Impact of the spatial repellents, metofluthrin on malaria incidence rates at two villages in Sumba, Indonesia by cluster-randomized, double-blind placebo-controlled trial

Clinical trial: ACTRN12611001050943

Din Syafruddin et al
Spatial Repellent (SR)

Spatial Repellent is one of the potential tools to explore.

Different from IRS/LLIN, SR does not require a tarsal contact of the vector to chemically-treated surface/space.

The core mechanism of action of an SR is inhibition of vector entry into a treated space by a chemical vapor.
Aim

To demonstrate that the spatial repellent (SR) could reduce the malaria attack rates in human population and to prove that the reduction associated with entomological correlates (proof-of-concept)
Trial end points

Primary: Protective efficacy of SR intervention on malaria incidence

Secondary: Anopheline mosquitoes attack rates in the house

Time frame: 31 Oct 2011 – 26 April 2012 (26 weeks)
Study site

Syafruddin et al., Malaria J, 8:8 2009

Sumba

SPR (%)
- 0
- < 5
- 5 - 10
- > 10

Samudera Indonesia

Sumba Timur

Sumbawa

Bima

Kupang

Kabupaten

Kabupaten

Sawu

Kabupaten

Kabupaten
Village Snapshot

Spirit Sumba
Study design (1)

- A randomized, double-blind, placebo-controlled trial
- 4 study clusters in 2 villages
- A total of 400 households were enrolled for mosquito coil placement- total population per cluster, ca 500 people
Study design (2)

- A cluster-block randomized sample of 45 men in each cluster (totally 180 men) were enrolled for malaria radical cure
- Subjects completed a supervised malaria radical cure (regardless of blood film status at enrolment) consisting of DHA/PP+PQ prior to the coil intervention
- Weekly monitoring of malaria infection during intervention

Inclusion Criteria:
Male >17 years of age, weight ≥40 kg, G6PD normal. No severe anaemia, No chronic illness, Sleeps in village >90% of nights during any given month. No plans for extended travel during study, Willingness to sign informed consent

Exclusion Criteria:
Men <17 years of age or female, Weight <40 kg, G6PD deficient and Haemoglobin of <8 mg/dL
Study design (3)

- Five sentinel houses selected per cluster and randomized as either 2 ‘active’, 2 ‘blank’ and 1 ‘no coil’

- Two identical appearing coils, either 4 active (metofluthrin 0.00975% AI) or 4 blank (inert ingredients only) placed inside each house, using a 90:10 distribution ratio of each treatment within a single study cluster (W1, W2, U1 and U2) each night beginning at 1800hr.

- Weekly monitoring of sentinel houses in each sub-cluster (5 houses each) by Human Landing Collection (HLC).
Study design (4)

- **Entomological Measures**
  - Indoor/outdoor HLC (biting densities)
  - Vector identification/incrimination (sporozoite infection)
  - Parity (age structure)
  - Resting collections (host preference)
  - Blood meal analysis
  - Larval habitat monitoring (population structure)
  - Climate (rainfall, temperature, RH, wind speed)
Study Implementation

- **HLC Methodology**
  - Two collectors per house
  - 1 positioned Indoor & 1 outdoor (~1m from house)
  - Collections for 50 min/hr, 1800-0600.
  - Rotate positions (in/out) each hour.
  - *Anopheles* morphologically ID; proportion parity dissections and sporozoite detection (ELISA/PCR)
RESULTS
Malaria status of men lives in active and blank coil clusters along the 6 month coil intervention

<table>
<thead>
<tr>
<th>Village</th>
<th>Cluster (Coil status*)</th>
<th>Develop malaria</th>
<th>Person Week (6 month)</th>
<th>Incidence rates</th>
<th>p value **</th>
<th>Rate Difference</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wainyapu</td>
<td>ACTIVE (W1)</td>
<td>21</td>
<td>594</td>
<td>0.0353</td>
<td>0.011</td>
<td>3.283</td>
<td>0.78 – 5.78</td>
</tr>
<tr>
<td></td>
<td>BLANK (W2)</td>
<td>45</td>
<td>660</td>
<td>0.0681</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Umbungedo</td>
<td>ACTIVE (U2)</td>
<td>6</td>
<td>794</td>
<td>0.0062</td>
<td>0.006</td>
<td>15.600</td>
<td>4.73 – 26.47</td>
</tr>
<tr>
<td></td>
<td>BLANK (U1)</td>
<td>20</td>
<td>959</td>
<td>0.0218</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>ACTIVE</td>
<td>27</td>
<td>1454</td>
<td>0.904</td>
<td>0.00001</td>
<td>2.732</td>
<td>1.463-4.001</td>
</tr>
<tr>
<td></td>
<td>BLANK</td>
<td>65</td>
<td>1553</td>
<td>2.324</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*) Unblinded after 6 month period

**) p value for comparing 2 person-time rates
**A**

CUMULATIVE INCIDENCE IN WAINYAPU
Active 90 - Placebo 90

**B**

CUMULATIVE INCIDENCE IN WAINYAPU
Active 10 - Placebo 10

**C**

CUMULATIVE INCIDENCE IN UMBUNGEDO
Active 90 - Placebo 90

**D**

CUMULATIVE INCIDENCE IN UMBUNGEDO
Active 10 - Placebo 10
### Sub-Cluster Effect Analysis

**Protection Independent of Neighbors**

<table>
<thead>
<tr>
<th></th>
<th>Active</th>
<th>Placebo</th>
<th>Odds Ratio</th>
<th>95% CI (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malaria</td>
<td>2</td>
<td>6</td>
<td>1.69</td>
<td>0.73 – 3.9</td>
</tr>
<tr>
<td>No Malaria</td>
<td>6</td>
<td>4</td>
<td>1.69</td>
<td>0.73 – 3.9</td>
</tr>
</tbody>
</table>

Insufficient statistical power to draw definitive conclusions regarding village level effects.
Protective efficacy on malaria Incidence

- Inactive coils
  - 59 infections among 1,296 person-weeks at risk
  - 2.367 infections/person-year

- Active coils
  - 25 infections in 1,381 person-weeks at risk
  - 0.9413 infections/person-year

\[
\frac{(2.324 - 0.904)/2.324} \times 100 = 61.1\% \text{ protective efficacy} \\
(95\%\text{CI} = 37\%-75\%)
\]
Entomological correlates
Overview: Entomological Findings

- Active breeding sites in Wainyapu cluster more consistent and productive with adult densities
- Larval collection: 11.8% of all females identified as *An. sundaicus* (note one temporary site [W2C] responsible for ~48% of entire collection)
- Distinct differences in anopheline densities between clusters
- Total HLC (26 wks)
  - \( W1+W2 = 1,603 \) \((3.1 \text{ An. sundaicus/person/night})\)
  - \( U1+U2 = 74 \) \((0.14 \text{ An. sundaicus/person/night})\)
Target species: *Anopheles sundaicus*

- HLC: $U1+U2 = 82.2\%$; $W1+W2 = 86\%$ of all anophelines
- Mean Indoor : Outdoor Ratio
  - $W1$ 1 : 1.8
  - $W2$ 1 : 1.85
  - $U1+U2$ 1 : 1.96
- Parity: predominantly parous
- Resting collections: 73\% of all anophelines captured were *An. sundaicus*.
- Sporozoite infection: Only *An. sundaicus* in clusters W1 and W2, all *P. falciparum* [15+/2,030]
- *An. sundaicus* is primary vector based on sporozoite infections and HLC data. *An. subpictus* s.l. regarded as secondary.
## EIR Calculation

\[
\text{EIR} = \left( \frac{\text{Positive ELISA Indoor}}{\# \text{ An. sondaicus Indoor}} \right) \times \left( \frac{\# \text{ An. sondaicus Indoor Person-Nights Indoors}}{\text{Placebo}} \right)
\]

### Table: Days to 1st Infective Bite

<table>
<thead>
<tr>
<th>Treat</th>
<th># Night</th>
<th># House Collector (In+Out)</th>
<th>Person-Night</th>
<th># An. sondaicus</th>
<th>Positive ELISA</th>
<th>EIR</th>
<th>Days to 1st Infective Bite</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>26</td>
<td>8 (8+8)</td>
<td>208 OUT 208</td>
<td>416 IN 247 OUT 452 TOTAL 699</td>
<td>2 IN 1 OUT 3 TOTAL</td>
<td>0.0156 IN 0.0078 OUT 0.0122 TOTAL</td>
<td>82</td>
</tr>
<tr>
<td>AI</td>
<td>26</td>
<td>8 (8+8)</td>
<td>208 OUT 208</td>
<td>416 IN 164 OUT 359 TOTAL 523</td>
<td>0 IN 2 OUT 2 TOTAL</td>
<td>0.0000 IN 0.0156 OUT 0.0122 TOTAL</td>
<td>82</td>
</tr>
<tr>
<td>No Coil</td>
<td>26</td>
<td>4 8</td>
<td>104 OUT 104</td>
<td>208 IN 324 OUT 484 TOTAL 808</td>
<td>5 IN 5 OUT 10 TOTAL</td>
<td>0.0296 IN 0.0296 OUT 0.0296 TOTAL</td>
<td>34</td>
</tr>
<tr>
<td></td>
<td>13 (W3)</td>
<td>5 10</td>
<td>65 OUT 65</td>
<td>130 IN 324 OUT 484 TOTAL 808</td>
<td>5 IN 5 OUT 10 TOTAL</td>
<td>0.0296 IN 0.0296 OUT 0.0296 TOTAL</td>
<td>34</td>
</tr>
</tbody>
</table>

### Indoor – Baseline

<table>
<thead>
<tr>
<th></th>
<th>EIR</th>
<th>Days to 1st Infective Bite</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>0.0110</td>
<td>91</td>
</tr>
<tr>
<td>AI</td>
<td>0.0105</td>
<td>95</td>
</tr>
<tr>
<td>No Coil</td>
<td>0.0122</td>
<td>82</td>
</tr>
</tbody>
</table>

### Indoor – Post Intervention

<table>
<thead>
<tr>
<th></th>
<th>EIR</th>
<th>Days to 1st Infective Bite</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>0.0156</td>
<td>64</td>
</tr>
<tr>
<td>AI</td>
<td>0.0000</td>
<td>INF</td>
</tr>
<tr>
<td>No Coil</td>
<td>0.0296</td>
<td>34</td>
</tr>
</tbody>
</table>
Cumulative attack rates of *An. sundaicus* pooled by village (indoor only)

**Cumulative Attack in Wainyapu (W1+W2) Indoor Only**

- **Week**: 1 to 26
- **Cumulative Density / Person**
  - Indoor - A.I
  - Indoor - Placebo

**Cumulative Attack in Umbungedo (U1+U2) Indoor Only**

- **Week**: 1 to 26
- **Cumulative Density / Person**
  - Indoor - A.I
  - Indoor - Placebo

**Wilcoxon Paired Test**: Statistically different densities between AI vs. Placebo ($p=0.0342$)

**CMLE Rate Ratio**: 32.9% reduction in attack rate for a person inside an active coil house ($p=0.04388$)

**Wilcoxon Paired Test**: No Significant difference in densities between AI vs. Placebo ($p=0.1562$)

**CMLE Rate Ratio**: Not applicable
Conclusions

1. Active coil in the homes of subjects was associated with a significant protective efficacy (60%) against new infections by plasmodial parasites.

2. No evidence of village-level effects, but this requires greater statistical power to ascertain.

3. Mosquito attack rate in the homes with SR was significantly reduced.

4. Reduction in mosquito attack rate might be associated with reduction in malaria attack rates.
Acknowledgement

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5. SOS Indonesia
   Michael Bangs

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