GM & GENE DRIVE MOSQUITOES: PRODUCT DEVELOPMENT PATHWAY

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RBM VCWG Expanding the Vector Control Toolbox

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<thead>
<tr>
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<th>Genetically modified – self-limited</th>
<th>Gene drive</th>
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<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>
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<td><strong>Potential impact</strong></td>
<td>Localized</td>
<td>Widespread</td>
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<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>
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<td><strong>Intended use</strong></td>
<td>a) Malaria elimination in small foci</td>
<td>To drive down malaria transmission across widespread, rural, high-burden areas where current tools are insufficient to get to elimination</td>
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<td>b) Controlling urban malaria outbreaks</td>
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<td></td>
<td>c) Data from GM self-limited releases can contribute to decision-making on gene drive</td>
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<td><strong>Timeline</strong></td>
<td>More likely to be available in the next 5 years</td>
<td>10+ years</td>
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DEFINITION OF PARADIGM/PRODUCT CLASS

GM self-limited
- Localized impact
- Short-term impact
- Large repeated releases needed, contributing to cost

Gene drive
- Transgenic
- Species-specific
- Implemented through rear- and-release
- Impact over a wide area
- Long-term impact
- Fewer releases needed, but long-term monitoring and engagement adds to cost
- Doesn't require user behavior change
PRODUCTS CURRENTLY UNDER EVALUATION

- **Transmission Zero**
  - An. gambiae gene drive

- **Lab development**
  - An. albimanus and An. stephensi self-limited
  - An. gambiae self-limited

- **Regulatory approvals for field testing**
  - Aedes aegypti self-limited (DENV, ZIKV)

- **Field trials**
  - No products for malaria control have made it to field trials yet!

- **Implementation**
GAPS THE PRODUCTS ARE MEANT TO ADDRESS

Regions with high transmission despite intervention scale-up

Outdoor biting

Elimination and prevention of reintroduction

The spatial distribution of Plasmodium falciparum malaria endemicity in 2019 in the WHO African Region.

Number of malaria cases

Year

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ONGOING EVALUATIONS AND HIGH-LEVEL RESULTS

Lab dynamics of self-limited and modeling potential field impact:
Facchinelli et al. 2019, Parasites & Vectors

Gene drive lab results: Adolphi et al. 2020, Nature Communications;
Hammond et al., pre-print under consideration at Nature Portfolio

Modeling potential impact of gene drive: North et al. 2020, BMC Biology
REMAINING RESEARCH QUESTIONS TO BE ANSWERED

• Laboratory-based safety assays – Does the product pose any risks from toxicity, changes to vector competence, etc.?
• Laboratory-based efficacy tests – What factors might change the potential impact, and can those be mitigated?
• Ecological research questions – What are the potential impacts from mosquito suppression or niche replacement?
• Delivery – How to rear and transport *Anopheles* mosquitoes in sufficient numbers without harming fitness? What would a release network need to look like?
• Capacity and Ownership – How do we successfully transfer the technology to scientists and implementers in malaria-endemic countries?
• Trial design – How do you design a trial to evaluate public health impact, when a traditional RCT isn’t possible?
• Evaluation – What data will be needed to make a decision on a gene drive release? What roles do national regulatory agencies, regional bodies, and WHO play?
• Engagement – What are the best ways to engage local communities in decision-making?
• Costs – What are the long-term costs, and cost efficacy?
ESTIMATED TIMELINE TO MARKET

Note: these are estimated, best-case scenarios for a very uncertain new product timeline!

**GM self-limited**

- Lab dev. and regulatory permits
- First field trials
- Implementation for select geographies

- Now
- 3 years
- 5 years
- 8 years
- 10 years
- Longer

- Regulatory studies, environmental risk assessments
- Regulatory process
- First field trial in isolated location
- Wider scale-up

**Gene drive**