Does Indoor Residual Spraying Provide Added Protection to That Provided By Insecticide Treated Nets in Preventing Malaria?

Results of an Incidence Cohort

Mary J. Hamel, M.D.
John Gimnig, PhD
KEMRI/CDC Research and Public Health Collaboration
In August 2008 the Kenya Division of Malaria Control (DOMC) conducted an IRS campaign - Area of perennial malaria transmission in western Kenya - Using longer lasting insecticide - Lambda-cyhalothrin capsule suspension (*Icon CS™*)  
  • Reportedly effective 3-6 months (WHOPES)

Second annual campaign conducted in April 2009 - Alphacypermethrin (*Fendona™*)  
  • Reportedly effective 4-6 months (WHOPES)

DOMC targeted every home in the selected district for IRS
Objectives

• Following the DOMC’s IRS campaign, to measure, through a prospective cohort study
  – the effectiveness of IRS plus ITNs compared to ITNs alone in reducing malaria incidence in an area of perennial malaria transmission
    • One district where DOMC recently applied IRS for the first time (Rachuonyo)
    • Adjacent district with similar malaria transmission levels where DOMC did not apply IRS (Nyando)
Rachuonyo (IRS) and Nyando (no-IRS) Districts, Nyanza Province, western Kenya

Data from community-based survey conducted in April 2009, prior to IRS campaign
Methods

• Incidence cohort from Nov 2008 – Nov 2009

• Randomly selected approximately 80 compounds within 1 km of 6 selected health facilities (~480 compounds total)
  – 3 health facilities in IRS district, 3 in non-IRS district
  – All compound members within selected compounds eligible if:
    • Over 6 months of age
    • Not pregnant

• ITN provided for every sleeping space in included compounds
  • Rachuonyo = “ITN+IRS” cohort
  • Nyando = “ITN, no-IRS” cohort
Enrollment

• Consented/assented participants
  – Interviewed
  – Urine pregnancy test for women of child bearing age
  – Blood sample for blood smear
  – Treated with artemether-lumefantrine (AL) to clear patent/sub-patent parasitemia
  – Provided ITN for every sleeping space
Follow-up

• Participants followed for 9 months or until first malaria parasitemia

• Monthly home visits
  – Questionnaire
  – Blood smear

• Any sick visit with history of fever or suspected malaria:
  – Rapid diagnostic test (RDT) for malaria for treatment
  – Blood smear for end point analysis
  – RDT or blood smear positive treated
Statistical Analysis

- Calculating malaria parasitemia incidence rates
  - Expected duration of minimum inhibitory concentration (MIC) for AL=10.5 days
  - Not “at risk” for new malaria infection 10.5 days after AL presumptive treatment at enrollment
  - Began measuring incidence rates 10.5 days after enrollment
  - Decreased time “at risk” by 10.5 days if AL given when BS negative

- Poisson regression model

- GEE to account for correlation within compound
  - In adjusted analysis, controlled for
    - housing type, baseline parasitemia
    - seasonality, ITN use as time varying variables

## Program and Study Timeline

<table>
<thead>
<tr>
<th></th>
<th>Jul 08</th>
<th>Au</th>
<th>Se</th>
<th>Oc</th>
<th>No</th>
<th>De</th>
<th>Ja 09</th>
<th>Fe</th>
<th>Ma</th>
<th>Ap</th>
<th>Ma</th>
<th>Ju</th>
<th>Jul</th>
<th>Au</th>
<th>Se</th>
<th>Oc</th>
</tr>
</thead>
<tbody>
<tr>
<td>IRS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enroll AL/ITNs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follow-up</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High Transmission Season</td>
<td><strong>Red</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Key:
- **Red**: High Transmission Season
- **Blue**: IRS
- **Green**: Enroll AL/ITNs
- **Purple**: Follow-up

Months:
- Jul 08
- Au
- Se
- Oc
- No
- De
- Ja 09
- Fe
- Ma
- Ap
- Ma
- Ju
- Jul
- Au
- Se
- Oc
### Cohort Baseline Characteristics, By District, November 2008

<table>
<thead>
<tr>
<th></th>
<th>ITN+IRS n=921</th>
<th>ITN, no-IRS n=886</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median age (range)</strong></td>
<td>12 (0.5-105)</td>
<td>12 (0.6-91)</td>
</tr>
<tr>
<td><strong>Household head completed 1° education</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>21%</td>
<td>32%*</td>
</tr>
<tr>
<td><strong>Housing: Traditional</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>10%</td>
<td>3%</td>
</tr>
<tr>
<td><strong>Semi-permanent</strong></td>
<td>64%</td>
<td>84%*</td>
</tr>
<tr>
<td><strong>Permanent</strong></td>
<td>26%</td>
<td>12%*</td>
</tr>
<tr>
<td><strong>Open Eaves</strong></td>
<td>90%</td>
<td>94%</td>
</tr>
<tr>
<td><strong>IRS in prior year</strong></td>
<td>74%</td>
<td>6%*</td>
</tr>
<tr>
<td><strong>Slept under ITN prior night</strong></td>
<td>28%</td>
<td>21%*</td>
</tr>
<tr>
<td><strong>Fever prior 2 weeks</strong></td>
<td>49%</td>
<td>33%*</td>
</tr>
</tbody>
</table>

* $p<0.05$. No significant difference in gender, repellent use, ITN use by age groups, fever prior 2 weeks in children <5, antimalarial or ACT use prior 2 weeks
## Cohort Baseline Blood Smear Results, By District, November 2008

<table>
<thead>
<tr>
<th></th>
<th>ITN+IRS n=921</th>
<th>ITN, no-IRS n=886</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>P. falciparum prevalence</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 mths - 4yr</td>
<td>8%</td>
<td>6%</td>
</tr>
<tr>
<td>5-14 yr</td>
<td>12%</td>
<td>9%</td>
</tr>
<tr>
<td>&gt;=15 yr</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td><strong>Geometric mean parasite density</strong></td>
<td>1008/uL</td>
<td>800/uL</td>
</tr>
</tbody>
</table>

*No significant difference in these parameters*
## Follow-up

<table>
<thead>
<tr>
<th></th>
<th>ITN+IRS</th>
<th>ITN, no-IRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Completed 9 month follow-up</td>
<td>792 (87%)</td>
<td>753 (86%)</td>
</tr>
<tr>
<td></td>
<td>7 died, 1 migration, 10 refusal</td>
<td>3 died, 15 refusal</td>
</tr>
<tr>
<td>Parasite period prevalence</td>
<td>13%</td>
<td>29%*</td>
</tr>
<tr>
<td>Geometric mean parasite density (parasites/uL)</td>
<td>1770</td>
<td>4292*</td>
</tr>
<tr>
<td>ITN use at 9 month visit</td>
<td>72%</td>
<td>98%*</td>
</tr>
</tbody>
</table>

*P<0.05
Unadjusted and Adjusted Malaria Parasitemia Incidence, ITN+IRS vs. ITN, no-IRS, by Age Group

<table>
<thead>
<tr>
<th>Age Group</th>
<th>ITN+IRS</th>
<th>ITN, no-IRS</th>
<th>Rate ratio (95% CI)</th>
<th>Adjusted Rate ratio* (95% CI)</th>
<th>Adjusted PE* % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>114</td>
<td>627</td>
<td>Events 570</td>
<td>0.41 (0.31,0.56)</td>
<td>61 (0.47,0.71)</td>
</tr>
<tr>
<td>6 mth – 4 yr</td>
<td>21</td>
<td>146</td>
<td>Events 133</td>
<td>0.34 (0.20,0.56)</td>
<td>70 (0.47,0.82)</td>
</tr>
<tr>
<td>5-14 yr</td>
<td>70</td>
<td>220</td>
<td>Events 186</td>
<td>0.43 (0.30,0.62)</td>
<td>59 (0.40,0.72)</td>
</tr>
<tr>
<td>≥15 yr</td>
<td>23</td>
<td>261</td>
<td>Events 251</td>
<td>0.39 (0.23,0.65)</td>
<td>57 (0.27,0.75)</td>
</tr>
</tbody>
</table>

*Adjusted for baseline parasitemia, housing type, and seasonality and ITN use as time varying variables. Interaction between district and ITN use.
Time to First Malaria Parasitemia, ITN+IRS vs. IRS, no-ITN cohorts, Nyanza Province, western Kenya

All Ages

6 Months to Four Years of Age

5 Years to 14 Years of Age

15 Years of Age and Older
Wall Bioassays to Measure Anopheline Mosquito Mortality following IRS in Rachuonyo District (ITN+IRS), Kenya
Number of *Anopheles* per House Before and After IRS, Rachuonyo (ITN+IRS) and Nyando Districts (ITN, no-IRS), Kenya

**IRS 1**

**IRS 2**

- **Nyando**
- **Rachuonyo**

*Chart shows the number of Anopheles per house before and after IRS in two different districts, Nyando and Rachuonyo, with data spanning from April 2008 to September 2009.*
Limitations

• Not blinded or randomized trial

• No IRS-only arm

• Differences in two districts at baseline
  – Tried to control for these

• Relatively short follow-up period
  – Insecticide resistance may develop with time
Summary

• In this non-randomized study, the combination of IRS and ITNs reduced malaria incidence in area of perennial transmission
  – Combination provided a greater benefit than ITNs alone
    • Reduction in malaria incidence by 61% overall – all in household are protected
    • Reduction in parasite density
  – Beneficial effect despite only 74% of households in the IRS+ITN cohort receiving IRS
    • PMI aims for 85% IRS coverage
• Reduction in ITN use observed in IRS+ITN cohort
  – Need to reinforce importance of ITN use
Discussion

• It may be that this area of East Africa is particularly suited to benefit from combination
  – Two primary vectors are *A. gambiae ss* and *A. Arabienses*
  – Anthrophilic mosquito population driven down by ITNs
  – Zoophilic population became primary vector with high ITN coverage, but may be driven down by IRS due to indoor resting behavior
  – If true, is assumption that we can reduce mosquito populations with IRS, then increase ITN coverage to maintain control valid?
Acknowledgments

- Peter Otieno
- Dr. Nabie Bayoh
- Dr. Kayla Laserson
- Dr. Larry Slutsker
- Dr. Simon Kariuki
- Vincent Were
- Dr. John Williamson
- Dr. John Vulule, KEMRI-CGHR Director

MTC Staff

DHMTs

Participants

Funders

- Malaria Transmission Consortium (MTC) supported by BMGF

The findings and conclusions in this presentation have not been formally disseminated by the Centers for Disease Control and Prevention and should not be construed to represent any agency determination or policy.
Time to First Malaria Parasitemia, 6 Months to 4 Years of Age

$p < 0.001$