New vector control strategies for Malaria Elimination

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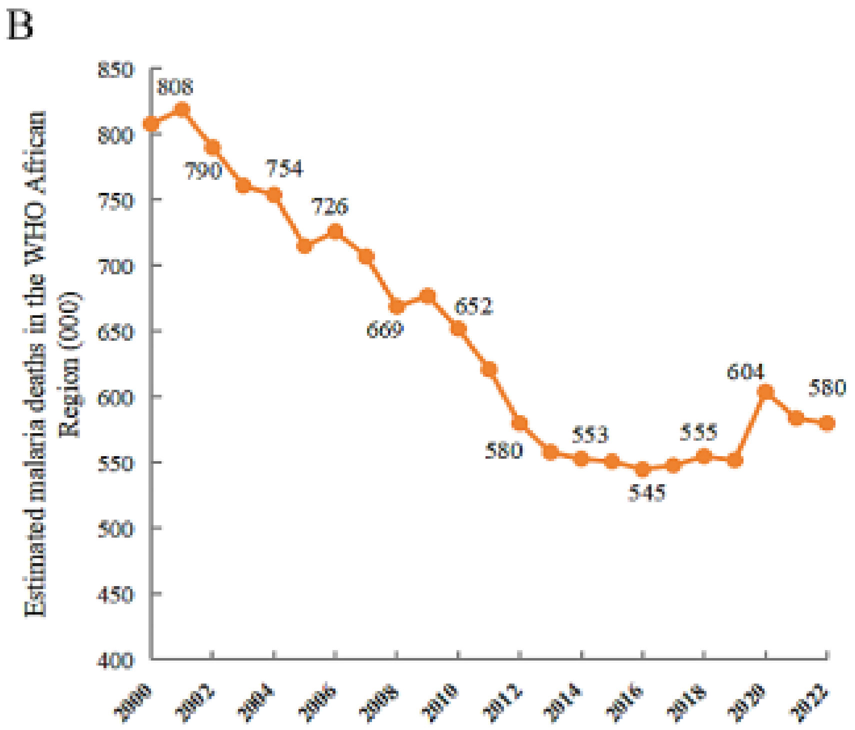
Presentation outline

- ❑ Background: Burden of malaria
- ❑ Need for Innovative Vector Control Strategies
- ❑ Non-Chemical and Non-Genetic Based Control Methods
- ❑ Genetic Based Control Methods
    - Release of Insects carrying a Dominant Lethal: RIDL
    - Sterile Insect Technique Principle
    - Wolbachia and IIT
    - Gene drives

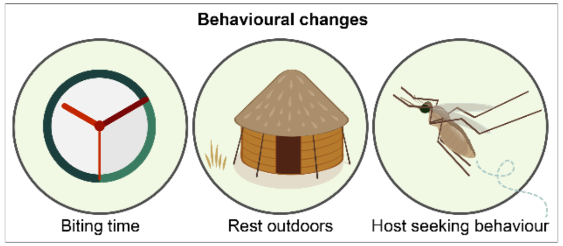
Malaria situation



- In 2022 ±249 million cases worldwide
- 94% (±233 million cases) were from countries in the WHO African region
- WHO African Region reduced from 370 to 226 per 1,000 populations at risk between 2000 and 2019
- increased to 232 per 1,000 populations at risk in 2020, mainly because of disruptions to health services during the COVID-19
- Global progress has now remained stagnant.
- high burden countries, mainly in sub-Saharan Africa, have seen an increase in cases and deaths

Need for complementary malaria vector control strategies

Vector behavioural change



Emerging new vectors
Secondary vectors

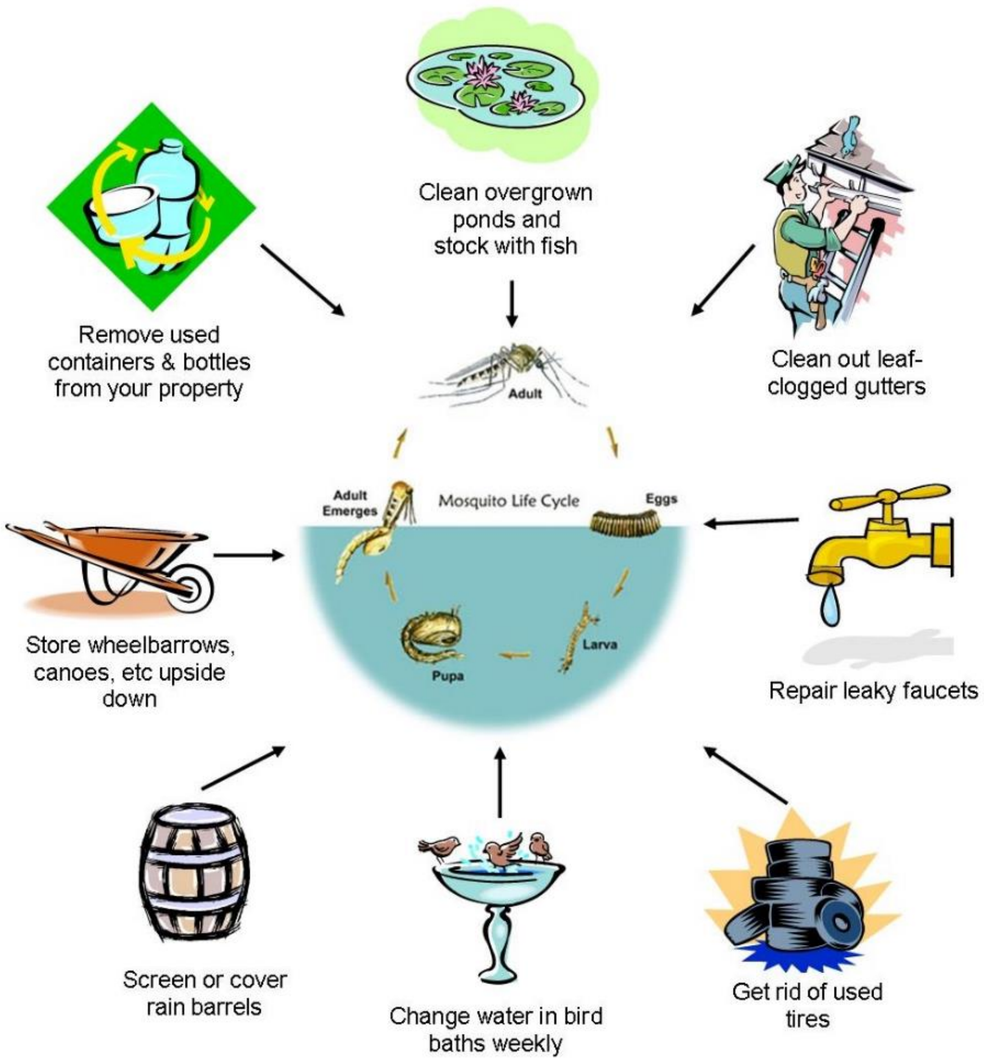
Insecticide resistance

Vector species	Pyrethroids		DDT		Organophosphates		Carbamates	
	Target-site	Metabolic	Target-site	Metabolic	Target-site	Metabolic	Target-site	Metabolic
An. gambiae s.s	✓	✓	✓	✓	✓		✓	✓
An. funestus s.s				✓				✓
An. arabiensis	✓		✓	✓	✓		✓	
An. culicifacies (C)	✓		✓					
An. culicifacies (B)	✓		✓	✓		✓		
An. stephensi	✓	✓	✓	✓		✓		
An. dirus				✓				
An. sacharovi				✓	✓	✓	✓	✓
An. albimanus		✓		✓	✓	✓	✓	

Poor intervention coverage

poverty,?
Substandard health services?

Neglected Technologies: Community education



Larval Source Management

- Environmental management (ecosystem compatible removal of mosquito breeding sites):

- Environmental modification (draining wetlands, constructing drainage canals, covering water tanks and stagnant water, land levelling, filling depressions and pools of water), environmental

- manipulation (irrigation management, clearing of vegetation, planting of trees, removal of trash)

Ecosystem compatible predators (larvivorous fish) and nematodes (under development)

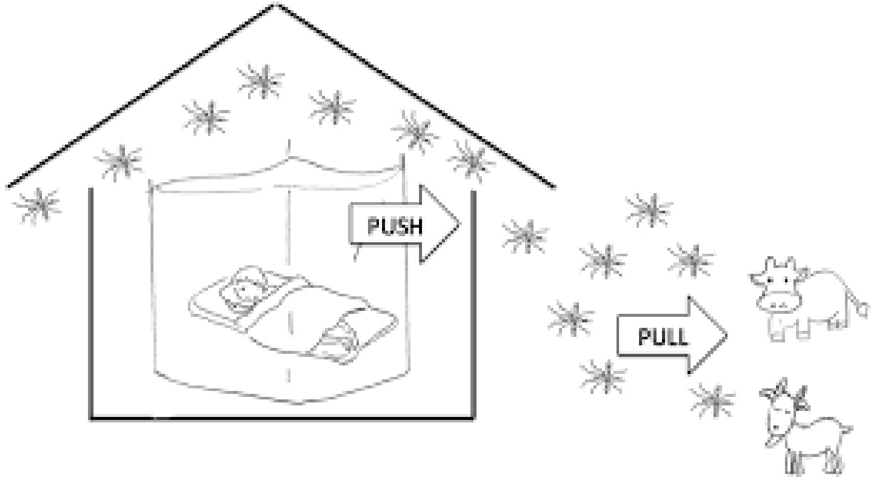
Bacterial larvicides (*Bacillus thuringiensis*)

Botanical larvicides (neem)

Chemical larvicides (Temophos)

Zooprophylaxis

Keeping cattle around homesteads



Spraying cattle with insecticides

Technologies under development: Attractive Toxic Sugar Bait (ATSB)

- Almost all mosquitoes, require a sugar meal shortly after emergence, and throughout their lives

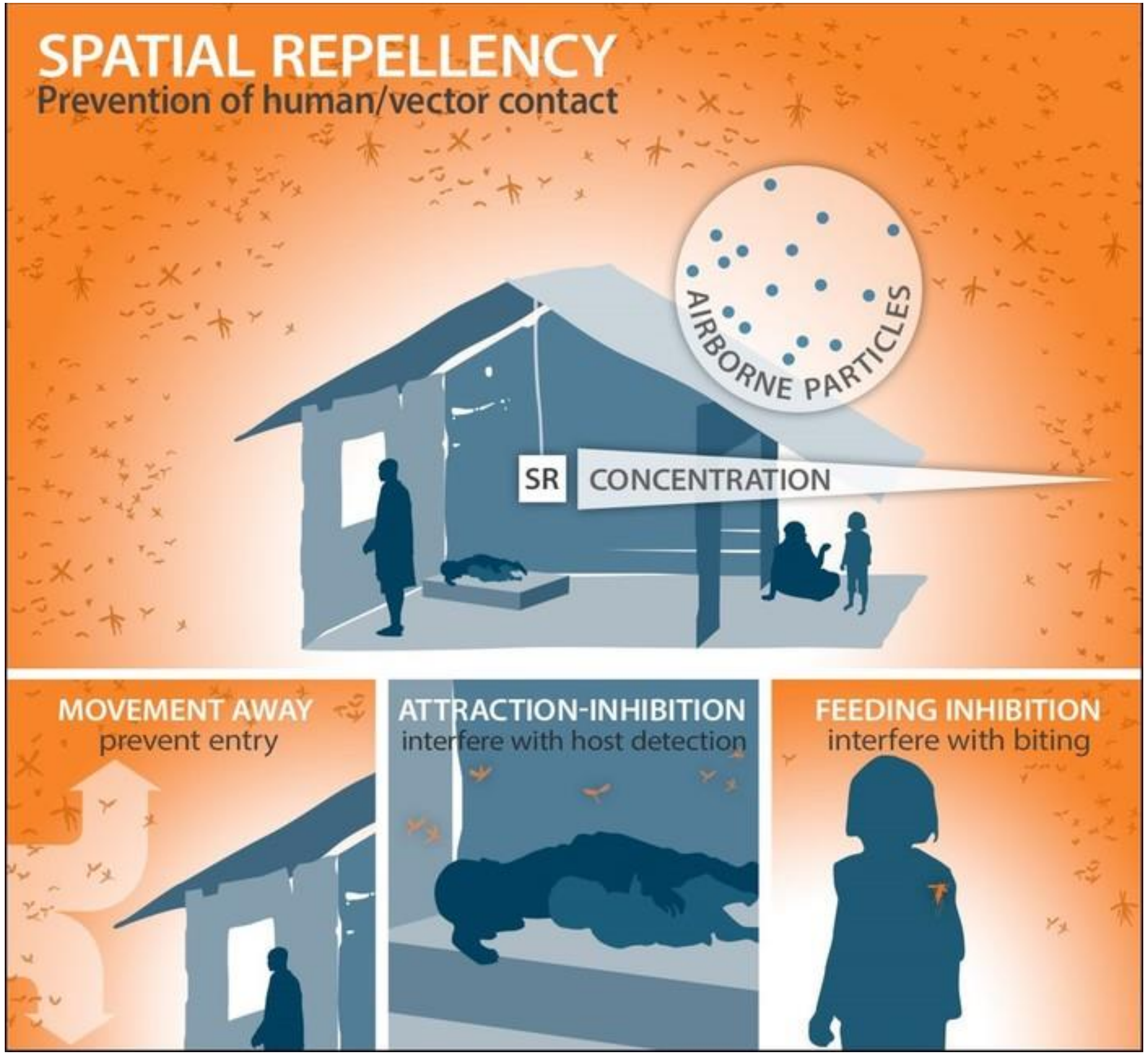
- Both male and female mosquitoes have low chances of mating, blood feeding, developing, and laying eggs without energy reserves formed from carbohydrates

- Comprises a bait with:
  - i) attractive to the species of interest (usually with a fruit or flower scent),
  - ii) contains an oral toxin mixed with sugar as a feeding stimulant

- bait stations, capitalize on resting and sugar seeking mosquitoes therefore placed where mosquitoes rest, and by attracting them from their natural sugar source

- sugar baiting methods have resulted in the control of multiple mosquito species and low impacts on non-target arthropods.

Use of spatial repellent for mosquito control

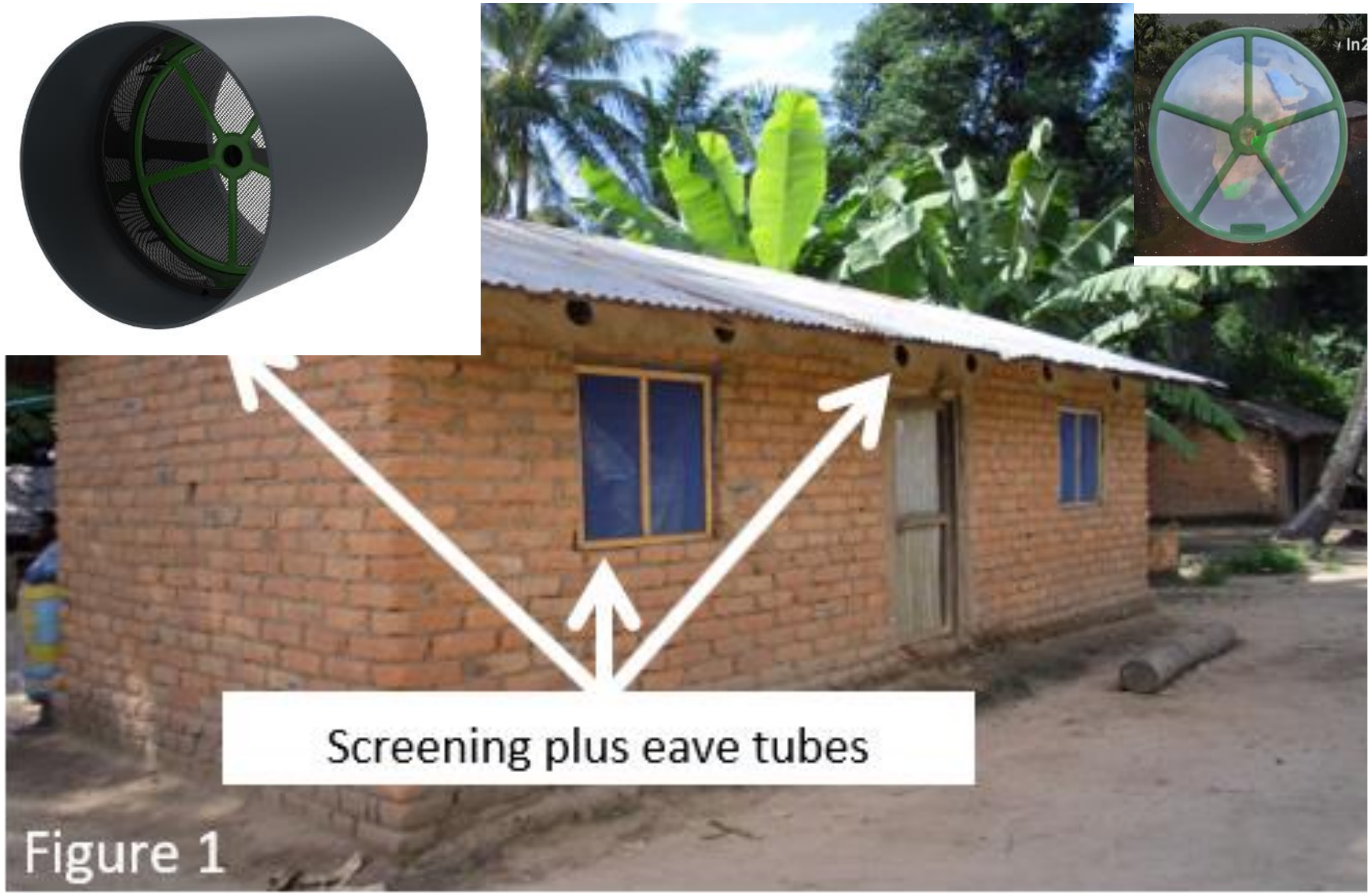


- Entomological outcomes in cRCT
- Malaria cases
- Safety assessment
- Community acceptance
- Trials in Indonesia 27.7% against 1st time malaria and a 60% decrease in infection
- Trials in Peru showed a 34.1 % protective efficacy against dengue and Zika
- In Tanzania 70% reduction in mosquito bites

69% reduction in blood-feeding

House screening

Eave Tubes

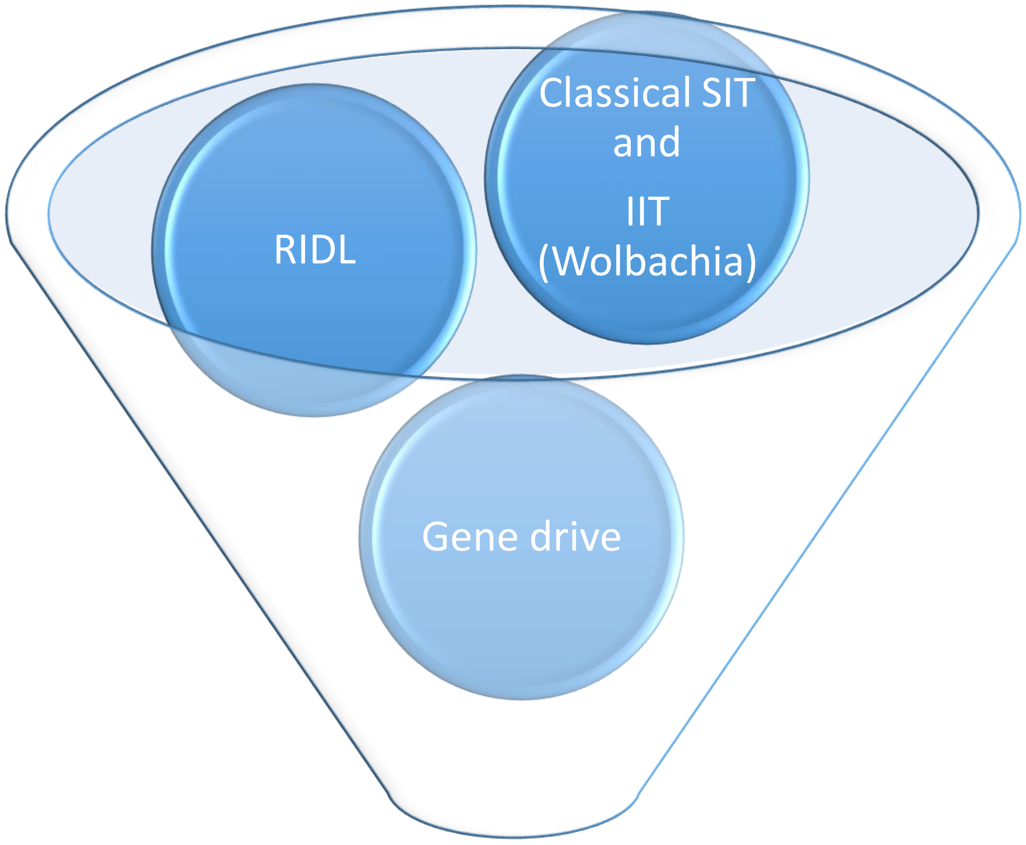


- EaveTubes consist of a PVC tube and insecticide treaded net on a disc
- Can work on all housing structures

- Eaves work as point source for human-scented air to lure mosquitoes /anophelines (warm air rises and escape through eaves.
- disc netting coated with special static charged insecticide capsule i.e. –vely charged and attract +ve charged mosquito (legs
- Gave 40% additional protection compared to LLINS

Emerging Mosquito Elimination approaches :Use of genetically modified mosquitoes (GMM)

Genetically engineering mosquitoes through either the introduction of novel genes or novel variants of genes into the mosquito genome to control their population



- ❑Released organisms do the hard job of finding difficult-to-reach niches.
- ❑Species-specific
- ❑Non-toxic

Strategic options for Genetic based approaches

Strategic options for SIT

- **Suppression**: To reduce vectors below transmission thresholds

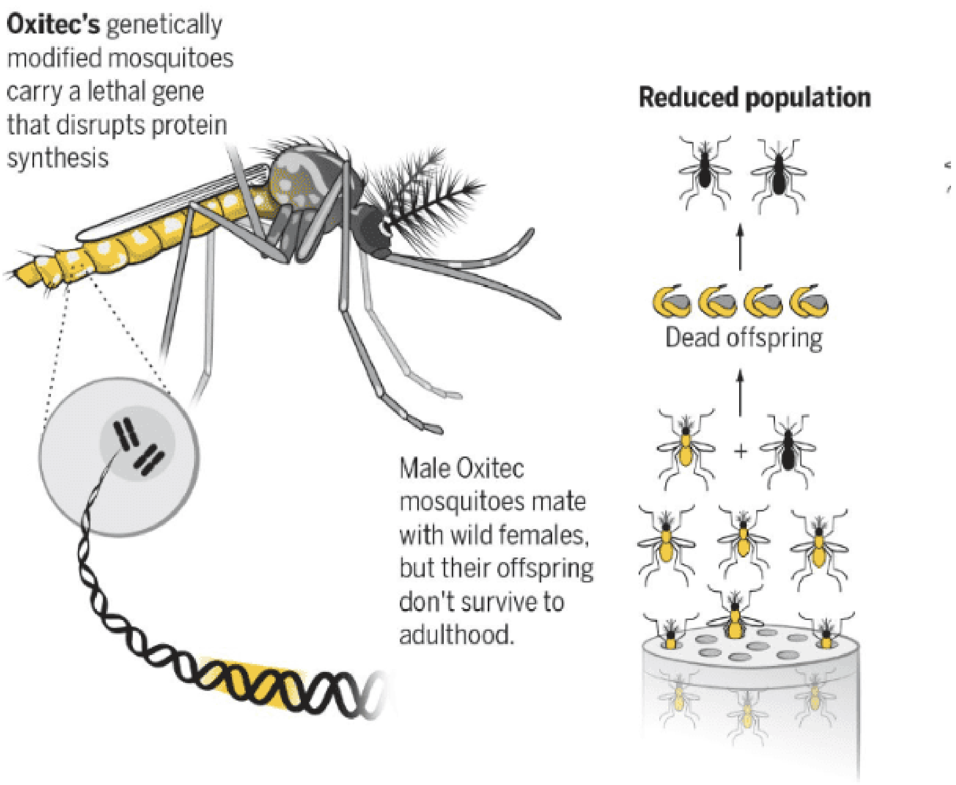
- **Containment**: To avoid the spread of introduced non-native species

- **Prevention**: To avoid the establishment of a non-native species

- **Eradication:** To develop areas free of major disease vectors, reduce costs and facilitate international trade or eliminate outbreaks of invasive species

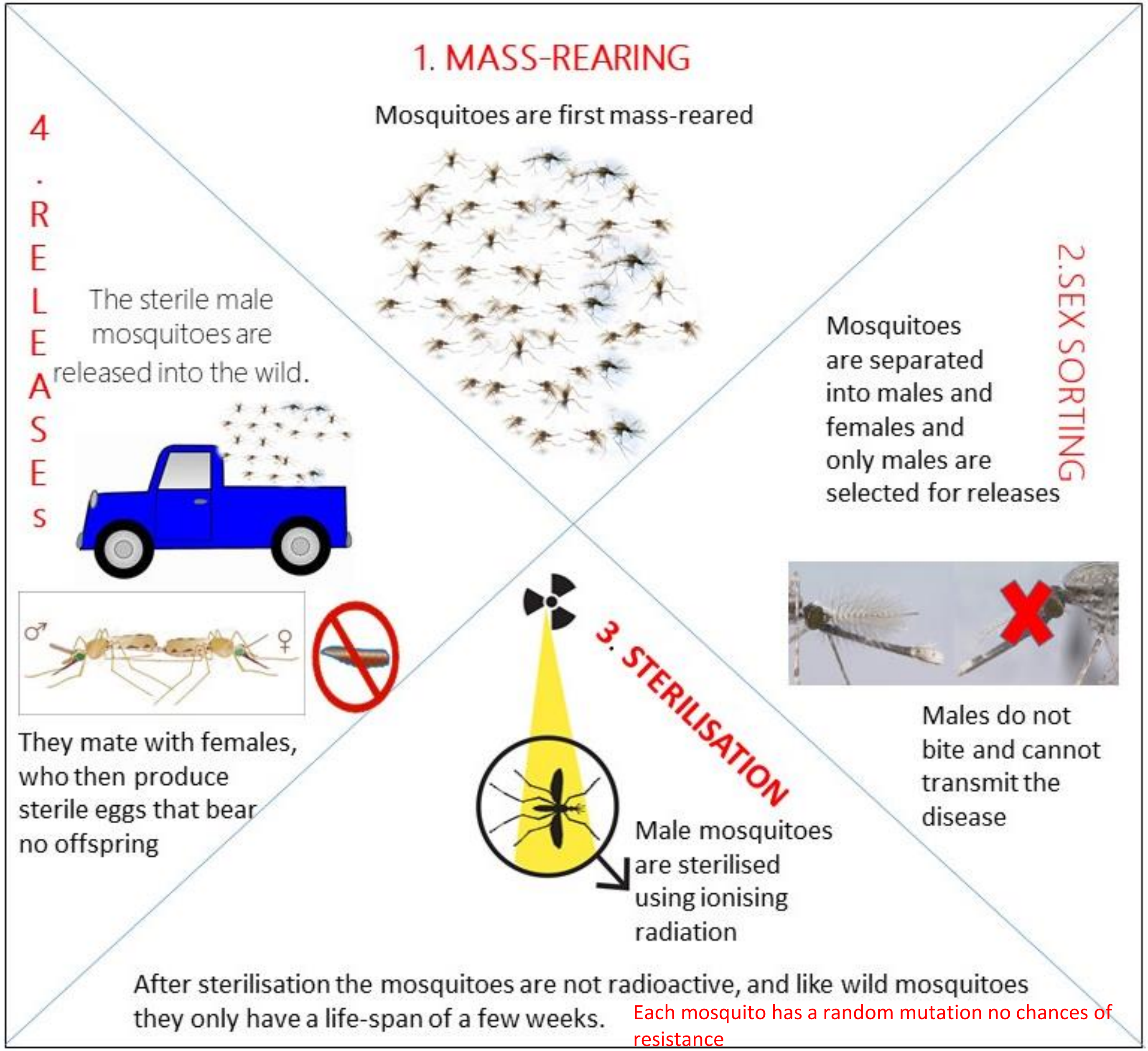
- **Population replacement**: Replacing a wild population with a genetically modified population (gene drives)

Release of Insects carrying a Dominant Lethal: RIDL

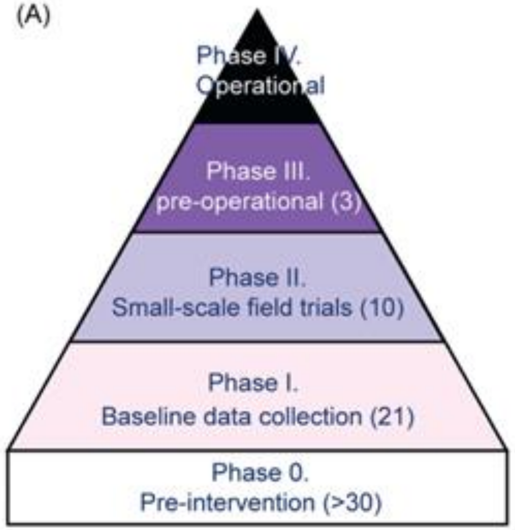


- Male mosquitoes are genetically engineered to possess a gene encoding a lethal factor.
- The lethal factor can be switched on and off
- Modified males are released into the wild to mate with wild females.
- The lethal gene is passed on to offspring, causing them to die before reaching adulthood
- Oxitec developed a strain with a lethal gene that is switched off when mosquitoes are reared in, allowing them to undergo development.
- Male mosquitoes reared in a tetracycline-rich lab environment are released to mate with wild mosquitoes and produce tetracycline-dependent larvae who would be unable to survive to adulthood, thus decreasing the wild population of mosquitoes.
- RIDL relies on sorting and releasing lab-raised mosquitoes.

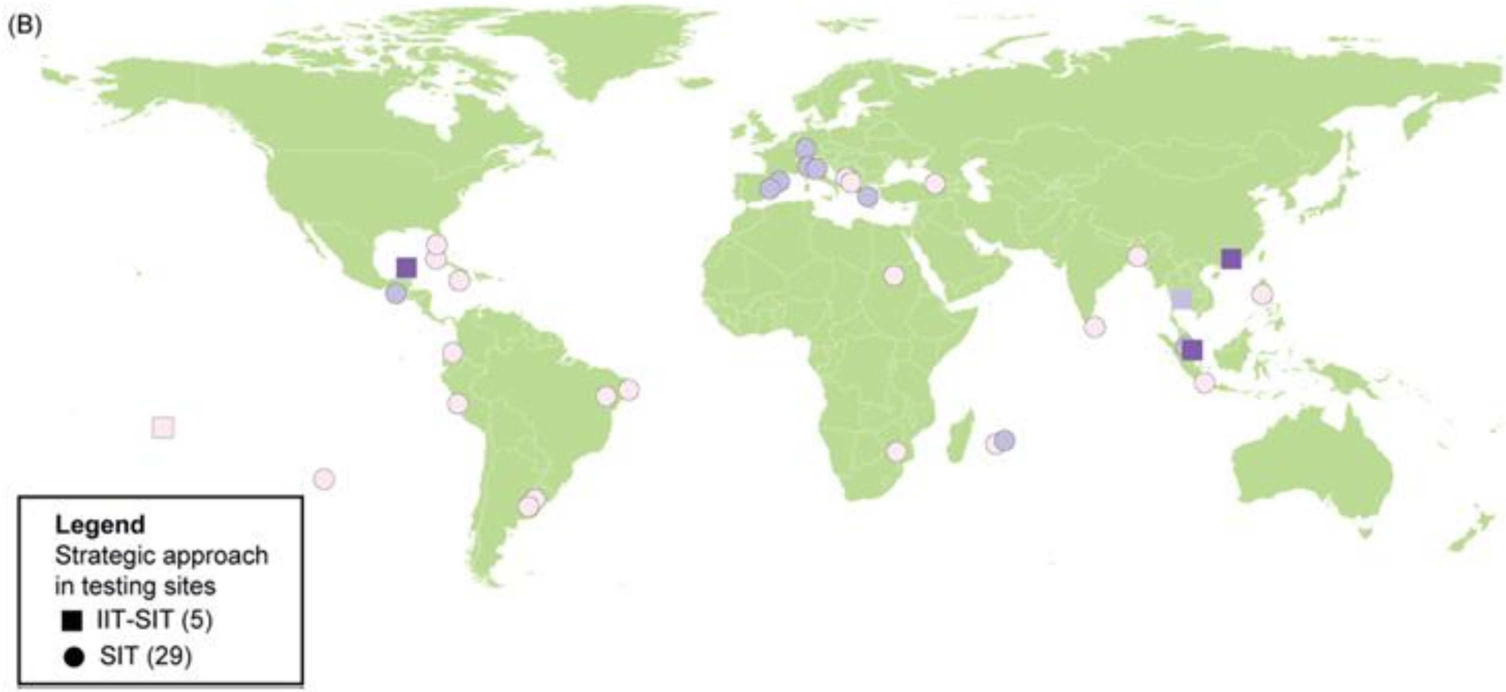
Sterile Insect Technique Principle



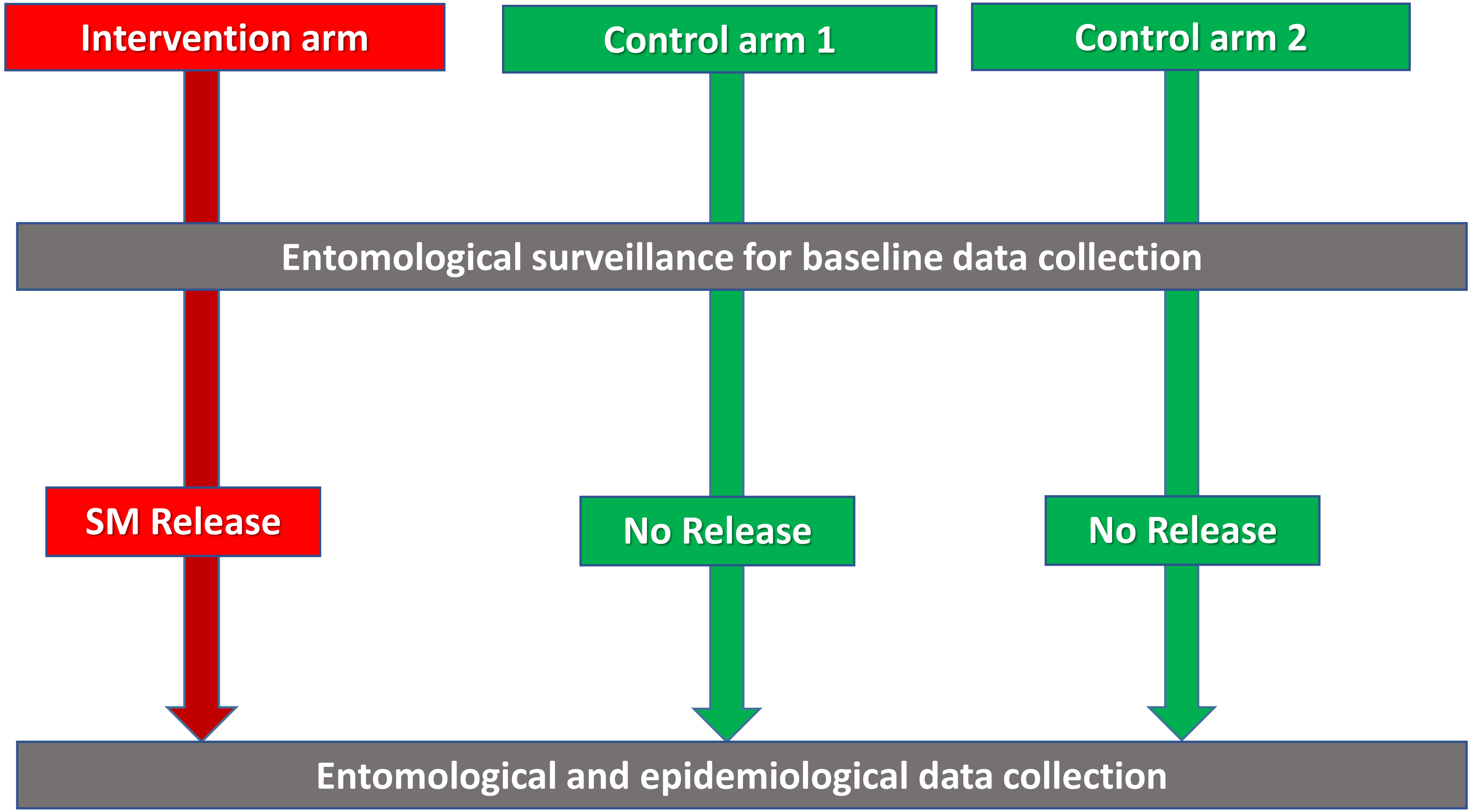
Advances in mosquito Sterile Insect Technique



Several field pilot trials and large scale trials have been completed in Greece, China, Cuba, Italy, and Spain (Bellini et al., 2013; Zheng et al., 2019; Gato et al., 2021; Tur et al. 2023; Balatsos et al., 2024).



Progress in South Africa



Key outcomes

- *An. arabiensis* population density
- Induced Sterility
- Proportion of female An. arabiensis mosquitoes that blood-fed on humans
- The proportion of female An. arabiensis mosquitoes infected with the Plasmodium parasite
- SIT KAP
- Mass rearing productivity

Mass rearing Capacity

<u>Key outcomes</u>

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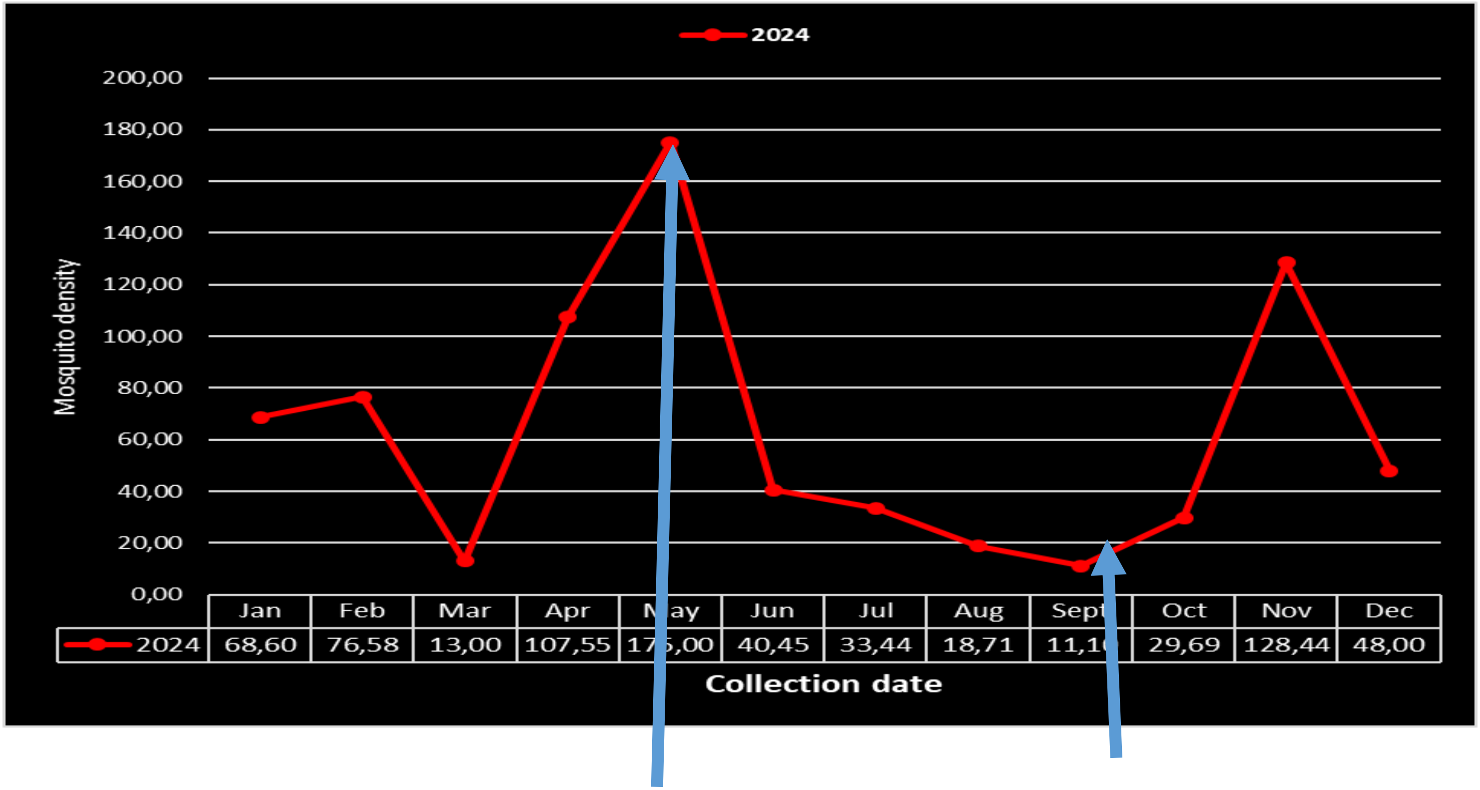
- ❑ SIT KAP
- ❑ Mass rearing productivity

Entomological Impact



1st release

Last release

- An immediate decline in the An. gambiae population density from 175 mosquitoes/month to 40.45 mosquitoes/month after the first releases
- There was a sudden rise of mosquitoes a month after the releases were stopped

- Sterile males were able to locate natural swarms
- inducing sterility in the wild population

Public health value

- Two-arm parallel cRCT over two malaria seasons

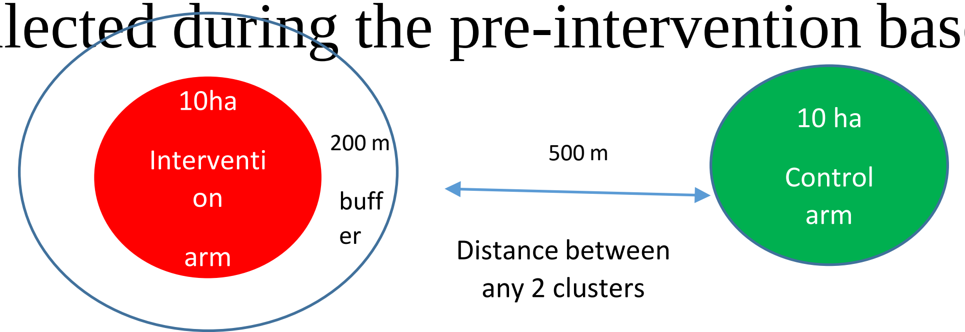
- 40 clusters, each consisting of an area of approximately 10 hectares and a human population of about 3000

- Clusters will be at least 500m apart and randomised 1:1 to

  1) control (standard of care vector control consisting of IRS and winter larviciding

  2) intervention (standard of care vector control consisting of IRS + winter larviciding plus weekly releases of sterile male An. arabiensis mosquitoes

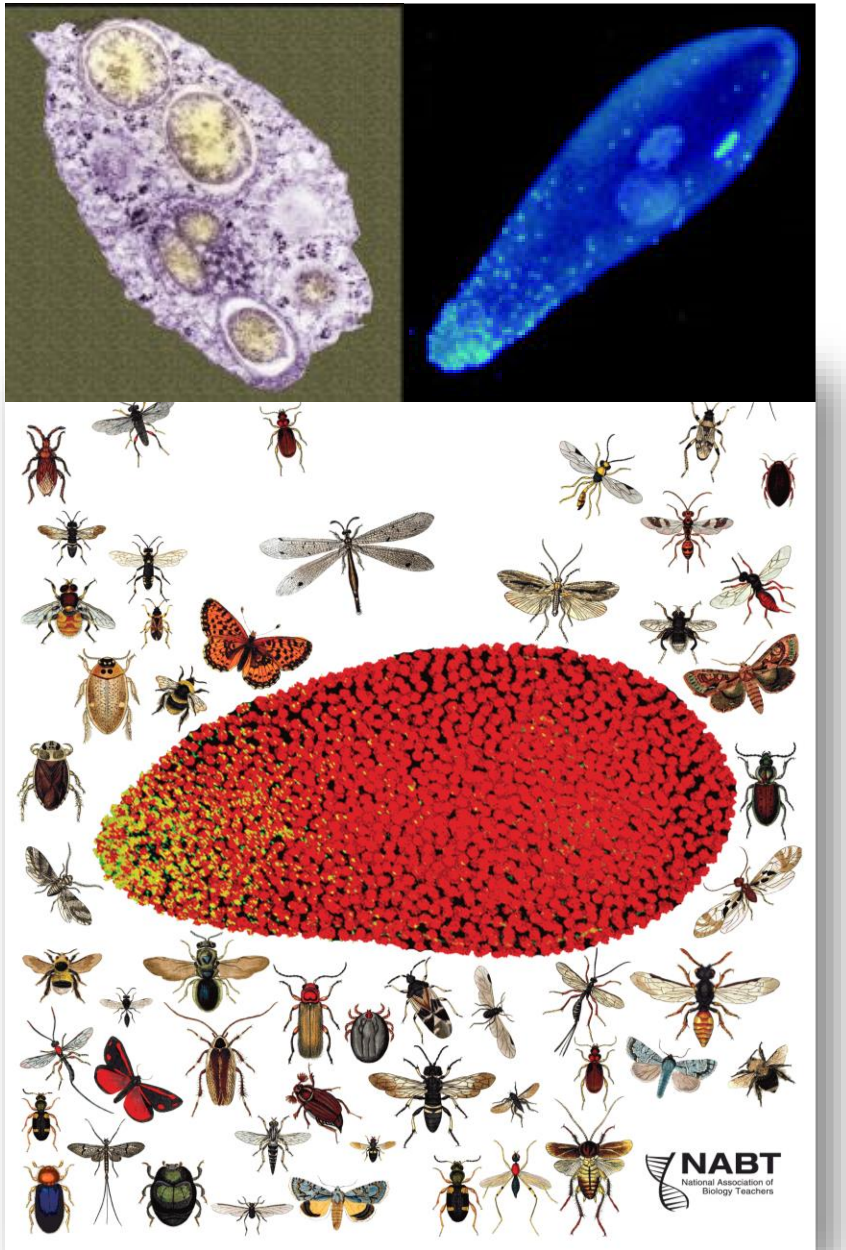
- Constrained randomisation to ensure balance in outcome measures between study arms using data collected during the pre-intervention baseline period



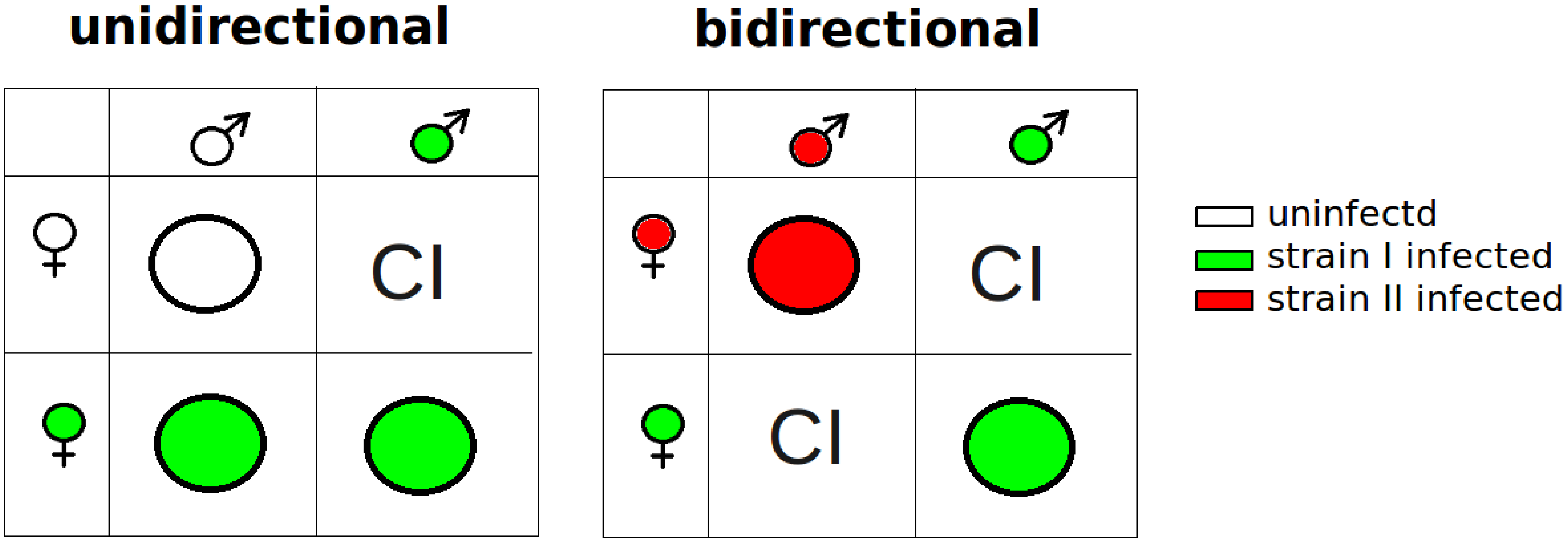
Wolbachia

- ❑Obligate intracellular Gram- symbiotic bacteria in insects that transmit from mother to offspring

- ❑Broad host range
  - Up to 65% of insects
  - but not present in malaria and the primary dengue mosquito vector *Aedes aegypti*
- ❑Can not survive outside of insects
- ❑Neither infect nor transmit to human or vertebrate animals
- ❑Manipulate insect reproduction for its own benefit



Cytoplasmic Incompatibility

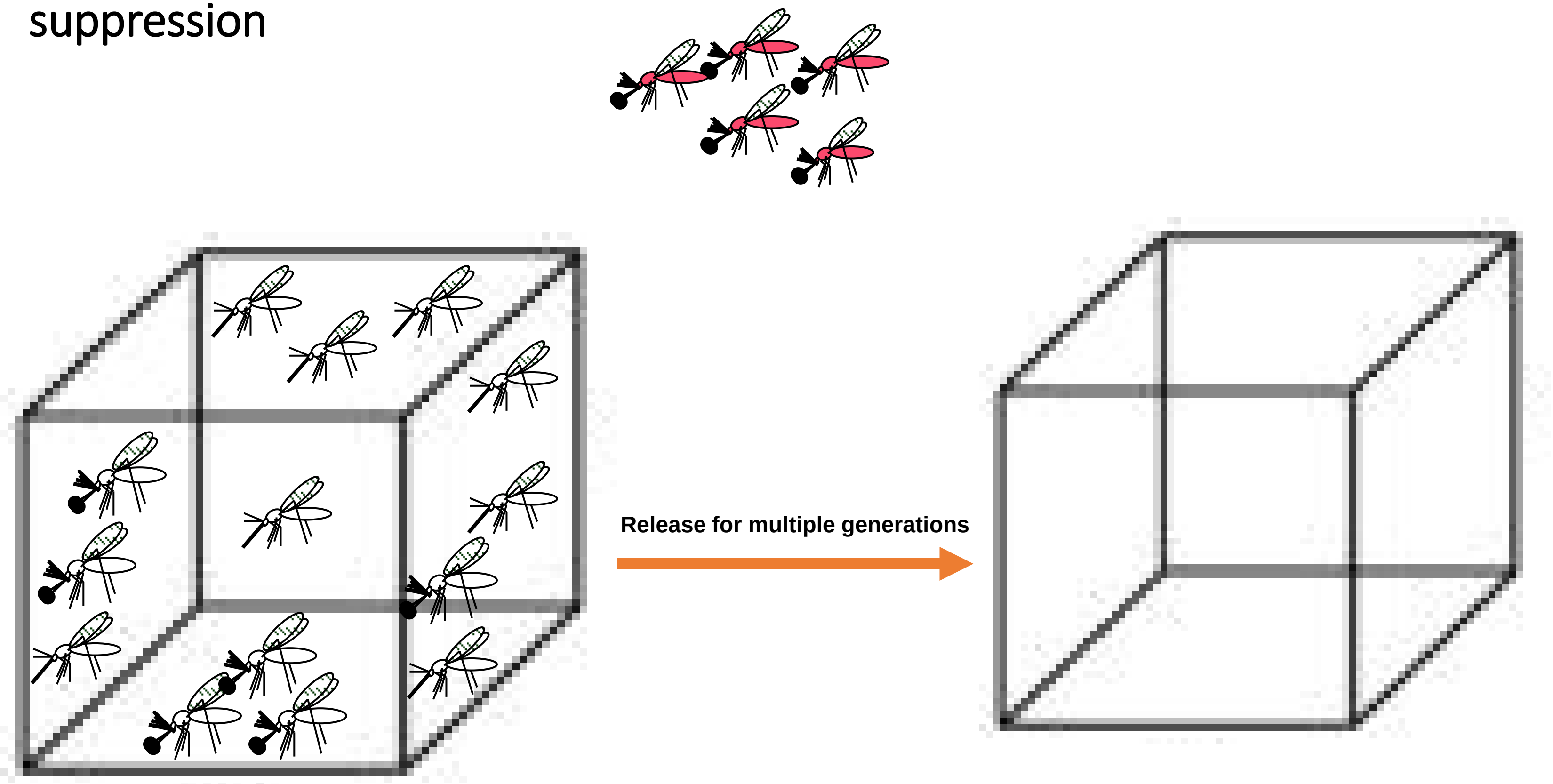


- ❑CI: Embryo death when an uninfected female mates with an infected male or a male infected with a different strain

LePage, D.P., et al. Nature, 2017; Shropshire, J.D., et al. PNAS, 2018

Application of CI for vector control

Release males carrying *Wolbachia* to induce female sterility for population suppression

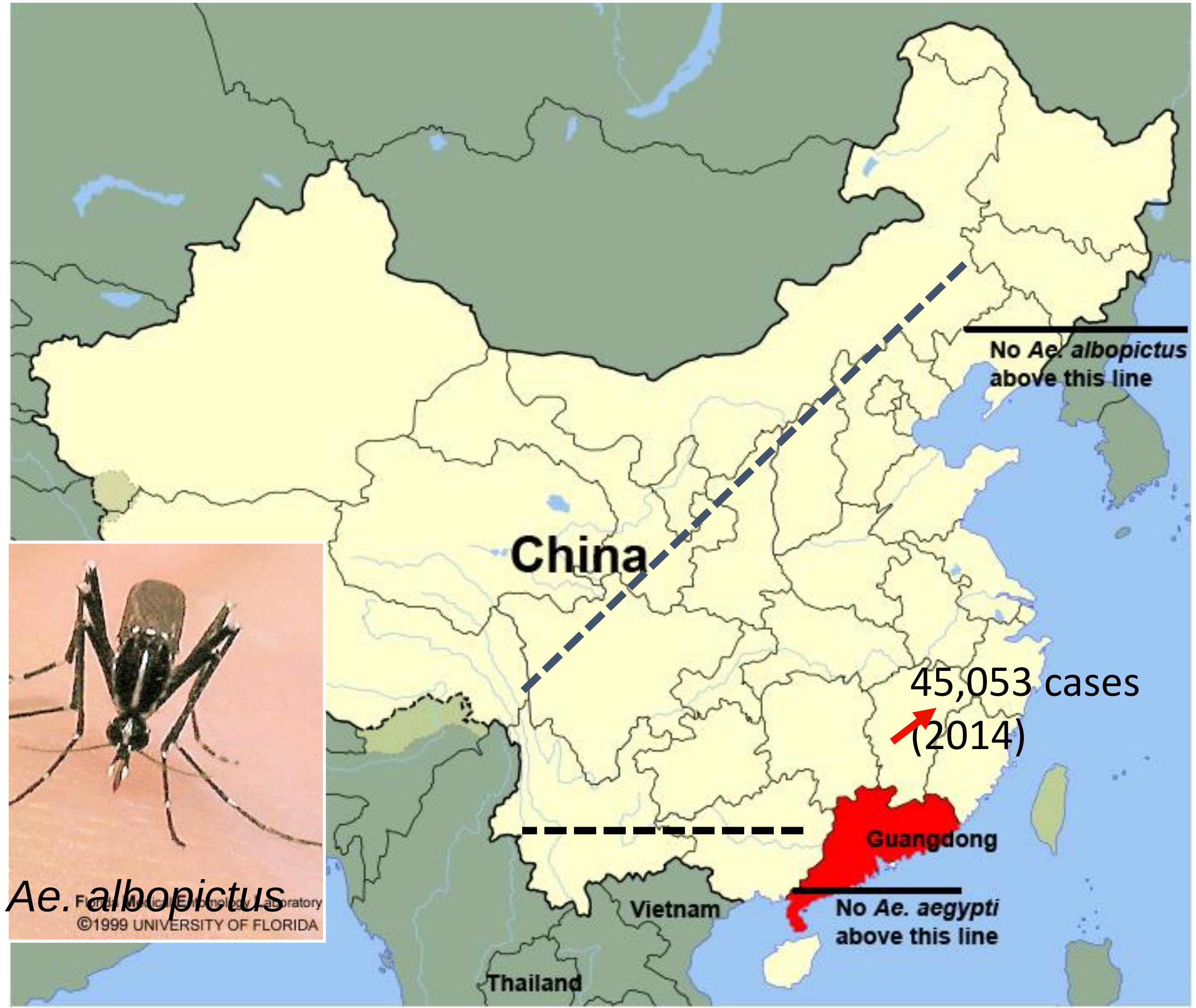


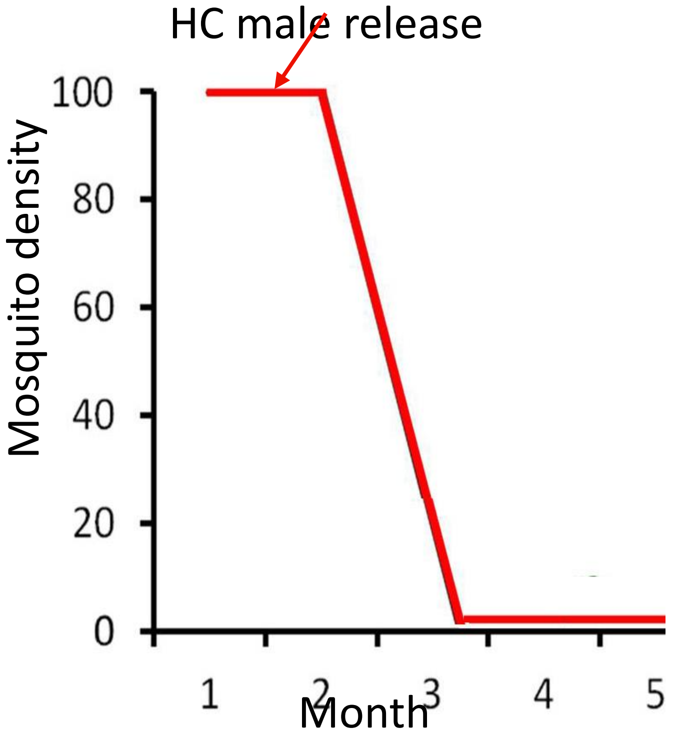
Incompatible Insect Technique, IIT

- Xi, Z. & Joshi, D. Chapter 14 of the book “Genetic Control of Arboviruses and Malaria”. 2016

Practical application of IIT

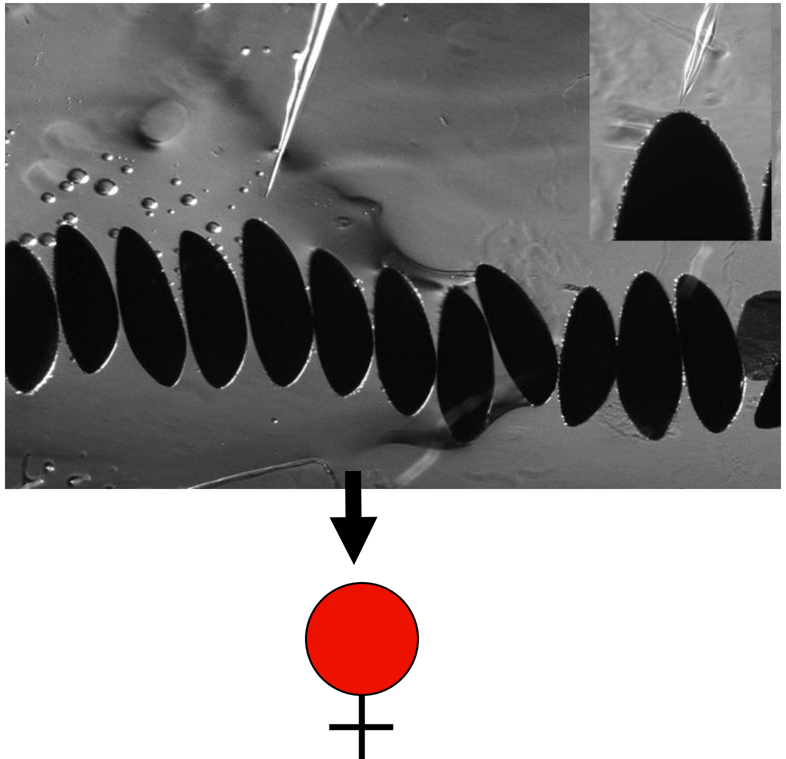
To eliminate the primary dengue vector *Aedes albopictus* in South China



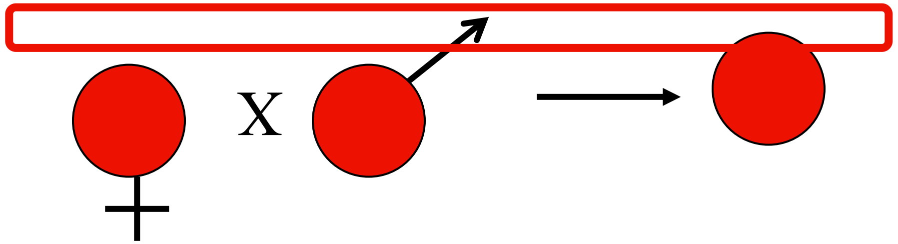


1. Mosquito line generation and characterization

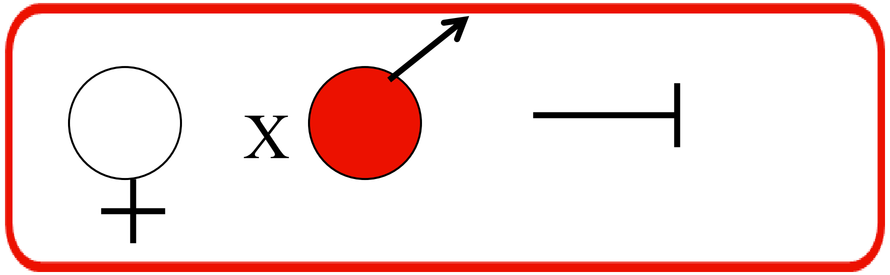
Embryonic microinjection to generate one *Wolbachia*-infected female as a "seed" for mass rearing



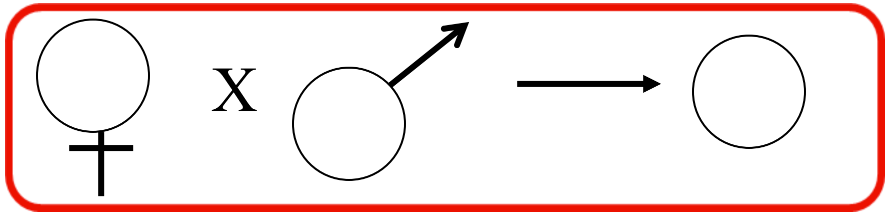
2. Mosquito mass rearing



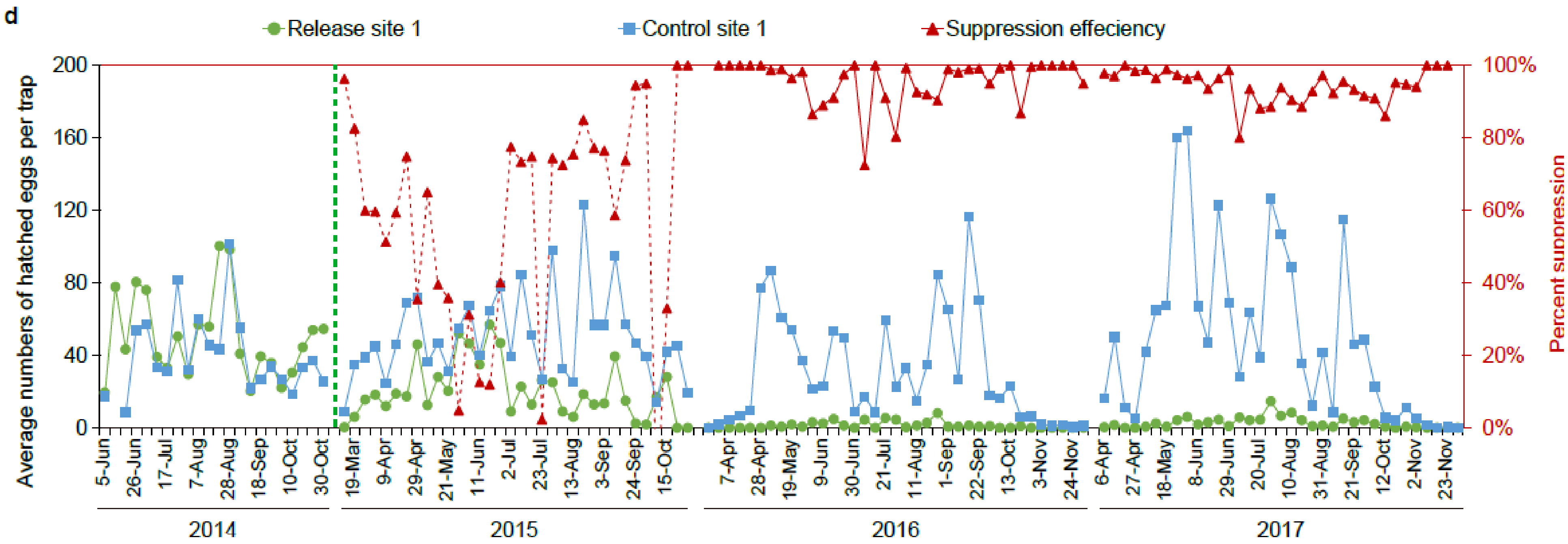
3. Field release



4. Field monitoring



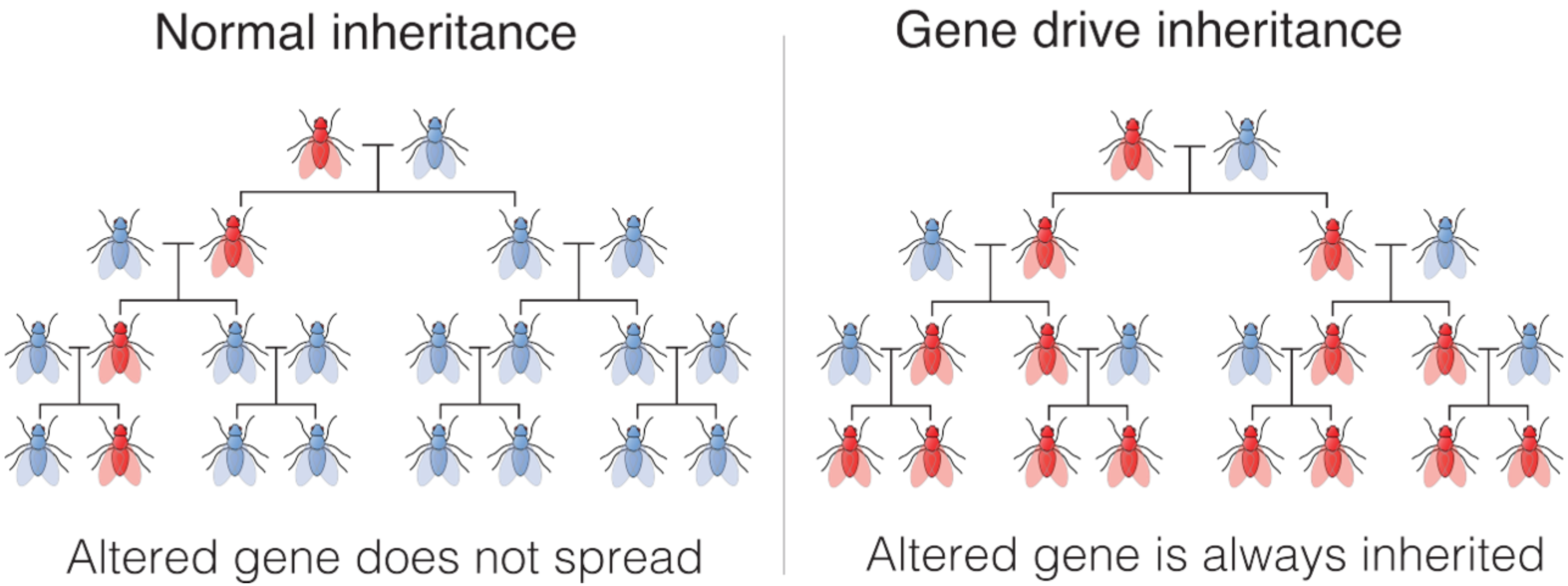
A yearly reduction of >94% in *Aedes* ***albopictus* larvae**, with no viable eggs for up to 13 weeks



Zheng, X., *et al.* Nature, 2019, 572 (7769):56-61

Trending novel approach: Gene drive

A technique that promotes the inheritance of a particular gene to increase its prevalence in a population

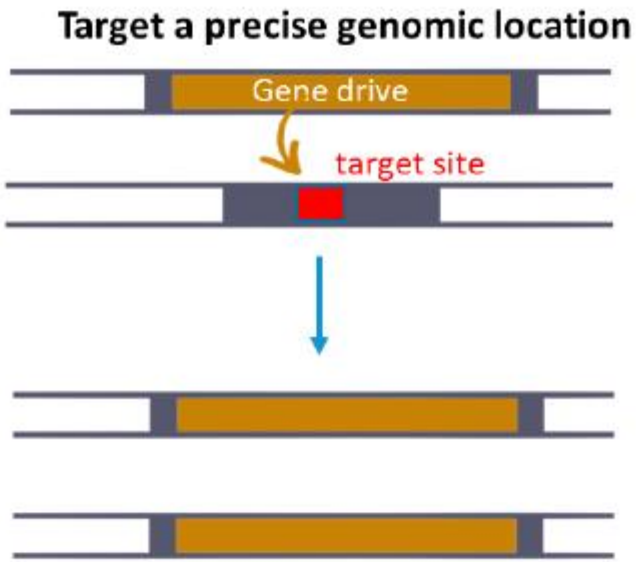


Mutant mosquitoes engineered to resist parasite development mosquito would pass on its new resistance genes to nearly all of its offspring The result: a gene that could spread through a wild population like wildfire.

WHAT IS NEW ABOUT GENE DRIVE APPROACHES

- ❑Species-specific
- ❑Self-sustaining mechanism
- ❑Biased gene transmission (from 50/50 to 100%)
- ❑Long-lasting and potentially more widespread

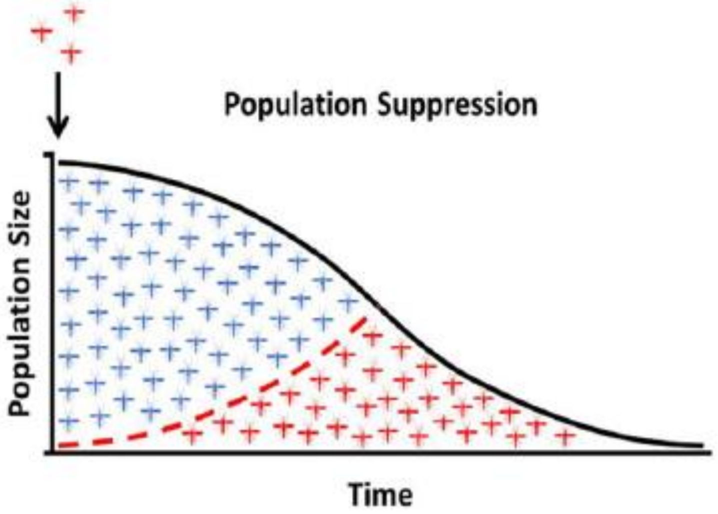
How does gene drives work

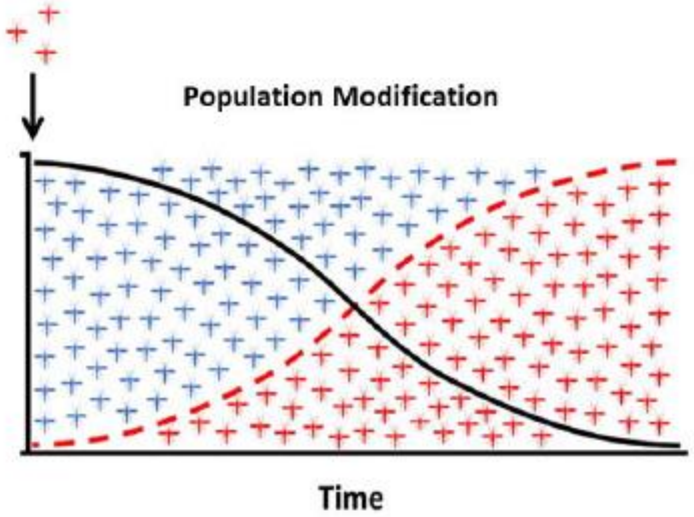


Both chromosomes now contain the gene drive

All offspring receive a copy of the gene drive

SPREAD GENES THAT SUPPRESS



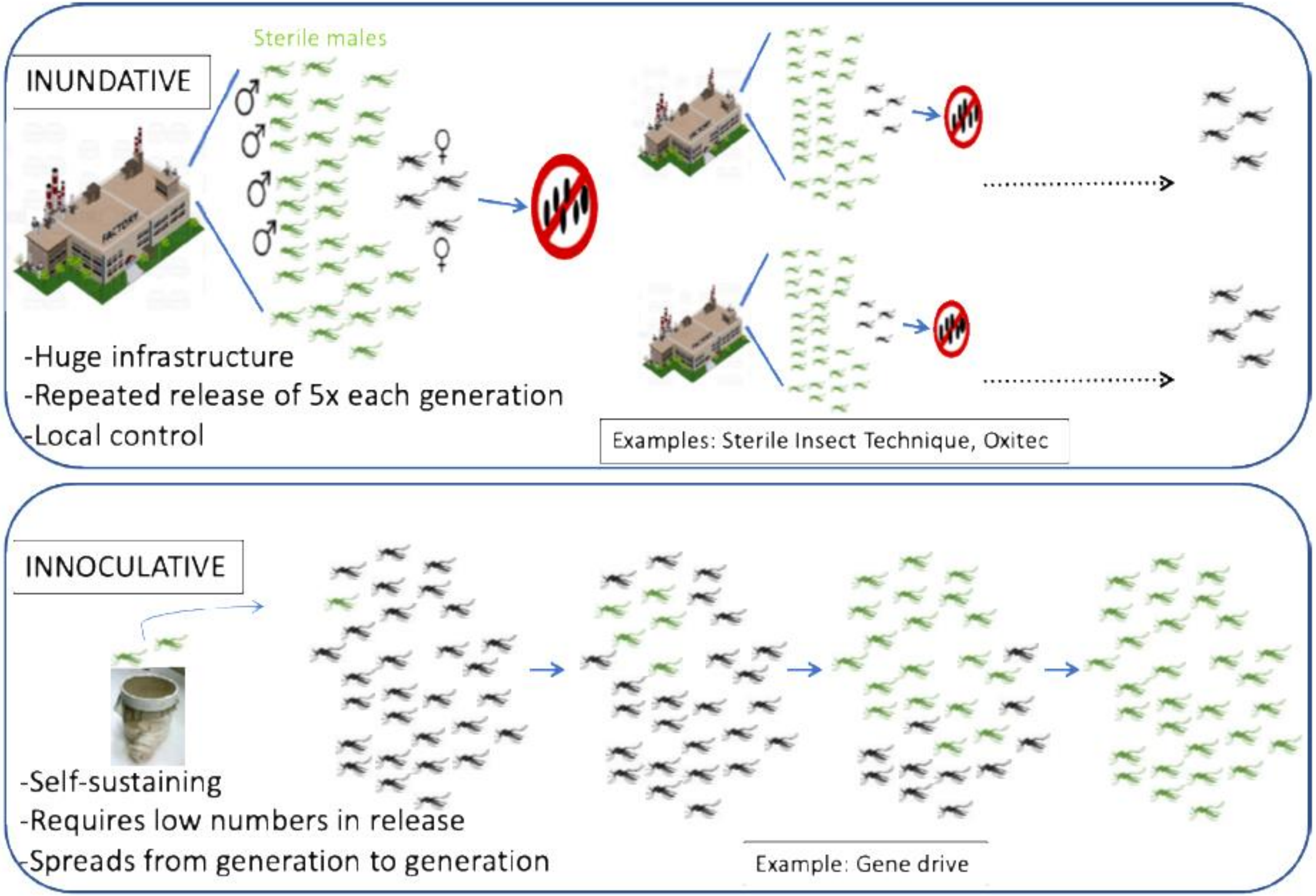


SPREAD GENES THAT MODIFY

Gene drives challenges

- Still under research to prove its effectiveness and safety
- Requires sexual reproduction: It can take many generations for drives to propagate across populations
- Agreed protocols for testing and levels of containment
- Not a magic bullet – like all technologies can be subject to resistance
- Negative public perception of GMOs in some countries

Difference between Gene drives and other GMM



Thank You