Non-inferiority of Guardian™ compared to Mosquito Shield™

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Volatile pyrethroid spatial repellents (VPSR) as public health intervention

Efficacy of a Spatial Repellent for Control of Malaria in Indonesia: A Cluster-Randomized Controlled Trial

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STUDY PROTOCOL

Evaluation of the protective efficacy of a spatial repellent to reduce malaria incidence in children in western Kenya compared to placebo: study protocol for a cluster-randomized double-blinded control trial (the AEGIS program)

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Study aim

To assess the non-inferiority of Guardian™, a 12 month-product compared to Mosquito Shield™, a 1-month product using standard WHO phase II experimental hut testing method.
Method

Treatment arms
~ Mosquito Shield™ vs Negative control
~ Guardian™ vs Negative control

Study design
~ 8 huts per arm for Guardian™(N= 768)
~ 4 huts per arm for Mosquito Shield™ (N= 128)
~ each product was evaluated for its full duration of efficacy

Study duration

<table>
<thead>
<tr>
<th></th>
<th>2022</th>
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<th>2023</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>J</td>
<td>J</td>
</tr>
<tr>
<td>Guardian</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Shield</td>
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</tbody>
</table>
Method

~ Experimental huts (28m³) ; male volunteers

~ One shift: 18:00 – 06:00 h

~ Collections: inside-net, resting on wall & floor, and window exit-traps

Primary endpoint
~ Number of *Anopheles arabiensis* mosquitoes blood-fed

Secondary endpoints
~ Proportion of *Anopheles arabiensis* mosquitoes blood-fed
~ Proportion of *Anopheles arabiensis* mosquitoes dead at 24 hours
Efficacy of Guardian™ in reducing blood-feeding

- Overall for Guardian™: ~ 83% (78 – 86%); p<0.001
- Overall for Mosquito Shield™: ~ 71% (65 – 76%); p<0.001
~ The WHO has set the non-inferiority margin at 7%

~ Analysis using regression models controlling for treatment volunteer study and date as fixed effects, huts as random effects since the treatments were fixed all throughout the study

~ Estimated odds ratio or a rate ratio that corresponds to a 7% difference relative to the outcome in the reference product
## Results

<table>
<thead>
<tr>
<th>Mosquito Shield™</th>
<th>Guardian™</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>Intervention</td>
</tr>
<tr>
<td>Anopheles arabiensis</td>
<td></td>
</tr>
<tr>
<td>N females entering</td>
<td>4,577</td>
</tr>
<tr>
<td>N females blood-fed (BF)</td>
<td>1,347</td>
</tr>
<tr>
<td>N females BF per hut night</td>
<td>6.7 (5.6, 8.1)</td>
</tr>
<tr>
<td>% reduction in number BF</td>
<td></td>
</tr>
<tr>
<td>% BF (95%CI)</td>
<td>34 (30, 38)</td>
</tr>
<tr>
<td>% reduction in proportion BF</td>
<td></td>
</tr>
<tr>
<td>N females dead</td>
<td>11</td>
</tr>
<tr>
<td>% 24-hour mortality (95% C.I.)</td>
<td>0.3 (0.1, 0.5)</td>
</tr>
</tbody>
</table>
Interpretation

Figure 1. Possible Scenarios of Observed Treatment Differences for Adverse Outcomes (Harms) in Noninferiority Trials

Reporting of Noninferiority and Equivalence Randomized Trials
Extension of the CONSORT 2010 Statement

Piaggio et al JAMA. 2012;308(24):2594-2604
## Non-inferiority results

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Reference</th>
<th>Candidate</th>
<th>delta</th>
<th>OR</th>
<th>CI</th>
<th>Test outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number blood fed</td>
<td>Shield™</td>
<td>Guardian™</td>
<td>1.07</td>
<td>0.63</td>
<td>0.47, 0.83</td>
<td>Non-inferior and superior</td>
</tr>
<tr>
<td><strong>Secondary:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proportion Blood fed</td>
<td>Mosquito Shield™</td>
<td></td>
<td>1.63</td>
<td>1.17</td>
<td>1.02, 1.35</td>
<td>Non-inferior</td>
</tr>
<tr>
<td>Proportion dead</td>
<td></td>
<td></td>
<td>0.54</td>
<td>0.71</td>
<td>0.22, 2.27</td>
<td>Indeterminate result</td>
</tr>
</tbody>
</table>
Non-inferiority results

Number blood fed

Proportion blood fed

Proportion dead
Conclusion

~ Tested continuously for 12 months Guardian™ was non-inferior and superior to Mosquito Shield™ tested for 32 days on the primary endpoint of number of blood fed mosquitoes

~ Guardian™ was also non-inferior to Mosquito Shield™ on the secondary endpoint of proportion of blood fed mosquitoes

~ We propose this a method for non-inferiority evaluations of spatial repellents
Special thanks: Olukayode Odufuwa, Dr. Amanda Ross and Prof. John Bradley