Defining strategies for controlling malaria transmission in areas of pyrethroid resistance using mixture LLIN and IRS

Mark Rowland
LSHTM
Presentation

• Recap CRT trial in Muleba of LLIN + bendiocarb vs LLIN alone
• Rationale and progress of current CRT in Muleba of Mixture LLIN +IRS
• Strategy for future deployment
Study area

- **Muleba, NW Tanzania**
- **Malaria transmission**
  - Epidemic prone
  - Two malaria seasons per year
- **Vectors**
  - 81% *An.gambiae*
  - 19% *An.arabiensis*
  - Pyrethroid resistance in *An.gambiae*
- **Control history**
  - 7 annual rounds of lambdacyhalothrin IRS before 2012 CRT
Trial design – supported by PMI

- Two arm community randomised trial with 25 clusters per arm

<table>
<thead>
<tr>
<th></th>
<th>Year 1: Baseline</th>
<th>Year 2: Intervention</th>
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<tbody>
<tr>
<td>Arm A</td>
<td>Pyrethroid IRS + LLINs</td>
<td>Bendiocarb IRS + LLINs</td>
</tr>
<tr>
<td>Arm B</td>
<td>Pyrethroid IRS + LLINs</td>
<td>LLINs</td>
</tr>
</tbody>
</table>

- Baseline year malaria prevalence in children: 9% and 23%
  Universal coverage of LLIN

**Objective:** Does IRS with bendiocarb (2 rounds) plus LLINs provide added protection against malaria compared to LLINs alone.

**Outcomes:**
- *P. falciparum* prevalence (PfPR) in children
- Entomological inoculation rate (EIR)

West et al. 2014, Plos Med
Muleba: Intervention coverage

<table>
<thead>
<tr>
<th>Reported LLIN coverage: moderate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Households owning ( \geq 1 ) LLIN</td>
</tr>
<tr>
<td>Households with enough LLINs</td>
</tr>
<tr>
<td>LLIN use</td>
</tr>
</tbody>
</table>

IRS coverage \( \approx 90\% \) in both spray rounds
### P. falciparum post-intervention surveys

#### Children 0.5-14 years

<table>
<thead>
<tr>
<th></th>
<th>Infection prevalence (%)</th>
<th>Odds Ratios</th>
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<tbody>
<tr>
<td></td>
<td>ITN</td>
<td>ITN and IRS</td>
</tr>
<tr>
<td><strong>Survey A (Feb)</strong></td>
<td>23.6</td>
<td>13.6</td>
</tr>
<tr>
<td><strong>Survey B (July)</strong></td>
<td>30.5</td>
<td>12.7</td>
</tr>
<tr>
<td><strong>Survey C (Oct)</strong></td>
<td>24.5</td>
<td>13.3</td>
</tr>
<tr>
<td><strong>All three surveys combined</strong></td>
<td>26.1</td>
<td>13.3</td>
</tr>
</tbody>
</table>

Major impact in survey B after transmission peak
Survey C was 6 months after 2\textsuperscript{nd} round of IRS
# Muleba, Tanzania: Results

<table>
<thead>
<tr>
<th></th>
<th>LLIN</th>
<th>IRS+LLIN</th>
<th>Ratio, [95% CI], p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection Prevalence in children, %</td>
<td>26·1</td>
<td>13·3</td>
<td>Odds Ratio=0·43, p=0·043</td>
</tr>
<tr>
<td>Mean A. gambiae s.l /HH (N)</td>
<td>1.7 (1892)</td>
<td>0.4 (1893)</td>
<td>Density Ratio=0.16, p=0.001</td>
</tr>
<tr>
<td>Sporozoite rate, % (N)</td>
<td>2.5 (3059)</td>
<td>1.8 (717)</td>
<td>Odds Ratio=0.73, p=0.607</td>
</tr>
<tr>
<td>EIR/month/hh</td>
<td>1.3</td>
<td>0.2</td>
<td>Rate Ratio=0.17 [0.03-1.08], p&lt;0.059</td>
</tr>
</tbody>
</table>

Conclusion: IRS with bendiocarb gave significant additional protection.

ITN use was protective regardless of whether the village had been sprayed, OR=0.83, 95%CI 0.70-0.98, p=0.03 (data not shown)
Anopheles density baseline & intervention

Bendiocarb IRS
Insecticide resistance trends between baseline and intervention years

% Mortality in *An.gambiae* in WHO tests

- High proportion of pyrethroid resistance, associated with lambda IRS (y1) and permethrin LN (y1 y2)
- Selection of carbamate resistance associated with bendiocarb IRS (y2)

Matowo et al. 2014, MVE
CDC light trap surveillance - molecular entomology

- 80% *An.gambiae* ss, 20% *An.arabiensis*
- 97% homozygous for *kdr*-east in *An.gambiae* s.s.
- *kdr*-east not present in *An.arabiensis*
- Ace-1^R^ not present (OP/carb. resistance)

Protopopoff et al. 2012, Malaria Journal
Characterisation of resistance using CDC bottle assay

<table>
<thead>
<tr>
<th>Strain</th>
<th>Treatment</th>
<th>% Mortality</th>
<th>KDT&lt;sub&gt;50&lt;/sub&gt; min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resistant (Muleba)</td>
<td>Permethrin</td>
<td>18</td>
<td>93</td>
</tr>
<tr>
<td>Resistant (Muleba)</td>
<td>Permethrin + PBO</td>
<td>93</td>
<td>44</td>
</tr>
<tr>
<td>Susceptible (Kisumu)</td>
<td>Permethrin</td>
<td>100</td>
<td>12</td>
</tr>
</tbody>
</table>

Indicates presence of MFO mechanisms in addition to kdr
Conclusions of first trial

• A high frequency of high level pyrethroid resistance is evolving
• The Muleba trial demonstrated that adding a non-pyrethroid IRS (bendiocarb) to LLINs provides additional protection against malaria
• A number of other trials have shown no added protection of IRS to ITN (e.g. Benin)
• Whether the combination is effective may depend on the insecticide used, level of ITN use, vector species, resistance (i.e. local definition)
• Need strategy for deploying non-pyrethroid IRS and combination LLINs against pyrethroid resistant populations
Defining future strategy : the new Muleba trial

- Evaluation of novel LN and IRS products, separately and together, against malaria transmitted by pyrethroid resistant mosquitoes
  - 4 arms factorial design : 12 clusters per arm
  - Olyset Plus LN (pyrethroid and PBO synergist)
  - *Actellic CS (long lasting OP IRS)

<table>
<thead>
<tr>
<th>LLIN Arms</th>
<th>LLIN + IRS Arms</th>
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<tbody>
<tr>
<td>Olyset LN</td>
<td>Olyset LN + IRS with pirimiphos methyl CS*</td>
</tr>
<tr>
<td>Olyset Plus LN</td>
<td>Olyset Plus LN + IRS with pirimiphos methyl CS*</td>
</tr>
</tbody>
</table>

Support: MRC / Wellcome Trust / DFID
‘Olyset Plus’ – synergist PBO

- Cone bioassay tests comparing Olyset with Olyset Plus
- Standard Olyset LN does not kill highly pyrethroid resistant strains
- Olyset Plus kills the resistant
  - An gambiae RSP (kdr),
  - An arabiensis (oxidase)
  - An gambiae Muleba (kdr and oxidase)
1. Actellic CS LLIRS: *Anopheles gambiae* mortality in experimental hut trial over 12 months

![Graph showing mortality percentages for different treatments]

Actellic CS gives prolonged residual control of pyrethroid resistant mosquitoes in Africa

Rowland et al. 2013, Plos ONE
Public health rationale of new Muleba trial

1. Olyset LN: current standard of care
2. Olyset LN + Actellic CS IRS: a strategy for high prevalence & epidemic prone areas
3. Olyset Plus: a future standard of care in areas with highly pyrethroid resistant *An gambiae*??
4. Olyset Plus + Actellic IRS: a future strategy of control in high prevalence areas with highly resistant mosquitoes. Time limited use of IRS

- Each of the 4 arms have a potential niche, collectively they should help define future policy in different transmission zones
New Muleba trial

Cluster mapping and first cross sectional survey completed
## Restricted randomisation

<table>
<thead>
<tr>
<th></th>
<th>Study arm 1</th>
<th>Study Arm 2</th>
<th>Study arm 3</th>
<th>Study arm 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LLIN</td>
<td>LLIN Plus</td>
<td>LLIN + IRS</td>
<td>LLIN Plus + IRS</td>
</tr>
<tr>
<td>Pf infection prevalence</td>
<td>67.0</td>
<td>60.6</td>
<td>64.7</td>
<td>65.0</td>
</tr>
<tr>
<td>ITN use (all residents)</td>
<td>30.4</td>
<td>26.4</td>
<td>27.5</td>
<td>26.6</td>
</tr>
<tr>
<td>% of HH in poorest tertile</td>
<td>29.2</td>
<td>30.7</td>
<td>36.6</td>
<td>38.7</td>
</tr>
</tbody>
</table>

Maximum difference in means between study arms:
- Pf infection prevalence: 7%
- ITN use (all residents): 10%
- % of HH in poorest tertile: 10%
Acknowledgements

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