections, and prevent onwards transmission from treated individuals
- However, primaquine has no effect on oocysts or sporozoites in already infected mosquitoes (Coleman et al. 1994), so there will be NO IMMEDIATE effect on mosquito-to-human transmission
- Ivermectin MDA targets the vector with mosquito-lethal endectocides which IMMEDIATELY suppresses mosquito-to-human transmission (Sylla et al. 2010, Kobylinski et al. 2011, Alout et al. 2014)
- Ivermectin MDA provides community-wide effect reducing number of new infections in treated and UNTREATED persons
- Disparate modes of action on transmission may make ivermectin plus primaquine MDA ideal

Ivermectin & Dihydroartemisinin-Piperaquine Trials

Goals: Determine safety, tolerability, pharmacokinetic interaction, and mosquito-lethal efficacy

PI: Dr. Menno Smit

- *P. falciparum*-infected Kenyan adults (x141)
- Randomized, double-blind, placebo controlled
- Three daily doses:
  - Dihydroartemisinin-Piperaquine (DHA-PQP) (120/960 mg) + Placebo
  - DHA-PQP + Ivermectin (300 µg/kg)
  - DHA-PQP + Ivermectin (600 µg/kg)
- Species: *An. gambiae* s.s.
- Mosquito membrane feed time points:
  0, 2d+4hr, 7d, 14d, 21d, 28d

(Smit et al. 2018)

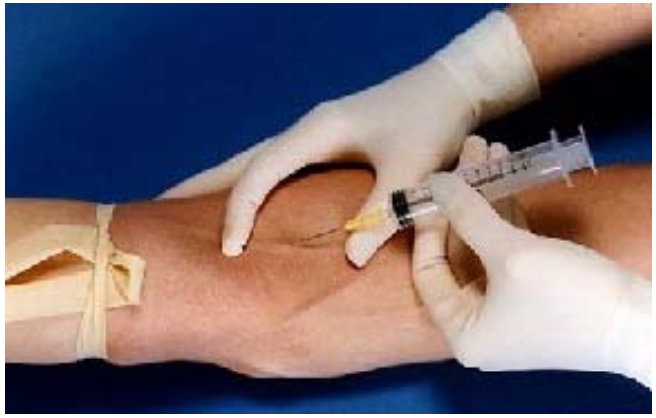
PI: Dr. Podjanee Jittamala

- Healthy Thai adults (x16)
- Sequential, no placebo
- Single dose:
  - Ivermectin (400 µg/kg)
  - Ivermectin + Primaquine (30 mg)
  - Ivermectin + DHA-PQP (120/960 mg)
  - Ivermectin + DHA-PQP + Primaquine
  5) Primaquine
  6) DHA-PQP
  7) DHA-PQP + Primaquine
- Species: *An. dirus* + *An. minimus*
- Mosquito membrane feed time points:
  0, 4hr, 1d, 2d, 3d, 6d, 10d

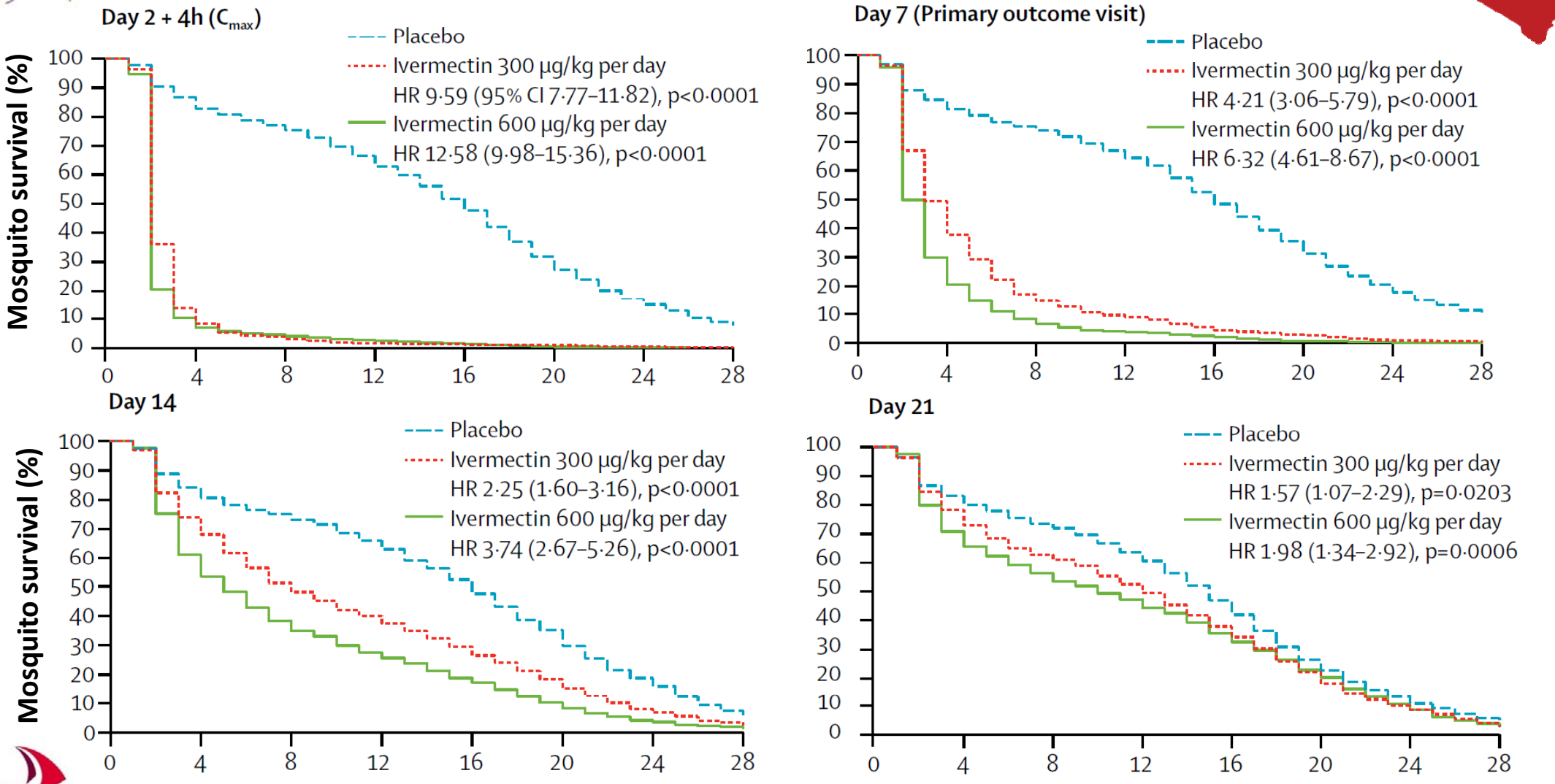
(unpublished data)

Mosquito Survival Studies

1) Venous whole blood collected
2) Membrane fed to mosquitoes: Kenya (100+) / Thailand (40)
3) Daily mosquito survival monitoring: Kenya (28 days) / Thailand (10 days)



An. gambiae Survival Results



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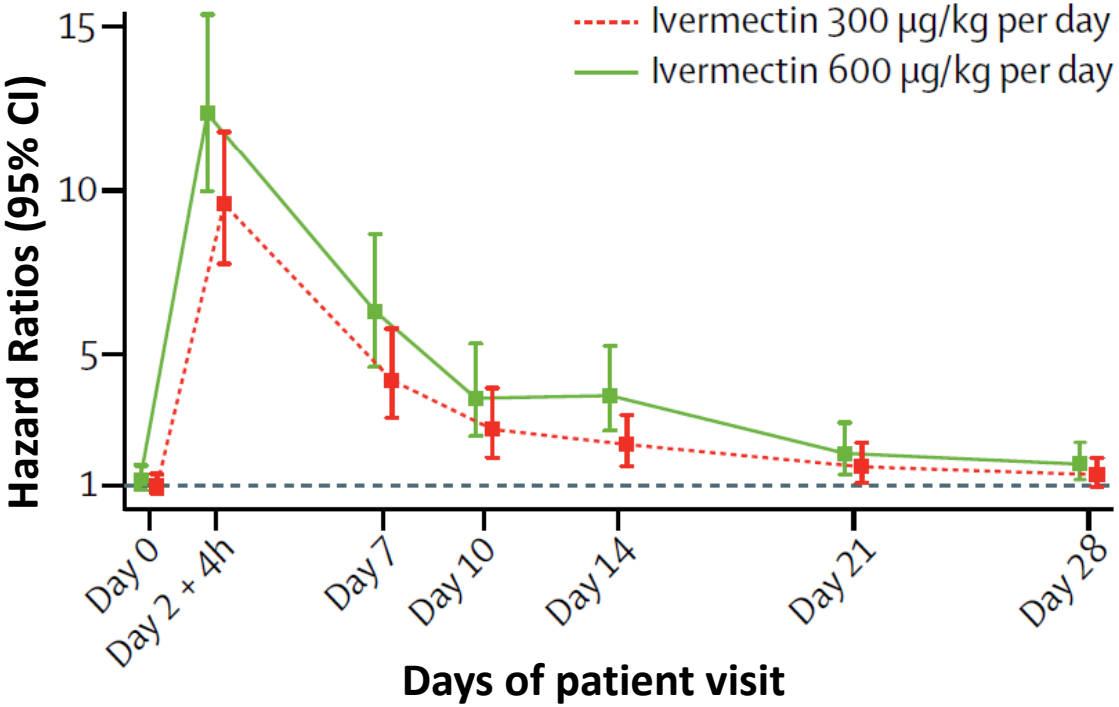
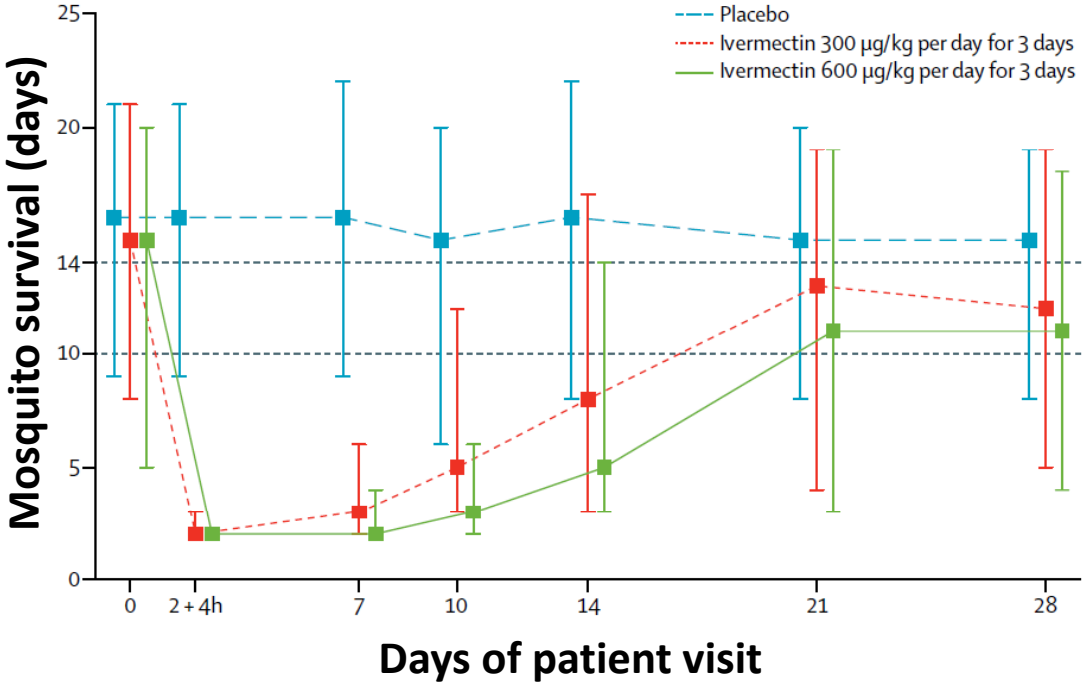
(Smit et al. 2018)

An. gambiae Survival Results

Hazard ratios for mortality by patient visit



Median survival by patient visit



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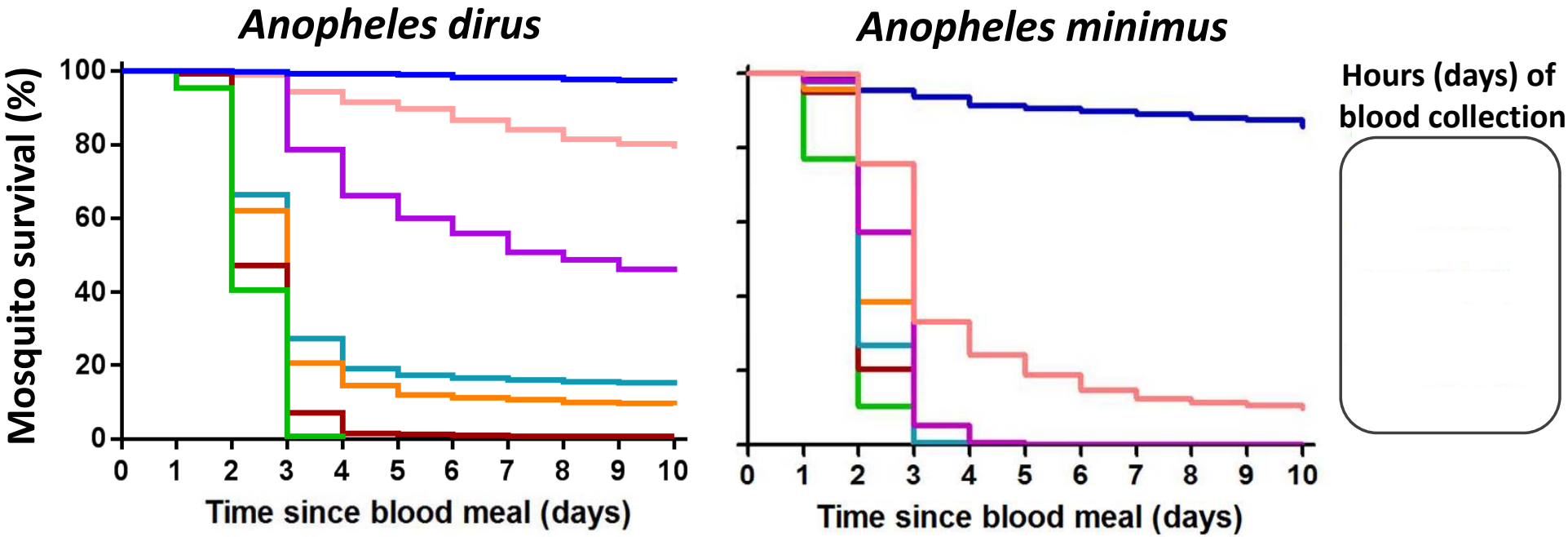
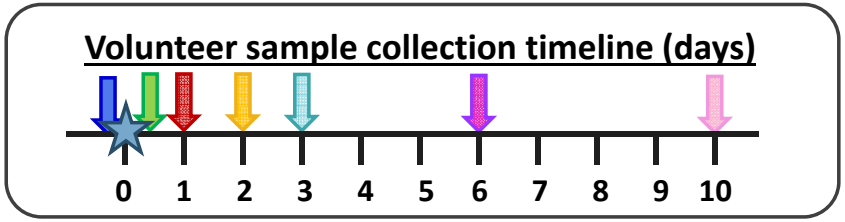
(Smit et al. 2018)

Ivermectin (400 µg/kg) mosquito survivorship results





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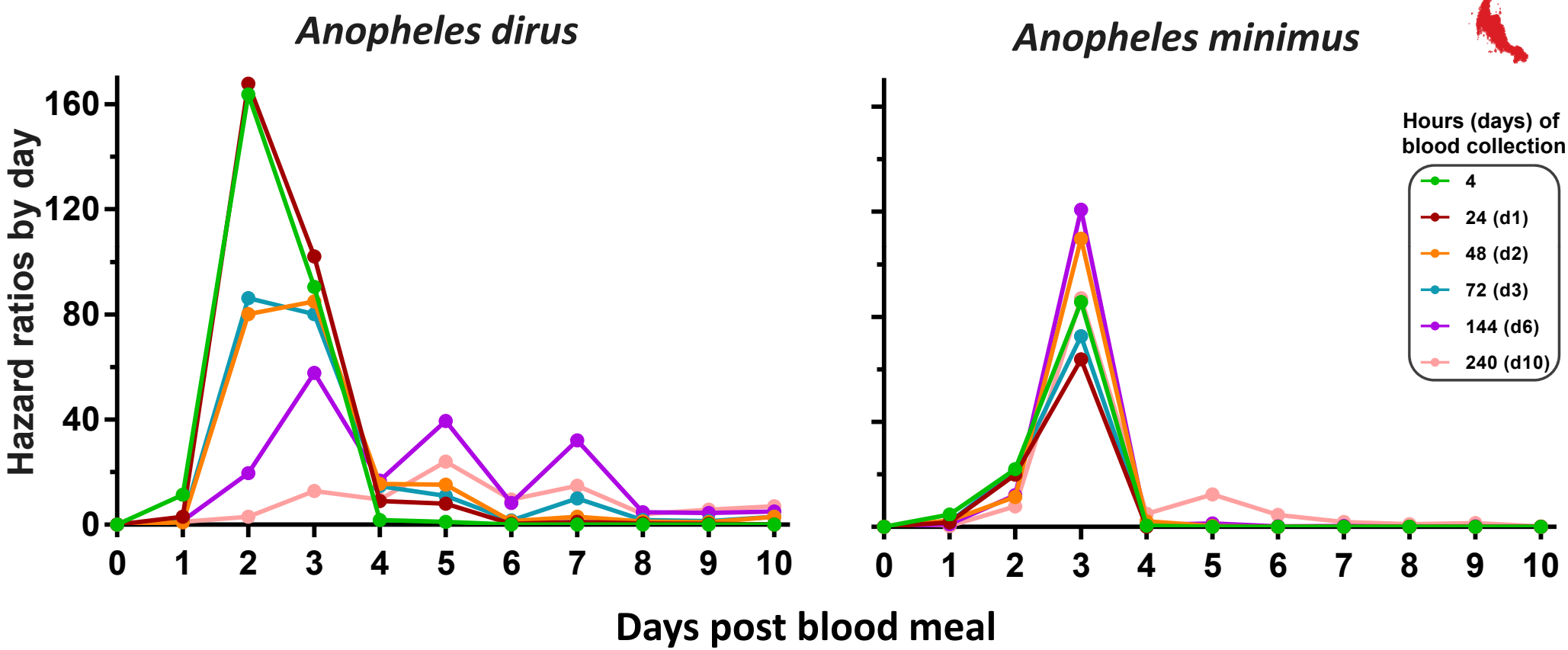
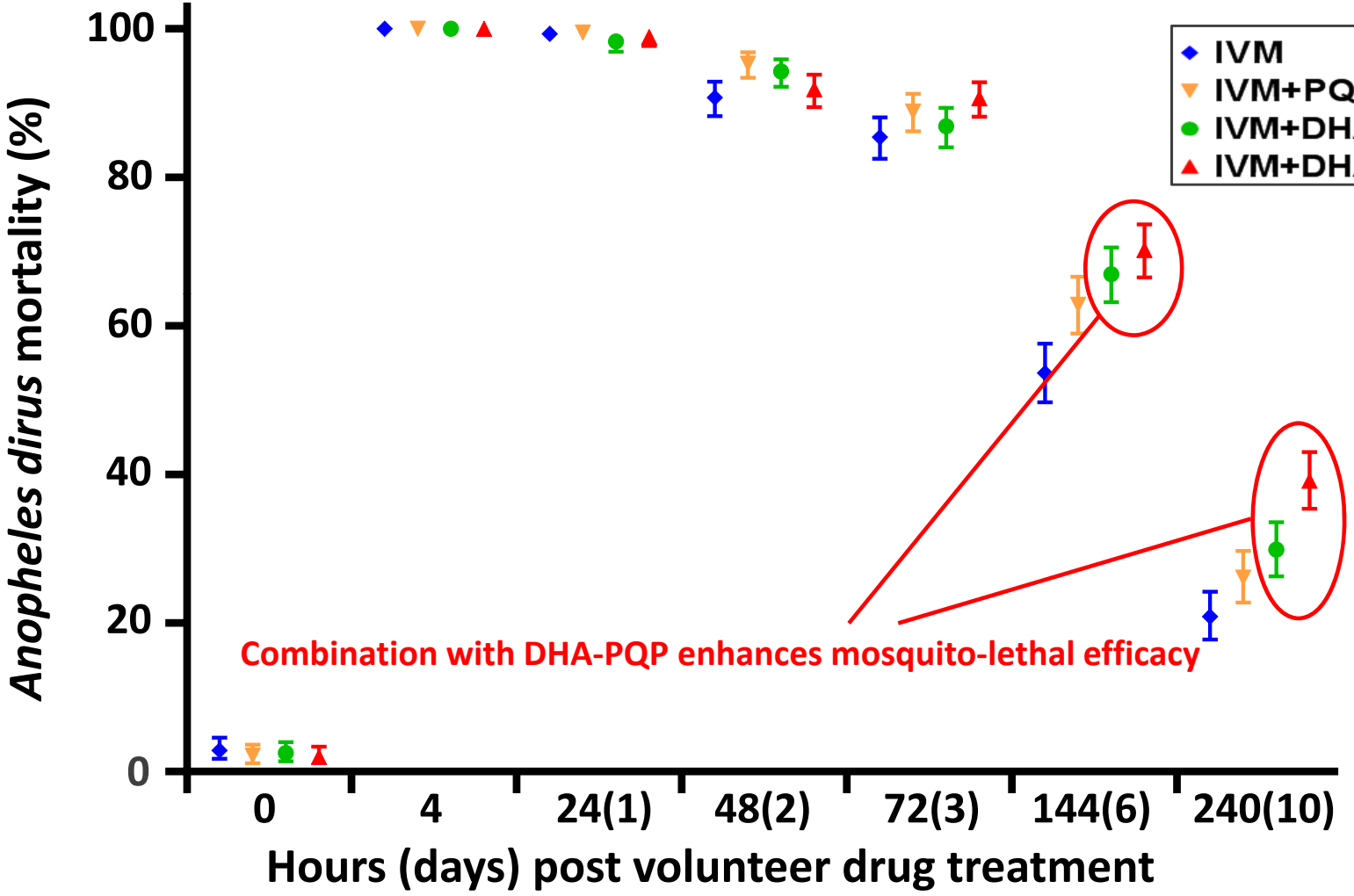
(unpublished data)

Hazard ratio for mosquito mortality by day

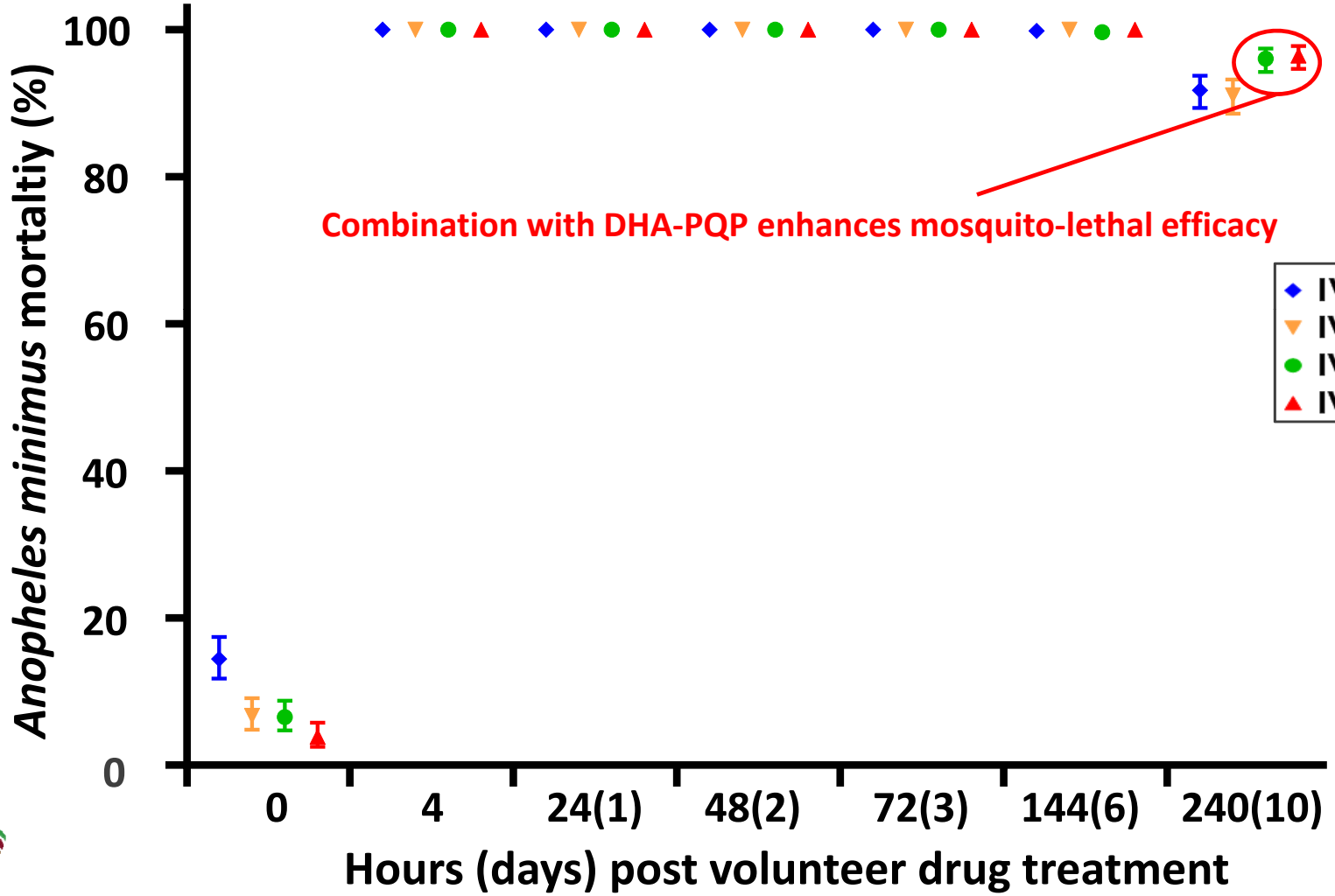


Mean mortality (95%CI) of *An. dirus* by regimen



(unpublished data)

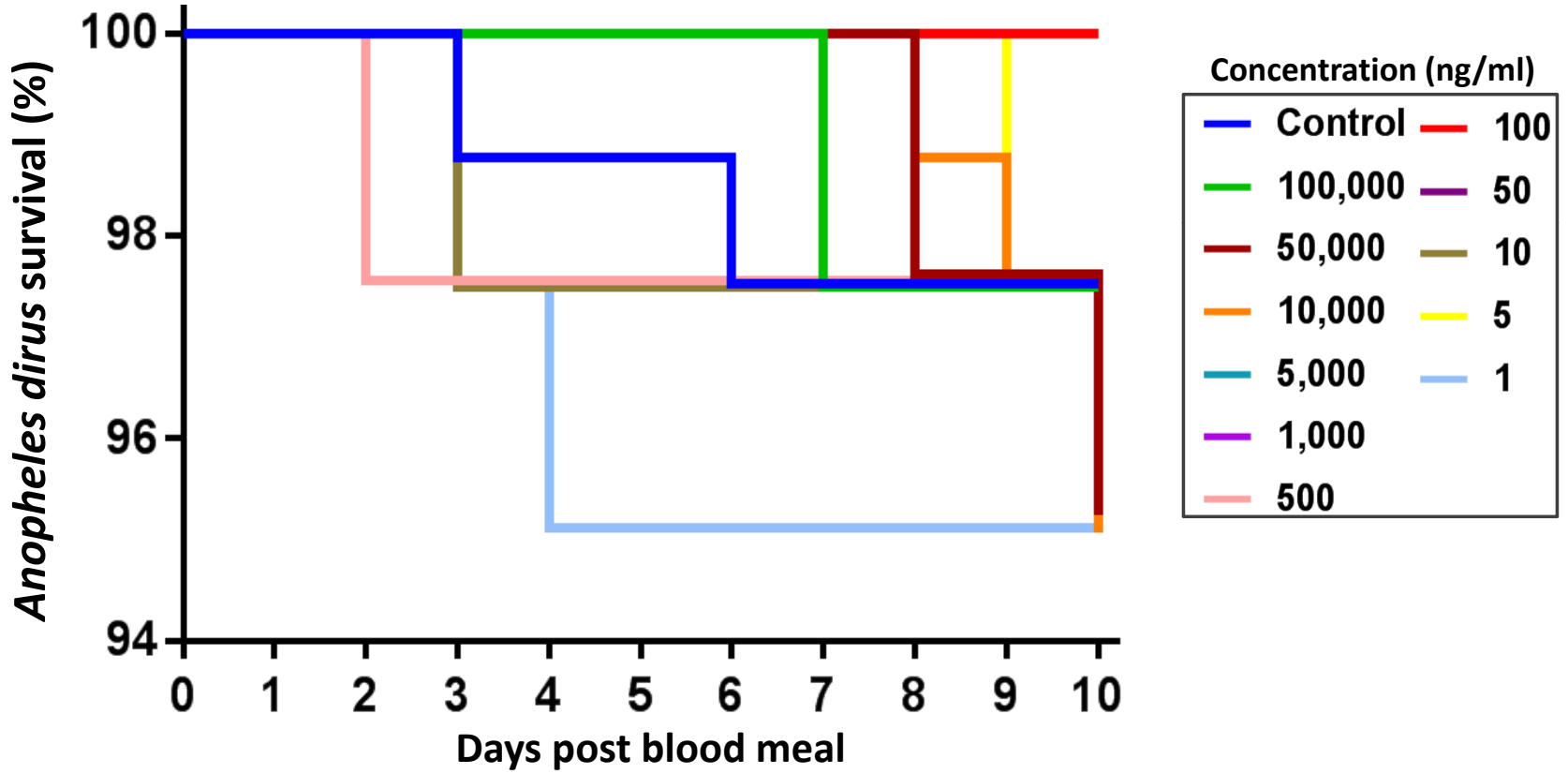
Mean mortality (95%CI) of *An. minimus* by regimen



(unpublished data)

Why is ivermectin and piperaquine combination more lethal?

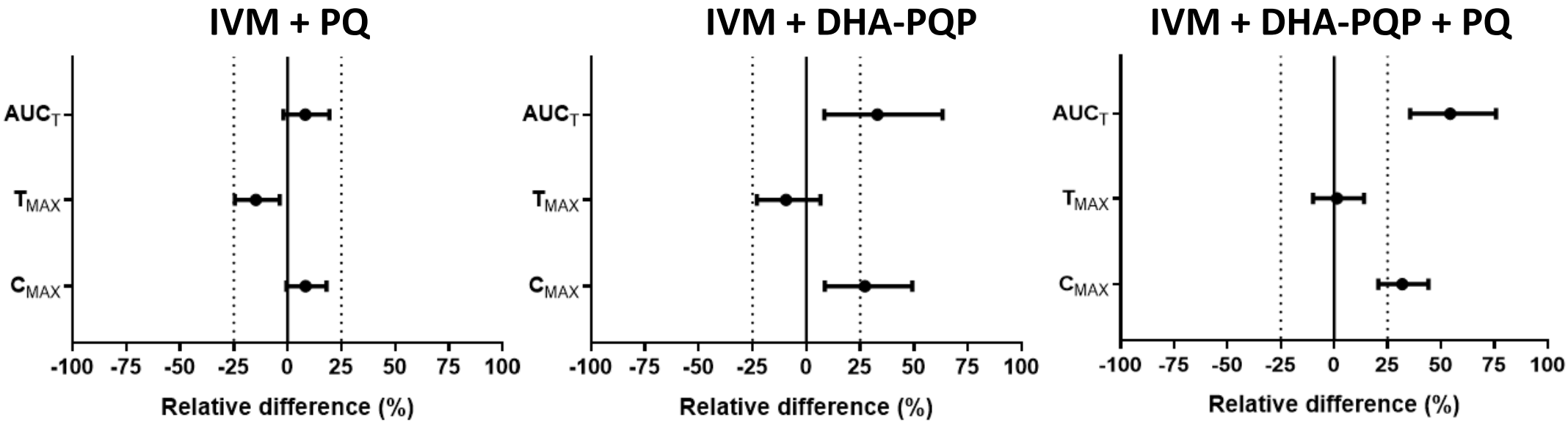
An. dirus survival after piperaquine ingestion



(unpublished data)

Non-compartmental pharmacokinetic interactions of ivermectin

- The exposure (AUC_{0-T} and C_{max}) of ivermectin is slightly increased when co-administered with primaquine (PQ)
- A significant increase in exposure observed when co-administered with DHA-PQP
- A significant additive increase in exposure observed when co-administered with DHA-PQP and PQ
  - DHA-PQP increases ivermectin bioavailability (34.2%) and absorption time (26.3%)



** Both ivermectin and piperaquine metabolized by CYP3A4 (Zeng et al. 1998, Lee et al. 2012) **

(unpublished data)

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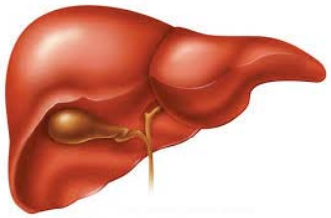
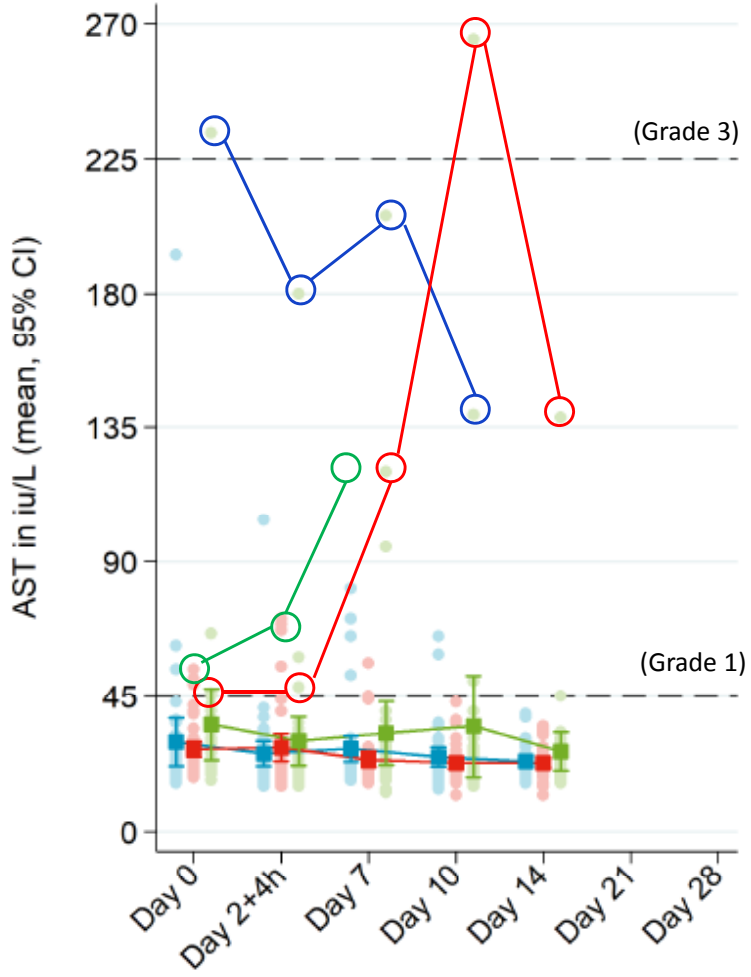
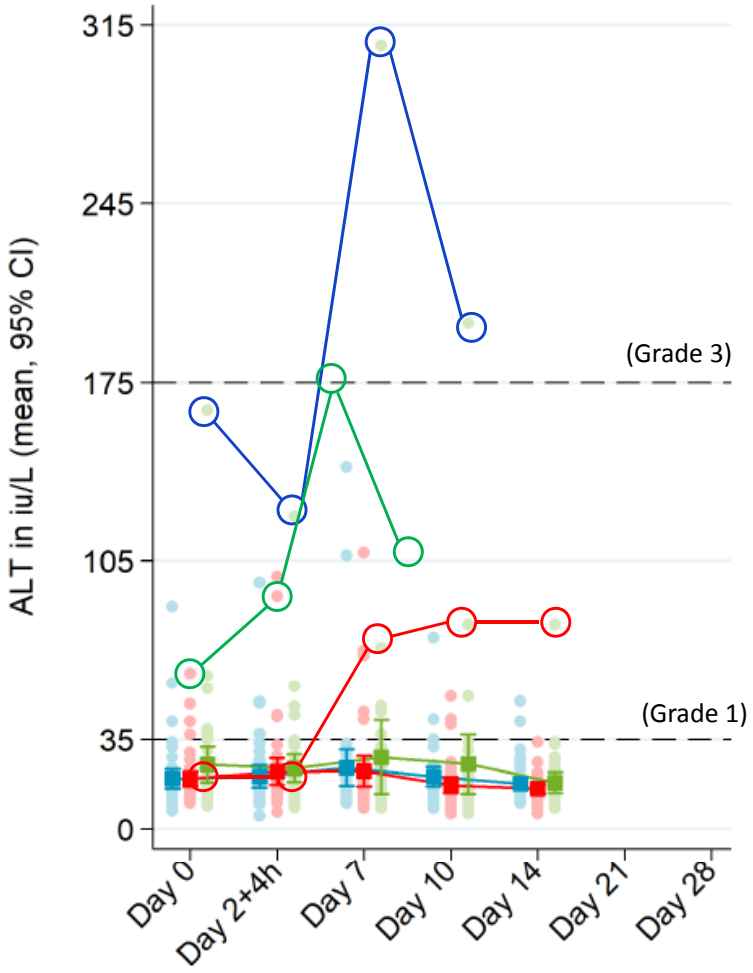


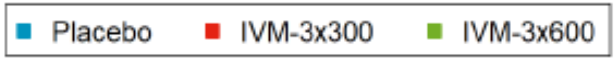
Clinical Results - Hepatobiliary

Aspartate Aminotransferase (AST)

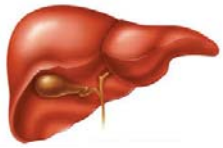


Alanine Transaminase (ALT)

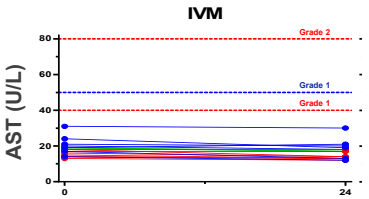


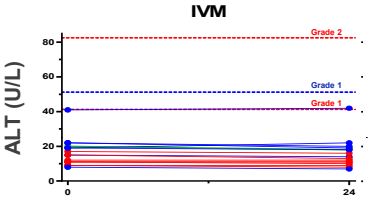


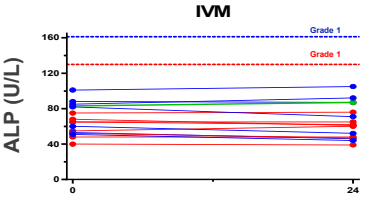
(Smit et al. 2018)

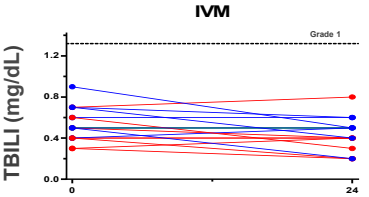


Hepatobiliary Results







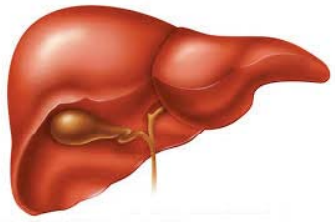


** No hepatotoxocity concerns for ivermectin alone **

- 4 non-drug related liver function AEs

Male ●

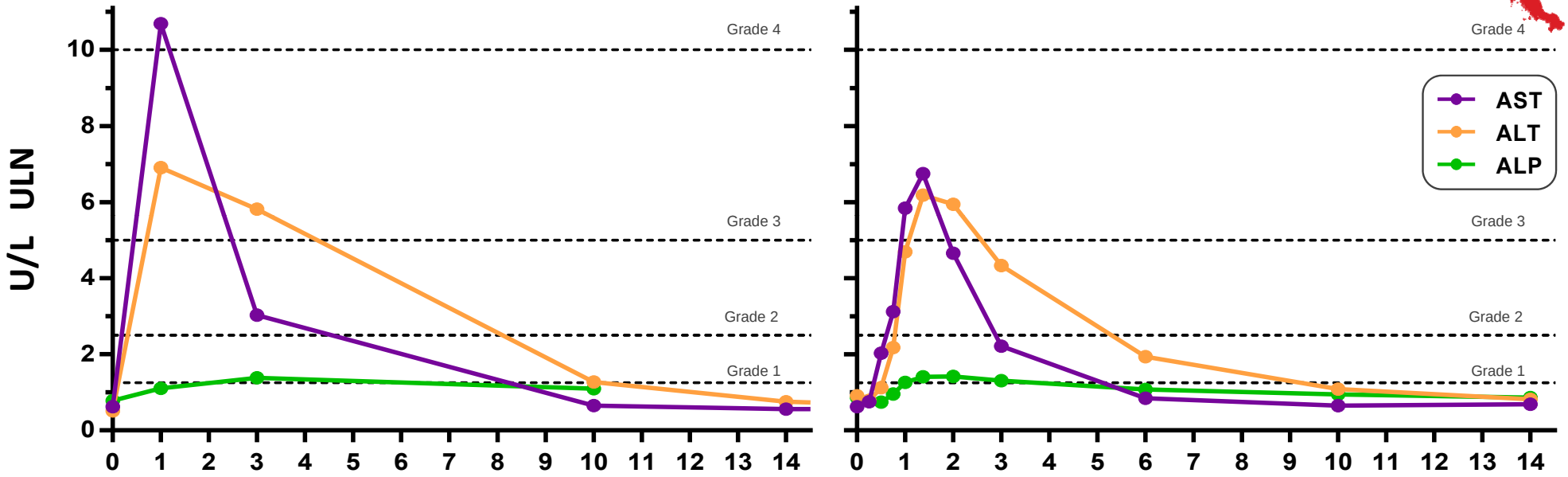
Female ●



Hepatobiliary Results

IVM+DHA-PQP

IVM+DHA-PQP+PQ

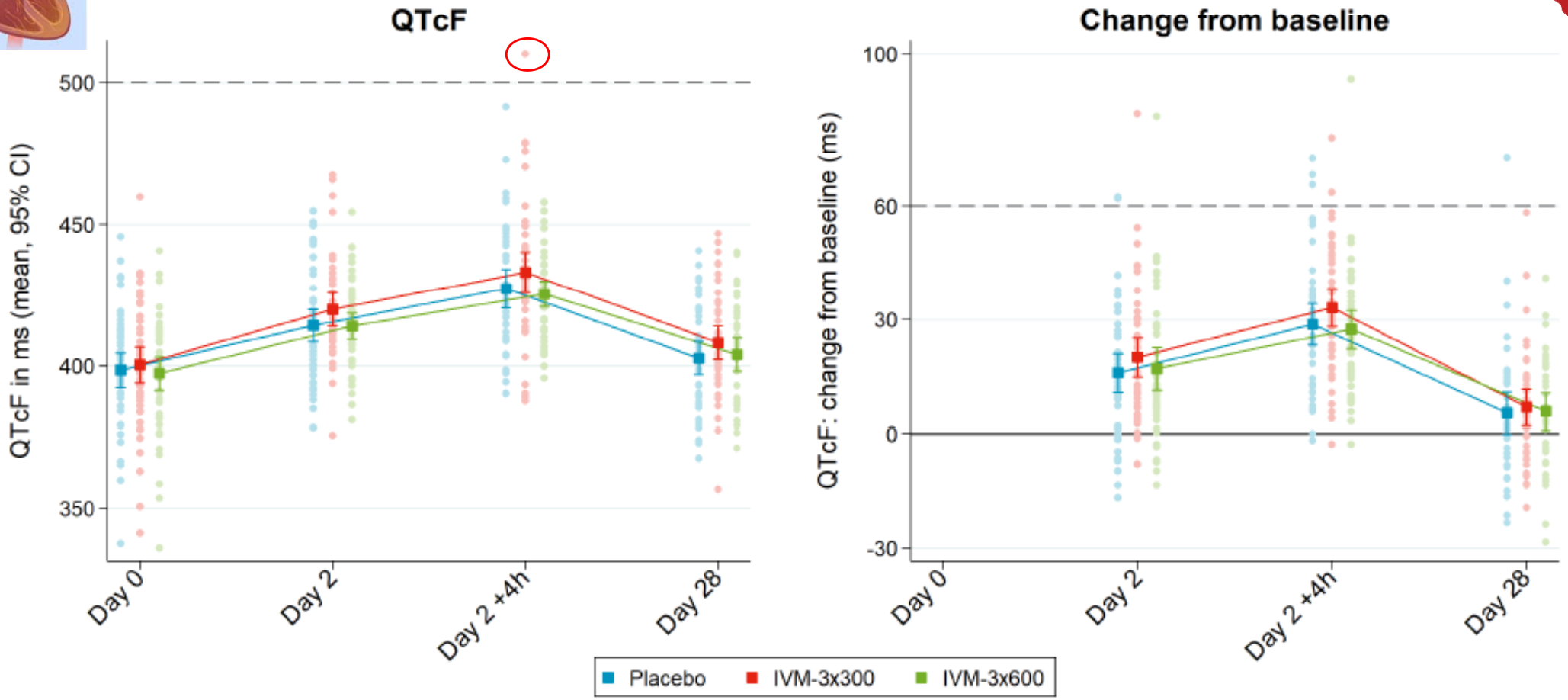


- Asymptomatic, transient elevation of liver enzymes, returning to normal within 10 days
- Female (40yo) negative findings for hepatobiliary ultrasonography, serum lipid profile, and serum hepatitis profile

** Bilirubin levels did not elevate, therefore no violation of Hy's law **

(unpublished data)

Effect of drug administration on QT interval

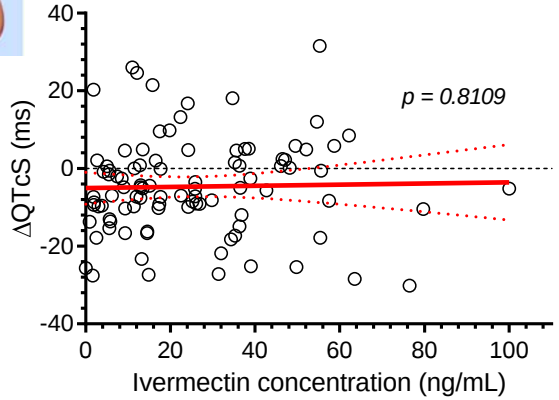


**** SAE in 24yo male: asymptomatic QT-prolongation (510ms) with T-wave inversion ****

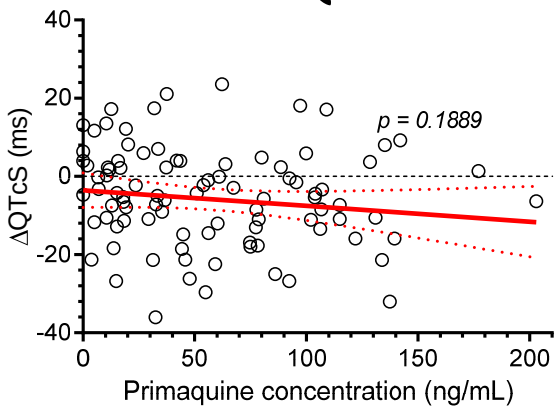
(Smit et al. 2018a)

Effect of drug concentrations on QT interval

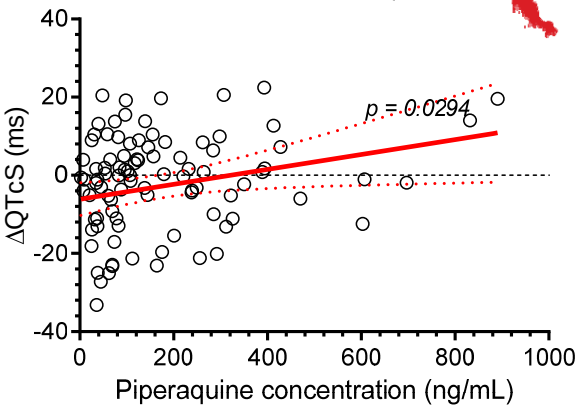
IVM



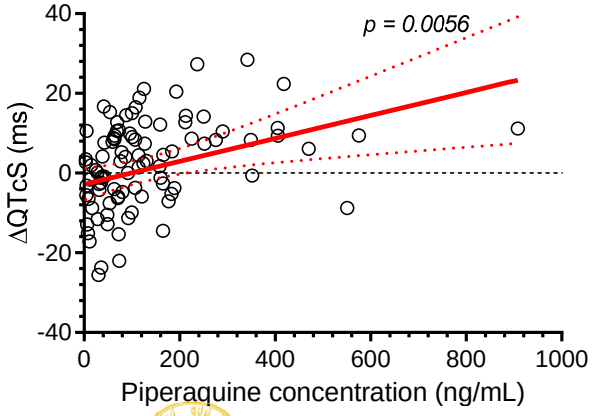
PQ



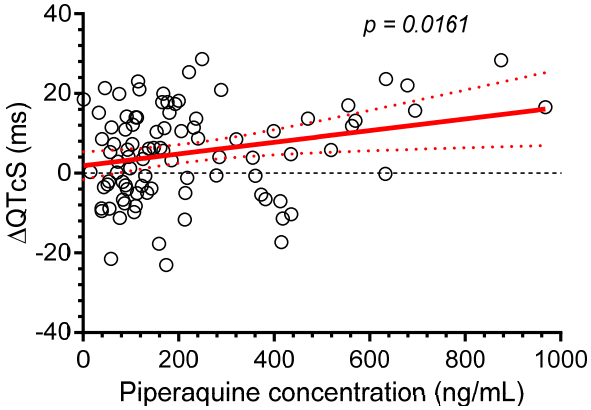
DHA-PQP



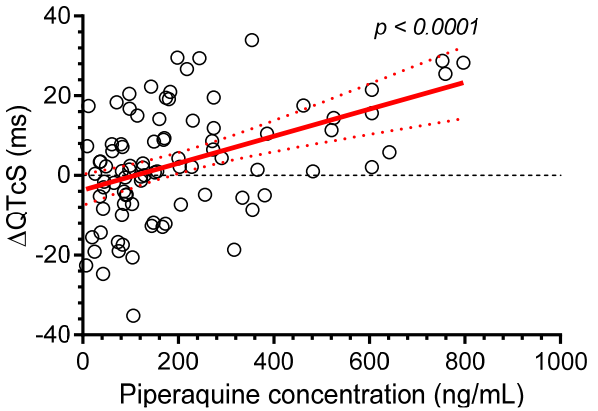
DHA-PQP + PQ



DHA-PQP + IVM



DHA-PQP + IVM + PQ



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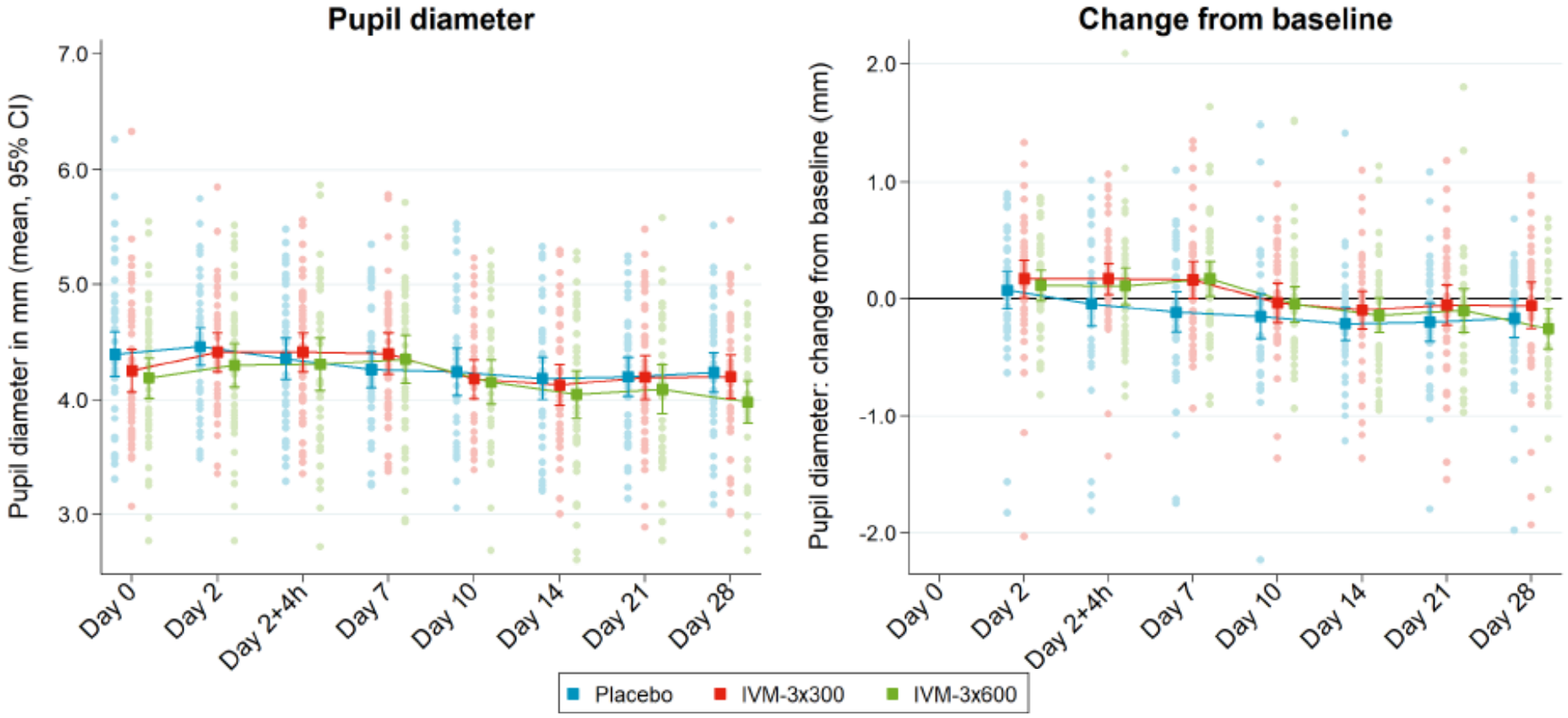
*** No QTc-interval >500 ms, and no change from baseline >60 ms (FDA limit) ***

Ocular Results



*** Transient minor visual disturbances (blurred vision) reported in x4 persons (IVM 3x600) and x2 persons (IVM 3x300) ***

- Ocular diameter not measured in Thai trial, no blurred vision reported by volunteers

(Smit et al. 2018)

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Additional Points

- Kenya – SAE anaphylaxis, urticaria and severe cramping after ivermectin 600 µg/kg + DHA-PQP single dose, discontinued study drug and administered chlorpheniramine and hydrocortisone, falciparum successfully treated with artemether-lumefantrine

- Kenya – All patients successfully cleared of *P. falciparum* infections

- Kenya – Ivermectin 300 µg/kg with DHA-PQP the ideal concentration, reduces costs, minimizes AEs, and has similar mosquito-lethal results

- Thailand – SAE Dengue infection, unrelated to study drugs

- Thailand – No safety concerns raised by ivermectin and primaquine (30mg) co-administration (G6PD normal)

- Thailand – co-administration of ivermectin and DHA-PQP leads to increased ivermectin concentrations, increased mosquito mortality, and may explain exceptional mosquito mortality from Kenya trial (not a LSTM conclusion)

- Thailand – surprising mosquito mortality results possibly due to ivermectin metabolites with mosquito-lethal activity

- Modelling work suggests that ivermectin 3x300 is not much more impactful on transmission than 1x400, especially if cost and logistics are considered (Slater in manuscript)

Ongoing ivermectin MDA studies for malaria vector control

Location	MDA Strategy	IVM (µg/kg x days)	First Results
The Gambia	Ivermectin + DHA-PQP	300 x 3	2019
Thailand	Ivermectin alone	400 x 1	2020
Guinea Bissau (Bijagos)	Ivermectin + DHA-PQP	300 x 3	2021
Burkina Faso	Ivermectin + SMC (<5yo SP-AQ)	400 x 1	2020
Kenya/Mozambique	Ivermectin alone + cattle MDA	400 x 1	2020

Ivermectin MDA Field Study in Thailand

- Collaboration between Mahidol University and AFRIMS
  - Dr. Jetsumon Sattabongkot Prachumsri (Principal Investigator)
- Field site – Rubber plantations in Southern Thailand
- Assess parameters of malaria transmission:
  Entomological (population age structure 1°, vector composition and density, sporozoite rate)
  Epidemiological (malaria prevalence 1°and clinical incidence, *Anopheles* salivary IgG response, drug-resistant parasite ratio, and anemia)
- Funded by Congressionally Directed Medical Research Program – Peer Reviewed Medical Research Program (W81XWH-16-2-0021)

Acknowledgements

Thailand Ivermectin & Eurartesim Study:

- **Volunteers for their participation**
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- **AFRIMS Department of Entomology Insectary, Malariology and Vector Biology & Control sections and Joi Larson for laboratory support**

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