Interceptor® G2

Experiences and effect of chlorfenapyr on Plasmodium

Susanne Stutz - BASF Global Public Health

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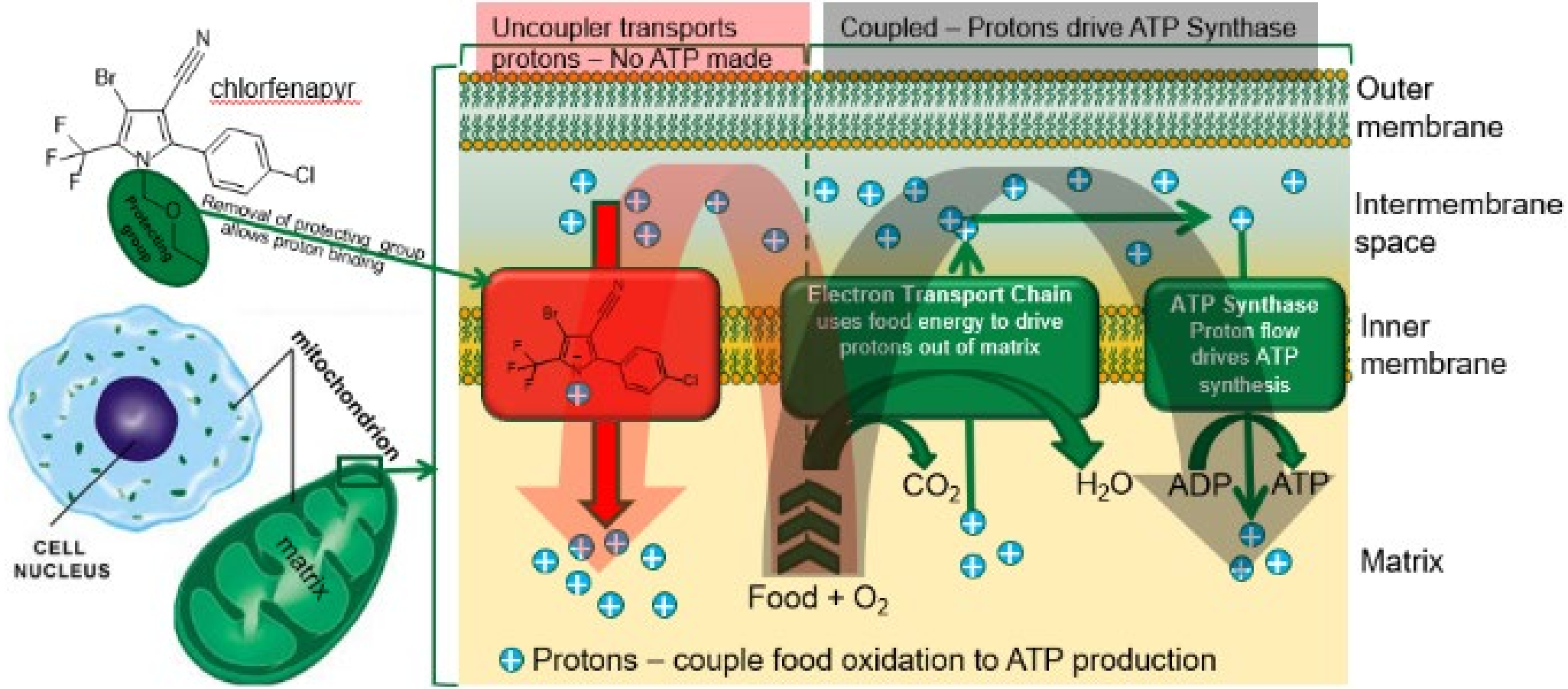
Chlorfenapyr – MoA disrupting the energy generation in mitochondria



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Interceptor® G2 - Epidemiological results from randomized controlled trial in Tanzania

Background to the Randomized Cluster Trials

- Interceptor® G2 is the first LLIN containing two adulticides (100 mg/m^2 alphacypermethrin and 200 mg/m^2 chlorfenapyr)
- It received the WHO recommendation in 2017 at the same time being asked to prove the Public Health impact meaning reduction of malaria cases when deployed
- WHO asked for two randomized cluster trials (RCT) lasting 2 seasons each
- The main objective of such a RCT is to assess the effectiveness of Interceptor® G2 compared to standard LLIN containing pyrethroids only for control of malaria in areas where the main malaria vectors are resistant to pyrethroid insecticides
- LSHTM has organized two RCT in Tanzania and Benin
- The RCT in Tanzania started February 2019 was completed mid 2021
- The RCT in Benin was completed mid 2022

➡ **Interceptor G2 technology has a broad range of data over 5 years studies**

Comparison between results from Tanzania and Benin

Tanzania[1]

- Overall 44% reduction in malaria incidence in children 6 months to 10 years in Interceptor® G2 arm compared to Interceptor® arm
- Stronger effect in year 1 (53% reduction) than in year two

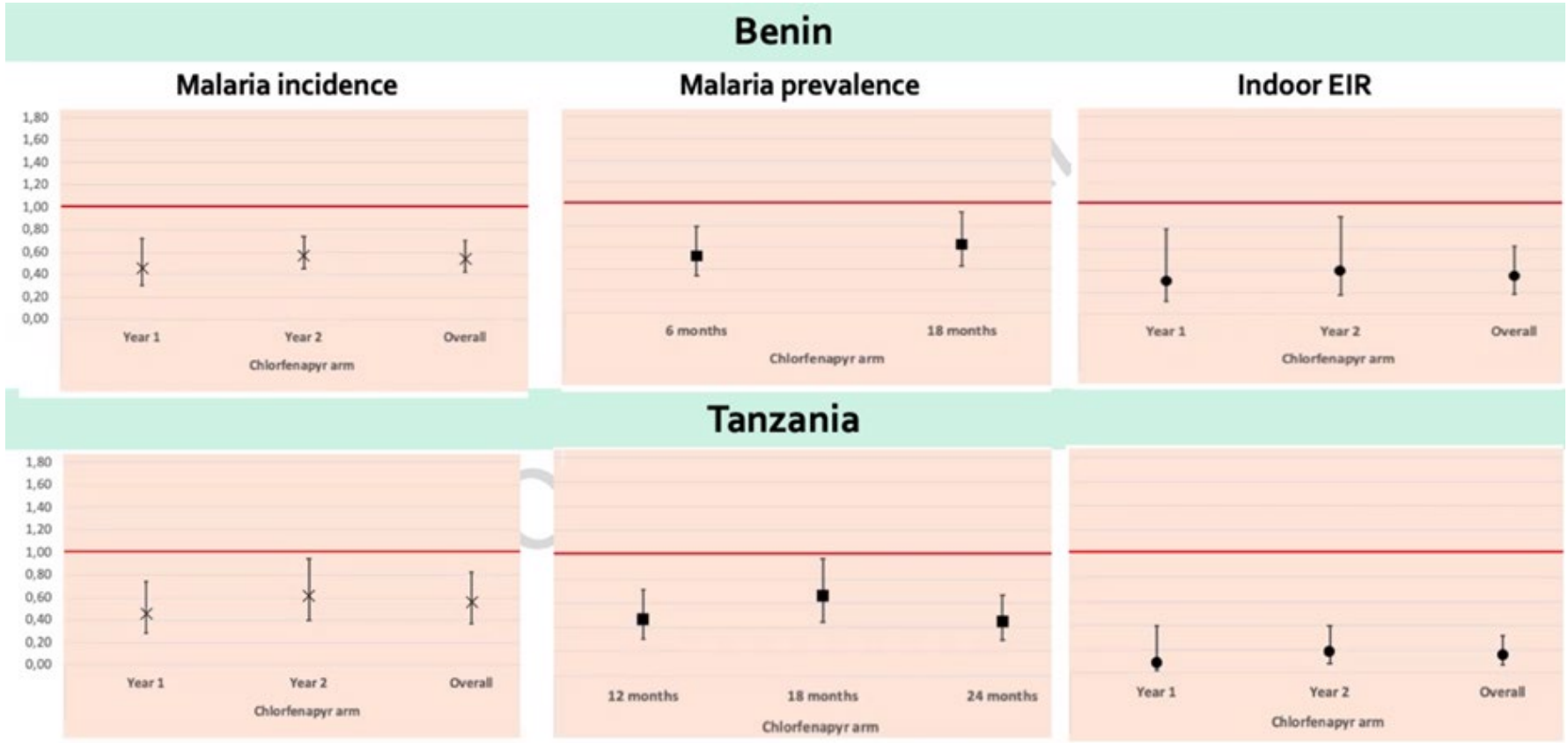
Benin[2]

- Reduction of malaria incidence was observed for both years in the CFP LLIN arm (46%)
- A stronger effect was observed in year 1 in comparison to year 2

1 J.F. Mosha, M.A. Kulkarni, E. Lukole, N.S. Matowo, C. Pitt, L.A. Messenger, E. Mallya, M. Jummame, T. Aziz, R. Kaaya, B.A. Shirima, G. Isaya, M. Taljaard, J. Martin, R. Hashim, C. Thickstun, A. Manjurano, I. Kleinschmidt, F.W. Mosha, M. Rowland, N. Protopopoff , The Lancet 2021, 399: 1227–41 „Effectiveness and cost-effectiveness of three types of dual active ingredient treated nets compared to pyrethroid long lasting insecticidal nets against malaria in an area with pyrethroid-resistant mosquitoes in Tanzania: A four arm, cluster-randomized trial”

2 M. Accrombessi, J. Cook, E. Dangbenon, B. Yovogan, H. Akpovi, A. Sovi, C. Adoha, L. Assongba, A. Sidick, B. Akinro, R. Ossè, F. Tokponnon, R. Aïkpon, A. Ogouyemi-Hounto, G. Gil Padonou, The Lancet 2022, doi.org/10.1016/S0140-6736(22)02319-4 „Efficacy of pyriproxyfen-pyrethroid long-lasting insecticidal nets (LLINs) and chlorfenapyr-pyrethroid LLINs compared with pyrethroid-only LLINs for malaria control in Benin: a cluster-randomised, superiority trial”

Comparison between results from Tanzania and Benin



Conclusions

- Interceptor® G2 more effective than standard LLIN
- WHO Guidelines for Malaria, Update 14 March 2023

New recommendation on pyrethroid-chlorfenapyr nets vs pyrethroid-only nets

WHO is issuing a strong recommendation for the deployment of pyrethroid-chlorfenapyr ITNs vs pyrethroid-only nets to prevent malaria in adults and children in areas where mosquitoes have become resistant to pyrethroids

New recommendation on pyrethroid-chlorfenapyr nets vs pyrethroid-PBO nets

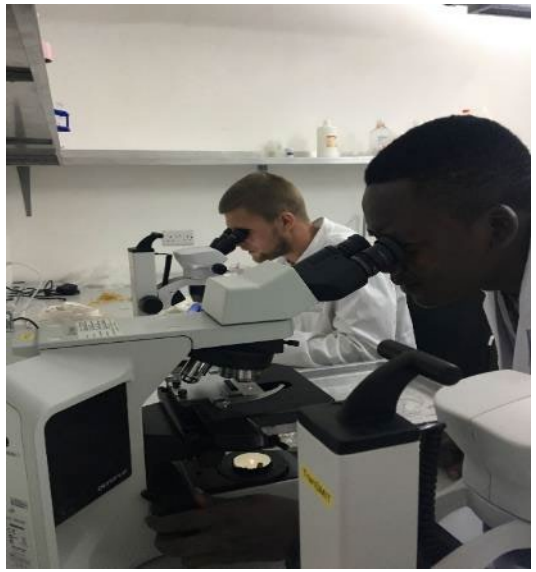
WHO is issuing a conditional recommendation for the deployment of pyrethroid-chlorfenapyr ITNs instead of pyrethroid-PBO nets to prevent malaria in adults and children in areas with pyrethroid resistance.

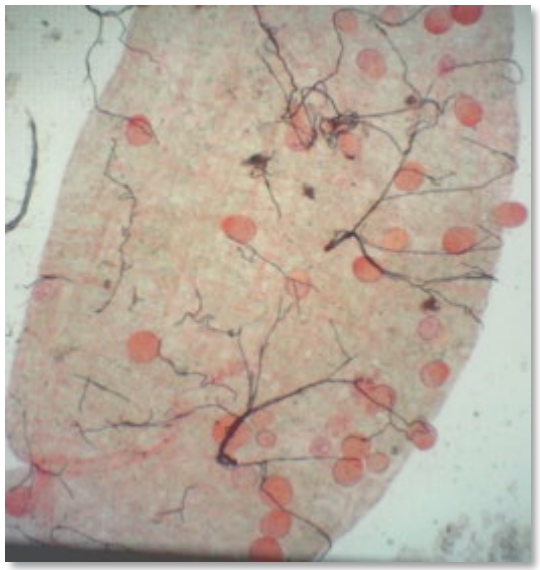
The Global Fund Replenishment Lyon 2019 : Bill Gates presents Interceptor® G2 as a new innovative tool to fight malaria

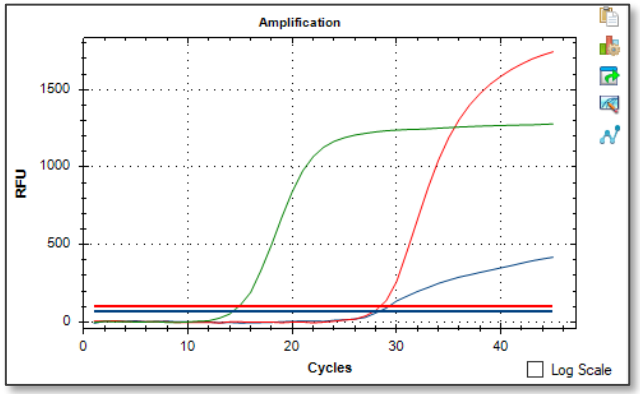
Chlorfenapyr provide additional transmission blocking effects even if a mosquito survives a sub-lethal dose

Modified WHO tunnel assay – scoring oozysts and sporozoites[1]

- Pyrethroid-resistant *Anopheles gambiae s.s.* (mixed-function oxidases and Vgsc-L995F *kdr* alleles)
- n = 3 x 100 mosquitoes/replicate
- Eight hours exposure in the tunnel to netting with 200 mg/m^2 chlorfenapyr
- Feeding with gametocytemic human blood
- Mortality scored 9 days post blood meal
- **Scoring of oocysts and sporozoites on day 8 and 16 after feeding**.







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

1 Kweyamba PA, Hofer LM, Kibondo UA, Mwanga RY, Sayi RM, Matwewe F,Austin JW, Stutz S, Brancucci N, Rottmann M, Moore SJ, Müller P, Tambwe MM, Sub-lethal exposure to chlorfenapyr reduces the probability of developing Plasmodium falciparum parasites in surviving Anopheles mosquitoes. In press.

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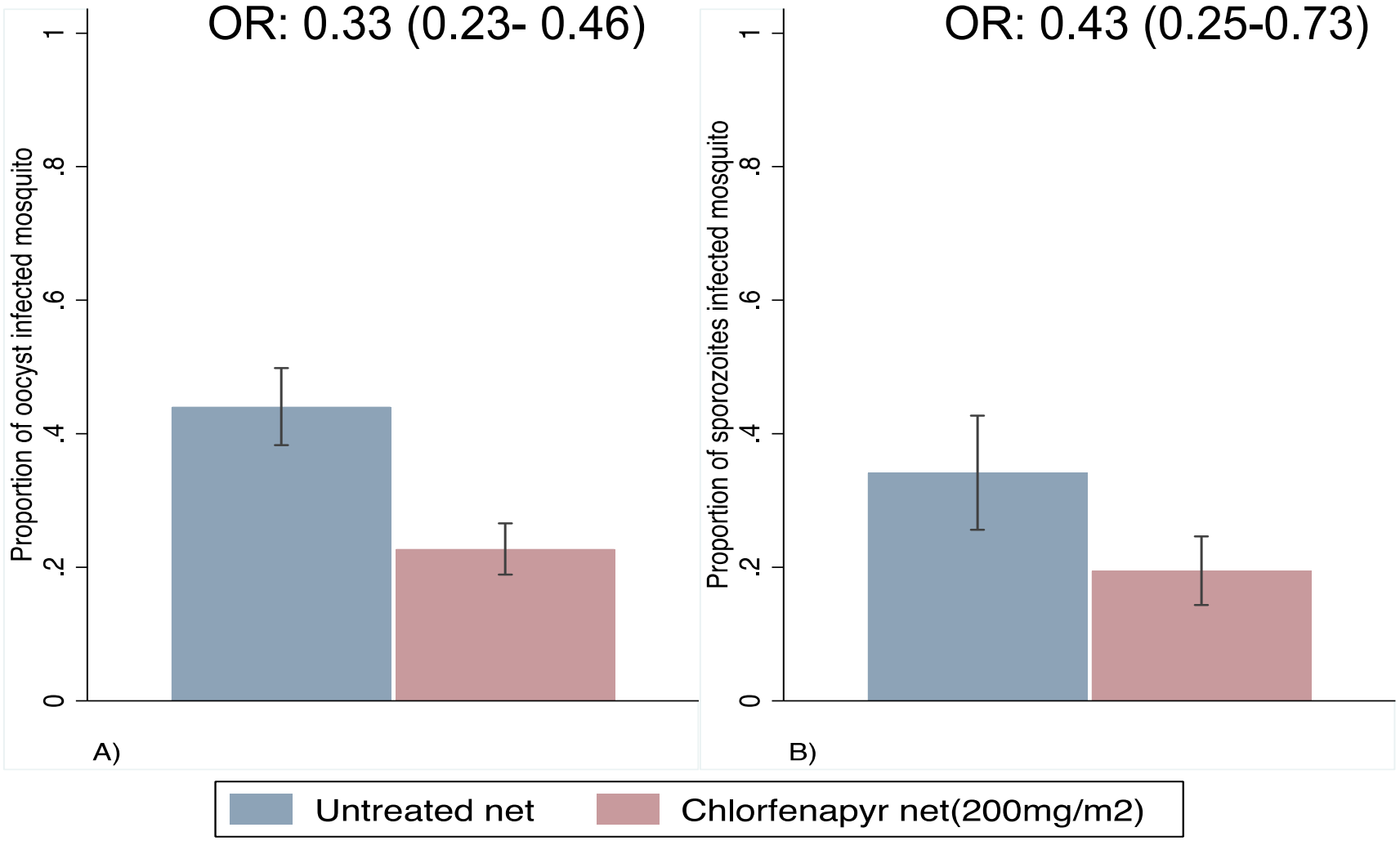
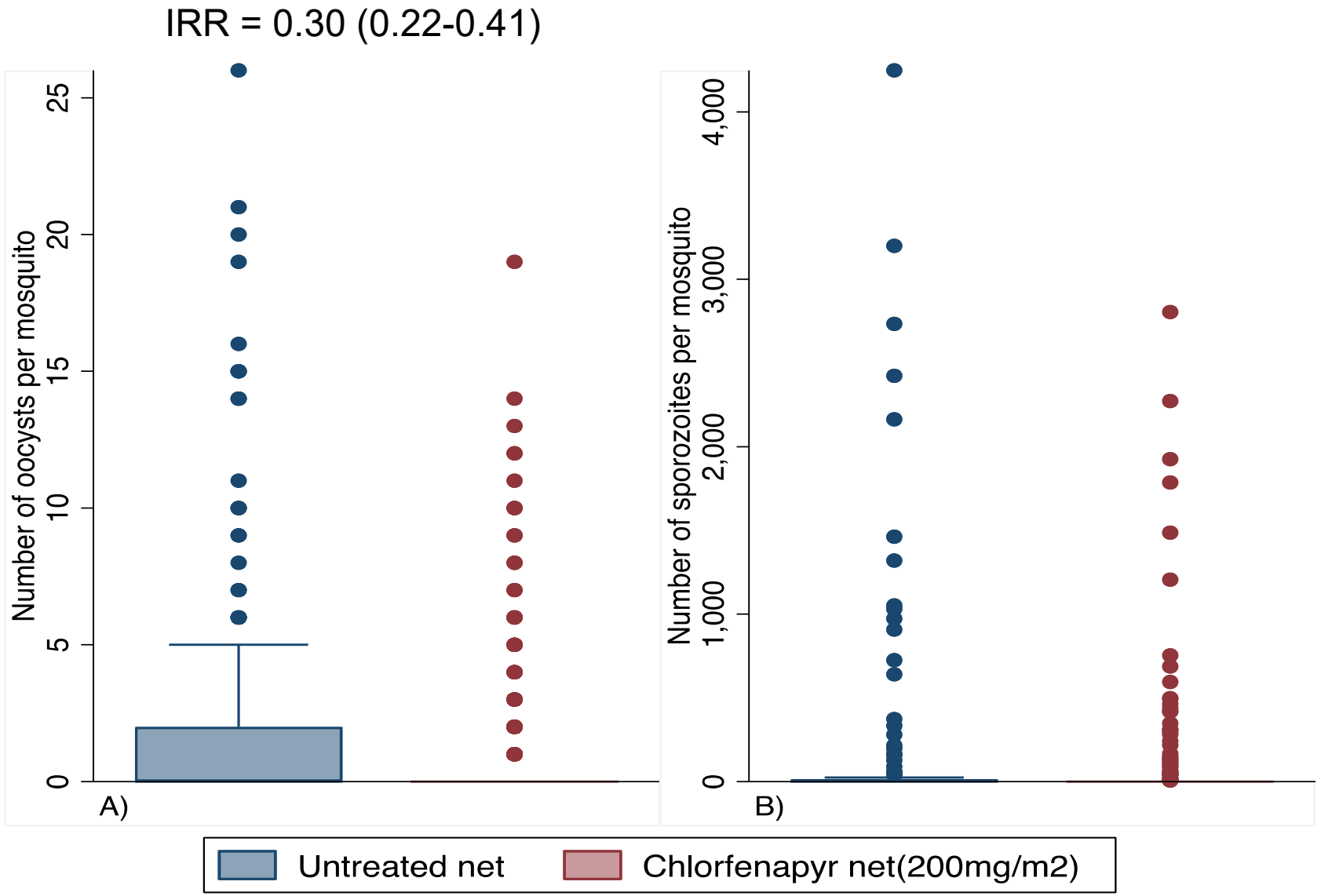
Effect of chlorfenapyr on Plasmodium parasites

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

Proportion of infected mosquitoes post chlorfenapyr exposure



Intensity of infection in mosquitoes post chlorfenapyr exposure



Incidents rate ratio (IRR) were derived from mixed effect negative binomial regression adjusted for study participant and treatment allocation

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Conclusions

- Chlorfenapyr substantially reduces the proportion of Plasmodium-infected mosquitoes and the intensity of infection at sub-lethal doses thus 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

Chlorfenapyr- a new a.i. for IRS

- Under evaluation by PQ
- Next step - start registrations in countries
- Brand Name

Sylando® 240 SC

Chlorfenapyr 240 SC

Chlorfenapyr in Public Health – a history

2007: First publication on the use of chlorfenapyr in VC

2009:Signature of Proof of Concept contract between IVCC, LSHTM and BASF to **evaluate the toxicity of chlorfenapyr on mosquitoes**

2010:Submission of Sylando®240 SC to WHOPES

2011:in vitro trials with chlorfenapyr and plasmodium at Swiss TPH

2011:Signature of project agreement between IVCC, LSHTM and BASF to **develop an long lasting mosquito nets based on chlorfenapyr**, Interceptor G2

2016, start of cooperation between Swiss TPH and BASF to prove that chlorfenapyr also acts on the **plasmodium** in a living mosquitoe

2017, Interceptor® G2 receives interims WHOPES recommendation for pyr only LN **2 RCT** needed for recommendation against resistant mosquitoes

2018 New Nets Project lead by IVCC, signature of copayment agreement

2019: First RCT in Tanzania starts

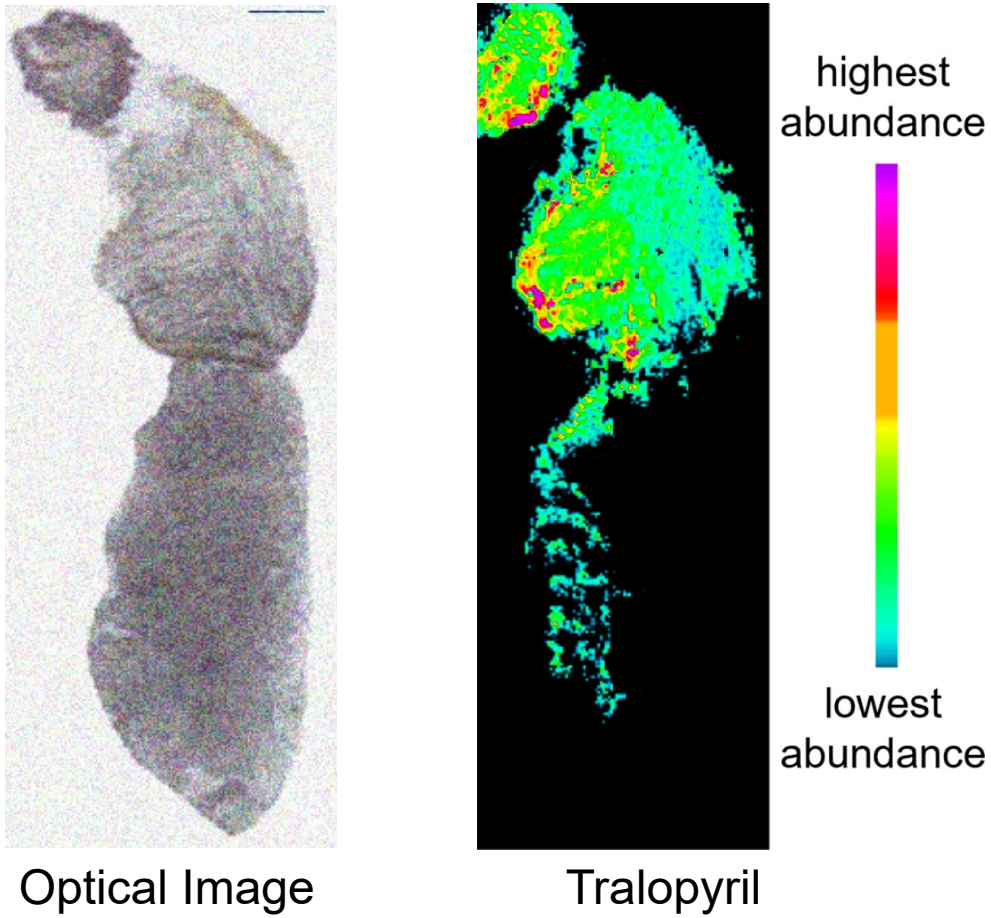
2022, proof on activity of chlorfenapyr in living mosquitoes infected by **plasmodium** demonstrated at IHI

March 2023: Recommendation of Interceptor® G2 by VCAG

2007 2010 2015 2020 2023

Chlorfenapyr- more to come from BASF

- Quantification of chlorfenapyr and its metabolite tralopyril in an individual mosquito
- Localization of tralopyril in the mosquitoe by MALDI Imagine



Optical Image

Tralopyril

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