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) 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)
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)
Indoor Proportion of Anopheles Species

- An. sundaicus: 72.50%
- An. tesellatus: 10.53%
- An. vagus: 7.83%
- An. kochi: 1.53%
- An. barbirostris: 0.53%
- An. indefinitus: 0.53%
- An. annularis: 0.53%
- An. subpictus: 0.53%
- An. maculatus: 0.53%
- An. flavirostris: 0.53%
- An. aconitus: 0.53%
RESULTS
Study Flow

Screened n = 231

Excluded n = 51
Reason for ineligibility:
- G6PD Def/Intermediate = 25
- Chronic Disease = 15
- Weight < 40 kg = 2
- Travel Plan = 2
- Sleep Outside for > 10% = 2
- Others (e.g., HLC personnel, live outside cluster) = 5

Enrolled n = 180

Withdrawn by Investigator before radical cure commenced n = 1

Following Radical Cure n = 179

Incomplete Radical Cure n = 9
Withdrawn by Investigator due to:
- Missed doses of radical cure drugs = 7
- HLC Personnel = 1
- Sign of Haemolysis in urine = 1

Completed Radical Cure n = 170

Participant to Follow Up W1 n = 43
Participant to Follow Up W2 n = 43
Participant to Follow Up U1 n = 43
Participant to Follow Up U2 n = 41
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>0.000001</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
CUMULATIVE INCIDENCE IN WAINYAPU
Active 90 - Placebo 90

Week
0,000 0,100 0,200 0,300 0,400 0,500 0,600 0,700 0,800 0,900 1,000
ACTIVE 90 PLACEBO 90

CUMULATIVE INCIDENCE IN WAINYAPU
Active 10 - Placebo 10

Week
0,000 0,100 0,200 0,300 0,400 0,500 0,600 0,700 0,800 0,900 1,000
ACTIVE 10 PLACEBO 10

CUMULATIVE INCIDENCE IN UMBUNGEDO
Active 90 - Placebo 90

Week
0,000 0,100 0,200 0,300 0,400 0,500 0,600 0,700 0,800 0,900 1,000
ACTIVE 90 PLACEBO 90

CUMULATIVE INCIDENCE IN UMBUNGEDO
Active 10 - Placebo 10

Week
0,000 0,100 0,200 0,300 0,400 0,500 0,600 0,700 0,800 0,900 1,000
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></td>
<td>(0.22)</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%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 *An. sundaicus*/person/night)
  - U1+U2 = 74 (0.14 *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**

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

<table>
<thead>
<tr>
<th>Treat</th>
<th># Night</th>
<th># House</th>
<th>Collector (In+Out)</th>
<th>Person-Night</th>
<th># An. sundiacus</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</td>
<td>(8+8)</td>
<td>208, 208, 416</td>
<td>247, 452, 699</td>
<td>2, 1, 3</td>
<td>0.0156, 0.0078</td>
<td>0.0122, 82</td>
</tr>
<tr>
<td>Al</td>
<td>26</td>
<td>8</td>
<td>(8+8)</td>
<td>208, 208, 416</td>
<td>164, 359, 523</td>
<td>0, 2, 2</td>
<td>0.0000, 0.0156</td>
<td>0.0122, 82</td>
</tr>
<tr>
<td>No Coil</td>
<td>26</td>
<td>4</td>
<td>8</td>
<td>104, 104, 208</td>
<td>324, 484, 808</td>
<td>5, 5, 10</td>
<td>0.0296, 0.0296</td>
<td>0.0296, 34</td>
</tr>
<tr>
<td></td>
<td>13 (W3)</td>
<td>5</td>
<td>10</td>
<td>65, 65, 130</td>
<td></td>
<td></td>
<td></td>
<td></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>Al</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>Al</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)**

<table>
<thead>
<tr>
<th>Week</th>
<th>Cumulative Density / Person</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
<td>30</td>
</tr>
<tr>
<td>4</td>
<td>40</td>
</tr>
<tr>
<td>5</td>
<td>50</td>
</tr>
<tr>
<td>6</td>
<td>60</td>
</tr>
<tr>
<td>7</td>
<td>70</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Week</th>
<th>Cumulative Density / Person</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>1.5</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
<td>2.5</td>
</tr>
<tr>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>7</td>
<td>3.5</td>
</tr>
</tbody>
</table>

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

Residents in the study sites:

1. Dr. Kate Aultman (Bill and Melinda Gates Foundation)

2. Drs. Daniel Lawson and Maude Maier (SC Johnson and Son Corp, USA)

3. Officials of the Southwest Sumba District Health Department

4. Parasitology and Entomology teams, field workers, data entry clerks and local volunteers
### Study team

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   - Hasanuddin  
   - Joko Hendarto  
   - Dian Sidik

4. **Sumba Foundation, Indonesia**  
   - Claus Bogh

5. **SOS Indonesia**  
   - Michael Bangs

6. **Department of Preventive Medicine and Biometrics, Uniformed Services University of the Health Sciences, Bethesda, MD USA**  
   - John Grieco  
   - Nicole Achee
Thank you