Lecture 4: **Stochastic models for arboviruses**

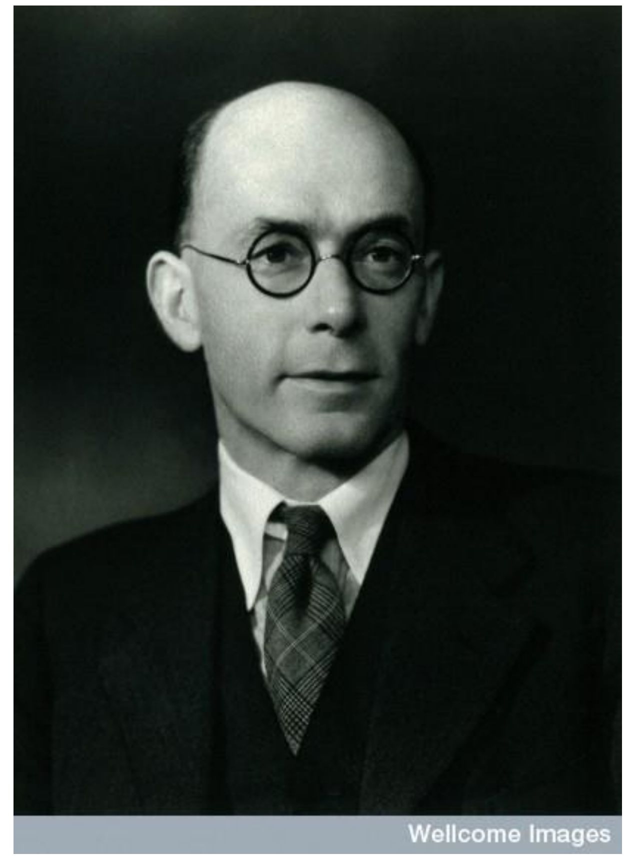
Ira Longini

The Ross-MacDonald Model for Vector Bourne Infectious Diseases

Sir Ronald Ross (1857-1932)
Liverpool School of Tropical Medicine

The 2nd Nobel Prize in Medicine 1902

"for his work on malaria, by which he has shown how it enters the organism and thereby has laid the foundation for successful research on this disease and methods of combating it"



George MacDonald
(1903-1967)
Director
Ross Institute and Hospital for Tropical Diseases
The London School of Hygiene & Tropical Medicine

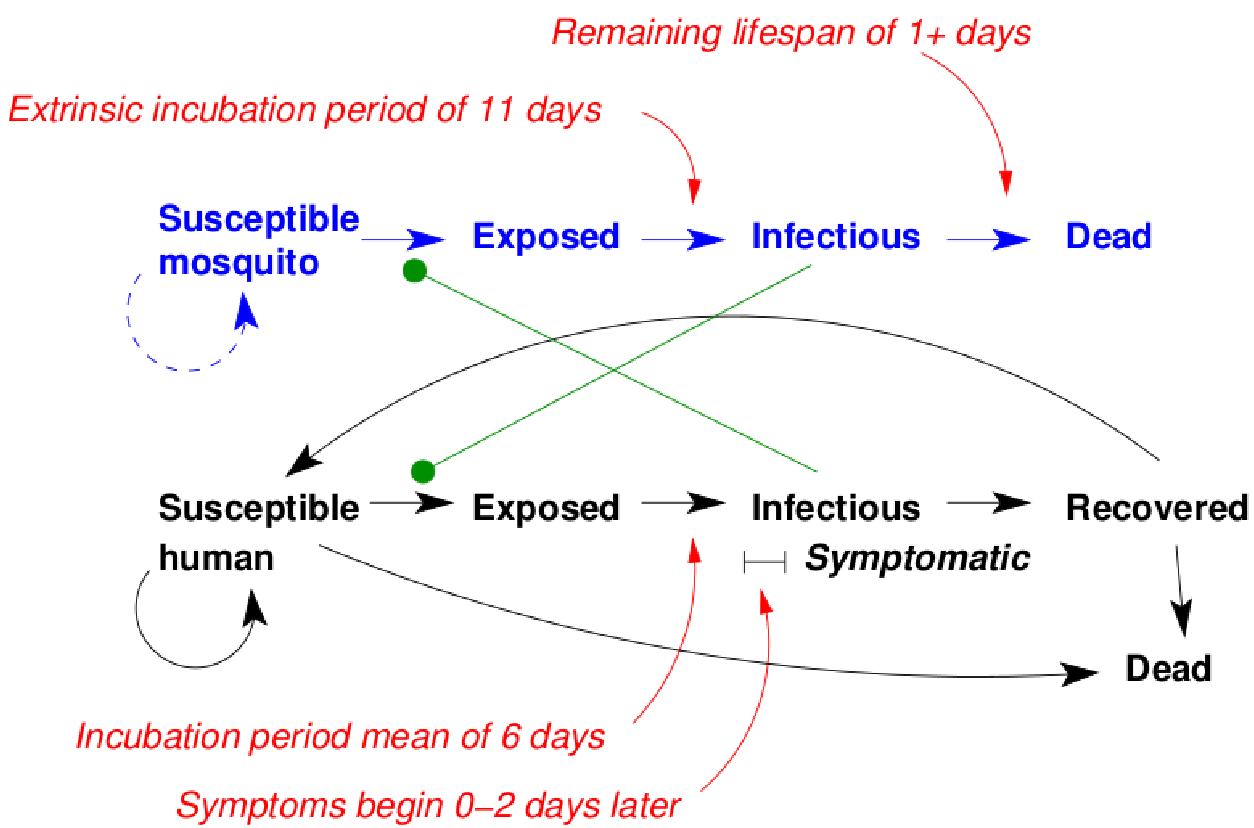
Model Structure

Simple deterministic model

Consider a S-I-S model for humans, and S-I model for mosquitoes

n_1 is the population size of humans.
n_2 is the population size of mosquitoes.
$m = \frac{n_2}{n_1}$ number of mosquitoes per person, a measure of mosquito density
$I_1(t)$ is the infection prevalence in humans, at time t.
$I_2(t)$ is the infection prevalence in mosquitoes, at time t.
a is mosquito biting rate.
b mosquito to human transmission probability, per bite
c human to mosquito transmission probability, per bite
$\gamma_1 = \frac{1}{D_1}$ is the recovery rate in humans.
$\gamma_2 = \frac{1}{D_2}$ is the death rate in mosquitoes.

Model: Natural history of dengue



- Human SEIR is linked to mosquito SEI model
- Humans and mosquitoes infect each other when they are in the same setting

Differential Equations

The initial value problem is

$$\begin{aligned}
\frac{dI_1(t)}{dt} &= abmI_2(t)(1 - I_1(t)) - \gamma_1 I_1(t), \\
\frac{dI_2(t)}{dt} &= acI_1(t)(1 - I_2(t)) - \gamma_2 I_2(t), \\
I_1(0) &> 0 \text{ and/or } I_2(0) > 0, \\
S_i(t) + I_i(t) &= 1, i = 1, 2, \forall t \geqslant 0.
\end{aligned}$$

This system has two equilibria as $t \to \infty$, one being $(I_1(\infty), I_2(\infty)) = (0, 0)$, and the other being in the interior of the SI-plane.

The largest eigenvalue of the linearized system at $(0, 0)$,is the basic reproductive number,

$$R_0 = \frac{ma^2bc}{\gamma_1\gamma_2} = ma^2bcD_1D_2 = (abD_2)(macD_1) = R_0^{2\to1}R_0^{1\to2}$$

hum inf by a mos # mosqitoes inf by a hum

Threshold Theorem:
If $R_0 \leq 1$,then $(0, 0)$ is globally asymptotically stable (GAS), and
if $R_0 > 1$,then the interior point $\left(\frac{R_0 - 1}{R_0 + \frac{ab}{\gamma_2}}, \frac{R_0 - 1}{R_0 + \frac{mab}{\gamma_1}}\right)$ is GAS.
e.g., $m = 5, a = 2, b = c = 0.1, D_1 = 5, D_2 = 5$, then $R_0 = 5.0$,
and the equilibrium infection prevalence is $(0.67, 0.40)$.

Differential Equations

The initial value problem is

$$\begin{aligned}
\frac{dI_1(t)}{dt} &= abmI_2(t)(1 - I_1(t)) - \gamma_1 I_1(t), \\
\frac{dI_2(t)}{dt} &= acI_1(t)(1 - I_2(t)) - \gamma_2 I_2(t), \\
I_1(0) &> 0 \text{ and/or } I_2(0) > 0, \\
S_i(t) + I_i(t) &= 1, i = 1, 2, \forall t \geqslant 0.
\end{aligned}$$

This system has two equilibria as $t \to \infty$, one being $(I_1(\infty), I_2(\infty)) = (0, 0)$, and the other being in the interior of the SI-plane.

The largest eigenvalue of the linearized system at $(0, 0)$, is the basic reproductive number,

$$R_0 = \frac{ma^2bc}{\gamma_1\gamma_2} = ma^2bcD_1D_2 = (abD_2)(macD_1) = R_0^{2\to1}R_0^{1\to2}$$

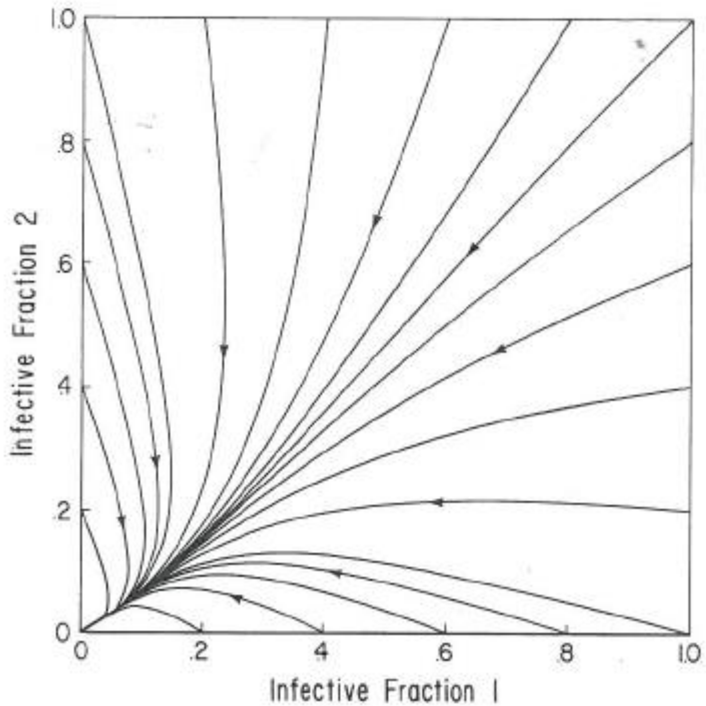
hum inf by a mos   # mosqitoes inf by a hum

Threshold Theorem: Epidemiological Folk Theorem for Host-Vector Systems

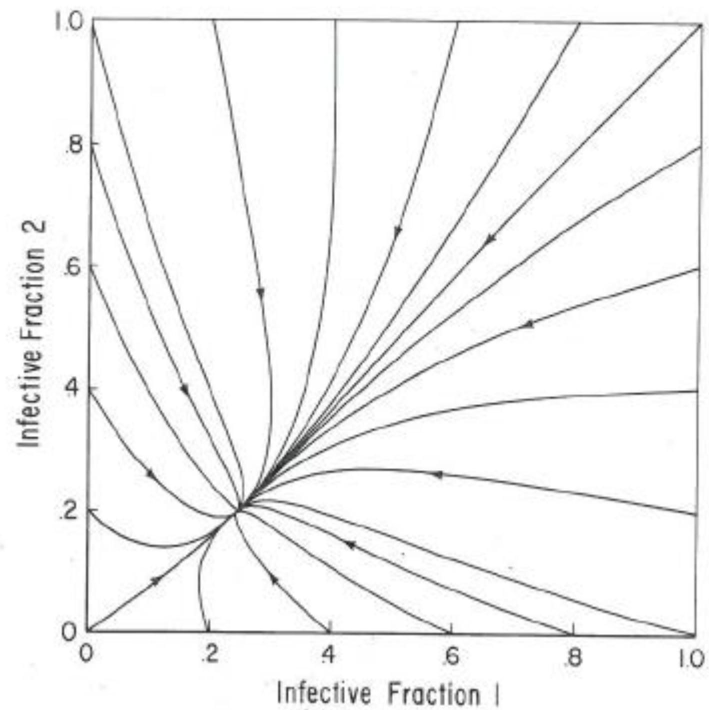
If $R_0 \leq 1$,then $(0,0)$ is globally asymptotically stable (GAS), and
if $R_0 > 1$,then the interior point $(\frac{R_0-1}{R_0+\frac{ab}{\gamma_2}}, \frac{R_0-1}{R_0+\frac{mab}{\gamma_1}})$ is GAS.

e.g., $m = 5, a = 2, b = c = 0.1, D_1 = 5, D_2 = 5$, then $R_0 = 5.0$,
and the equilibrium infection prevalence is $(0.67, 0.40)$.

Typical $I_1 I_2$ - plane phase portraits*



$R_0 \leq 1$



$R_0 > 1$

*Source: Hethcote, *Math Bosci* 28, 335-56 (1976).

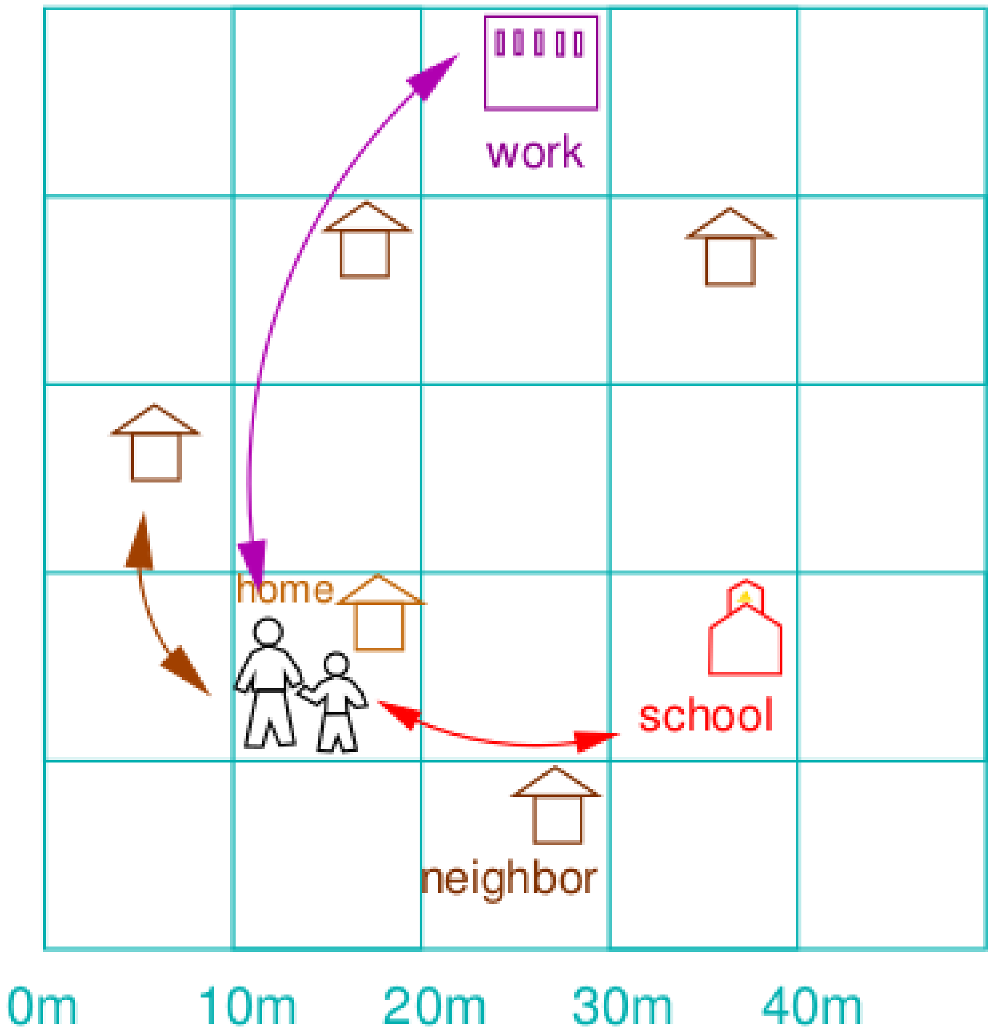
Basic Reproductive Number

$$R_0 = ma^2bcD_1D_2 = (abD_2)(macD_1) = R_0^{2\to1}R_0^{1\to2}$$

- Transmission decreases as a quadratic with decreasing biting rate, *a*
- Transmission decreases linearly with decreasing mosquito density, *m*
- Transmission decreases as a quadratic with vaccination if vaccine has both VE_S, through *b*,and VE_I, through *c*.

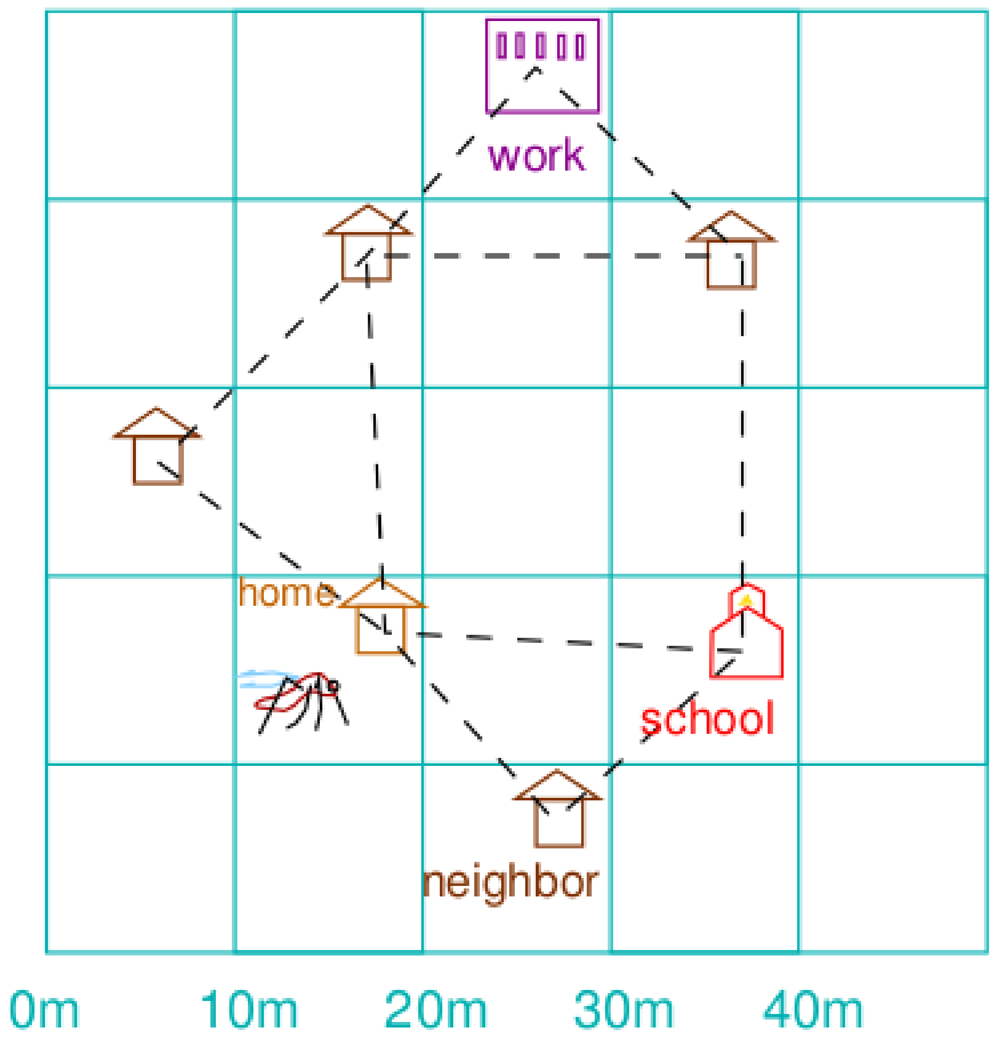
Stochastic models

Model: human movement



- People are at home in the morning and evenings.
- People may go to work or school during the day.

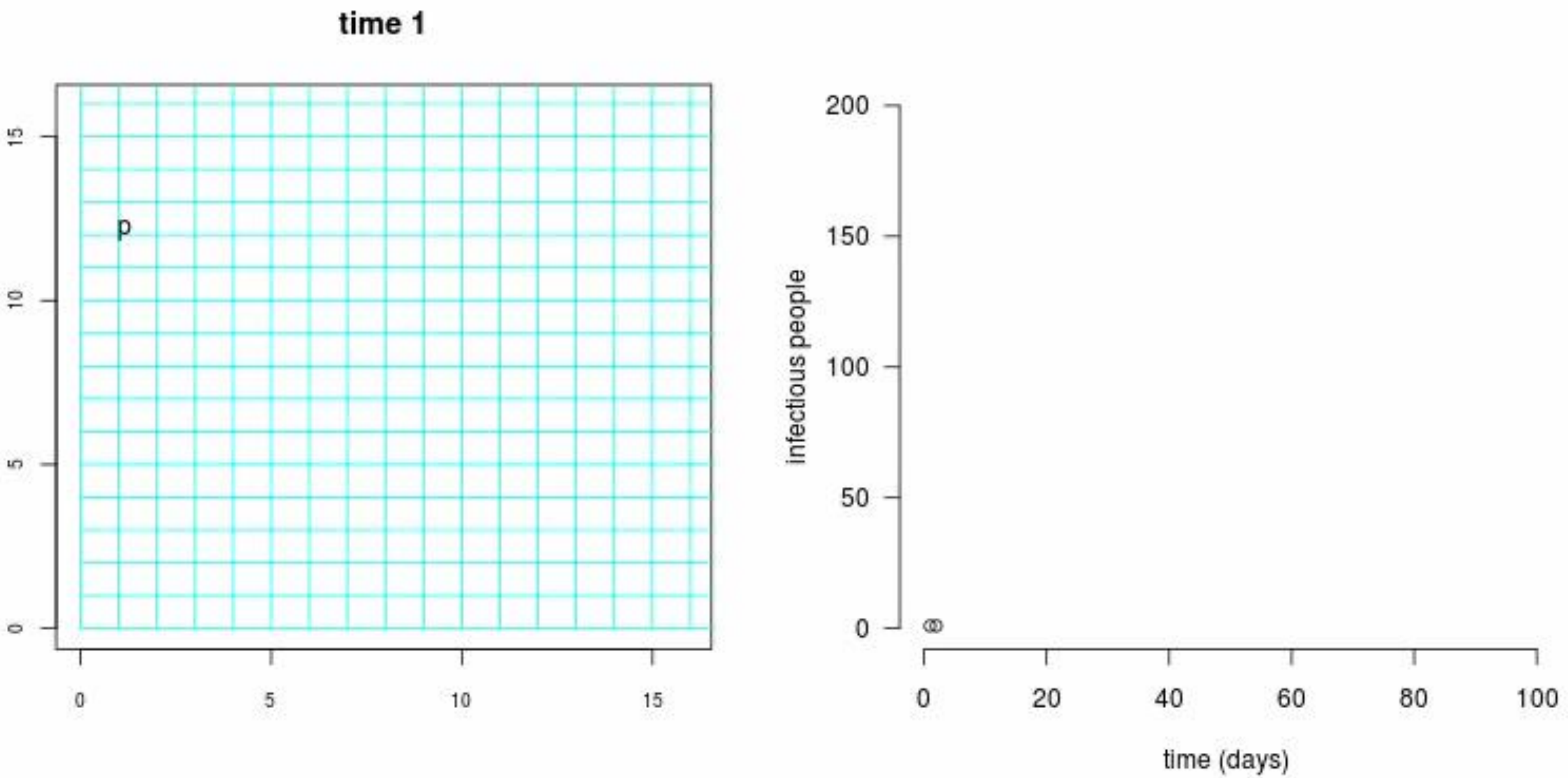
Model: mosquito movement



- Each mosquito is associated with a setting (house, workplace, school).
- Mosquitoes often migrate to adjacent setting.
- Occasionally, mosquitoes migrate to distant setting.

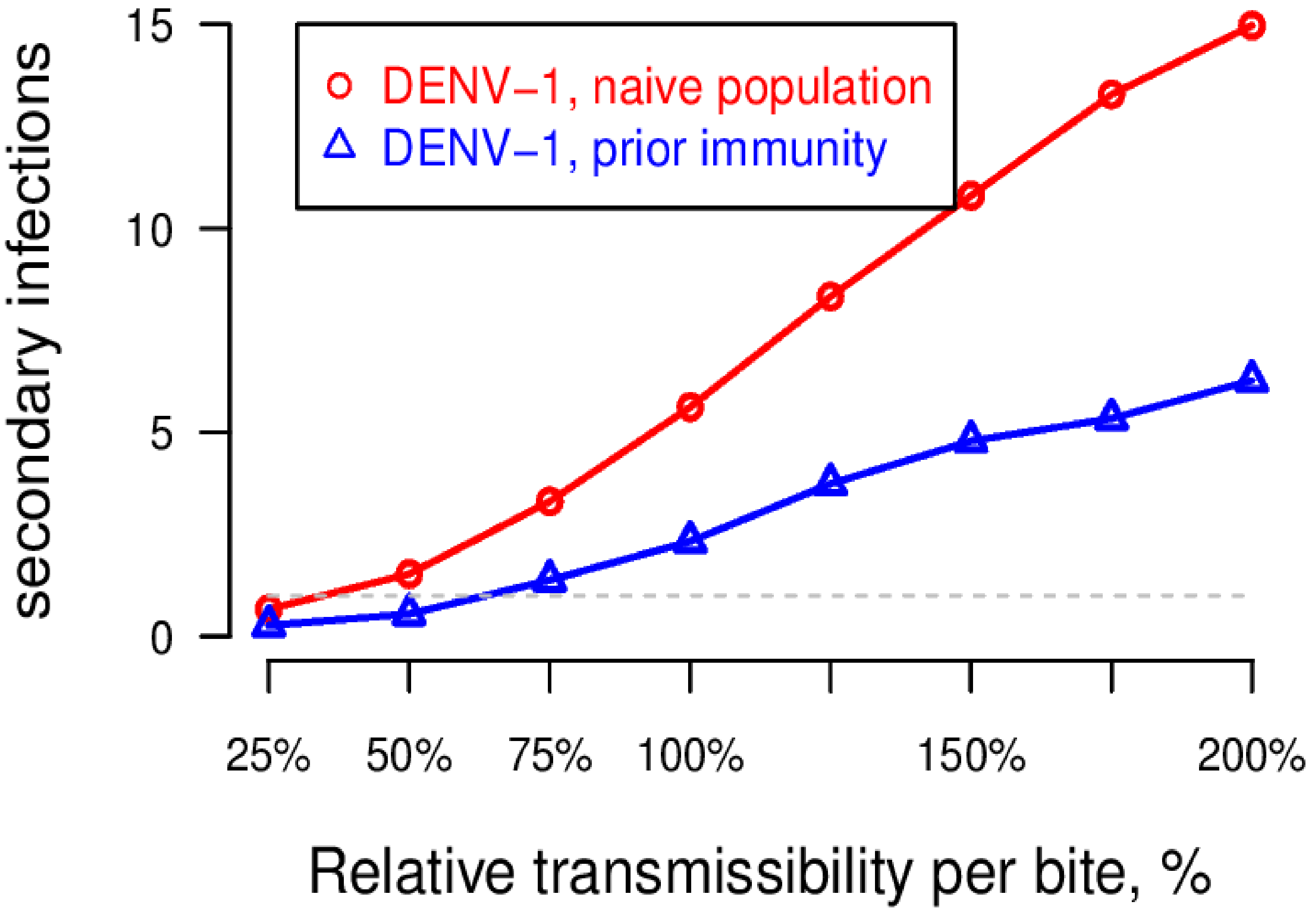
Simplified Model

- Small community of 16 x 16 households
- 40 “transmission settings” scattered among households.
- No age structure
- 1 initial case



- p = infected human
- m = exposed mosquito
- m = infectious mosquito

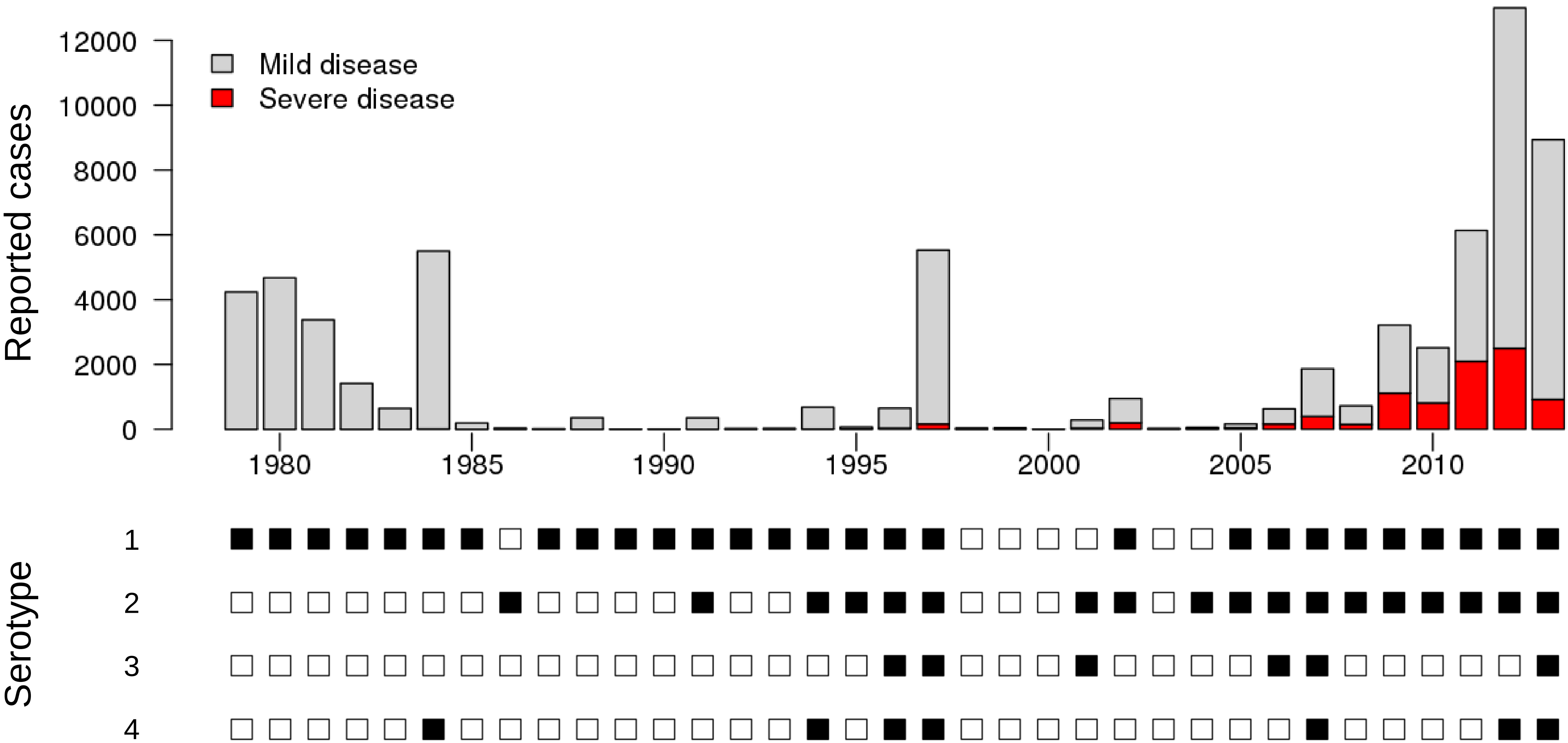
Modeled relationship between mosquito biting rate and R_0 and R



Current dengue intervention use and impact modeling

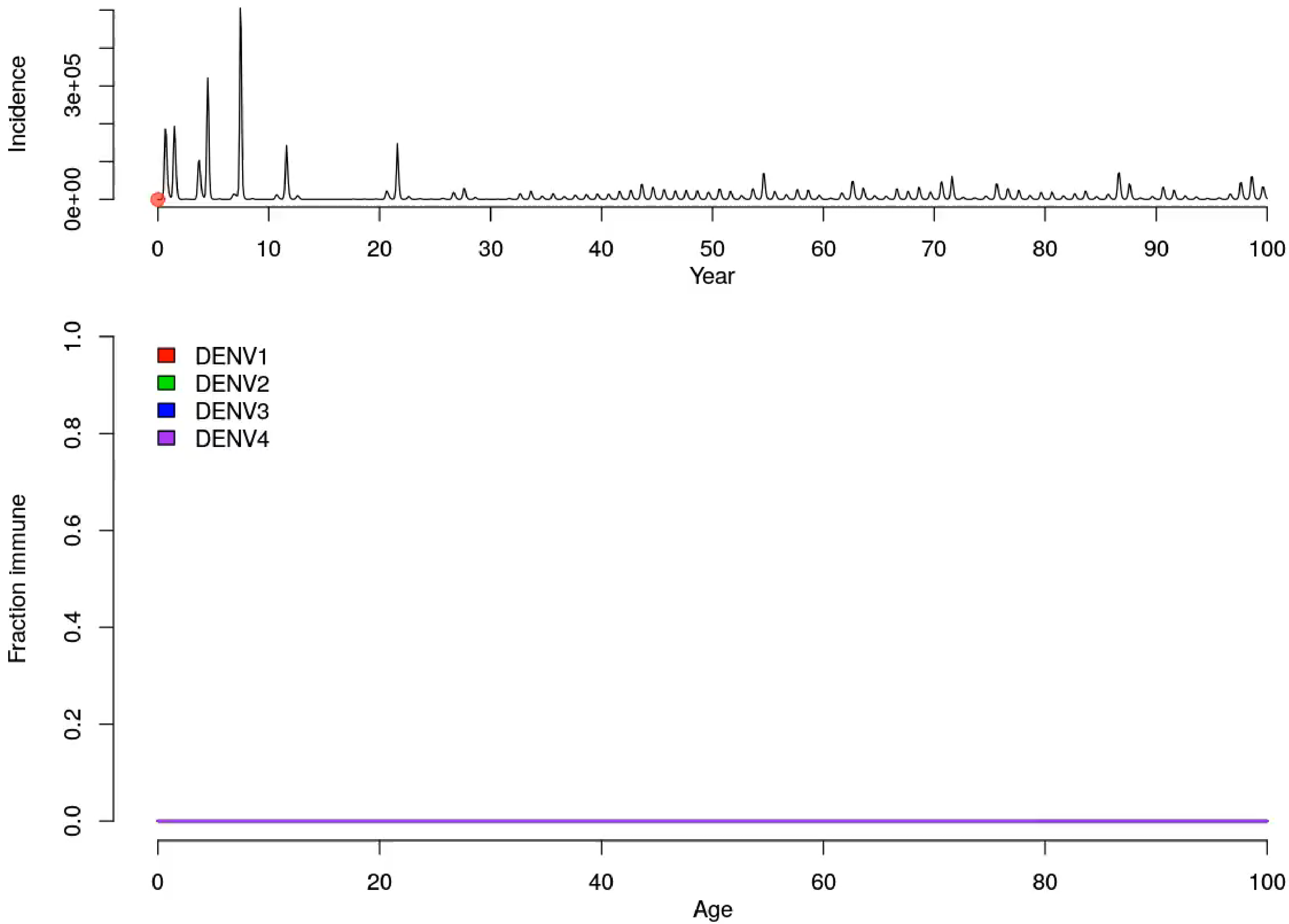
- Vaccine effectiveness depends on
  - Force of infection of each serotype
  - Mix of serotypes circulating
  - Level of immunity in the population
  - Age structure of the population
    - Change immunity patterns
    - Level of exposure
- Vector control
  - Need to establish the relationship between vector control methods and dengue illness and infection

Dengue in Yucatan, 1979-2013



Hladish *et al*. PLOS NTDs (2016)

Simulated immune profile



Agent based model

- People
- Home
- Day location
- Age
- Infection state
- Immune state
- May stay home if sick

- Mosquitoes
- Location
- Age
- Infection state
- May move once per day

PLOS | NEGLECTED TROPICAL DISEASES

RESEARCH ARTICLE

Projected Impact of Dengue Vaccination in Yucatán, Mexico

Thomas J. Hladish[1,2]*, Carl A. B. Pearson[2], Dennis L. Chao[3¤a], Diana Patricia Rojas[4], Gabriel L. Recchia[5¤b], Héctor Gómez-Dantés[6], M. Elizabeth Halloran[3,7,8], Juliet R. C. Pulliam[1,2], Ira M. Longini[2,9]

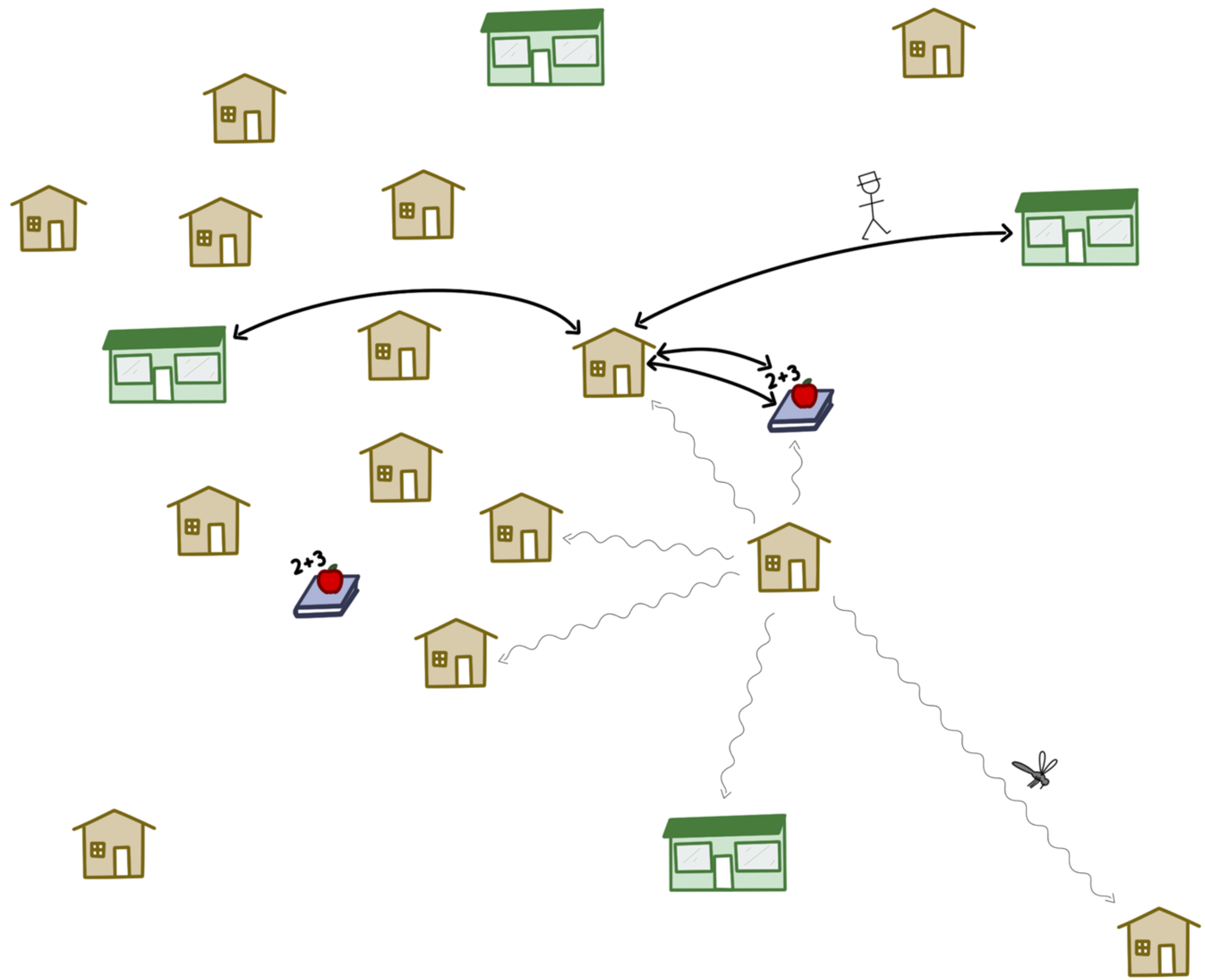
1 Department of Biology, University of Florida, Gainesville, Florida, United States of America, **2** Emerging Pathogens Institute, University of Florida, Gainesville, Florida, United States of America, **3** Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Research Center, Seattle, Washington, United States of America, **4** Department of Epidemiology, University of Florida, Gainesville, Florida, United States of America, **5** Institute for Intelligent Systems, University of Memphis, Memphis, Tennessee, United States of America, **6** Health Systems Research Center, National Institute of Public Health, Cuernavaca, Morelos, Mexico, **7** Center for Inference and Dynamics of Infectious Diseases, Seattle, Washington, United States of America, **8** Department of Biostatistics, University of Washington, Seattle, Washington, United States of America, **9** Department of Biostatistics, University of Florida, Gainesville, Florida, United States of America

¤a Current Address: Institute for Disease Modeling, Intellectual Ventures, Bellevue, Washington, United States of America
¤b Current Address: Centre for Digital Knowledge, Centre for Research in the Arts, Social Sciences and Humanities (CRASSH), University of Cambridge, Cambridge, Cambridgeshire, United Kingdom
* tjhladish@gmail.com

Citation: Hladish TJ, Pearson CAB, Chao DL, Rojas DP, Recchia GL, Gómez-Dantés H, et al. (2016) Projected Impact of Dengue Vaccination in Yucatán, Mexico. PLoS Negl Trop Dis 10(5): e0004661. doi:10.1371/journal.pntd.0004661

Abstract

Dengue model overview



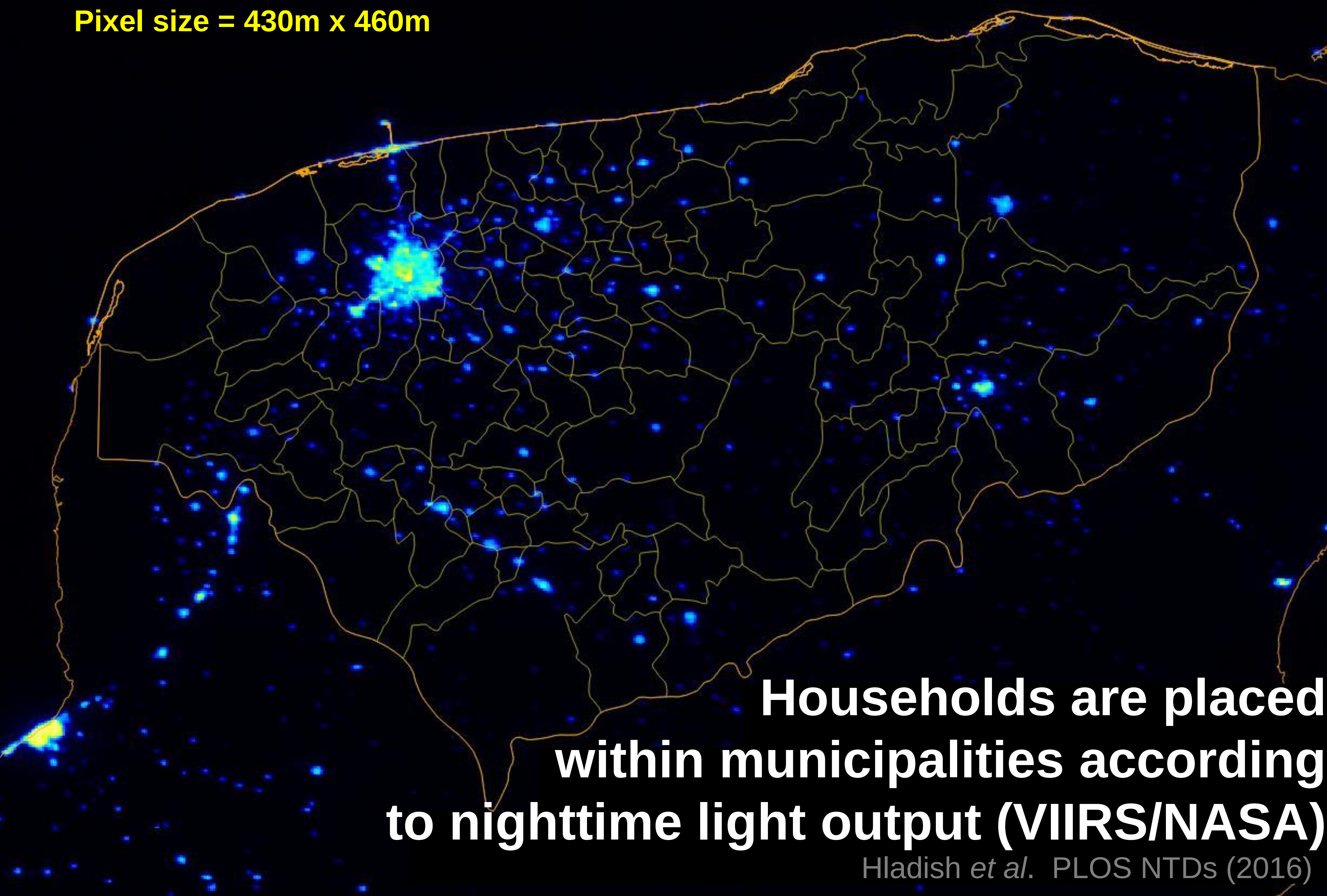
- 1.82 million people
  - 38% employed
  - 28% in school
  - 34% stay at home

– 376k Households (5% sample, municipality)

– 96k Workplaces (size, postal code)

– 3.4k Schools (postal code)

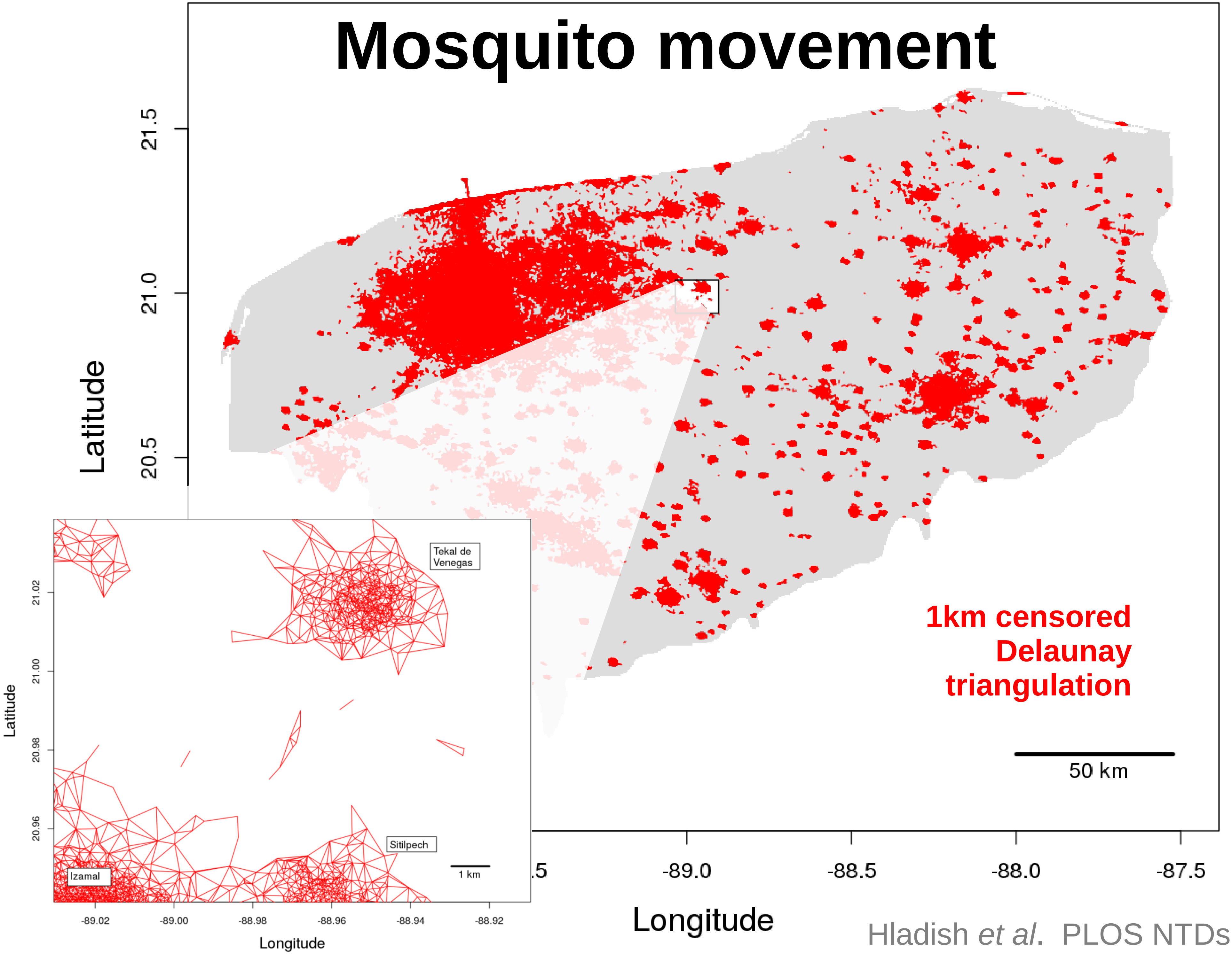
Hladish *et al*. PLOS NTDs (2016)



Households are placed within municipalities according to nighttime light output (VIIRS/NASA)

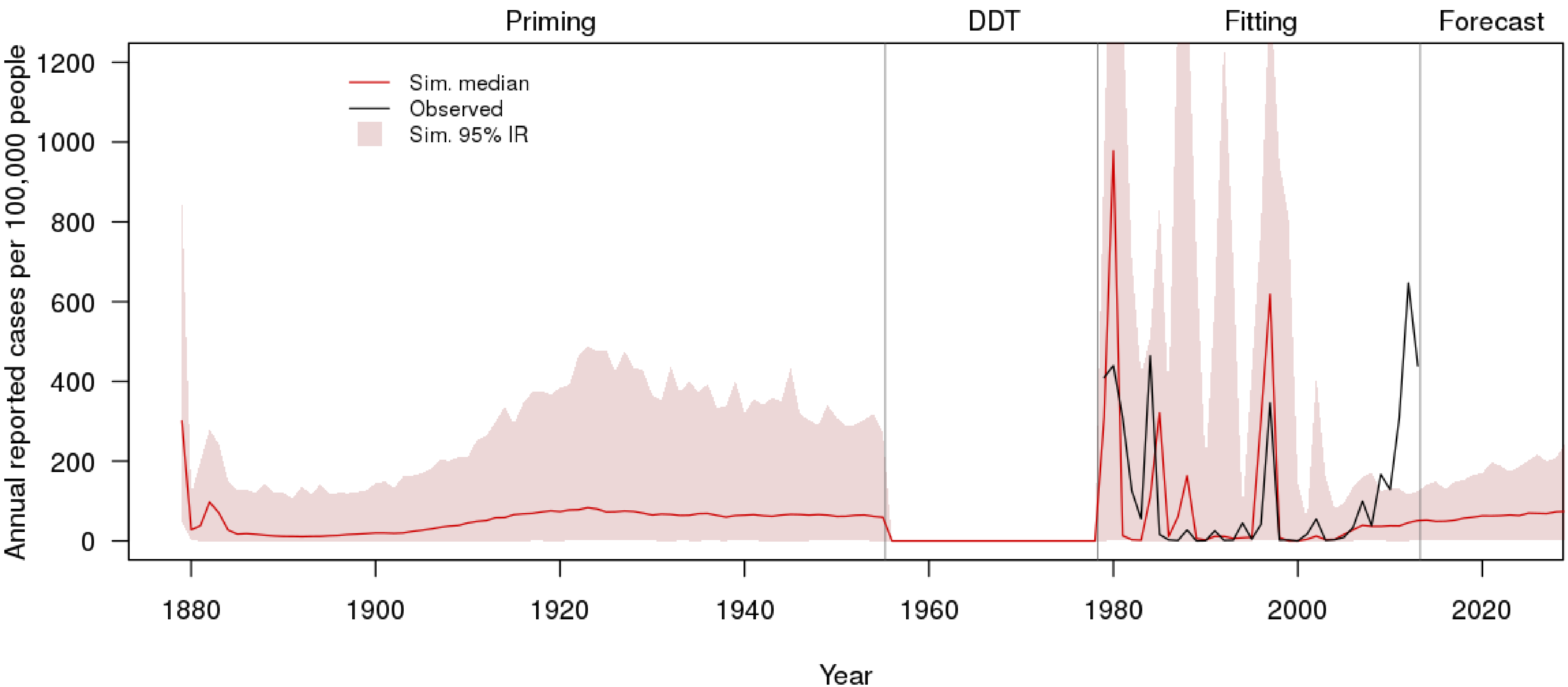
Hladish *et al*. PLOS NTDs (2016)

Mosquito movement



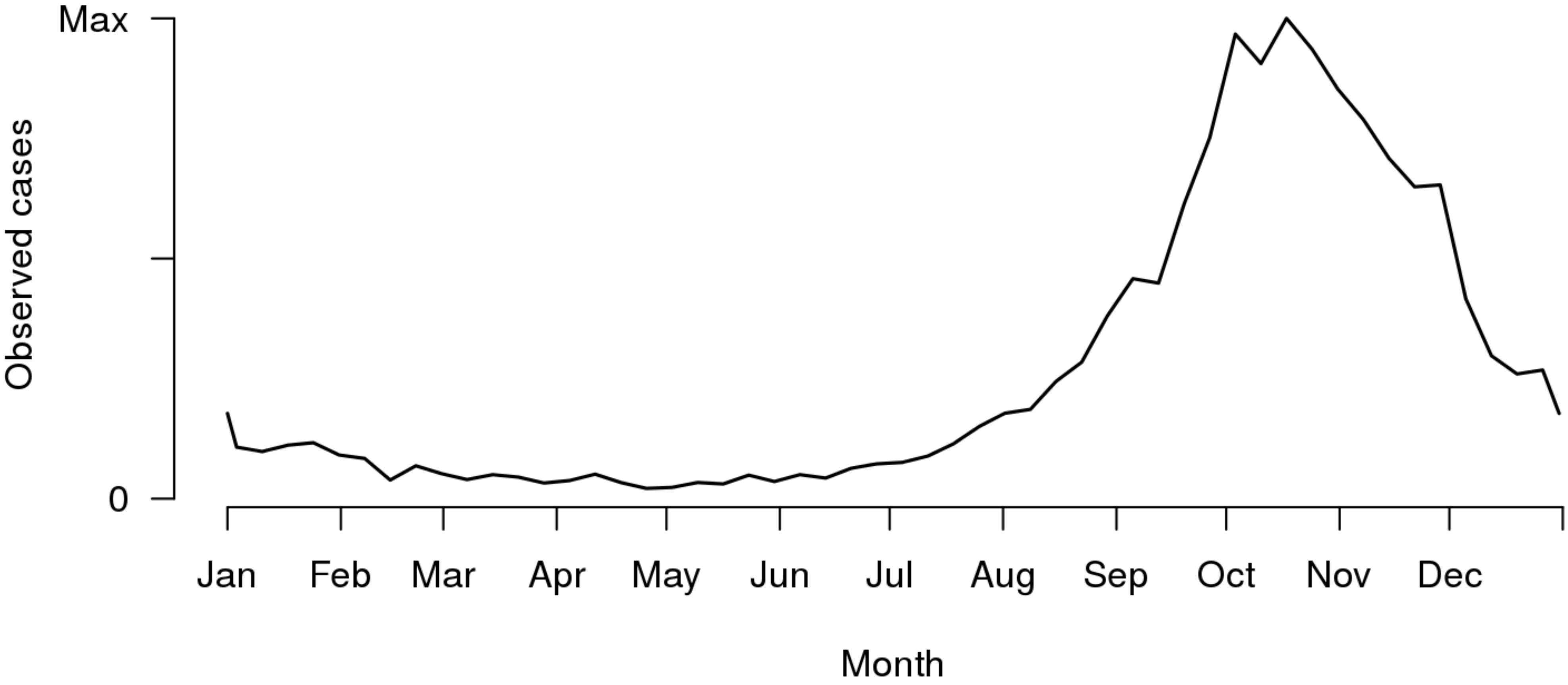
Hladish *et al*. PLOS NTDs (2016)

Reconstruct the past, forecast the future

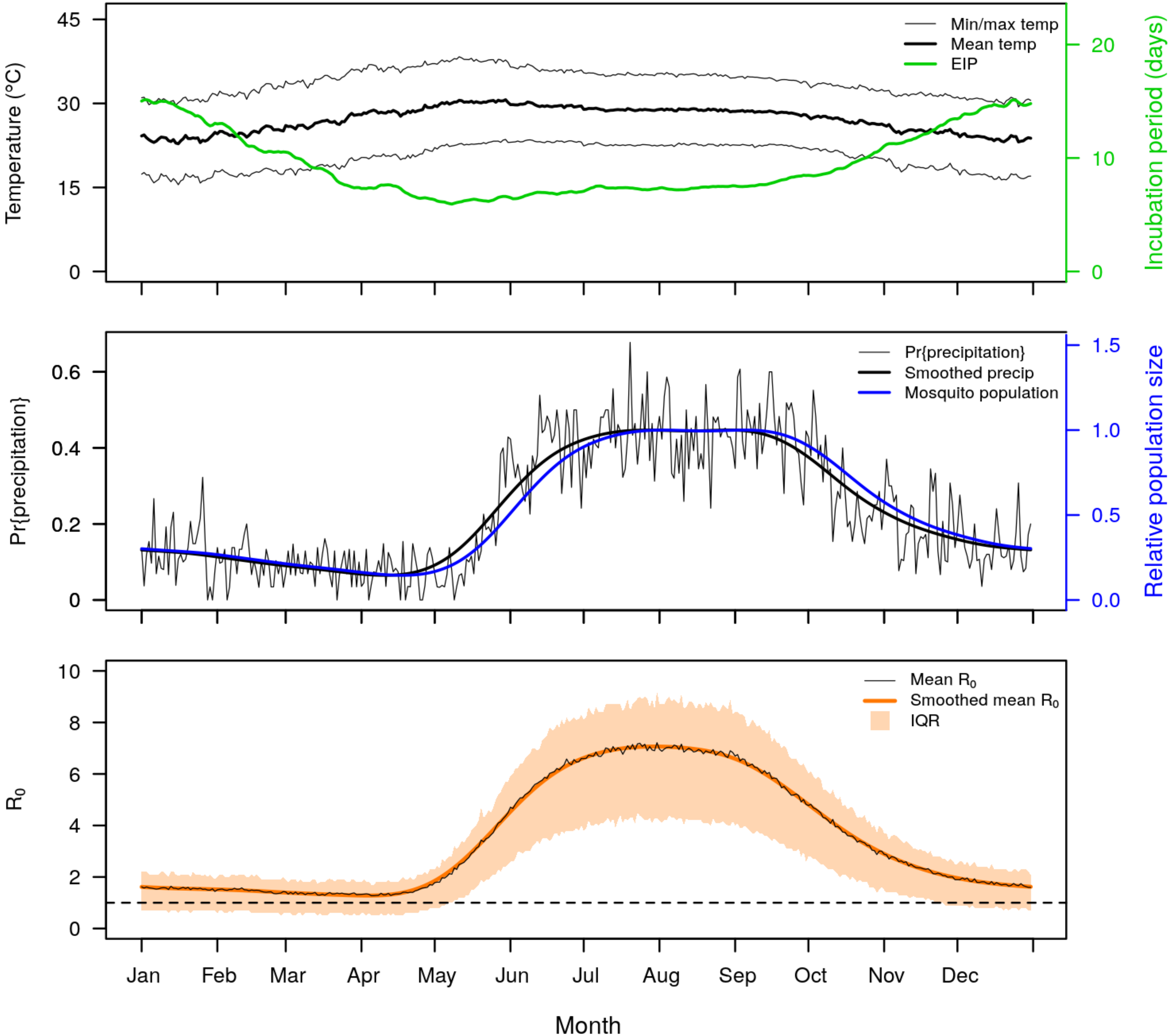


Hladish *et al*. PLOS NTDs (2016)

Observed seasonality (1995-2011)

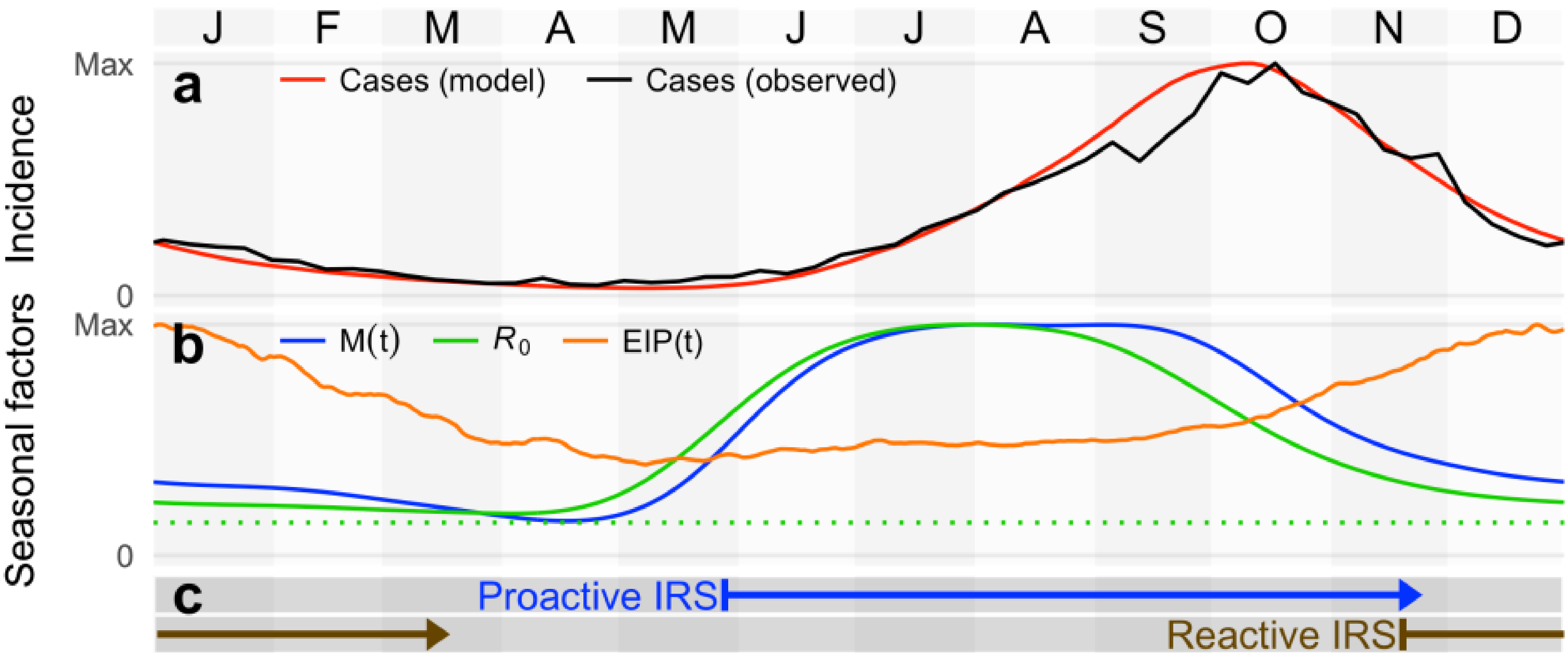


Hladish *et al*. PLOS NTDs (2016)



Min/max temp
Mean temp
EIP
Temperature (°C)
Incubation period (days)
45
30
15
0
20
10
0
Pr{precipitation}
Smoothed precip
Mosquito population
Pr{precipitation}
Relative population size
0.6
0.4
0.2
0
1.5
1.0
0.5
0.0
Mean R0
Smoothed mean R0
IQR
R0
10
8
6
4
2
0
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Month

Dengue seasonality in Yucatan, 1995-2015



Yucatan Simulation with Vaccination

http://tjhladish.github.io/d3_dengue_map/mex.html

Vector Control

Hladish TJ, Pearson CAB, Rojas DP, Gomez-Dantes H, Halloran ME, Vazquez-Prokopec GM, Longini IM: Effectiveness of indoor residual spraying for reducing dengue burden. *PLoS Neglected Tropical Diseases* (In print).

Indoor residual spraying*

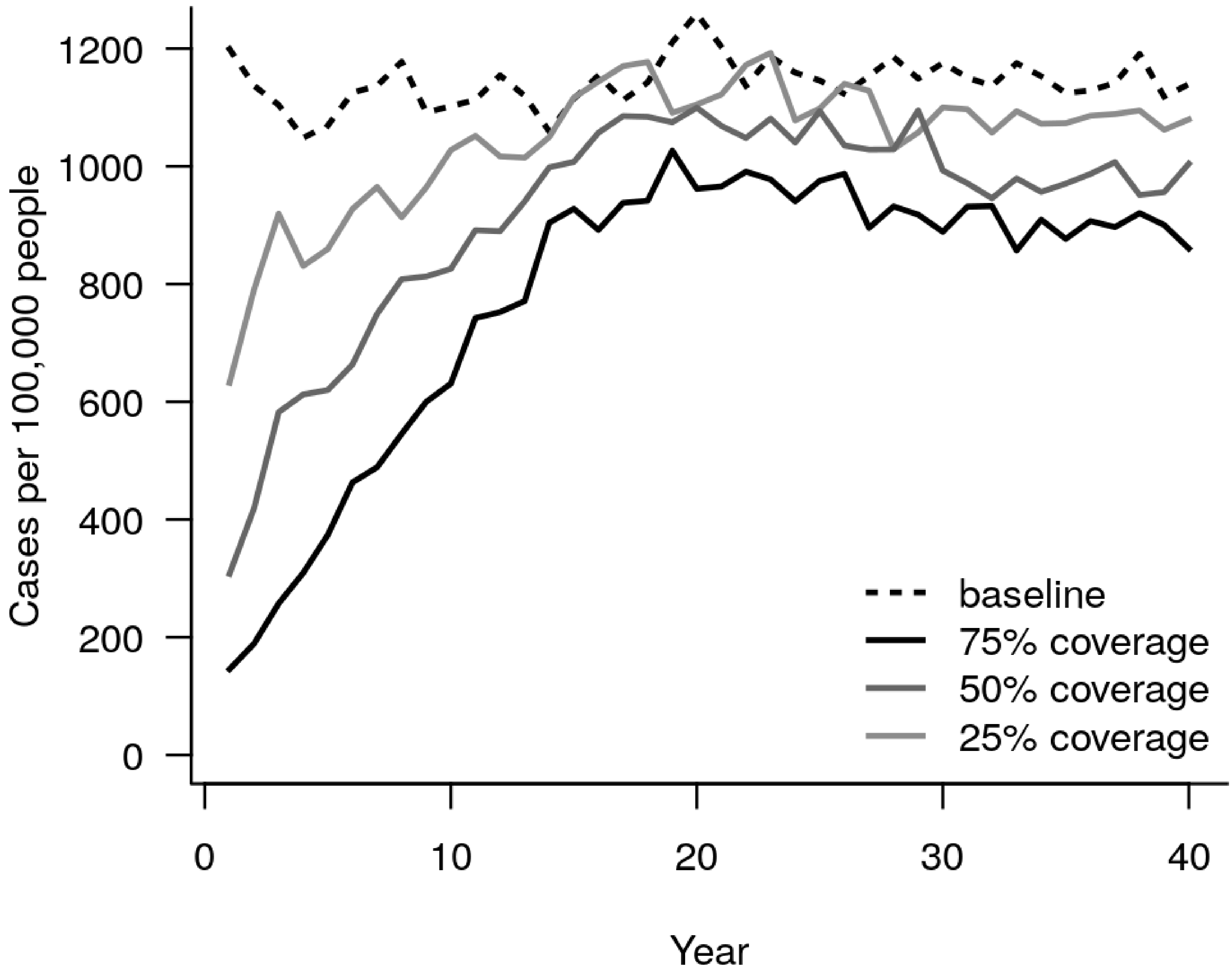
- Coverage: Treat 25/50/75% of houses per year
- Efficacy: 80% reduction in equilibrium pop size in treated houses
  - Corresponds to 13% daily mortality due to IRS
- Treatment lasts 90 days

Campaigns last 1/90/365 days

52 different start dates (1 and 90 day campaigns)

*Efficacy & durability based on Vazquez-Prokopec et al, *Science Advances* (2017)

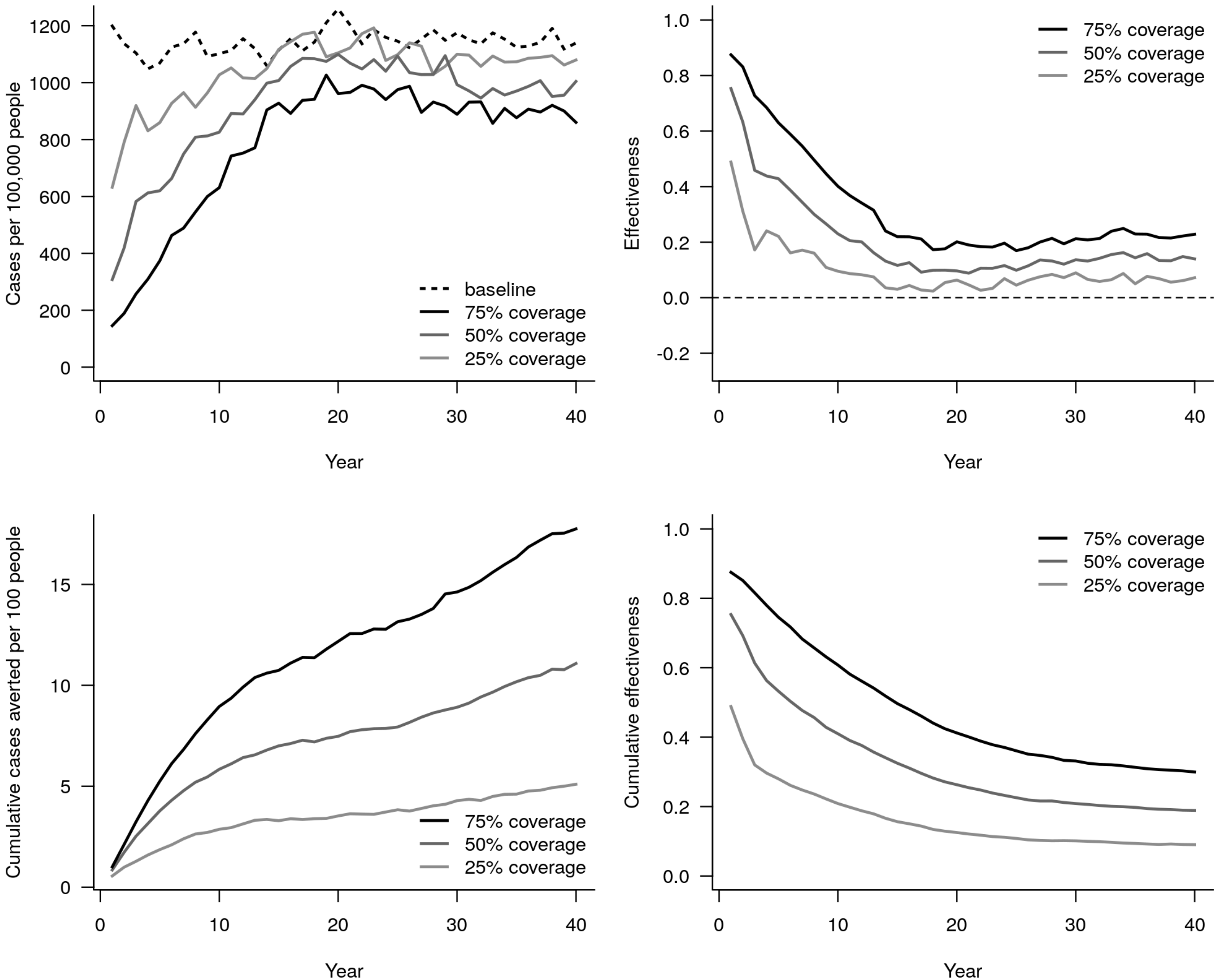
Simulated impact of IRS (90-day campaign, 90-day durability, late May start)



Overall Effectiveness

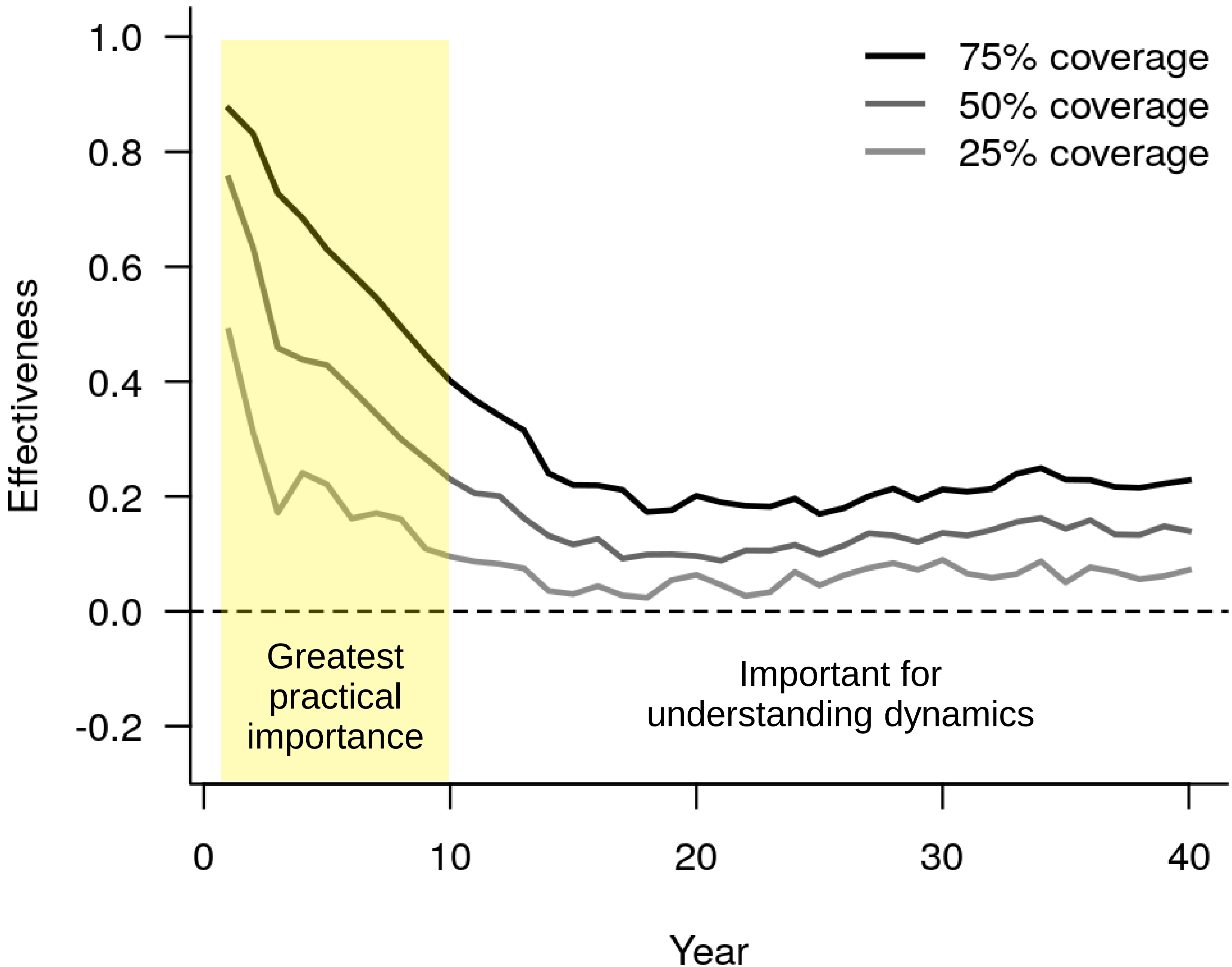
- Overall effectiveness based on incidence
  - Effectiveness = 1 - $\frac{\lambda_1}{\lambda_0}$
  - $\lambda_0 =$ dengue incidence with no intervention
  - $\lambda_1 =$ dengue incidence with intervention
- Overall effectiveness can also be based on cumulative incidence

Simulated impact of IRS (90-day campaign, 90-day durability, late May start)

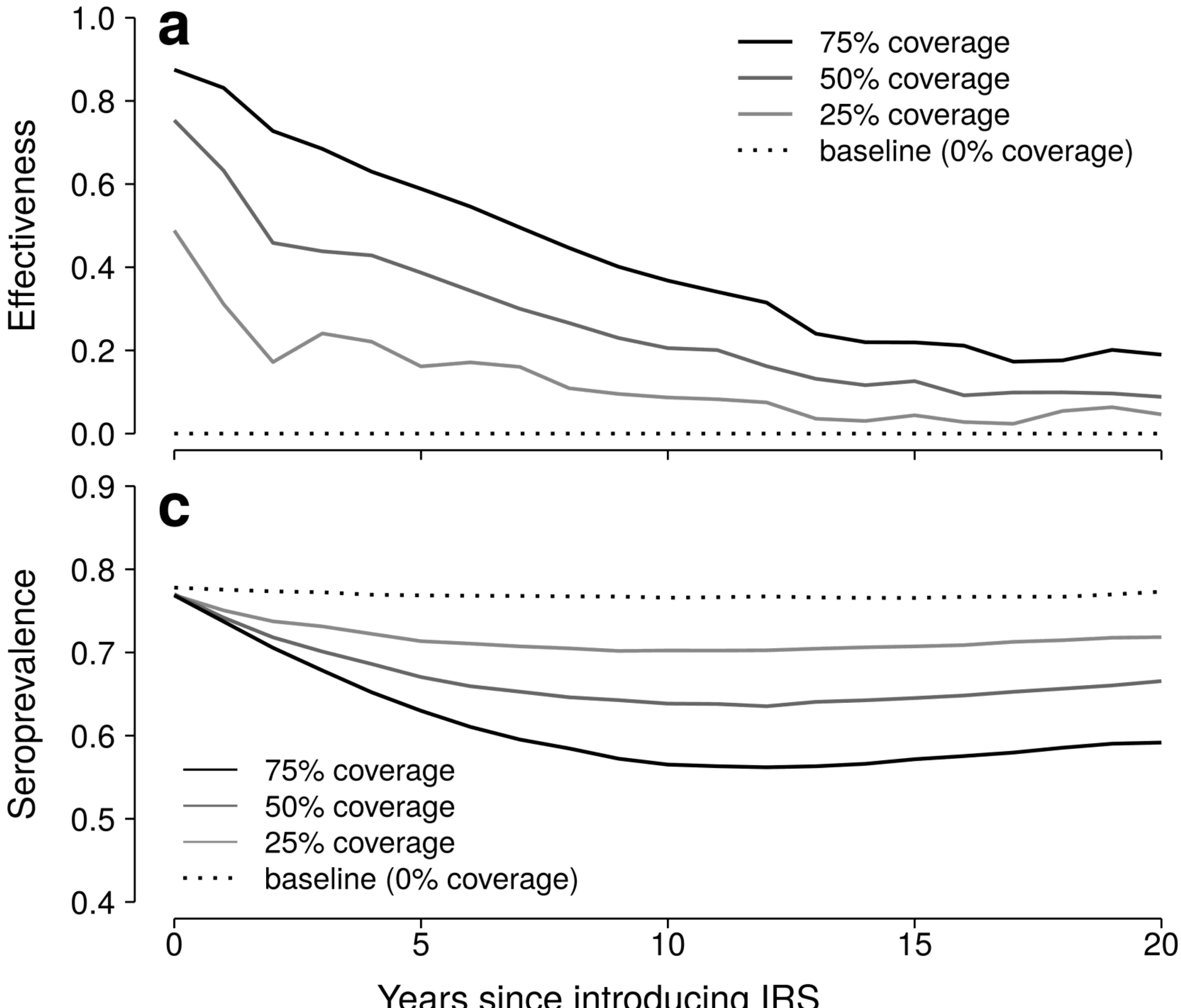


Effectiveness decreases for 15 years, then levels out. Why?

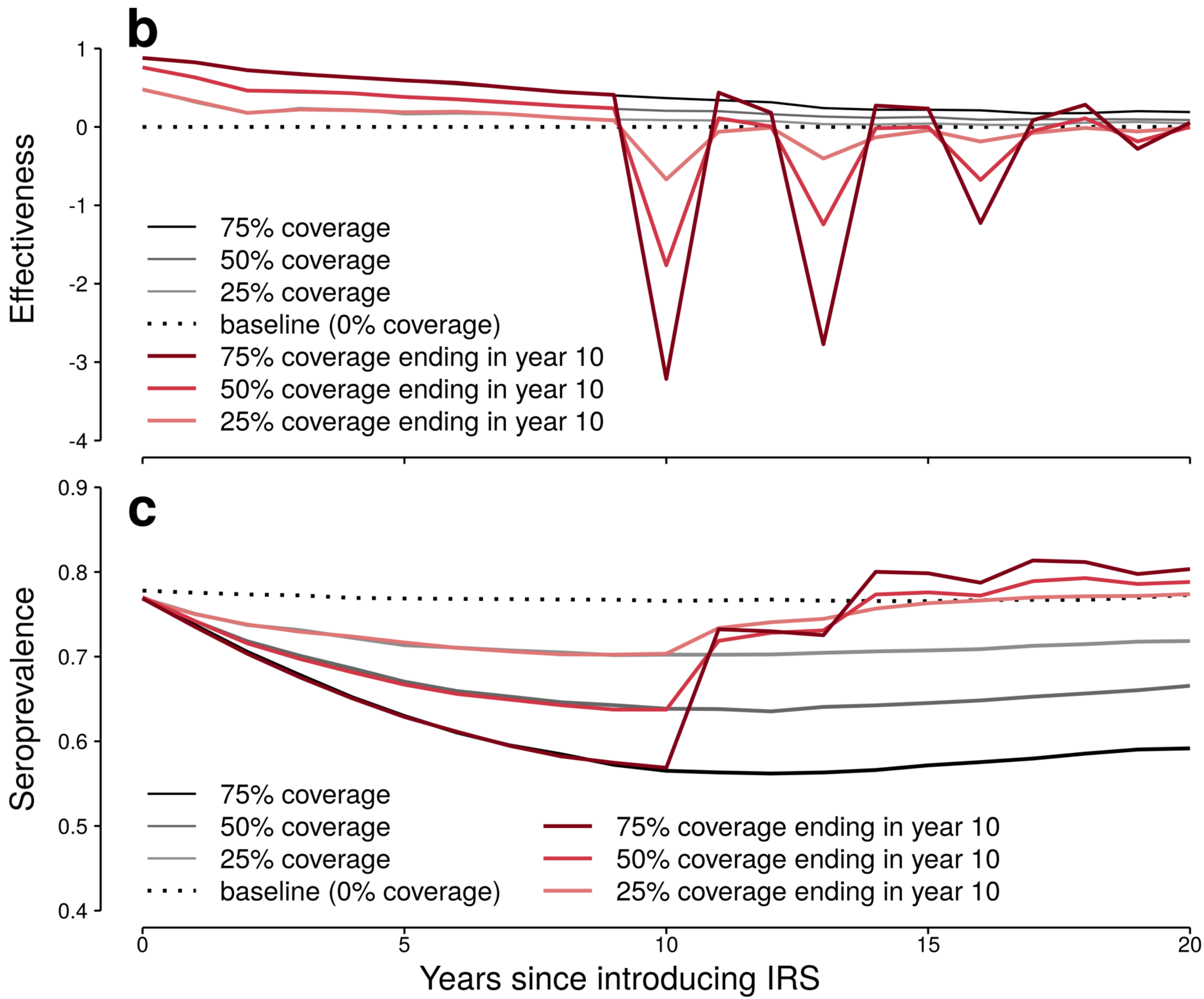
(90-day campaign, 90-day durability, optimal timing: late May start)



Population immunity drives long-term IRS effectiveness



What happens if IRS is abruptly stopped,
or mosquitoes suddenly evolve resistance?


b
c
Effectiveness
Seroprevalence
75% coverage
50% coverage
25% coverage
baseline (0% coverage)
75% coverage ending in year 10
50% coverage ending in year 10
25% coverage ending in year 10
Years since introducing IRS
1
0
-1
-2
-3
-4
0.9
0.8
0.7
0.6
0.5
0.4
0
5
10
15
20

Vaccines

- What should we expect if:
- a vaccine is introduced that works as an asymptomatic natural infection?
- a durable, efficacious vaccine is introduced?
- these are done alongside new vector control?

Dengue vaccines pipeline

Vaccine Candidate	Manufacturer	Vaccine Type	Mechanism of attenuation or inactivation	Clinical Phase
CYD Dengvaxia	Sanofi Pasteur	Live Attenuated	Yellow Fever vaccine backbone, premembrane and envelope proteins from wildtype dengue virus	III finished
DENVax	Takeda	Live Attenuated	Wildtype DEN2 strain attenuated in primary dog kidney cells and further attenuated by mutation in NS3 gene	III pending
TV003/TV005	NIAID and Butantan Institute	Live Attenuated	Wildtype strains with genetic mutations	III pending
TDENV PIV	GSK and WRAIR	Purified Inactivated	Formalin inactivated	I
V180	Merck	Recombinant Subunit	Wildtype premembrane and truncated envelope protein via expression in the Drosophila S2 cell expression system	I
D1ME100	NMRC	DNA	Premembrane and envelope proteins of DENV1 are expressed under control of the human cytomegalovirus promoter/enhancer of the plasmid vector VR1012	I

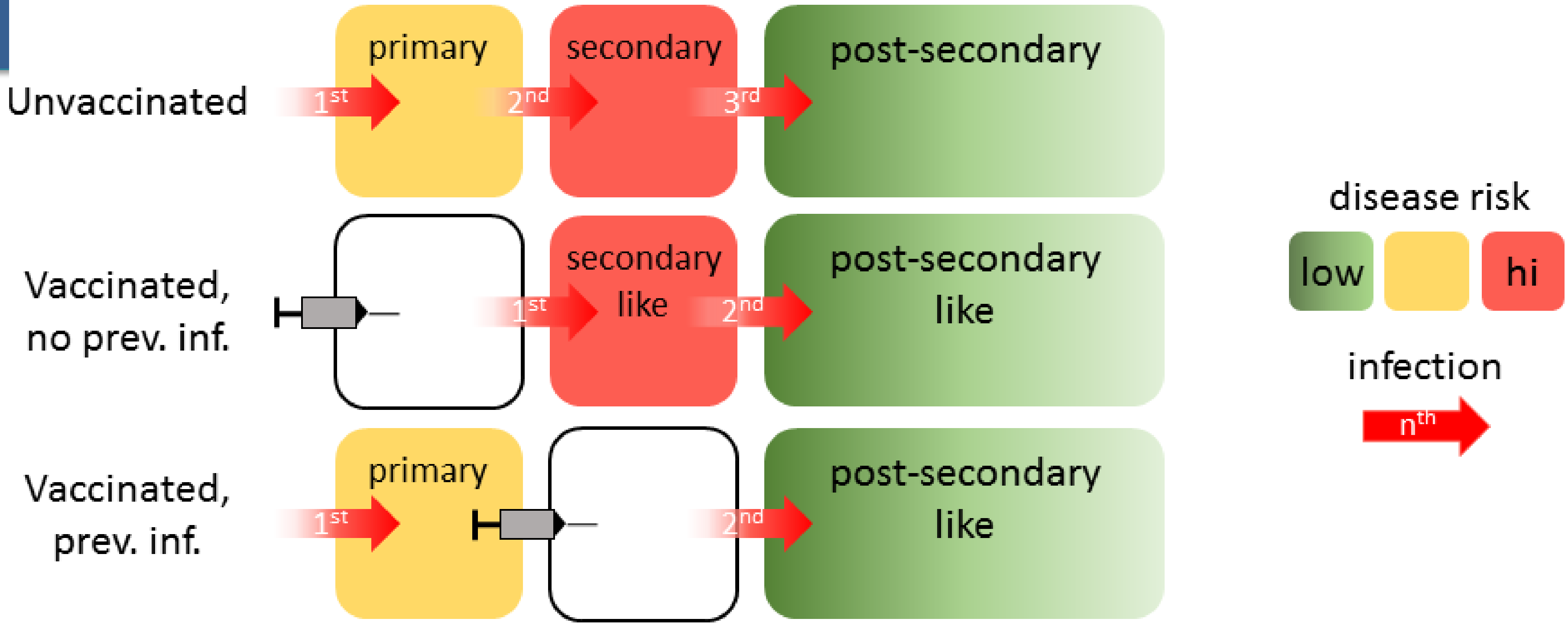
Dengvaxia assumptions:

- Vaccine replaces a non-specific natural infection
- Provides cross-immunity that wanes linearly over 2 years
- 3 doses, 6 months apart
- 9-year-old routine; catchup to 50

70% efficacious vaccine assumptions:

- Leaky protection, homogenous across serotypes and serostatus
- Durable
- 1 dose
- 2-year-old routine; catchup for 2+ years

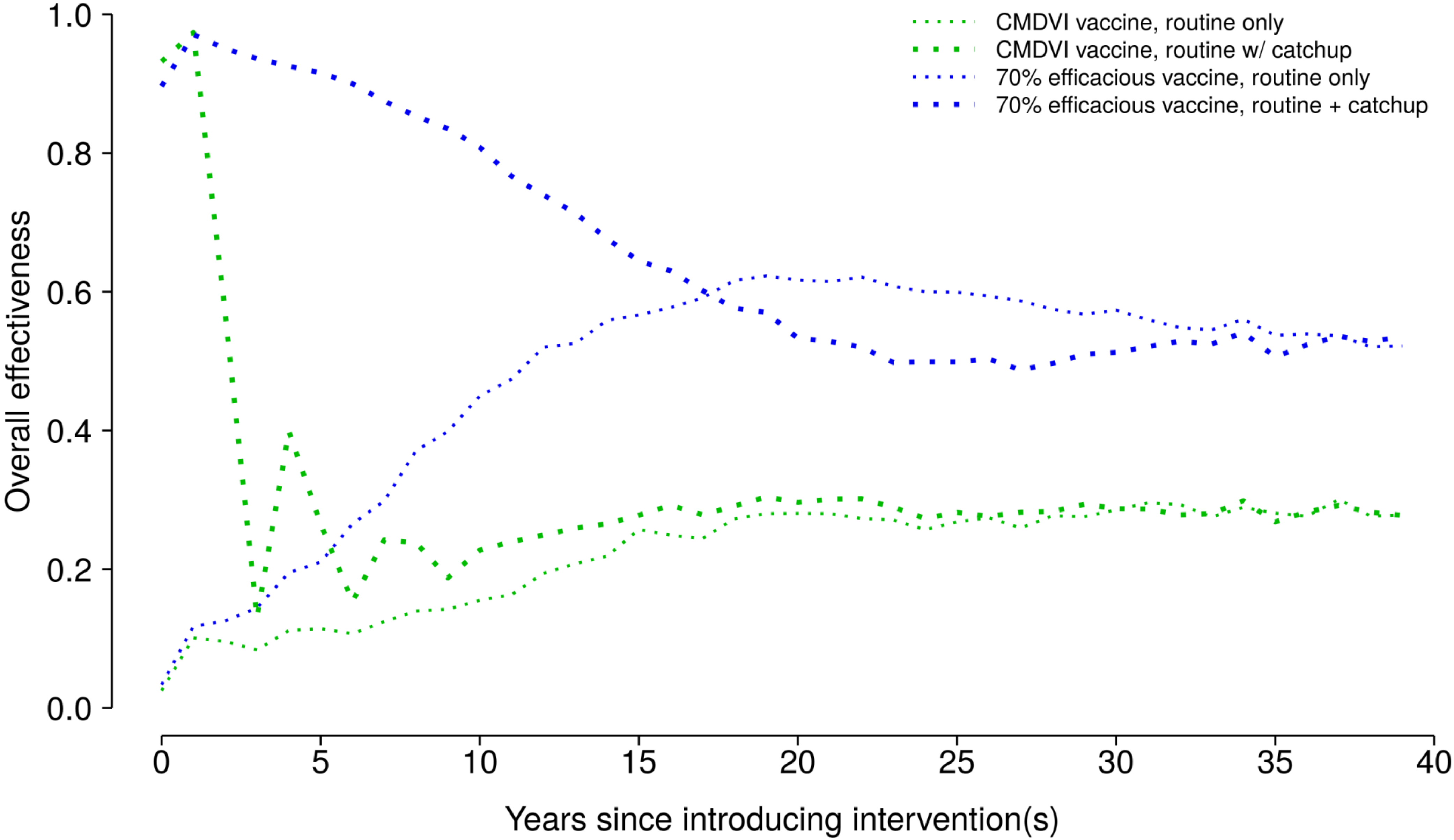
Explanatory hypothesis about vaccine action for Dengvaxia (CYD-TDV) by Sanofi Pasteur



Assumes that vaccination primes the immune system similarly to infection:

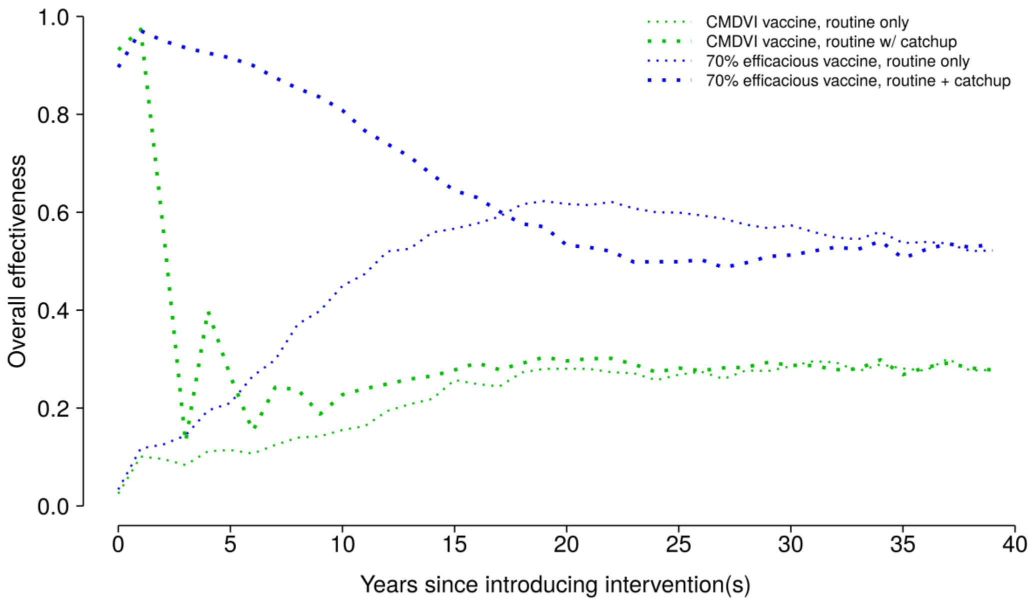
- Temporary high degree of cross-immunity in at least seronegative recipients
- Seronegatives primed to secondary-like (more severe) infection once cross-immunity wanes
- Seropositives boosted so that future infections are tertiary-like (less severe)

Vaccination only

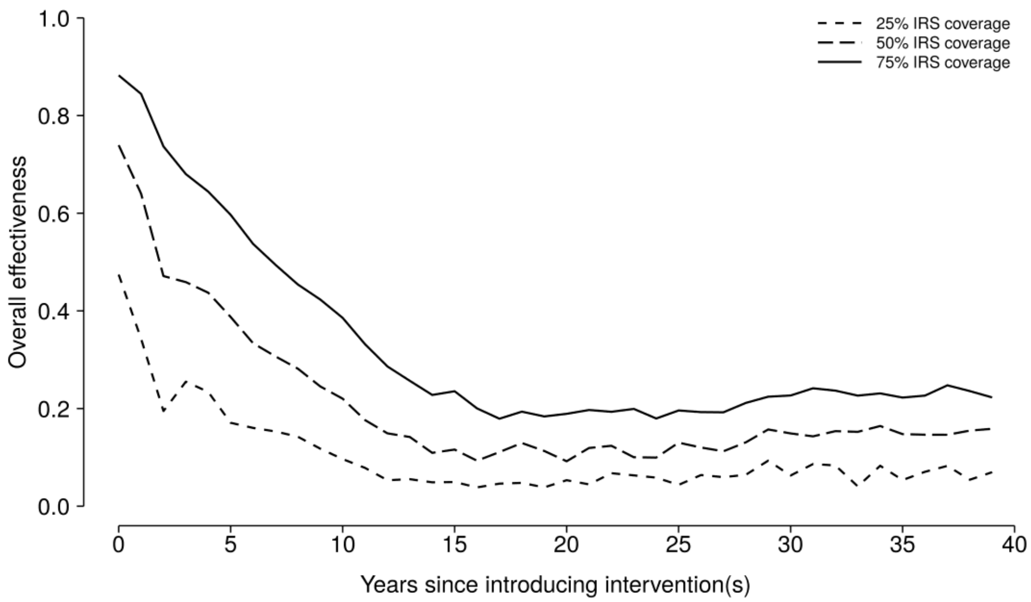


CMDVI – Comparative modeling of dengue vaccine impact (Dengvaxia)

Vaccine only

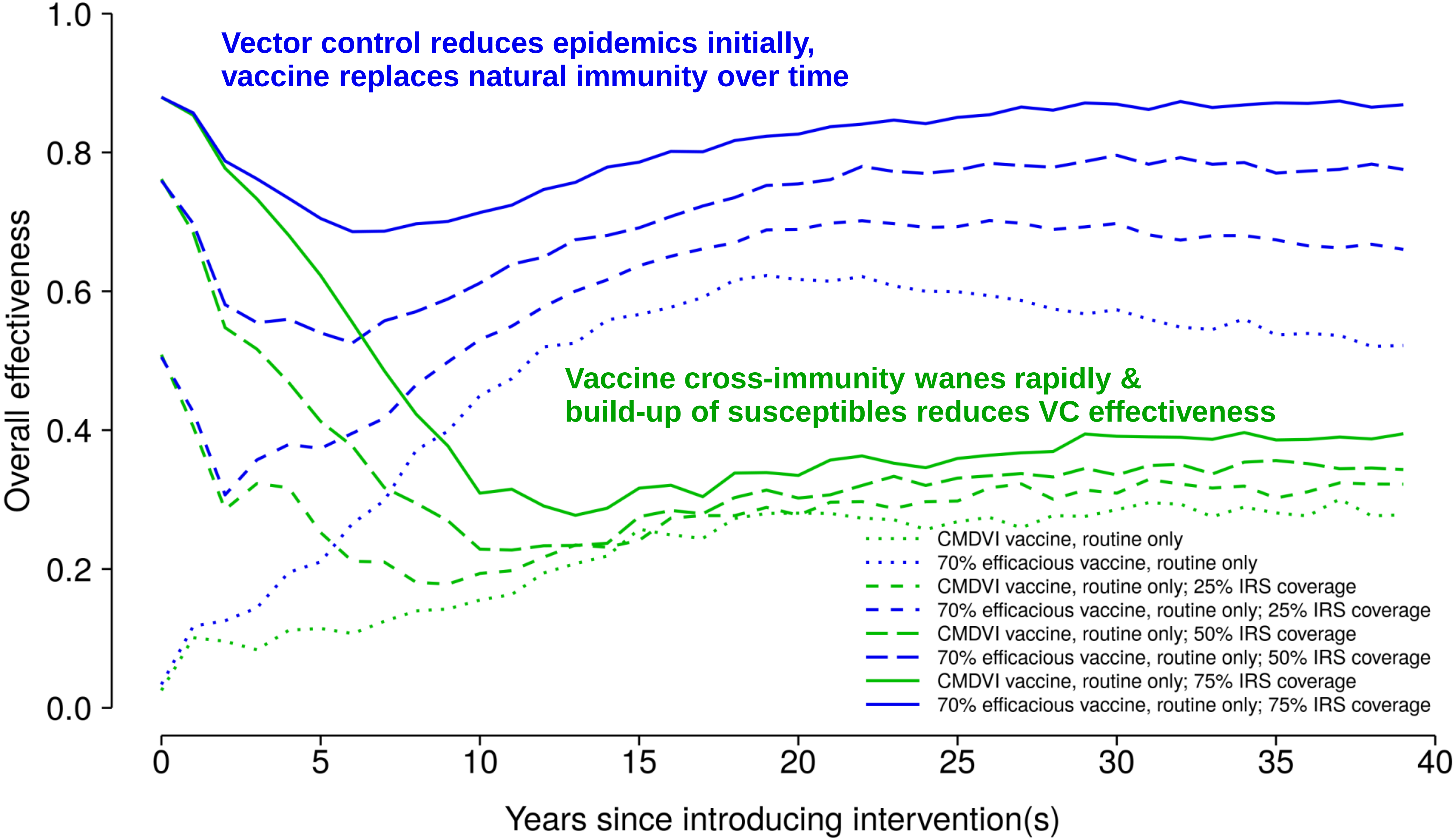


Vector control only

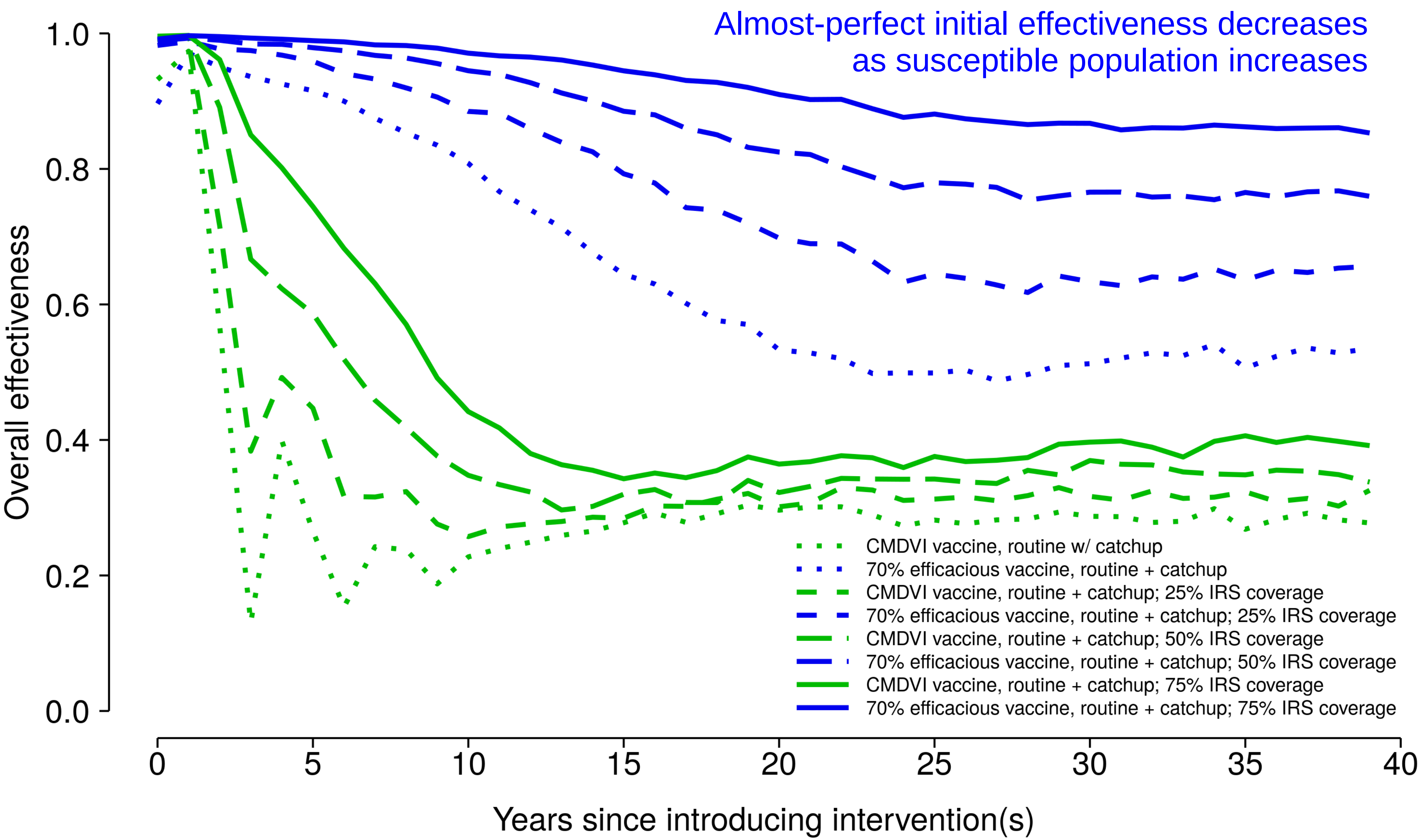


- Catchup vaccination and vector control both provide early effectiveness that decreases as susceptible population increases
- Effectiveness of routine vaccination by itself builds over ~20 years, but plateaus before reaching high effectiveness

Routine vaccination + new vector control



Routine vaccination w/ catchup + new vector control



Conclusions Vaccines + Vector Control

- The only way to achieve high effectiveness, i.e., 80%, is to combine an efficacious vaccine with at least 50% IRS
  - With a less efficacious vaccine about 40% effectiveness is possible
- Combing routine vaccination with modest vector control = routine vaccination with catchup

WHO Sanofi vaccine modelling exercise

Members of CMDVI (in authorship order, with joint first authors starred): Stefan Flasche*, Mark Jit*, Isabel Rodríguez-Barraquer*, Laurent Coudeville*, Mario Recker*, Katia Koelle*, George Milne*, Tom Hladish*, Alex Perkins*, Derek Cummings, Ilaria Dorigatti, Daniel Laydon, Guido España, Joel Kelso, Ira Longini, Jose Lourenco, Carl A.B. Pearson, Robert C. Reiner, Luis Mier-y-Terán-Romero, Kirsten Vannice, Neil Ferguson

WHO: Raymond Hutubessy and Joachim Hombach

Members of the CMDVI economics subgroup: Celina Martelli, Dagna Constenla, Donald Shepard, Vittal Mogasale, Yot Teerawattanon (+literature review support from Sarah Cox)

Members of the SAGE dengue working group, especially Maria Novaes, Stephen Thomas and Terry Nolan

Members of IVIR-AC, especially Philippe Beutels

Results of this work are published in Flasche, et al.: The long-term safety, public health impact, and cost-effectiveness of routine vaccination with a recombinant, live-attenuated dengue vaccine (Dengvaxia): A model comparison study. *PLoS Medicine.* http://dx.doi.org/10.1371/journal.pmed.1002181 (2016).

The Strategic Advisory Group of Experts (SAGE) on immunization met on 12 – 14, April 2016 in Geneva, Switzerland

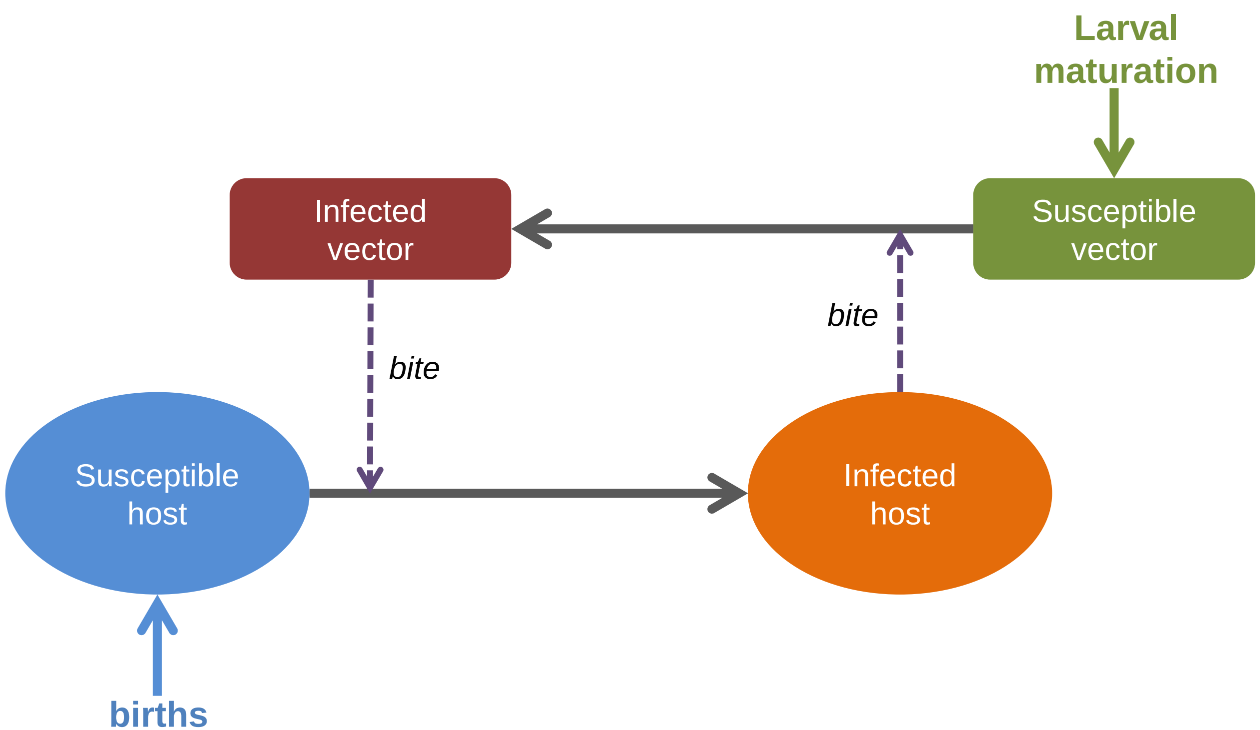
One vaccine under consideration was Denvaxia, including evidence from 7 mathematical models that were independently constructed and implemented, but with some degree of coordination

Models and groups

Group	Model type	Fitted to trial	Vectors	Trans ∝ symptoms	Demography
Sanofi Pasteur	Deterministic non-spatial	Yes (both, pre LTFU)	Yes	Yes	Brazil
Johns Hopkins + Univ Florida	Deterministic non-spatial	Yes (both)	Yes	Yes	Brazil
Imperial College London	Deterministic non-spatial	Yes (both)	Yes	Yes	Brazil
Duke Univ	Deterministic non-spatial	Calibrated	No	No	Brazil
Univ Florida	Stochastic spatial	No	Yes	Yes	Mexico
Univ Western Australia	Stochastic spatial	No	Yes	No	Thailand
Notre Dame Univ	Stochastic spatial	No	Yes	Yes	Peru
Exeter+Oxford Univs	Stochastic spatial	Yes (CYD14)	Yes	No	Generic (65 y mean lifespan)

Common features

- 4 serotypes – homologous and heterologous immunity
- Vectors (all but 1 model)
- Stratified by host age
- Flexible representations of immunity, disease, seasonality
- Standardised outputs for this exercise



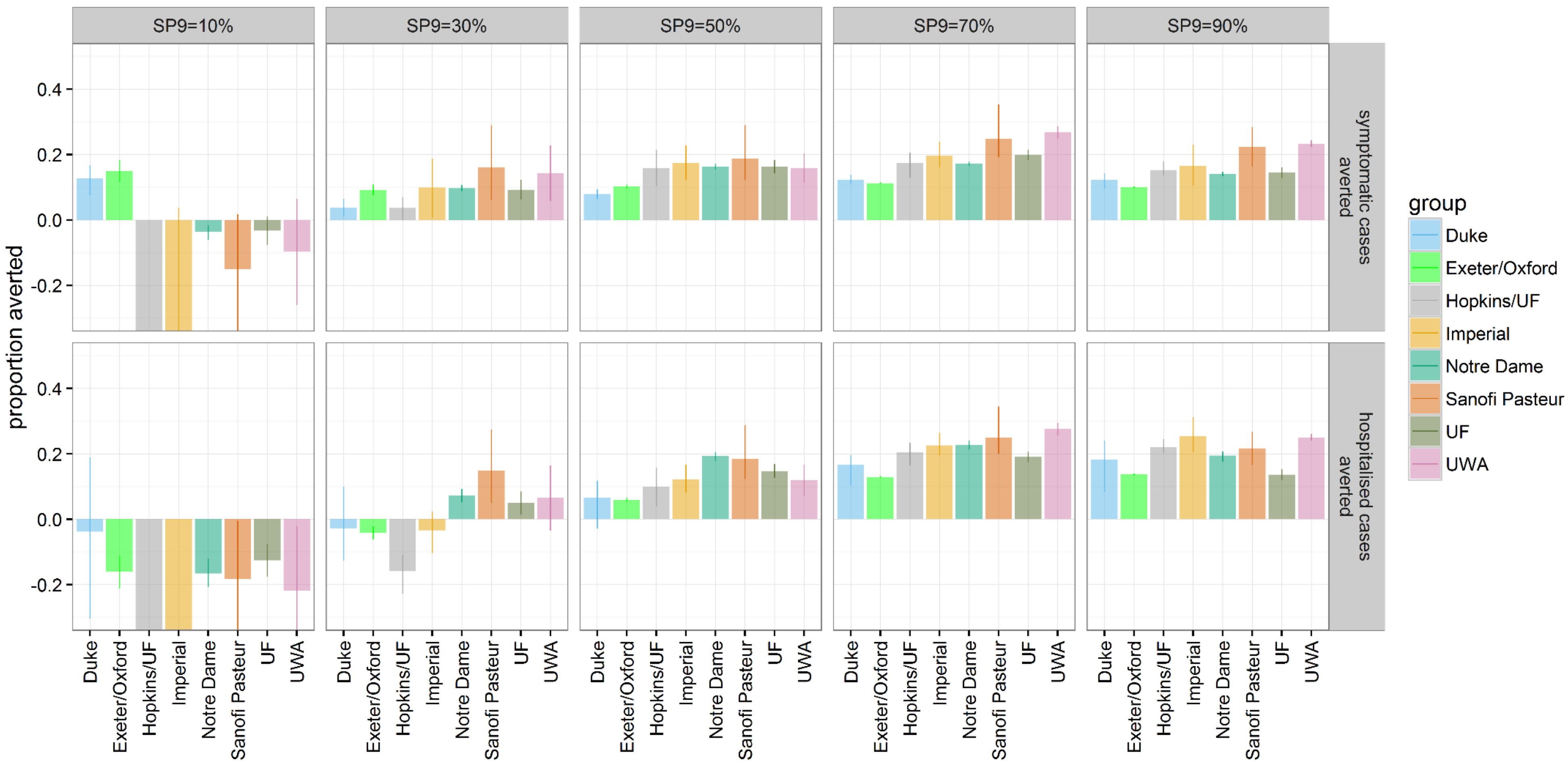
Scenarios to model

These scenarios were chosen in discussion with SAGE dengue WG as those which were most useful for SAGE decision making

- Base case scenario: routine vaccination of 9 year olds at 80% coverage with 3 doses per recipient
- Alternative scenarios
  - 50% coverage
  - Alternative ages of vaccination between 10-18 years
  - Catch-up campaign at 80% coverage of 10-17 years in the first year of vaccination
- Time horizon of 30 years.

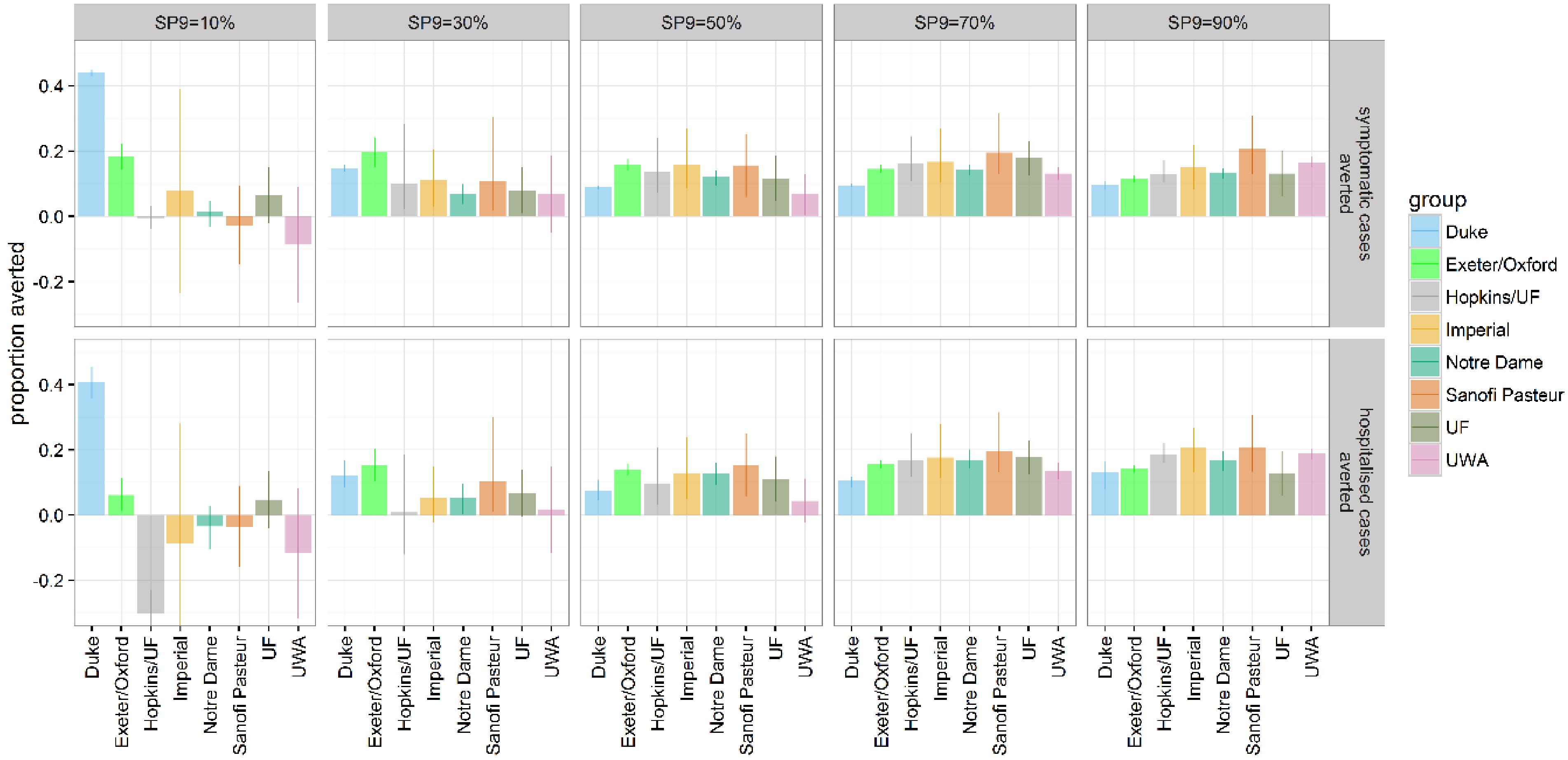
Reference scenario: cases averted (%) over 30 years

Routine vaccination at 9y with 80% coverage. All groups show negative impacts in SP9=10%; more mixed results for SP9=30% setting. For SP9=50% and above, no negative impacts at the population level predicted.



Reference scenario: cases averted (%) in 10 years

Magnitude of positive impact in 50-90% settings v similar to 30 year time horizon, but with a 10 year time horizon, only SP9=10% scenario still shows negative vaccine impact (SP9=30% now positive).



Population vs individual impact

- This vaccine has highly positive benefits for some recipients (seropositives)
- But may have negative impacts for recipients who seronegative when vaccinated, at least if evaluated over a 10-30 year timescale
- Risk over decades (or lifetime) hard to assess – e.g. none of the current models account for variability in exposure within populations
- Potential negative impact has not been proven – but is perhaps the most plausible interpretation of the CYD14 hospital phase data
- Only vaccinating 9+ year olds reduces the likelihood that a recipient will be seronegative, but not necessarily the impact if they are
- In theory, the subset with potentially negative outcomes could be identified
- More than most vaccines, this poses challenges for decision-makers (and individuals) in weighing up population vs individual impacts

SAGE recommendations in a nutshell

1. SAGE recommended countries consider introduction of CYD--TDV only in geographic settings (national or subnational) with high endemicity, as indicated by seroprevalence of approximately 70% or greater in the age group targeted for vaccination or other suitable epidemiologic markers.
2. Dengue vaccine introduction should be a part of a comprehensive dengue control strategy together with a communication strategy, well--executed and sustained vector control, the best evidence--based clinical care for all patients with dengue, and robust dengue surveillance.
3. Decisions about introduction require careful assessment at the country level, including consideration of local priorities, national and subnational dengue epidemiology, predicted impact and cost--effectiveness with country--specific hospitalization rates and costs, affordability and budget impact.

http://www.who.int/immunization/sage/meetings/2016/april/SAGE_April_2016_Meeting_Web_summary.pdf?ua=1

SAGE recommendations (full statement)

SAGE considered the results of a comparative mathematical modelling evaluation of the potential public health impact of CYD--TDV introduction done by 7 different groups. There was agreement across the different models that in high transmission settings, the introduction of routine CYD--TDV vaccination in early adolescence could reduce dengue hospitalizations by 10--30% over the period of 30 years, representing a substantial public health benefit. The modelling predicted that the vaccine would be less beneficial in low transmission settings, due to the higher proportion of seronegative individuals, where the vaccine has less protective effect.

SAGE recommended countries consider introduction of CYD--TDV only in geographic settings (national or subnational) with high endemicity, as indicated by seroprevalence of approximately 70% or greater in the age group targeted for vaccination or other suitable epidemiologic markers. The vaccine is not recommended when seroprevalence is below 50%. Dengue vaccine introduction should be a part of a comprehensive dengue control strategy together with a communication strategy, well--executed and sustained vector control, the best evidence--based clinical care for all patients with dengue, and robust dengue surveillance.

Decisions about introduction require careful assessment at the country level, including consideration of local priorities, national and subnational dengue epidemiology, predicted impact and cost--effectiveness with country--specific hospitalization rates and costs, affordability and budget impact.

http://www.who.int/immunization/sage/meetings/2016/april/SAGE_April_2016_Meeting_Web_summary.pdf?ua=1

Thank You