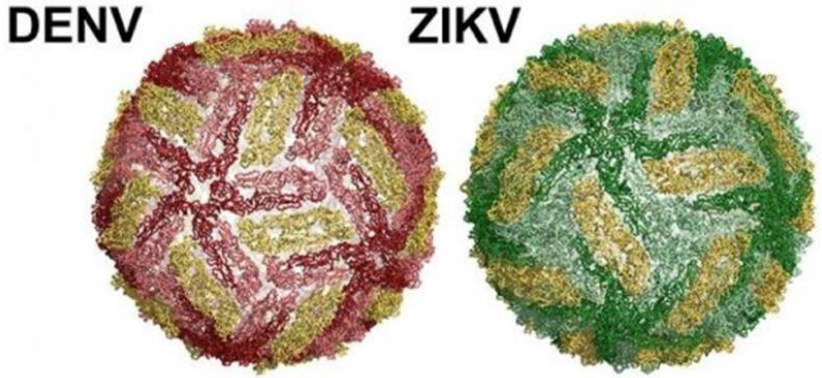
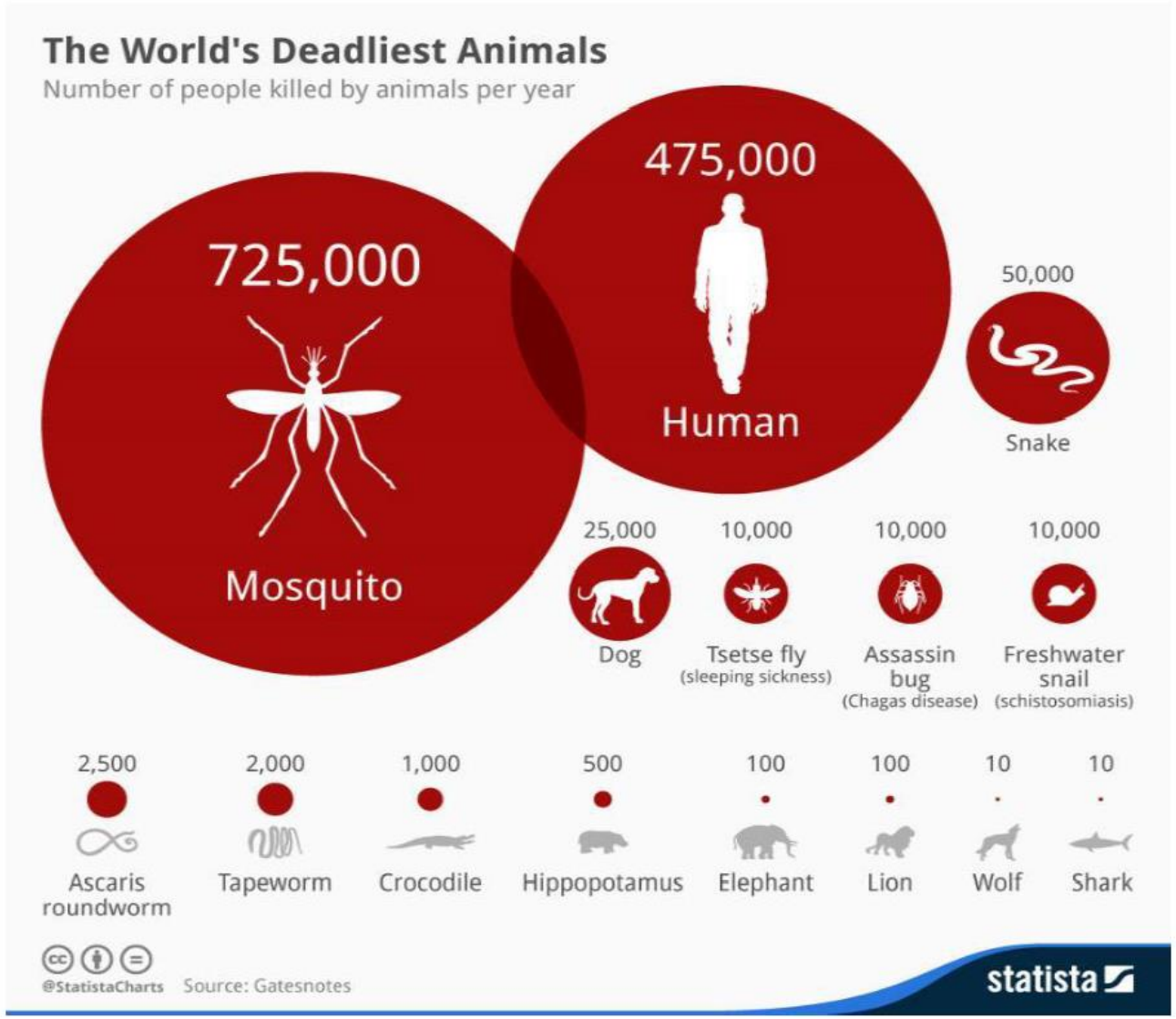
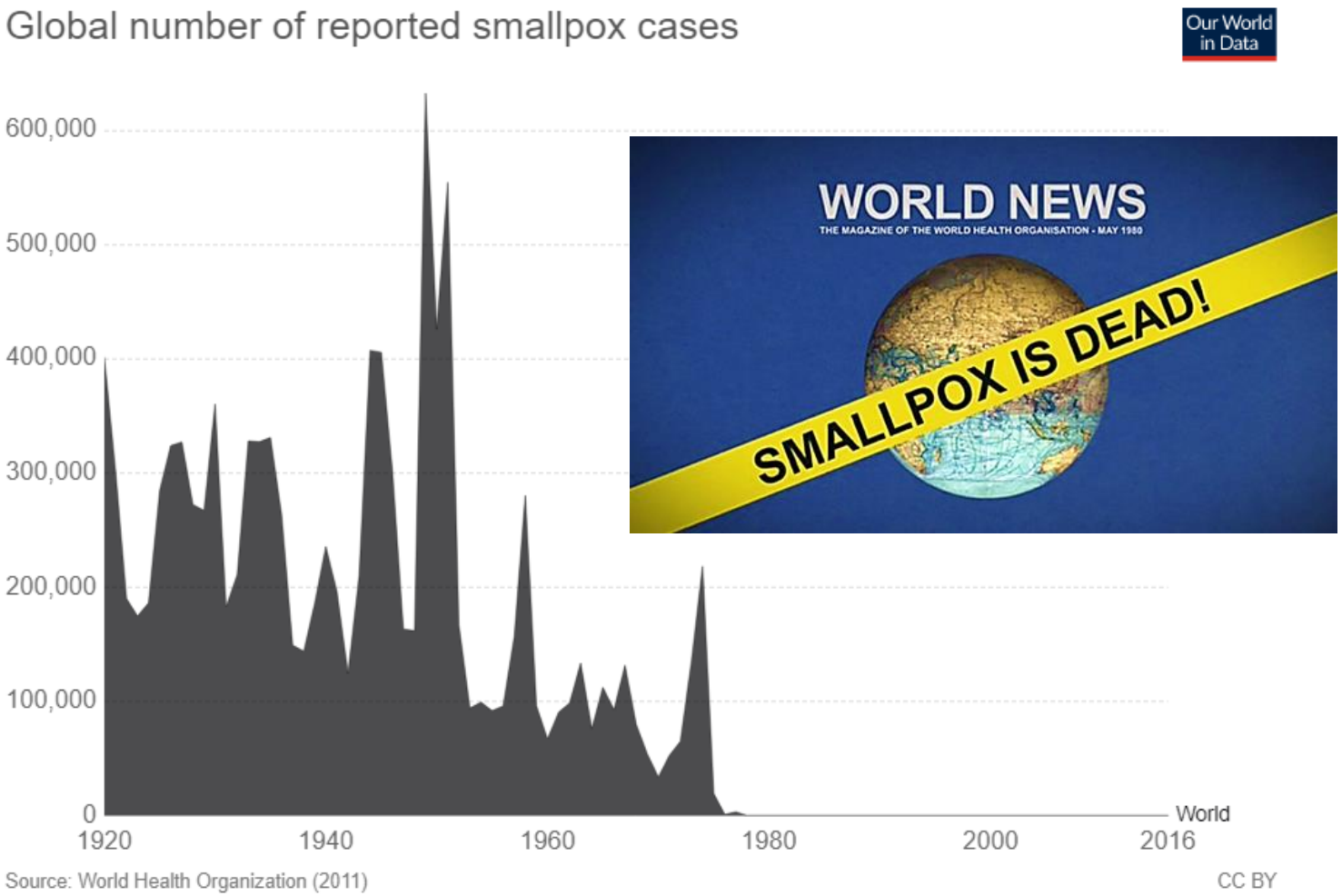
Why do we need a gene drive mosquito?

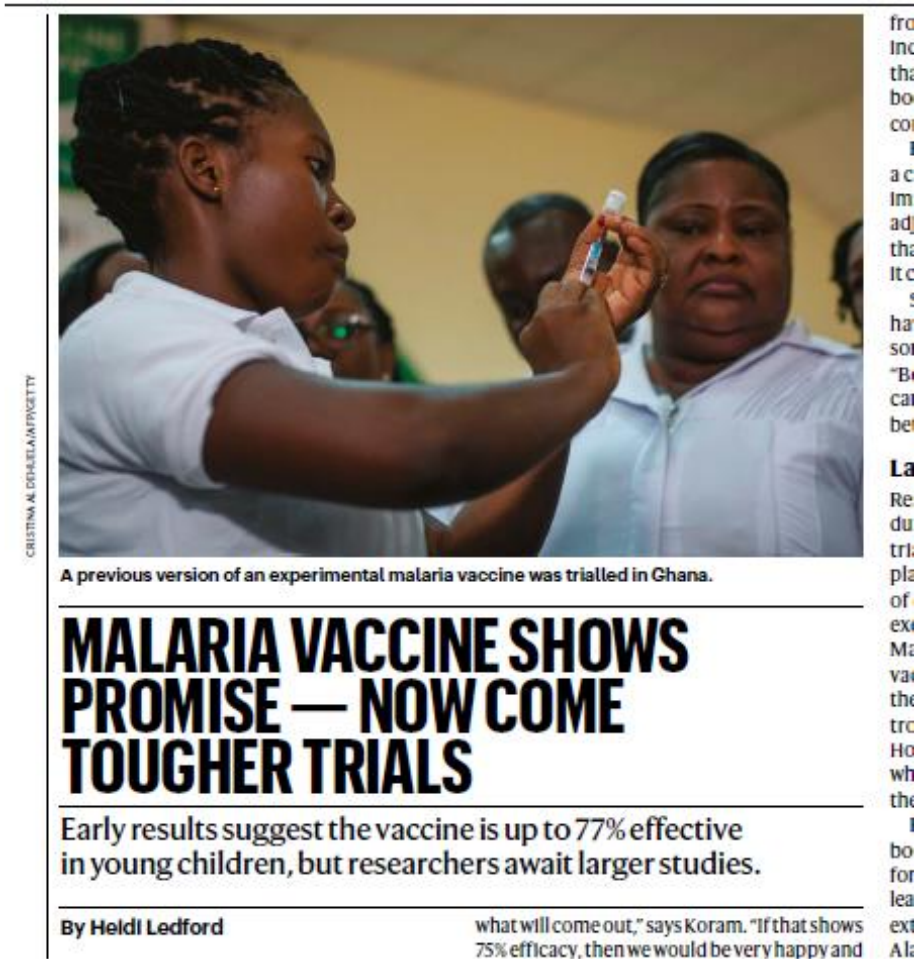


Chun-Hong Chen
National Health Research Institutes


The World's Deadliest Animals
Number of people killed by animals per year
725,000
Mosquito
475,000
Human
50,000
Snake
25,000
Dog
10,000
Tsetse fly
(sleeping sickness)
10,000
Assassin bug
(Chagas disease)
10,000
Freshwater snail
(schistosomiasis)
2,500
Ascaris roundworm
2,000
Tapeworm
1,000
Crocodile
500
Hippopotamus
100
Elephant
100
Lion
10
Wolf
10
Shark
@StatistaCharts
Source: Gatesnotes
statista

There is no effective vaccine for Malaria, Dengue and Zika yet





CRISTINA ALDEHUELA/AFP/GETTY

A previous version of an experimental malaria vaccine was trialled in Ghana.

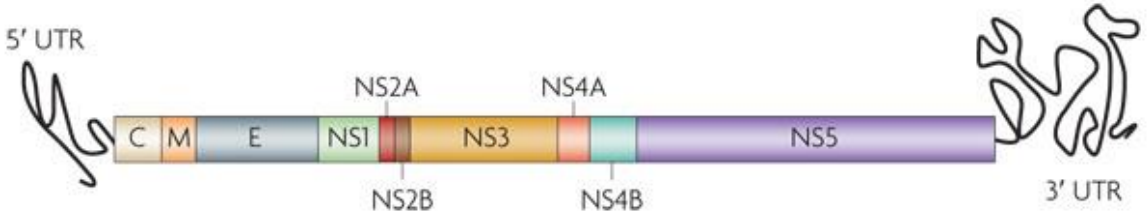
MALARIA VACCINE SHOWS PROMISE — NOW COME TOUGHER TRIALS

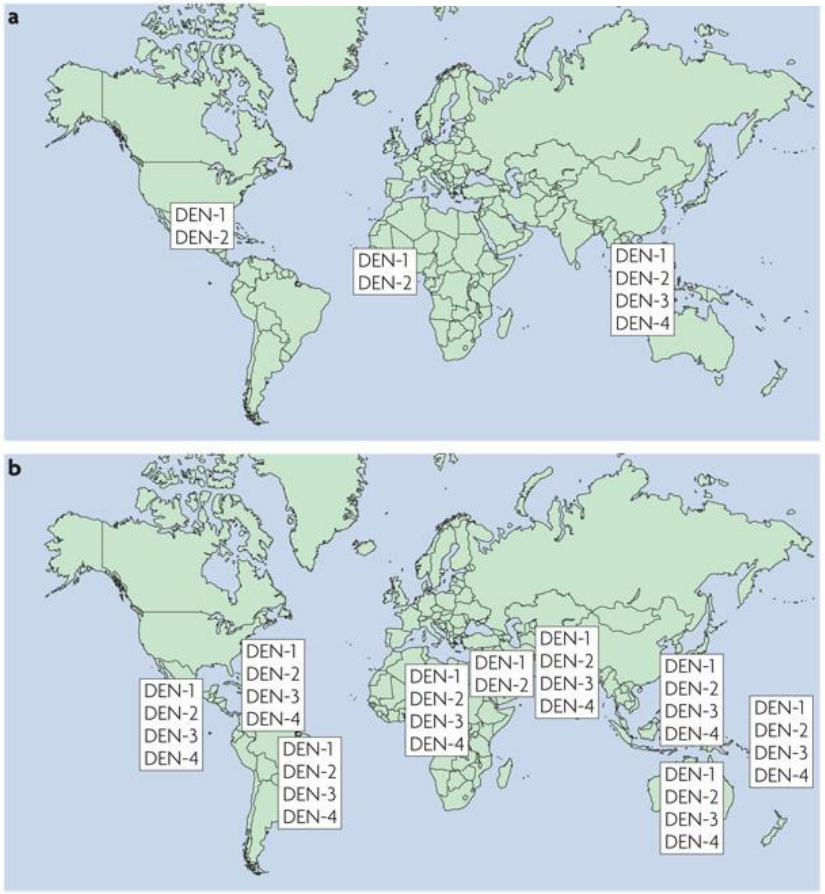
Early results suggest the vaccine is up to 77% effective in young children, but researchers await larger studies.

By Heidi Ledford

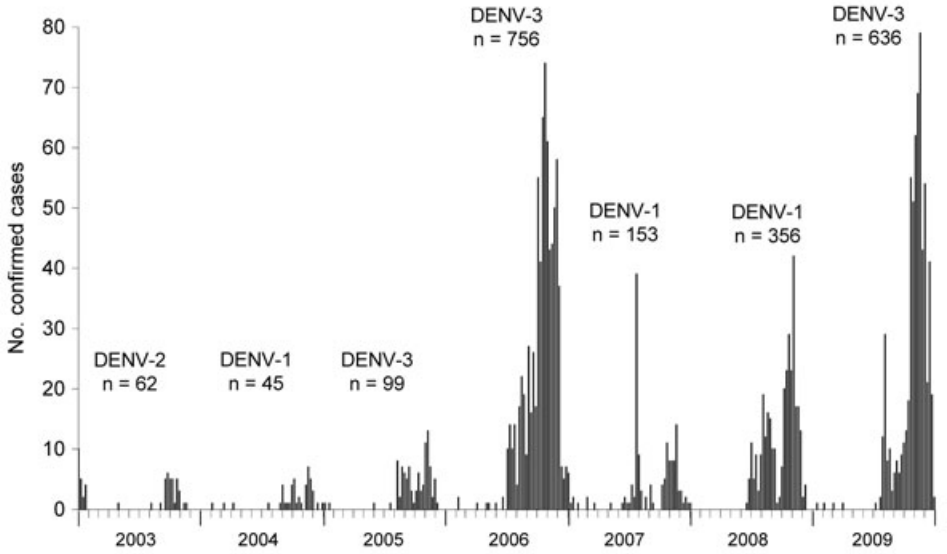
what will come out," says Koram. "If that shows 75% efficacy, then we would be very happy and

Dengue consists of four closely related but antigenically distinct viral serotypes (DEN1-4) All four serotypes can cause the full spectrum of disease.





Nature review of Microbiology 2010



Dengue Outbreaks , Kaohsiung City, Taiwan, 2003–2009

Taiwan CDC

There are limited drugs for Malaria, Dengue and Zika

The plasmodium parasite is spread by female Anopheles mosquitoes

Anopheles gambiae

Anopheles funestus

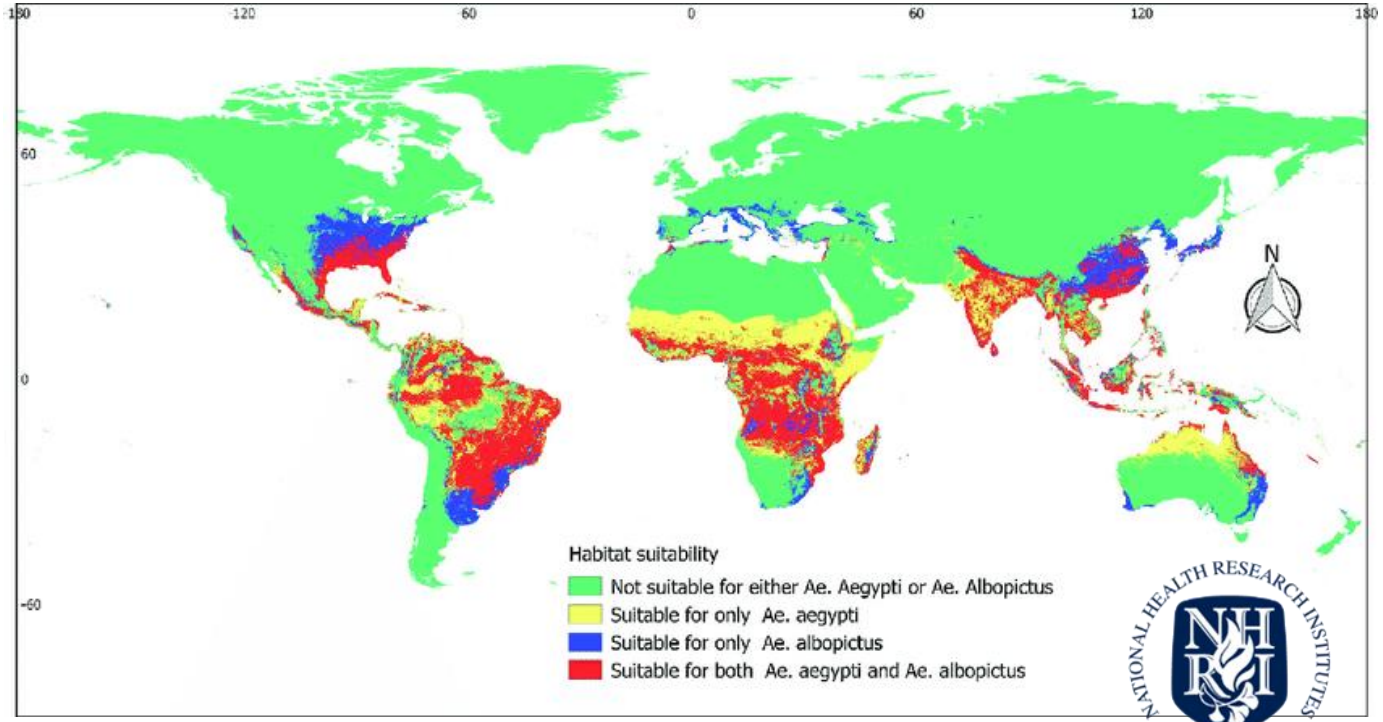
Dengue is spread through the bite of the female mosquito (Aedes)

Aedes aegypti

- These Mosquitoes Live In Tropical, Subtropical, And In Some Temperate Climates.
- They Are The Main Type Of Mosquito That Spread Zika, Dengue, Chikungunya, And Other Viruses.
- Because *ae. Aegypti* mosquitoes Live Near And Prefer To Feed On People, They Are More Likely To Spread These Viruses Than Other Types Of Mosquitoes.

Aedes albopictus

- These mosquitoes live tropical, subtropical, and temperate climates, but can live in a broader temperature range and at cooler temperatures than *Ae. Aegypti.*
- Because these mosquitoes feed on animals as well as people, they are less likely to spread viruses like
- Zika, dengue, chikungunya and other viruses.



The traditional methods for mosquito control did not change too much in past decades

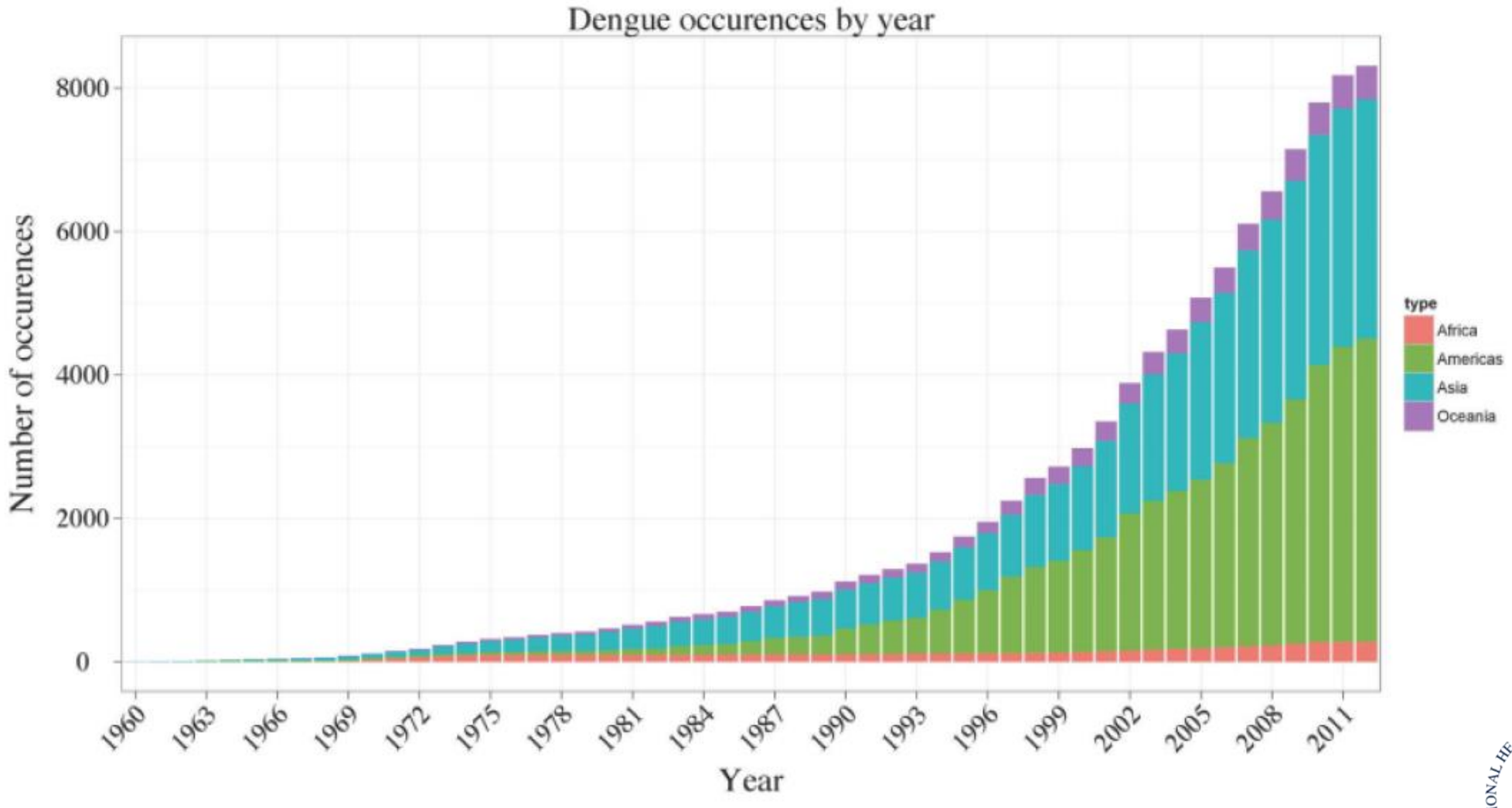
1950-1980

1981-2005

2006-2021

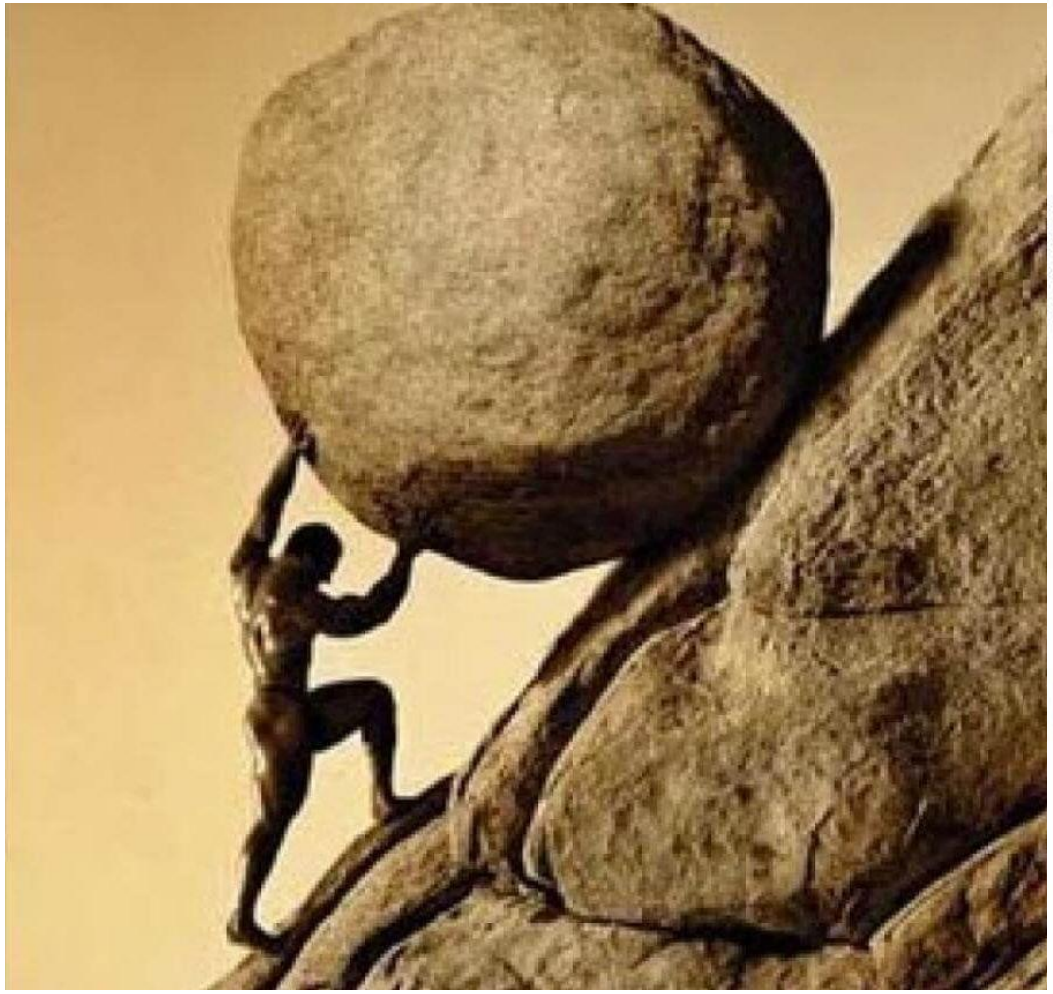
A typical mosquito treatment lasts about 30 days, but most less two weeks.

WHO: Failure of mosquito spraying to stop dengue raises questions for battle against Zika



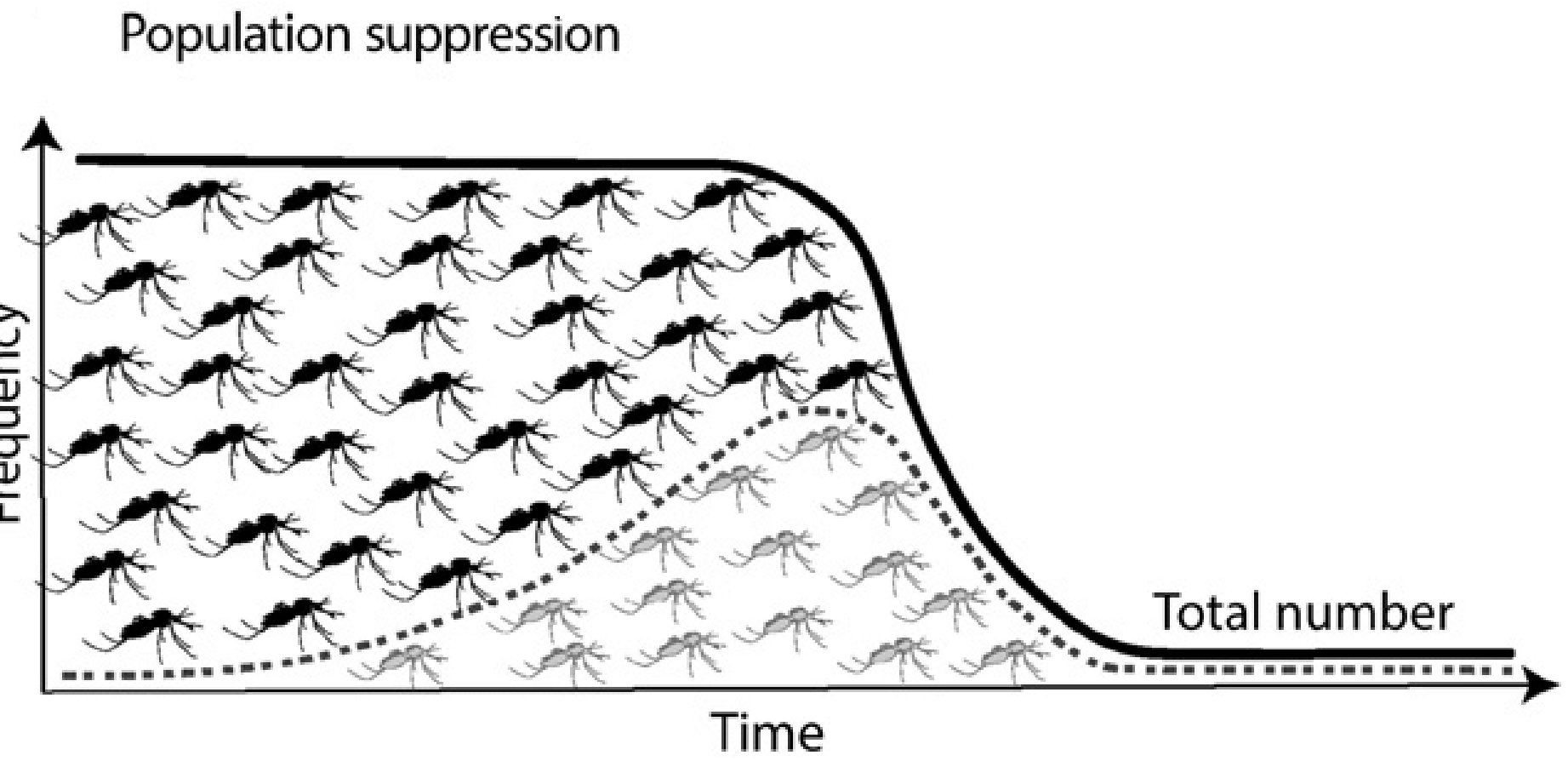
Mosquito source reduction also cost huge labor and cost

The traditional mosquito control works pretty much like the work of Sisyphus



We need new tools for preventing vector borne diseases.

Two Major strategies for mosquito control : population suppression and population replacement



Chemical Frogging

Source reduction

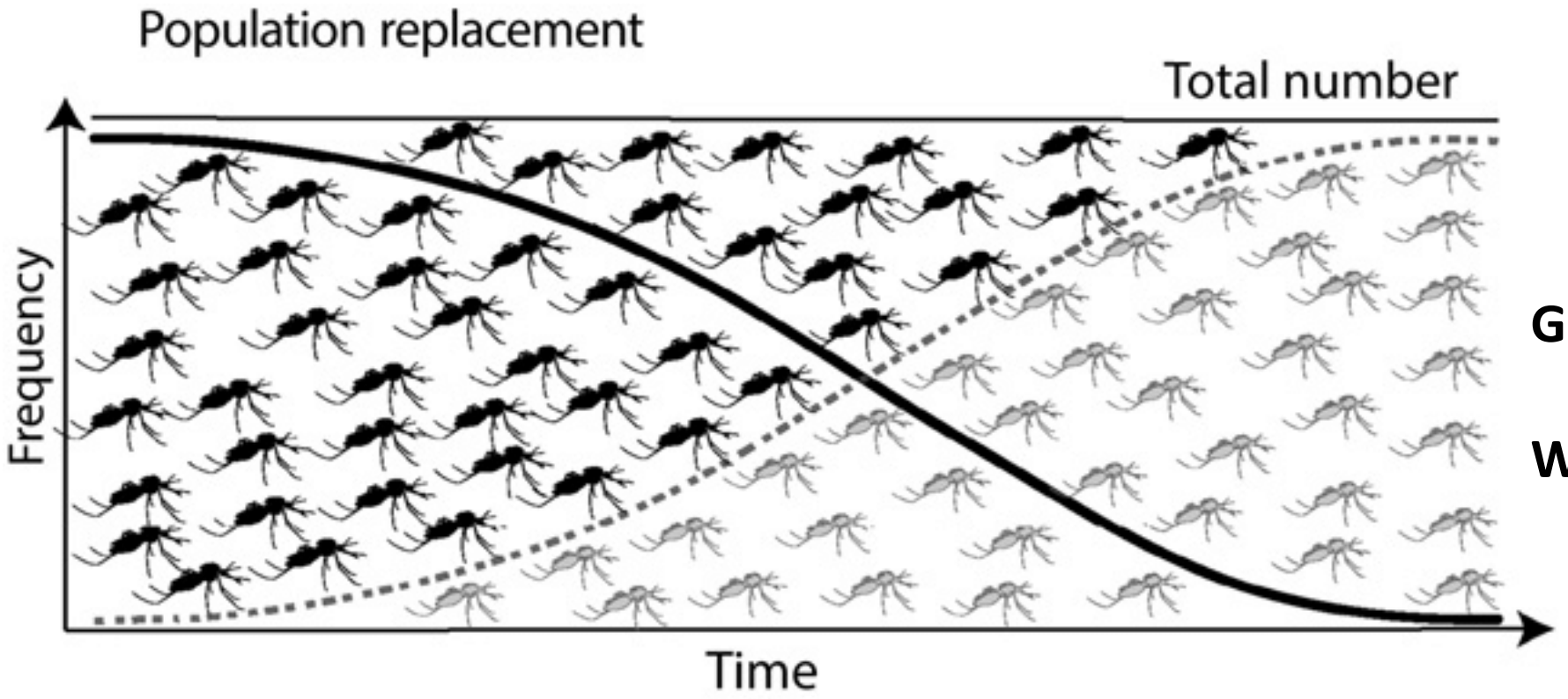
SIT

Transgenic Oxitec

Wild Type

SIT, or Oxitec male

Two Major strategies for mosquito control : population suppression and population replacement



Gene drive

Wolbachia infected mosquito

Wild Type

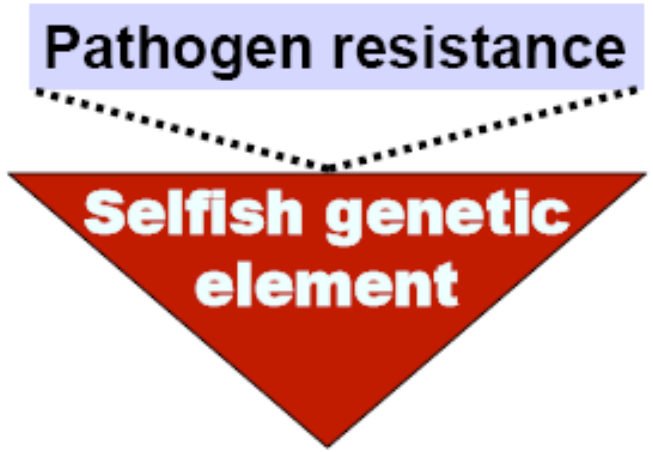
Gene Drive or Wolbachia infected mosquito

Two Major Goals:

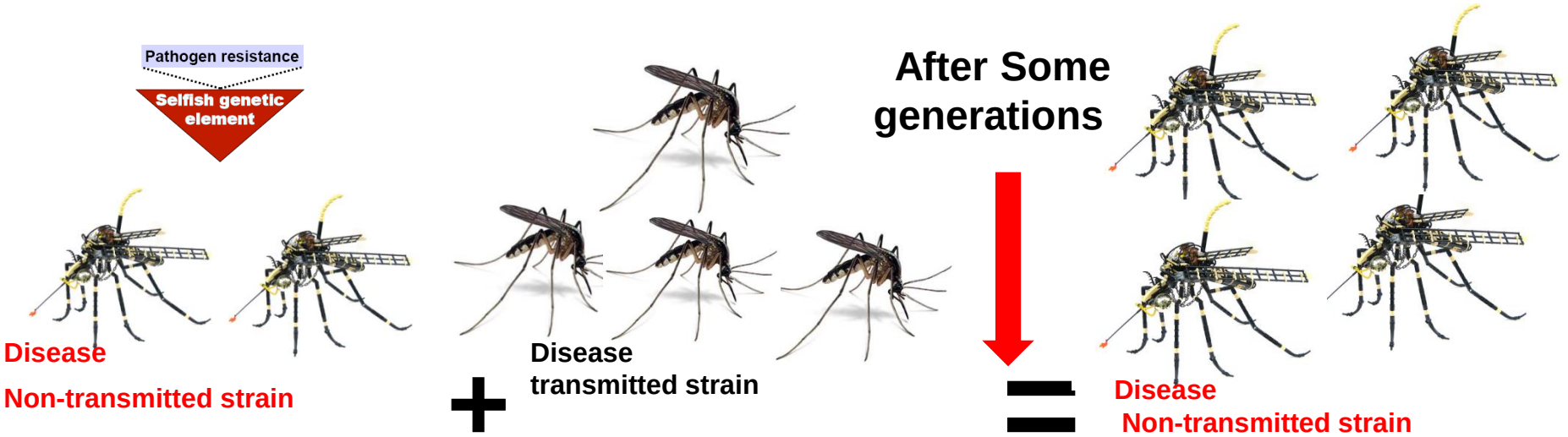
Effector genes for Malaria or Dengue Virus resistance

A driver gene for spreading the effector gene into population

The solution: Link genes for pathogen resistance with a selfish genetic element



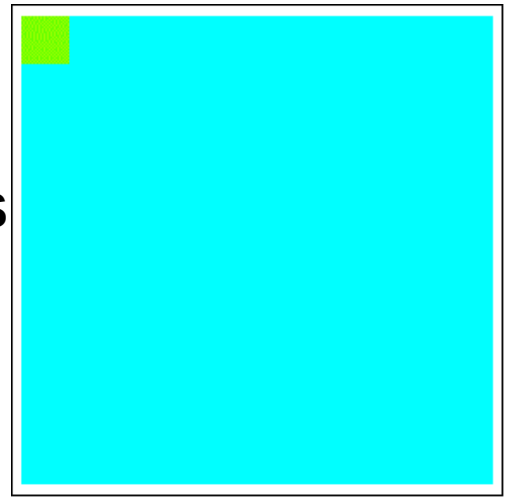
The Idea of Gene drive for disease control



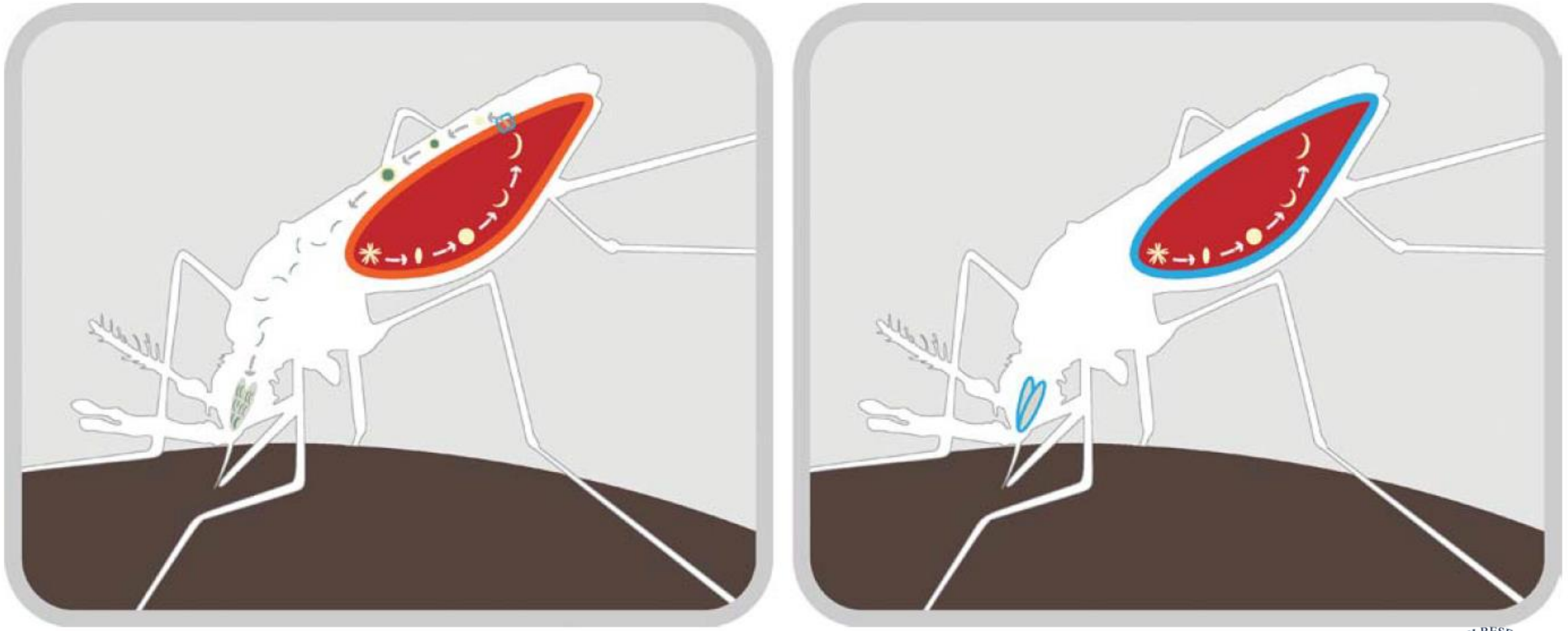
100% WT

50% WT, 50%NTS

100% NTS



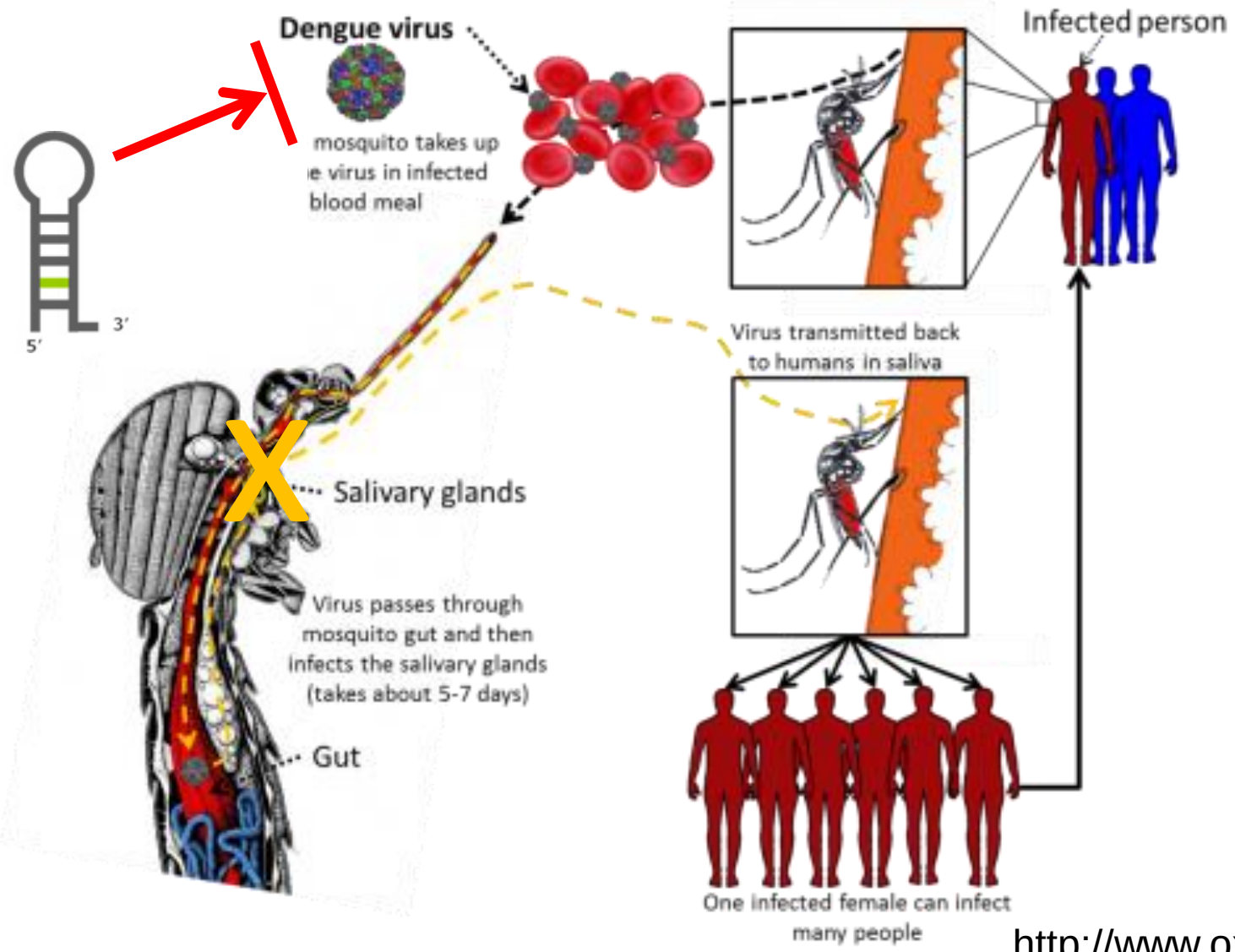
Transgenic anopheline mosquitoes impaired in transmission of a malaria parasite Nature (2002)



doi:10.1371/journal.pmed.1000020.g001

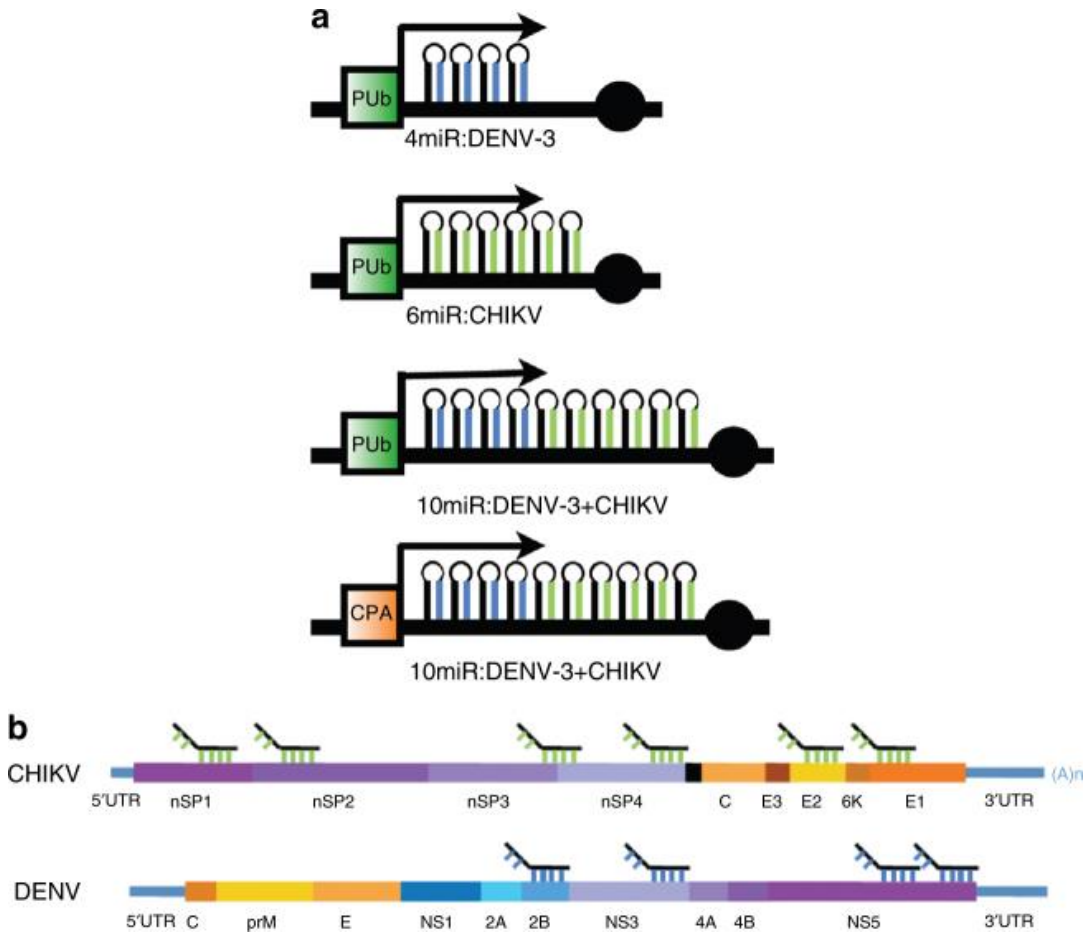
Figure 1. Mechanism for Blocking Malaria Transmission in the Mosquito

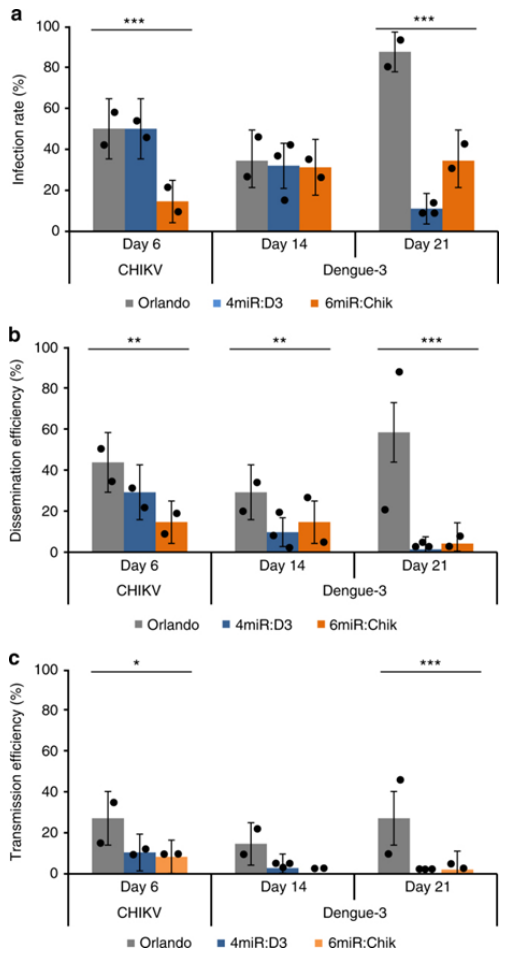
The life cycle of the dengue virus

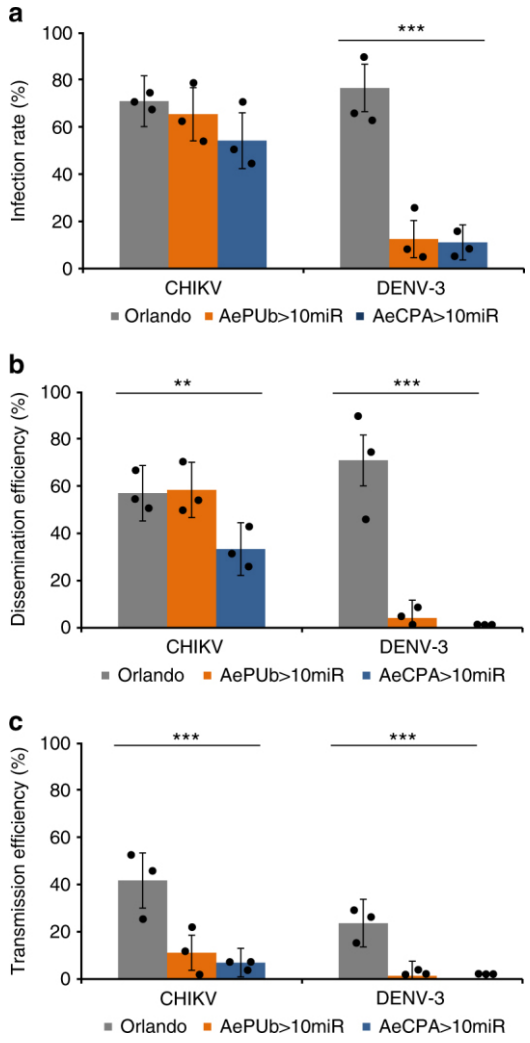


http://www.oxitec.com/

Anti-DENV/CHIKV phenotype of transgenic AePUb>10miR and AeCPA>10miR mosquitoes suppress Dengue and CHIKV replication

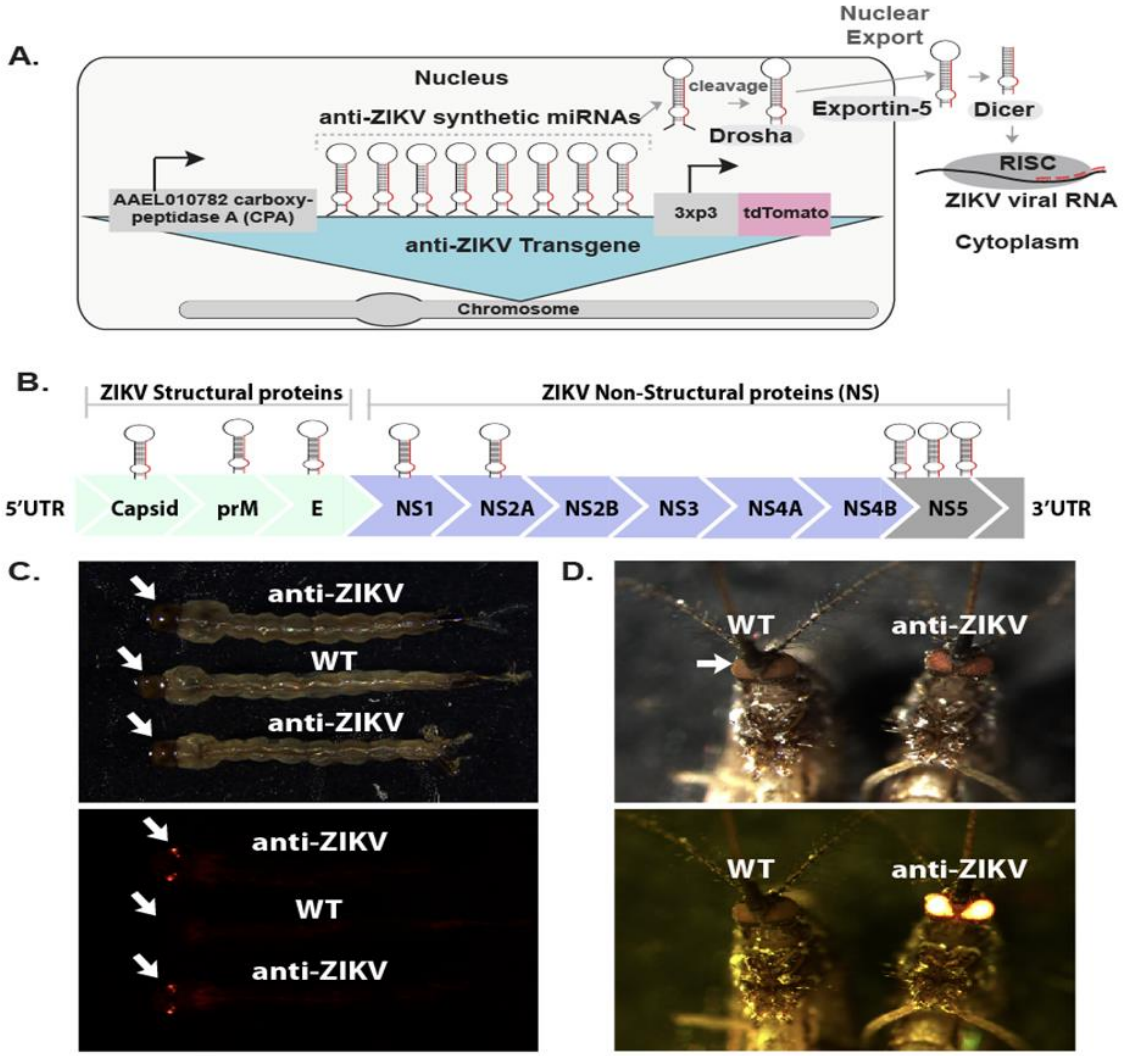


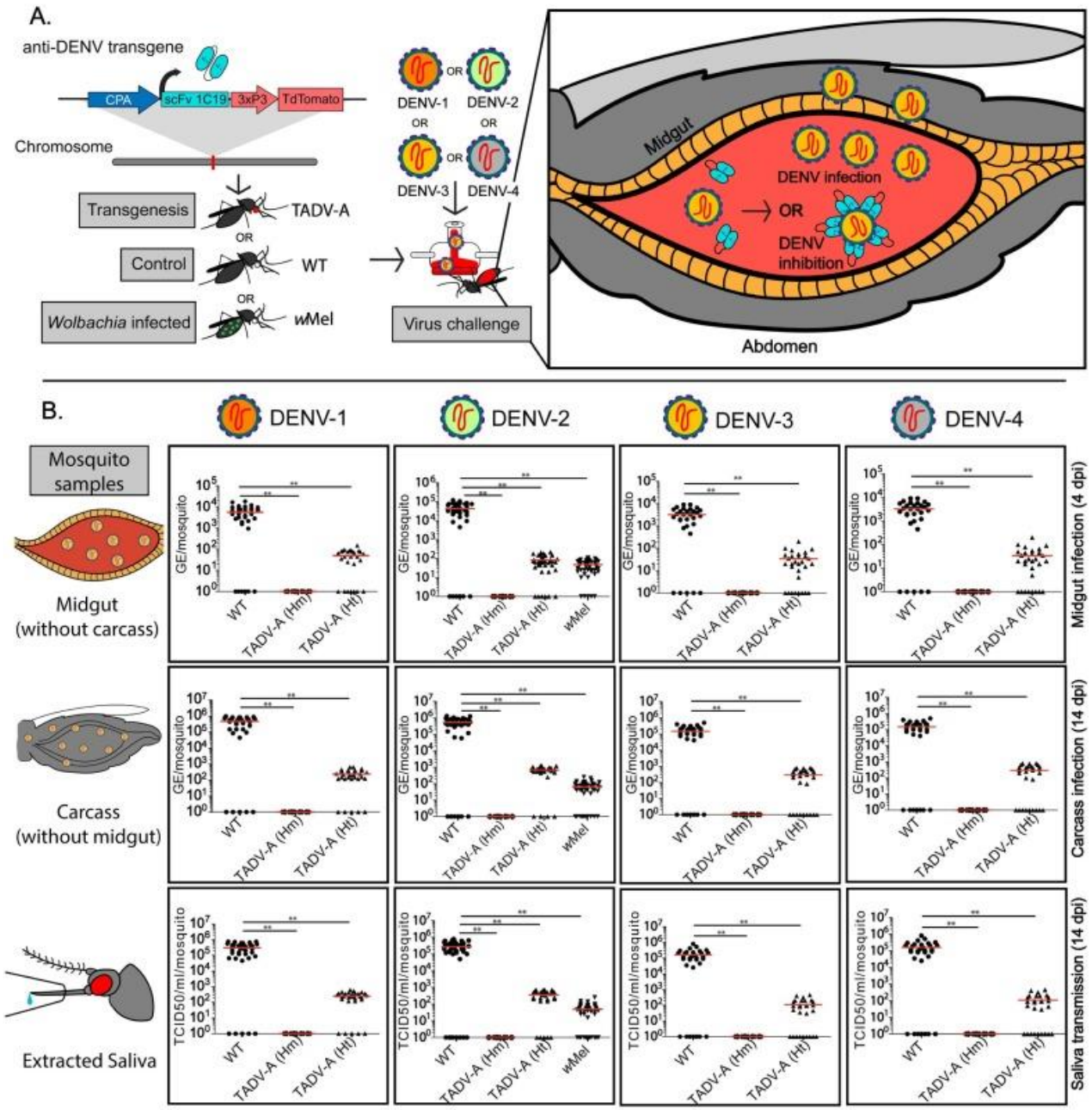




Yen, P.S., James, A.A., **CHEN, C.-H.**, Failloux A.B., 2018. miRNA-based transgenic *Aedes aegypti* mosquitoes reduce the transmission of arboviruses from two distinct families. ***Nature communication Biology***

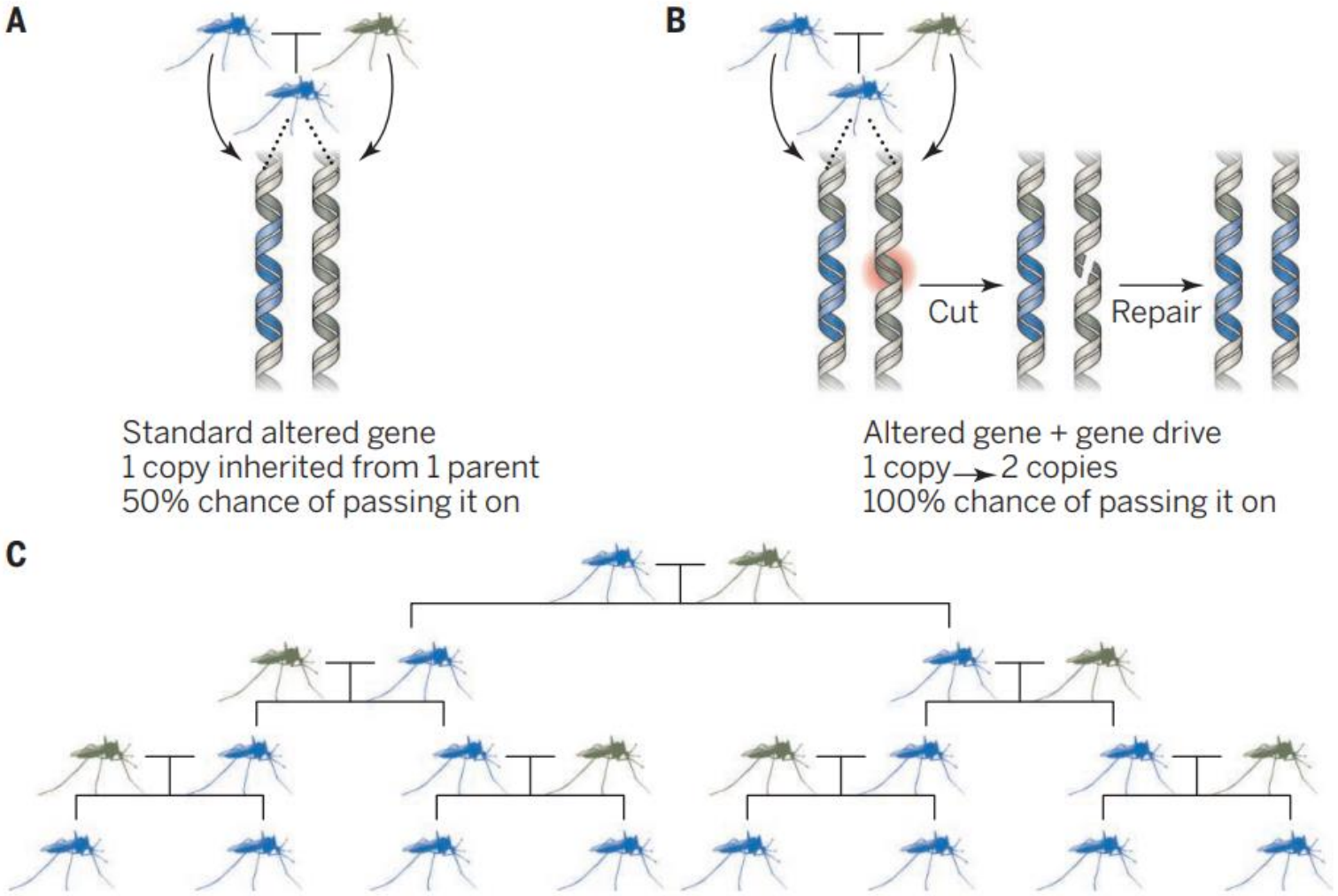
Refectory design for Zika and four types of DENV





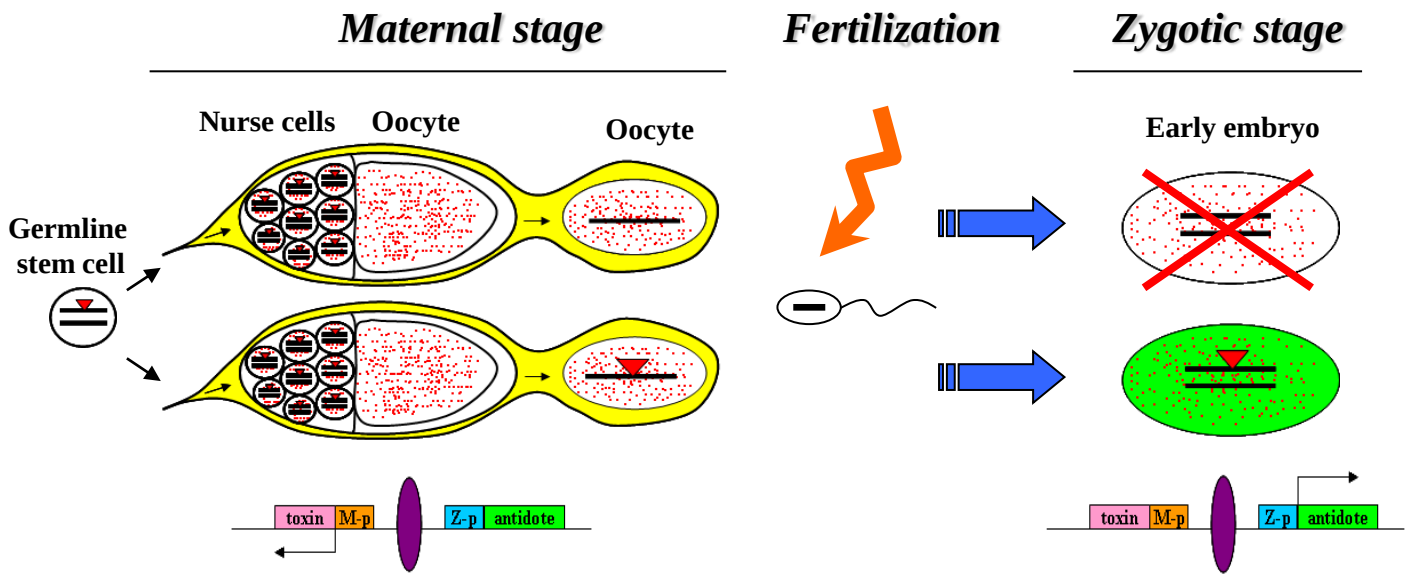
2018 PLOS Pathogen
2019 PNAS

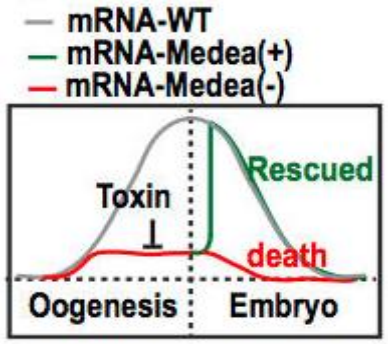
Gene Drive

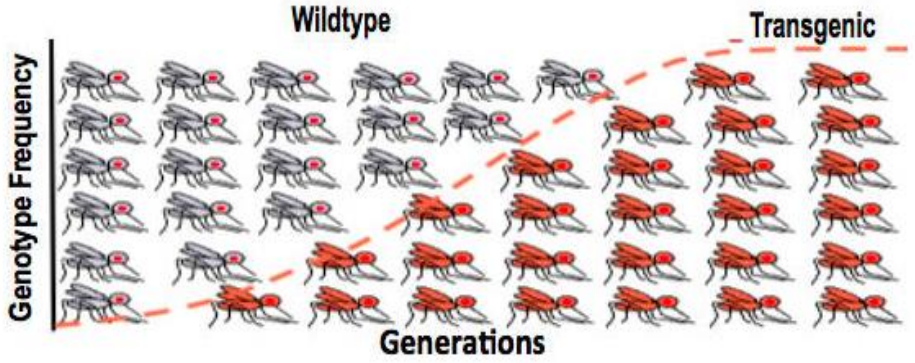


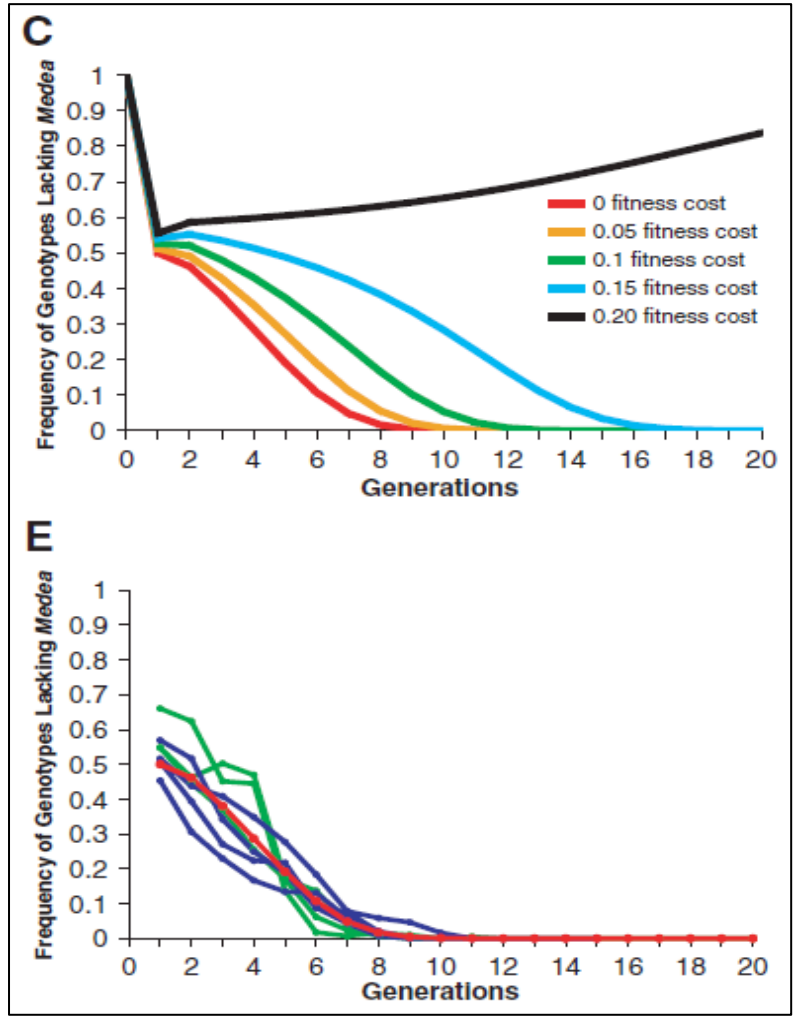
Science. 2014:Vol. 345, Issue 6197, pp. 626-628

Medea drives population replacement in *Drosophila*



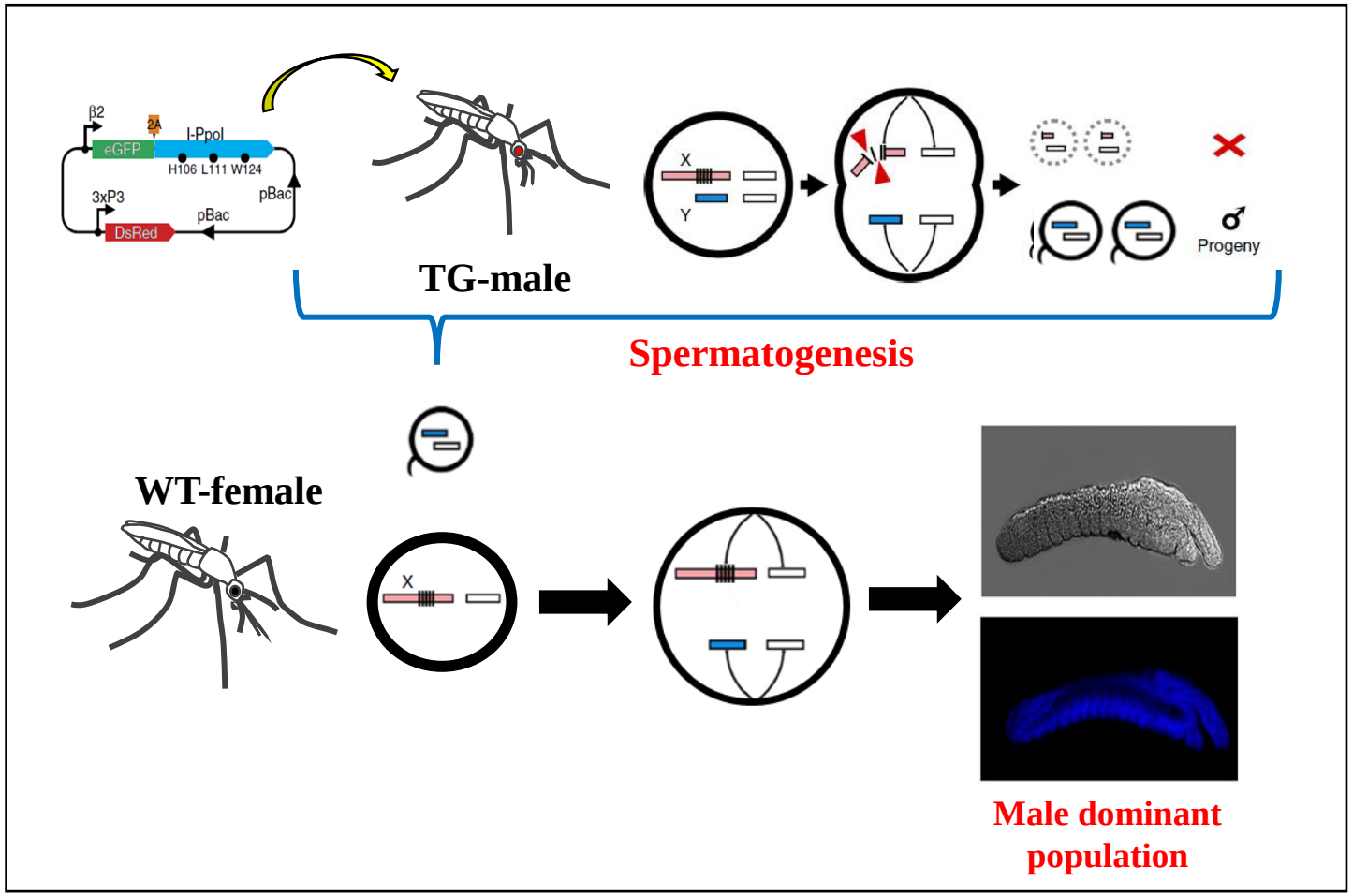


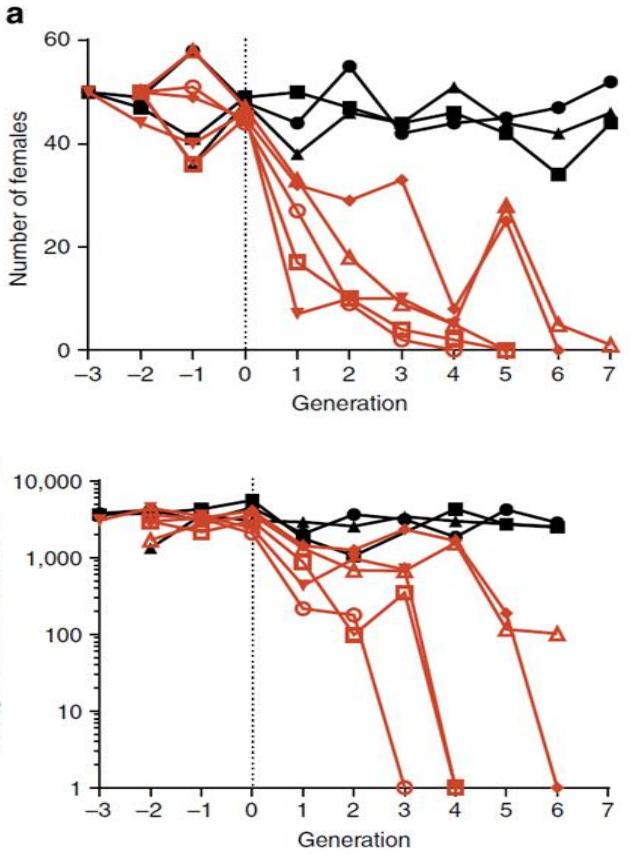




Science. 2007 Apr 27;316(5824):597-600.

Transgenic ^{gfp}111A-2 males that contained a modified intron-encoded endonuclease_I-PpoI suppress wild-type mosquito caged populations





Nat Commun. 2014 Jun 10;5:3977.

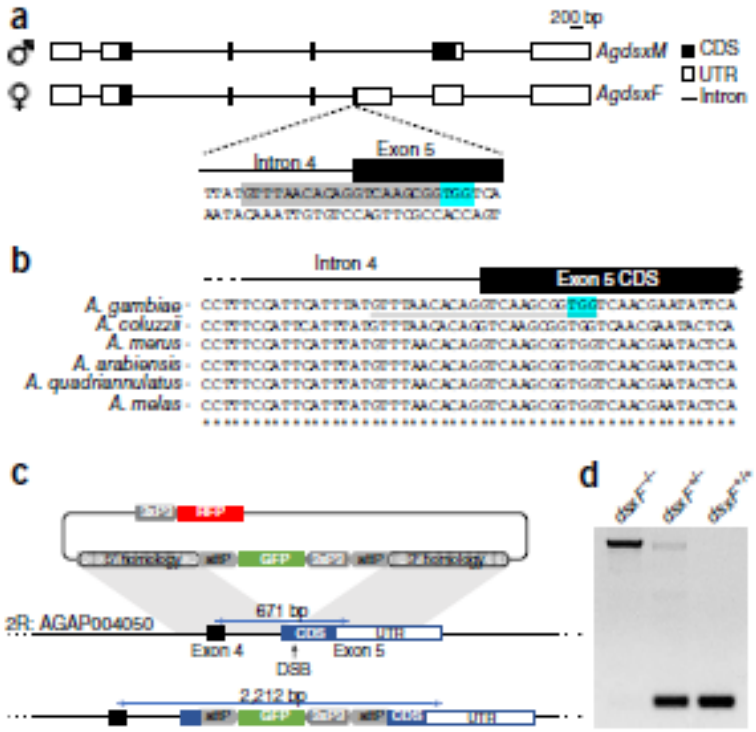
ARTICLES

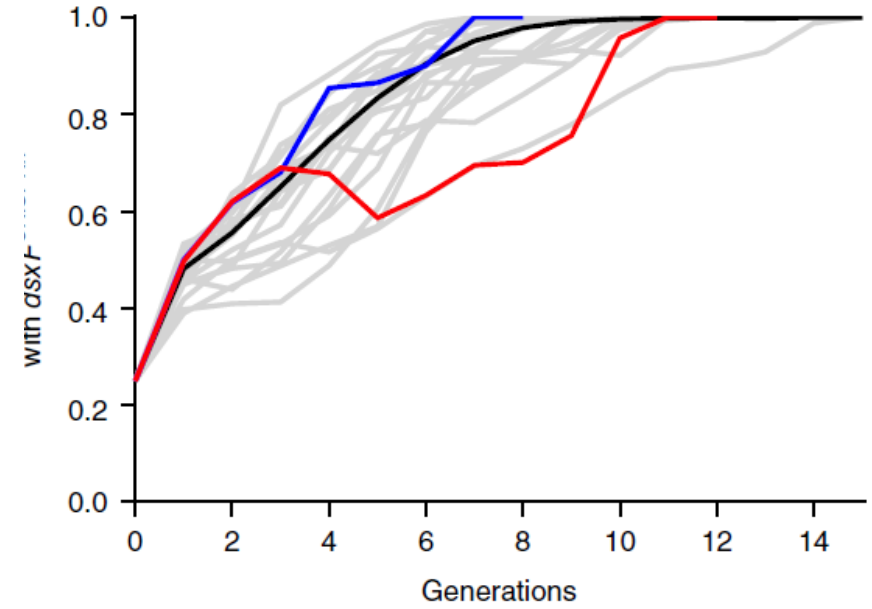
nature biotechnology

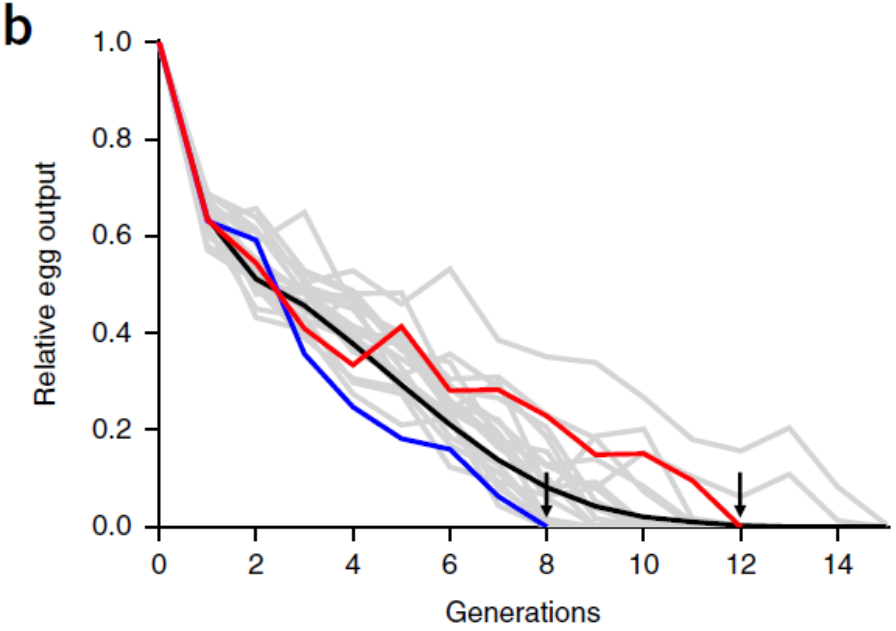
OPEN

A CRISPR–Cas9 gene drive targeting *doublesex* causes complete population suppression in caged *Anopheles gambiae* mosquitoes

Kyros Kyrou[1,2], Andrew M Hammond[1,2], Roberto Galizi[1], Nace Kranjc[1], Austin Burt[1], Andrea K Beaghton[1], Tony Nolan[1] & Andrea Crisanti[1]







Three take home messages

1 We need new tools for preventing vector borne diseases.

2 Gene drive once developed, there is less need for repeating re-release. It might mean less cost.

3 Gene drive is more specific than other control methods. It only aims for specific species.

Guann-Yi Yu
NHRI TW

Omar Akbari
UCSD

Anna-Bella FAILLOUX
Pasteur France

Grant support by NHRI, MOST