

Gene Drives for Malaria Control

(and what has the ILSI Research Foundation been doing about it?)

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Contents of My Presentation

What is Malaria and why do we need new tools to combat it?

What is a gene drive, and how might that help?

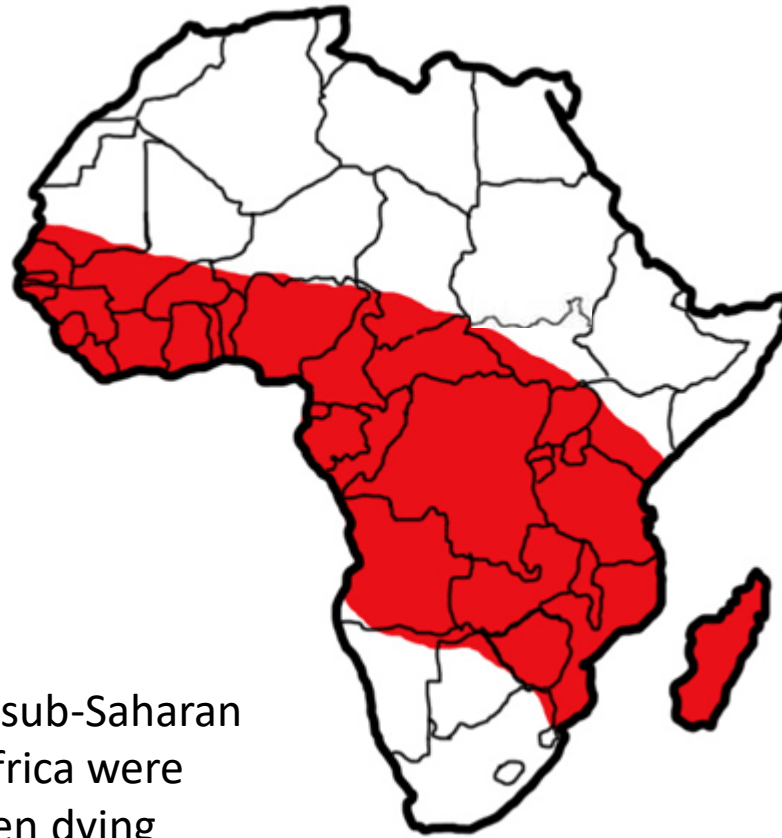
What has the ILSI Research Foundation been doing in this area?

Malaria is the Most Common Parasitic Disease of Humans

Malaria result from infection by the *Plasmodium falciparum* parasite.



Anopheles gambiae



Nearly 90% of all deaths from malaria are found in sub-Saharan Africa. In 2012, 482,000 children in Sub-Saharan Africa were killed from malaria, with an estimated 1,300 children dying each day.

Malaria Impedes Poverty Reduction

In addition to loss of life, Malaria creates a huge economic burden

Malaria costs sub-Saharan economies about \$12 Billion a year

- Medical costs
- Lost Productivity/Absenteeism
- Lost educational opportunities
- Permanent health impacts including on brain development
- Loss of investment and tourism

Together with HIV/AIDS, malaria is one of two diseases specifically targeted by the Millennium Development Goals

- Because of the huge economic burden

Great Progress Has Been Made - But it is at Risk

Through a combination of cost effective methods for preventing malaria

- Indoor Residual Spraying (IRS) of insecticides
- Long Lasting Insecticide-treated Nets (LLINS)
- Environment and behavior modification
 - Removing breeding areas
 - Encouraging people to stay indoors at night

These methods are reaching their limits of effectiveness and are at risk

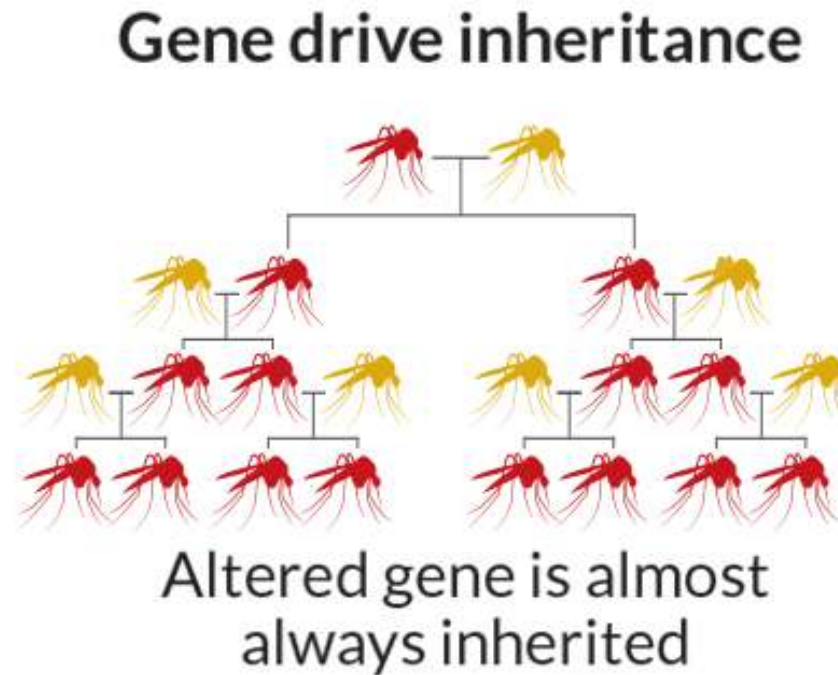
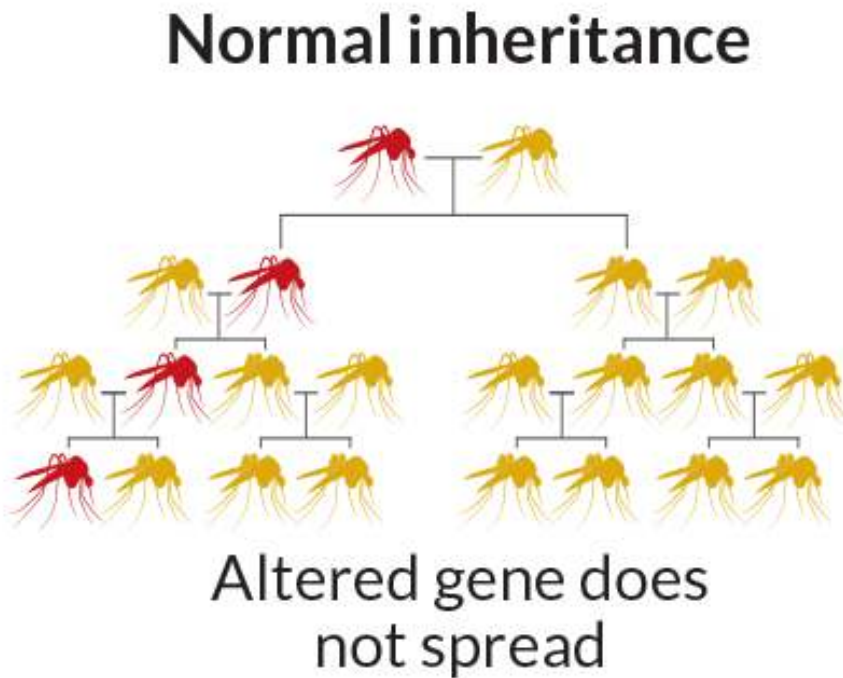
- Insecticide resistance
- Drug resistant parasites
- Unsustainable funding
- Behavior change in target vector mosquitos
 - Biting shifting to daylight hours to avoid bed nets and IRS

What Can Be Done?

In 2003, Austin Burt at Imperial College London suggested that “gene drives” could be used to modify vector mosquito populations and reduce the incidence of malaria

What’s a gene drive?

Gene Drives Alter Inheritance to Spread a Trait Through Populations



Gene Drives Occur in Nature

And are in fact very common

- Every known genome contains at least one active “selfish” gene
- The P element in *Drosophila melanogaster* – first observed in the 1950s appears to have since spread to every population of wild *Drosophila* in the world.

The first proposed gene drives for malaria control were homing endonuclease systems

- Naturally occurring enzymes which target DNA sequences, which they cut in order to copy the sequence containing the gene
- This system has actually been used in the laboratory to insert traits in *Anopheles* mosquitoes

But natural gene drives are challenging to engineer for effective gene drives carrying desirable traits

Two Ways You Might Use a Gene Drive to Control Malaria

Population Suppression

- Drive a trait into a population of vector mosquitos that causes the population to crash
- “Driving Y” Chromosome in *Aedes aegypti* is a natural drive that does this
- Most proposed suppression methods alter the sex ration to reduce the availability of females
- This would remove (or severely reduce) the mosquito population in the environment

Population Replacement

- Drive a trait into the population that alters its ability to transmit malaria
- Resistance alleles
- This method keeps the mosquito (and the gene drive) in the environment

The Discovery of CRISPR-Cas9

In 2014, Esvelt et. al. describes a method for making a CRISPR Cas9 gene drive

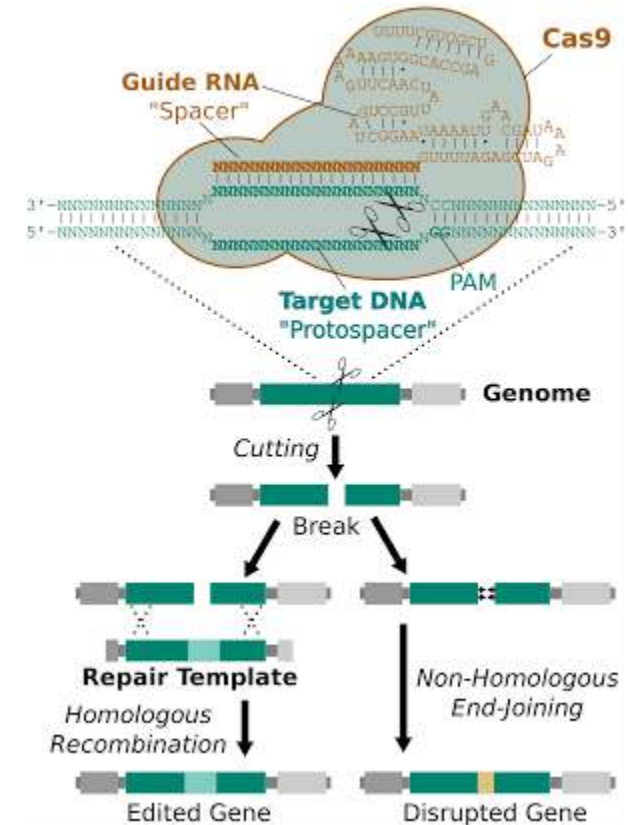
- CRISPR = Clustered Regularly Interspaced Repeats
- Cas = CRISPR associated protein

Cas proteins recognize a DNA sequence, and can cut it

- Just like a homing endonuclease
- But are MUCH easier to work with and “program” to target sequences of choice

This immediately changes the outlook for practical use of gene drives

- And everyone freaks out...



<http://www.sculptingevolution.org/research/tools>

Where Does the ILSI Research Foundation Come In?

In early 2016, the Foundation for the National Institutes of Health approached ILSI RF

- Based on our body of work with environmental risk assessment of GE crops
- To help them put together a workshop to begin discussion about what would be needed for environmental risk assessment of gene drive in *Anopheles gambiae* for malaria control

What they were after was a Problem Formulation Exercise

- An ordered scoping process to help determine what potential harms might occur to the environment
- And identify the sort of information you might use to estimate the likelihood of those harms occurring

Workshop: Problem Formulation for the use of Gene Drive in *Anopheles gambiae* for Malaria Control

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)



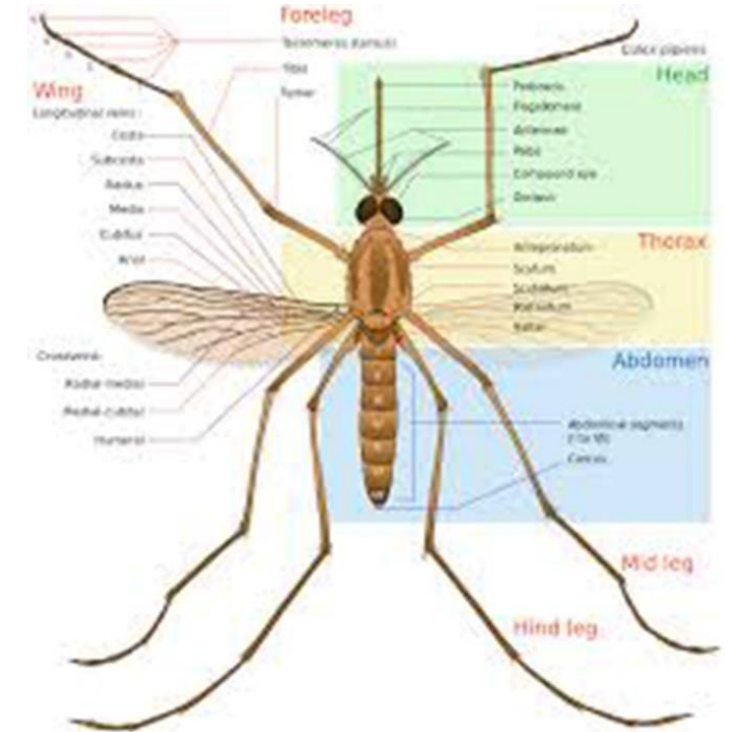
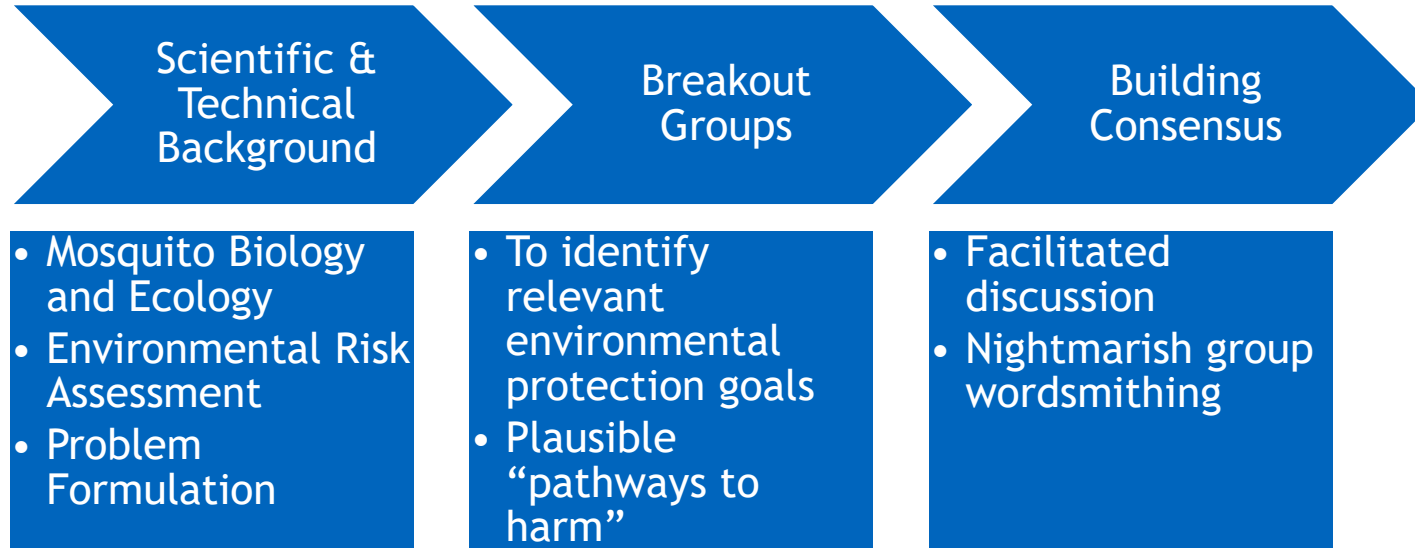
Purpose of the Workshop

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 collecting data in support of risk assessment

Provide a rational starting point for regulators to think about the use of this technology for this particular application

Three Day Structure



Consensus Points



Non-Pertinent Broad Protection Goals:

- Soil Quality
- Air Quality
- Natural Resources (other than biodiversity)
- Agricultural Production (excluding animal health)

Am. J. Trop. Med. Hyg., 96(3), 2017, pp. 530–533

doi:10.4269/ajtmh.16-0726

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Perspective Piece

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

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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.

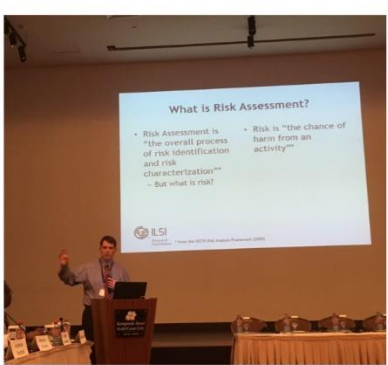
Consultations

Subsequent to the Reston Workshop, the New Partnership for African Development (NEPAD) suggested that it would be useful to take this methodology to more direct consultations with African regulators and stakeholders

Proposed a series of regional workshops

- Accra, Ghana in October 2016
- Nairobi, Kenya in July 2017
- Gaborone, Botswana in July 2017
- Libreville, Gabon in February 2018 (coming soon!)

Structure of the workshops is very similar to the activity in Reston



Some Observations

International experts are much more comfortable excluding protection goals or concluding pathways to harm are implausible than regulators

- Some of this stems from high familiarity and trust in published literature
- It will be interesting to see if/how this changes over time

Socio-economic considerations are difficult for people to exclude from their thoughts on mosquito and malaria control

- Including some lengthy pathways involving lots of human decision points
- Previous experience with vector control programs is useful
- Previous experience with biocontrol organisms may be useful

Problem Formulation methodology is very useful in this context

- And it is clear that the assessments are likely to consider very different things than for GE crops
- Biocontrol risk assessments are much more relevant

Next steps

FOR GENE DRIVE

Getting the technology to work

- This is not a trivial endeavor

Generating the data needed to inform risk assessment and decision making

Encouraging governments and international organizations to think about a pathway to use

FOR ILSI RESEARCH FOUNDATION

Publish the results of the African consultations

Continue to work with stakeholders to refine the necessary risk assessment framework to support decision making on gene drive

Acknowledgments

ILSI Research Foundation Staff

- Dr. John Teem
- Ms. Libby Williams
- Ms. Karen Christianson

FNIH

NEPAD

Participants in all the workshops

Thank you!

http://www.ajtmh.org/content/journals/10.4269/ajtmh.16-0726#html_fulltext