

Evidence Base for New Dual-AI Nets

Interceptor ® G2

Interceptor® G2 (IG2) is a second-generation LLIN developed by <u>BASF</u> with a combination of chlorfenapyr and alphacypermethrin to control insecticide resistant mosquitoes. This novel mode of action in vector control exploits mosquito enzymatic systems against themselves and shows no cross-resistance to other insecticide classes. Unlike pyrethroids, the chlorfenapyr target site of activity is not the insect nervous system. Instead, chlorfenapyr acts, after being metabolized by P450 enzymes at the cellular level, by disrupting respiratory pathways and proton gradients through the uncoupling of oxidative phosphorylation within the mitochondria. The IG2 net has a <u>WHO prequalification listing</u>. Previously the net was evaluated and given an interim recommendation by the <u>20th WHOPES Working Group</u>.

There have been several experimental hut trials conducted with IG2 nets. Overall, the hut trial results show that IG2 nets demonstrate improved efficacy and wash resistance compared to standard alpha-cypermethrin nets against pyrethroid resistant mosquitoes.

A Chlorfenapyr Mixture Net Interceptor® G2 Shows High Efficacy and Wash Durability against Resistant Mosquitoes in West Africa.

Efficacy of Interceptor® G2, a new long-lasting insecticidal net against wild pyrethroid-resistant Anopheles gambiae s.s. from Côte d'Ivoire: a semi-field trial.

Which intervention is better for malaria vector control: insecticide mixture long-lasting insecticidal nets or standard pyrethroid nets combined with indoor residual spraying?

<u>Evaluation of efficacy of Interceptor® G2, a long-lasting insecticide net coated with a mixture of chlorfenapyr and alphacypermethrin, against pyrethroid resistant Anopheles gambiae s.l. in Burkina Faso.</u>

Efficacy of interceptor® G2, a long-lasting insecticide mixture net treated with chlorfenapyr and alpha-cypermethrin against Anopheles funestus: experimental hut trials in north-eastern Tanzania.

Furthermore, a <u>randomised controlled trial</u> was conducted in Tanzania showing that after two years, IG2 ITNs provided significantly better protection than standard ITNs (44% lower incidence and 55% lower odds of infection compared to standard ITNs). Trial results indicate that IG2 nets would be more cost-effective over a 2-year period, in an area with highly pyrethroid-resistant mosquitoes, than standard, pyrethroid-only nets.

Royal Guard®

Royal Guard® (RG) is an ITN developed by <u>Disease Control Technologies</u> to provide vector control through both the personal protection of traditional mosquito knockdown and mortality, as well as a reduction in fecundity of any mosquitoes that manage to survive exposure to the products pyrethroid active ingredient. The intended benefit of the insect growth regulator, pyriproxyfen, is to reduce the fecundity of adult female mosquitoes and, therefore, yield an overall reduction in the vector population by inhibiting egg laying, larval-pupal transformation and the emergence of functioning young adult mosquitos. The RG net has a <u>WHO prequalification listing</u>.

Hut trials using RG have been conducted in Tanzania and <u>Benin</u>, demonstrating equal or superior performance in comparison to the reference DuraNet®. RG demonstrated superiority over DuraNet® by significantly reducing the offspring of surviving wild free-flying pyrethroid resistant blood-fed mosquitoes exposed to the net.

One <u>epidemiological trial conducted using Olyset Duo</u>®, containing a pyrethroid and pyriproxyfen, showed additional impact over standard pyrethroid nets against clinical malaria. Separately, a randomised controlled trial conducted in Tanzania using Royal Guard showed no effect on malaria incidence, with an indication of reduced prevalence, although not statistically significant.

Ongoing/Upcoming New Net Evaluations

A cluster-randomized controlled trial including both IG2 and Royal concluded in <u>Benin</u> in March 2022 and has been submitted to the Lancet. Another trial is underway in <u>Uganda</u> comparing Royal Guard and PBO ITNs. Additional evidence is being collected through effectiveness pilot evaluations as part of the <u>New Nets Project</u>. Effectiveness pilots include enhanced passive case detection, cross-sectional surveys, enhanced entomology, and anthropology data collection. Below is a summary of preliminary effectiveness pilot results.

Country	Type of study	Main findings on differential ITN performance	Reference
Burkina Faso*	Observational – through 24 months	 The IG2 ITNs district saw a 25% greater reduction in malaria incidence, and PBO ITNs a 16% greater reduction, than standard ITNs two cumulative years after distribution. Changes in prevalence were biased by seasonal malaria chemoprevention (SMC) implementation in 2021, and all districts saw reductions in under 5 prevalence regardless of ITN type. Modelled estimates will disentangle the effects of SMC and evaluate the effects of new nets two years post-distribution. 	New Nets Project interim results (July 2022)
Northern Mozambique*	Observational – through 12 months	 The IG2 ITN district saw a 75% greater reduction in malaria incidence compared to standard ITN district. The RG ITN district saw a 64% greater reduction compared to the standard ITN district. Reductions in prevalence were also largest in the IG2 and RG districts, 42% and 29% respectively, compared to 7% in the standard district. The IG2 district also had the lowest rate of reported ITN use and ownership while demonstrating the largest gains in malaria reduction. 	
Western Mozambique*	Observational – through 12 months	 The district where IG2 ITNs were distributed saw a 26% greater reduction in malaria incidence than the standard ITN district. Reductions in the PBO and standard district were similar. Prevalence went down slightly in the standard ITN district (12%) but substantially (by more than 66%) in both the IG2 and PBO districts. 	
Nigeria*^	Observational – through 12 months	SMC was implemented in the IG2 and RG ITN districts in 2021. Modelled estimates will evaluate the effect of dual-active ingredient ITNs compared to standard ITNs.	
Rwanda*	Observational – through 24 months	 IG2s conferred an additional 13% reduction in malaria incidence compared to standard ITNs. Standard ITNs with IRS conferred an additional 29% reduction in malaria incidence compared with standard ITNs only. Prevalence was below 5.2 % at all time points in all districts in this very low burden setting, ranging from 1.2% to 0.3% two years post-distribution. 	

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*Final results are anticipated in early 2023 ^Funding for Nigeria pilot split between New Nets Project and Global Fund	
Alongside the above work, the <u>ESSENTIALS</u> project funded by the Bill and Melinda O experimental hut studies involving IG2 and/or RG since 2020. These trials, using a contained have taken place in Benin, Burkina Faso, and Tanzania and a final round of trials is standard outputs of knockdown, mortality and blood feeding, mosquito longevity, been monitored. The results have been shared with Imperial College and have been dual-active ingredient nets.	ombination of new, aged, and washed nets, planned for Malawi in 2022. In addition to the fecundity and ability to re-feed have also