Dengue

- Viral infection (flavivirus: an arbovirus) that affects humans

- Principal vector: *Aedes aegypti*

  (the yellow fever mosquito)

- Day-biting mosquito

- Anthropophilic mosquito species: highly associated with humans

  Lays eggs in human-associated water containers and other places where rainwater collects
  (e.g. blocked rain gutters)

Dengue

- Viral infection (flavivirus: an arbovirus) that affects humans

- Four serotypes of the virus

  Each confers permanent immunity in people

  Temporary cross immunity between serotypes

  Antibody dependent enhancement

Highly Variable Symptoms

- Highly variable infection, with wide spectrum of outcomes:

  inapparent infection,

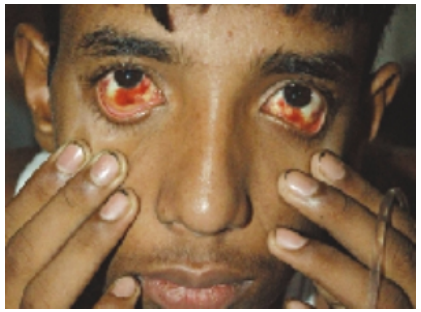
  mild and severe flu-like illness with severe joint pain
  "classic dengue": "break-bone fever"

  severe dengue

  dengue shock syndrome (DSS)
  dengue haemorrhagic fever (DHF)

- Untreated, DHF death rate can be 20%+,
  but treatment reduces this to 1%.

- Antibody-dependent enhancement (ADE)?



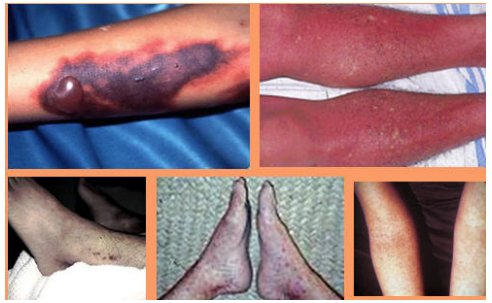
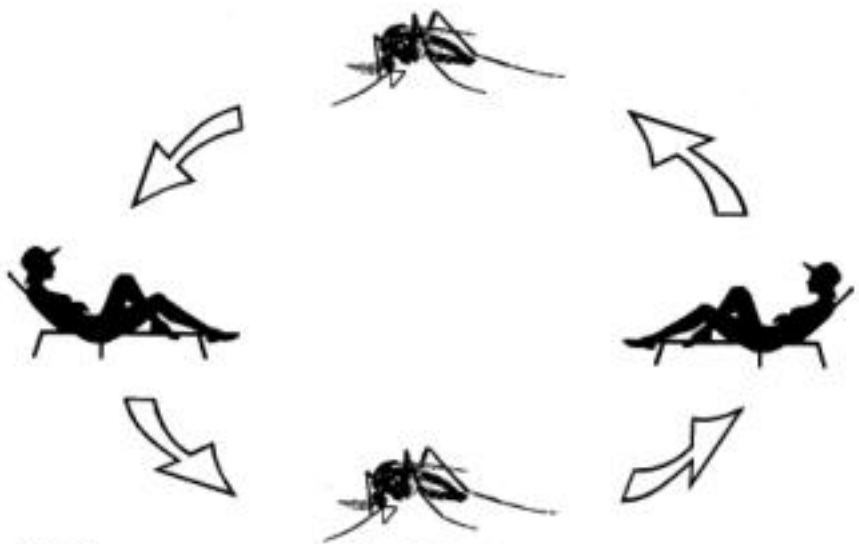


Image credits: UN, New York Times, unknown

Dengue Lifecycle

Key fact 1 : Adult female mosquitoes need blood to produce eggs

(Rudyard Kipling: The female of the species is more deadly than the male)



1. Adult female mosquito bites infected person
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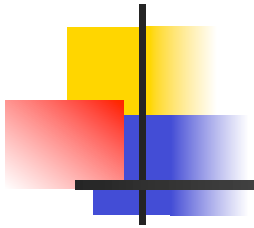
   average intrinsic incubation period ~ 4-5 days
   average human infectious period ~ 4-5 days

   (cycle repeats)

Key fact 2 : Adult female mosquitoes live for about 3 weeks (highly dependent on conditions)

Key fact 3 : Lifecycle involves the mosquito biting twice at appropriate times



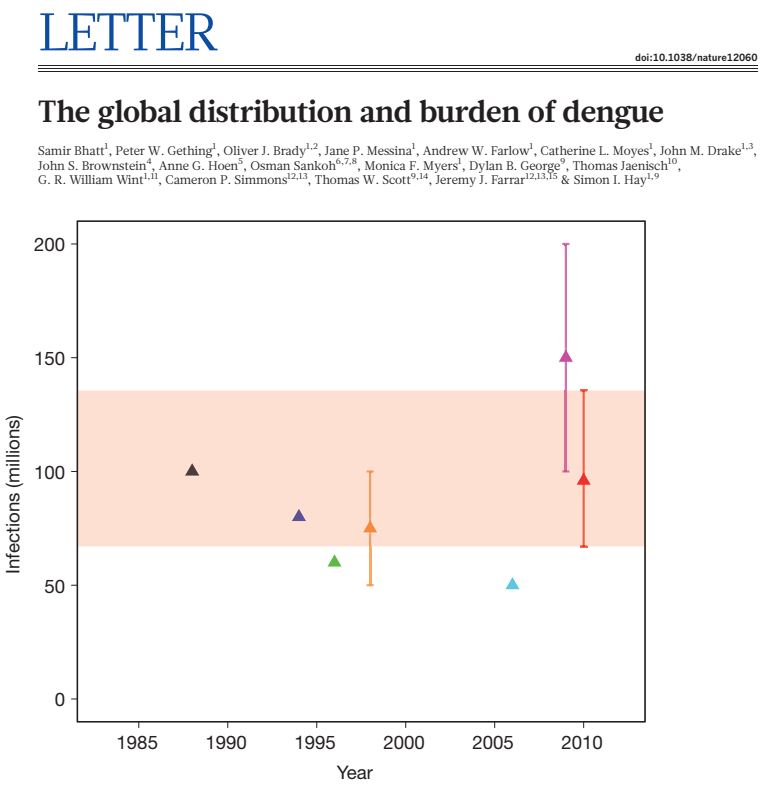
PART I : Data and Descriptive Analyses

Burden of Dengue

- Variability in symptoms hinders assessment of dengue burden based on case data
- Attempts to estimate burden reviewed and improved in Bhatt et al. (2013) Nature

doi:10.1038/nature12060

- Previously published estimates of apparent infections, together with credible interval based on a statistical risk mapping approach applied to an assembly of dengue occurrence records
- Estimate occurrence of an additional 294 (217-392) million inapparent infections
- Can we do better than case data? *Yes… see later*



LETTER

doi:10.1038/nature12060

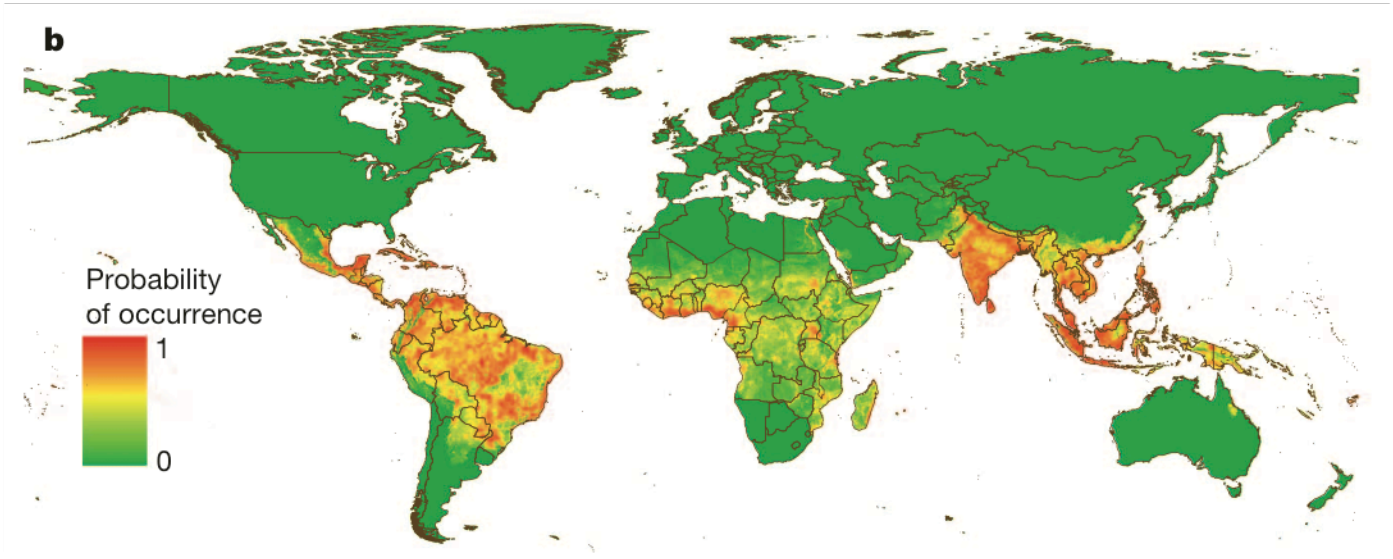
The global distribution and burden of dengue

Samir Bhatt[1], Peter W. Gething[1], Oliver J. Brady[1,2], Jane P. Messina[1], Andrew W. Farlow[1], Catherine L. Moyes[1], John M. Drake[1,3], John S. Brownstein[4], Anne G. Hoen[5], Osman Sankoh[6,7,8], Monica F. Myers[1], Dylan B. George[9], Thomas Jaenisch[10], G. R. William Wint[1,11], Cameron P. Simmons[12,13], Thomas W. Scott[9,14], Jeremy J. Farrar[12,13,15] & Simon I. Hay[1,9]

Global Distribution of Dengue

- Probability of dengue occurrence at the 5km x 5km scale

  based on map-based statistical approach



- South East Asia, India, South America
- Likely underappreciated in Africa
- Note US/Mexico border

US/Mexico Border

- Gubler 1998:

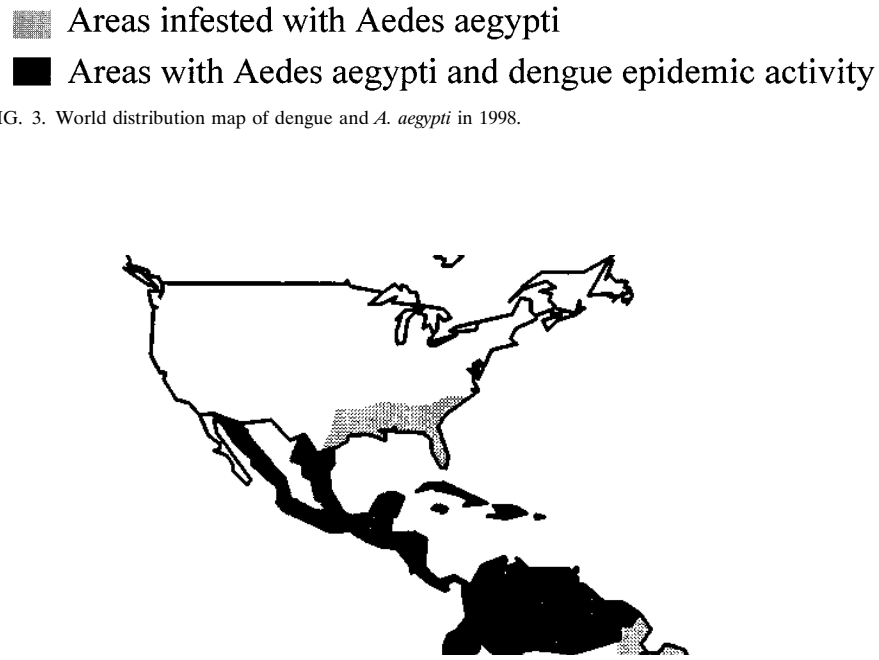
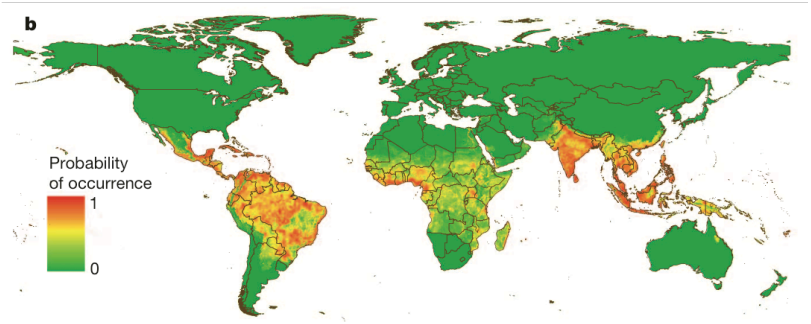


FIG. 3. World distribution map of dengue and *A. aegypti* in 1998.

- *Aedes aegypti* doesn't know about the border, but dengue does?

Expansion of Dengue

- Viewed as an emerging infectious disease



- Demographic and social changes, particularly population growth and urbanization
- Lack of effective mosquito control
  Reinvasion of *Ae. aegypti* in South America
- Expansion of the range of *Ae. aegypti* mosquito
  increased number of larval habitats in tropical regions (plastic containers and tyres)
- Increased international trade and travel: dispersal of mosquito and virus

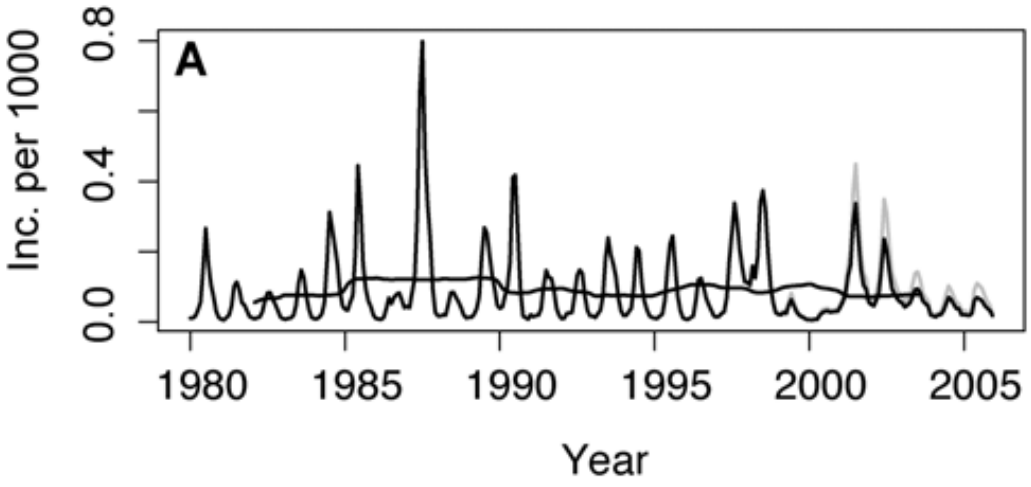
- Potential for climate change to make things worse?

Temporal Patterns of Incidence

- Repeated epidemics : annual or multi-annual period

Incidence of dengue disease in Thailand, 1981-2005

(Cummings et al. PLoS Medicine, 2009)



- Oscillatory behavior driven by human immunity:
  - explosive epidemic
  - susceptible population depleted : self-limiting epidemic
  - susceptibles replenished by births (slower process)
    - importance of demographic processes (birth rate)

Temporal Patterns of Incidence

- Serotype-specific immunity leads to temporal patterns in serotype-specific incidence

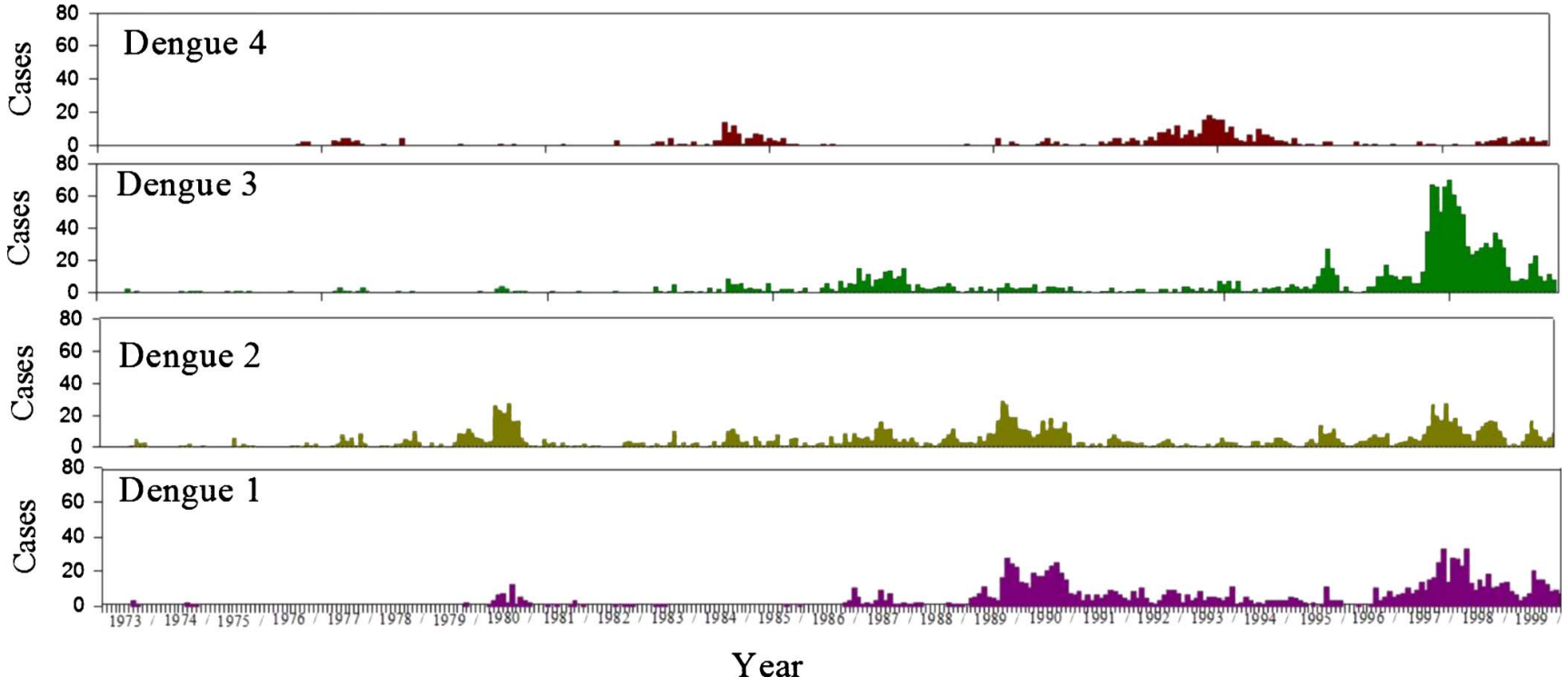


FIG. 7. (Color online) Frequency of detection of each of the four Dengue virus types per month at the Queen Sirikit National Institute for Child Health from 1973 to 1999. Reprinted from [16].

Molecular Epidemiology: Phylogeny of DENV

Inferring the Rate and Time-Scale of Dengue Virus Evolution

S. Susanna Twiddy, Edward C. Holmes, and Andrew Rambaut

Department of Zoology, University of Oxford, Oxford, United Kingdom

Dengue is often referred to as an emerging disease because of the rapid increases in incidence and prevalence that have been observed in recent decades. To understand the rate at which genetic diversification occurs in dengue virus and to infer the time-scale of its evolution, we employed a maximum likelihood method that uses information about times of virus sampling to estimate the rate of molecular evolution in a large number of viral envelope (E) gene sequences and to place bounds around the dates of appearance of all serotypes and specific genotypes. Our analysis reveals that dengue virus generally evolves according to a molecular clock, although some serotype-specific and genotype-specific rate differences were observed, and that its origin is more recent than previously suggested, with the virus appearing approximately 1000 years ago. Furthermore, we estimate that the zoonotic transfer of dengue from sylvatic (monkey) to sustained human transmission occurred between 125 and 320 years ago, that the current global genetic diversity in the four serotypes of dengue virus only appeared during the past century, and that the recent rise in genetic diversity can be loosely correlated both to human activities such as population growth, urbanization, and mass transport and to the emergence of dengue hemorrhagic fever as a major disease problem.

Mol. Biol. Evol. 20(1):122–129. 2003
DOI: 10.1093/molbev/msg010

Molecular Epidemiology: Phylogeny of DENV-3

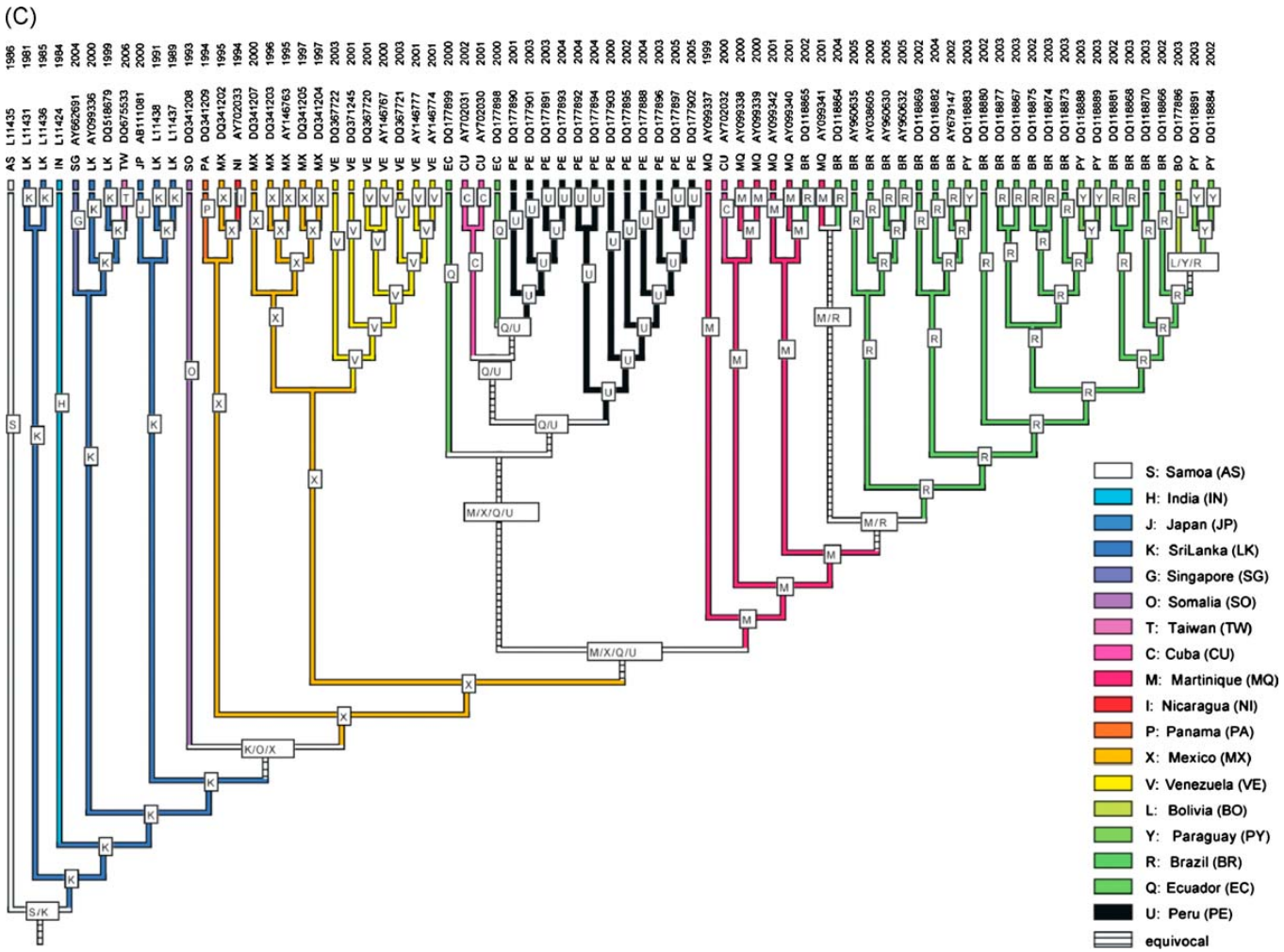


Fig. 2. (*Continued*).

Molecular Epidemiology: Phylogeny of DENV

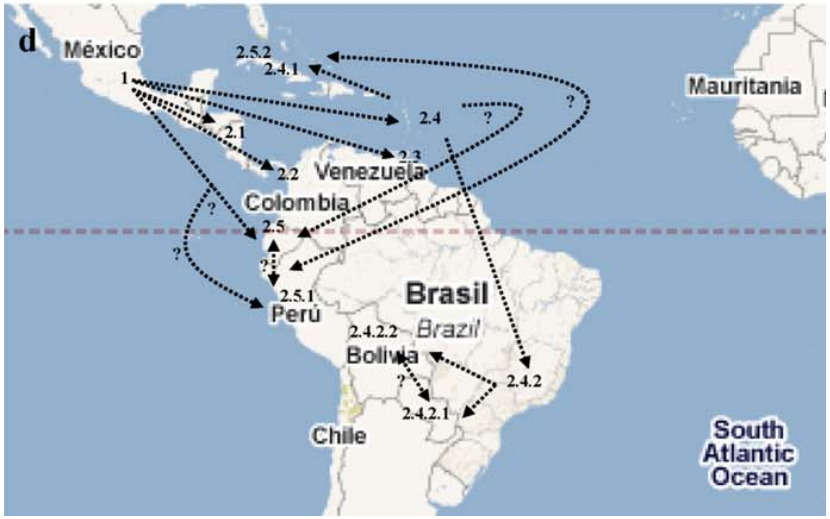
- Inferences from phylogenetic analysis of molecular epidemiology data:

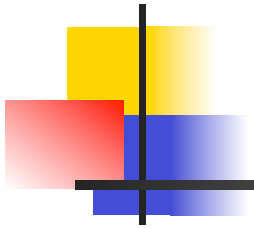
- DENV entered human population between 125 and 320 years ago
- Increase in genetic diversity occurred relatively recently in this history

- Origin of DENV-3 in human about 1890

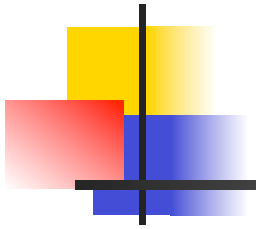
- Diversity of main DENV-3 genotypes occurred between mid sixties and mid seventies

Inferred Migration Patterns





PART II : Understanding Transmission Dynamics



Mathematical Modeling

Tools of mathematical modeling have been used to

interpret observed dynamical patterns

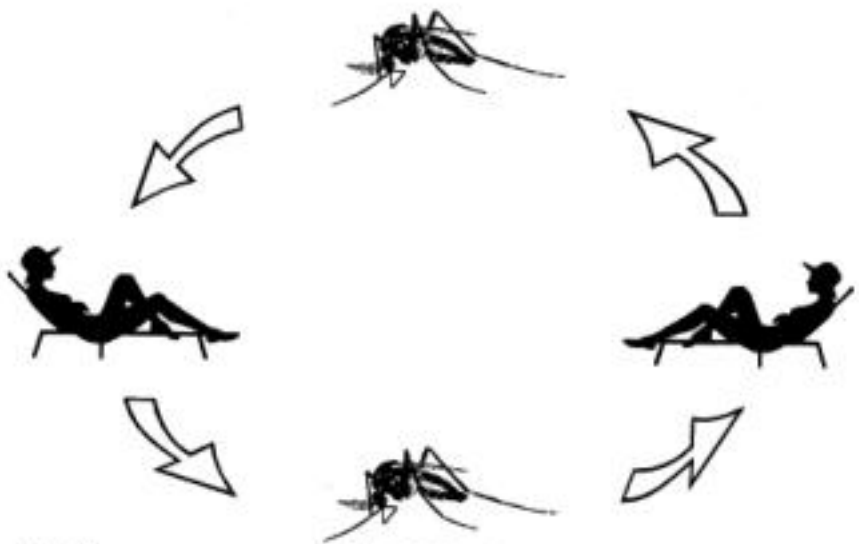
and

inform our understanding of transmission processes

Dengue Lifecycle

Key fact 1 : Adult female mosquitoes need blood to produce eggs

(Rudyard Kipling: The female of the species is more deadly than the male)



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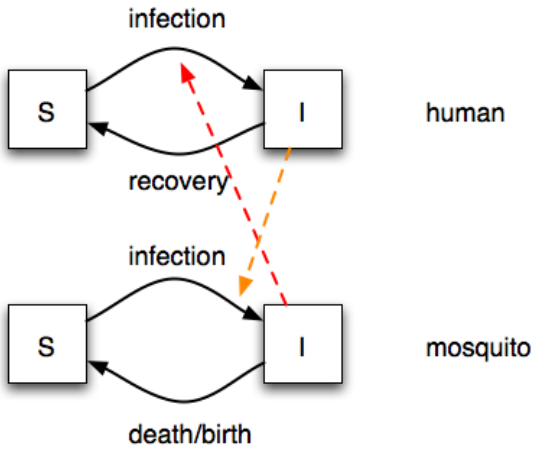
   (cycle repeats)

Key fact 2 : Adult female mosquitoes live for about 3 weeks (highly dependent on conditions)

Key fact 3 : Lifecycle involves the mosquito biting twice at appropriate times

History: The Ross Model



- Developed for malaria, but widely used for other vector-borne infections
- Very simple model (just two equations)
- Asymmetry in the transmission term:

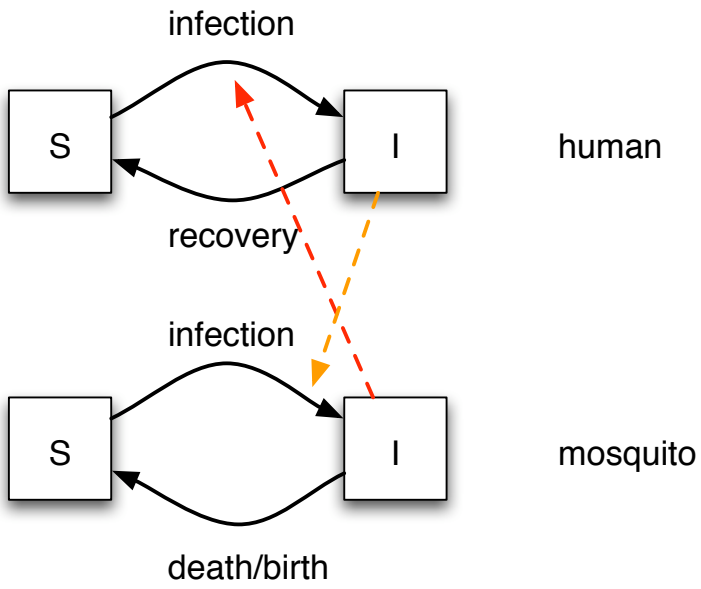
the rate at which mosquitoes bite humans is **proportional to the number of mosquitoes** but **independent of the number of people**

(idea is that mosquitoes only need a certain number of blood meals, so as long as there are sufficiently many humans around…)

- Very simple behavior: infection can invade and persist if the basic reproductive number (R_0) is greater than one

- Basic reproductive number is the average number of secondary infections that result if a single infectious individual is introduced into an entirely susceptible population

The Ross Model



- Assume constant host (human) population size

  H humans, of which Y are infectious

  $H - Y$ susceptible humans

  Humans recover to susceptible state ("SIS" infection in humans)

- Assume constant vector (mosquito) population

  V mosquitoes, of which I are infectious

  $V - I$ susceptible mosquitoes

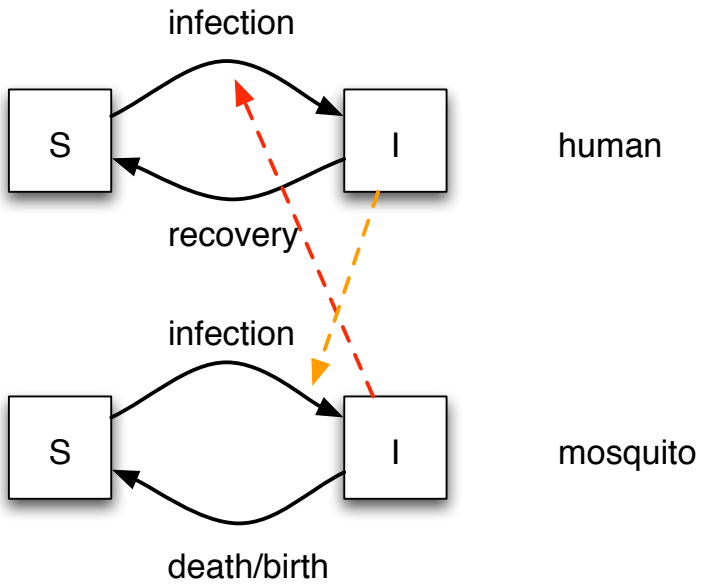
  Infected mosquitoes never recover ("SI"), but when they die, they are replaced by a susceptible mosquito

  (no need to worry about susceptible deaths)

The Ross Model

- Key assumption: rate at which mosquitoes bite humans is proportional to the number of mosquitoes but independent of the number of humans

  Mosquitoes have a certain appetite for blood, and there are sufficiently many humans around to satisfy this



- Each vector bites at rate k

  Probability p of transmission per bite when infectious vector bites susceptible host

  Define $\alpha = k\,p$

  Probability q of transmission per bite when susceptible vector bites infectious host

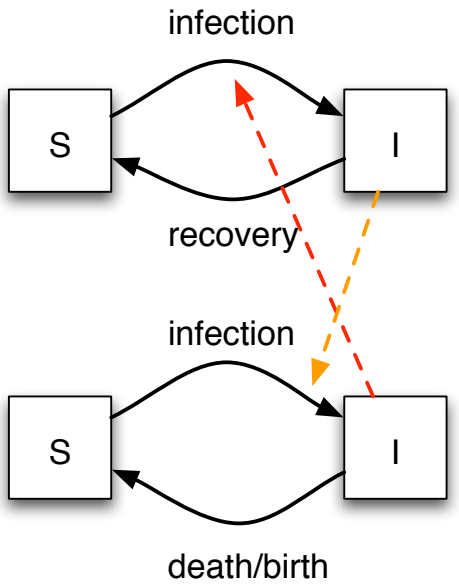
  Define $\beta = k\,q$

- Total biting rate is $k\,V$
  linear in V, but independent of H

The Ross Model

- Key assumption about biting rate leads to transmission terms that are:
  proportional to *numbers* of mosquitoes, *fractions* of human population

- Assume constant recovery rate, ξ , for an infectious human
- Constant death rate, δ , for a vector



human

$$\dot{Y} = \alpha I\left(\frac{H-Y}{H}\right) - \xi Y,$$

Infectious humans

mosquito

$$\dot{I} = \beta(V-I)\frac{Y}{H} - \delta I.$$

Infectious mosquitoes

Basic Reproductive Number

$$\dot{Y} = \alpha I\left(\frac{H-Y}{H}\right) - \xi Y, \qquad \text{Infectious humans}$$

$$\dot{I} = \beta(V-I)\frac{Y}{H} - \delta I. \qquad \text{Infectious mosquitoes}$$

$1/\xi$ average duration of infection

$1/\delta$ average lifespan of infected mosquito

α transmission parameter mosquito to human (biting rate × transmission prob.)

β transmission parameter human to mosquito (biting rate × transmission prob.)

When infection is rare, *rates* of transmission per infected individual are approximately

α mosquito to human

$\beta V/H$ human to mosquito

One infected mosquito causes an average of α/δ new human infections R_0^{VH}

One infected human causes an average of $\beta V/(\xi H)$ new mosquito infections R_0^{HV}

For entire lifecycle: $$R_0 = R_0^{HV} R_0^{VH} = \frac{\beta \alpha V}{\xi \delta H}$$

In the **deterministic model**, R_0>1 guarantees invasion (and persistence) of infection

success of invasion does not depend on whether an infectious host or vector arrives

The Basic Reproductive Number

$$R_0 = ma^2 bcD_H D_M P$$

The average number of secondary infections when infection is introduced into an entirely susceptible population is the product of:

- the number of mosquitoes per person (m)
- the square of the rate at which a single mosquito bites (a)
- transmission probabilities between host and vector (b,c)
- average duration of infection in humans (D_H)
- average lifespan of infected mosquito (D_M)
- **probability that mosquito survives the extrinsic incubation period** (P)

The Basic Reproductive Number

$$R_0 = ma^2 bcD_H D_M P$$

Herd immunity: controlling spread of infection requires reduction of R_0 below one

e.g. by :

- reducing number of vectors
- reducing encounters between humans and vectors
- reducing duration of infection
- reducing number of susceptible humans
- …

Need to better understand encounters between humans and vectors

Traditional Control of Mosquito-Borne Infections

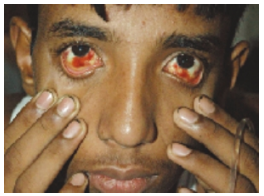
- Modify environment

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

- 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



Dengue Vaccine

- Sanofi-Pasteur vaccine
- Somewhat mixed results in clinical trials
- Differential effectiveness against different serotypes, with noticeably lower protection against DENV-2
- 30.2% effective in a phase IIb trial in Thailand, due to prevalence of DENV-2
- 56% effective in phase III trial in Asia (only 34.7% effective against DENV-2)
- 60.8% effective in a South American phase II trial
- Reduced number of severe dengue cases by 80%
- Less effective for individuals without prior exposure to dengue
  (e.g. tourists!)

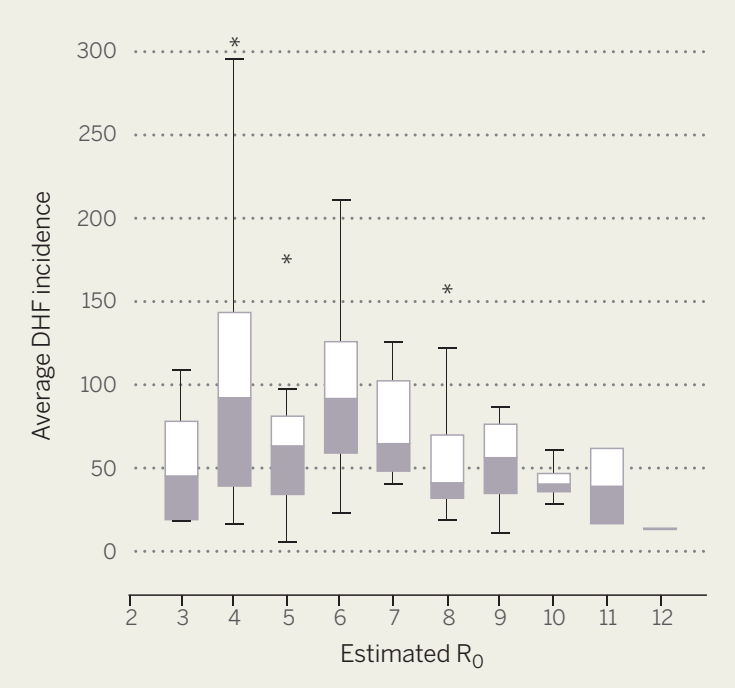
A Cautionary Note

Decreases in dengue transmission may act to increase the incidence of dengue hemorrhagic fever

Yoshiro Nagao* and Katia Koelle†‡

2238–2243 | PNAS | February 12, 2008 | vol. 105 | no. 6

- Complicated relationship between infection, disease and cross-immunity between serotypes can lead to counterintuitive impacts of control



Back to the Basic Reproductive Number

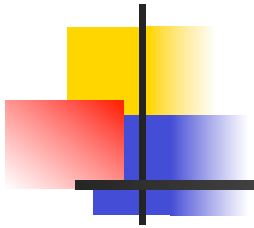
$$R_0 = ma^2 bcD_H D_M P$$

So now we know everything… unfortunately not

R_0 is easy to write down in terms of model parameters, but some are difficult to measure directly

Typically estimate R_0 by some indirect method (e.g. epidemic growth rate, age-specific seroprevalence curve, level of infection at equilibrium, inter-epidemic period)

Estimates for dengue collected in a recent review (Nishiura 2006) ranged from 1.3 through 27
Most of the more plausible sounding estimates were between 3 and 6

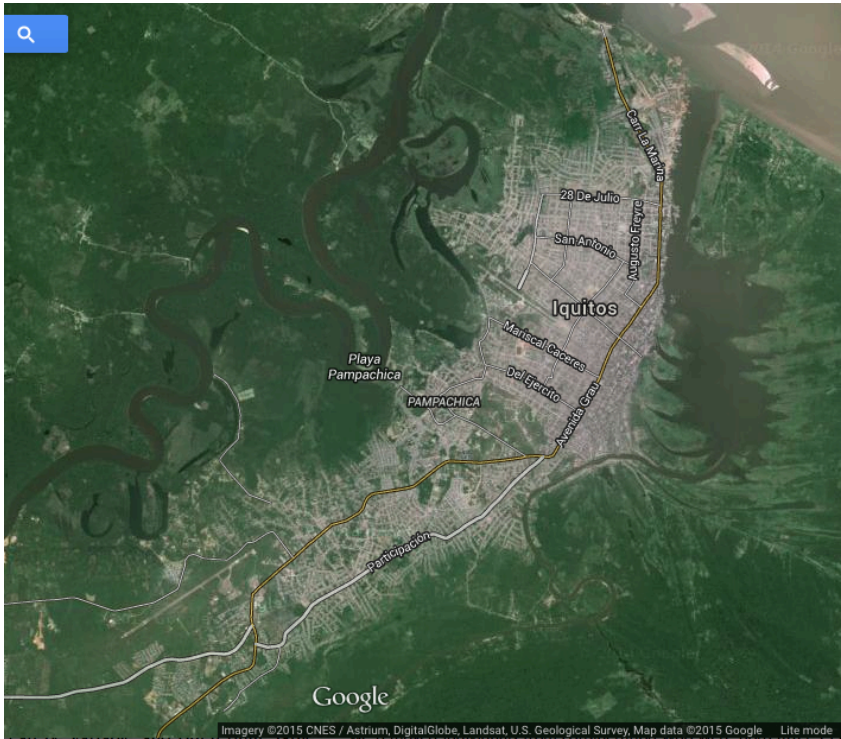


PART III : More Detailed Epidemiological Investigations

Long-Term Epidemiological Monitoring Projects

Some notable long-term epidemiological and entomological studies

Tom Scott, UC Davis: Iquitos, Peru Late 1990s-present



Long-Term Epidemiological Monitoring Projects

Tom Scott, UC Davis: Iquitos, Peru Late 1990s-present

Many types of ongoing study:

- Active surveillance, infection clusters
- Longitudinal cohort studies
- Human movement studies
- Human infectiousness studies (current)
- Entomological surveys

Cohort Studies and Force of Infection

Recall problems with case data

Cohort studies: test individuals for seroconversion against different serotypes periodically

Problem: learn that person X has seroconverted some time between two tests, but not the exact time

statistical approaches to impute the seroconversion time or to find the average rate of seroconversion at a given point in time

Time-varying, serotype-specific force of infection of dengue virus

Robert C. Reiner, Jr.[a,b,1], Steven T. Stoddard[a,b], Brett M. Forshey[c], Aaron A. King[a,d], Alicia M. Ellis[a,e], Alun L. Lloyd[a,f], Kanya C. Long[b,g], Claudio Rocha[c], Stalin Vilcarromero[c], Helvio Astete[c], Isabel Bazan[c], Audrey Lenhart[h,i], Gonzalo M. Vazquez-Prokopec[a,j], Valerie A. Paz-Soldan[k], Philip J. McCall[h], Uriel Kitron[a,j], John P. Elder[l], Eric S. Halsey[c], Amy C. Morrison[b,c], Tadeusz J. Kochel[c], and Thomas W. Scott[a,b]

www.pnas.org/cgi/doi/10.1073/pnas.1314933111

Cohort Studies and Force of Infection

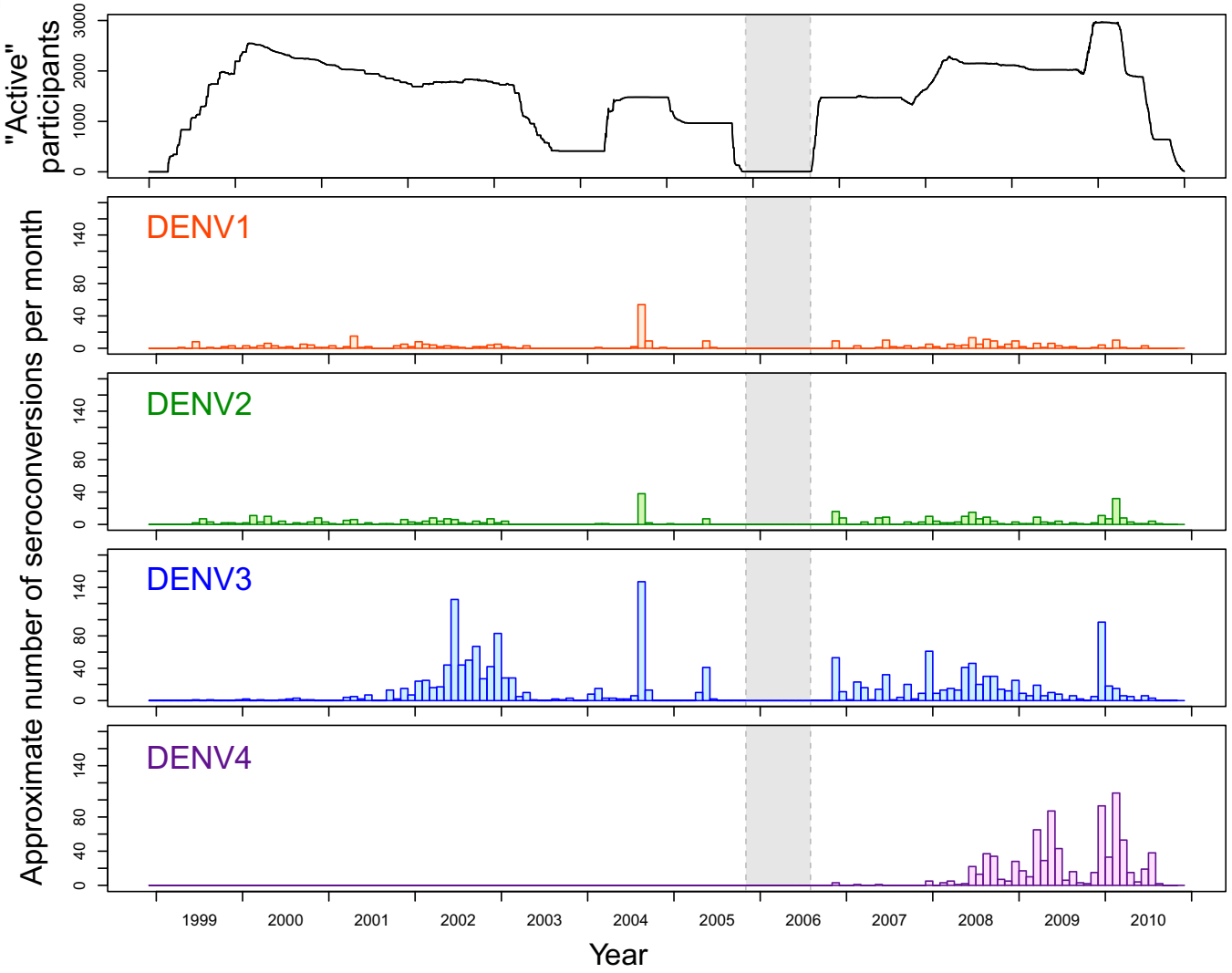
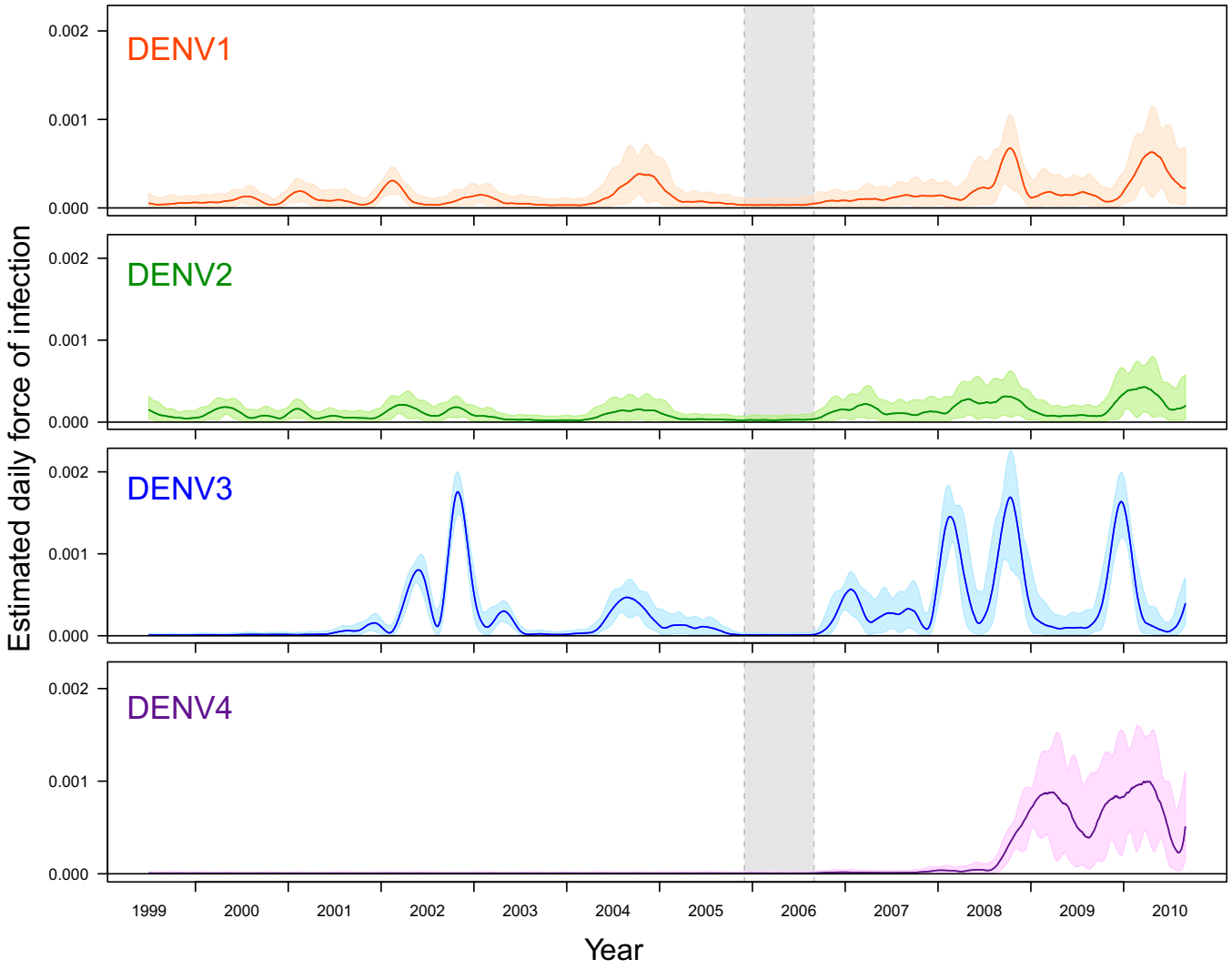
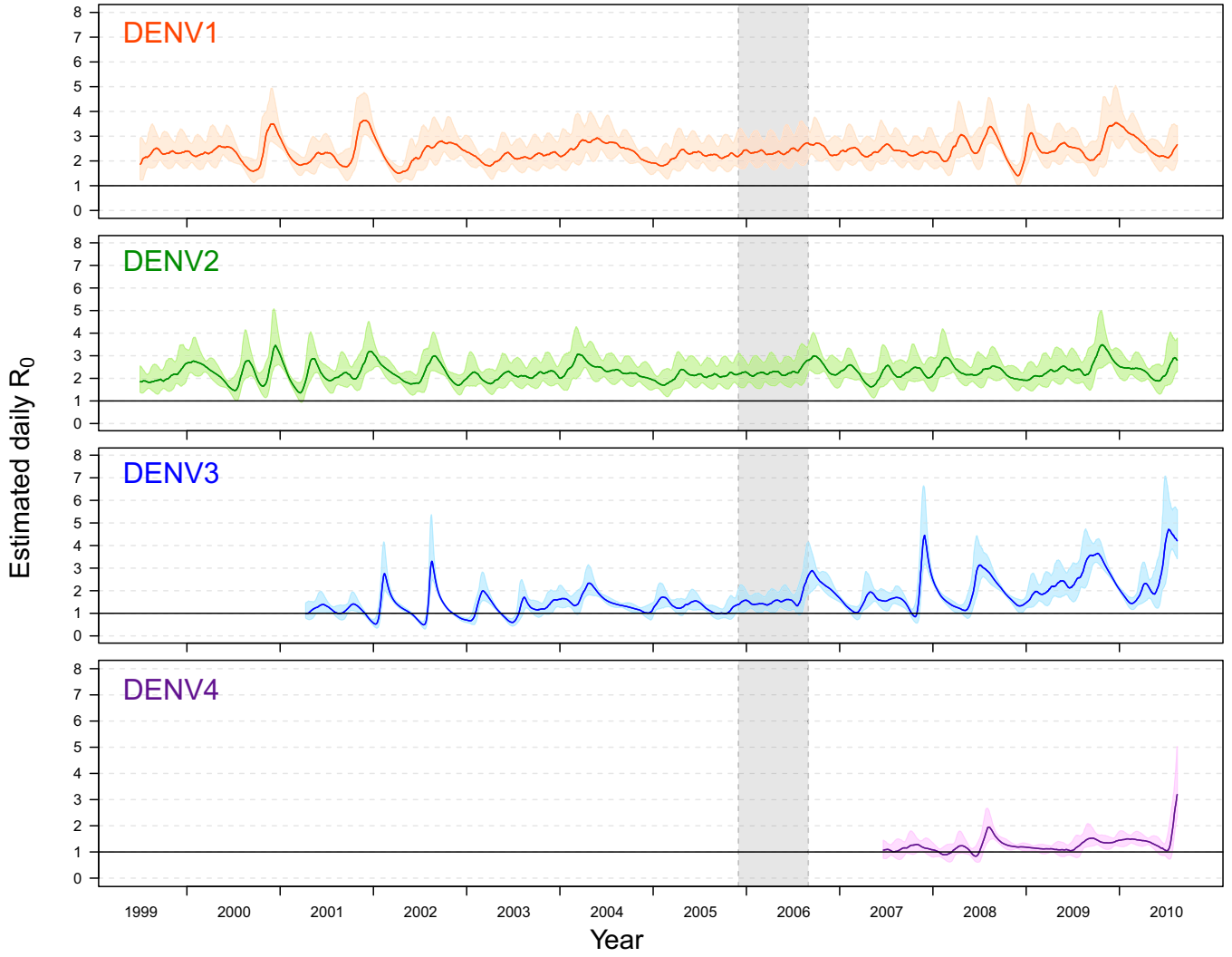


Fig. 1. Summary of participants and interval-censored infections. The top panel shows the total number of active participants across cohort studies from 1999 to 2010. The absence of a cohort study from late 2005 to mid-2006 is indicated by the gray shaded region. Remaining panels: After applying the se-

Cohort Studies and Force of Infection



Cohort Studies and Force of Infection



Big Question: How Important Are Heterogeneities?

Mosquito and human populations are highly structured and heterogeneous:

age structure of mosquito population




spatial structure:
containers and houses


Iquitos, Peru (Pictures from Amy Morrison and Google Earth)

How much does this matter for the spread of dengue?

Big Question: How Important Are Heterogeneities?

- Examples of Heterogeneities:
  differences in infectiousness or susceptibility
  differing chances of getting bitten or of biting
  differing productivities of different houses
  mixing patterns of populations (e.g. spatial structure)

- 80/20 "rule" (Woolhouse et al.)
  80% of all transmission is due to 20% of all individuals

- Example: de Benedictis et al. (2003):

DNA profiling of blood meals in *Ae.* aegypti collected in 22 houses in Florida, PR
about 100 residents, field workers and visitors connected to the houses
identified sources of 80% of the blood meals

Feeding non-random ($P=2.4\times10^{-17}$) with a bias towards young adults and males

Three people accounted for 56% of the meals

How much does this matter for the spread of dengue?

Determinants of Heterogeneous Blood Feeding Patterns by *Aedes aegypti* in Iquitos, Peru

Kelly A. Liebman[1]*, Steven T. Stoddard[1], Robert C. Reiner, Jr.[1,2], T. Alex Perkins[1,2], Helvio Astete[3], Moises Sihuincha[4], Eric S. Halsey[5], Tadeusz J. Kochel[6], Amy C. Morrison[1,3], Thomas W. Scott[1,2]

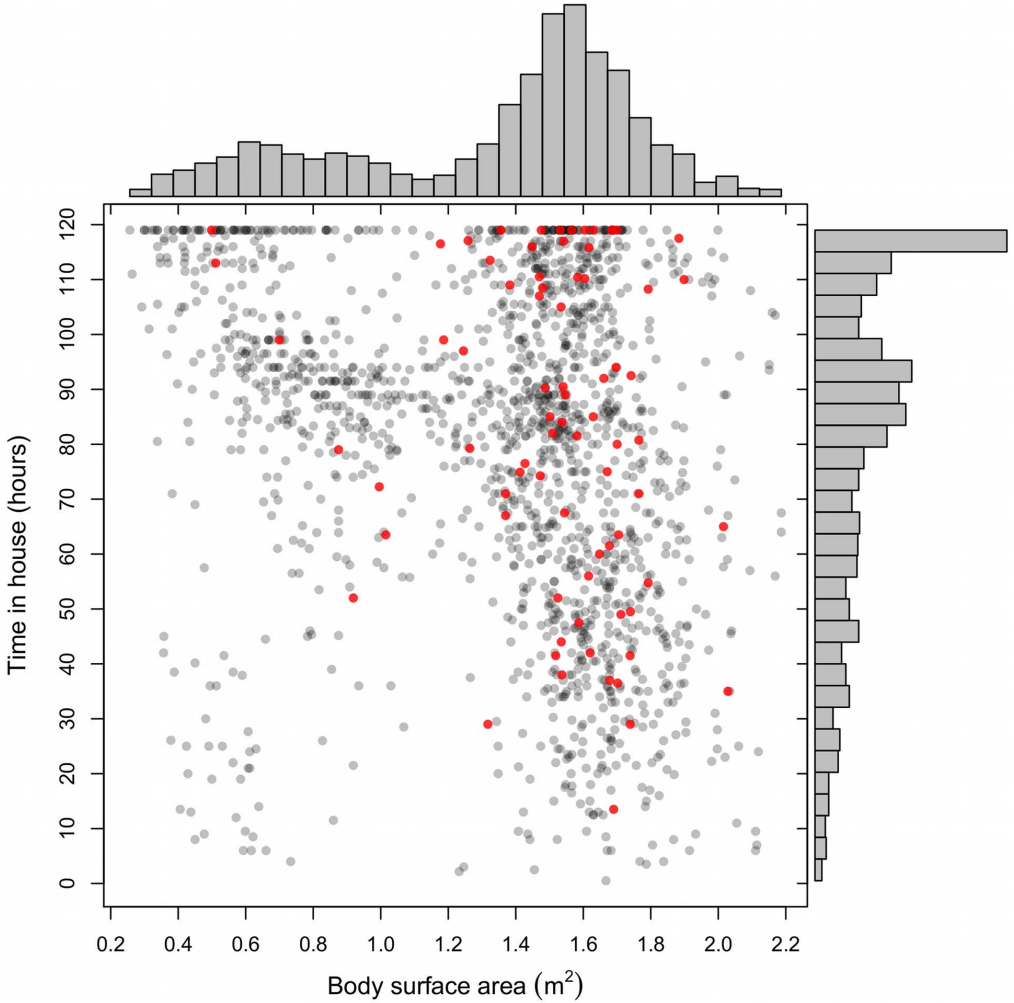


Figure 2. Joint distributions of reported total weekly time in a house and body surface area across all study participants measured on eight separate occasions. Red dots indicate individuals whose blood was identified in mosquitoes.

PLoS Negl Trop Dis 8(2): e2702. doi:10.1371/journal.pntd.0002702

Big Question: How Important Are Heterogeneities?

- Heterogeneity often increases R_0 , and by a factor that reflects the degree of heterogeneity

  R_0 is multiplied by $1 + CV^2$

  High degree of heterogeneity means that CV^2 is much larger than one and that the naïve value of R_0 (ignoring heterogeneity) can be a severe underestimate

  In the setting of malaria in Africa, Dave Smith and colleagues obtained a wide range of estimates of R_0 (IQR: 30-815). *Are things as bad for dengue?*

- Increase in R_0 due to heterogeneity facilitates disease invasion/persistence, but prevalence is lower than in homogeneous situation

- Reduction in prevalence and/or eradication is more difficult using uniform control measures, but targeted control can be highly beneficial IF you can identify and reach the relevant subpopulation

  (Florida, PR example: those three people contributed enormously to transmission)

Big Question: How Important Are Heterogeneities?

- Populations are far from spatially ‘well-mixed’

- Movement patterns of people?
  GPS tracking data, cellphone tracking

- Where do people get infected?

  Important as WHO guidelines recommend localized spraying around the homes of infected individuals

  Tom Scott/Uriel Kitron’s activity space study in Iquitos

- Movement of people likely to be more important than movement of mosquitoes for spread of dengue

Using GPS Technology to Quantify Human Mobility, Dynamic Contacts and Infectious Disease Dynamics in a Resource-Poor Urban Environment

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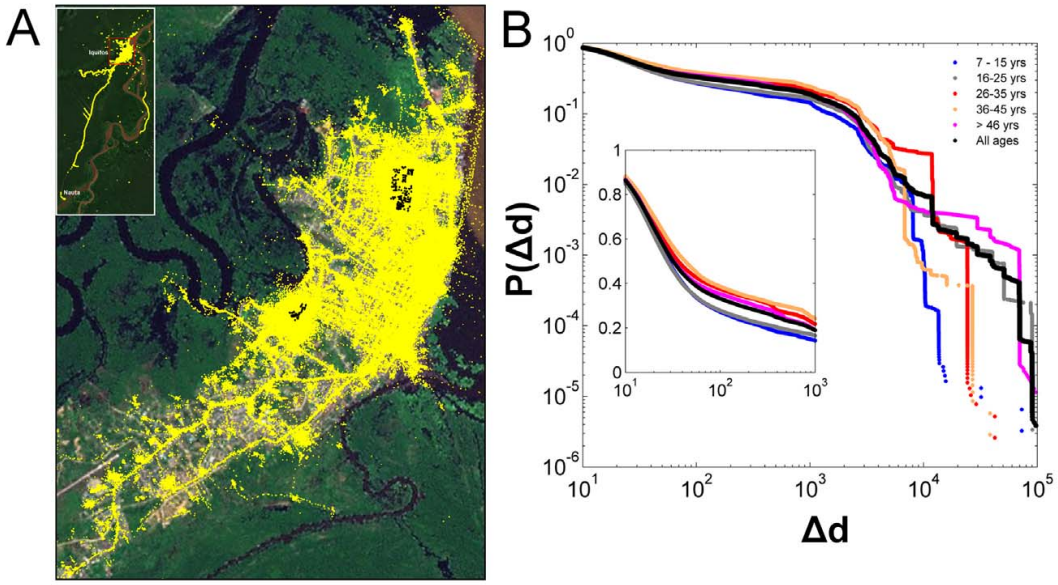

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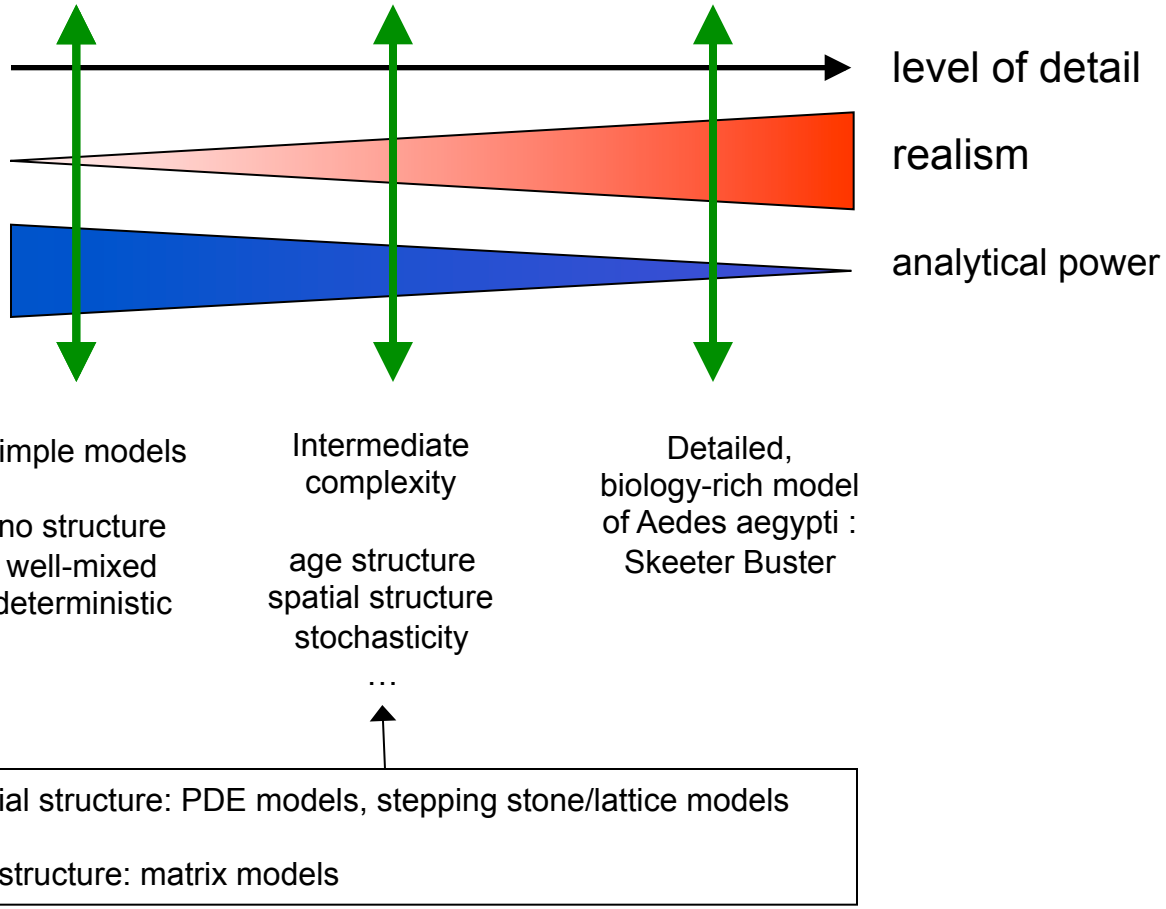
Simple and Complex Models



Theme underlying our research: what level of complexity is appropriate for modeling various aspects of the population and disease system?

New Genetic Control Methods

Two broad alternative approaches:

1. Reduce number of mosquitoes

   population suppression or eradication

2. Replace existing mosquito population with one that is less able to transmit the infection

   population replacement

   Wolbachia symbiont

Wolbachia Protects Mosquitoes Against Dengue Infection

A *Wolbachia* Symbiont in *Aedes aegypti* Limits Infection with Dengue, Chikungunya, and *Plasmodium*

Moreira et al. (2009, Cell: **139**, 1268) found that the popcorn strain of *Wolbachia* protects mosquitoes against dengue infection

In one set of experiments: feeding mosquitoes dengue-infected blood led to dengue infection in

70 % of non-*Wolbachia* mosquitoes (*n* = 40)

65 % of antibiotic treated *Wolbachia* mosquitoes (*n* = 40)

5 % of *Wolbachia mosquitoes* (*n* = 40)

Double whammy: life shortening and virus protection

Stochastic Model: Invasion Probabilities

Stochastic model: reinterpret rates of deterministic model as transition rates (probabilities) describing discrete transitions

event	transition	rate at which event occurs	probability of transition in time interval $[t, t+\mathrm{d}t]$
infection of host	$Y \to Y+1$	$\alpha I((H-Y)/H)$	$\alpha I((H-Y)/H)\mathrm{d}t$
infection of vector	$I \to I+1$	$\beta(V-I)(Y/H)$	$\beta(V-I)(Y/H)\mathrm{d}t$
recovery of host	$Y \to Y-1$	ξY	$\xi Y\,\mathrm{d}t$
death of vector	$I \to I-1$	δI	$\delta I\,\mathrm{d}t$

Neither invasion nor persistence are guaranteed when $R_0 > 1$

Use branching process formulation to describe (approximate) invasion process

corresponds to assuming no. of susceptible hosts ≈ H and no. of susceptible vectors ≈ V

equivalent to linearizing system about infection free equilibrium

(Bartlett 1964, Griffiths 1972, Ball 1983)

Need to use multi-type (two-type) branching process

Stochastic Model: Invasion Probabilities

Recall analysis from simple infection model

If infected individual causes infections randomly at rate β (Poisson process), and recovery process occurs at rate γ (exponential distribution of duration of infection, average = $1/\gamma$)

Number of offspring, Z , has **geometric distribution**, with mean $R_0 = \beta/\gamma$

Branching process formulation utilizes generating function

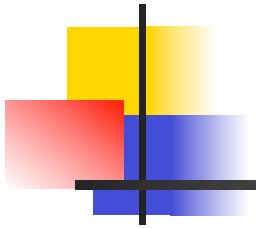
$$G_Z(s) = E[s^Z] = 1/(1 + R_0(1-s))$$

Solve fixed point equation and find probability of extinction starting from one infective

Invasion ("major outbreak") said to occur if branching process does not go extinct

If $R_0 > 1$, invasion occurs with probability $1-1/R_0$

If $R_0 < 1$, invasion occurs with probability 0



Two-type Branching Process

Notation:

X_{HH} number of secondary host infections caused (directly) by one infectious host

X_{HV} number of secondary vector infections caused (directly) by one infectious host

X_{VH} number of secondary host infections caused (directly) by one infectious vector

X_{VV} number of secondary vector infections caused (directly) by one infectious vector

Note: $X_{HH} = X_{VV} = 0$

Two-type Branching Process

Generating functions:

Recall: $X_{HH} = X_{VV} = 0$

Hosts: $$G_H(s_H, s_V) = E\left[s_H^{X_{HH}}\, s_V^{X_{HV}}\right] = E\left[s_V^{X_{HV}}\right]$$

Vectors: $$G_V(s_H, s_V) = E\left[s_H^{X_{VH}}\, s_V^{X_{VV}}\right] = E\left[s_H^{X_{VH}}\right]$$

If X_{HV} ~ Geometric, mean R_0^{HV} and X_{VH} ~ Geometric, mean R_0^{VH}, then

$$G_H(s_H, s_V) = \frac{1}{1 + R_0^{HV}(1 - s_V)} \quad \text{and} \quad G_V(s_H, s_V) = \frac{1}{1 + R_0^{VH}(1 - s_H)}$$

Probability that an epidemic does not occur is found by solving

$$G_H(s_H, s_V) = s_H \quad \text{and} \quad G_V(s_H, s_V) = s_V$$

Two-type Branching Process

$$G_{\mathrm{H}}(s_{\mathrm{H}}, s_{\mathrm{V}}) = \frac{1}{1 + R_0^{\mathrm{HV}}(1 - s_{\mathrm{V}})} \quad \text{and} \quad G_{\mathrm{V}}(s_{\mathrm{H}}, s_{\mathrm{V}}) = \frac{1}{1 + R_0^{\mathrm{VH}}(1 - s_{\mathrm{H}})}$$

Probability that an epidemic does not occur is found by solving

$$G_{\mathrm{H}}(s_{\mathrm{H}}, s_{\mathrm{V}}) = s_{\mathrm{H}} \quad \text{and} \quad G_{\mathrm{V}}(s_{\mathrm{H}}, s_{\mathrm{V}}) = s_{\mathrm{V}}$$

Notice G_{H} does not depend on s_{H} and G_{V} does not depend on s_{V}, so we can suppress unimportant arguments and write

$$G_{\mathrm{H}}(s_{\mathrm{V}}) = s_{\mathrm{H}} \quad \text{and} \quad G_{\mathrm{V}}(s_{\mathrm{H}}) = s_{\mathrm{V}}$$

So we have to solve

$$G_{\mathrm{H}}(G_{\mathrm{V}}(s_{\mathrm{H}})) = s_{\mathrm{H}} \quad \text{or (equivalently)} \quad G_{\mathrm{V}}(G_{\mathrm{H}}(s_{\mathrm{V}})) = s_{\mathrm{V}}$$

Notice, this should not be a surprise because composing the two generating functions gives the generating functions for the two-step processes V➔H➔V and H➔V➔H , i.e. following one complete lifecycle.

Stochasticity: Invasion Probabilities

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

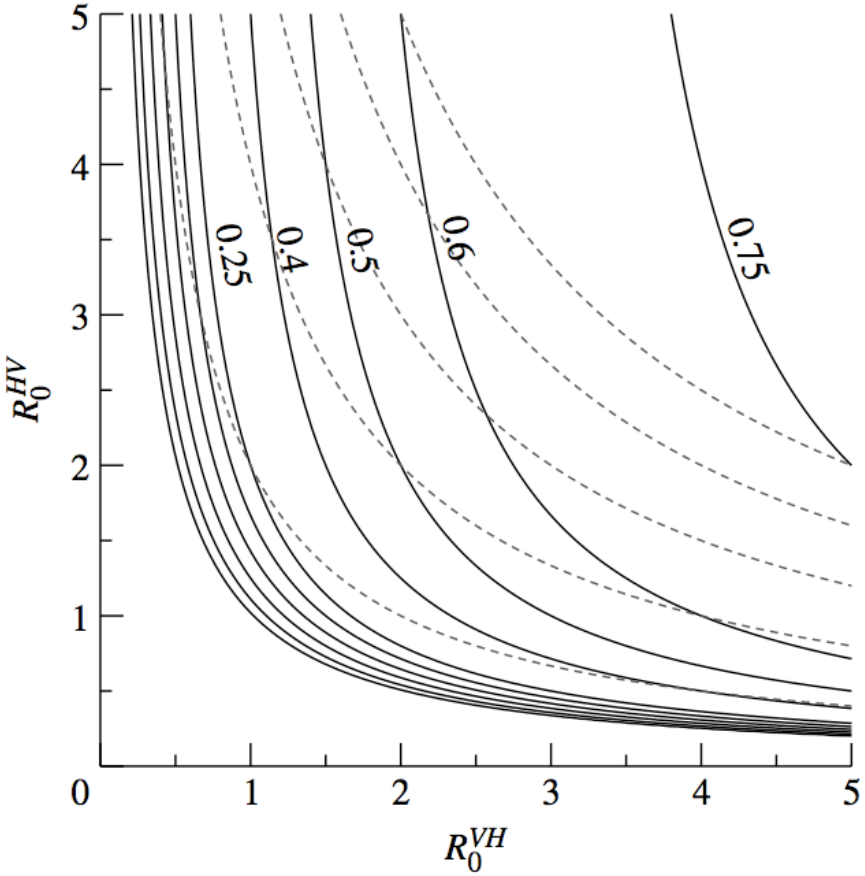
Invasion is more likely if introduction occurs via the type with the higher R_0

Stochasticity: Invasion Probabilities

Invasion probability from one infective vector

Contours of equal invasion probability (solid)

Contours of equal overall R_0 (dashed)



For a given R_0 , invasion probability is larger if R_0^{VH} is greater than R_0^{HV}

(Look at topmost dashed curve: R_0 = 10

if vector to host R_0 is 5, inv. prob. = 0.75

if vector to host R_0 is 2, inv. prob. = 0.6)

Stochasticity: Variation Around Endemic Equilibrium

Deterministic model

If $R_0 > 1$ the system approaches a stable endemic equilibrium

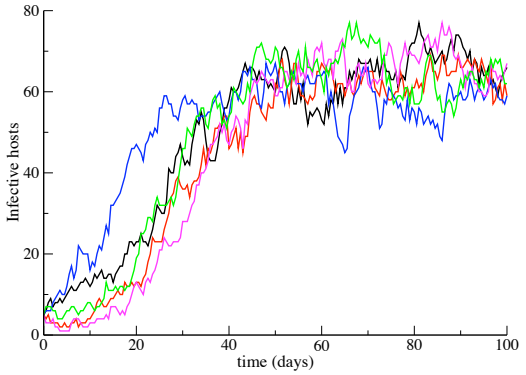
Stochastic model, $R_0 > 1$

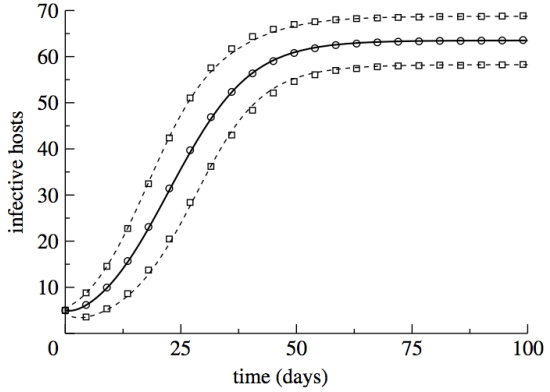
If invasion is successful, system approaches endemic state

Variation is seen between realizations

Realizations continue to fluctuate about equilibrium of the deterministic model

mean +/- standard deviation :





Stochasticity: Variability About Endemic Equilibrium

Use moment equations to quantify how (e.g.) variance of *I* changes over time

Use the general result $$\frac{d}{dt}E\left[f(Y,I)\right]=\sum_j E\left[\lambda_j(Y,I)\cdot\Delta f(Y,I)_j\right]$$

to derive the following set of moment equations:

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

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

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

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

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

Stochasticity: Variability About Endemic Equilibrium

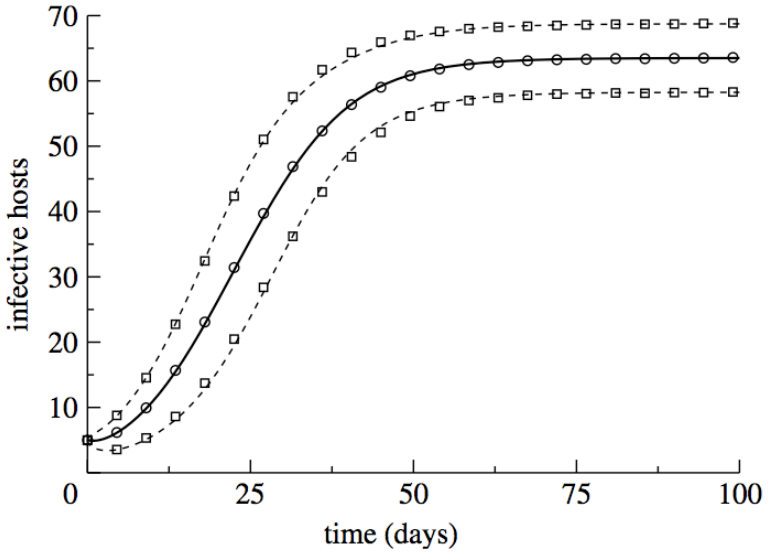
Stochastic process is nonlinear, so moment equation set is not closed

- first order moment equations involve second order moments
- second order moment equations involve third order moments
- must use moment closure approximation e.g. multivariate normal approximation
  - assumes that third order central moments are zero
  - e.g. $E\left[\left\{(Y-E[Y])^2\right\}\left\{I-E[I]\right\}\right]=0$ -- gives E[Y^2I] in terms of lower moments

Often gives a good approximation:

Curves: from moment equations + MVN

Symbols: numerical estimates of moments based on 10 000 realizations of the model



Quasi-Stationary Distribution

(*y* , *i*) = (0 , 0) is an absorbing state of the Markov chain model
(no infection!)

Eventually, infection will go extinct, although timescale could be very long

Look at probabilities conditional on non-extinction: $q_t(y,i) = P\left\{Y(t) = y, I(t) = i \,\middle|\, Y(t) + I(t) > 0\right\}$

$$= \frac{P\left\{Y(t) = y, I(t) = i\right\}}{1 - P\left\{Y(t) = I(t) = 0\right\}}$$

Quasi-stationary distribution is $\lim_{t\to\infty} q_t(y,i)$

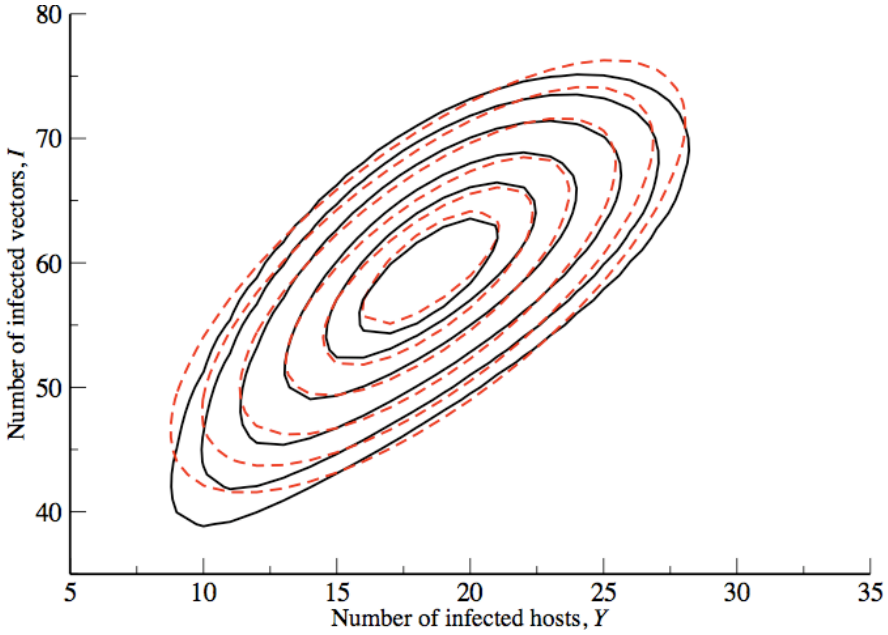
Can find this by forming a rate matrix *Q* (paper uses notation *A*), eliminating rows and columns corresponding to the absorbing states, and finding the normalized left eigenvector associated with the largest eigenvalue

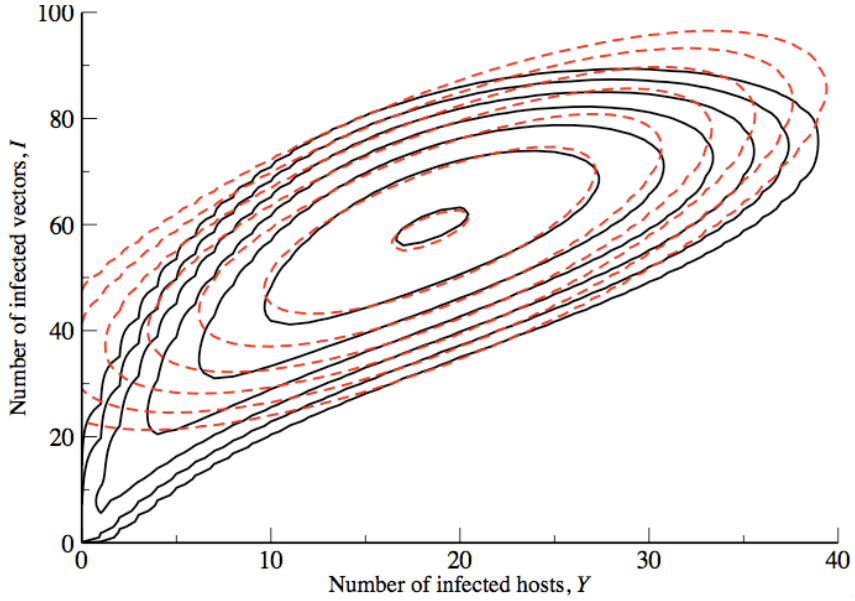
Matrix is large, but sparse

Stochasticity: Variability About Endemic Equilibrium

Comparison between exact calculation of quasi-stationary distribution (Nåsell, 1991; black curves) and that obtained using moment equations + MVN (red curves)

Works well, although notice discrepancies in the tails, particularly if the distribution has noticeable weight near boundaries





(Nåsell (1991) Math. Biosci. **107**, 187.)

Further directions…

Ross model is highly simplified:

Latent period in both vector (“extrinsic incubation period”) and host (“intrinsic incubation period”)

Population dynamics of mosquitoes
Demography of human population

Human infection is more likely SIR (or SEIR) than SIS
- increases variability about endemic equilibrium

Heterogeneity in populations
- populations are not well-mixed (e.g. spatial distribution)
- mosquitoes prefer to bite some people rather than others (80-20 rule…)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IT'S TOO MUCH FOR THEM