Advances in Gene Drive for Vector-borne Disease Control

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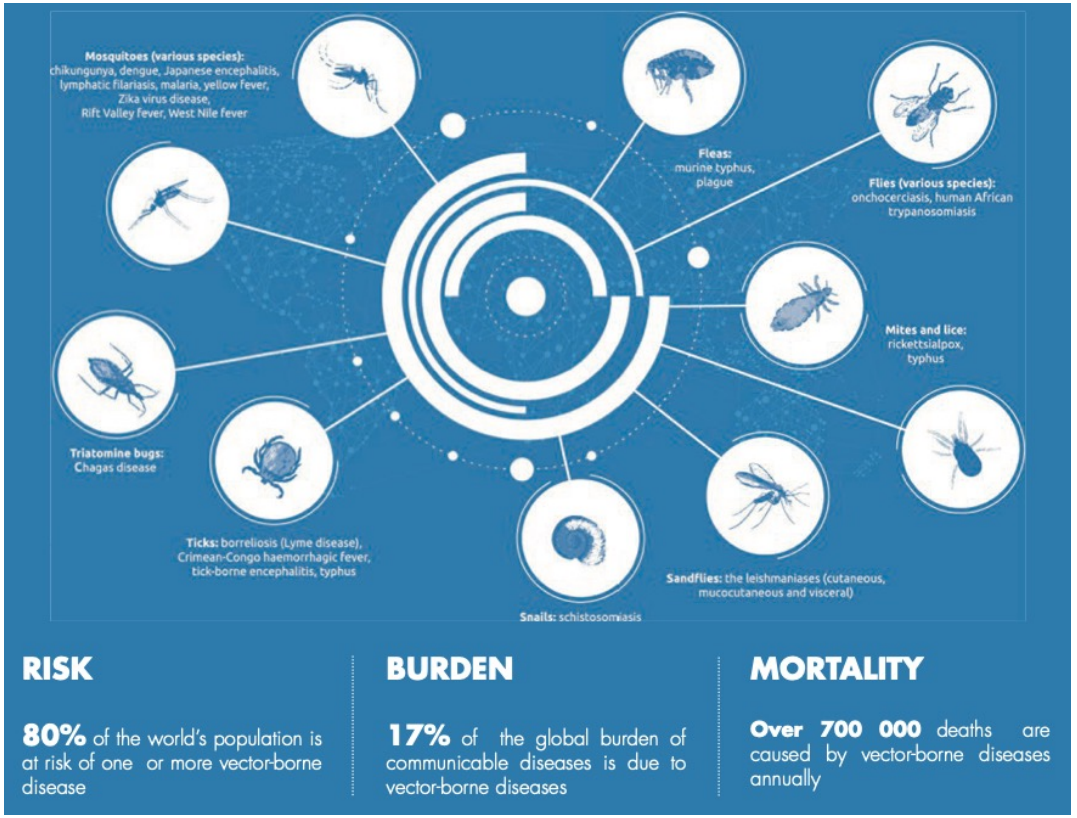
Outline

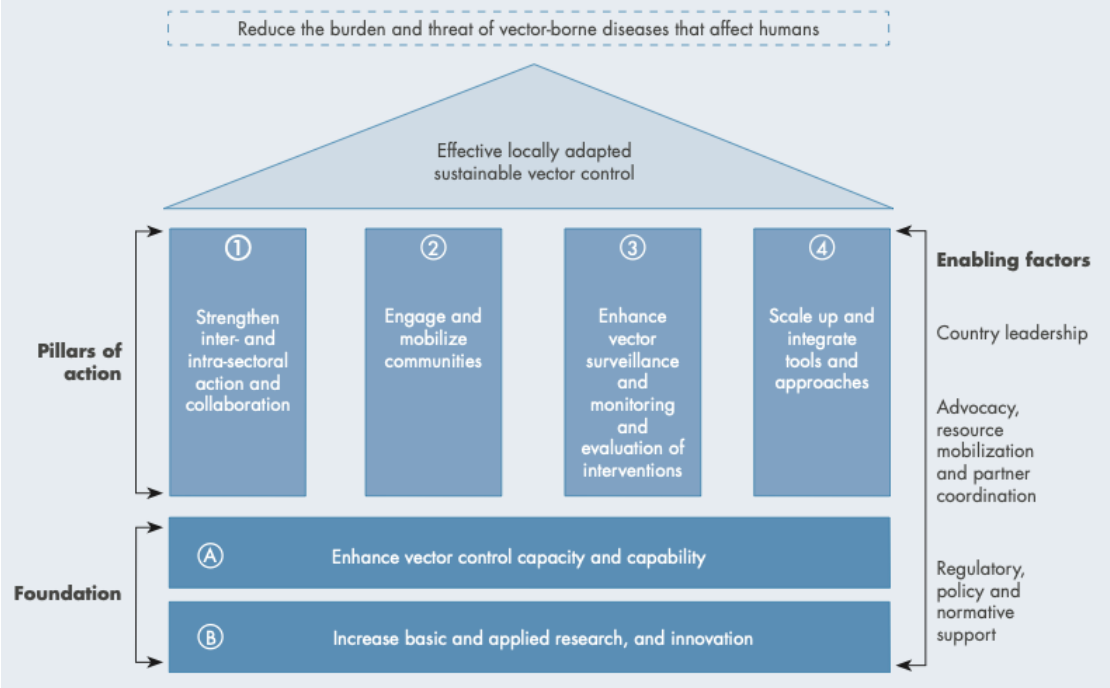
- Introduction
- Mosquito Genetic Transformation
- Gene Drive Technologies
- Applications of Gene Drive Technologies
- Transmission Zero (T0) project

Introduction

Why Vector-borne Diseases?

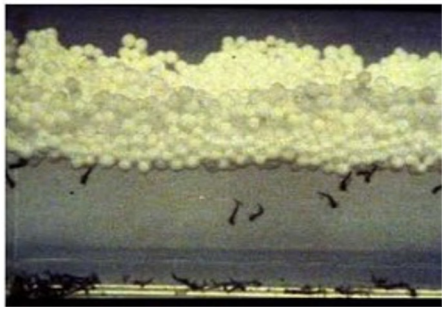


Response Framework



Mosquito Genetic Transformation

Why Genetically Modify Mosquitoes?



What Makes a Mosquito Good Malaria Vector?

FACTORS:

Host feeding behaviour
(human biting preference?)

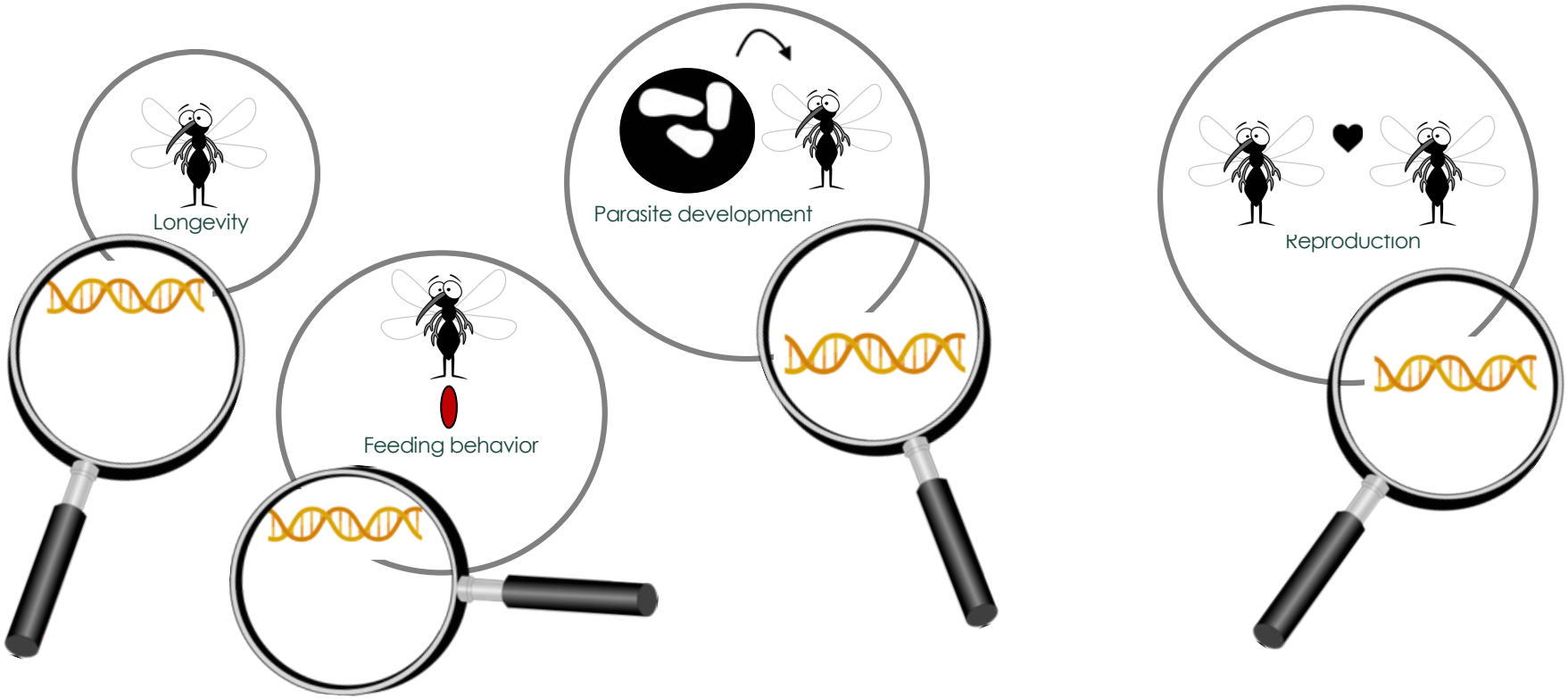
Vector susceptibility
(immunity to parasite?)

Vector longevity
(sufficient time for parasite to develop?)

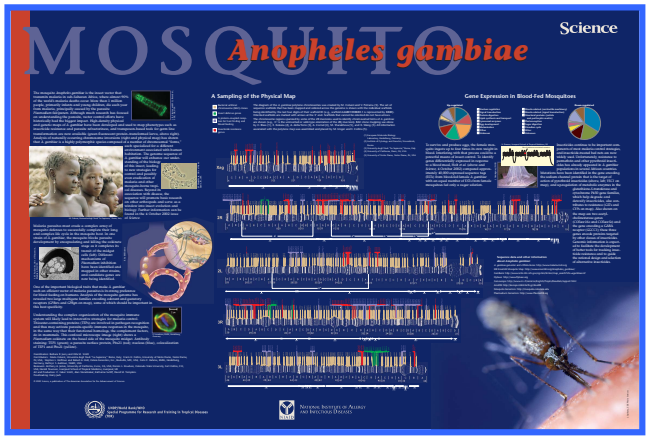
Vector density
(high reproductive rate?)

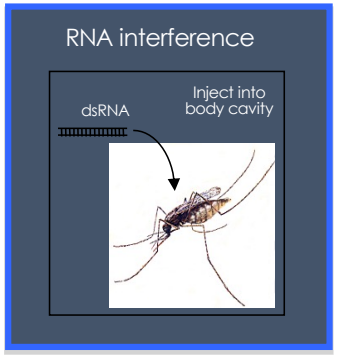
Habitat preference
(frequency of contact with human host?)
(preference for man-made habitats?)

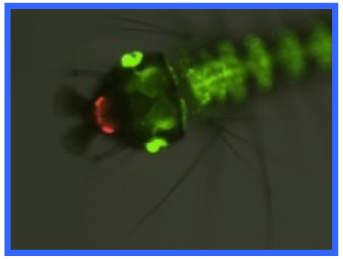
Vector Competence is Genetically Determined

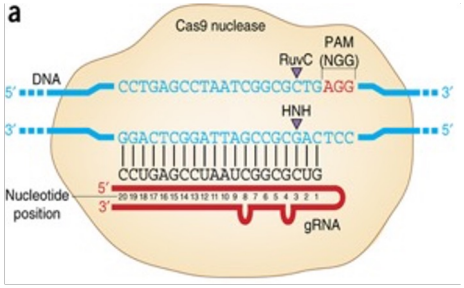


Genetic Tools to Study the Biology of Mosquitoes





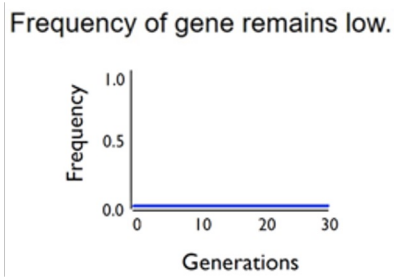




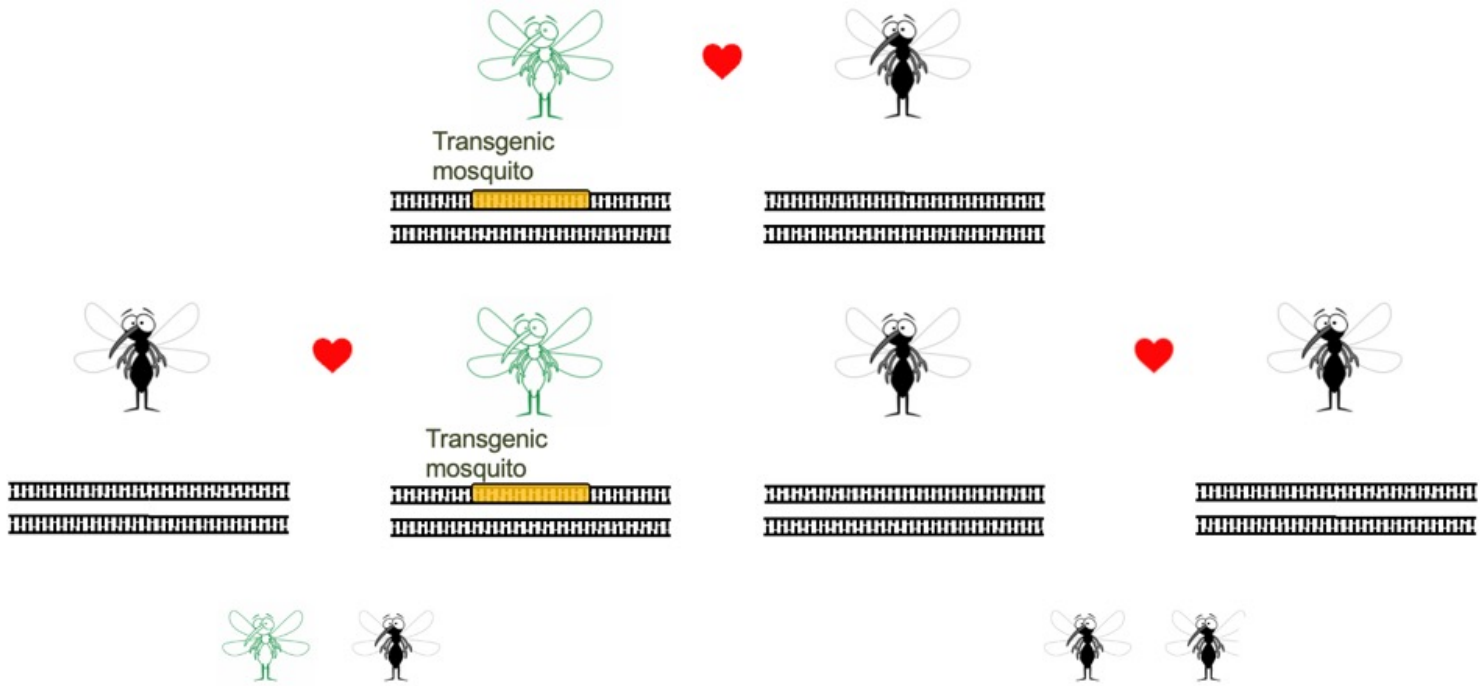
Holt et al., Science 2002
Catteruccia, Nolan et al., Nature 2000
Blandin et al., EMBO Reports 2002

Genetic Modified Mosquitoes….cont'd

- Resistance to parasite
- Insecticide susceptibility
- Behavioural change
- Sterility

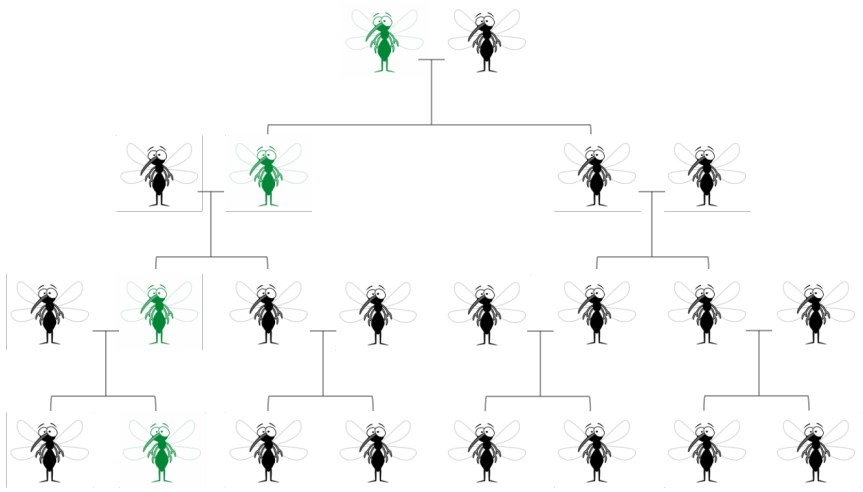


Mendelian Inheritance



Mendelian Inheritance….cont'd

The frequency of a genetic modification in a population will not increase above its release frequency

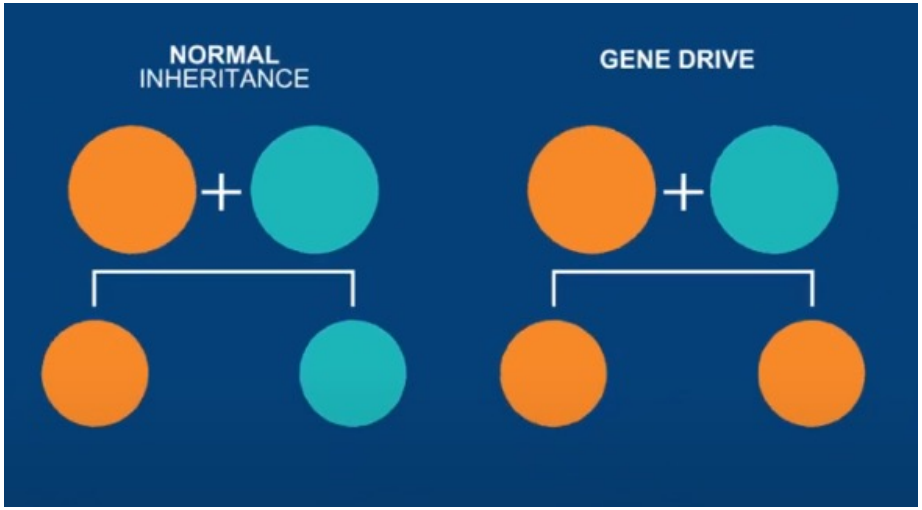


Altered gene does not spread

Genetic modifications like all genetic traits is transmitted to half of the progeny and will not increase above release frequency

Gene Drive Technology

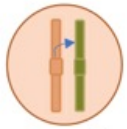
What is Gene Drive?



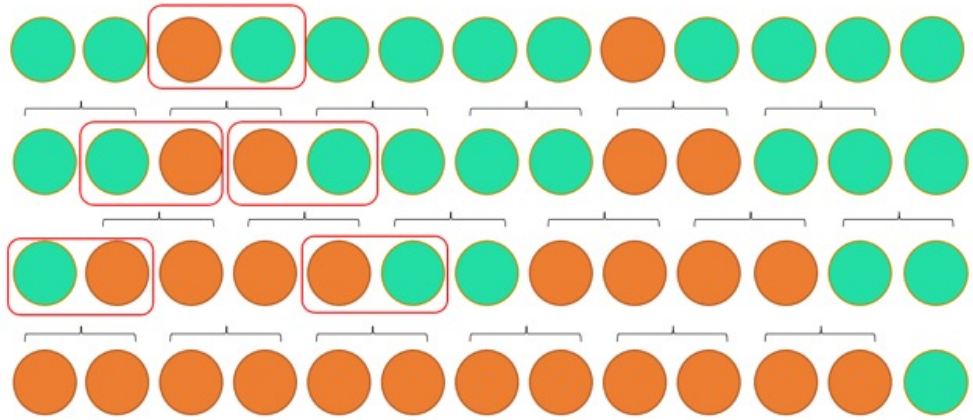
- Natural genetic phenomenon.
- It is any genetic element that is able to bias its own inheritance among offspring.
- Requires sexual reproduction.

Gene drives could make a selected trait to become increasingly common within a specific species.

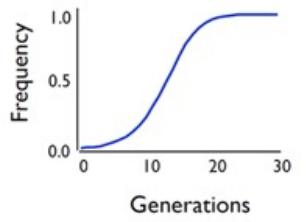
Gene Drive Inheritance in a Population



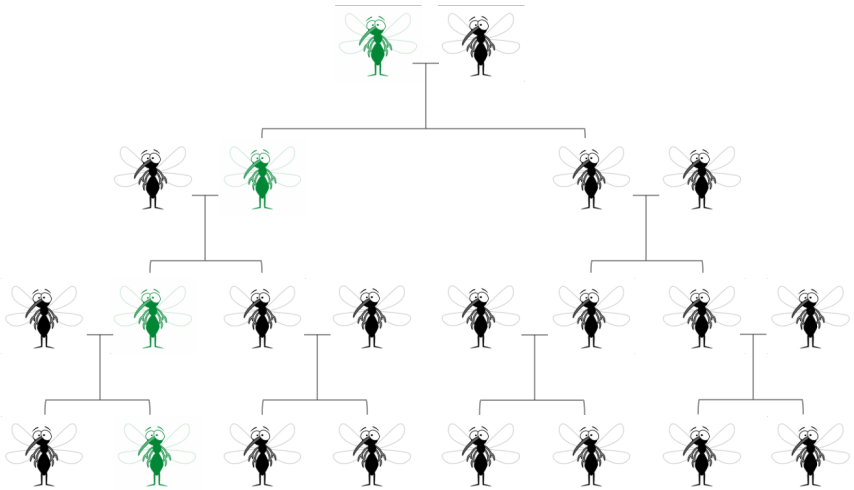
gene drive



Can transform an entire population in a few generations

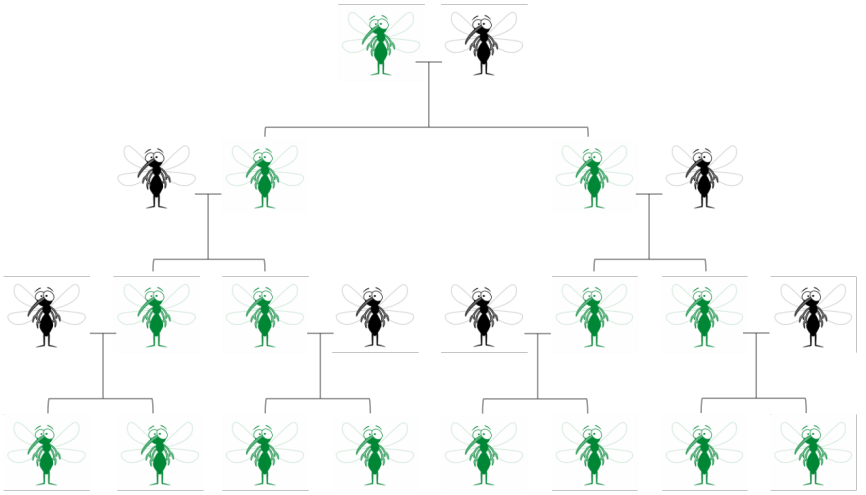


Gene Drive Inheritance….cont'd



Altered gene does not spread

Gene drive inheritance in mosquitoes

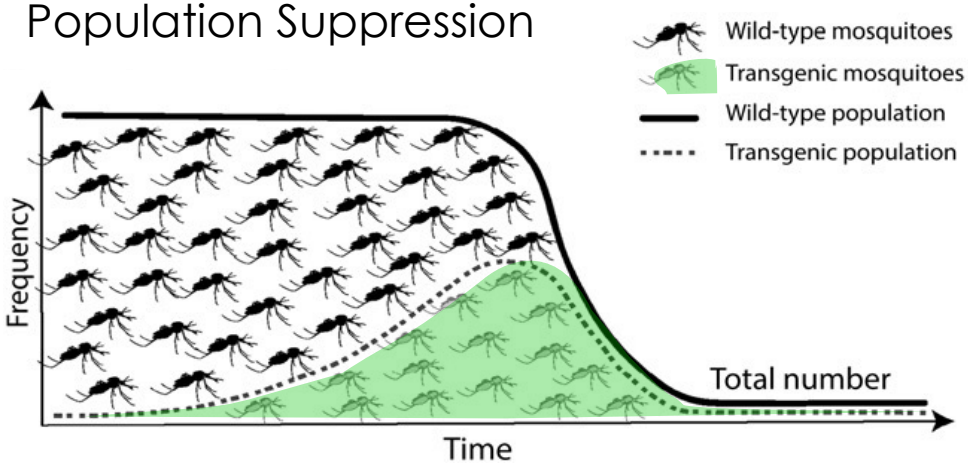


Altered gene is always inherited

Gene drive → Super Mendelian Inheritance

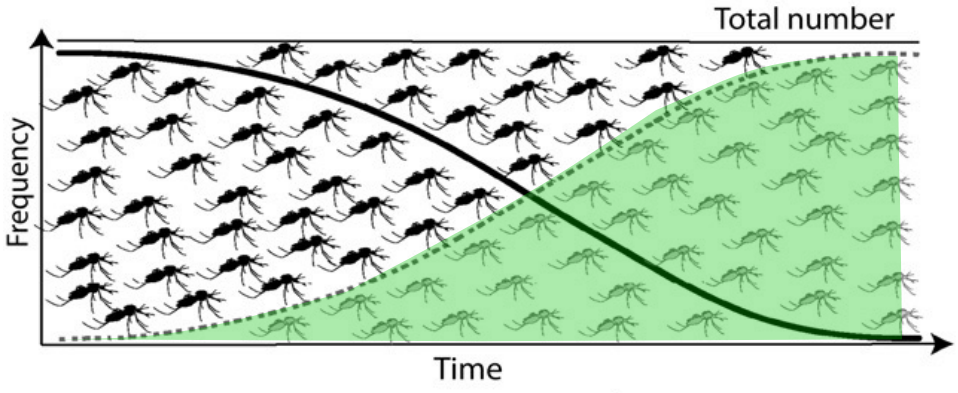
Gene Drives for Vector-borne Disease Control

Population Suppression



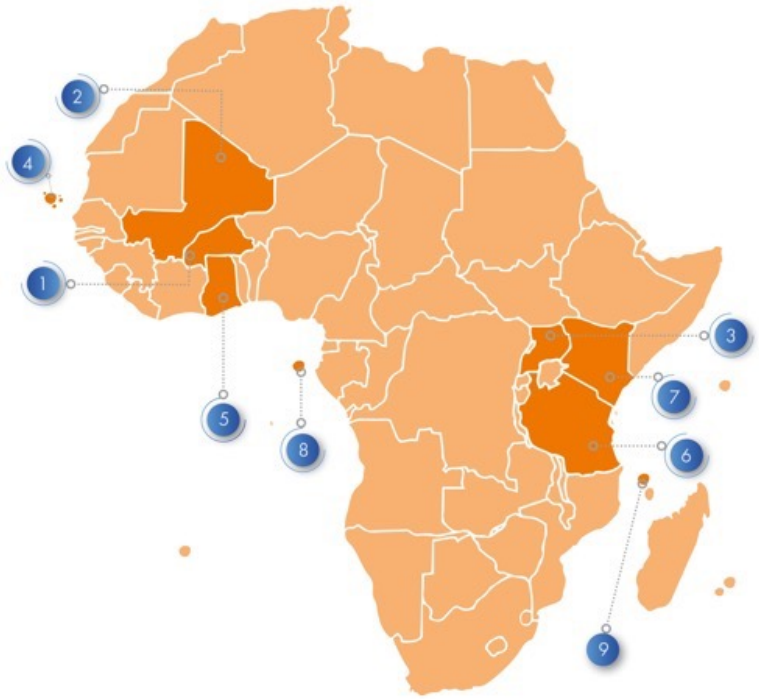
Gene drive disrupts an essential mosquito gene

Population modification (replacement)



Gene drive propagates antimalarial effect

Who Works on Gene Drive Mosquitoes in Africa?



Works on gene drive mosquitos in Africa

1 **Burkina Faso** Mosquito suppression

2 **Mali** Mosquito suppression

3 **Uganda** Mosquito suppression

4 **Carpe Verde** Mosquito suppression

5 **Ghana** Ecological

6 **Tanzania** Mosquito replacement

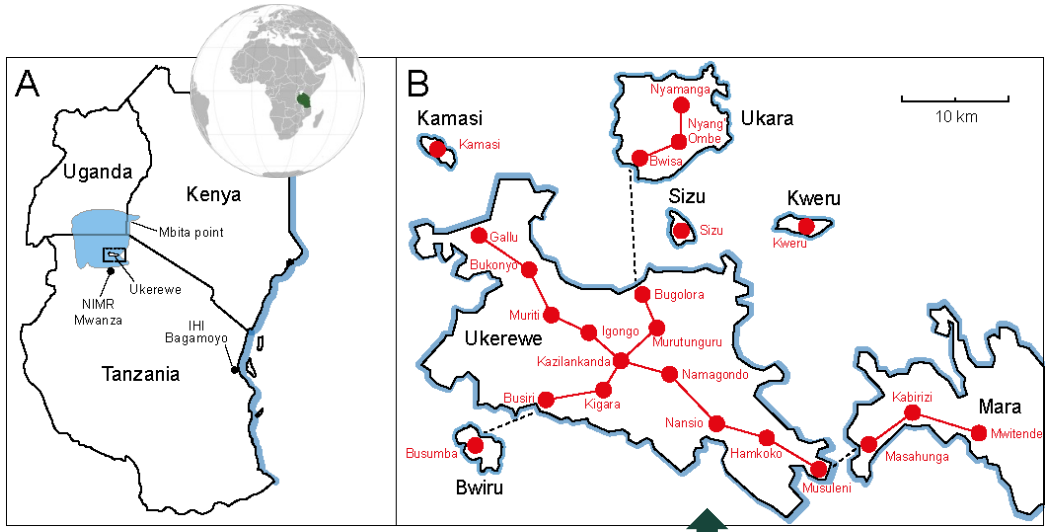
7 **Kenya** Advocacy

8 **Sao Tome, Principe** Mosquito replacement

9 **Comoros** Mosquito replacement

Transmission Zero (T0) project

Who is transmission zero ?



IMPERIAL

IFAKARA HEALTH INSTITUTE

Swiss TPH

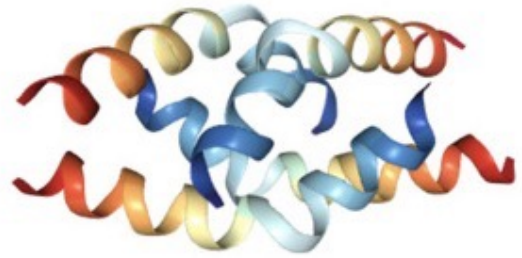
- Collaboration:
  - Imperial College London
  - Ifakara Health Institute
  - NIMR
  - Swiss TPH
- Focus on population modification
- Transgenic work at IHI Bagamoyo
- Field work in Ukerewe district (Lake Victoria).

Transgenic Mosquitoes Developed

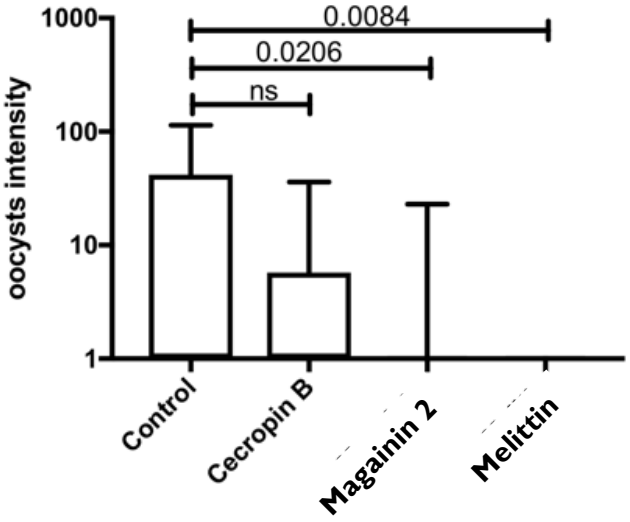
MM-CP strain expressing antimicrobial peptides (AMPs)

Two Antimicrobial Peptides as Effectors

Magainin 2 - GIGKFLHSAKKFGKAFVGEIMNS
(Xenopus laevis)

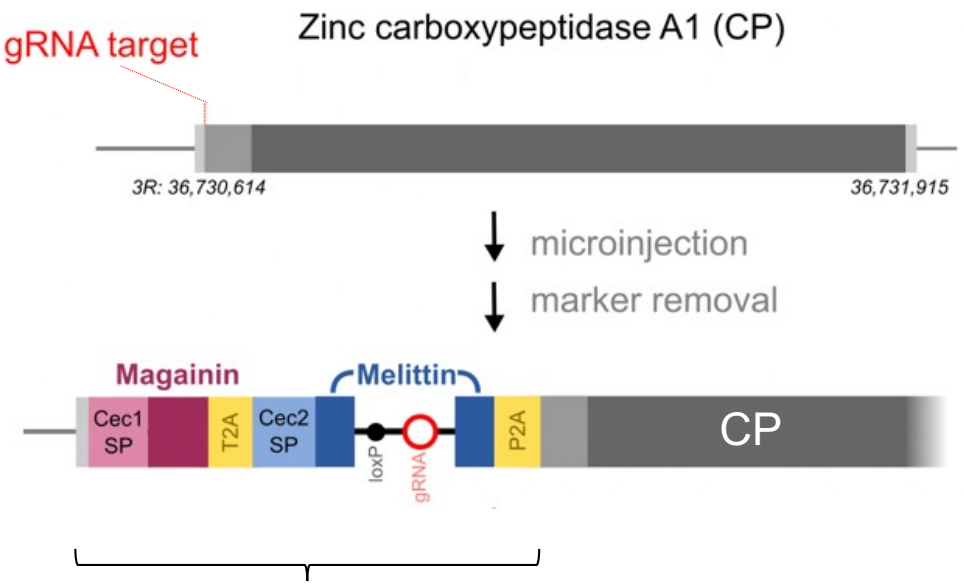


Melittin - GIGAVLKVLTTGLPALISWIKRKRQQ
(Apis mellifera)



Magainin2 & Mellittin block *P. falciparum* transmission in the SMFA when spiked into the bloodmeal

Expression of Magainin2 & Melittin from a mosquito midgut gene



Tiny genetic modification

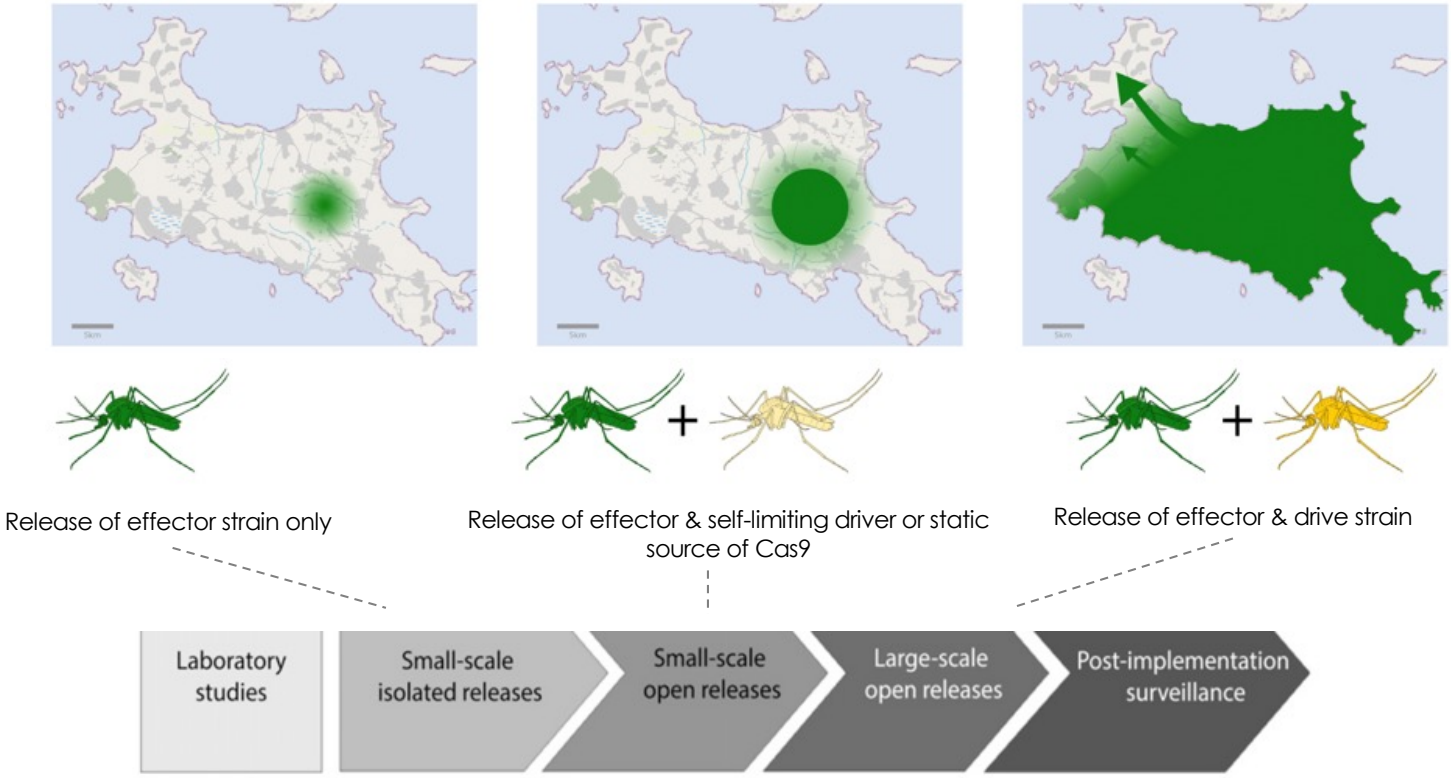
(0.8 kb transgene) i.e. 800 letters/ 278,000,000 letters

Phased Approach to Testing & Deployment

Trial phase	Phase 1	Phase 2	Phase 3	Phase 4
Scale of research	Laboratory studies → Population cage studies	Physically-, ecologically-, or genetically-confined studies → Small-scale isolated releases	Small-scale open releases → Large-scale open releases	Post-implementation surveillance
Potential efficacy endpoints	• Increase in frequency of gene drive system • Impact on vectorial capacity	• Increase in frequency of gene drive system • Spread of gene drive system • Stability of gene drive system, including effector genes • Impact on vectorial capacity	• Increase in frequency of gene drive system • Spread of gene drive system • Stability of gene drive system • Resistance to drive • Impact on vectorial capacity • Impact on malaria	• Impact on vectorial capacity • Resistance to drive • Impact on malaria
Source of potential safety endpoints	• Environmental risk assessment (ERA) informed by laboratory and insectary studies of modified mosquitoes	• ERA • Entomological, epidemiological, and ecological data from field location • Mathematical modelling of gene drive at field location	• ERA • Data and modelling from Phase 2 trials	• Data and modelling from Phase 3 trials
Criteria to move to next phase	• Pre-determined performance milestones based on Target Product Profile (TPP) • ERA indicates gene drive system will do no more harm to human health than wild-type mosquitoes of the same genetic background, and no more harm to the ecosystem than other conventional vector control interventions	• Pre-determined performance milestones based on Target Product Profile (TPP) • ERA indicates gene drive system will do no more harm to human health than wild-type mosquitoes of the same genetic background, and no more harm to the ecosystem than other conventional vector control interventions	• Pre-determined performance milestones based on Target Product Profile (TPP) • ERA indicates gene drive system will do no more harm to human health than wild-type mosquitoes of the same genetic background, and no more harm to the ecosystem than other conventional vector control interventions	• Pre-determined performance milestones based on field data
Biosafety considerations in African context	• Persistence and spread of low threshold gene drive mean that Phases 1 to 4 represent a continuum of biosafety considerations for field trials • Need for additional precautions beyond those for other genetically modified organisms in order to avoid escape into the environment in Africa	• Guarantee of physical confinement in Africa becomes uncertain when escape of small numbers of mosquitoes capable of self-sustaining gene drive could lead to their establishment in a local mosquito population	• Series of trials of increasing size, duration, and complexity conducted at single or multiple locations effectively constituting limited implementation of gene drive vector control across Africa	• Monitoring of gene drive system and resistance to drive

Connolly et. al., 2024

Phased Approach to Testing & Deployment….cont'd



WHO, 2021


Ahsanteni