



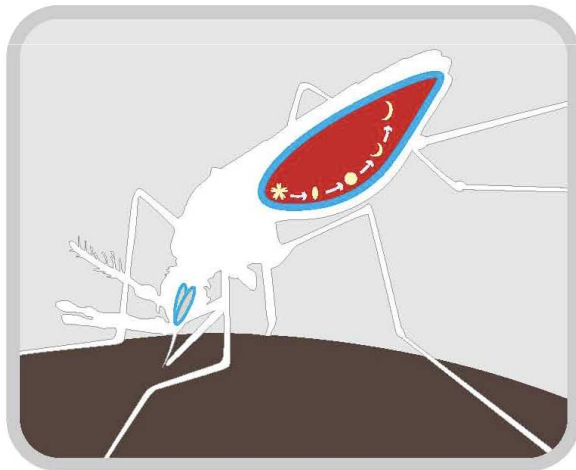
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Medicine and Hygiene, November 18-22, 2009**



Can mosquitoes engineered with gene drive systems be contained?

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**refractory
gene**

**gene drive
system**

Physical containment cannot be guaranteed



- Some **breaches of containment** are difficult to protect against:
 - **Lightning** or **earthquakes**
 - **Leakage** of water containing **eggs** or **larvae**
 - **Sabotage** and **burglary**
 - **Human error**
- Gene drive systems **enhance** the **invasiveness** of introduced genes.

Q1: How likely is it that mosquitoes with gene drive systems will persist following an accidental release?

Public support for a confined trial



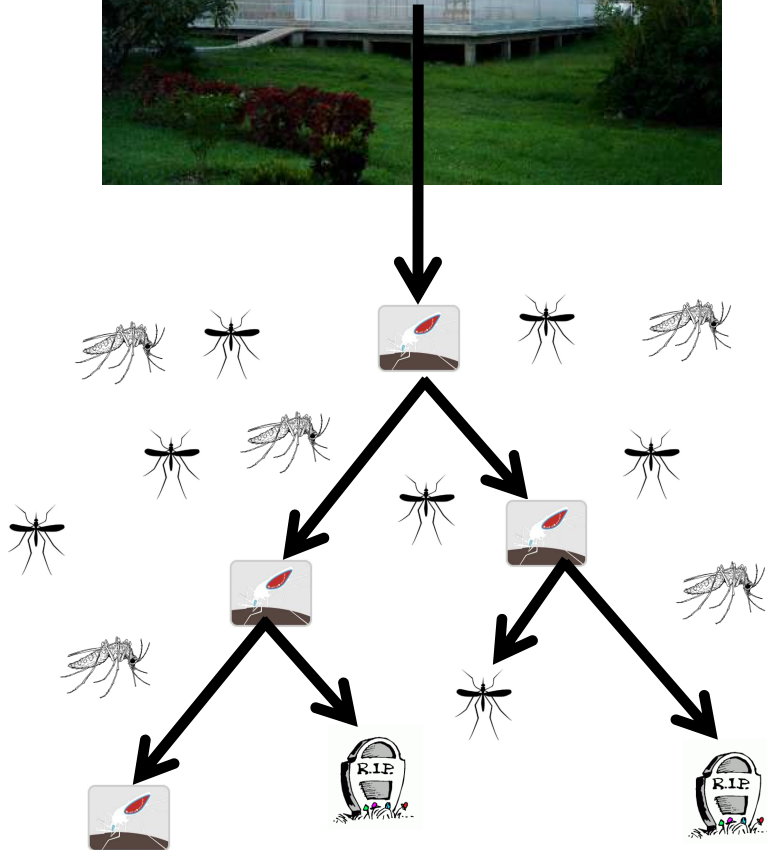
- **Public attitude surveys** in **Mali** suggest that people would like to see a **successful confined trial** before accepting a release:

“I would have to see an example of modified mosquitoes reducing malaria in another village before I believe this claim”

72-year-old man, Tienfala, Mali

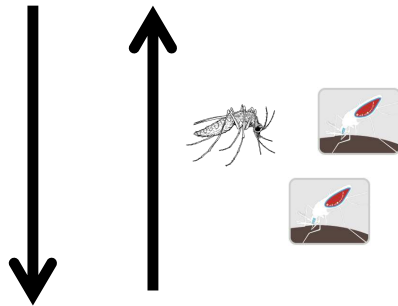
Q2: Is it possible to confine a release of mosquitoes engineered with a gene drive system to a single village?

Methods: Estimating invasiveness



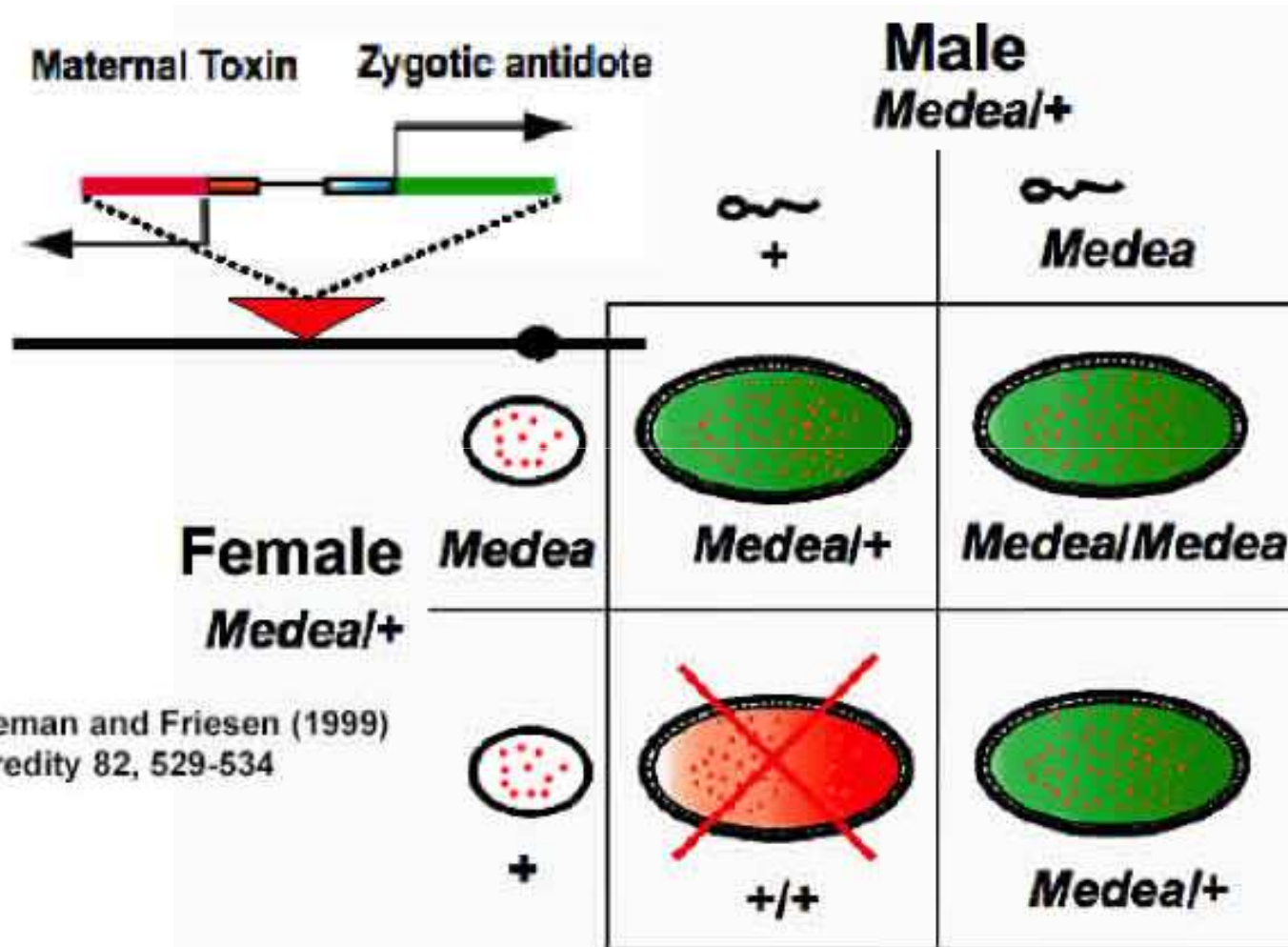
- A small number of GM mosquitoes escape into an **infinite population of wild-types**.
- **Mating and death** of GM mosquitoes is modeled in **continuous time**.
- **Patterns of inheritance** are specific to each **gene drive system**.
- Calculate **probability** that the **transgene is lost**.

Methods: Predicting confinement



- The **gene drive system** is **introduced** into **one population**.
- This population **exchanges migrants** with a population of **wild-types**.
- The **inheritance pattern** of each gene drive system is used to calculate **genotype frequencies** in the **next generation**.
- Question: Is there a **critical migration rate** at which the gene drive system takes over the new population?

Medea



Beeman and Friesen (1999)
Heredity 82, 529-534

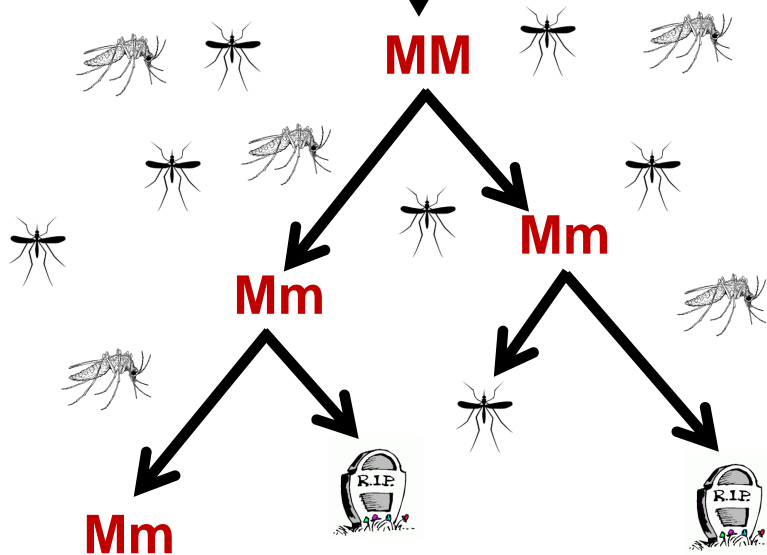
Medea is moderately invasive following an accidental release



$$e_{MM} = \frac{1}{1 + (1+r)(2-s)(1-e_{Mm})}$$

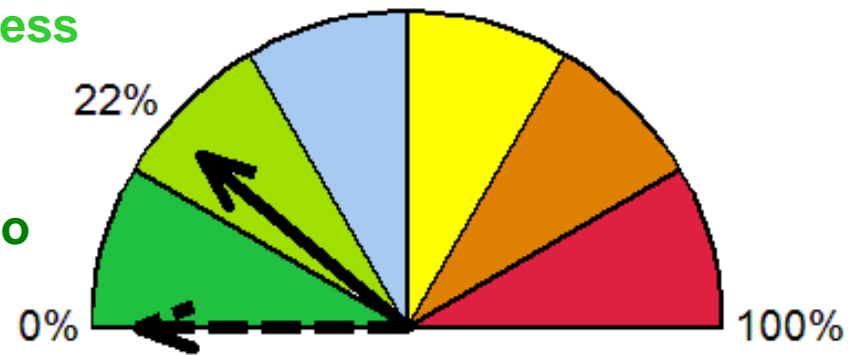
$$e_{Mm} = \min \left\{ \frac{2}{(1+r)(2-hs)}, 1 \right\}$$

Persistence probability of 10 mosquitoes with *Medea*:



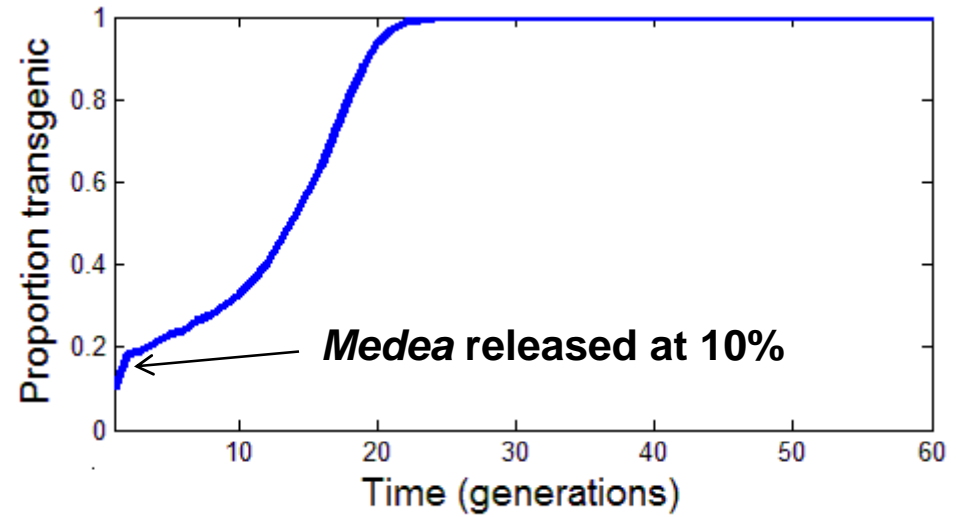
5% fitness benefit

5% or no fitness cost

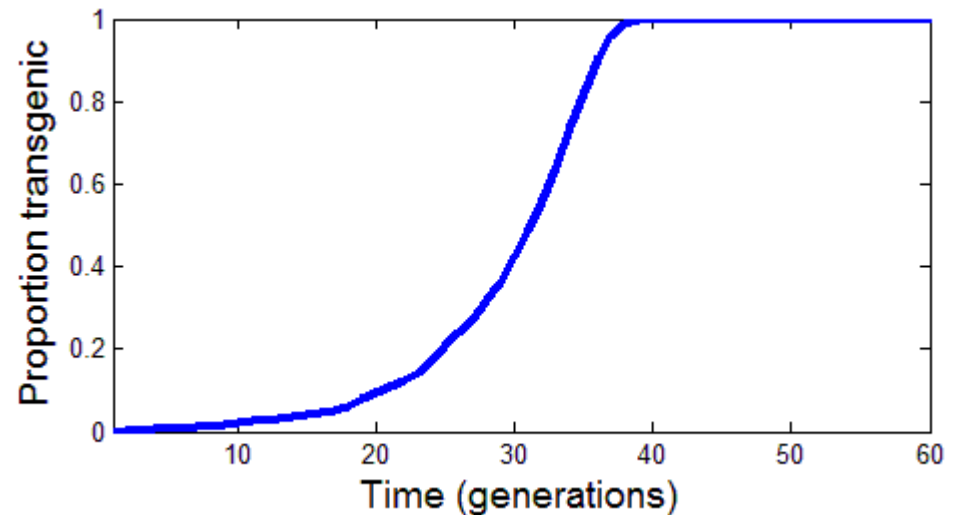
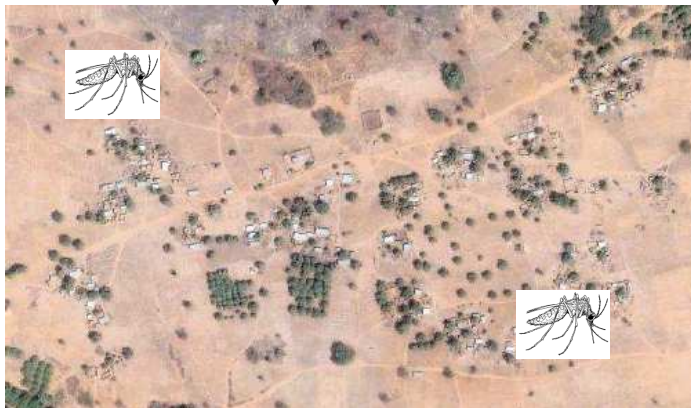


MODERATELY INVASIVE

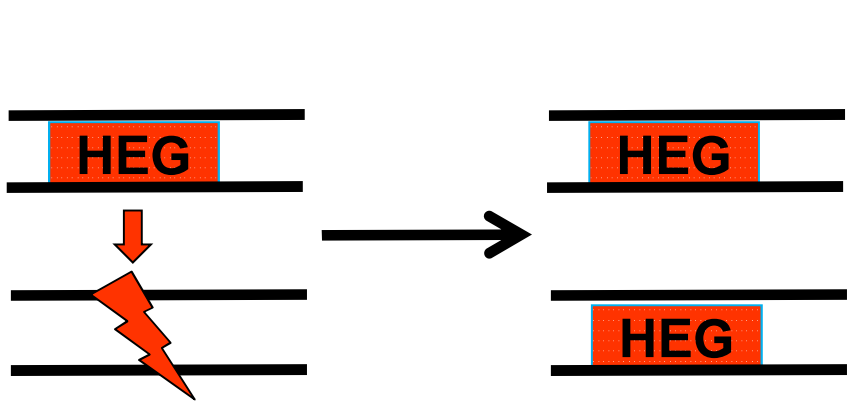
Medea is able to spread between villages with small migration rates



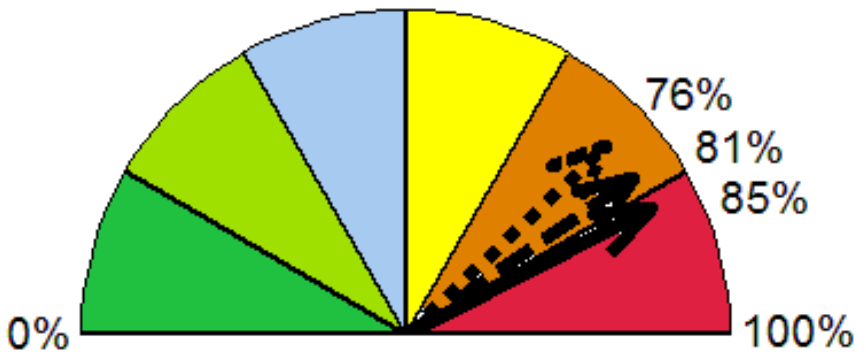
Migration rate = 1% /gen



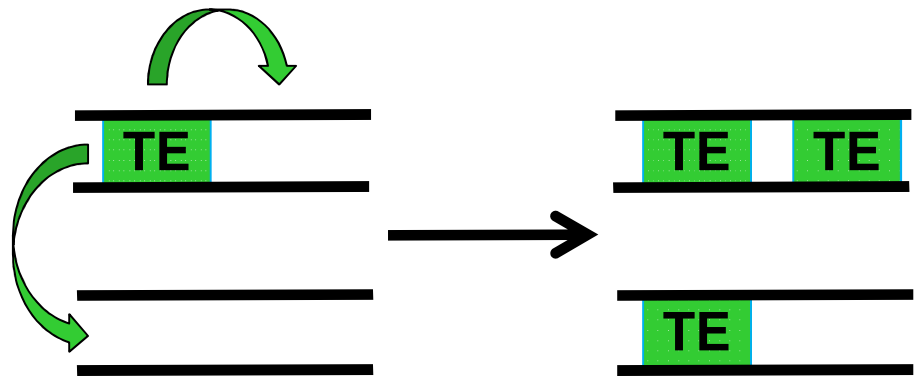
Homing endonuclease genes and transposable elements are also highly invasive



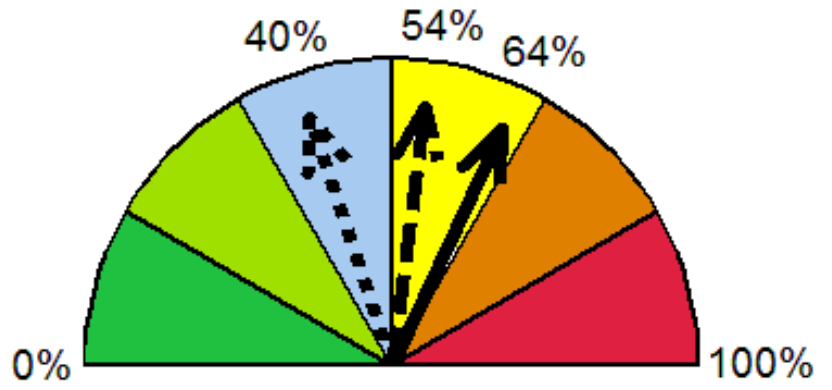
Persistence probability of 10 mosquitoes with the HEG:



EXTREMELY INVASIVE

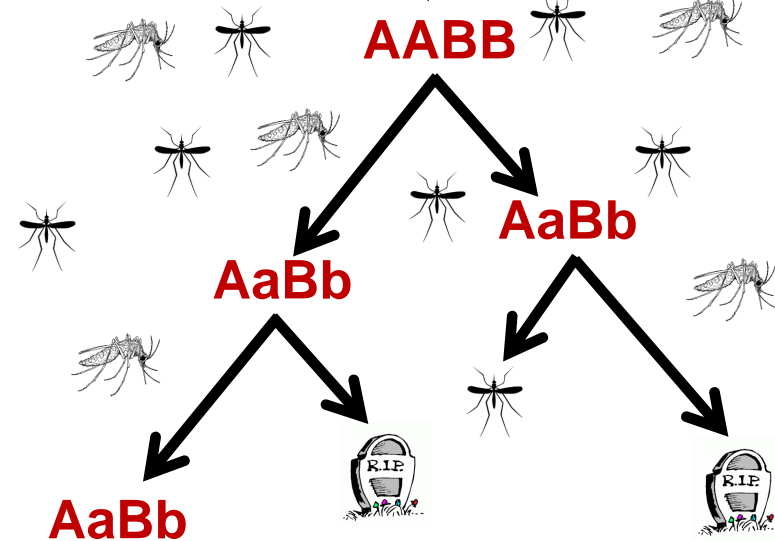
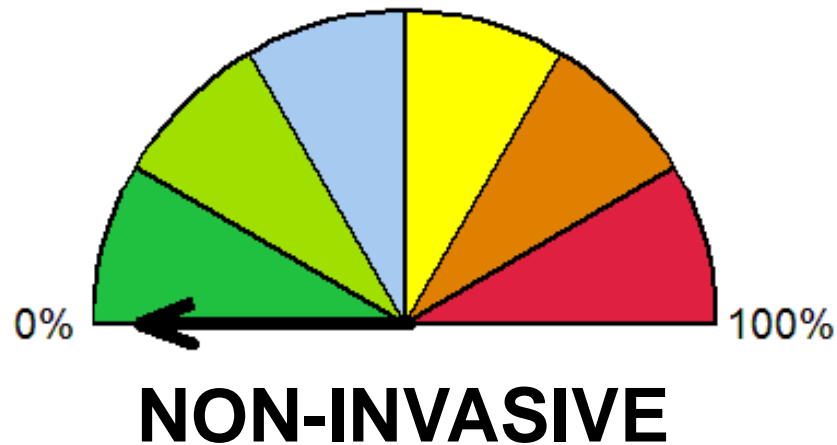
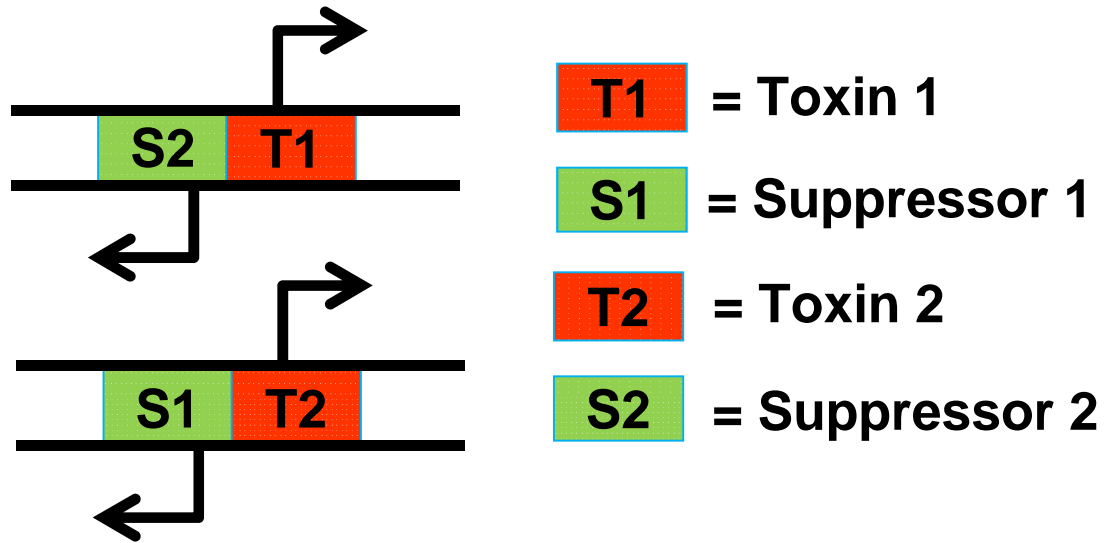


Persistence probability of 10 mosquitoes with the TE:

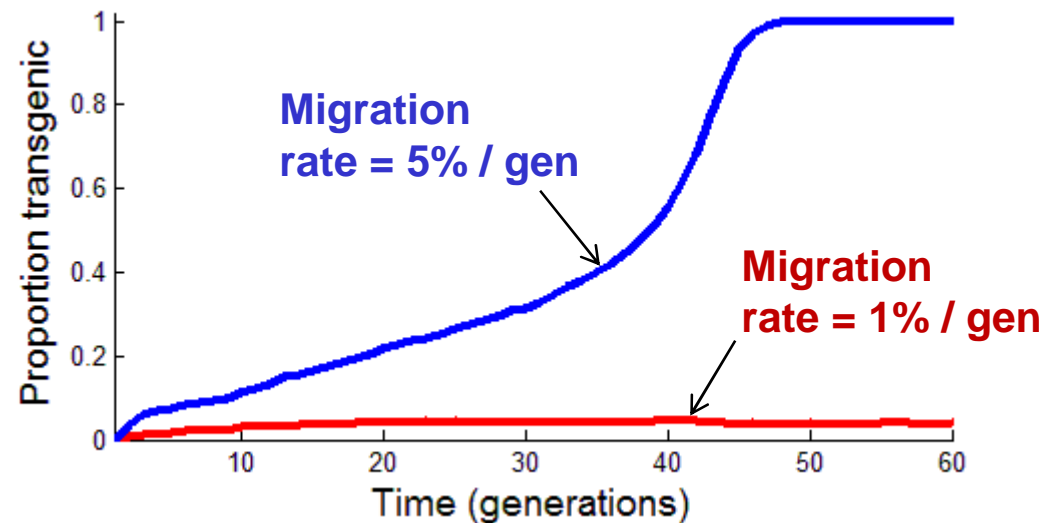
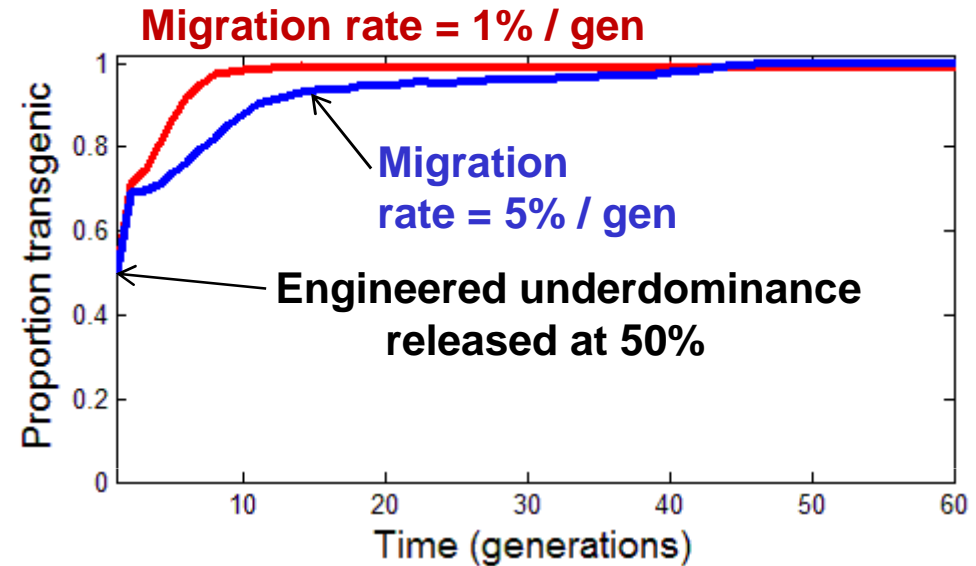
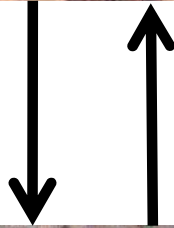


VERY INVASIVE

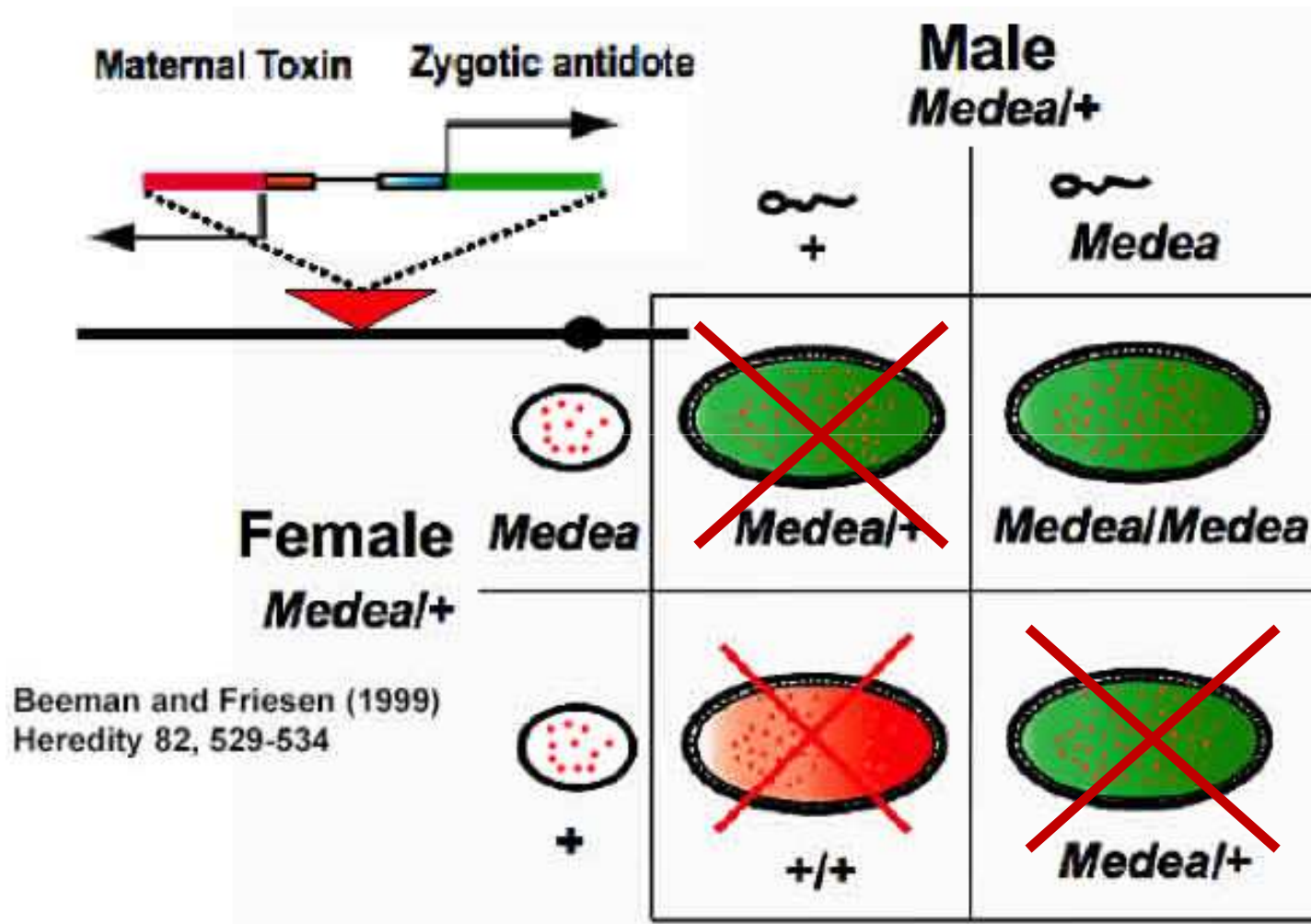
Engineered underdominance does not spread following an accidental release



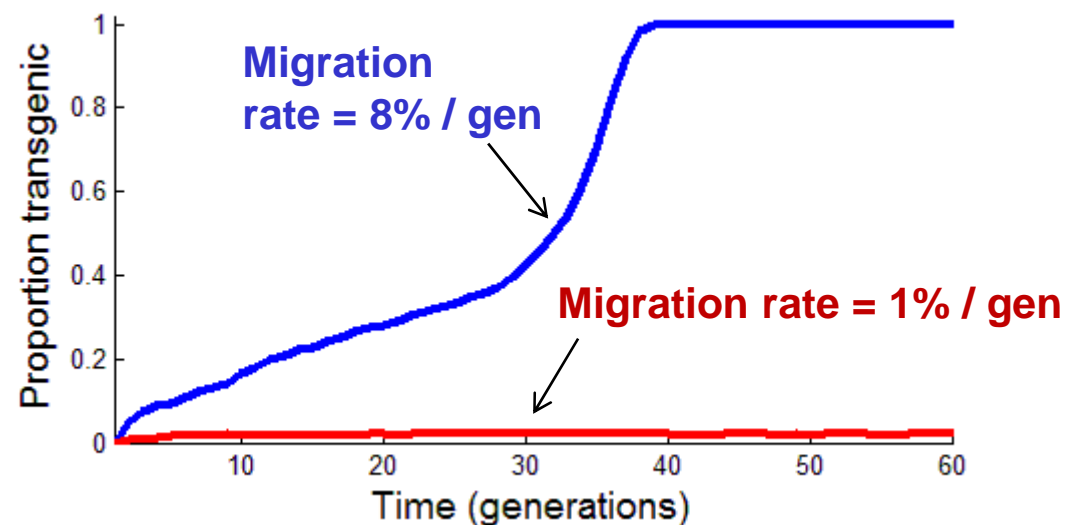
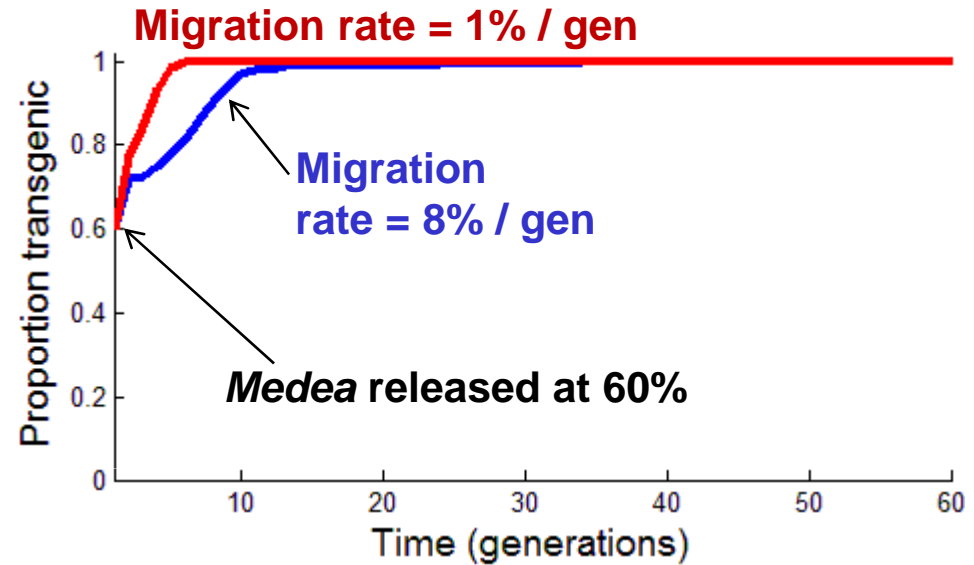
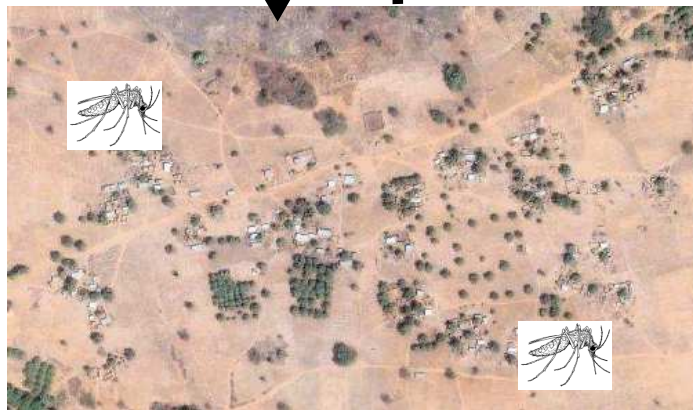
Engineered underdominance can be confined to the release population for migration rates $< 5\%$



Medea with a recessive antidote



Medea with a recessive antidote can be confined to the release population for migration rates $< 8\%$



Conclusions

Invasive gene drive systems are very difficult to contain.

Gene drive systems such as **HEGs** and **transposable elements** have **very high persistence probabilities** and can **spread** into **adjacent populations**.

It may be possible to confine gene drive systems with thresholds to cages and single populations.

Migration thresholds for **engineered underdominance** and *Medea* with a **recessive antidote** are greater than **migration rates** measured between **neighboring villages** in **Mali**.

Acknowledgements

- **UCLA:**

- **Prof Charles Taylor**
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(mathematical modeling)



- **Caltech:**

- **Prof Bruce Hay**
(molecular biology)
- **Catherine Ward**
(mathematical modeling)

Perspectives of people in Mali, West Africa to transgenic mosquitoes for malaria control:

- Sunday 22nd November, 11am
- Room: Virginia AB