Update on the Development of Gene Drive Mosquitoes for Malaria Control

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Genetic biocontrol is an umbrella term for a set of approaches.

Make a genetic change to cause a desired effect...

Inject mosquito egg with plasmid DNA

Modified mosquito

...then release into a wild population to mate

Release of modified

Mating between modified and wildtype

Impact based on modification
Genetic biocontrol of insects is an 80-year-old concept

Observations of natural gene drive stretch back ~100 years

The concept of its use for vector control is over 80 years old

Genetically sterile biocontrol also dates to the 1940s

Detailed genetic biocontrol timeline: www.geneconvenevi.org/gene-drive-timeline
Genetic biocontrol is a persistently attractive approach because of a unique combination of potential benefits

<table>
<thead>
<tr>
<th>Potential benefits of genetic biocontrol</th>
<th>African Union and WHO recognize potential</th>
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<tbody>
<tr>
<td><strong>Efficacy</strong>: Genetic biocontrol approaches have locally eliminated species</td>
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<td><strong>Mechanism of action</strong>: Generally independent from other control MOAs</td>
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<td><strong>Specificity</strong>: Primary impact is on the target organism</td>
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<td><strong>Area-wide effect</strong>: No individual-level behavior is required for benefits</td>
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Background figure: PubMed records for “gene drive” from 1990 (1) to 2021 (100)
Key parameters: target outcome of the modification, and how long the modification persists after a release

**Target outcome**
- Population suppression
- Population modification
- Fertility reduction/lethality
- Sex ratio distortion
- Pathogen transmission blocking

**Persistence**
- None or rapid decline (no drive)
- Indefinite (drive)
Non-drive approaches like SIT and Oxitec typically require large, sustained releases and have impact localized to the release area.

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When the modification doesn’t drive, it is maintained in the population through sustained releases. Population suppression with sustained releases lasts over time. Population recovers after releases stop (unless it is eliminated).
Self-sustaining gene drive approaches like Target Malaria typically require small, sparse releases to have wide, sustained impact.

**Persistence**
- When the modification drives...

**Release approach**
- ...small releases are sufficient to achieve impact over time

**Spatial extent**
- Impact area grows as drive spreads from release area

- Population suppression after modification reaches high prevalence
- Suppression is sustained until elimination or resistance
Self-sustaining population modification (transmission-blocking) approaches like UCMI and Transmission Zero are similar

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Transmission blocking increases as modification increases in prevalence
Transmission blocking is sustained (until resistance)
Split-drive-type approaches are designed to decay after 10s-100s generations of persistence near the release area.

 Persistence

Drive ramps up then down over time

 Release approach

Increase and decrease of modification depend on releases

 Spatial extent

Little drive outside of the release area

Transmission blocking increases as modification increases in prevalence

Transmission blocking is sustained until drive fades and modification decays
To achieve impact, there is a general balance between persistence and release requirements, with many possible variations

- Wide range of intended persistence is possible
  - Sterile (no persistence)
  - Male bias / daughterless (rapid decay)
  - Split drive / daisy drive (drives for 10s-100s of generations, then decays)
  - Self-sustaining / autonomous (intended to drive indefinitely)

- Persistence has implications for spatial spread, but other mechanisms control spread directly
  - Threshold drive (drive only above threshold prevalence)
  - Private allele / tethered drive (drive only in specific genetic background)
Recent progress on genetic biocontrol for malaria has been impressive, with important steps ahead to achieve impact

- **Lab science**
- **Regulatory approvals: research**
- **Regulatory approvals: products**
- **Production and delivery**
- **Environmental studies**
- **Safety and efficacy studies**
- **Policy and funding**
- **Monitoring and adjustment**

**Malaria impact**

**Current state of genetic biocontrol for malaria**
- Spectacular successes in lab experiments (efficacy, safety)
- First release of GM Anopheles mosquitoes, in Burkina Faso
- Field trial site selection and characterization underway
- National and regional regulatory capacity developing
Many open questions for consideration, but also many domains to draw on to inform the answers

- Enabling regulatory and policy environments for approaches that may spread across national borders
- Design of field trials and transition to implementation at scale
- Role of genetic control and reversal as risk mitigation tools
- Cost-effective use cases for localized genetic biocontrol
- Priorities for next-generation product development

Genetic biocontrol for other applications
GM animals and crops
Conventional biocontrol
Conventional vector control for malaria
Invasive species management

GM animals and crops
Conventional biocontrol for other applications
Genetic biocontrol for malaria
Invasive species management
GeneConvene
Thank you!

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www.GeneConvene.org
www.GeneConveneVI.org
The mission and approach of the GeneConvene Global Collaborative

Mission

Advance best practices and informed decision making for the development of genetic biocontrol technologies to improve public health

Identifying and Addressing Key Questions

Providing Technical Advice

Strengthening Capacity and Sharing Information