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Sub-lethal exposure to chlorfenapyr kills *Plasmodium* parasites in surviving insecticide-resistant *Anopheles* mosquitoes

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Efficacy of Interceptor® G2 LLIN measured in RCTs

Prevalence in children 18 months post LLIN distribution

Country	Group	Prevalence	OR	95% CI	*p*-value
Benin	Pyrethroid only LLIN	28.0%	1	-	-
	Pyriproxyfen-pyrethroid LLIN	26.9%	0.92	0.63 – 1.35	0.67
	Chlorfenapyr-pyrethroid LLIN	**15.7%**	**0.47**	**0.32 – 0.69**	**0.0002**
Tanzania	Pyrethroid only LLIN	52.3%	1	-	-
	PBO-pyrethroid LLIN	43.3%	0.76	0.52 – 1.12	0.1699
	Pyriproxyfen-pyrethroid LLIN	50.6%	0.98	0.67 – 1.44	0.9184
	Chlorfenapyr-pyrethroid LLIN	**25.6%**	**0.66**	**0.45 – 0.97**	**0.0365**

Accrombessi *et al.* (2023) Lancet S0140-6736(22)02319-4

Mosha *et al.* (2022) Lancet 399: 1227–41

Can we reproduce RCT results *in silico*?

Use of OpenMalaria transmission model to reproduce the Tanzanian RCT *in silico*

	LLIN				
Tanzania	Pyrethroid only LLIN	52.3%	1	-	-
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Mathematical modelling of IG2 efficacy in OpenMalaria

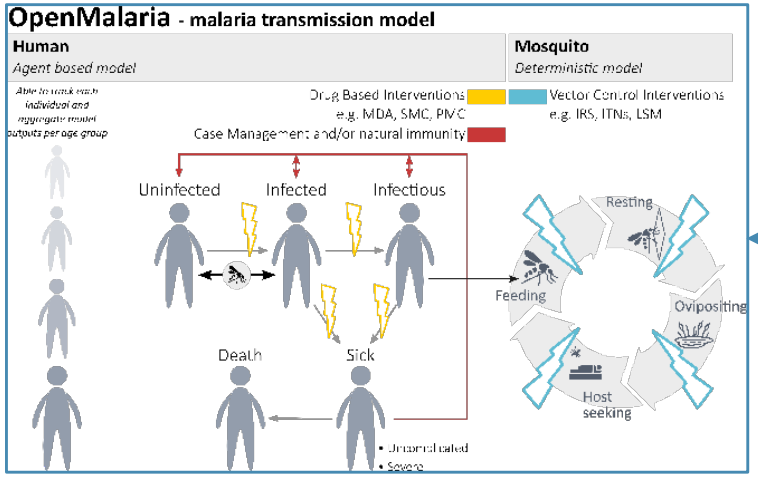
Predict the deterrency and killing effects on mosquitoes

Experimental hut trials
Pyrethroid only
PBO-pyrethroid
Chlorfenapyr-pyrethroid

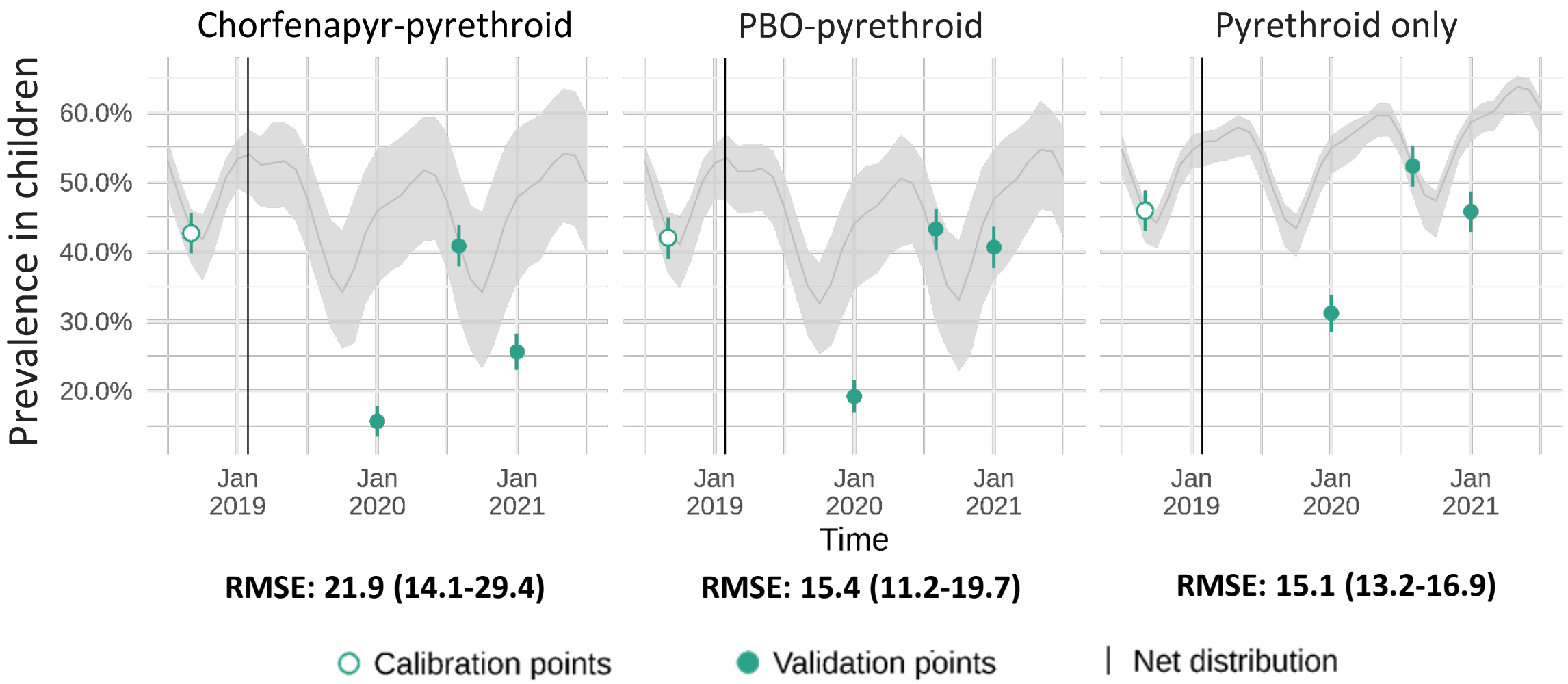
Estimate additional effect of
PBO-pyrethroid vs pyrethroid only
Chlorfenapyr-pyrethroid vs pyrethroid only

+

Parameterisation of pyrethroid net in OpenMalaria according to Briët *et al.* Mal J 2013, 12:77, with increased insecticide-resistance)



Effect of IG2 in RCT is greater than expected from hut trials



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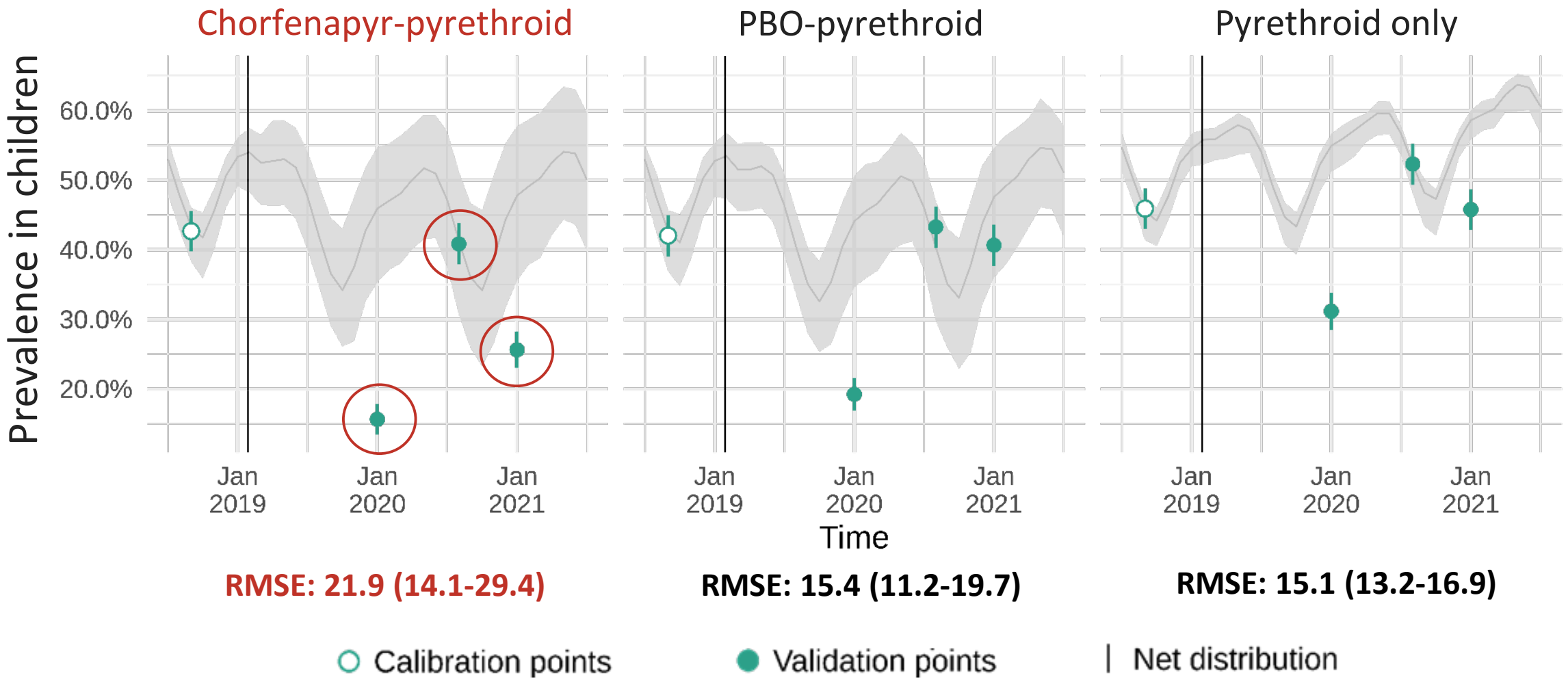
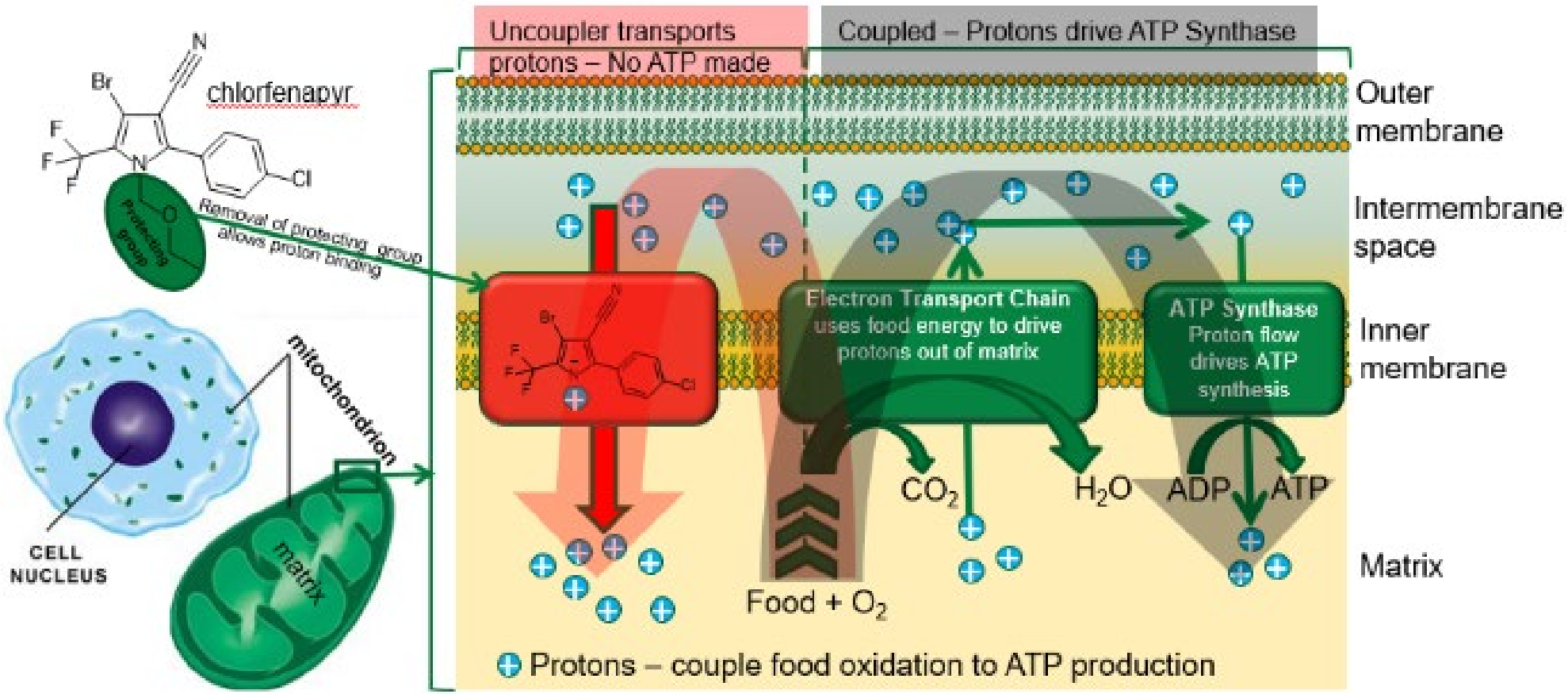


Does chlorfenapyr provide additional transmission blocking effects even if a mosquito survives a sub-lethal dose?

Chlorfenapyr disrupts the production of ATP



BASF Corporation. 2013. Insecticide Mode of Action Technical Training Manual. Crop Protection Division, Global Strategic Marketing, Insecticides. Research Triangle Park, NC,27709 USA. 74pp.

Determining chlorfenapyr dose that induces 30-50% mortality

Modified WHO tunnel assay

- Net samples: chlorfenapyr only (100 and 200 mg/m^2) and untreated net
- Pyrethroid-resistant *Anopheles gambiae s.s. kdr*
- *n* = 3 x 100 mosquitoes/replicate
- 8 hours exposure

Blood meal upon exposure to chlorfenapyr

- Mosquitoes removed from tunnel
- Blood feeding with human blood
- Mortality scored 9 days post blood meal

Determining chlorfenapyr dose that induces 30-50% mortality

Mortality rates 9 days post blood-feeding in *Anopheles gambiae s.s. kdr*

Net sample	Mortality	95% CI	OR	95% CI	*p*-value
Untreated	28.5%	22.0% – 35.0%	1	-	-
Chlorfenapyr 100 mg/m^2	36.2%	23.6% – 48.9%	1.46	1.12 – 1.90	0.005
Chlorfenapyr 200 mg/m^2	43.0%	43.0% – 50.6%	1.87	1.87 – 2.43	<0.001

ORs and *p*-values derived from mixed-effects logistic regression

→ Net samples with 200 mg/m^2

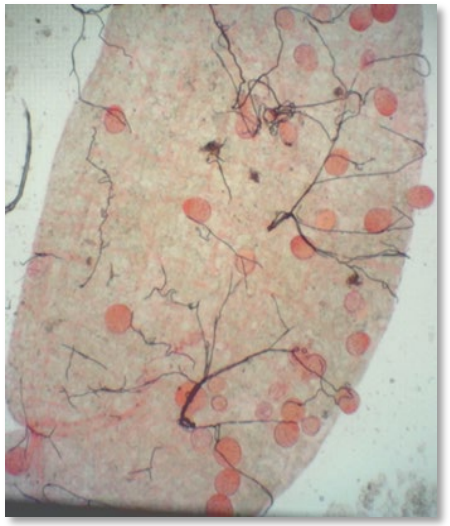
Experiment repeated with blood from gametocytaemic carriers

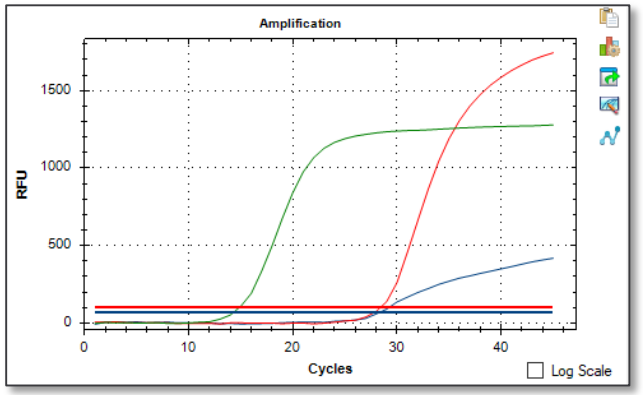
- Blood collected from microscopically confirmed gametocytaemic carriers with >3 gametocites per 500 RBCs.

Modified WHO tunnel assay – scoring oozysts and sporozoites

Following exposure in the tunnel

- Blood feeding with human blood
- Scoring mortality 9 days post blood meal
- **Scoring of oocysts and sporozoites**



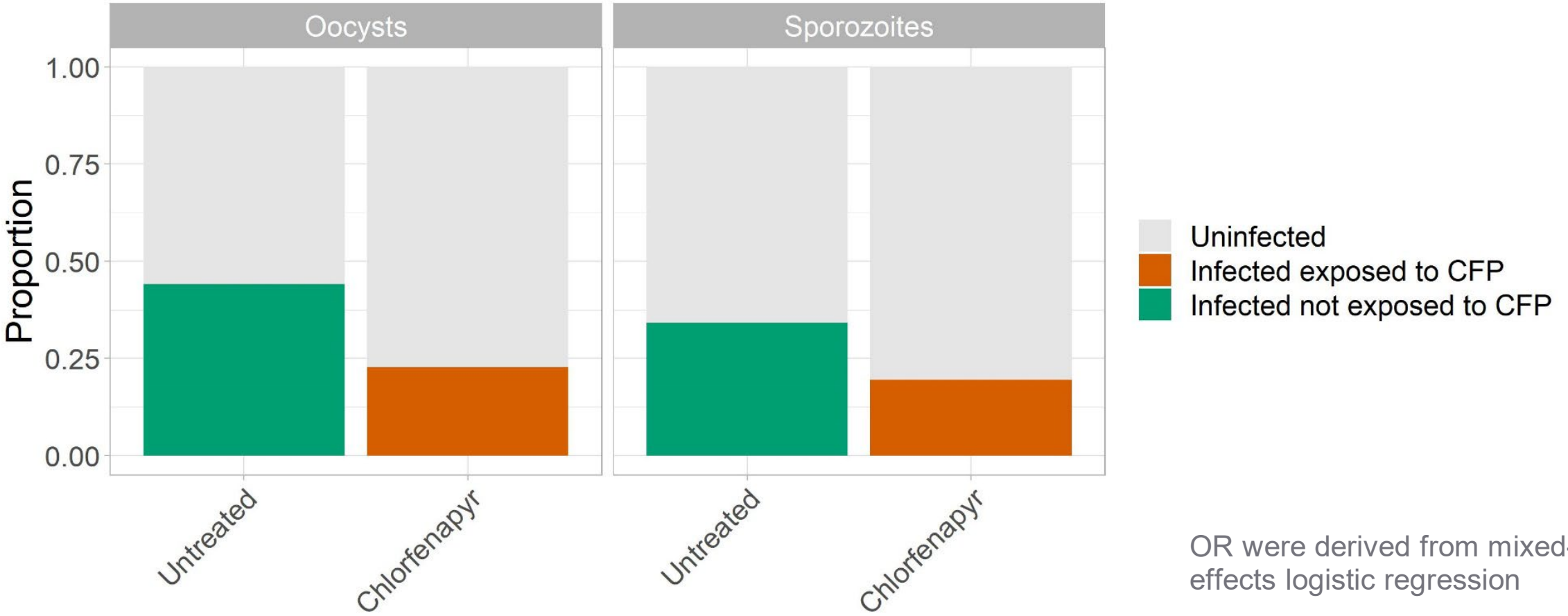


Bass, C. et al. (2008) Malar J **7,** 177

Proportion of infected mosquitoes post chlorfenapyr exposure

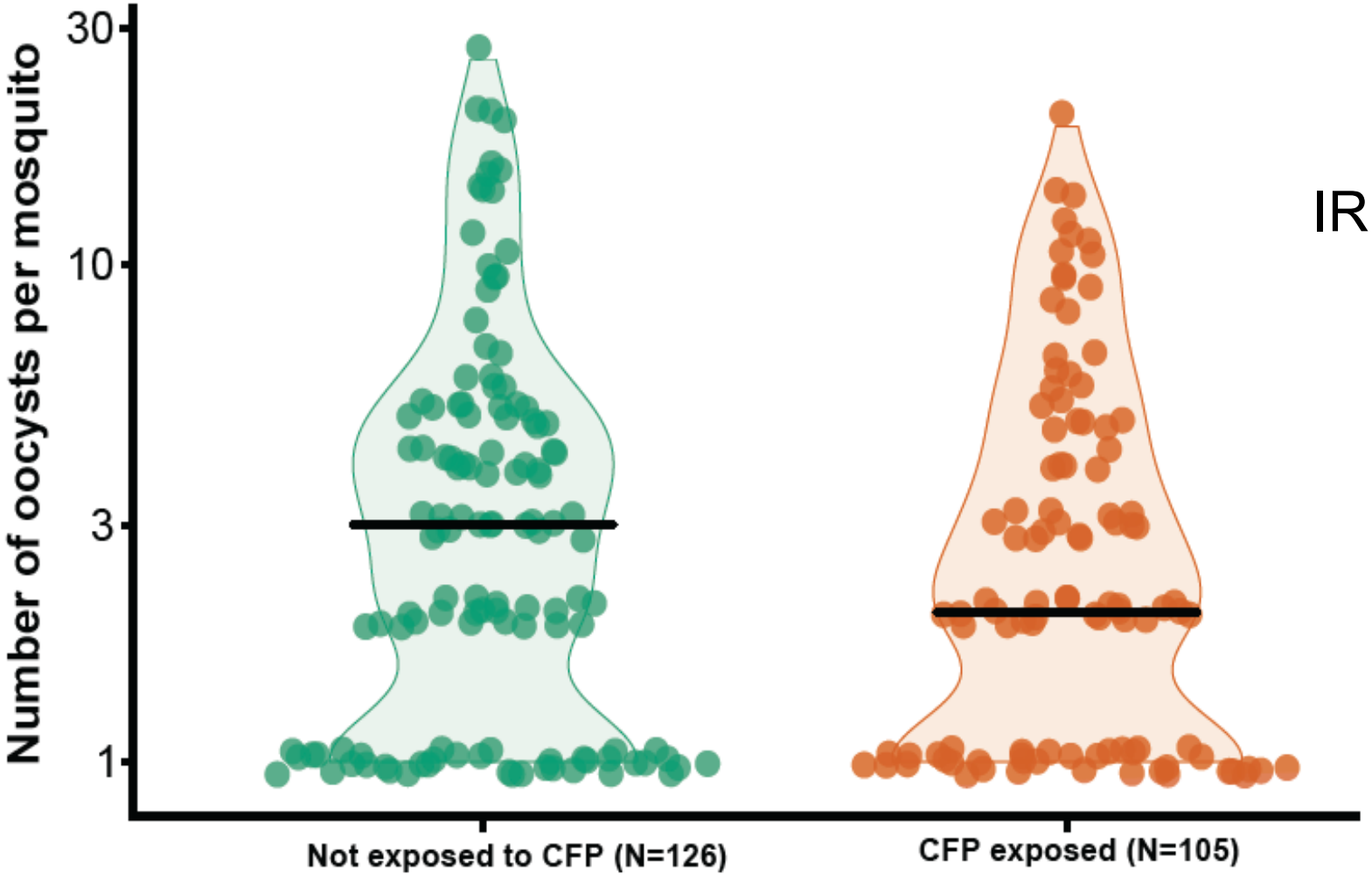
OR: 0.33 (0.23- 0.46) OR: 0.43 (0.25-0.73)

n = 286 *n* = 462 *n* = 120 *n* = 231



OR were derived from mixed-effects logistic regression

Intensity of infection in mosquitoes post chlorfenapyr exposure



IRR = 0.30 (0.22-0.41)

IRR were derived from mixed effect negative binomial regression adjusted for study participant and treatment allocation

Conclusions

- Chlorfenapyr substantially reduces the proportion of *Plasmodium*-infected mosquitoes and the intensity of infection at sub-lethal doses
- Chlorfenapyr will further decrease the occurrences of malaria in communities beyond killing mosquitoes
- A possible explanation is that chlorfenapyr disrupts ATP production not only in the mosquito but also in the *Plasmodium* parasite
- Ongoing studies are further exploring the nature of this mechanism and chlorfenapyr's overall ability to affect malaria transmission

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