Implications of insecticide resistance for malaria vector control

Outcomes from a multi-country evaluation

RBM Vector Control Working Group 12th Annual Meeting

9 February 2017; Geneva, Switzerland

Global **Malaria** Programme

World Health Organization

Multi-country evaluation (2009 – 2016+)

Primary objectives

- To assess trends in insecticide resistance status and underlying mechanisms in main malaria vector species in response to different interventions.
- To determine the impact of insecticide resistance in malaria vectors on the protective effectiveness of LLINs and IRS, and therefore on malaria disease burden.

Study design considerations

Required:

- common study design across all countries
- standardisation of methods, outcomes and measurements
- adequate statistical power, hence replication in many places (clusters)
- observational design since resistance cannot be randomly assigned

Epidemiological endpoints:

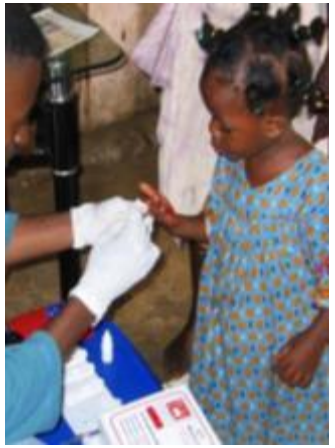
- Active case detection in cluster cohorts
- Active infection detection in cluster cohorts
- Prevalence of infection in clusters
- ➢ Effectiveness of nets measured by comparing incidence in users with incidence in non-users of LLINs

Methods published: Kleinschmidt et al. *Malaria Journal.* 2015;14:282.

Epidemiological component Entomological component

Cluster (village)

Test regularly for malaria infection/ and or disease



Collect data on whether they sleep under ITNs

Collect larvae at local breeding site, raise to adults…

.. and test susceptibility to insecticide (WHO 2013)

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Outcomes

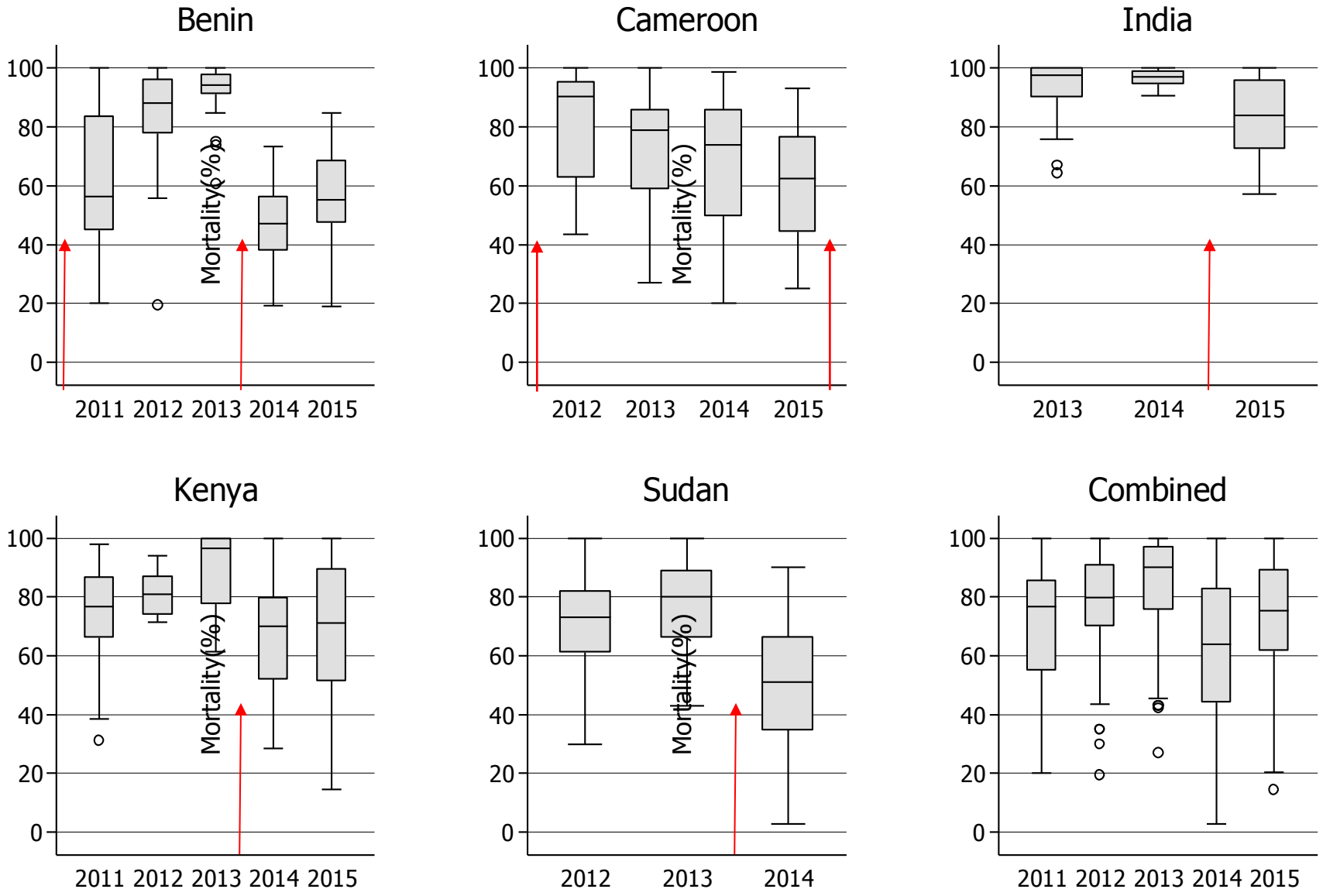
1. Time trends in resistance (bioassay mortality)
2. Impact of resistance on:
   - Effectiveness of LLINs (personal protection only)
   - Effectiveness of IRS (Sudan only)
3. Association between resistance and malaria morbidity

Evaluation areas

EVALUATION AREAS		BENIN	CAMEROON	INDIA	KENYA	SUDAN
Region/s		Département de Plateau	North Region	Kondagaon, Chhattisgarh	Western Kenya	Gezira, Gedarif and Kassala States
Sub-region/s		Ifangni Sakété Pobé Kétou	Garoua Mayo Oulo Pitoa	Keshkal	Bondo Nyando Rachuonyo Teso	El Hoosh Galabat Hag Abdalla New Halfa
***PfPR* $_{2–10}$ endemicity class** [a]		High	High	Low	High	Low
Baseline *P. falciparum* incidence		1.4 / year	0.6 / year	0.015 / year	1.4 / year	0.03 / year
Key vector/s		*An. gambiae s.s.*	*An. arabiensis* *An. gambiae s.s.* *An. coluzzii* *An. funestus*	*An. culicifacies*	*An. gambiae s.s.* *An. arabiensis* *An. funestus*	*An. arabiensis*
Baseline pyrethroid susceptibility [b]		20–100%	43–100%	86–100%	1–100%	47–100%
Evaluation design						
Number of clusters, by intervention	**LLINs**	32	38	80	50	70
	LLINs + IRS	0	0	0	0 [c]	70 [d]
Main indicator		Active case detection incidence				
Av. number children in cohort, per cluster		70	80	80	80	200

[a] proportion of 2–10 year olds in the general population that are infected with *P. falciparum*, averaged over the 12 months of 2010 as estimated by Malaria Atlas Project (MAP); low = 0% < *PfPR* $_{2–10}$ ≤ 5%; intermediate = 5% < *PfPR* $_{2–10}$ ≤ 40%; high = *PfPR* $_{2–10}$ > 40%; [b] mortality as measured in standard WHO susceptibility tests with the insecticide used in local LLINs; [c] IRS with deltamethrin and lambda-cyhalothrin in Rachuonyo and Nyando in 2012 only; [d] IRS with bendiocarb but with deltamethrin in Galabat in 2011 and 2012.

Time trends in resistance (bioassay mortalities)



Arrows indicate LLIN distributions

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Time trends in resistance (bioassay mortalities): linear

Country	Average mosquito mortality decrease per year, % (95% CI)	p
5 Countries Combined*	**4.6** (3.3- 5.7)	<0.001
Benin**	**3.6** (0.7-6.2)	0.009
Cameroon**	**6.1** (4.3-7.9)	<0.001
India**	**5.7** (3.6-7.7)	<0.001
Kenya**	**2.9** (1.1-4.7)	0.001
Sudan**	**11.3** (7.9-14.8)	<0.001

*adjusted for country, **adjusted for district

- Significant trend in increasing phenotypic resistance over time across all study areas

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Protection due to LLINs: infection prevalence in net users v non-users

Benin, Cameroon, Kenya, India and Sudan

1. Individuals sleeping under LLINs had lower risk of infection than those not sleeping under LLINs; OR=0.68 [95% CI 0.56 – 0.83]
2. No evidence that LLIN effectiveness varied with insecticide resistance as measured by WHO tube tests (p = 0.496)
3. Historical comparison (Lengeler 2004, based on cluster randomised trials): OR=0.87 (13% protective efficacy for infection prevalence) – same order of magnitude as current study

Protection due to LLINs: clinical incidence in net users v non-users

Benin, Cameroon, Kenya

- Individuals sleeping under LLINs had lower risk of infection than those not sleeping under LLINs; Rate Ratio=0.56 [95% CI 0.40 – 0.79]

Sudan

- No observed benefit for those sleeping under LLINs; Rate Ratio=1.41[95% CI 0.89- 2.24]

- No evidence that LLIN effectiveness varied with insecticide resistance as measured by WHO tube tests (p = 0.426)
- Historical comparison (Lengeler, 2004, based on cluster randomised trials): Rate Ratio=0.50

Protection due to IRS: change from deltamethrin to bendiocarb

- *Galabat, Sudan* - Malaria incidence in areas with LLINs versus LLINs + IRS with deltamethrin (2012) or bendiocarb (2013-2014)

Year	Study Arm (n=13 clusters per arm)	Cases	Annual Incidence, Cases per 1000 per year	Mean Incidence, Cases per 1000 per year	Overall effect of 2013/2014 vs 2012	Interaction
2012	LLIN+IRS (deltamethrin)	126	47.2	47.2	1	
2013	LLIN+IRS (bendiocarb)	82	28.1	24.6	0.52[0.36-0.75; p<0.001]	0.55 [0.34-0.89; p=0.014]
2014	LLIN+IRS (bendiocarb)	65	21.3			
2012	LLIN	117	44.4	44.4	1	
2013	LLIN	155	52	42.1	0.95[0.68-1.31; p=0.75]	1
2014	LLIN	98	32.3			

- IRS with deltamethrin had no added impact in addition to LLINs in the presence of pyrethroid resistance but switching to IRS with bendiocarb halved incidence

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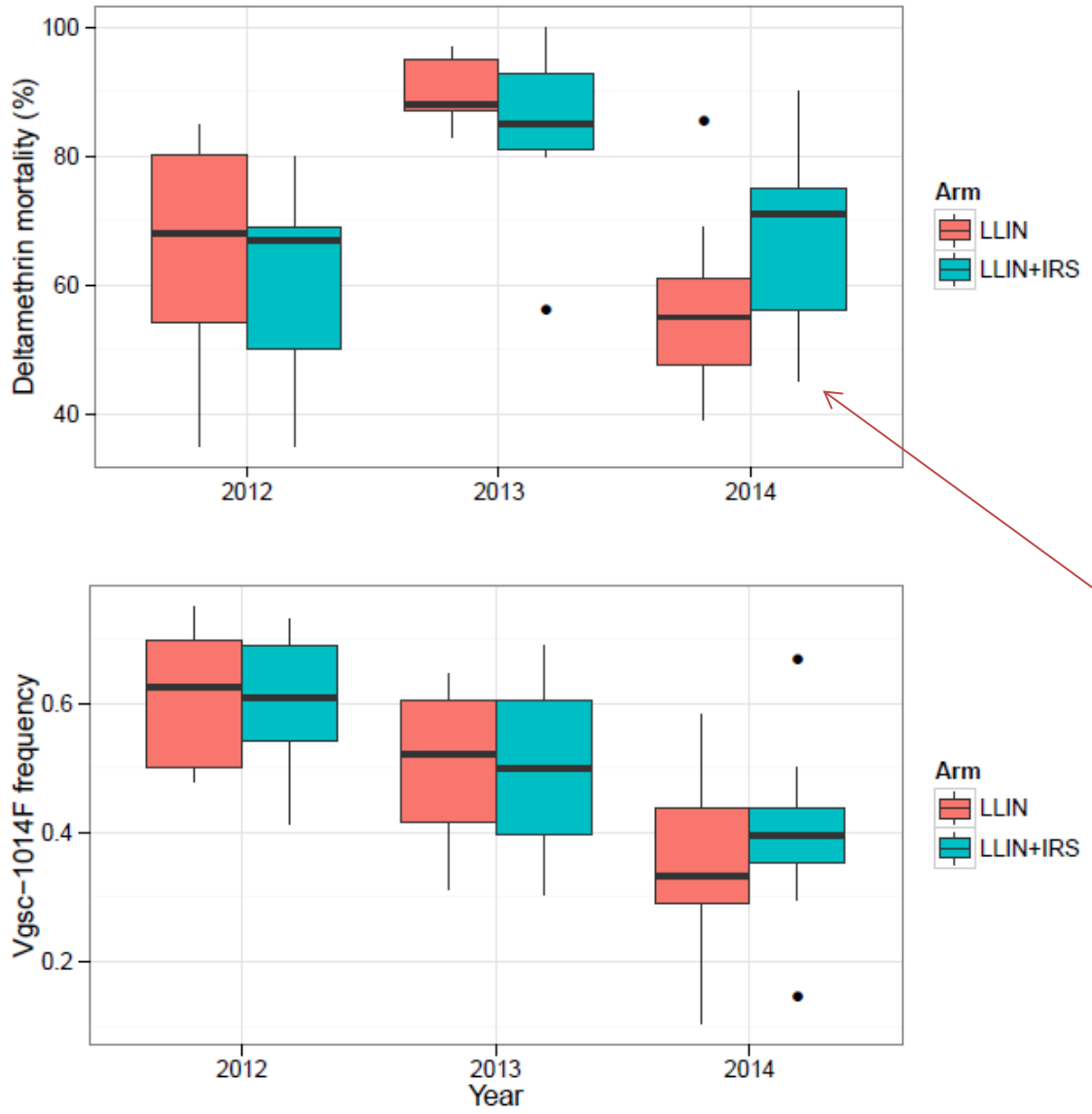
Resistance increase less marked in LLIN + non-pyrethroid IRS areas



- Change in deltamethrin mortality (upper panel) and *Vgsc-1014F* frequency (lower panel) across study years and between LLIN only and LLIN + IRS intervention arms
- In 2014 there was significantly higher mortality (less resistance) in the LLIN + IRS arm compared to the LLIN only arm (p = 0.038)

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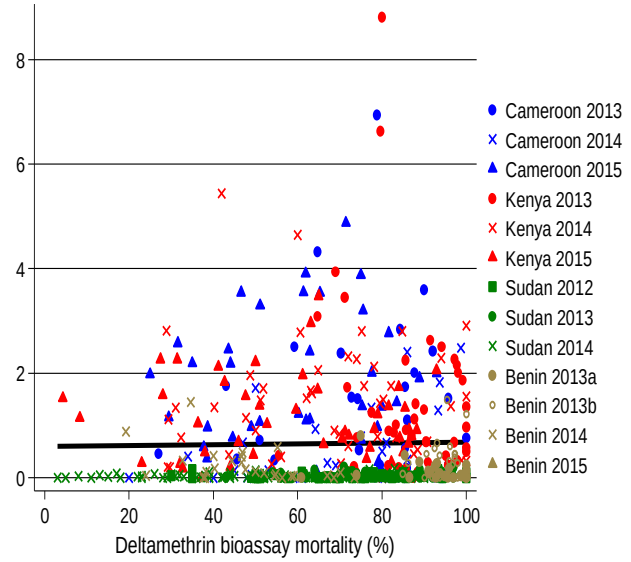
Association between pyrethroid resistance and malaria morbidity

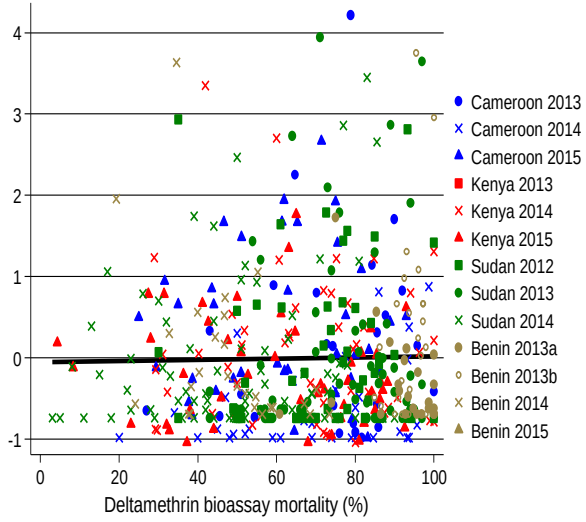
Global analysis (excluding India)

- Effect of a 10% increase in bioassay mortality: RR = 0.99 (0.91, 1.07), p = 0.736
- i.e. across all locations, there was no evidence of an increase in case incidence associated with pyrethroid resistance
- Similar observation for infection prevalence (p = 0.93)

Case incidence (all countries, cluster level)



Case incidence (standardised by country)



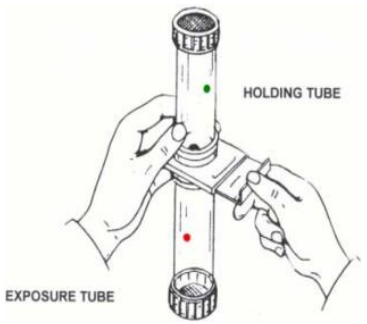
Figures provided by I. Kleinschmidt, 2016

Conclusions

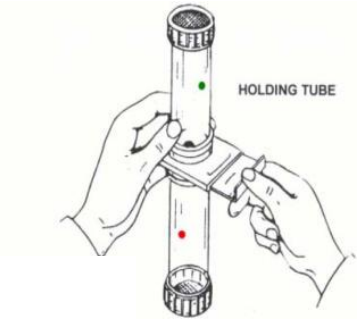
1. Insecticide resistance was highly variable between years and was heterogeneous on a relatively fine scale. There was a significant trend of increasing pyrethroid resistance in the main malaria vector species.
2. There was no evidence of an association between malaria disease burden and pyrethroid resistance across all locations.
3. There was evidence that LLINs provided personal protection against malaria in areas with pyrethroid resistance. There was no difference detected in LLIN effectiveness between higher and lower pyrethroid resistance.
4. There was evidence from an area (Galabat) with high LLIN coverage that IRS with an insecticide to which there is resistance provided no additional protection whereas IRS with an insecticide to which there is susceptibility almost halved malaria incidence relative to LLINs alone.
5. The development of pyrethroid resistance was slower in areas with LLINs plus a non-pyrethroid IRS than in an area with LLINs only.

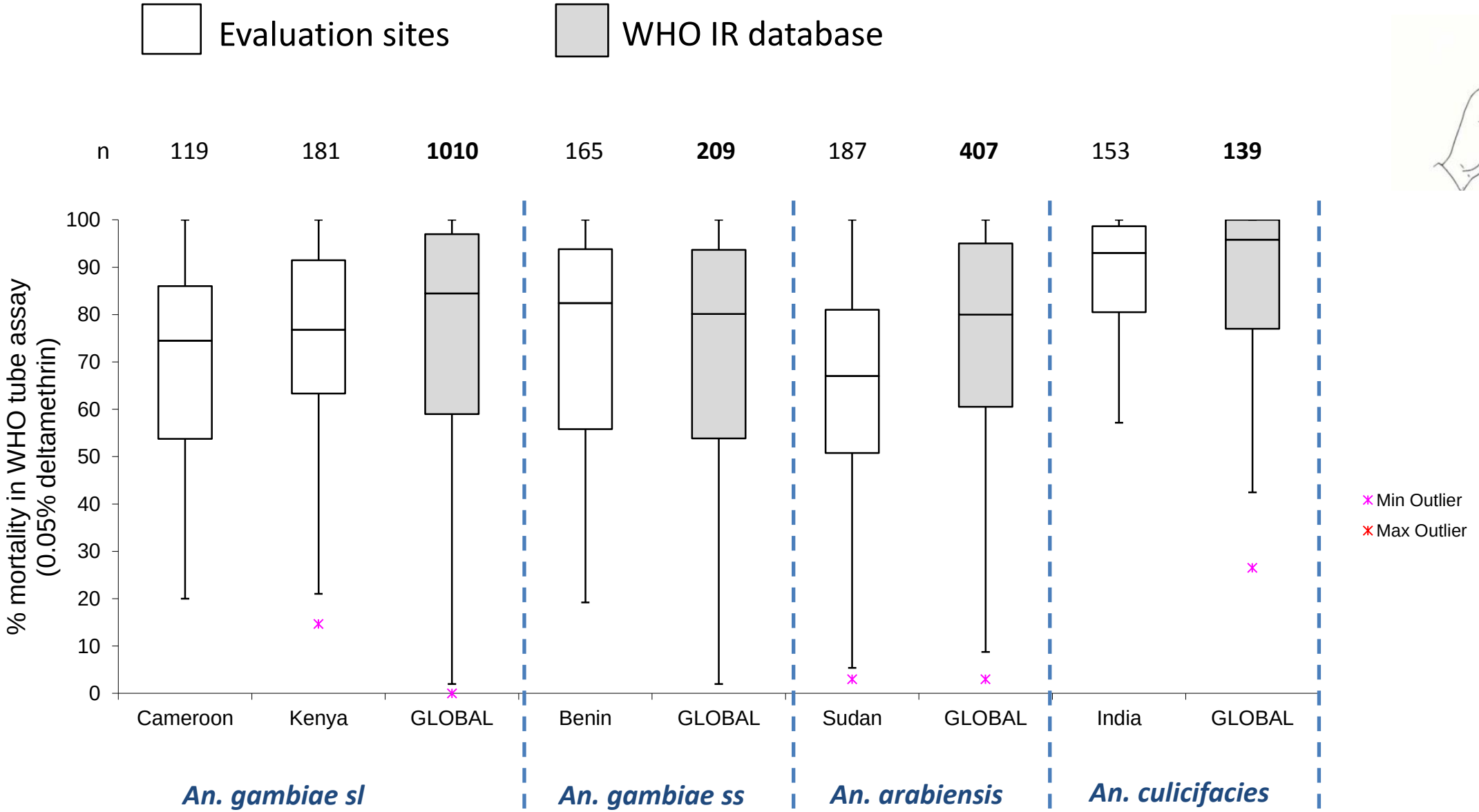
Limitations

1. **Resistance indicator**: pragmatic decision to generate data for maximum number of clusters using standard single-dose fixed-time exposure assay (one test per cluster per time point = over 78,000 specimens tested)
2. **Species composition and behaviour**: data not comprehensive enough for explanatory power
3. **Community effect**: unable to measure this; contribution of personal versus community protection not quantifiable
4. **Not worst case scenario**: but over evaluation period the resistance levels observed were similar to that reported more broadly



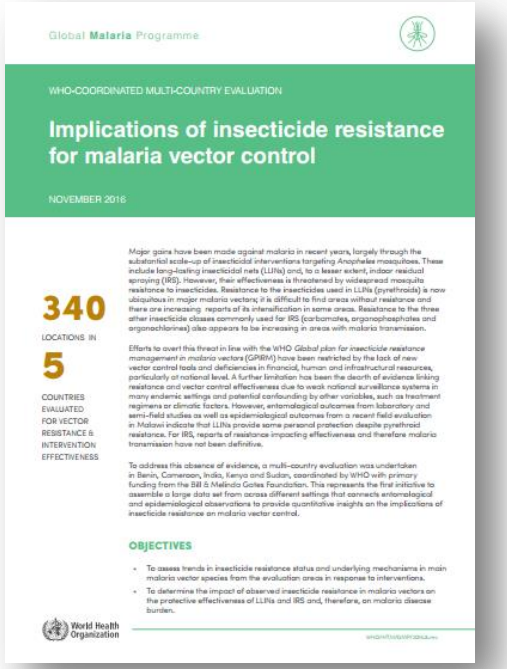
Resistance levels across evaluation sites similar to elsewhere





Implications for malaria vector control and surveillance

- **Universal coverage** with effective vector control of all at-risk populations is essential to protect against malaria. LLINs continue to provide protection even in the face of resistance.
- Despite gains made against malaria, transmission is still occurring. **New tools and strategies are required** to reach elimination in line with the Global Technical Strategy for Malaria (2016 – 2030), including to address insecticide resistance and residual transmission.
- Countries are urged to develop and implement **national insecticide resistance monitoring and management plans**.
- Better **measures of insecticide resistance** are needed.

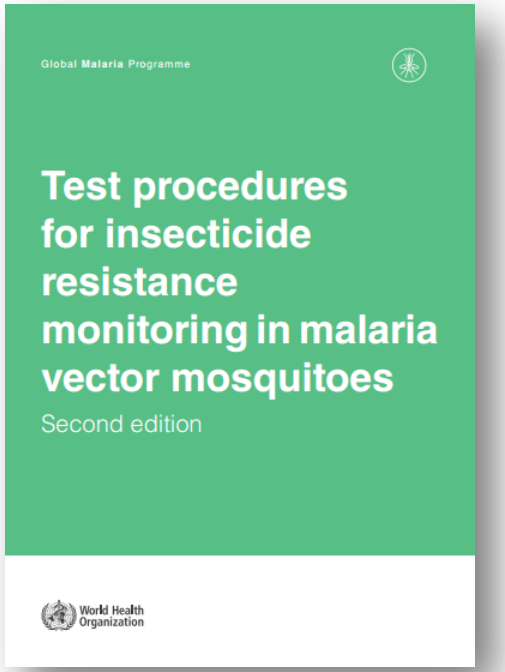


Information note available on WHO/GMP website

Updated WHO test procedures for insecticide resistance monitoring

Includes:

- **Intensity bioassay**: measures the strength of insecticide resistance in a mosquito population
- **Synergist-insecticide bioassay** – indication of the involvement of metabolic mechanisms in insecticide resistance



Test procedures and webinar available on WHO/GMP website

Acknowledgements

Implementation

Benin

Cameroon

India

Kenya

Sudan

Support & coordination

Technical Steering Committee

Thank you

Video of full presentations from the session at the ASTMH 65th annual meeting in Atlanta are available through the MESA Knowledge Hub