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

Eskindir Loha¹, Wakgari Deressa², Taye Gari¹, Meshesha Balkew², Oljira Kenea², Tarekegn Solomon¹, Alemayehu Hailu², Bjarne Robberstad³, Meselech Assegid², Hans J. Overgaard⁴, Bernt Lindtjørn³

¹Hawassa University, Hawassa, Ethiopia, ²Addis Ababa University, Addis Ababa, Ethiopia, ³University of Bergen, Bergen, Norway, ⁴Norwegian University of Life Sciences, Aas, Norway
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*
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

Taye Gari¹, ⁴*, Oljira Kenea³, Eskindir Loha¹, Wakgari Deressa², Alemayehu Hailu², ⁴, Meshaesha Balkew³, Teshome Gebre-Michael³, Bjarne Robberstad⁴, Hans J. Overgaard⁵, ⁶, ⁷ and Bernt Lindtjørn⁴

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

Wakgari Deressa¹*, Eskindir Loha², Meshesha Balkew³, Alemayehu Hailu¹,⁷, Taye Gari²,⁷, Oljira Kenea³, Hans J. Overgaard⁴,⁵,⁶, Teshome Gebremichael³, Bjarne Robberstad⁷ and Bernt Lindtjørn⁷

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

<table>
<thead>
<tr>
<th></th>
<th>IRS +LLIN</th>
<th>LLIN</th>
<th>IRS</th>
<th>Routine</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of clusters</strong></td>
<td>44</td>
<td>44</td>
<td>44</td>
<td>44</td>
<td>176</td>
</tr>
<tr>
<td><strong>Households</strong></td>
<td>1,618</td>
<td>1,388</td>
<td>1,527</td>
<td>1,538</td>
<td>6,071</td>
</tr>
<tr>
<td><strong>Population</strong></td>
<td>9,104</td>
<td>8,038</td>
<td>8,567</td>
<td>8,839</td>
<td>34,548</td>
</tr>
<tr>
<td><strong>Population/cluster</strong></td>
<td>207</td>
<td>183</td>
<td>195</td>
<td>201</td>
<td>196</td>
</tr>
</tbody>
</table>
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

### Assessment for eligibility (n=207 clusters)

### Randomized (n=176 clusters, 6,071 households, 31,275 people)

<table>
<thead>
<tr>
<th>Allocation</th>
<th>IRS + LLIN</th>
<th>IRS</th>
<th>LLIN</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Allocated</strong></td>
<td>Allocated for intervention (N=44 clusters,</td>
<td>Allocated for intervention (N=44</td>
<td>Allocated for intervention (N=44 clusters,</td>
<td>N=44 clusters, 1538 households</td>
</tr>
<tr>
<td></td>
<td>1,618 households)</td>
<td>clusters, 1,527 households)</td>
<td>clusters, 1,388 households)</td>
<td></td>
</tr>
<tr>
<td><strong>Received</strong></td>
<td>Received allocated intervention: First IRS</td>
<td>Received allocated intervention: First</td>
<td>Received allocated intervention: First</td>
<td></td>
</tr>
<tr>
<td></td>
<td>round (N=1,551 households), Second IRS</td>
<td>round (N=1,474 households), Second</td>
<td>round (N=1,392 households), Second round</td>
<td></td>
</tr>
<tr>
<td></td>
<td>round (N=1,519 households), Third IRS</td>
<td>round (N=1,427 households)</td>
<td>round (N=1,388 households)</td>
<td></td>
</tr>
<tr>
<td><strong>Did not</strong></td>
<td>Did not receive allocated intervention: First</td>
<td>Did not receive allocated intervention:</td>
<td>Did not receive allocated intervention:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IRS round (N=67 households), Second round</td>
<td>IRS round (N=53 households), Second</td>
<td>IRS round (N=100 household), All rounds</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(N=99 households), Third IRS round</td>
<td>round (N=135 households), Third IRS</td>
<td>(N=7 households)</td>
<td></td>
</tr>
<tr>
<td><strong>Lost to follow up</strong></td>
<td>Lost to follow up (N=143 household, 682</td>
<td>Lost to follow up (N=194 households,</td>
<td>Lost to follow up (N=121 household,</td>
<td>Lost to follow up (N=163 household,</td>
</tr>
<tr>
<td></td>
<td>people)</td>
<td>822 people)</td>
<td>658 people)</td>
<td>824 people)</td>
</tr>
<tr>
<td><strong>Discontinued</strong></td>
<td>Discontinued intervention (N=234 household)</td>
<td>Discontinued intervention (N=263</td>
<td>Discontinued intervention: Only 8.4%</td>
<td></td>
</tr>
<tr>
<td><strong>Newly joined</strong></td>
<td>897 people</td>
<td>household)</td>
<td>had at least one net at 2 years</td>
<td></td>
</tr>
<tr>
<td><strong>Analysed</strong></td>
<td>Analysed (N=1612 household, 9068 individuals)</td>
<td>Analysed (N=1,520 household, 8,521</td>
<td>Analysed (N=1,388 household, 8,038</td>
<td>Analysed (N=1,538 household, 8,839</td>
</tr>
<tr>
<td></td>
<td></td>
<td>people)</td>
<td>people)</td>
<td>people)</td>
</tr>
<tr>
<td><strong>Excluded from</strong></td>
<td>Excluded from analysis (N=6 household, 36</td>
<td>Excluded from analysis (N=7 household,</td>
<td>Excluded from analysis (N=0)</td>
<td>Excluded from analysis (N=0)</td>
</tr>
<tr>
<td></td>
<td>individuals)</td>
<td>46 people)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

**Notes:**

- The study was designed to assess the effectiveness of IRS + LLIN compared to IRS alone and LLIN alone, with a control group receiving no intervention.
- The study included 207 clusters initially, of which 176 were randomized.
- The sample included 6,071 households and 31,275 people.
- The analysis was performed on 1,612 households and 9,068 individuals for the IRS + LLIN group, 1,520 households and 8,521 people for the IRS group, 1,388 households and 8,038 people for the LLIN group, and 1,538 households and 8,839 people for the control group.
- The study accounted for losses to follow-up, discontinuation of the intervention, and newly joined households in the analysis.

---
Result

- 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)

<table>
<thead>
<tr>
<th>Arm</th>
<th>Incidence (95% CI) per 10,000 person-weeks of observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>IRS+LLIN</td>
<td>2.99 (2.67-3.35)</td>
</tr>
<tr>
<td>LLIN</td>
<td>2.92 (2.58-3.3)</td>
</tr>
<tr>
<td>IRS</td>
<td>3.01 (2.68-3.39)</td>
</tr>
<tr>
<td>Routine</td>
<td>2.72 (2.41-3.08)</td>
</tr>
<tr>
<td>Overall</td>
<td>2.91 (2.74-3.09)</td>
</tr>
</tbody>
</table>
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

![Bar chart showing impact on human biting rate across different conditions. The chart compares mean bites per person per night for control, IRS, LLINs, and IRS + LLINs both indoors and outdoors.]
Intervention challenge: LLIN use

- Lower LLIN use than expected
Intervention challenge: Functional survivorship of LLIN

Hypothetical survival curves of defined median survival

- 1 year
- 2 year
- 3 year
- 4 year
- 5 year
- 6 year
- 7 year
- 8 year
- 9 year

Nets surviving in functional conditions in %

Years since distribution

4%
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]
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

The Research Council of Norway