Novel Strategies for Controlling Mosquito-Borne Diseases: New Challenges for Modelers

Alun L. Lloyd

Biomathematics Graduate Program and Department of Mathematics
North Carolina State University

In collaboration with: Fred Gould, Krisztian Magori, Yunxin Huang and Matthieu Legros
Department of Entomology, NCSU

Dengue

- Dengue

  Virus (flavivirus: an arbovirus)

  Four serotypes

  Vector: *Aedes aegypti* (and others)

- 50 million cases per year
- Severe flu-like illness with severe joint pain
  "classic dengue": "break-bone fever"

- About 1% of cases lead to dengue haemorrhagic fever (DHF)
  Untreated, DHF death rate can be 20%+, but treatment reduces this to 1%.

Image credits: UN, New York Times, unknown

Traditional Control of Mosquito-Borne Infections

- Insecticides
    - Spraying (vector population suppression)
    - Insecticide-laced bed nets
        - *Ineffective against mosquitoes that mainly bite during the day* (e.g. *A. aegypti*)
    - Insecticide resistance, safety, off-target killing



- Drug treatment
    - Not always available
    - Major problems with drug resistance
    - Side effects


Image credits: C. Curtis, Tjeerd Wiersma, J. Davis, epocrates.com

- Vaccines
    - Antigenically diverse pathogens
        - dengue: four serotypes, ‘immune enhancement’
        - vaccine that is not protective against all four serotypes could lead to more cases of DHF

Genetic Approaches I

- Sterile male release
  Introduce a **large** number of sterile mosquitoes (e.g. radiation sterilized):

  Those wild-type females that mate with released sterile males will have no offspring
  Sterile females will have no offspring

Problems:

- Sterility does not get passed on to future generations
- Density-dependence

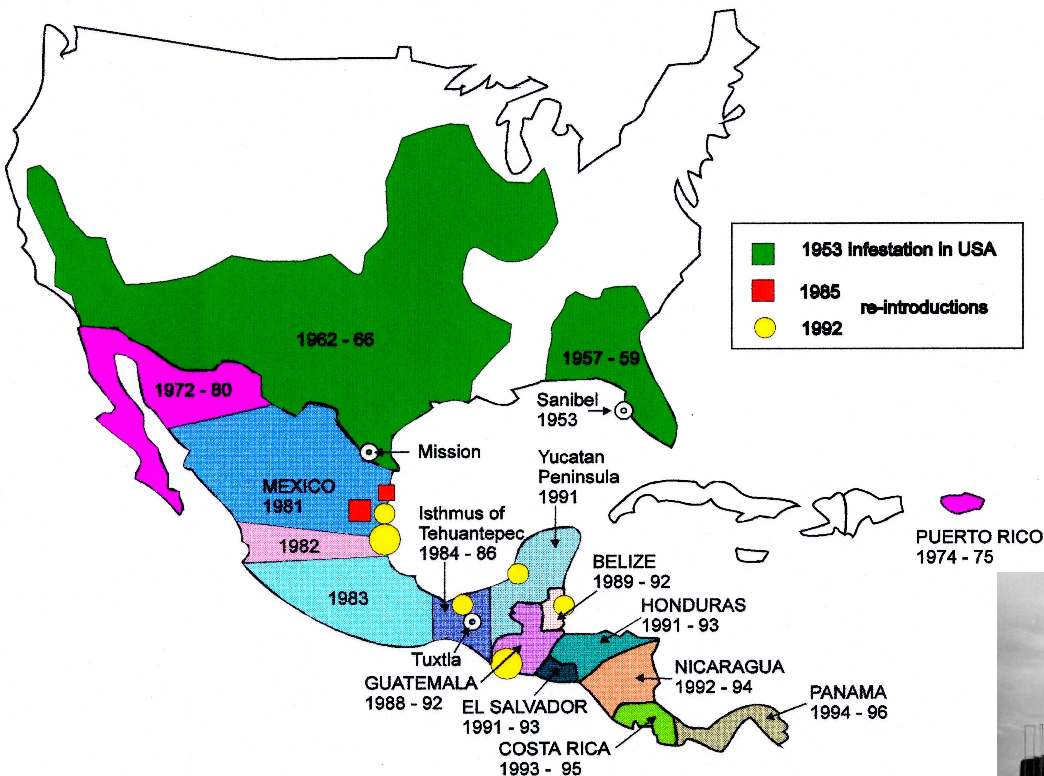
The success of this approach requires the production and release of a **large** number of sterile insects on an ongoing basis

It can work: the screwworm fly has been eradicated from the US, and as far south as the Panama Canal

Image credit: John Kucharski ARS-USDA

Screwworm fly Eradication

Screw-worm fly, *Cochliomyia hominivorax*, distribution and eradication



Genetic Approaches II

Vector Population Replacement:

Produce a mosquito that is unable to transmit infection, and cause it to become more widespread than (i.e. *replace*) the wild-type mosquito

Genetic engineering (transgenics) approaches:

- Shorten lifespan of mosquito to below extrinsic incubation period of pathogen
- Co-opt (hijack) insect's immune response (e.g. RNAi) to attack virus
- Make infection lethal to insect ('death on infection')

Problem: resulting mosquito is typically less fit (has fewer offspring), so trait will not spread through the population (outcompeted by wild-type)

Need a genetic drive mechanism to aid the spread of the desired gene

non-Mendelian inheritance: gene is passed on to more than 50% of offspring

Many mechanisms: Medea, Wolbachia, transposons, …

A lot of highly impressive molecular biology going on in this area

Modeling Tasks

Will such approaches work? We need to model multiple processes at multiple scales

- Population dynamics and genetics of mosquito
- Disease transmission

A. aegypti have a close relationship with humans, laying eggs in water containers

Low dispersal rates

Household-based transmission

Iquitos, Peru

Highly stochastic, spatially heterogeneous, seasonally forced system

What level of detail do we need? We use a spectrum of models, from simple to complex

Stochasticity: Invasion Probabilities

Branching process approximation to Ross model (Bartlett 1964, Griffiths 1972, Ball 1983)

If R_0 (=$R_0^{HV}R_0^{VH}$) > 1, then major outbreak probabilities are

$$1 - \frac{R_0^{HV} + 1}{R_0^{HV}(R_0^{VH} + 1)}$$ following the introduction of a single infectious vector

$$1 - \frac{R_0^{VH} + 1}{R_0^{VH}(R_0^{HV} + 1)}$$ following the introduction of a single infectious host

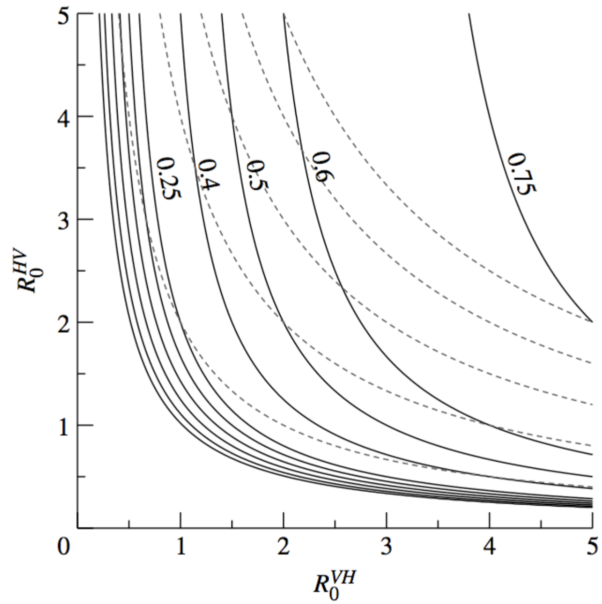
Asymmetry in invasion probability:

if $R_0^{HV} \neq R_0^{VH}$, it matters whether an introduction occurs via host or vector, even if the overall R_0 is the same

Invasion probability from one infective host

Contours of equal invasion probability (solid)

Contours of equal overall R_0 (dashed)



Lloyd et al. (2007) J. R. Soc. Interface **4**, 851.

Invasion Probabilities in Heterogeneous Case

Multi-type branching process approximation (Griffiths 72, Ball 83, Becker & Marschner 90)

Two host, one vector with exponential infectious periods

Heterogeneity: vector has preference for one host over the other
    Vector makes fraction γ_1 of its bites on host type 1

This is the only heterogeneity

20% of hosts are of type 1

Solid curves: introduction of single infective vector

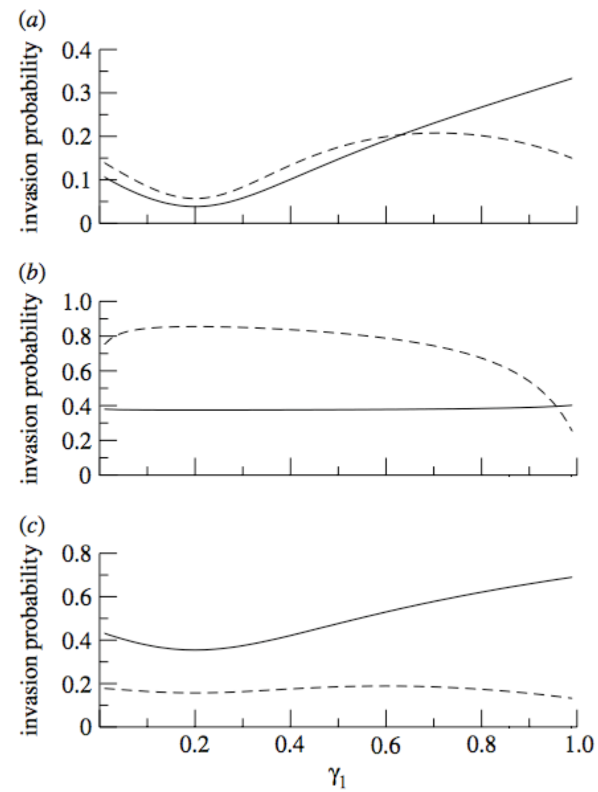
Dashed curves: introduction of single infective host

(a) and (b): transmission probs host to vector, vector to host are roughly equal.

Ten times as many vectors in (b) than in (a)

(c) assumes marked asymmetry in transmission probabilities host ←→ vector ,few vectors

Complexity of patterns, differences between what is seen for hosts and vectors



Lloyd et al. (2007) J. R. Soc. Interface **4**, 851.

Stochasticity: Variability About Endemic Equilibrium

Use moment equations (e.g Isham, 1991)
to estimate variances and covariances

$$\frac{d}{dt}E(Y) = \alpha E(I) + \frac{\alpha}{H}E(YI) - \xi E(Y) \quad (3.17)$$

$$\frac{d}{dt}E(I) = \frac{\beta V}{H}E(Y) - \frac{\beta}{H}E(YI) - \delta E(I) \quad (3.18)$$

$$\frac{d}{dt}E(Y^2) = \alpha E(I) + \xi E(Y) + \frac{\alpha(2H-1)}{H}E(YI) - 2\xi E(Y^2) - \frac{2\alpha}{H}E(Y^2 I) \quad (3.19)$$

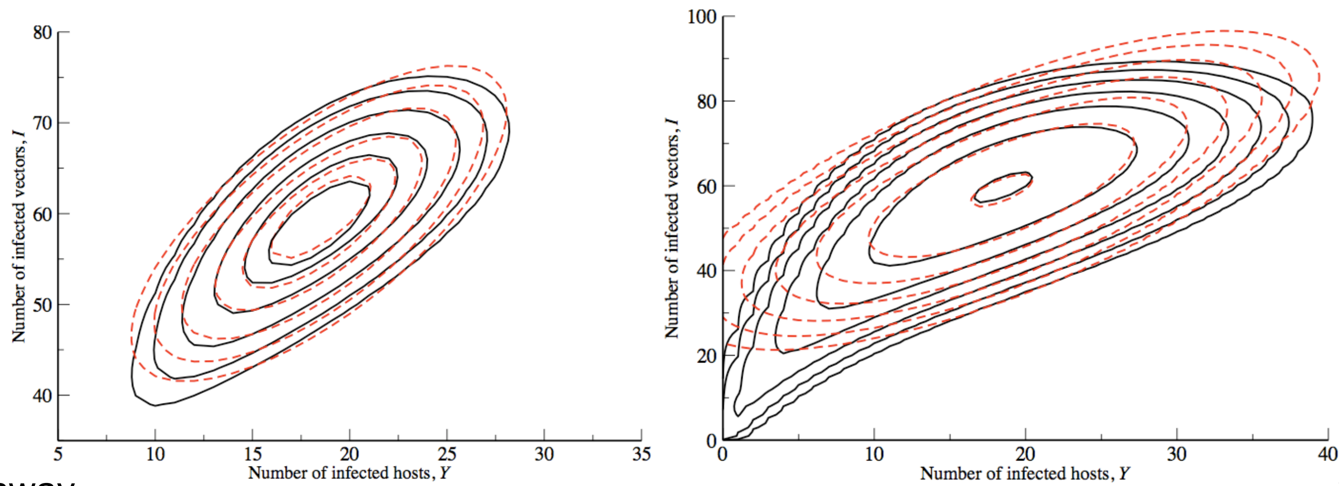
$$\frac{d}{dt}E(I^2) = \delta E(I) + \frac{\beta V}{H}E(Y) - 2\delta E(I^2) + \frac{\beta(2V-1)}{H}E(YI) - \frac{2\beta}{H}E(YI^2) \quad (3.20)$$

$$\frac{d}{dt}E(YI) = \alpha E(I^2) - (\xi+\delta)E(YI) + \frac{\beta V}{H}E(Y^2) - \frac{\alpha}{H}E(YI^2) - \frac{\beta}{H}E(Y^2 I) \quad (3.21)$$

Nonlinear system, so set is not closed
Must use moment closure approximation
e.g. multivariate normal approximation

Can obtain an approximation to the
quasi-stationary distribution about the endemic equilibrium (red dashed curves)

Results can be
compared to
exact calculation
of Nåsell (1991)
(solid black curves)



Works well, provided that
numbers don't stray too far away
from the equilibrium

(Nåsell (1991) Math. Biosci. **107**, 187. Lloyd et al. (2007) J. R. Soc. Interface **4**, 851.)

Stochasticity: Variability About Endemic Equilibrium

Approach can be extended to heterogeneous situations

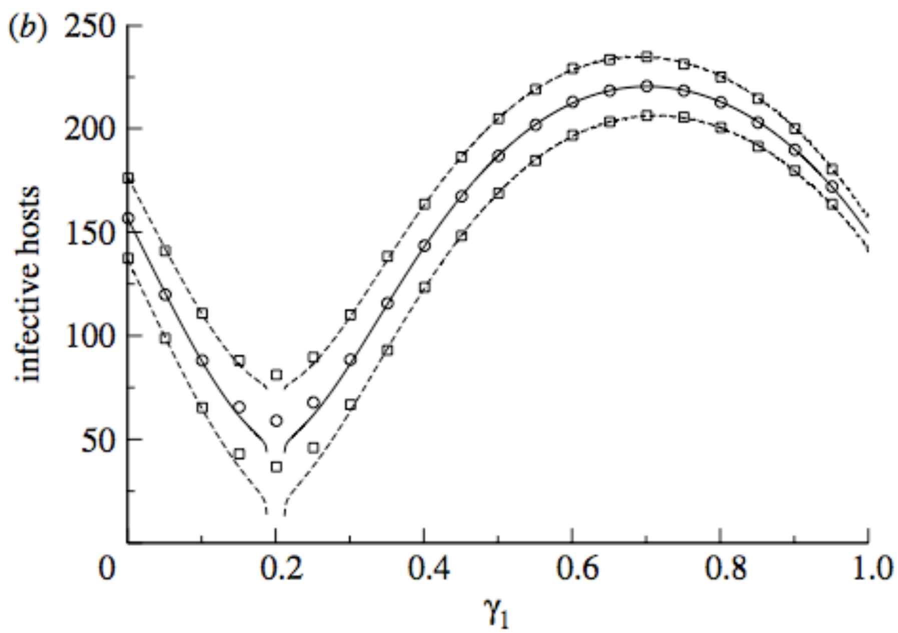
Size of moment equation set increases rapidly: for an *m* host, *n* vector system there are $(m+n)(m+n+3)/2$ equations for the 2nd order set

Automate process using maple (generate PDE for cumulant generating function, expand in a Taylor series, identify terms)

Example: Two host, one vector model
(20% of hosts are type 1, 80% of hosts are type 2)

Non-trivial relationship between variability and mean level of infection

For this small population, moment equations break down near $\gamma_1 = 0.20$



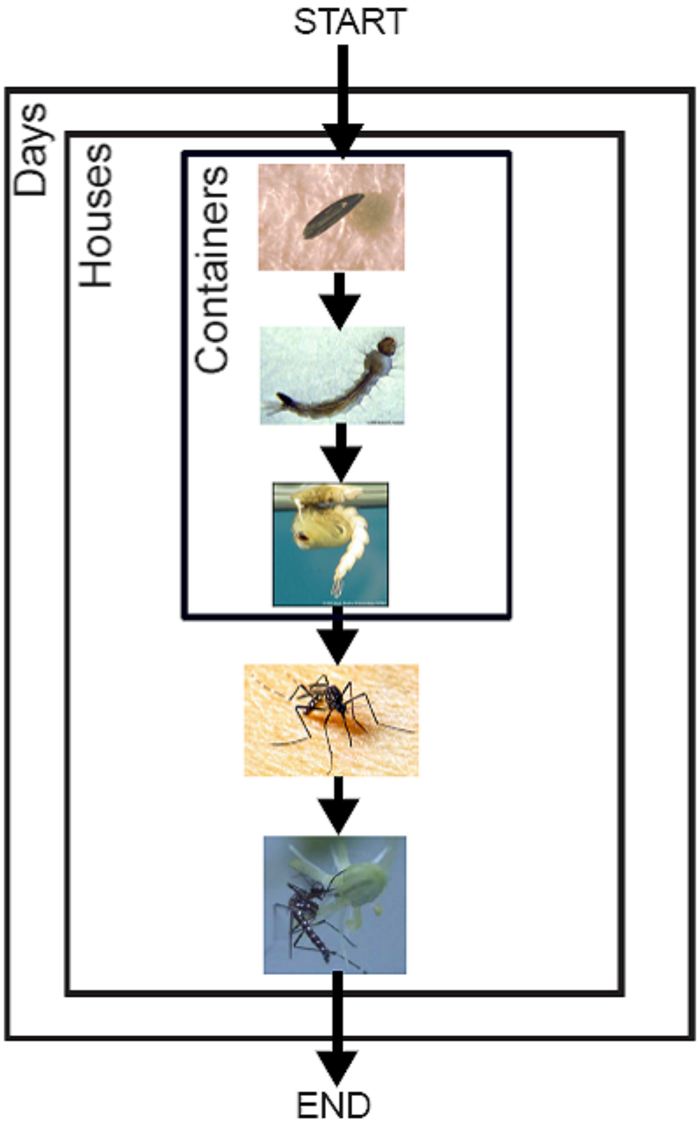
Lloyd et al. (2007) J. R. Soc. Interface **4**, 851.

Skeeter Buster

General characteristics:

- Species-specific
- Cohort and stage based
  - eggs, larvae, pupae, adults
- Detailed biology
  - larval and pupal development
  - track weights of cohorts
- Weather-dependent (temperature and rainfall)
- Spatially explicit
  - containers and houses
- Stochastic

Based on an earlier model
(CIMSiM: Focks *et al.*, 1993)



Skeeter Buster

More details:

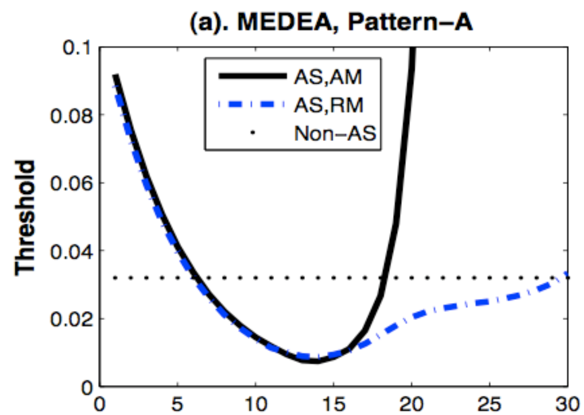
- Daily timestep
- Each container's water level and food content are tracked
  - water gain (rain, human filling), loss (evaporation, human emptying)
  - nutrient input (falling from vegetation, dead pupae), output (consumption)
- Water level important for egg laying and egg development (dessication)
- Larvae compete for food
- Enzyme kinetics-based equations model growth and development of immatures
- Female adult weights and gonotrophic cycle are tracked
  - Female mosquitoes bite when they need blood (allows egg production)
- Mating between males and females, depends on sizes
  - larval and pupal development
  - track weights of cohorts
- Movement: currently random, but could depend on resident population (e.g. females might migrate in search of a mate if no males are present)
- Fertilization of females? One-time deal, or multiple matings? Sperm choice?

Skeeter Buster Results

Effects of container heterogeneity and spatial structure are crucial

Mosquito dispersal pattern is very important for the spread of a gene
- Typically, *A. aegypti* disperse over short distances (nearby houses), but any long-range dispersal has a major impact

Age structure is important
- Releases of different-aged individuals (e.g. eggs, pupae, adults) can have dramatically different outcomes: reproductive value



Stochastic effects play an important role

Multiple releases may be beneficial for many strategies

Impact on Dengue?

Work in progress: linking ecological model to epidemiological model

How effective does the anti-pathogen gene need to be?

What fraction of the wild-type population needs to be replaced?

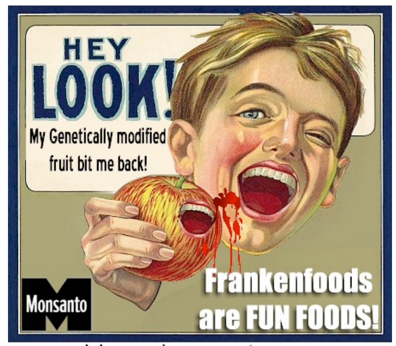
Even if we cannot achieve fixation of the transgene, can we significantly impact transmission, e.g. reduce R_0 below one?

Investigate negative consequences (e.g. recent paper by Koella that suggested vector control could, under certain circumstances, lead to an increase in dengue hemorrhagic fever)

So Everything is Looking Good?

Use of this technology raises important ethical and societal questions

- Government regulation (look to transgenic crops as a model)
- Public acceptance (again, transgenic crops…)



oldamericancentury.org

Project involves working with regulatory bodies, health officials, engaging the public, education

and honestly evaluating the risks (e.g. virus evolving resistance to anti-pathogen gene, loss of linkage between drive and effector genes)

Very cautious approach

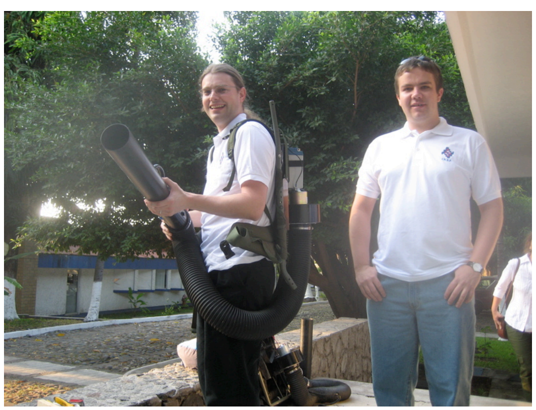
Field Trials and Ecological Studies

Very cautious approach:
Initial work involves releases in controlled, enclosed, environments (large cages)

Field site: Tapachula, Mexico (Hurricane risk…)
cultural sensitivity

Modelers need to know detailed information about
the ecology of the mosquito in Tapachula

Field work will be carried out by a large team
of entomologists and ecologists (US and local)



Acknowledgements

Funding:

National Institutes of Health

Bill and Melinda Gates Foundation
(Grand Challenges in Global Health)

At NC State: Fred Gould (NCSU entomology)

Krisztian Magori, Yunxin Huang and Matthieu Legros

Elsewhere… members of the Gates project: UC Irvine, Tony James (PI)

UC Davis: Tom Scott, Amy Morrison

Caltech: Bruce Hay, Catherine Ward

Cornell: Laura Harrington

Colorado State: Ken Olson, Bill Black, Jonathan Carlson

Oxitech (Didcot, UK): Luke Alphey

Texas A&M: Craig Coates

Notre Dame: David Severson

Oswaldo Cruz Inst., Brazil: Claudio Struchiner

Virginia Tech: Zhijian Tu


WWW.SEASPACE.CN
IT'S TOO MUCH FOR THEM