The Impact of Next-Generation Long-Lasting Insecticidal Nets on Insecticide Resistance: cRCT Results from Benin and Tanzania

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15th April 2024 – 19th Annual RBM Vector Control Working Group Meeting

PY-PBO ITNs & PY-CFP ITNs Have Begun to Replace PY ITNs

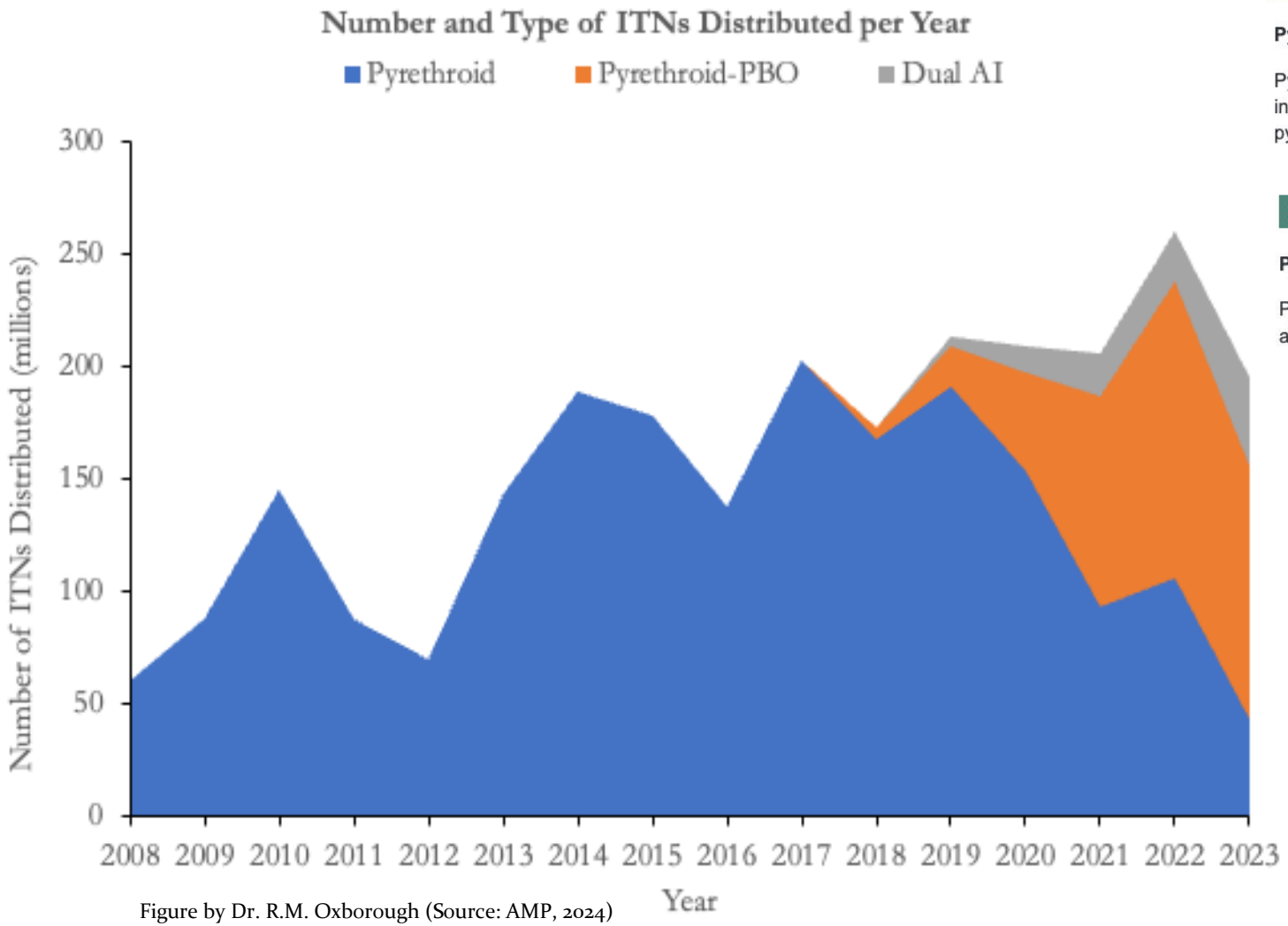


Figure by Dr. R.M. Oxborough (Source: AMP, 2024)

Conditional recommendation for, Moderate certainty evidence

Pyrethroid-PBO ITNs (2022)

Pyrethroid-PBO ITNs instead of pyrethroid-only LLINs can be deployed for the prevention and control of malaria in children and adults in areas with ongoing malaria transmission where the principal malaria vector(s) exhibit pyrethroid resistance.

Strong recommendation for, Moderate certainty evidence

Pyrethroid-chlorfenapyr ITNs vs pyrethroid-only LLINs (2023)

Pyrethroid-chlorfenapyr ITNs should be deployed instead of pyrethroid-only LLINs for prevention of malaria in adults and children in areas with pyrethroid resistance.

- WHO policy recommends use of PBO-ITNs and CFP-ITNs in areas with pyrethroid resistance
- 58% of ITNs (112.6 million) delivered to sub-Saharan Africa in 2023 were PBO-ITNs
- PY ITNs decreased to to 22% (39.8 million) in 2023
- Since 2018, 404 million PY-PBO ITNs were delivered to sub-Saharan Africa
- **What impact is mass distribution of new nets having on insecticide resistance selection?**

Large-Scale, Longitudinal Insecticide Resistance Monitoring

Lancet 2022; 399: 1227–41

Effectiveness and cost-effectiveness against malaria of three types of dual-active-ingredient long-lasting insecticidal nets (LLINs) compared with pyrethroid-only LLINs in Tanzania: a four-arm, cluster-randomised trial

Jacklin F Mosha, Manisha A Kulkarni*, Eliud Lukole, Nancy S Matowo, Catherine Pitt, Louisa A Messenger, Elizabeth Mallya, Mohamed Jumanne, Tatu Aziz, Robert Kaaya, Boniface A Shirima, Gladness Isaya, Monica Taljaard, Jacklin Martin, Ramadhan Hashim, Charles Thickstun, Alphaxard Manjurano, Immo Kleinschmidt, Franklin W Mosha, Mark Rowland, Natacha Protopopoff*

Lancet Planet Health 2023; 7: e673–83

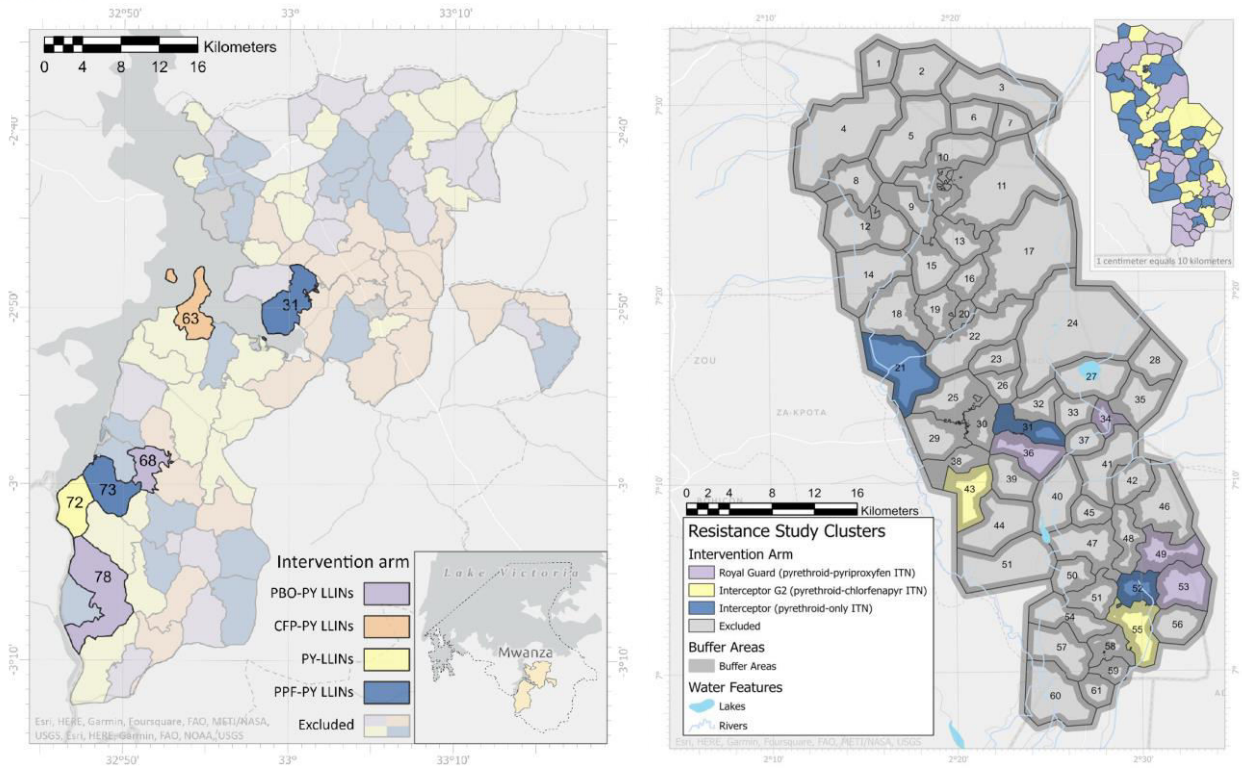
Effects of next-generation, dual-active-ingredient, long-lasting insecticidal net deployment on insecticide resistance in malaria vectors in Tanzania: an analysis of a 3-year, cluster-randomised controlled trial

Louisa A Messenger, Nancy S Matowo, Chad L Cross, Mohamed Jumanne, Natalie M Portwood, Jackline Martin, Eliud Lukole, Elizabeth Mallya, Jacklin F Mosha, Robert Kaaya, Oliva Moshi, Bethanie Pelloquin, Katherine Fullerton, Alphaxard Manjurano, Franklin W Mosha, Thomas Walker, Mark Rowland, Manisha A Kulkarni, Natacha Protopopoff

Lancet 2023; 401: 435–46

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

Manfred Accrombessi, Jackie Cook*, Edouard Dangbenon, Boulais Yovogan, Hilaire Akpovi, Arthur Sovi, Constantin Adoha, Landry Assongba, Aboubacar Sidick, Bruno Akinro, Razaki Ossè, Filémon Tokponnon, Rock Aïkpon, Aurore Ogouyemi-Hounto, Germain Gil Padonou, Immo Kleinschmidt, Louisa A Messenger, Mark Rowland, Corine Ngufor, Natacha Protopopoff†, Martin C Akogbeto†*



- **Tanzania cRCT**: Interceptor G2, OlysetPlus, Royal Guard *vs.* Interceptor (control)
- **Benin cRCT**: Interceptor G2, Royal Guard *vs.* Interceptor (control)
- PY CDC intensity bottle bioassays; PBO pre-exposure bioassays; CFP and PPF CDC bottle bioassays
- Tanzania n=47,258; Benin n=19,292 mosquitoes

Interceptor G2 Had Variable Impact on PY Resistance Over 3 Years

Intervention Arm 1: Interceptor® G2

Active Ingredients: Alpha-cypermethrin + chlorfenapyr

Modes of action: Neurotoxin + mitochondrial inhibitor

- **Tanzania cRCT**: no escalation of PY resistance over 3 years in *Anopheles funestus* s.l.
- **Benin cRCT**: significant increase in PY resistance over 3 years in *Anopheles gambiae* s.l. (predominantly *Anopheles coluzzii*)
- Minimal reduction in complete susceptibility to CFP in both sites

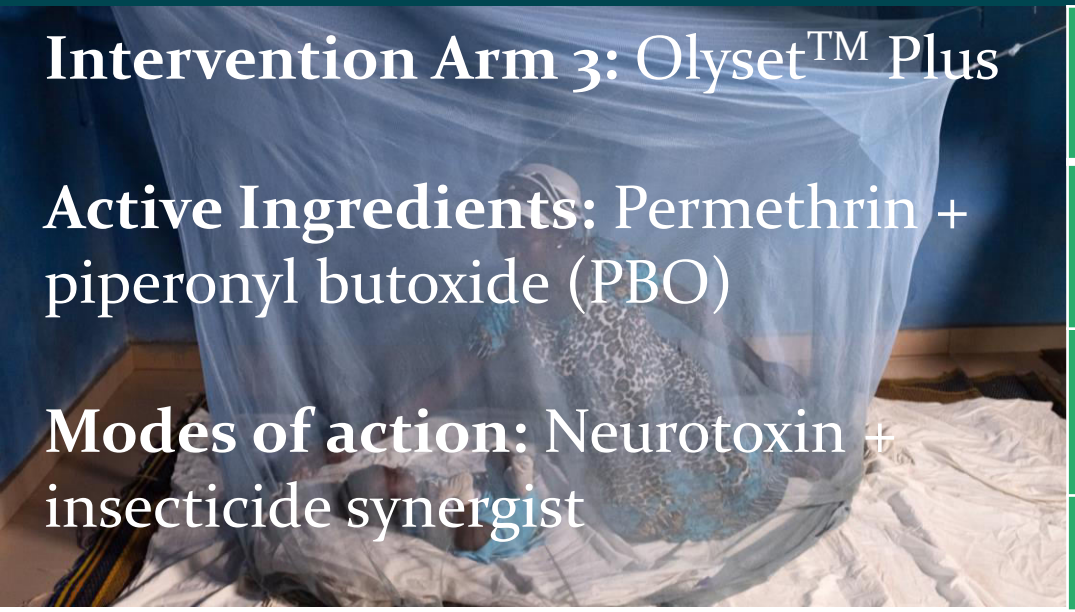
TANZANIA

Insecticide	LD50 [95% CI]			Relative Median Potency by Year
	Year 1	Year 2	Year 3	
Alpha-cypermethrin	**0.42** [0, 3.13] (n = 404)	**1.55** [0, 7.34] (n = 870)	**0.99** [0, 5.68] (n = 743)	1 vs. 2: 0.27 [0, 1.43] 1 vs. 3: 0.42 [0, 2.34] 2 vs. 3: 1.56 [0.27, 36.44]
Permethrin	**0** (n = 607)	**0** (n = 594)	**0** (n = 651)	1 vs. 2: 3.80e-05 1 vs. 3: 0 2 vs. 3: 8.92
PBO + Permethrin	**0.02** [0, 0.82] (n = 362)	**0.1** [0, 2.53] (n = 594)	**0.26** [0, 3.95] (n = 883)	1 vs. 2: 0.17 [0, 2.28] 1 vs. 3: 0.07 [0, 0.91] 2 vs. 3: 0.4 [0, 2.69]

BENIN

Insecticide	LD50 [95% CI]			Relative Median Potency by Year
	Year 1	Year 2	Year 3	
Alpha-cypermethrin (cluster 43)	**44.48** [35.82, 55.26] (n = 482)	**77.98** [62.12, 98.74] (n = 509)	**97.51** [77.30, 124.89] (n = 492)	1 vs. 2: 0.57 [0.39, 0.80] 1 vs. 3: 0.46 [0.29, 0.65] 2 vs. 3: 0.80 [0.57, 1.11]
Alpha-cypermethrin (cluster 55)	**39.79** [32.66, 48.73] (n = 503)	**42.20** [31.84, 56.08] (n = 508)	**124.82** [98.74, 163.01] (n = 439)	1 vs. 2: 0.94 [0.66, 1.32] 1 vs. 3: 0.32 [0.15, 0.52] 2 vs. 3: 0.34 [0.16, 0.56]

PY Resistance Escalation and Loss of Synergy in Olyset Plus Arm



Intervention Arm 3: Olyset™ Plus

Active Ingredients: Permethrin + piperonyl butoxide (PBO)

Modes of action: Neurotoxin + insecticide synergist

Insecticide	LD50 [95% CI]			Relative Median Potency by Year
	Year 1	Year 2	Year 3	
Alpha-cypermethrin	**33.26** [23.54, 47.41] (n = 551)	**35.81** [27.18, 47.20] (n = 706)	**70.22** [50.15, 102.64] (n = 673)	1 vs. 2: 0.93 [0.59, 1.44] 1 vs. 3: 0.47 [0.26, 0.78] 2 vs. 3: 0.51 [0.3, 0.79]
Permethrin	**47.09** [13.10, 174.93] (n = 164)	**306.02** [130.17, 8246.03] (n = 624)	**2635.29** [264.98, 3.98e+06] (n = 731)	1 vs. 2: 0.15 [0, 0.58] 1 vs. 3: 0.02 [0, 0.28] 2 vs. 3: 0.12 [0, 1.18]
PBO + Permethrin	---	**7.26** [2.87, 12.95] (n = 813)	**61.73** [45.08, 83.19] (n = 1178)	2 vs. 3: 0.12 [0.04, 0.25]

TANZANIA

- **Tanzania cRCT**: significant increase in PY resistance over 3 years in *Anopheles funestus* s.l. and loss of PBO synergy
- In year 3, LD95 for PBO + permethrin was 50-fold times the diagnostic dose
- No PBO-ITN arm in Benin cRCT for comparison
- Large-scale, randomized longitudinal monitoring data for PBO-ITNs needed from West Africa

PY Resistance Escalation In Control Arm (Not As Extreme?)

Control Arm: Interceptor®

Active Ingredient: Alpha-cypermethrin

Mode of action: Neurotoxin

- **Tanzania cRCT**: significant increase PY resistance and loss of PBO synergy over 3 years in *Anopheles funestus* s.l. **BUT not as extreme as PBO-ITN arm(?!)**
- **Benin cRCT**: significant increase in PY resistance over 3 years in *Anopheles gambiae* s.l. (predominantly *Anopheles coluzzii*)

TANZANIA

Insecticide	LD50 [95% CI]			Relative Median Potency by Year
	Year 1	Year 2	Year 3	
Alpha-cypermethrin	**9.52** [3.68, 16.96] (n = 670)	**76.20** [45.05, 155.03] (n = 695)	**59.16** [32.52, 119.83] (n = 552)	1 vs. 2: 0.12 [0.03, 0.31] 1 vs. 3: 0.16 [0.04, 0.40] 2 vs. 3: 1.29 [0.57, 3.15]
Permethrin	**13.27** [7.70, 19.49] (n = 981)	**35.83** [23.34, 51.16] (n = 734)	**168.79** [114.33, 272.65] (n = 644)	1 vs. 2: 0.37 [0.18, 0.63] 1 vs. 3: 0.08 [0.02, 0.18] 2 vs. 3: 0.21 [0.09, 0.40]
PBO + Permethrin	**0.28** [0.01, 3.13] (n = 194)	**5.54** [1.86, 10.51] (n = 760)	**43.06** [29.66, 58.57] (n = 957)	1 vs. 2: 0.05 [0.002, 0.56] 1 vs. 3: 0.01 [0.00, 0.08] 2 vs. 3: 0.13 [0.04, 0.27]

BENIN

Insecticide	LD50 [95% CI]			Relative Median Potency by Year
	Year 1	Year 2	Year 3	
Alpha-cypermethrin (cluster 21)	**35.69** [28.92, 44.01] (n = 484)	**75.77** [60.66, 95.53] (n = 509)	**144.92** [112.60, 190.65] (n = 512)	1 vs. 2: 0.47 [0.32, 0.66] 1 vs. 3: 0.25 [0.15, 0.37] 2 vs. 3: 0.52 [0.36, 0.74]
Alpha-cypermethrin (cluster 31)	**38.69** [23.05, 64.74] (n = 409)	**58.16** [37.28, 89.86] (n = 527)	**112.37** [72.32, 188.88] (n = 479)	1 vs. 2: 0.67 [0.27, 1.25] 1 vs. 3: 0.34 [0.08, 0.74] 2 vs. 3: 0.52 [0.20, 0.96]

Key Discussion Points

- The market share of ITNs delivered to sub-Saharan Africa is now dominated by PBO-ITNs, followed by dual-A.I. ITNs
- A concerning escalation of PY resistance and parallel loss of PBO synergy was observed with *Anopheles funestus* s.l. exposed to PBO-ITNs in Tanzania
- CFP-ITNs displayed variable performance between sites – does this reflect differences in relative community-level ITN durability, IR mechanisms between major vector species, fitness costs or initial phenotypic resistance intensities?
- **How can we better optimize programmatic decisions regarding PBO-ITN and CFP-ITN deployment?**

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