STAYING AHEAD OF RESISTANCE & BUILDING TRANSFORMATIVE TOOLS

A quick look at the BMGF malaria vector control portfolio

Dr. Helen Jamet, Deputy Director, Vector Control, Malaria Program Strategy Team

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Three strategic goals define Pathway to Eradication

1. **Drive down burden**
   - In the short- and medium-term, scale surveillance + data-driven sub-national optimization, chemoprevention & case management in high burden settings to reduce deaths and cases.

2. **Shorten the endgame**
   - Create enabling environment for winning endgame in high endemic SSA by investing in next-gen surveillance systems, MDR Pf elimination, and accelerating endgame R&D today.

3. **Get ahead of resistance**
   - Mitigate emergence of drug & insecticide resistance by eliminating Pf in the GMS, developing a robust pipeline of AIs and analyzing entomological and genetic epi data to quickly respond to threats.

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**Total malaria cases**
- 219M cases today

**Total malaria deaths** (often a leading indicator)
- 469K deaths today

**WHO GTS death reduction targets**
- Current trend
- What we can achieve

**Current trend**
- If resistance is not countered

**What we can achieve**
- 469K deaths today
VECTOR CONTROL PORTFOLIO INVESTMENT AREAS

**Insecticidal interventions**
- Discover, optimize, and translate new insecticide active ingredients (AIs) to fight resistance
- Develop new AI combinations into LLINs and IRS to fight insecticide resistance
- Develop novel insecticide delivery systems for community transmission prevention
- Tools for improved surveillance
- Vector control product launch & life cycle management
- Develop long lasting endectocides

**Genetically Based Vector Control**
- Create & test platforms to test GM mosquitoes
- Develop self-limiting mosquito constructs
- Develop self-sustaining GM mosquito constructs with gene drive
- Develop endosymbiont-based interventions

**Vector surveillance**
- Tools for improved vector surveillance
- Improve entomological surveillance & data use
## INSECTICIDAL INTERVENTIONS

### Stage of development

<table>
<thead>
<tr>
<th>Pre-development</th>
<th>Development</th>
<th>Field Trials</th>
<th>Implementation</th>
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| • Active Ingredient insecticide discovery  
  • 3 novel AIs (IVCC)  
  • Exploration of traditional Chinese medicine library | • LLINs  
  • 2 x novel AIs with pyrethroids (IVCC)  
  • 1 x PBO LLIN | • IRS  
  • 2 x new molecules (submitted to PQ)  
  • PBO net field stability | • Next generation LLINs |
| • ATSB  
  • Identifying long range attractants  
  • Investigating alternative AIs  
  • Active ingredient discovery (volatiles/repellents) | • ATSB  
  • Product development  
  • Product optimization  
  • Manufacturing scale-up) | • Eave Tubes & window screening*  
  • Spatial repellents** | |

* RCT complete; proof of concept of insecticidal window screens continuing  
** Completed
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## HOW DO WE REPLACE PYRETHROIDS?

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<tr>
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<th>Strengths</th>
<th>Weaknesses</th>
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<tbody>
<tr>
<td>New AI</td>
<td>Delivers new insecticide that fits TPP for intended use</td>
<td>Very few companies capable of new AI development</td>
</tr>
<tr>
<td></td>
<td>Offers novel target site mode of action</td>
<td>High cost</td>
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<tr>
<td></td>
<td>No pre-existing background resistance</td>
<td>Long time to market</td>
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<tr>
<td></td>
<td></td>
<td>High failure rate even at late stages</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Relatively high CoGs for new AI</td>
</tr>
<tr>
<td>Repurposing</td>
<td>Eliminates highly risky development process</td>
<td>For LLIN especially – few insecticides meet the TPP requirements</td>
</tr>
<tr>
<td></td>
<td>Relatively short time to market</td>
<td>Very few compounds that provide BFI/Personal Protection hence combining with Pyrethroids</td>
</tr>
<tr>
<td></td>
<td>Relatively low cost for of development</td>
<td>Not always possible to access chemistry and regulatory package.</td>
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<tr>
<td></td>
<td>Potential: Many companies do not screen for activity vs. resistant mosquitoes.</td>
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ATTRACTION TARGETED SUGAR BAIT CONCEPT

A device that presents an attractive sugar-meal laced with a lethal toxicant to mosquitoes and other flying, biting insects

Use case

- Outdoor application
- Offers insecticide to mosquito through mechanism other than contact, opening up wider choice of insecticides and potential for resistance management
- Targets both male and female mosquito populations
- Reduces transmission by impacting adult mosquito survival, shifting towards greater proportion of younger uninfected females
## GENETIC BASED VECTOR CONTROL

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<table>
<thead>
<tr>
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<th>Development</th>
<th>Field Trials</th>
<th>Implementation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lab development</strong></td>
<td></td>
<td>Regulatory approvals for field testing</td>
<td>Field Trials</td>
<td>Implementation</td>
</tr>
<tr>
<td><strong>Pre-development</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Development</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Field Trials</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td><strong>Implementation</strong></td>
<td></td>
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<td></td>
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<tr>
<td>• Self limited</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• An. albimanus &amp; An. stephensi (Oxitec)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Gene drive</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>• Target Malaria</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Transmission Zero</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• UCI*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Self-limited</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• An. gambiae (Target Malaria)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• No products for malaria control have made it to field trials yet</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Self-limited</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Aedes aegypti (DENV, ZIKV) (Oxitec)**</td>
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</tr>
</tbody>
</table>

* Prior investment by BMGF, deprioritized in 2019
** Not funded by BMGF
### DEFINITION OF PARADIGM/PRODUCT CLASS

<table>
<thead>
<tr>
<th></th>
<th><strong>Self-limited</strong></th>
<th><strong>Gene drive</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Product description</strong></td>
<td>A mosquito strain that is modified so that only male offspring are produced</td>
<td>A mosquito strain that is modified with a construct that copies itself. The construct can either decrease mosquito populations (suppression) or make them unable to transmit malaria (replacement).</td>
</tr>
<tr>
<td><strong>Potential impact</strong></td>
<td>Localized</td>
<td>Widespread</td>
</tr>
<tr>
<td><strong>Timespan</strong></td>
<td>Transgenic mosquitoes die off after releases halt</td>
<td>Transgenic mosquitoes continue to increase and spread after releases halt</td>
</tr>
</tbody>
</table>
| **Intended use**          | a) Malaria elimination in small foci  
  b) Controlling urban malaria outbreaks  
  c) Data from GM self-limited releases can contribute to decision-making on gene drive                                                                                                                                                                                                 | To drive down malaria transmission across widespread, rural, high-burden areas where current tools are insufficient to get to elimination                                                                                                                                                                                                                       |
| **Timeline**              | More likely to be available in the next 5 years                                                                                                                                                                                                                                                                                                   | 10+ years                                                                                                                                                                                                                                                                                                                                                       |
## Stage of development

<table>
<thead>
<tr>
<th>Discovery</th>
<th>Early / Preclinical</th>
<th>Mid / Proof of concept</th>
<th>Late Dev/ Launch</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Novel isoxazoline</td>
<td>• Long acting oral ivermectin formulation</td>
<td>• Isoxazoline class</td>
<td>• Multiple trials of 1-3d standard ivermectin with and without DHA/PQP MDA (modelling suggest low impact)*</td>
</tr>
<tr>
<td></td>
<td>• Long acting injectable ivermectin</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Not funded by BMGF
LONG-ACTING ENDECTOCIDES IN COMBINATION WITH OTHER INTERVENTIONS TO REDUCE COVERAGE NEEDS

Endectocide MDA alone is effective when the duration is ≥ 60 days; however MDA combining an ACT with an endectocide of ≥14 days increase the impact above either alone (right).

Longer duration of activity and multiple rounds of endectocide allow tradeoff with high coverage in SMC (above).

SI = systemic insecticide

SOURCE: Selvaraj et al. Malar J (2019) 18:307; Figs 2d, 3 a & c, & 4d.
**VECTOR SURVEILLANCE**

![Proportional Shortfalls in Staffing Capacities of National Malaria Control Programmes](image)

**Table 7** Summary assessment of laboratory analytical techniques for malaria vectors by expert informants

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Mosquito identification</th>
<th>Insecticide resistance</th>
<th>Sporozoite detection</th>
<th>Age grading</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Morphology¹</td>
<td>PCR²</td>
<td>WHO CDC bottle</td>
<td>CS-ELISA</td>
</tr>
<tr>
<td>Training requirement</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Human Resource Needs</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Complexity of Method</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Costs/Logistics/Supplies³</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Specimen quality</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>In-country capability</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Interpretation of result⁴</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Technical consistency</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

a. Yellow indicates a moderate level of training required
b. Red indicates significant requirements for use including high level of training, human resources, complex methodology, costs, need for quality specimens, which impacts technique uptake and use
c. Green indicates few impediments (few logistics concerns, low costs or in-country capability present) for use
d. Yellow indicates variability in Interpretation of results and technical consistency
e. ‘+‘ not expressly addressed by informants

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Source: Russell et al. Malar J (2020) 19:422

PRIORITIES FOR NEW TECHNIQUES

• **Human Landing Catch replacement** to determine biting rates

• **Age grading of mosquitoes** to determine age structure of mosquito populations, with new techniques

• **Surface active ingredient detection** using a quantitative, non bioassay method

• **Field applicable rapid assays** for species identification, insecticide resistance frequency and mechanisms, sporozoite rates

• **Automated multiple parameter analyses** for:
  - adult density, species ID, insecticide resistance status and sporozoite infection
  - Characterization of larval habitats (remote sensing with drones, satellite imagery, other)
Thank you for listening