Combining long-lasting insecticidal nets and indoor residual spraying for malaria prevention in Ethiopia: Results from a cluster randomized controlled trial

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Background

- Interventions against malaria
  - Long lasting insecticidal net (LLIN)
  - Indoor residual spraying (IRS)
  - Others
- The need for the study
  - Paucity of evidence: Effect of combined use versus single intervention
  - The dominant vector is *An. arabiensis*

Pilot study

Gari *et al. Malar J (2016) 15:145*
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Malaria Journal

RESEARCH Open Access

Malaria incidence and entomological findings in an area targeted for a cluster-randomized controlled trial to prevent malaria in Ethiopia: results from a pilot study

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Purpose: to get ICC for the sample size computation

Study Period

- Pilot study: August – December 2013

- Main study: September 2014 – January 2017
  - Weekly data collection for 121 weeks

Study protocol

Deressa *et al. Trials* (2016) 17:20
DOI 10.1186/s13063-016-1154-2

Trials

STUDY PROTOCOL Open Access

Combining long-lasting insecticidal nets and indoor residual spraying for malaria prevention in Ethiopia: study protocol for a cluster randomized controlled trial

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Trial registration: PACTR201411000882128 (8 Sep 2014)

Primary objective

- To determine whether the combined use of LLINs and IRS with propoxur provides additional protection against malaria (*P. falciparum* and/or *P. vivax*) among all age groups in the study area compared to LLINs or IRS alone.

Secondary objectives

- Effect on entomological parameters: human biting rates, mosquito resting density, longevity, sporozoite rates and entomological inoculation rate
- Effect on haemoglobin (Hb) concentration among children

Methods: Design

- 2x2 factorial cluster randomized controlled trial
- Four arms:
  - LLIN plus IRS
  - LLIN alone
  - IRS alone
  - Control

Methods: Population

	IRS +LLIN	LLIN	IRS	Routine	Total
Number of clusters	44	44	44	44	176
Households	1,618	1,388	1,527	1,538	6,071
Population	9,104	8,038	8,567	8,839	34,548
Population/cluster	207	183	195	201	196

Methods: Population

Entomology

- 4 clusters (24 HHs) in each arm (random selection)
  - Followed every second week in each malaria season

Methods: Intervention

- IRS (Propoxur)
  - Once per year (3 rounds)
  - Coverage: 96%, 93% and 94%
  - 100% effective (test conducted on an insecticide susceptible insectary colony of *An. arabiensis*)

- LLIN (PermaNet 2.0) distribution
  - Once for all households (combination and LLIN-alone arms)
    - National guideline
  - Coverage 100%
  - Bio-efficacy: 80% of LLINs met WHO PES effectiveness criteria (after 2 years)

Study Profile

Assessed for eligibility (n=207 clusters)			
Randomized (n=176 clusters, 6,071 households, 31,275 people)			
Allocation			
IRS + LLIN	**IRS**	**LLIN**	**Control**
Allocated for intervention (N=44 clusters, 1618 households)	Allocated for intervention (N= 44 clusters, 1527 households)	Allocated for intervention (N=44 clusters, 1388 households)	N=44 clusters, 1538 households
Received allocated intervention: First IRS round (N= 1551 Households), Second IRS round (N=1519 households), Third IRS round (N=1529 households); For LLIN (N=1618 households)	Received allocated intervention: First round (N=1474 Households), Second round (N=1392 household), Third IRS round (N=1427 households)	Received allocated intervention (N= 1388 households)	
Did not receive allocated intervention: First IRS round (N=67 households), Second round (N=99 households), Third IRS round (N=89 households), All rounds (N=6 households); For LLIN (N=0)	Did not receive allocated intervention: First round (N=53 Households), Second round (N=135 Households), Third IRS round (N=100 household), All rounds (N=7 households)	Did not receive allocated intervention (N=0 households)	
Follow-up			
Lost to follow up (N= 143 household, 682 people)	Lost to follow up (N=194 households, 822 people)	Lost to follow up (N=121 household, 658 people)	Lost to follow up (N=163 household, 824 people)
Discontinued intervention (N=234 household)	Discontinued intervention (N=263 household)	Discontinued intervention: Only 8.4% had at least one net at 2 years	
Newly joined 897 people	Newly joined 830 people	Newly joined 740 people	Newly joined 806 people
Analysis			
Analysed (N=1612household, 9068 individuals)	Analysed (N=1520 household, 8521 people)	Analysed (N= 1388 household, 8038 people)	Analysed (N= 1538 household, 8839 people)
Excluded from analysis (N=6 household, 36 individuals)	Excluded from analysis (N=7 household, 46 people)	Excluded from analysis (N=0)	Excluded from analysis (N=0)

Result

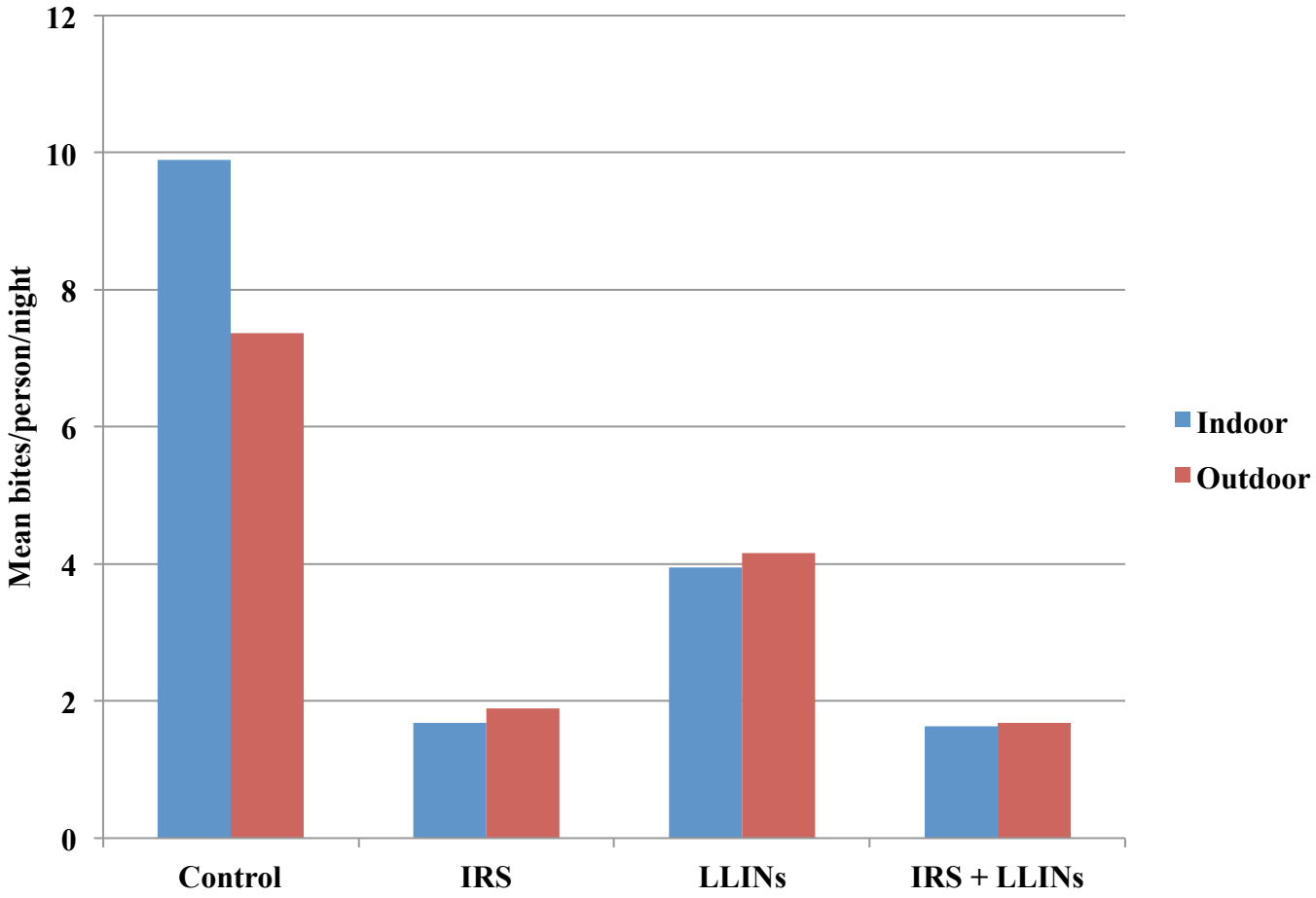
Arm	Incidence (95% CI) per 10,000 person-weeks of observation
IRS+LLIN	2.99 (2.67-3.35)
LLIN	2.92 (2.58-3.3)
IRS	3.01 (2.68-3.39)
Routine	2.72 (2.41-3.08)
Overall	**2.91 (2.74-3.09)**

- 1081 malaria cases (70% *P. falciparum* and more among children)
- No difference in incidence of malaria among the arms (adjusted for main material of the roof)

Impact on host seeking density

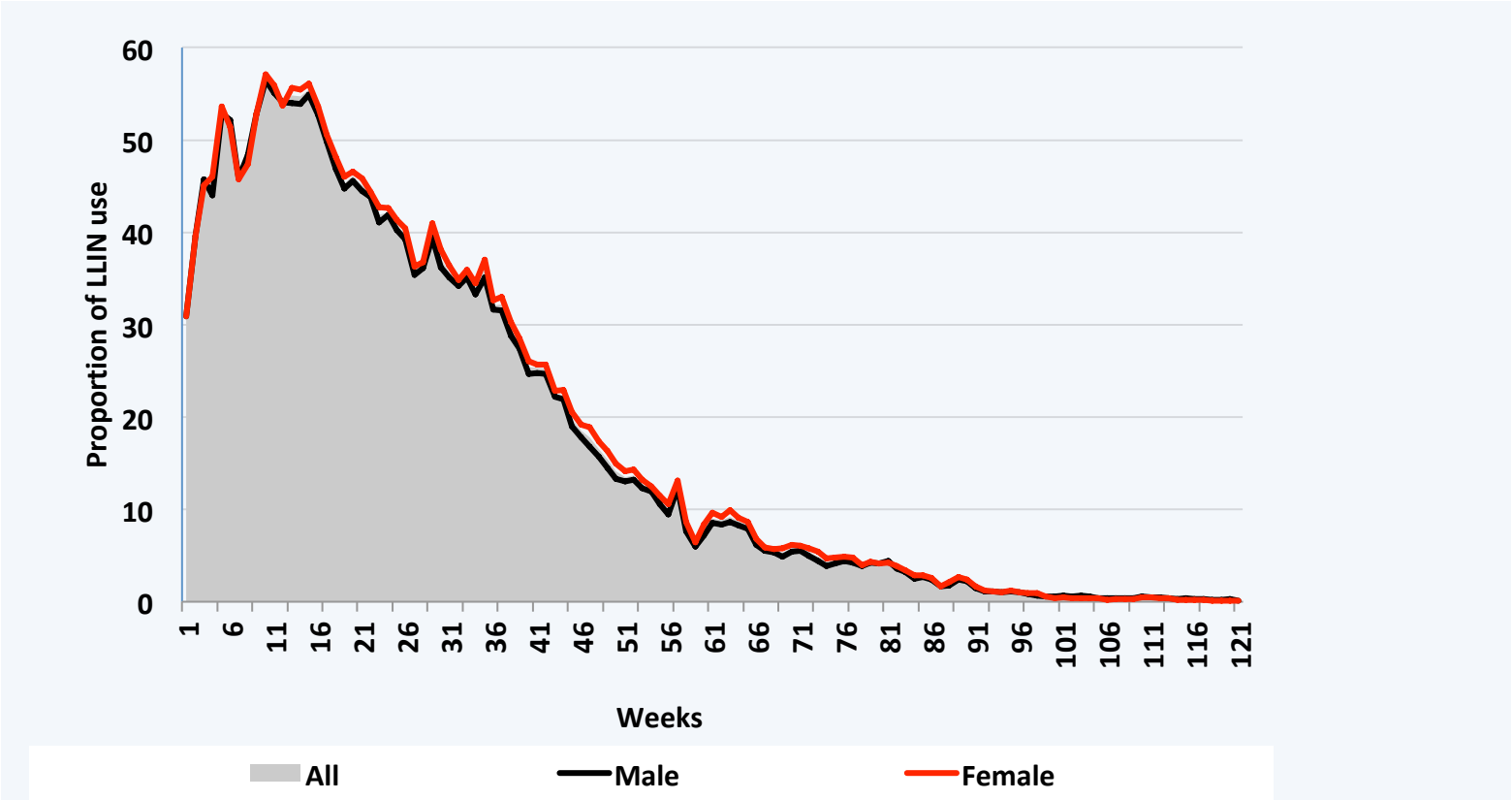
- Less mosquitoes in three interventions arms compared to the control arm
- More reduction in the IRS than LLIN arm
- No impact of adding LLIN to IRS

Impact on human biting rate

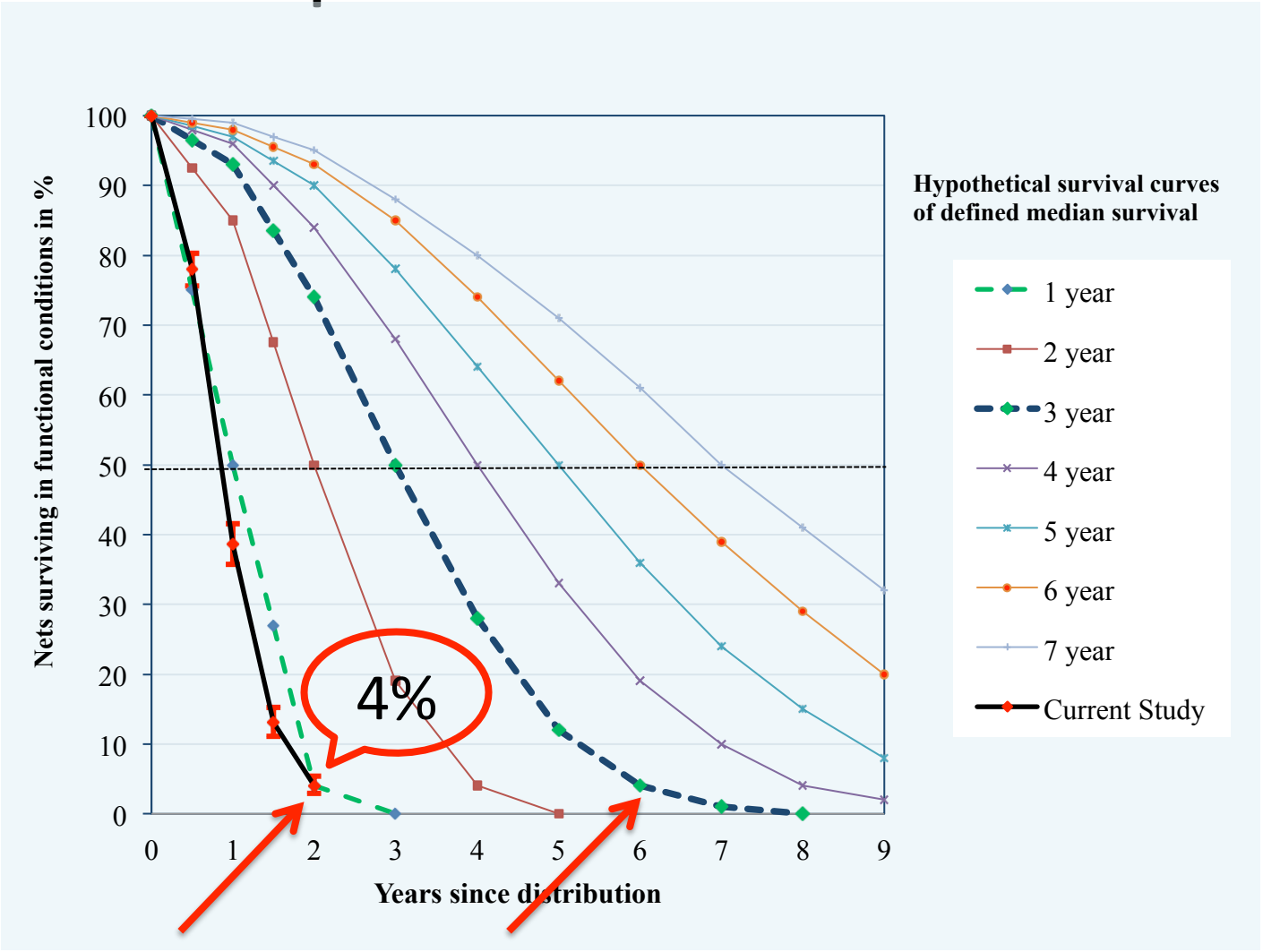


Intervention challenge: LLIN use

- Lower LLIN use than expected



Intervention challenge: Functional survivorship of LLIN



Intervention challenge: Unintended use

Unintended uses of LLIN

- Productive activities
- Household bedding support needs
- Clothing and related services
- Outdoor services
- Income support
- As insect repellents and protection from bugs, flees, spiders and other crawlers

Unexpected event: severe drought

- Decreased rainfall mainly in 2015
  - Low incidence of malaria (about 37% of what we had expected)
  - The prevalence of malnutrition: Stunting increased from 45% to 52% during the trial period
- Prevalence of anemia (baseline 28%) increased in 2015 (36%) but decreased at the end of 2016 (29%) [no difference among the arms]

Kenea et al. Parasites & Vectors (2016) 9:527
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Parasites & Vectors

RESEARCH Open Access

Human-biting activities of *Anopheles* species in south-central Ethiopia

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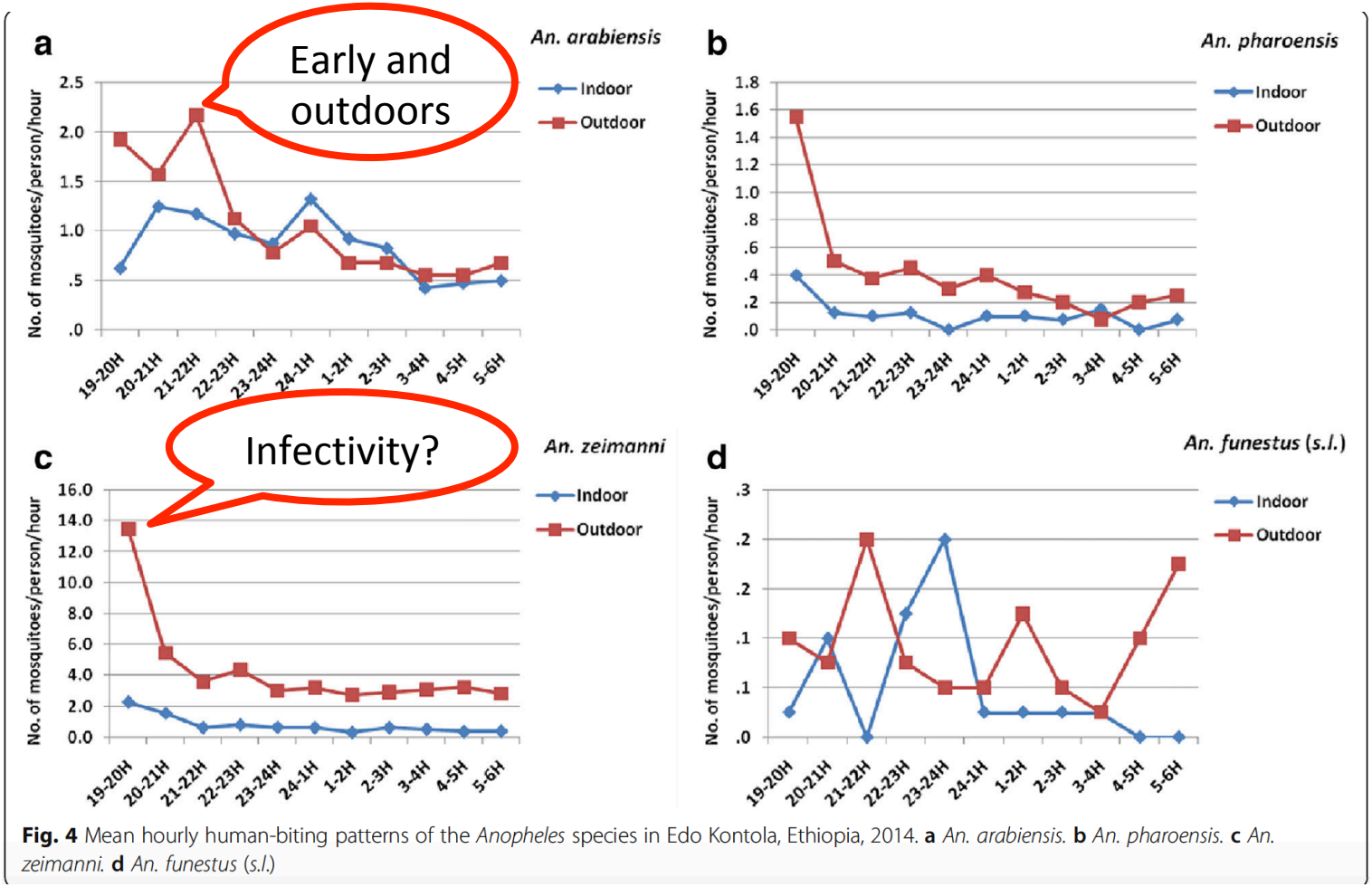

Fig. 4 Mean hourly human-biting patterns of the *Anopheles* species in Edo Kontola, Ethiopia, 2014. **a** *An. arabiensis*. **b** *An. pharoensis*. **c** *An. zeimanni*. **d** *An. funestus* (*s.l.*)

All tested mosquitoes were negative for Sporozoites

Data quality?

- Randomization: all clusters for both epidemiological and entomological studies
  - Arms were fairly similar at baseline (except for main material of the roof)
- Weekly visits to each household for 121 weeks
- Missing cases?
  - Accessible diagnostic (RDT, microscopy) and treatment facilities
  - Active and passive search for cases
  - A prevalence study: randomly selected 5500 individuals [1100 households] (≈0.5%)
- Coverage and usage of interventions followed
- Bio-efficacy of LLIN
- Efficacy of Propoxur

Conclusion

- No added effect of combining IRS + LLIN
- No societal protection of the interventions
- Residual transmission?

- Does the LLIN or IRS strategy work for low incidence settings?
  - What additional interventions are needed to eliminate malaria (zero transmission)?

Acknowledgements

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