Results of the Workshop: “Problem Formulation for the Use of Gene Drive in Mosquito”

Andrew F Roberts, PhD
Director
Center for Environmental Risk Assessment (CERA)

September 20, 2016
Contents of My Presentation

• Brief introduction to the workshop
• How did we conduct the problem formulation exercise?
• Summary of conclusions
• Next steps
Workshop: Problem Formulation for the use of Gene Drive in Mosquito

• Took place in Reston, Virginia, May 25-27, 2016
• 47 participants
  ▪ Wide geographic representation
• Funding provided by the Foundation for the National Institutes of Health (FNIH)
Purpose of the Workshop

• To begin conversations about Environmental Risks associated with the use of gene drive for malaria control
• To identify areas where researchers and development programs should be thinking about collected data in support of risk assessment
• Provide a rational starting point for regulators to think about the use of this technology
Day 1: Scientific and Technical Background

- Biology of *Anopheles* mosquitoes
- What is Gene Drive?
- Applications of Gene Drive in Malaria Control
  - Population suppression
  - Population alteration
- Modeling the potential benefits of malaria control
Day 1: Scientific and Technical Background

• What is Risk Assessment, and why do we do it?
• Introduction to Problem Formulation
• Problem Formulation Case Example: *Aedes aegypti* OX513A
• Environmental Protection Goals and Priorities in a Sub Saharan Country
• Introduction to the case study
Day 2: Breakout Groups

- Case Study Document
  - 10 pages of background material (similar to Day 1 presentations)
  - Four hypothetical examples of the use of gene drive in *Anopheles gambiae*

- Workbook - walking through Problem Formulation
  - Identification of pertinent protection goals
  - Refining protection goals and identifying plausible pathways to harm
  - Identifying information (data) that would be useful to determine likelihood of risk
Protection Goal: Water Quality

Harm: Aquatic organism population adversely affected (e.g., less larvae breeding in the water impacts nutrient cycle)

Pathway to Harm

- Less larvae breeding in the water
- Less microorganisms (e.g., algae) consumed and processed
- Less processed nutrients available to aquatic organisms
- Nutrient cycle adversely affected
- Aquatic organism populations (e.g., plants) adversely affected

Plausibility: Low

A large fraction of habitats are temporary and do not support complex communities.

Knock-in Suppression: Same
Protection Goal: Human Health

Harm: Human health is adversely affected by a change in the phenotype of the mosquito, thereby increasing the ability to transmit malaria

Pathway to Harm

- Off target effect on the target organism
- Pleiotropic/multiple, unexpected effects of transgene or knock out process
- Effects leading to change in phenotypes
- Increased transmission of malaria

Examples:
- Response to chemicals
- Longevity
- Aestivation and desiccation
- Ability to transmit other pathogens – broaden vector competence
- Lack of females leads to increased male competition
- Timing of feeding

Plausibility: Yes

Further research on the consequences of mutation of target and off-target effects is necessary.

Knock-in Suppression: Same
Day 3: Building Consensus

• Morning session spent with each group presenting their results
• Afternoon session was a discussion of consensus points, based on the morning’s presentations.
Consensus Points

- Human Health
- Animal Health (i.e. livestock)
- Biodiversity
- Water Quality

Pertinent Broad Protection Goals

Non-Pertinent Broad Protection Goals:
- Soil Quality
- Air Quality
- Natural Resources (other than biodiversity)
- Agricultural Production (excluding animal health)
General Statement on Exposure Related to Species Specific Population Suppression And Population Alteration Strategies

• Population Suppression
  • Gene Drive Mosquitos for population suppression are designed to eventually reduce in numbers in the environment over a relevant time.

• Population Alteration
  • Gene Drive Mosquitos for population alteration are designed to persist in the environment over a relevant time.
Human Health

• The relevant interaction for human health is biting
  ▪ Incidental exposure through inhalation, ingestion, etc. is not likely to result in any significant levels of exposure leading to harm to human health

• Proteins introduced into *Anopheles gambiae*, including components of the gene drive and markers, should be considered with respect to toxicity and allergenicity potential.

• Horizontal gene flow to humans is extremely unlikely to occur.
Human Health

• Because *Anopheles gambiae* is an important disease vector, consideration should be given to potential alterations in disease transmission
  - This includes altered *P. falciparum* transmission or virulence, other human malarial transmission as well as altered transmission of other diseases.
Biodiversity (General Consensus Statements 1 of 2)

• *Anopheles gambiae* is not a “keystone” species in the environment and is not known to provide any non-redundant ecosystem services
  ▪ Changes in population size or even elimination of *Anopheles gambiae* from a particular environment are unlikely to harm biodiversity or ecosystem services. This is based on existing knowledge and experience with vector control programs.
Biodiversity (General Consensus Statements 2 of 2)

• *Anopheles gambiae* interacts with other species by feeding on them, being consumed as prey, or competing with them.
  - These interactions may require consideration for species of relevance to the assessment such as threatened, endangered, or valued species
  - Incidental contact between organisms and *Anopheles gambiae* carrying gene drives is not likely to lead to harms to those organisms, compared to interactions with other *Anopheles gambiae*. 
Biodiversity (Refined harms and priorities for consideration)

• *Anopheles gambiae* is not known to be the sole or primary food source for any organism, with the possible exception of a few species of spider known to prefer Anophelines.

• Removing *Anopheles gambiae* from the environment is unlikely to harm species that feed on it, due to the availability of other prey, including Anophelines.
  - Birds, bats, fish etc.
  - This is primarily relevant for suppression strategies

• Consideration should be given to any proteins introduced into *Anopheles gambiae* (including gene drive components or markers) for toxicity to other species
Biodiversity (Gene Flow)

- Gene flow to other species within the *Anopheles gambiae* s.l. complex through hybridization is likely, and does not create additional pathways to harm.
- Horizontal gene transfer is not likely to occur to other organisms on any relevant time scale and is not a pertinent pathway to harm.
Animal Health (livestock)

- Potential harm could result from altered pathogen transmission dynamics to livestock.
- Harm resulting from other mechanisms, including toxicity from introduced proteins, was considered unlikely.
Other Considerations (1 of 2)

• The use of gene drives in *Anopheles gambiae* should be considered as a complementary strategy to other vector control methods and malaria mitigation strategies.

• The potential harms identified for the use of gene drive in *Anopheles gambiae* should be considered in the context of other vector control methods and malaria mitigation strategies.
Other Considerations (2 of 2)

• Failure to sustain a successful malaria vector control strategy can have harmful effects on malaria incidence.
  ▪ This is not unique to gene drive, and would be the same for other malaria control or eradication techniques
  ▪ The ability to control resurgence needs be sustained and effective additional control methods need to be available
Conclusion

• The consensus points from the workshop provide a good starting point for a case specific risk assessment
• They are not intended to be immutable
  ▪ Rather to allow developers and risk assessors to focus their efforts on the areas that are likely to be important for risk assessment
• These results have been submitted for peer review to the American Journal of Tropical Medicine and Hygiene (AJTMH)
  ▪ Currently under peer review
• Additional workshops are planned for West, Southern and East Africa
Thank you!
www.ilsirf.org