New Paradigms – spatial and individual repellents: current knowledge and future directions

Dr Sarah J Moore

Work performed in collaboration with Sheila Ogoma, Fredros Okumu, Peter Sangoro, Lena Lorenz, John Grieco, Nigel Hill, Nicole Achee

Roll Back Malaria Vector Control Working Group Meeting
Optimizing Evidence for Vector Control Interventions Work Stream
Tuesday 7th February 2012
Malaria transmission

Control using existing mainstream vector control tools LLINs and IRS

Integrated Vector Management

Evaluation of complementary means of vector control

Development of additional tools to combat residual transmission

Residual Transmission

Time
Early evening feeding behaviour of malaria vectors


Data from papers on mosquito bionomics using human landing catch published within the last five years.
Aren’t bednets enough for malaria control in Africa?

Data from papers on mosquito bionomics measured by human landing catch published within the last five years
A Cryptic Subgroup of *Anopheles gambiae* Is Highly Susceptible to Human Malaria Parasites

Michelle M. Riehle,1,2,4 Wamdaogo M. Guelbeogo,1,4 Awa Gneme,1 Karin Egliemeier,1 Inge Holm,1 Emmanuel Bischoff,1 Thierry Garnier,1 Gregory M. Snyder,2 Xuanzhong Li,4 Kyriacos Markianos,4 N’Fale Sagnon,3 Kenneth D. Vernick2,3†

Population subgroups of the African malaria vector *Anopheles gambiae* have not been comprehensively characterized owing to the lack of unbiased sampling methods. In the arid savanna zone of West Africa, where potential oviposition sites are scarce, widespread collection from larval pools in the peridomestic human habitat yielded a comprehensive genetic survey of local *A. gambiae* population subgroups, independent of adult resting behavior and ecological preference. A previously unknown subgroup of exophilic *A. gambiae* is sympatric with the known endophilic *A. gambiae* in this region. The exophilic subgroup is abundant, lacks differentiation into M and S molecular forms, and is highly susceptible to infection with wild *Plasmodium falciparum*. These findings might have implications for the epidemiology of malaria transmission and control.

Riehle at al Science February 2011
**Figure 2** Household ownership of bed nets, defined as at least one per house, of any bed net type and whether treated or untreated, in Asembo (site of bed net trial in the late 1990s) and Seme (no bed net trial) from 1995 through 2008. Arrows indicate the initiation of subsidized national distribution of bed nets through health clinics to pregnant women and children < 5 years (2004) and a mass campaign during which 3.4 million nets were distributed for free to children < 5 years in all endemic regions of Kenya (2006).

**Figure 7** Proportion of adult female *A. gambiae* s.l. mosquitoes collected west of Kisumu and identified as *A. gambiae* s.s. (top, black bars) or *A. arabiensis* (bottom, green bars). Data from 1970 through 2003 are compiled from published data (see Additional File 1), and data from 2003 onwards are from the current study.

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**Anopheles gambiae:** historical population decline associated with regional distribution of insecticide-treated bed nets in western Nyanza Province, Kenya

M Nabile Bayoh1,2, Derrick K Mathias1,2, Maurice R Odiere1,2, Francis M Mutuku1,2, Luna Kamau3, John E Gimnig4, John M Vulule1, William A Hawley4, Mary J Hamel3,4, Edward D Walker4

Analysis of *Anopheles arabiensis* Blood Feeding Behavior in Southern Zambia during the Two Years after Introduction of Insecticide-Treated Bed Nets

Christen M. Fornadel,* Laura C. Norris, Gregory E. Glass, and Douglas E. Norris

*The W. Harry Feinstone Department of Molecular Microbiology and Immunology, The Johns Hopkins Malaria Research Institute, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland.*

Total *Anopheles arabiensis* mosquitoes caught each hour by human landing catch pairs December-April, Mucha, Zambia.
<table>
<thead>
<tr>
<th>Region</th>
<th>Vector</th>
<th>Vector Behaviour</th>
<th>Trial Type</th>
<th>Intervention / control</th>
<th>Sample Size</th>
<th>outcome</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pakistan</td>
<td>An. culicifacies, An. stepphensi</td>
<td>Early evening/outdoor</td>
<td>RCT</td>
<td>Mosbar vs no intervention</td>
<td>1148 people, over 6 months</td>
<td>56% reduction <strong>SIGNIFICANT</strong> (p=0.004) OR 0.44 (0.25-0.76)</td>
<td>Rowland et al (2004a) TMIH</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>92% reduction in malaria</strong> <strong>SIGNIFICANT</strong> (p&lt;0.001) OR 0.08 (0.01-0.61)</td>
<td>Rowland et al (2004b) TMIH</td>
</tr>
<tr>
<td>Bolivia</td>
<td>An. darlingi</td>
<td>Early evening/outdoor</td>
<td>RCT</td>
<td>PMD vs clove oil in addition to LLIN</td>
<td>4008 individ over 6 months</td>
<td><strong>P. vivax 80% reduction</strong> <strong>SIGNIFICANT</strong> (P&lt;0.001) IRR, 0.20 (0.11-0.38)</td>
<td>Hill et al (2007) BMJ</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>P. falciparum 82% reduction</strong> NOT SIGNIFICANT IRR, 0.18 (0.02 -1.40)</td>
<td></td>
</tr>
<tr>
<td>Peru / Equador</td>
<td></td>
<td></td>
<td>RCT</td>
<td>Mosbar vs no intervention</td>
<td>8272 individ over 1 year</td>
<td><strong>P. falciparum 0% reduction</strong> <strong>P. vivax 26% reduction</strong> NOT SIGNIFICANT</td>
<td>Kroeger et al (1997) AJTMH</td>
</tr>
<tr>
<td>Thailand</td>
<td>An. maculatus, An. minimus (A?)</td>
<td>Early evening/outdoor</td>
<td>RCT</td>
<td>20% DEET and thanaka vs thanaka alone</td>
<td>897 pregnant women</td>
<td><strong>P. falciparum 28% reduction</strong> (incidence 10.6% vs 14.8%) NOT SIGNIFICANT <strong>P. vivax 9% reduction</strong> (incidence 21.1% vs 26.4%) NOT SIGNIFICANT</td>
<td>McGready et al (2001) AJTMH</td>
</tr>
<tr>
<td>Tanzania</td>
<td>An. arabiensis</td>
<td>Early evening/outdoor</td>
<td>RCT</td>
<td>15% DEET vs placebo lotion in addition to LLIN</td>
<td>1950 person years at risk per arm</td>
<td><strong>P. falciparum 13% reduction</strong> Cluster Rate ratio 0.87 (cluster risk 47.37 vs 54.14 per 1000 person years ) NOT SIGNIFICANT</td>
<td>Onyango et al in prep for Int J Epi</td>
</tr>
</tbody>
</table>
Topical repellents consistently fail to be used correctly. How do we improve compliance for long term use?
Target: - long lasting passive spatial repellents to maximise coverage
ARR (Advancing Repellents to Recommendation) team

AIM: To attain formal acceptance and recognition for the use of spatial repellent strategies from global health authorities as a valuable vector control tool for disease transmission intervention, by providing the evidence needed for decision making

**Objective 1.** Document spatial repellency (SR) as an effective mechanism of action for vector control

**Objective 2.** Demonstrate a spatial repellent will impact disease at the community level
Endpoints currently measured by behavioural assays

Feeding inhibition
*Mosquitoes don’t bite indoors or outdoors*

Repellency
*Mosquitoes move away*

Deterrence
*Prevents house entry*

Toxicity
*Mosquitoes die indoors & outdoors*
Phase 1: Document spatial repellency (SR) as an effective mechanism of action for vector control

Objective 1: To measure changes in human-vector contact under assay conditions

Objective 2: To devise effective repellent testing methodologies to measure changes in human-vector contact

1 What is the primary mode of action of currently registered active ingredients against key vector species (insecticide resistant and insecticide susceptible)

2 what is the optimum dose of molecule needed?

3 Over what distance does that protection extend?

4 where should the molecule be placed and in what format to maximise efficacy?

5 safety – is this dose within no observed effect levels for inhalation toxicity?
Lorenz et al submitted

Ogoma et al in preparation

Grieco et al 2007 PLoS ONE

Okumu et al 2012 PLoS ONE
Phase 2: Demonstrate a spatial repellent will impact disease at the community level

• Define specific **end points** for measuring SR in intervention studies

• Develop **standardized protocols** to correlate SR vector behavior endpoints with malaria incidence during intervention

• Demonstrate an individual and community level **reduction in malaria incidence**

• Determine if there is **diversion** of vectors from spatial repellent-treated areas to untreated locations
Hill, N. et al. A household randomised controlled trial of the efficacy of Transfluthrin coils alone and in combination with long-lasting insecticide treated nets on the prevalence of *Plasmodium falciparum* malaria infection in Yunnan Province, China *In preparation for BMJ*
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<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Coils</th>
<th>LLINs</th>
<th>Coils + LLINs</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>P. falciparum</em> Incidence (1000 person years)</td>
<td>6.45</td>
<td>1.46</td>
<td>0.55</td>
<td>0.36</td>
</tr>
<tr>
<td>Odds Ratio of being <em>P. falciparum</em> positive (95% Confidence Interval [CI])</td>
<td>1</td>
<td>0.23 (0.10, 0.49)</td>
<td>0.09 (0.03, 0.28)</td>
<td>0.05 (0.01, 0.23)</td>
</tr>
<tr>
<td>Age-adjusted OR (95% CI)</td>
<td>-</td>
<td>0.23 (0.11, 0.50)</td>
<td>0.09 (0.03, 0.28)</td>
<td>0.06 (0.01, 0.23)</td>
</tr>
<tr>
<td><em>p</em>-value$^+$</td>
<td>-</td>
<td>0.0002</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Protective efficacy (95% CI)</td>
<td>-</td>
<td>77% (50, 89)</td>
<td>91% (72, 97)</td>
<td>94% (77, 99)</td>
</tr>
<tr>
<td><em>P. vivax</em> Incidence (1000 person years)</td>
<td>7.00</td>
<td>1.46</td>
<td>1.66</td>
<td>0.53</td>
</tr>
<tr>
<td>Odds Ratio of being <em>P. vivax</em> positive (95% Confidence Interval [CI])</td>
<td>1</td>
<td>0.20 (0.09, 0.44)</td>
<td>0.21 (0.10, 0.47)</td>
<td>0.07 (0.02, 0.24)</td>
</tr>
<tr>
<td><em>p</em>-value$^+$</td>
<td>-</td>
<td>&lt;0.0001</td>
<td>0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Protective efficacy (95% CI)</td>
<td>-</td>
<td>80% (56, 91)</td>
<td>79% (53, 90)</td>
<td>93% (76, 98)</td>
</tr>
</tbody>
</table>

$^+$P-values for unadjusted and age-adjusted odds ratios were identical.
Next steps

1. WHO guidelines on Spatial Repellent testing methodology currently being drafted
2. Clinical trial of metofluthrin coils underway in Indonesia
3. Target Product Profile of optimal passive product devised
4. Clinical trial of optimal passive products planned against a range of malaria vectors