Imperial College London

MRC Centre for Outbreak Analysis and Modelling

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Vector control strategies for malaria

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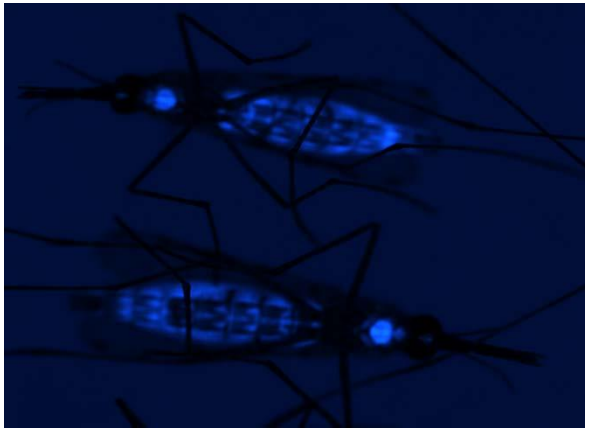
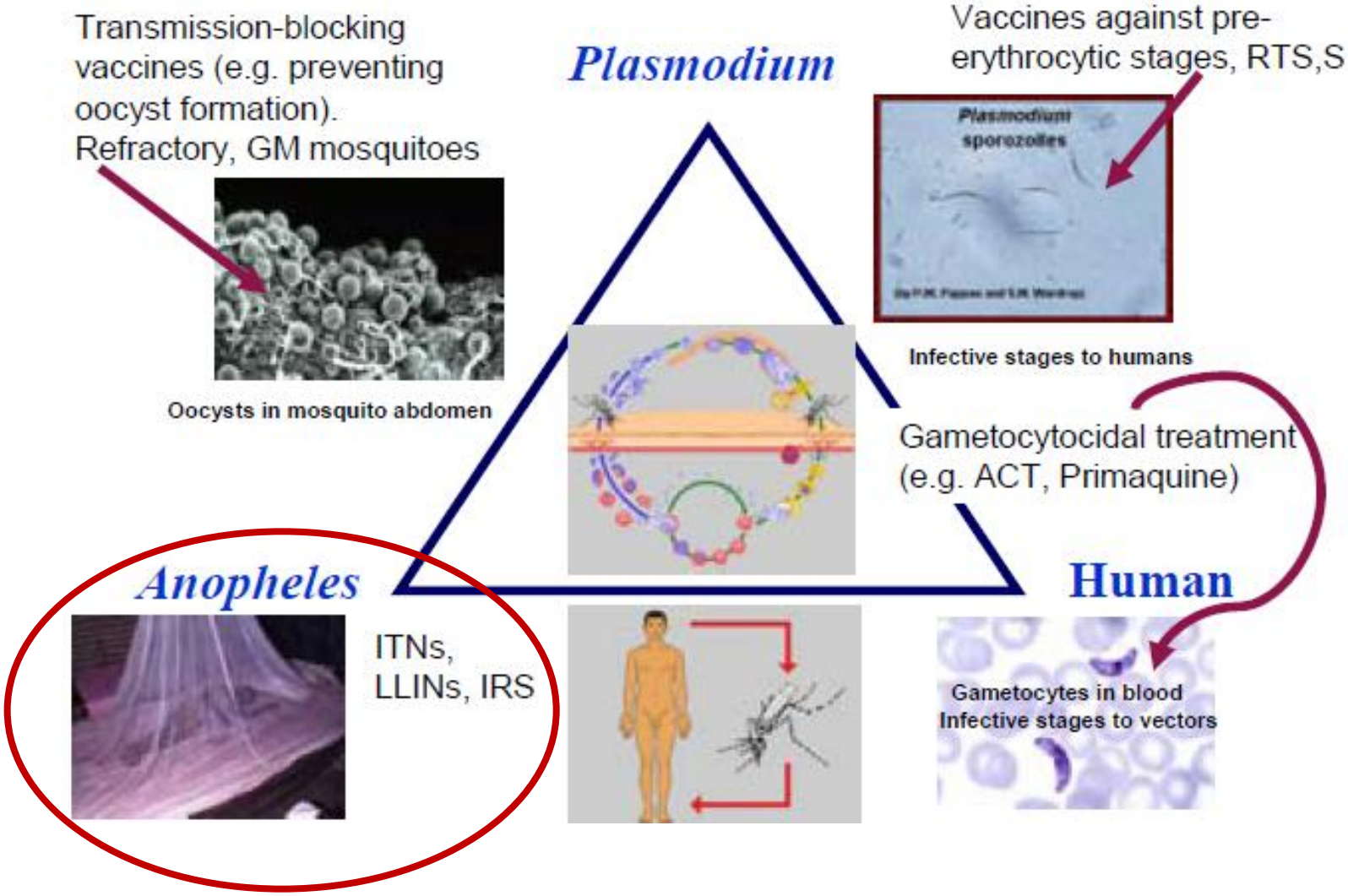
Historically successful control methods

Traditional methods

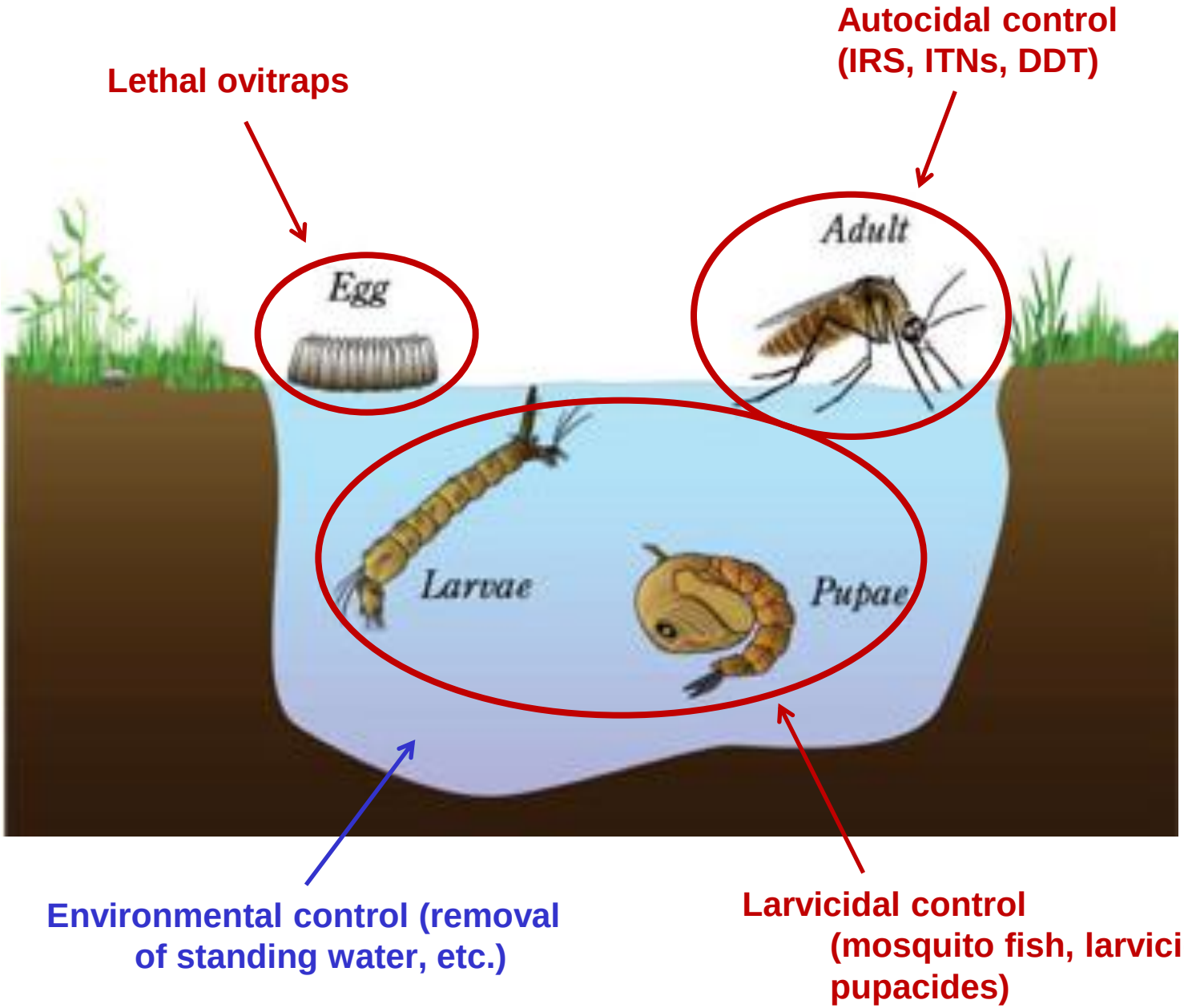


Recent advances and challenges

The triangle of malaria transmission



Mosquito life cycle



Mosquito life cycle (more detailed)

Spatial and contact repellants, physical barriers to prevent mosquito entry into houses

Zooprophylaxis, insecticide-treated cattle, odour-baited traps

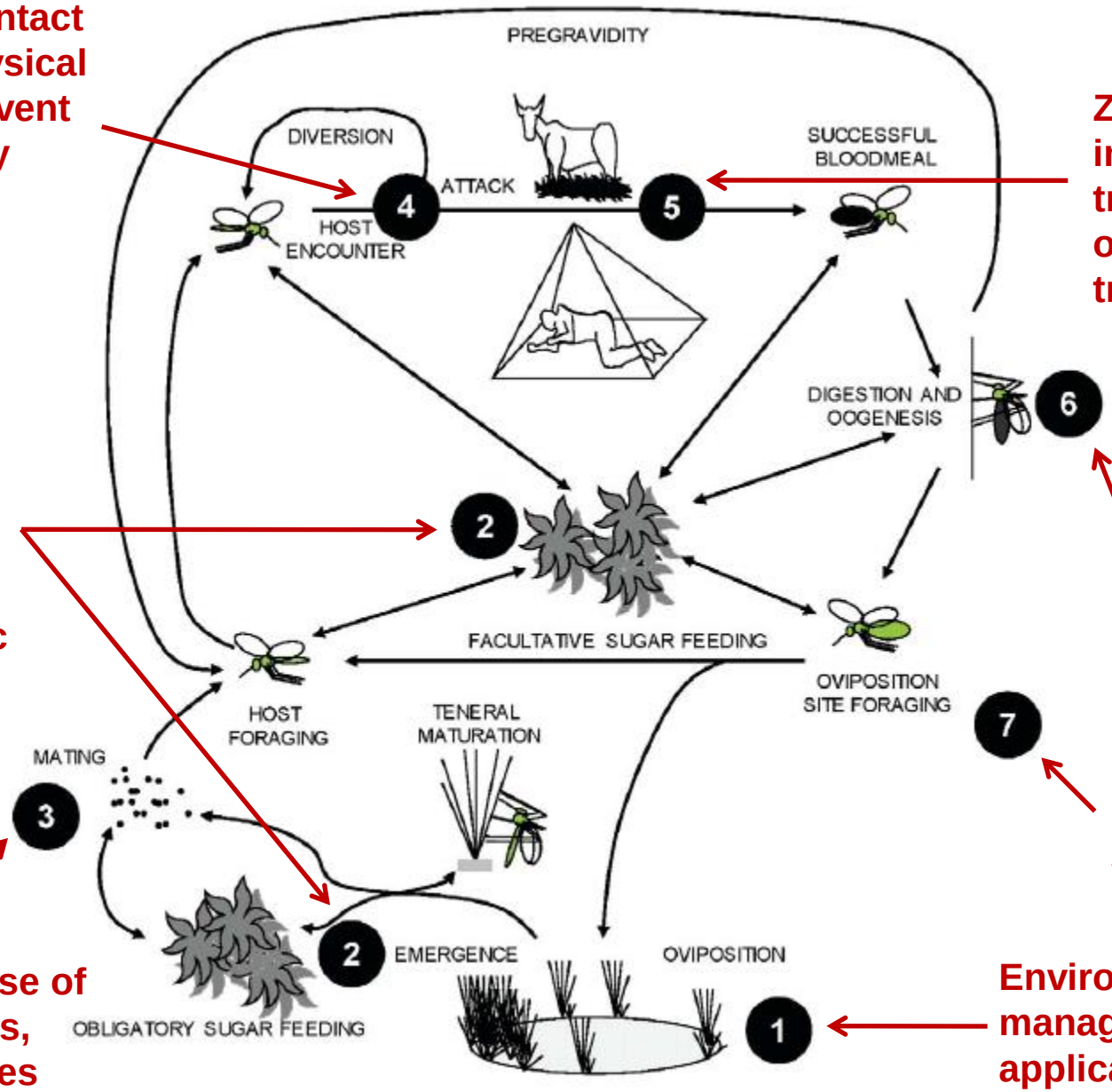
Insecticide application to natural sugar sources, toxic sugar baits, paratransgenic bacteria

Adult contamination with biological and chemical agens

Pheromone trapping, release of GM mosquitoes, GM sterile males

Environmental management of water sources

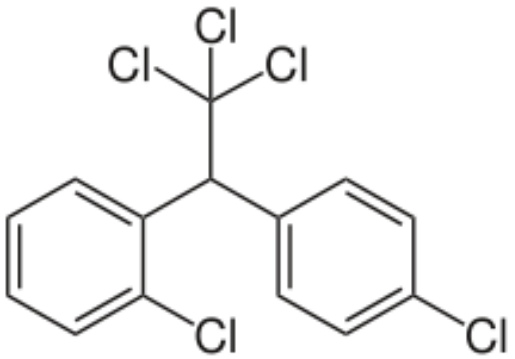
Environmental management, direct application of larvacides, pupacides



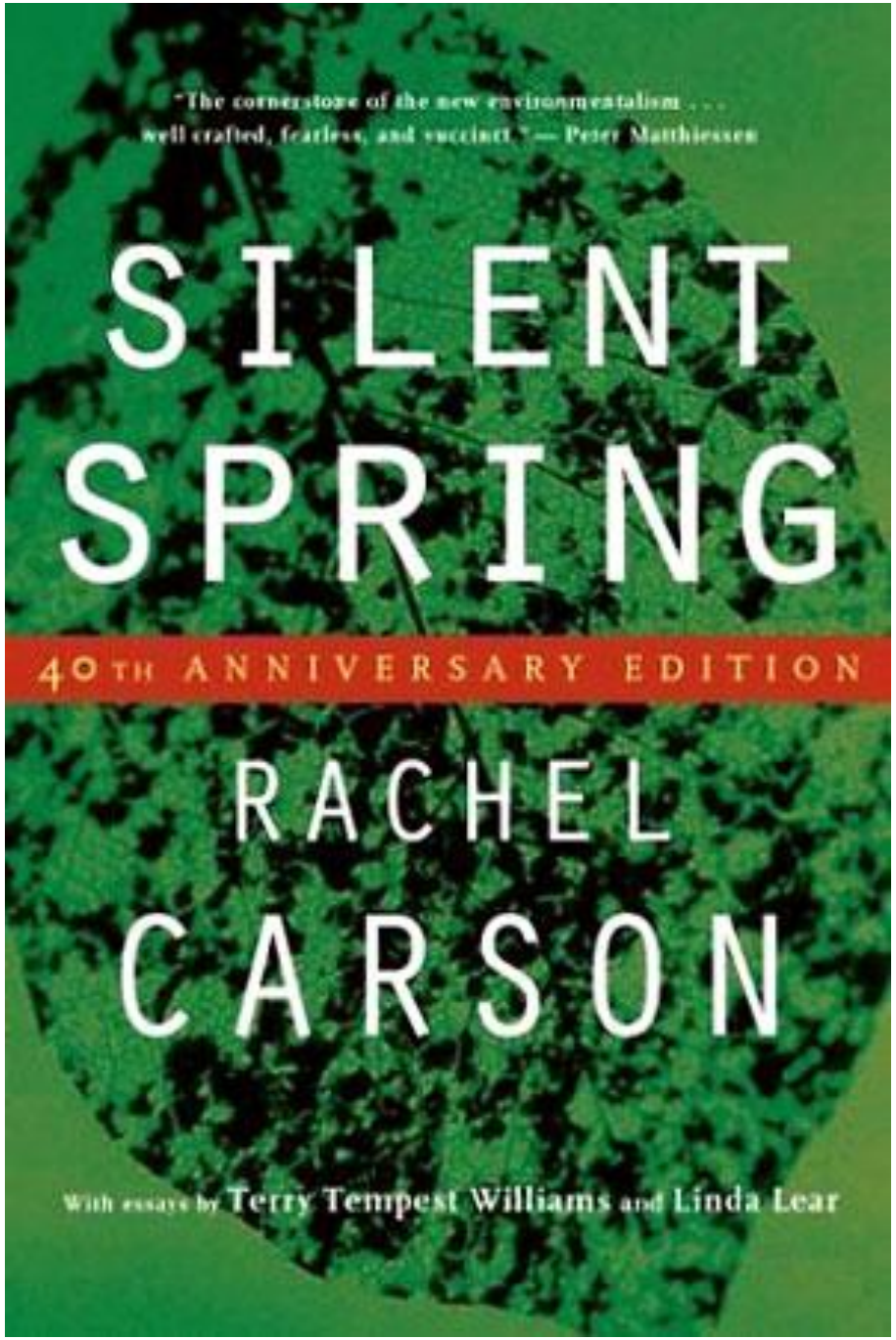
Malaria elimination in the US and Europe

- **US:**
  - **Malaria** was **prevalent** in many parts of the **US until** the **early 20th century**; and **remained** in the **South until 1951**.
  - **Vector control programs** assisted in its **elimination**:
    - **Draining wetland** breeding grounds,
    - Use of the pesticide **DDT**.

- **Southern Europe:**
  - **Malaria** was **present** in **southern Europe** for **centuries**.
  - The word “malaria” comes from Italian (“mal aria” = “bad air”).
  - It was **eradicated** from **Europe** in the **1950s** using similar tools:
    - **Draining wetlands**,
    - **Spraying** with **DDT**.



- **DDT:**
  - **First synthesized** in **1874**.
  - **Insecticidal properties** discovered in **1939**.
  - **Opens Na channels** in **neurons**, causing them to **fire all at once**, followed by **spasms/death**.
  - **Nobel Prize** in **1948** for the "discovery of the **high efficiency** of **DDT** as a **contact poison** against **several arthropods**".
  - Also used as an **agricultural insecticide**.
  - **Widespread use 1950-1980**.
  - **Now** produced only in **India**.



- **Silent Spring:**
  - **Published** in **1962**.
  - **Inspired by** widespread **concern** about **pesticides** and the **environment**.
  - **Title** refers to a **spring without bird songs**.
  - **Facilitated** the **US ban** of **DDT** in **1972** (but this doesn't apply outside the US).
  - The **Global Malaria Eradication Campaign** had already **abandoned DDT** due to **resistance** in **1969**.
  - The **2001 Stockholm Convention on Persistent Organic Pollutants** includes an **exemption** for **malaria control**.

RachelWasWrong.org

CEI

Sponsor

RachelWasWrong.org is a project of the Competitive Enterprise Institute.

Global Malaria Control Programme (1955)

- Launched by the **WHO** in **1955**.
- **Focused** on **DDT** as a vector control tool.

- **Initial success** in **eliminating malaria** from:
  - **Taiwan**;
  - The **Caribbean**;
  - The **Balkans**;
  - **Northern Australia**;
  - Parts of **Northern Africa**;
  - Much of the **South Pacific**.

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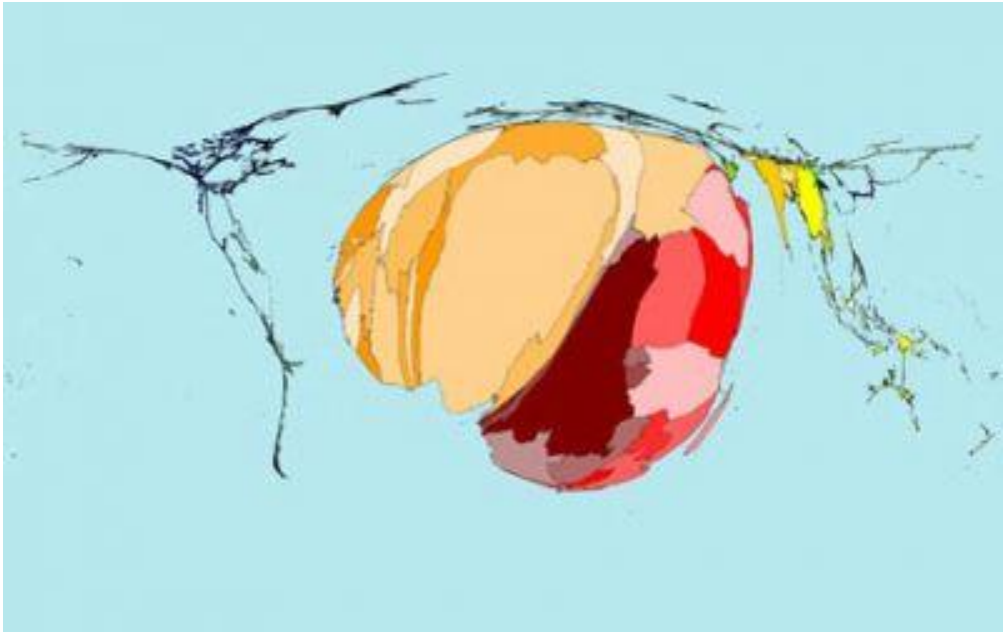
- **Reduced mortality** in:
  - **India**;
  - **Sri Lanka**.

- **Wasn't applied** in **sub-Saharan Africa** due to **perceived difficulties**.

- **Resistance** began to **emerge** and the **goal** of **eradication** was **abandoned** in **1969**.

Control in Africa has been more difficult

- **Possible reasons:**
  - Africa is a **huge continent**, much of which is **climatically suitable** for **mosquitoes**.
  - The **environment** and **rainy season** in many parts of **Africa** make **removal of standing water** very **difficult**.
  - **Lack** of **educational** and **medical infrastructure** to fight the disease.
  - **Traditional thatched housing** provides **entry points** for **mosquitoes**.



- E.g. **Kankiya**, Northern **Kenya**, **1960s**:
  - 11 rounds of **MDA**, 8 rounds of **IRS** with **DDT**.
  - **Parasite prevalence** dropped from **19% to 1%**; but **increased** again **after interventions**.

The Garki Project

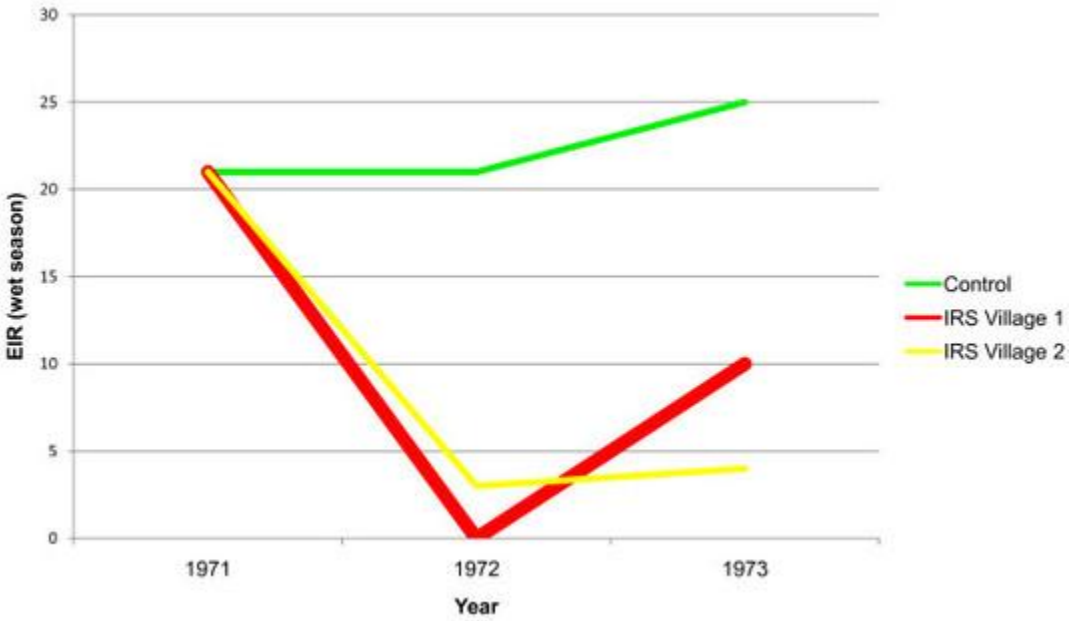
- **Garki**, Northern **Kenya**, **1969-1976**:
  - **169 study villages**.
  - Each **sprayed** with **propoxur** (a **carbamate insecticide**).
  - **Drugs** given in **60 villages** at **10 week intervals**.
  - **Larvicide** every 2 weeks in **2** small **village clusters**.
  - **Parasite prevalence** dropped to **1%** in the **dry season**, **5%** in the **rainy season**.
  - However, **no interruption of transmission**.
  - **Prevalence increased after interventions**.

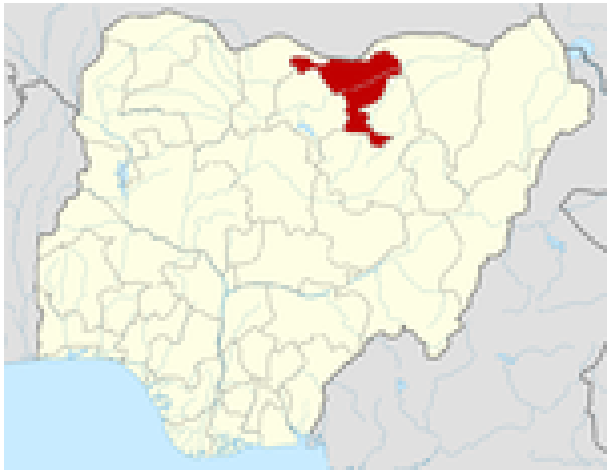

THE GARKI PROJECT

Research on the Epidemiology and Control of Malaria in the Sudan Savanna of West Africa

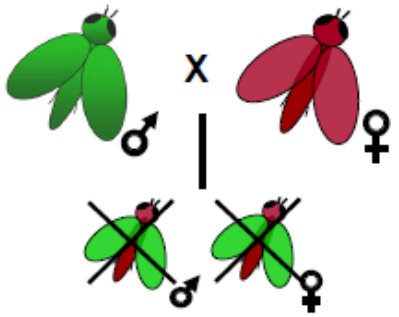
by

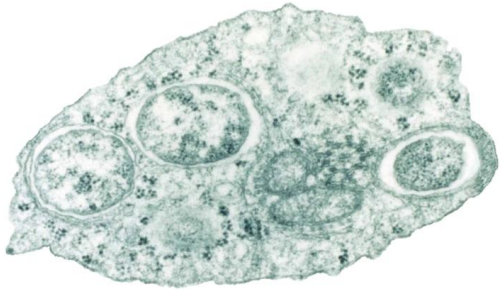
WORLD HEALTH ORGANIZATION

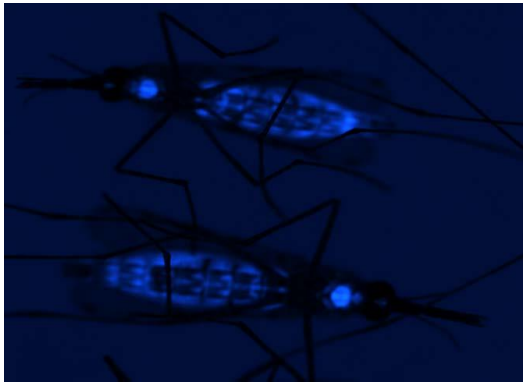




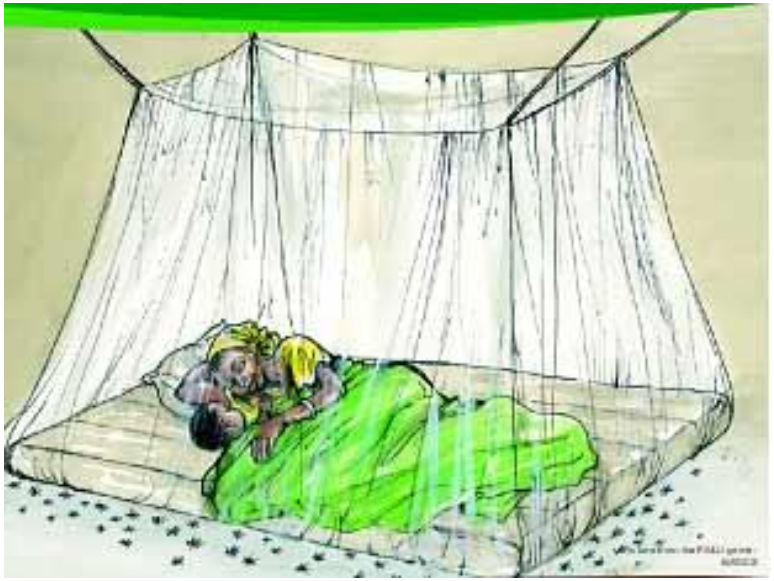
Malaria control in endemic parts of Africa will require using many interventions at the same time







Bed nets (ITNs, LLINs)



•The **main personal protection measure**.

•Protects against **malaria-transmitting mosquitoes** (mainly ***Anopheles gambiae***) that tend to **bite at night**.

•**Insecticide-impregnated** to provide **additional protection** (however, levels of **insecticide resistance** should be **monitored**).

•**Distribution** has **historically** been **poor**, but this is **improving**:

- •**WHO Roll Back Malaria**
- •**President's Malaria Initiative**

•However, **proper use** is always an **issue**.

•**Pros:**

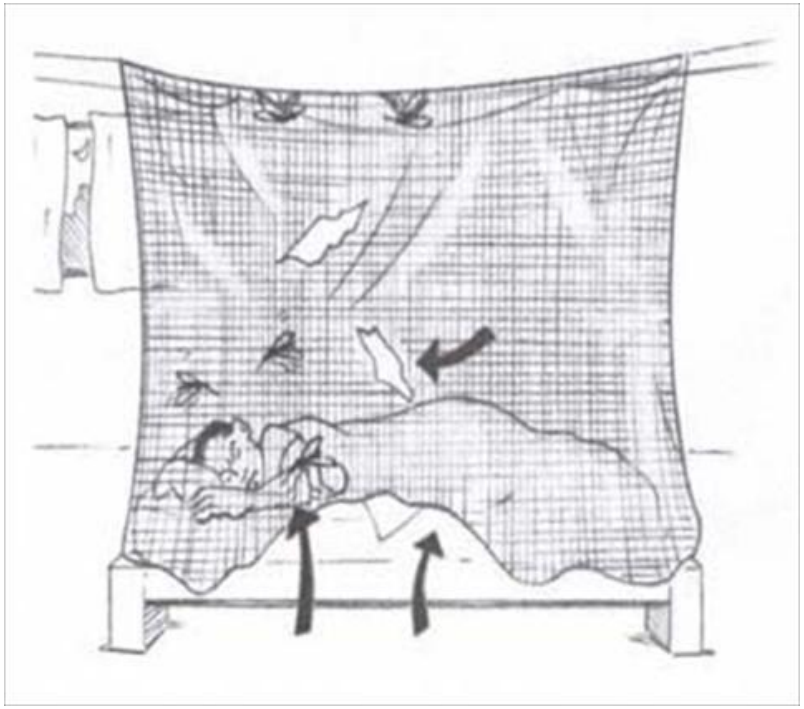
- •**Effective** if **used properly** (can provide a **30-60% reduction** in **malaria morbidity**, and can **delay emergence** of **drug resistance** in the **parasite**).

Great photo op!

Why bed nets are not enough

- **Cons:**
  - **ITNs** are **not always used properly**.
  - Some people **don't believe** that **malaria** is **transmitted** by **mosquitoes**, and therefore don't use ITNs.
  - People **don't like nets**.

  - Even if **people** use ITNs, they can still be **bitten late at night**, **before they go to bed**, when they are outside socializing or eating.
  - **Nets** often end up having **holes**, which mosquitoes can fly through.
  - If **not tucked in**, mosquitoes can fly between the net and bed.
  - **Nets** can often make **contact** with the skin, making the **skin accessible** to mosquitoes.



  - **Mosquitoes** are becoming **resistant** to the **insecticides** used to treat nets (it is therefore necessary to **evaluate which insecticides** to use in **different places**).

Indoor residual spraying (IRS)

•Applying a **long-lasting insecticide** (with a hand-compression sprayer) to the **inner walls** of a house.
•**Mosquitoes** are **driven away** or **killed** when they **rest** on **treated walls**.

•Can use one or more **insecticides** from:
- •**DDT**;
- •**Pyrethroids** (6 choices, e.g. **deltamethrin**);
- •**Carbamates** (2 choices, e.g. **bendiocarb**);
- •**Organophosphates** (3 choices, e.g. **malathion**).

•**Pros:**
- •**Results** are **comparable** to **ITNs** (**good** if **properly implemented**).

•**Cons:**
- •**Benefits** are only seen **if** a **majority** of **residents** are **involved**.
- •**Many residents oppose insecticide use**:
  - •**Health concerns**.
  - •May also **kill beneficial insects**, e.g. **wasps** that kill **caterpillars** that destroy thatched **roofs**.

Darwin's mosquitoes

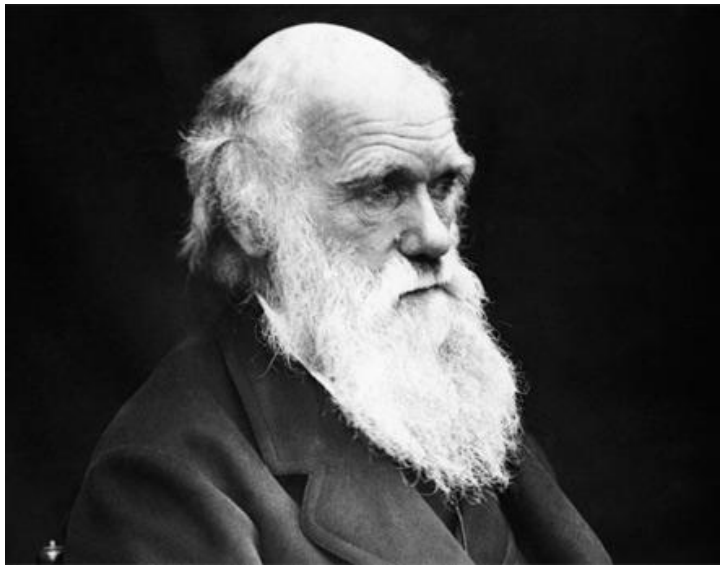
- The **more ITNs** and **IRS** are **used**, the **more mosquitoes resistant** to **insecticides** will be **favored** in the population.

- This **increases** the **rate** at which **insecticide-resistant alleles spread** into the **population**.

- **Resistance** can be:

  1. **Physiological**:
     - **Mutations** in the **Na channel gene** confer resistance.
     - **Up-regulation** of **genes expressing cytochrome P450**.

  2. **Behavioral**:
     - **Selection for**:
       - **Mosquitoes** that **rest outdoors** (e.g. ***An. gambiae***).
       - **Mosquitoes** that **feed earlier** at night.

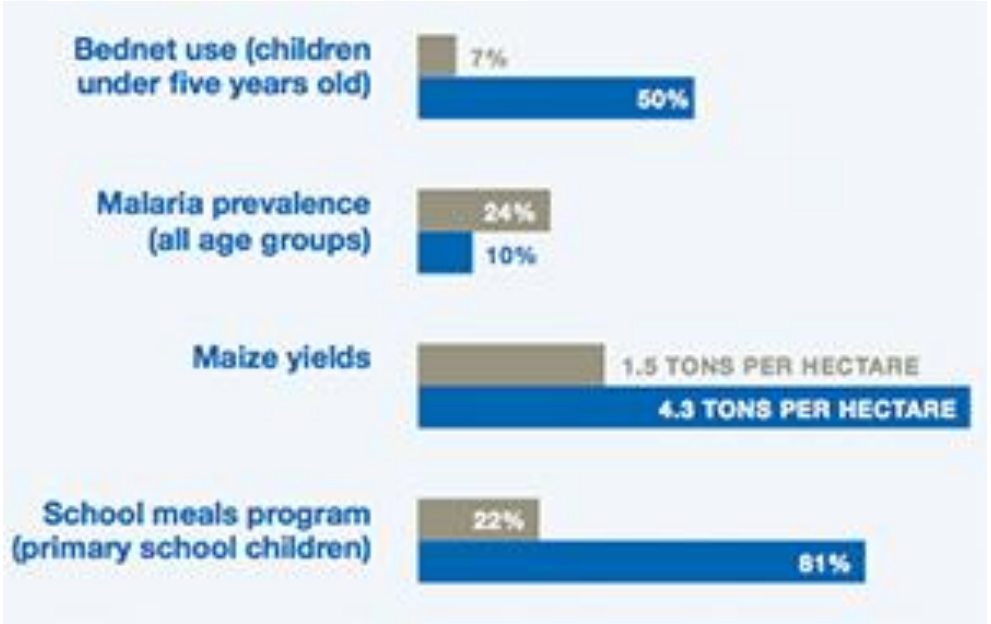


Education and sustainability

Millennium Villages

•**Strategies** that require **active human involvement** (e.g. **ITNs**) also **require education** on **disease causation**.

• **Millennium Villages**
  - •**Holistic approach**:
    - •**Education**,
    - •**Agriculture** & **jobs** (leading to **economic self-sufficiency**),
    - •**Clean water** & **health care** (including **bed nets**).



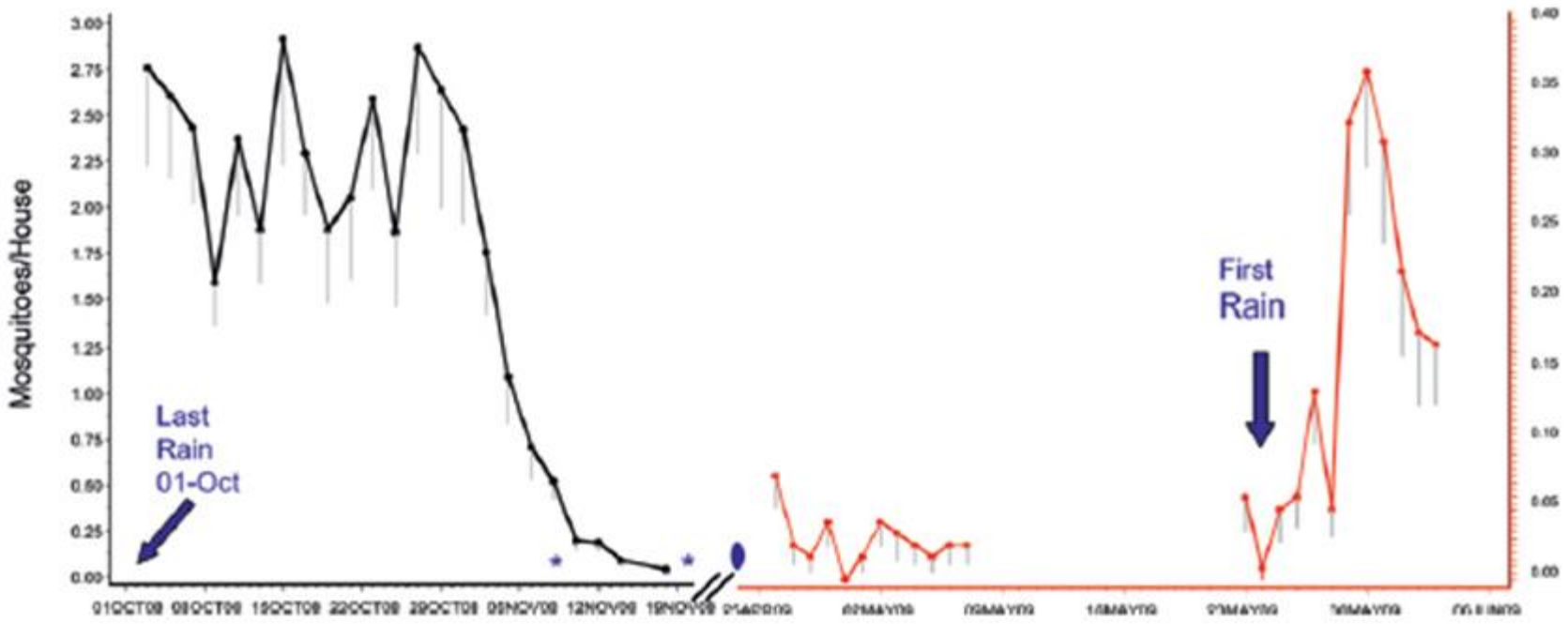
Environmental management

- **Prevent mosquitoes** from **breeding**, **nesting** and **feeding** through **environmental modifications**.

- Thus **suppress** the **mosquito population**.

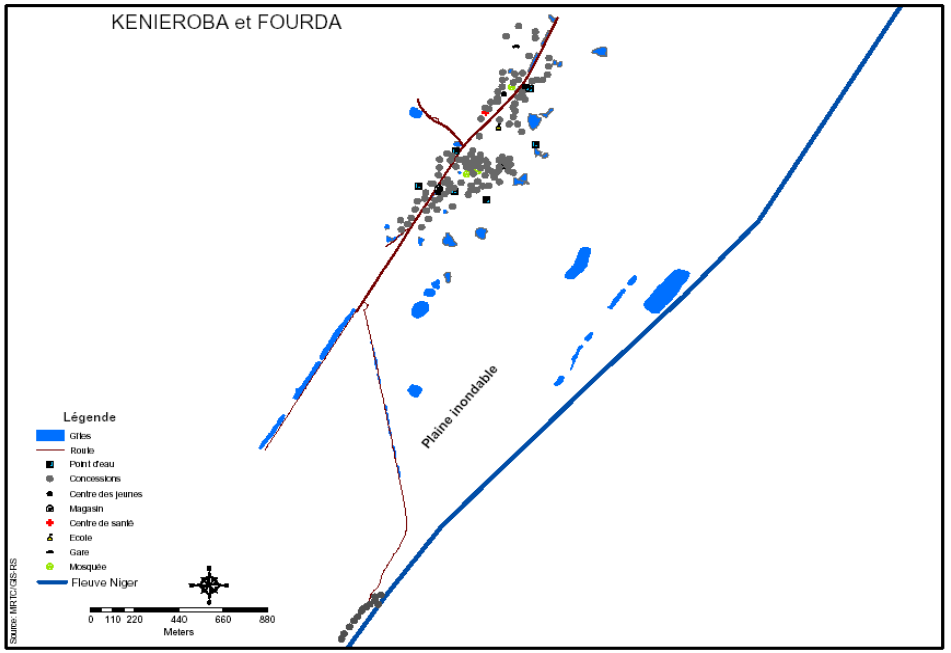
- **Methods:**
  - **Removal** of **stagnant water** (**draining swamps**, **removing old tires**).
    - **Not always possible**, given the rainy season in some environments.
  - Investing in **more secure housing**, **windows**, **doors**, **screens**.
  - **Monitor agriculture**, **construction**, **irrigation** (these activities can generate **breeding sites**).
  - **Apply oil** to some **water sources** (environmental issues).

- Requires **collaboration** between **community members** and **vector control officers**.



- **Rainy season:**
  - **Many** standing **water sources**.
  - Apply an **insecticide when** the **rains start** that **lasts until** the **end** of the **rainy season**.

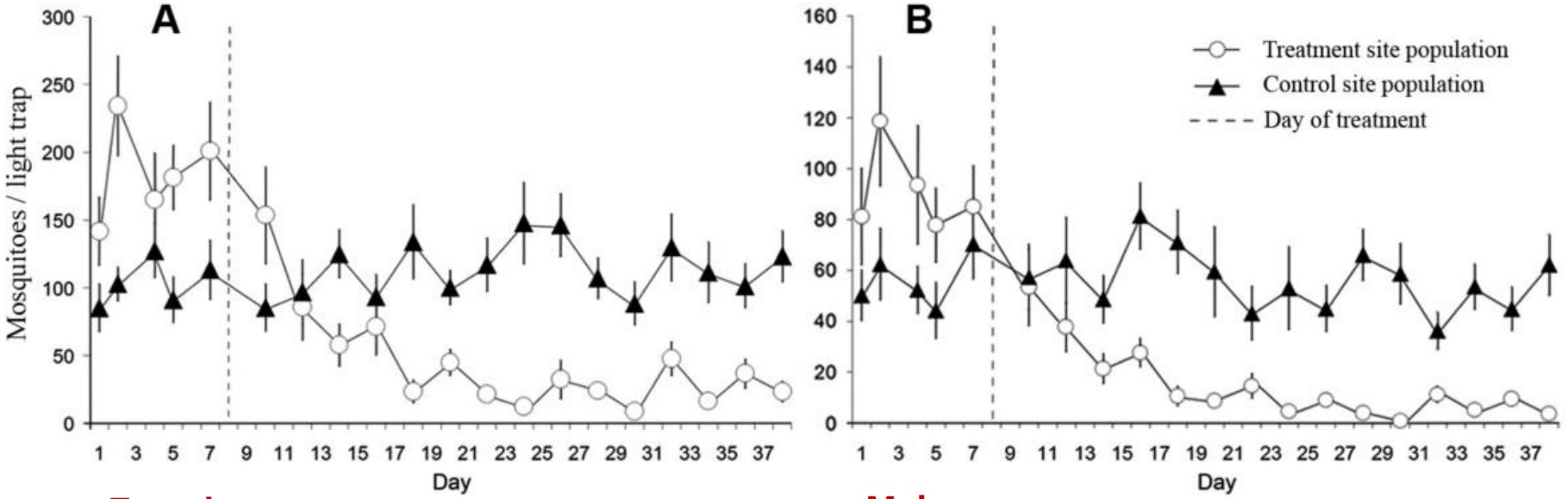
- **Dry season:**
  - **Target permanent water sources**.
  - E.g. small spots of **water** on the **side** of the **river bed**.



AttractiveToxic Sugar Bait

- **Mosquito sugar feeding:**
  - **Both sexes sugar feed** from **flowers**, etc.
  - **Females** require **blood** to produce **eggs**.

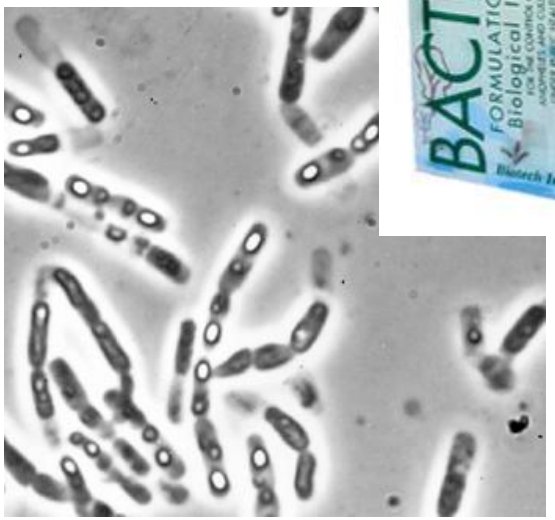
- **Toxic sugar bait**
  - **Spray sugar feeding sites** with **toxic sugar bait**.
  - Provide **bait stations** with **sheltered, sprayed vegetation**.
  - **Most effective** in **dry locations**.



Females **Males**

Larvacides

- **Control** of **larvae** through:
  - **Chemical poisons**.
  - **Infectious agents**:
    - **Bacteria**, **fungi**.
    - **Dead spores** of the soil bacterium ***Bacillus thuringiensis israelensis***.
      - **Interfere** with **larval digestive system**.
      - Can be **dropped** from **helicopter**.
  - **Biocontrol agents**:
    - **Predatory fish** and **nematodes** that feed on larvae.
    - **Dragonflies** (consume larvae).



- **Pros:**
  - **Complement other control strategies**.
- **Cons:**
  - Need to **consider environmental feasibility**, **consequences**.

Insecticide-treated cattle (ITC)

- **Pros:**
  - **Complements other strategies** in **locations** where **vectors** are largely **zoophilic**.
    - Has been **successfully trialed** in **Pakistan**.
- **Cons:**
  - **African field trials** have been **less successful**.
    - **Mosquitoes** tend to **feed** from **legs of cattle**.
    - **Cattle rub** their **legs** on the **ground** when they sleep/sit, leading to a **short insecticidal half-life**.
    - **Mosquitoes feed** for **shorter times** on **treated cattle**.

Table 1. Percentage of mosquitoes observed feeding successfully on clean (untreated) or insecticide-treated Zebu cattle and the percentage of flies observed on the legs

Species	Treatment	*n*	Fed (%)	On leg (%)
An. arabiensis	Clean	98	78	95
	Treated	67	40	97
An. pharoensis	Clean	90	68	98
	Treated	29	31	97
An. tenebrosus	Clean	340	56	93
	Treated	478	43	86

Odor-baited traps

- **Lure-and-kill strategy**:
  - **Traps emit chemicals** to **mimic** a **mammal's scent**:
    - **CO_2** (propane-burning device),
    - **Lactic acid**,
    - **Sugary scent**.
    - **Smelly socks** also **produce attractive odors**.
  - **Females** are **drawn towards** the **trap**, **sucked in**, and **collected**.
  - **Useful** for **monitoring**; but typically too **inefficient** for **suppression**.

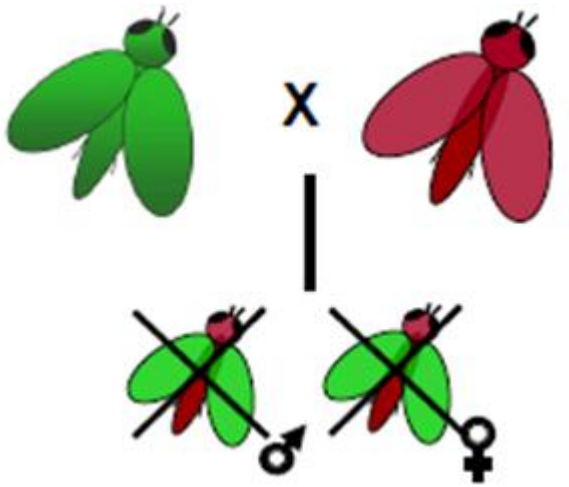
- **Lethal ovitraps**:
  - Also use the **lure-and-kill** strategy.
  - **Females lay eggs** in the **trap**, which are **unable to emerge**.
  - **Number of eggs** can **help identify** mosquito **breeding hotspots**.

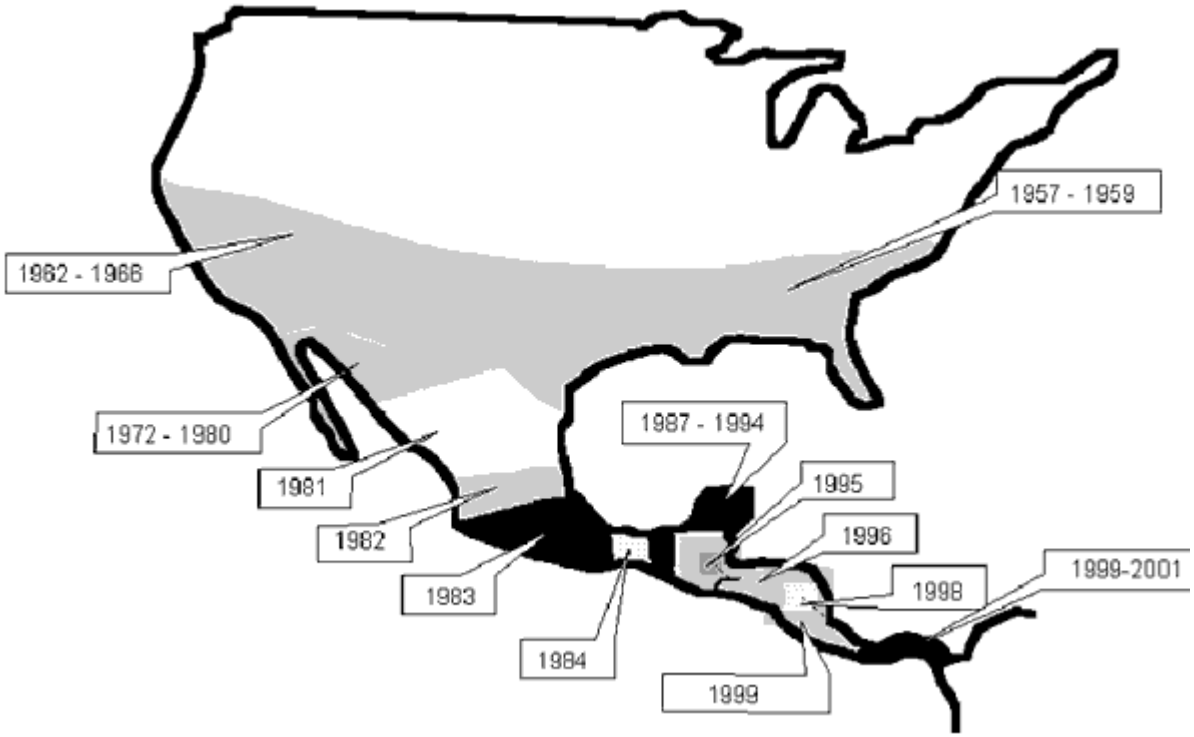
IN BRIEF

Nasty Foot Stench Could Help Fight Malaria

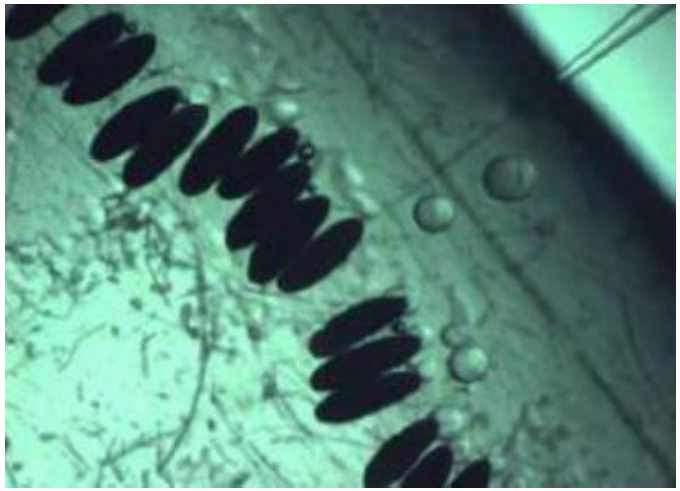
Sterile insect technique (SIT)

- Make **mosquitoes sterile** through **exposure** to **radiation**.
- Need to work out **appropriate dose** so that:
  - **Mosquitoes** are still **competitive**;
  - **Offspring** are **unviable**.
- **Successfully** applied for **New World Screw-worm**.





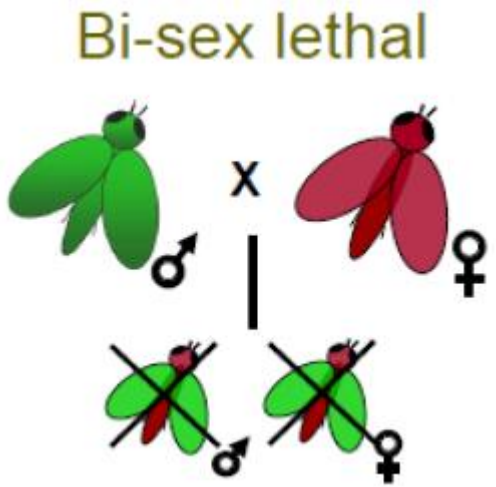
GM sterile mosquitoes

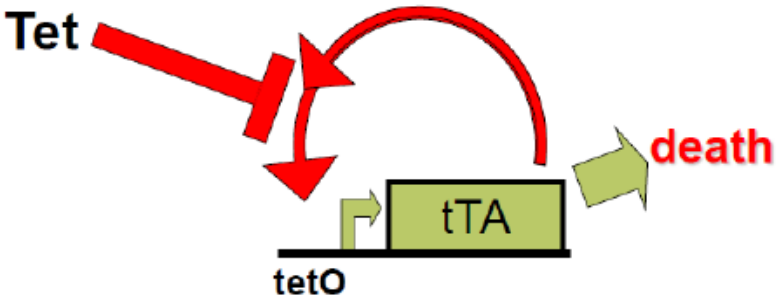


- **Genetic approach to SIT:**
  - **Repression** of **Insects** using a **Dominant Lethal** allele (RIDL).
  - **Mosquitoes** having at least **one copy** of the **RIDL** allele **can't fly**.
  - This effect is **repressible** (by **Tetracycline**).
  - **Provide Tetracycline** during **rearing**.
  - **Release homozygous males** (can't bite).
  - **All offspring** should be **unviable**.
  - **Population** should **decline**.

- **Pros:**
  - **Species-specific**.
  - **Genetic sexing** methods are **available**.
  - **GM males** are **more fit** than **irradiated males**.

- **Cons:**
  - **Requires continued release**.



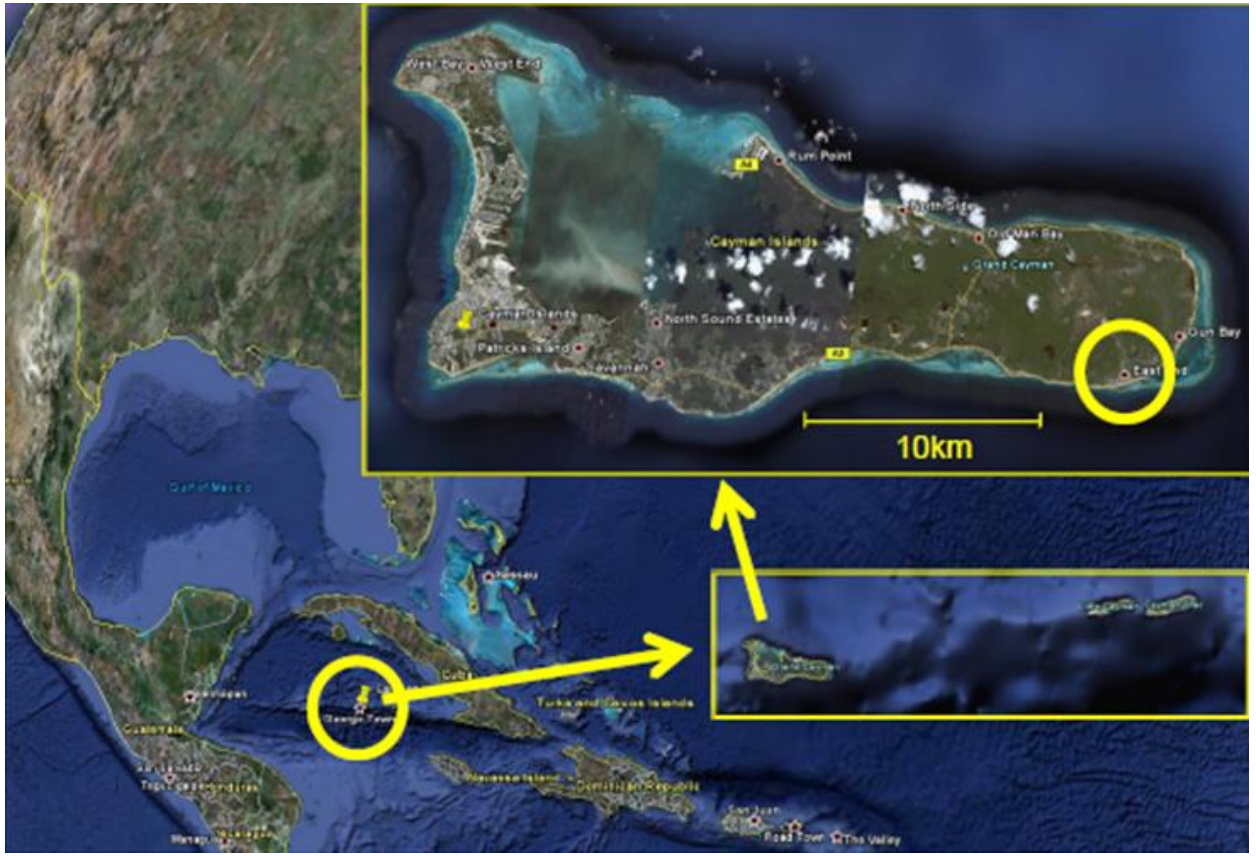


Genetically-modified mosquitoes released for no reason

27-01-11

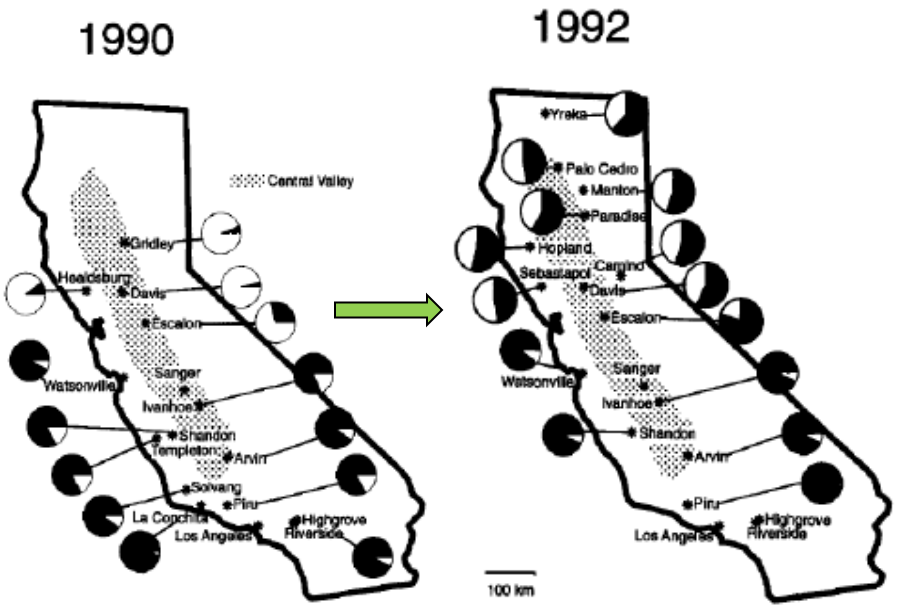
SCIENTISTS in Malaysia have unleashed giant, DNA-altered mosquitoes into the environment for the hell of it.

The scientists will now have to release an absolutely enormous frog



Wolbachia

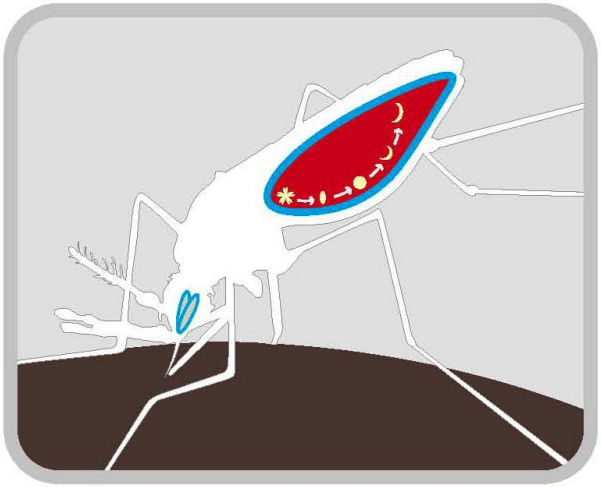
- ***Wolbachia*:**
  - Is an **inherited intracellular bacterium** capable of manipulating its host's reproductive biology to **favor its spread** through a population.
  - Is **capable of spreading** over a **large geographical area**; as seen in California, 1990-1992.



- **wMelPop strian:**
  - Has several **beneficial features** for **dengue control** in *Ae. aegypti*:
    - **Reduced mosquito lifespan**.
    - **Reduced dengue viral load**.
    - **Reduced** ability to obtain **blood meals** with age.

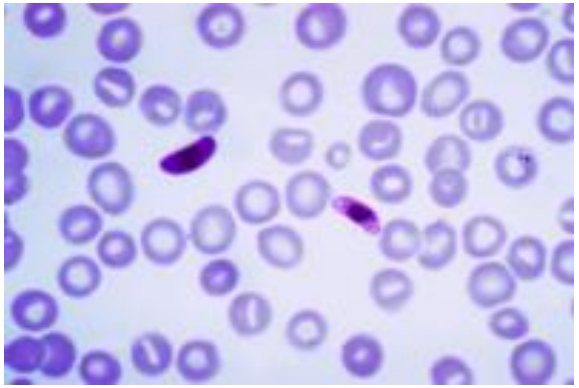
Disease refractory mosquitoes

- **Candidate disease-refractory genes:**



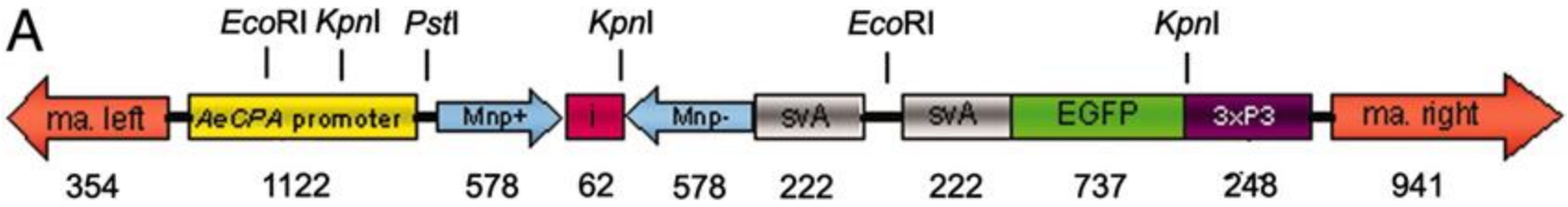
  - A **transgene** has been engineered in ***Anopheles stephensi*** that confers **resistance to rodent malaria** by preventing passage of the parasite through the gut following ingestion.

  - **Antibodies** are being studied that **kill malaria parasites** within the mosquito.

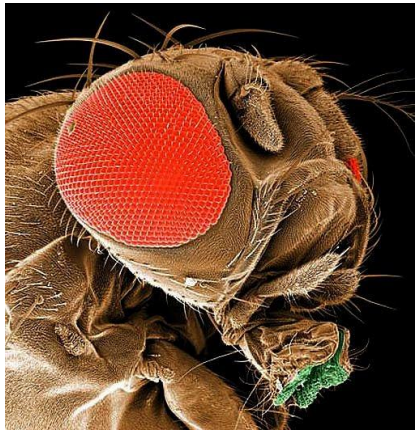


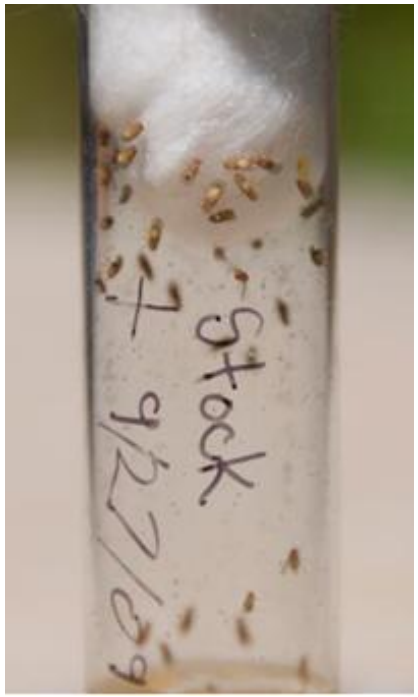
  - **Genes** that govern **refractoriness** in **natural populations** are being searched for.

  - A **dengue refractory gene** in ***Aedes aegypti*** has been engineered by taking advantage of a **natural antiviral pathway** in the mosquito and placing it under the control of a **blood-meal specific promoter**.

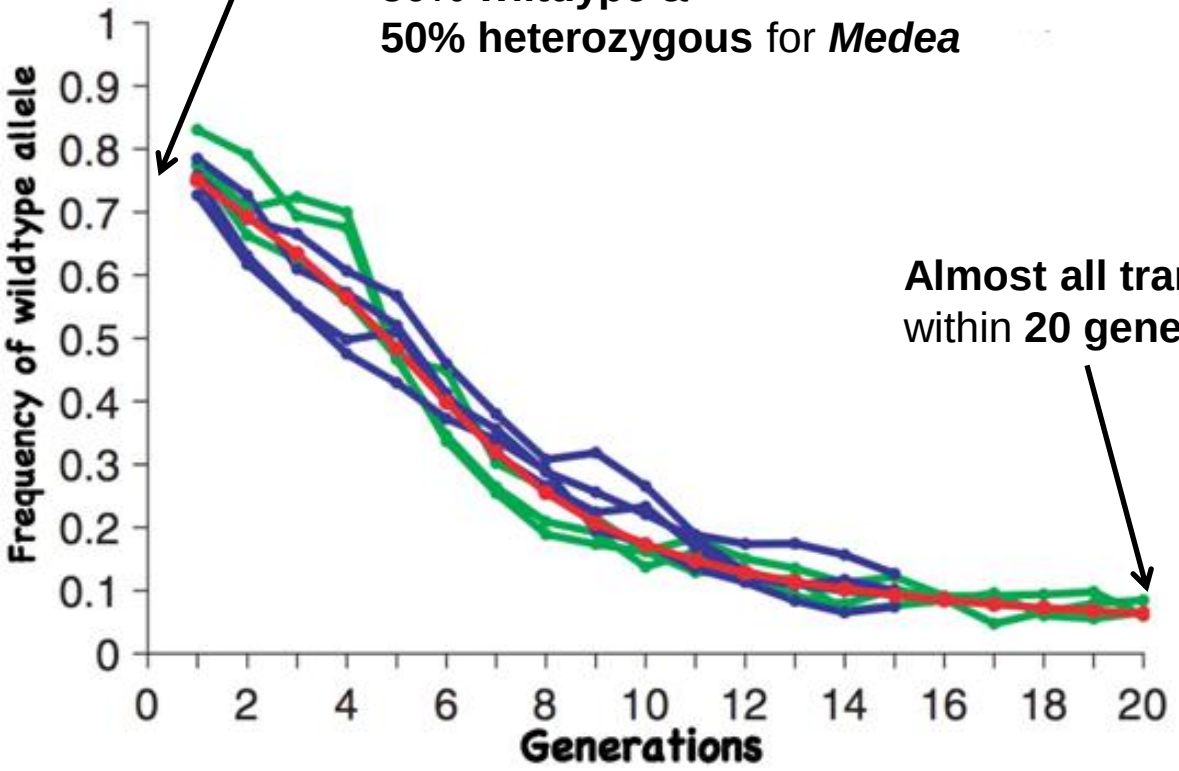


Refractory genes can be driven into a population using *Medea*





Initial population is
50% wiltdype &
50% heterozygous for ***Medea***

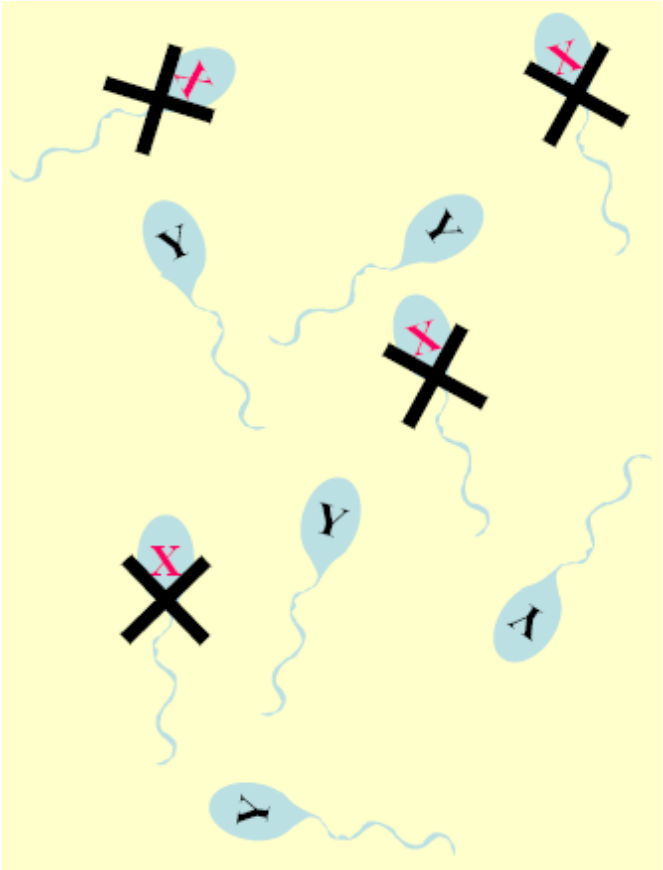


Almost all transgenic
within **20 generations**

X shredders

- **Homing endonuclease genes** on the **Y chromosome** that:
  - Cut a specific site on the **X chromosome**.
  - Reduce the number of **X chromosomes** in the **sperm**.
  - Create a **male bias** in the population.

- They are predicted to cause a **population crash**:
  - A **high male bias** leads to a population crash.
  - Combined with **gene drive**, this could lead to a **cascade of crashes**.



Make:

technology on your time

The Most Useless Machine!
page 94 »

AMAZING GADGETS YOU CAN BUILD!

PLUS: MOSQUITO BLASTER:
IT'S REAL!
HOW THEY DID IT
PAGE 48

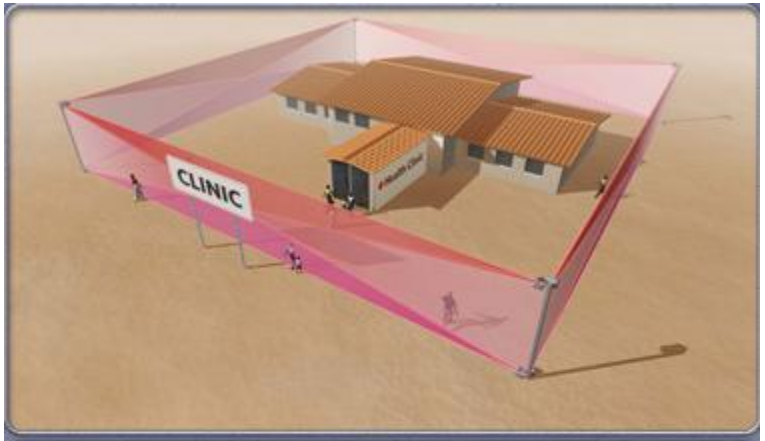
18 FUN HOW-TO PROJECTS

- MAGIC TALKING MIRROR
- TINY AUTO GYROCAR
- SOLAR SUBWOOFER
- HULA HOOP POOL WARMER

Eric Johanson and Intellectual Ventures' new malaria weapon, the Photonic Fence.

O'REILLY

makezine.com



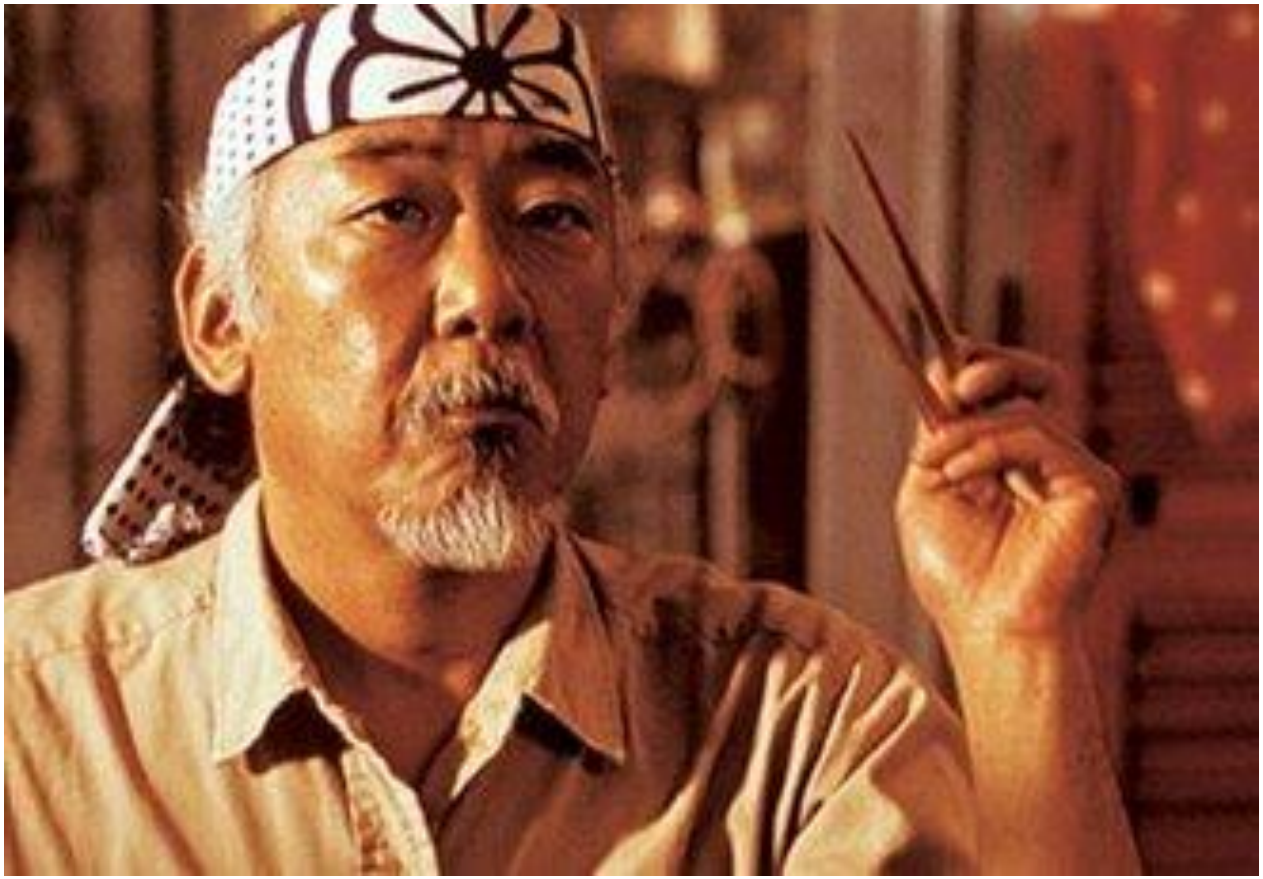
Clinic

IV's system could protect a health clinic with fence-like planes of light, which would detect and kill mosquitoes passing through them. The light beams, shown in red here for clarity, would actually be composed of infrared photons and hence invisible to the human eye. Insects other than mosquitoes would pass through the fence unharmed.

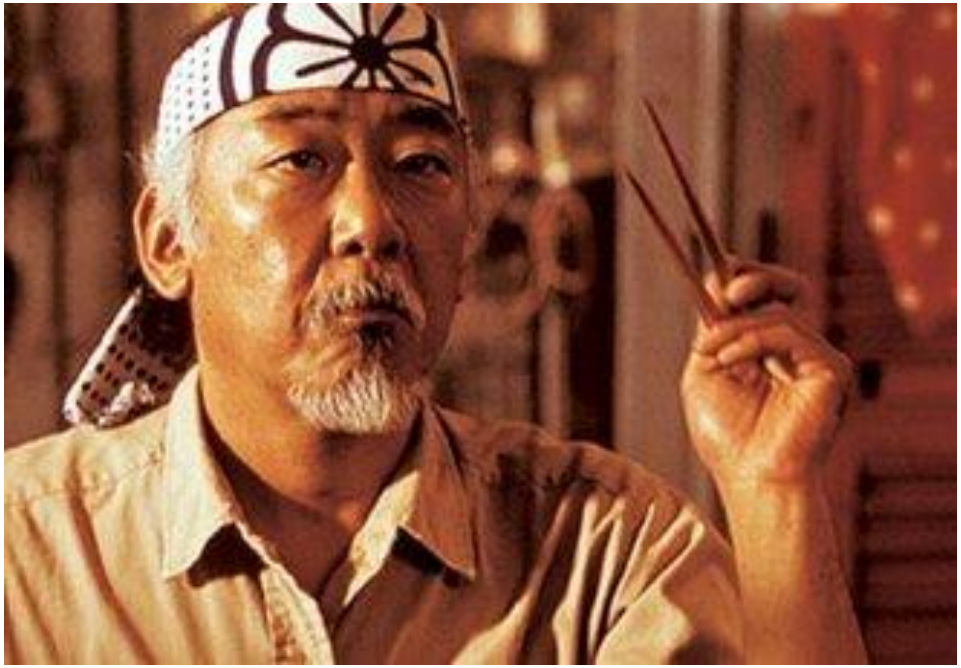
Backyard

Mosquitoes are an annoyance and carry diseases such as West Nile Fever even in regions where malaria has been eradicated. IV's new technology could one day turn your backyard into a no-fly zone for mosquitoes and other low-flying pests.

The Mr Myagi technique



Capacity building



- **Successful vector control** should be **information-based**:
  - Need to understand **vector biology, ecology, behavior, genetics, environment**.
  - Need to know **available resources** (**health centers**, etc.) to assess **cost-effectiveness**.

- To this end, **need** to **ensure**:
  - Adequate levels of **local staff** at **all levels**.
  - **Career path** for **young people** in the area, so that there will **always** be a group of **local experts** in the country.
  - **Financial resources** for **training**.

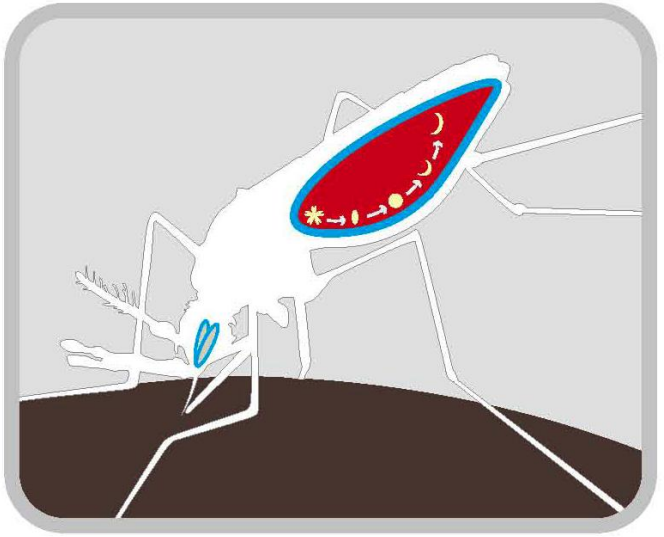
- **Local research institutions** and **control centers** can then **disseminate information** on **optimal** local control **strategies**.

Should we release GM mosquitoes?

Q1. What are the **potential risks**?
Do they **differ** from **other strategies**?
What are the **potential benefits**? Do the **benefits outweigh** the **risks**?

Q2. How do the **fundamental principles** of **medical ethics** apply to **GM mosquitoes**?
Are there **intrinsic ethical issues** specific to **genetic engineering**?

Q3. Would it be **possible** to **gain approval** for a **GM sterile release**?
Would it be **possible** to **gain international approval** for **GM mosquitoes** that would **spread across national borders**?



Risk/benefit analysis

Anticipated benefits to participants	Possible risks to participants
•If the project works: •**Reduction of the prevalence of vector-borne diseases** in the community.	•Risks to **human health**: •**Increased capacity** for the mosquito to **transmit target** or **non-target pathogens**. •**Enhanced survival/reproductive capacity.** •**Increased human biting rate.** •**Female bias** in wild mosquito sex ratio. •**Decreased susceptibility** of mosquitoes to **other control measures.**
•Independent of project success: •**Education** about vector-borne diseases. • Access to **insecticide-treated bed nets** & other disease control interventions.	•Risks to the **environment**: •**Disruption** of an essential **ecological function**. •**Horizontal gene transfer** to non-target organisms via viruses, microbes, etc. •**Disruption** of normal **interactions** between **non-target organisms** and the **environment**. •Detrimental effects on **farming communities**.

Four fundamental principles of medical ethics (Belmont Report)

1. Benificence
2. Non-maleficence

} **Risk-benefit analysis**
Ethical experimental design

Precautionary principle

3. Autonomy

Informed consent

Right to health

{ **Individual consent**
Community consent
Approval by elected officials
Referenda

4. Justice

Distributive justice ← **Site selection**
Rawlsian justice
Compensatory justice
Procedural justice

Additional issues

{ **1. Intrinsic issues of genetic engineering**
2. Animal rights concerns

Is a regional agreement possible? The case of Zambia and GM food aid

- **Gene drive systems** are capable of **self-propagating across national borders**.
- The **Cartagena Protocol** would require that **every country in which the mosquito lives sign the international agreement**.

- **The case of Zambia:**
  - In **2002**, **famine** threatened many lives in **southern Africa**.
  - **Food aid** was offered by the **US**, but was likely to contain **GM corn**.
  - **Zambia rejected** the corn, even after it was **milled**.

- ***Wolbachia*-infected mosquitoes:**
  - **Capable** of **spreading** across **international borders**.
  - **Released** in **Australia** in **2011 without international consideration**.