Problem formulation for the environmental risk assessment of gene drive modified mosquitoes

ANDREW F ROBERTS, PHD

ILSI RESEARCH FOUNDATION

ILSI Research Foundation

About Us

As a non-profit, public charitable organization, the ILSI Research Foundation collaborates with experts to respond to relevant issues that have a global impact through applied research, capacity building, education and outreach.

Our Work

All programs are for public benefit and focus on contributing to long-term solutions. This includes:

Sustainable Nutrition Security

Environmental Risk Assessment of Genetically Engineered Crops

Environmental Risk Assessment of Gene Drives

Genetically Engineered Food and Feed Safety Assessment

Biosafety Capacity Building

Contents of My Presentation

Introduction to gene drives and their potential applications in mosquitoes

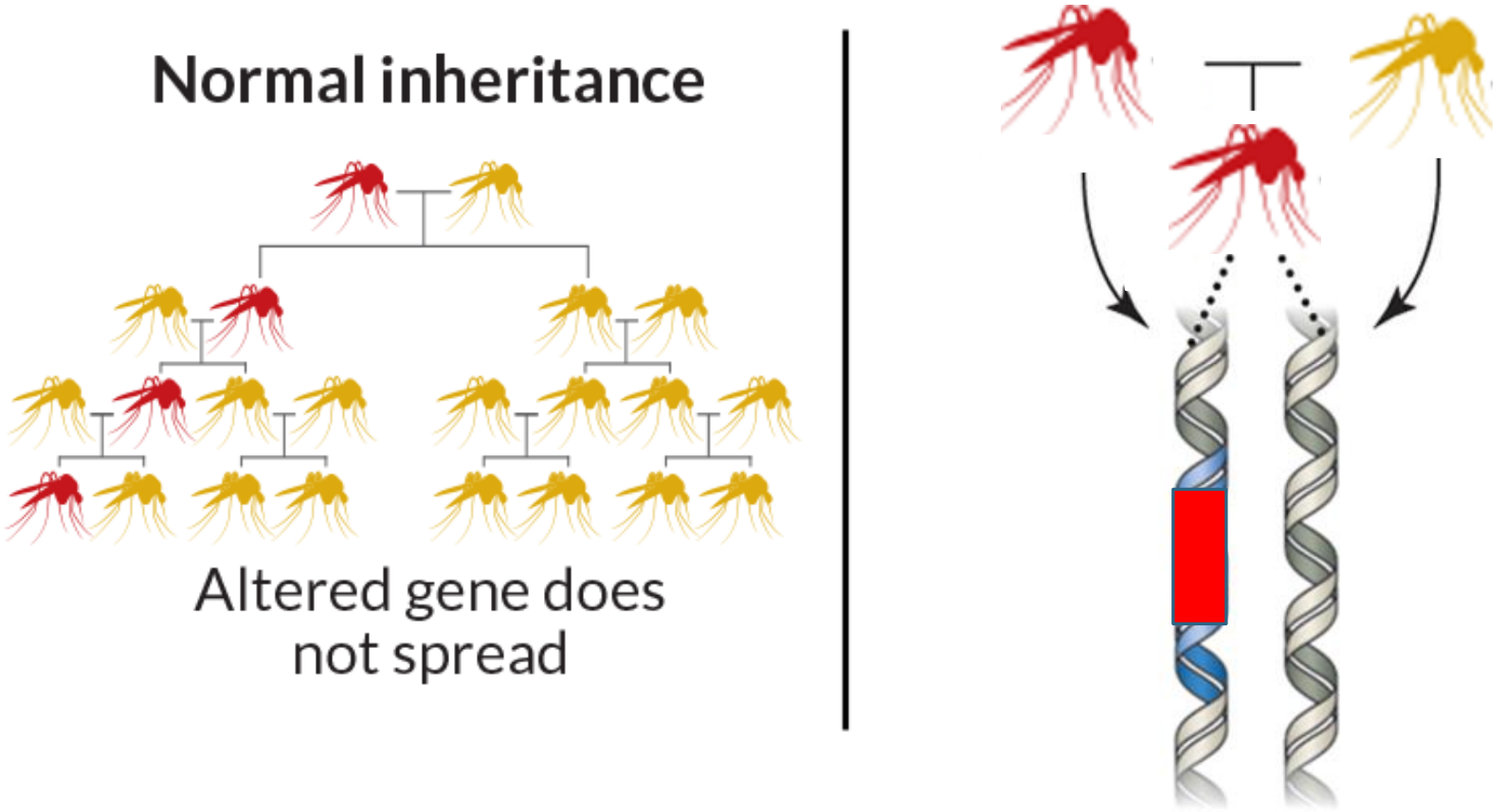
Description of the workshops and consultations involving problem formulation exercises

Conclusions from these exercises

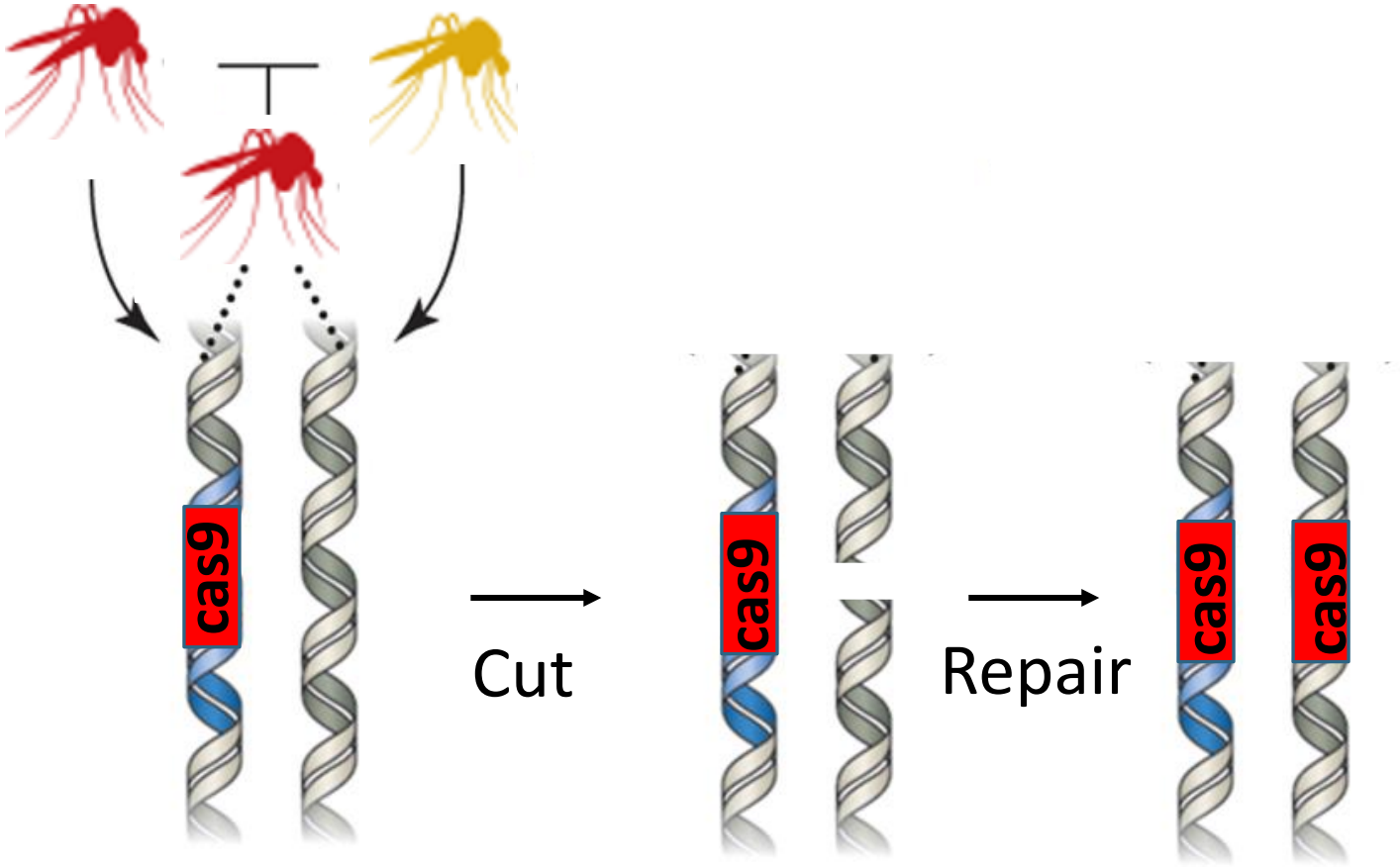
- Broad protection goals with relevance to this use of gene drives in *Anopheles gambia* for control of malaria

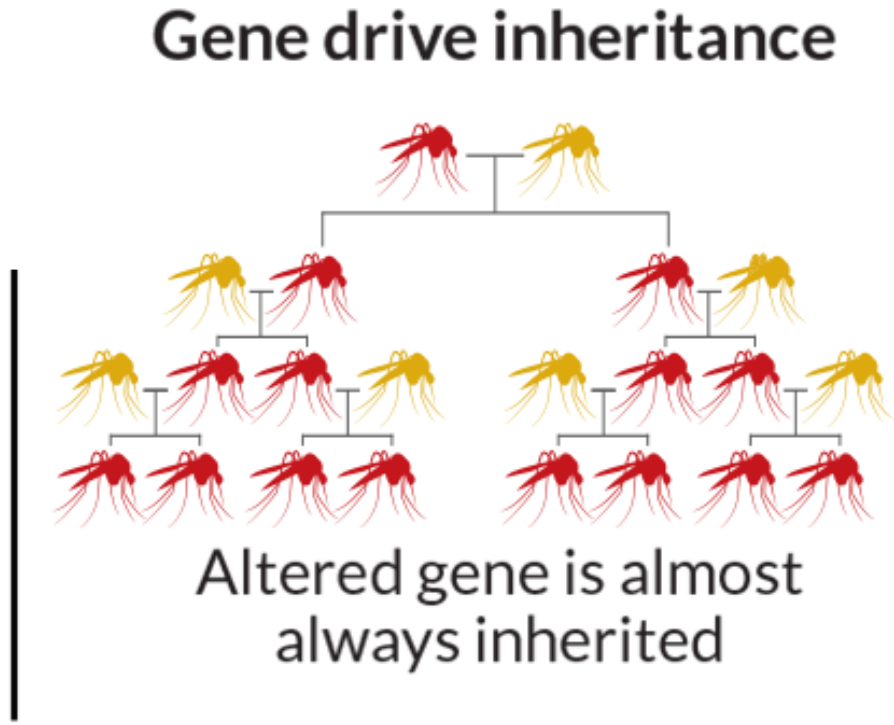
What is a gene drive?

Normal Inheritance of the Trait Will Not Cause it to Spread in the Population



Gene Drive Inheritance of the Trait Will Cause it to Spread in the Population





Genetic Biocontrol in the Form of a "Gene Drive" Mosquito May Be a Tool to Eradicate Malaria

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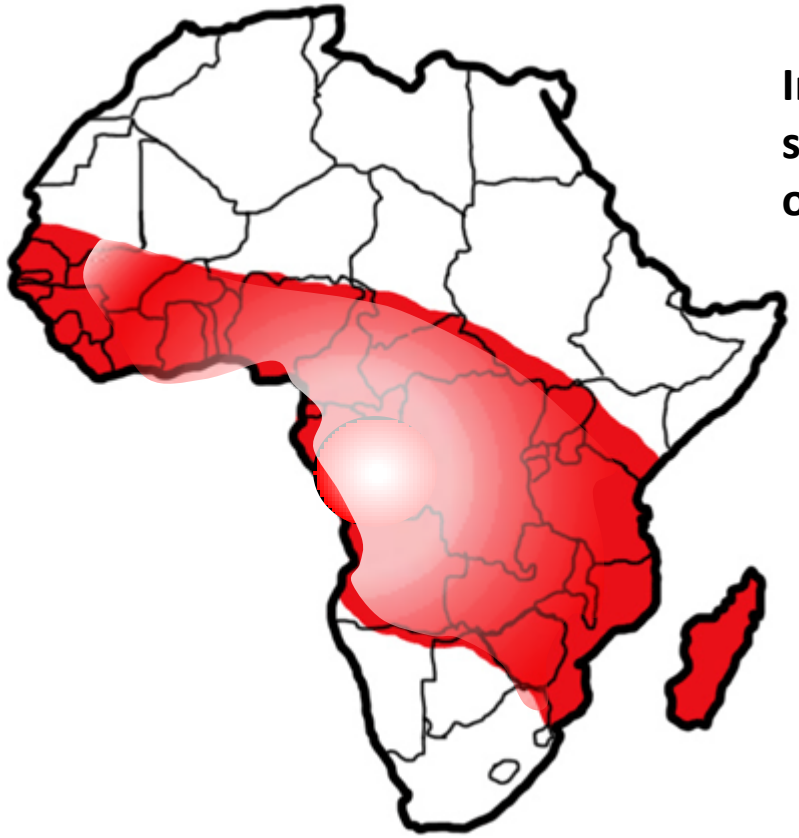
Starts with the introduction of a genetically modified mosquito containing a gene drive construct into a target population.

Over time, the mosquito mates within the population and a new trait spreads into the population that wasn't there before.



In theory, a gene drive can be started with a very small number of genetically modified mosquitoes.

Once a gene drive is introduced it is expected to "drive" through an entire population (again, in theory).

What are the risks to the environment of initiating a gene drive in *Anopheles gambiae* to control malaria?

Five Workshops and Consultations Including Problem Formulation Exercises

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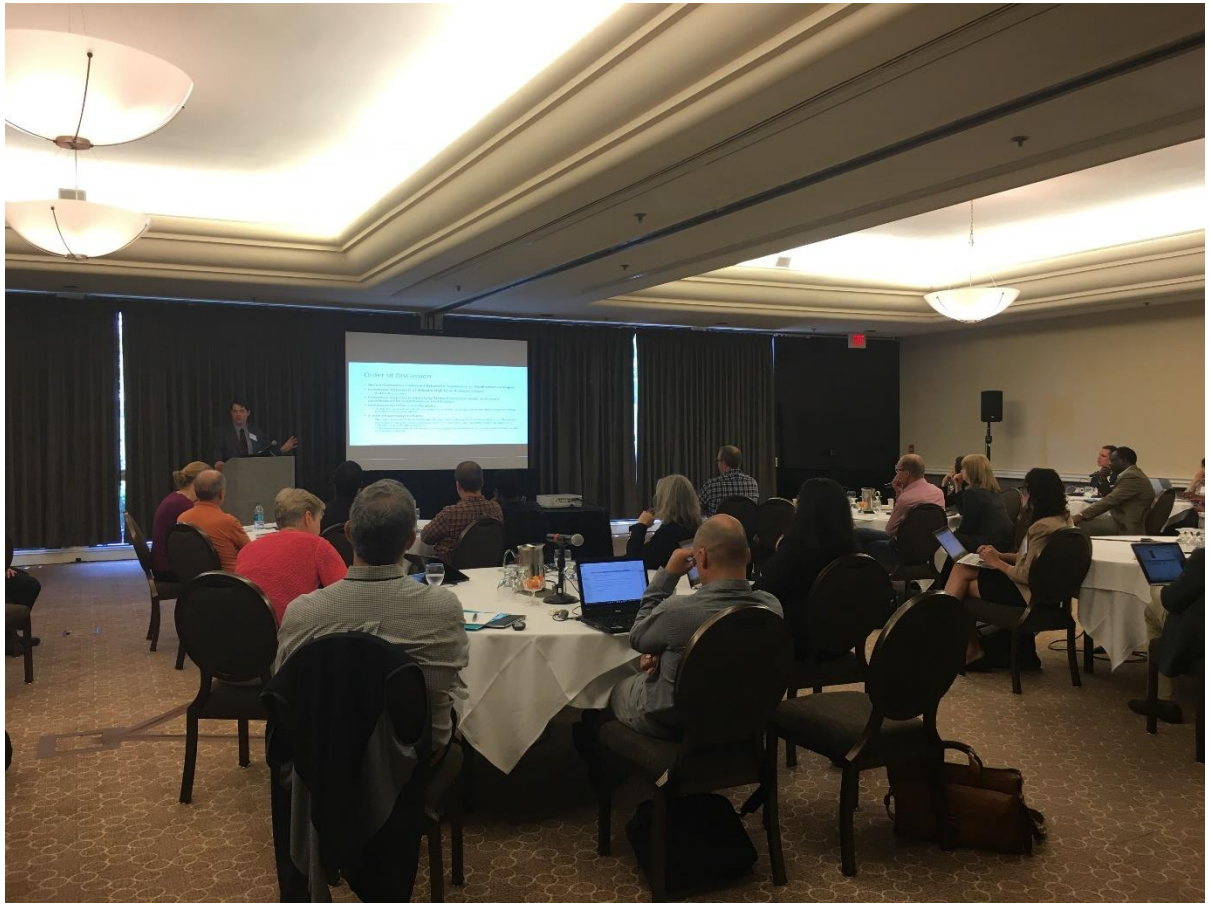
Workshop

- Reston, Virginia, May 25-27, 2016

Consultations

- Accra, Ghana, Oct. 17-19, 2016
- Nairobi, Kenya, June 20-22, 2017
- Gabarone, Botswana June 26-28, 2017
- Libreville, Gabon, Feb. 20-22, 2018



Purpose of the Workshop and Consultations

To begin conversations about environmental or ecological risks that may be associated with the use of gene drive mosquitos for malaria control in Africa

To identify areas where researchers and development programs should be thinking about collecting data in support of risk assessment

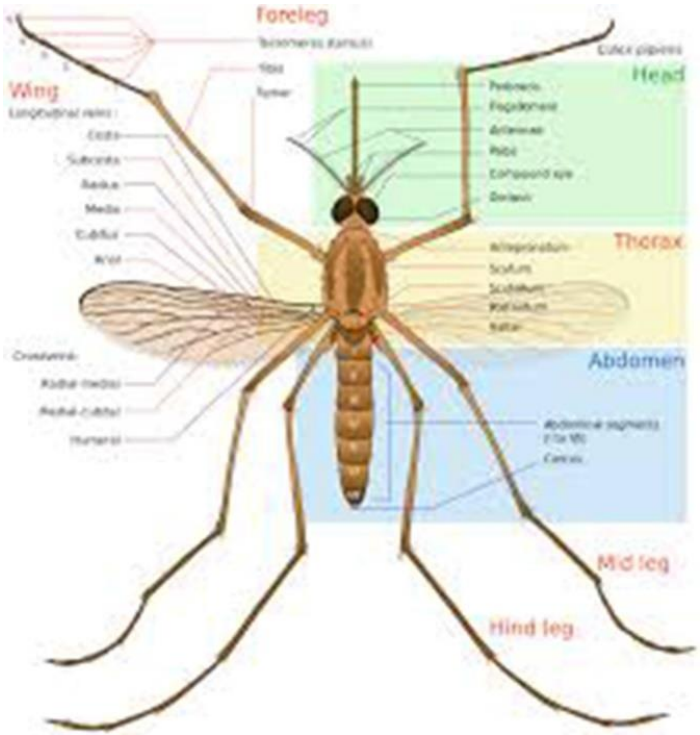
Provide a rational starting point for developers, researchers, and regulators to think about the use of gene drive technology for malaria control

Structure of the Workshop/Consultations

Day 1: Information to Inform Problem Formulation

Day 2: Breakouts using Hypothetical Case Studies

Day 3: Review and Discussion



Scientific & Technical Background → Breakout Groups → Review and Discussion

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Perspective Piece

Results from the Workshop "Problem Formulation for the Use of Gene Drive in Mosquitoes"

Andrew Roberts,[1]* Paulo Paes de Andrade,[2] Fredros Okumu,[3] Hector Quemada,[4] Moussa Savadogo,[5] Jerome Amir Singh,[6,7] and Stephanie James[8]

[1]*Center for Environmental Risk Assessment, International Life Sciences Institute Research Foundation, Washington, District of Columbia;* [2]*Department of Genetics, Federal University of Pernambuco, Recife, Brazil;* [3]*Ifakara Health Institute, Environmental Health and Ecological Sciences Thematic Group, Dar es Salaam, Tanzania;* [4]*Institute for International Crop Improvement, Donald Danforth Plant Science Center, Saint Louis, Missouri;* [5]*African Biosafety Network of Expertise, NEPAD Agency, Ouagadougou Node, University of Ouagadougou, Burkina Faso;* [6]*Centre for the AIDS Programme of Research in South Africa, University of KwaZulu-Natal, Durban, South Africa;* [7]*Dalla Lana School of Public Health, University of Toronto, Ontario, Canada;* [8]*Foundation for the National Institutes of Health, Bethesda, Maryland*

Abstract. Reducing the incidence of malaria has been a public health priority for nearly a century. New technologies and associated vector control strategies play an important role in the prospect of sustained reductions. The development of the CRISPR/Cas9 gene editing system has generated new possibilities for the use of gene-drive constructs to reduce or alter vector populations to reduce malaria incidence. However, before these technologies can be developed and exploited, it will be necessary to understand and assess the likelihood of any potential harms to humans or the environment. To begin this process, the Foundation for the National Institutes of Health and the International Life Sciences Institute Research Foundation organized an expert workshop to consider the potential risks related to the use of gene drives in *Anopheles gambiae* for malaria control in Africa. The resulting discussion yielded a series of consensus points that are reported here.

Consensus Points

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

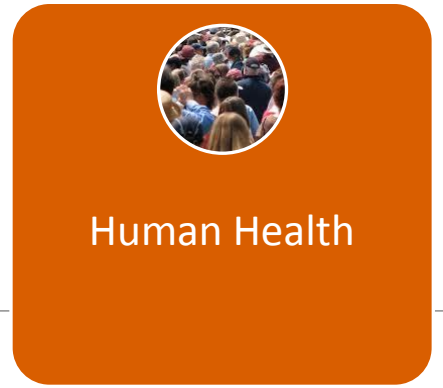
Population Suppression

- 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 encoded by genes 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)

Biodiversity

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)

Biodiversity

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)

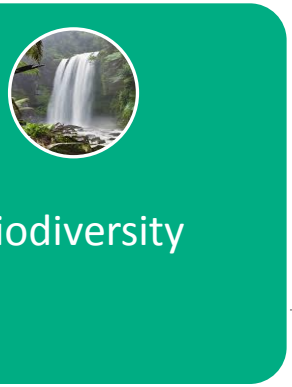
Biodiversity

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

My Thoughts

These activities are incredibly valuable, but they do have limits

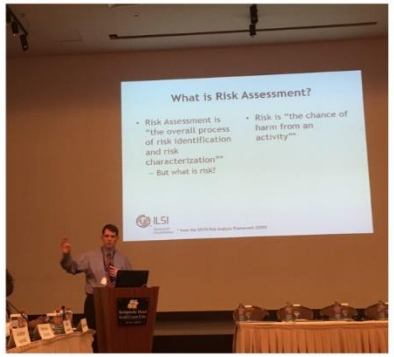
- It is impossible to exhaustively discuss pathways to harm in three days
- Many differences between groups were caused by differences in available expertise to supply missing information

The most discussed protection goals (by a wide margin) involved human health and biodiversity

- Human health considerations were almost always related to altered gene transmission
- Biodiversity considerations were nearly always related to harm to predators of mosquitos

Water Quality was a distant third

- This was typically mitigated by the types of habitat *An. gambiae* lives in
- Participants in Africa were generally more inclined to view water quality effects as a plausible pathway to harm


What is Risk Assessment?
• Risk Assessment is "the overall process of risk identification and risk characterization""
– But what is risk?
• Risk is "the chance of harm from an activity""


Gene Drives to Target Snails- A Case Study in Problem Formulation

Acknowledgments

I want to acknowledge the incredibly hard work of all the people participating in all of these events, although I can't possible name them all:

Colleagues at the ILSI Research Foundation

- John Teem (especially for slides), Libby Williams, Karin Christianson, and Layla Tarar

Foundation for the National Institutes of Health

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New Partnership for African Development

- Initiating, organizing managing and hosting the consultations in Africa

Speakers at all five workshops

Participants in Reston, Accra, Nairobi, Gabarone, and Libreville

Thank you!

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