Lecture 4: **Stochastic models for arboviruses**

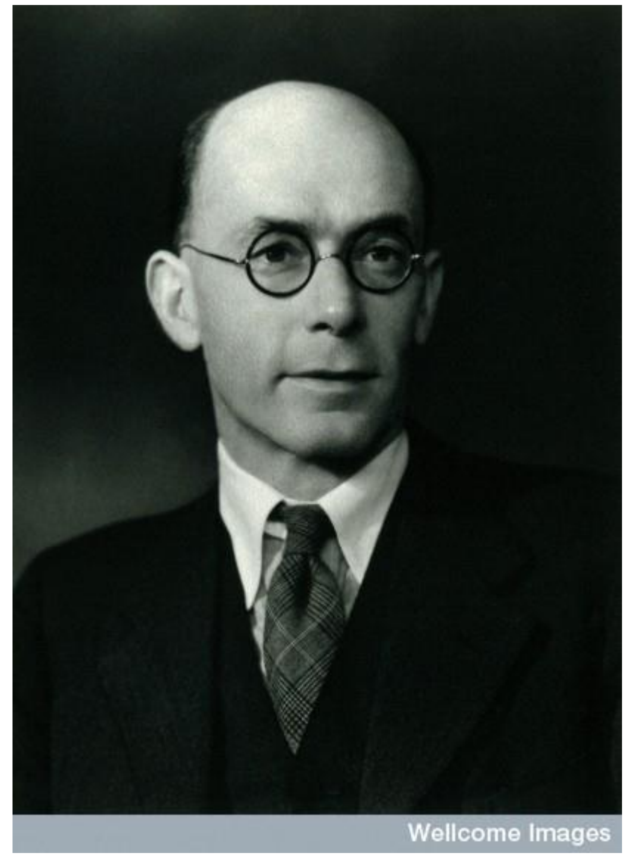
Ira Longini

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.

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

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

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hum inf
by a mos

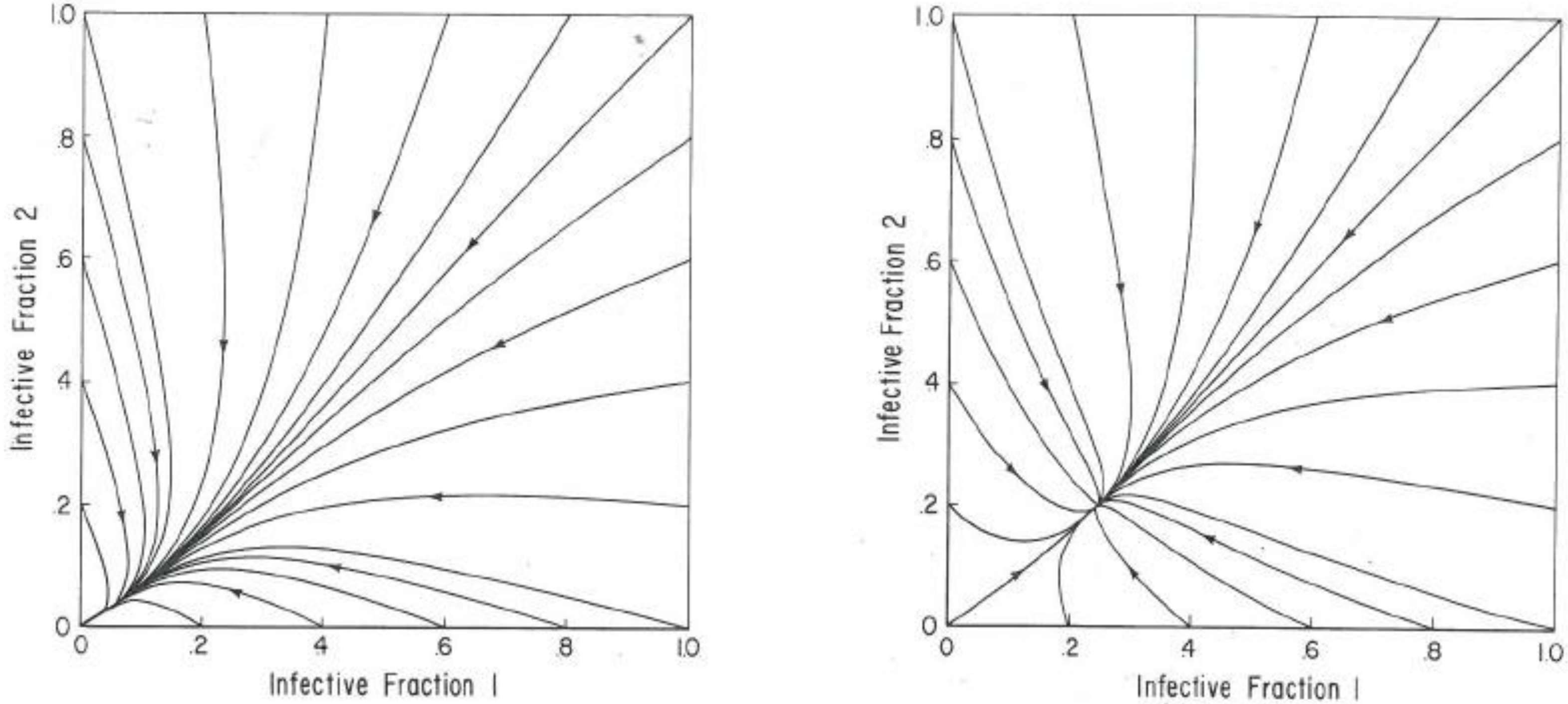
mosqitoes inf
by a hum

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_1I_2 - plane phase portraits*



$R_0 \leq 1$ $\qquad$ $R_0 > 1$

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

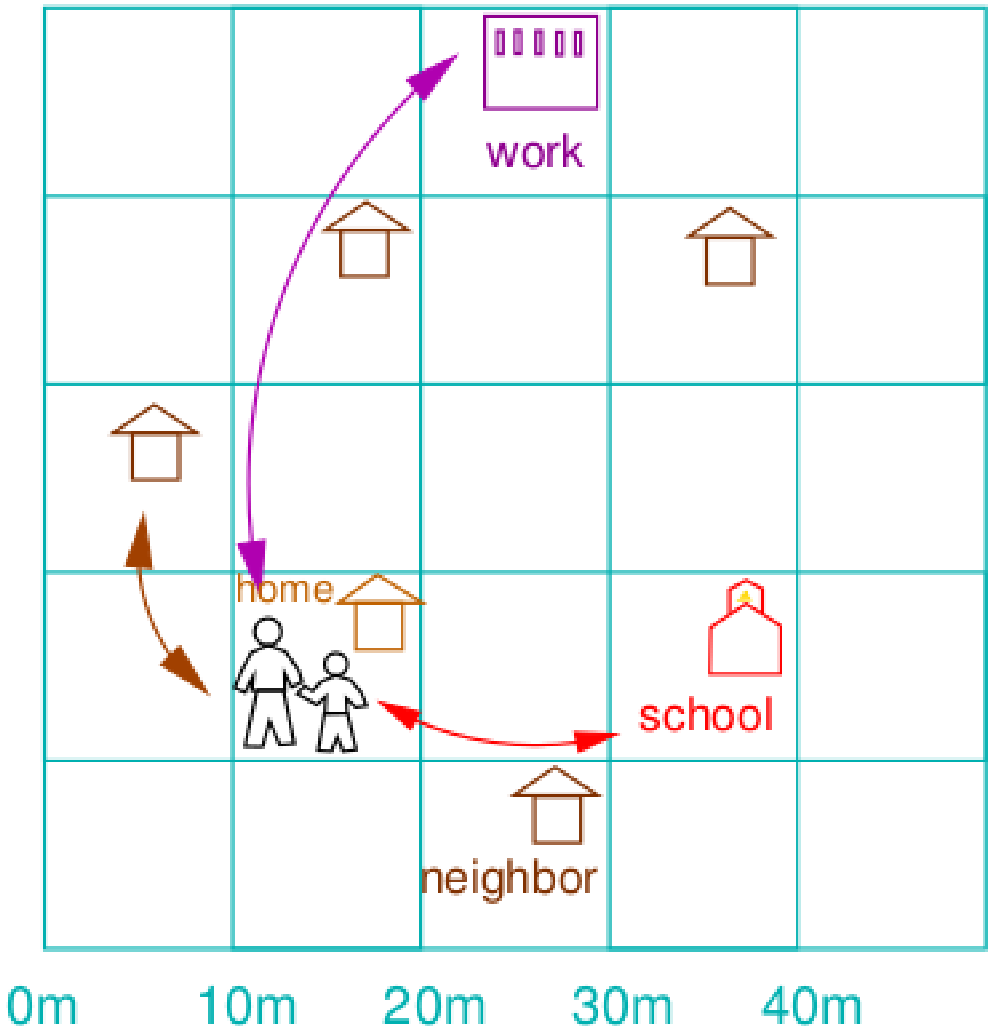
Basic Reproductive Number

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

- 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*.

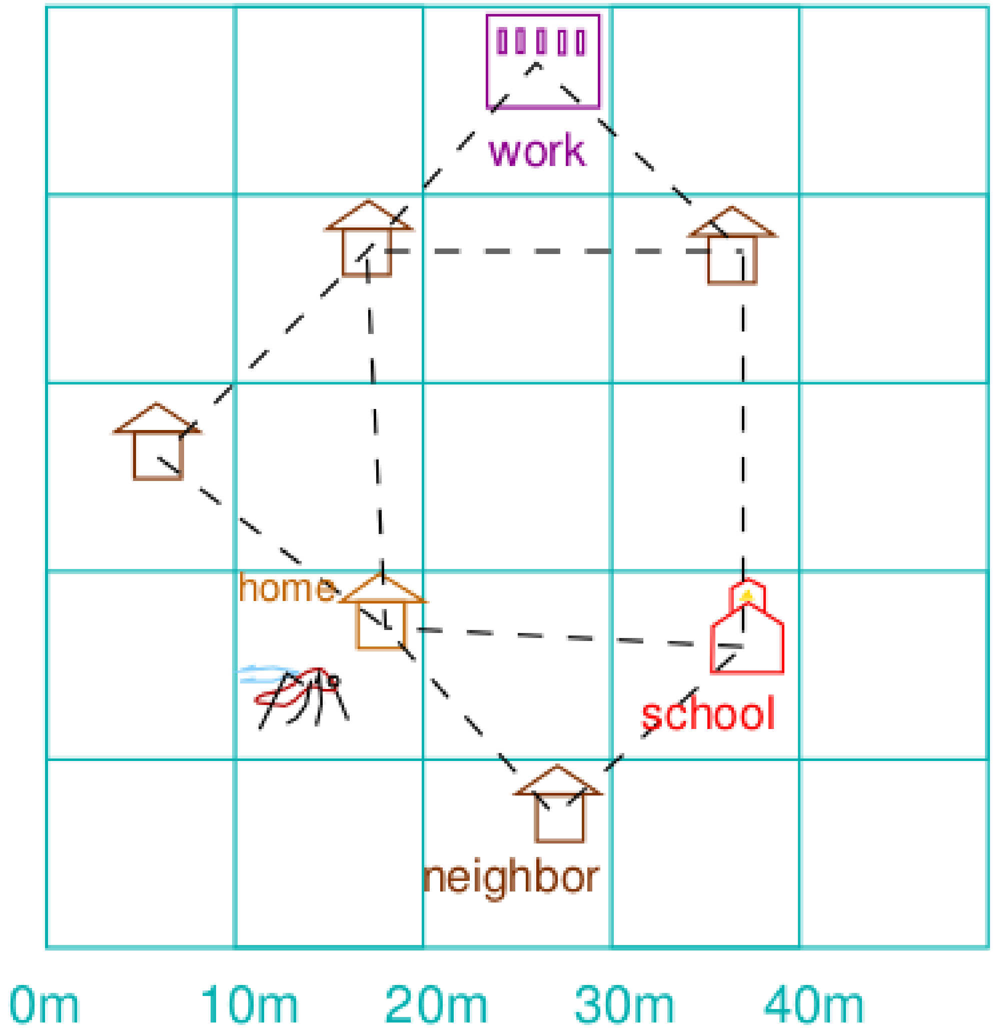
Stochastic models

Model: human movement



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

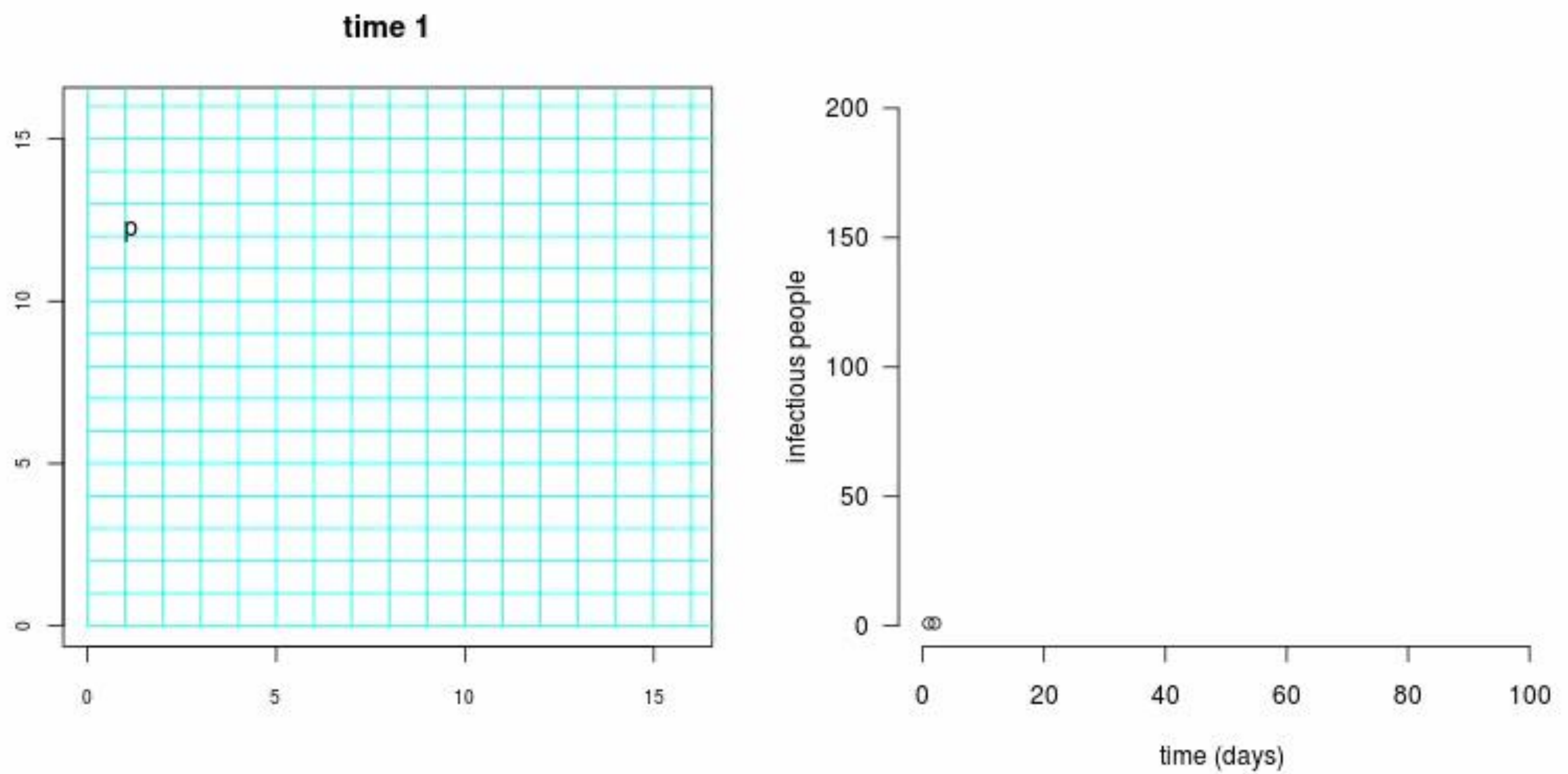
Model: mosquito movement



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

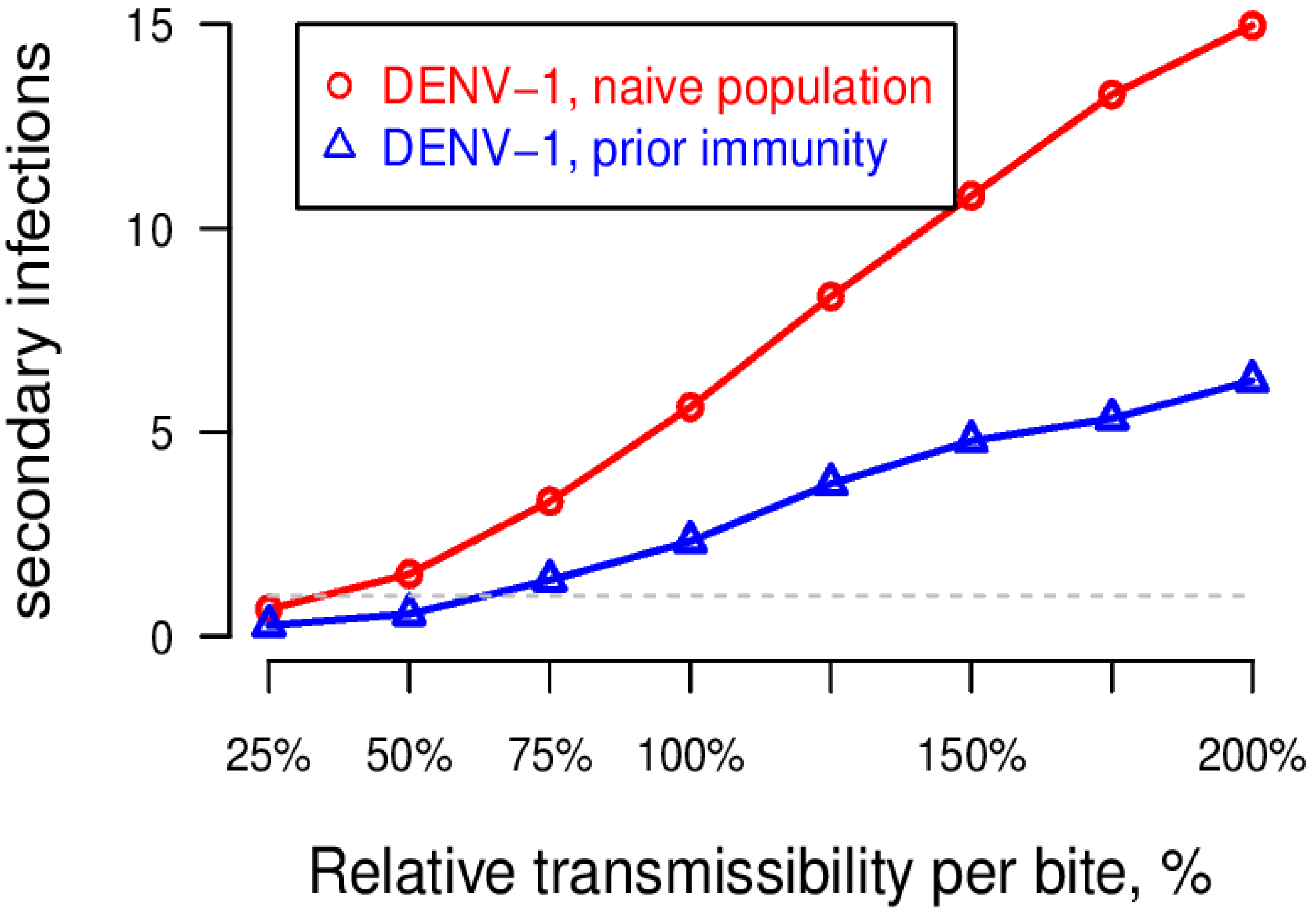
Simplified Model

- 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

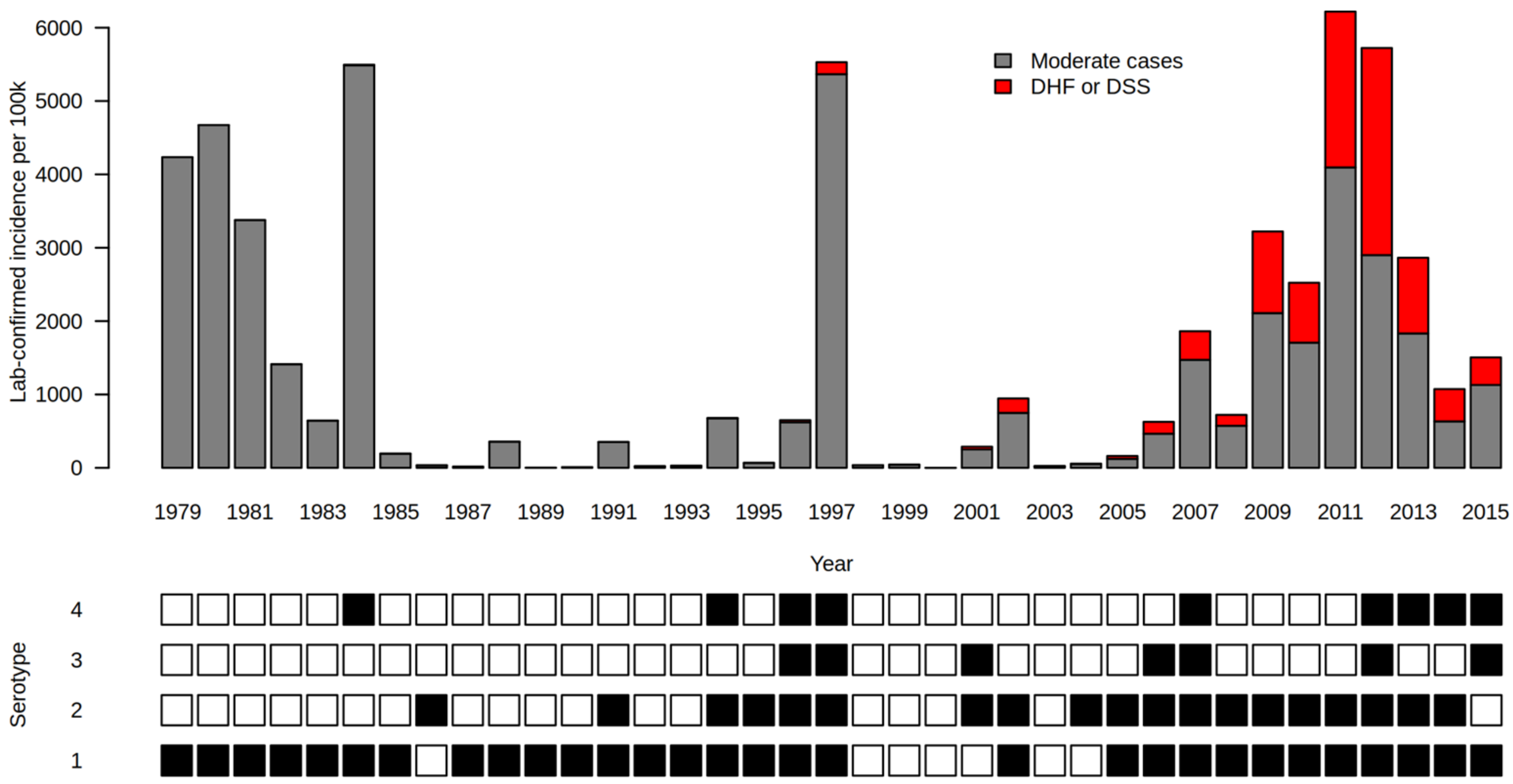
Modeled relationship between mosquito biting rate and R_0 and R



Current dengue intervention use and impact modeling

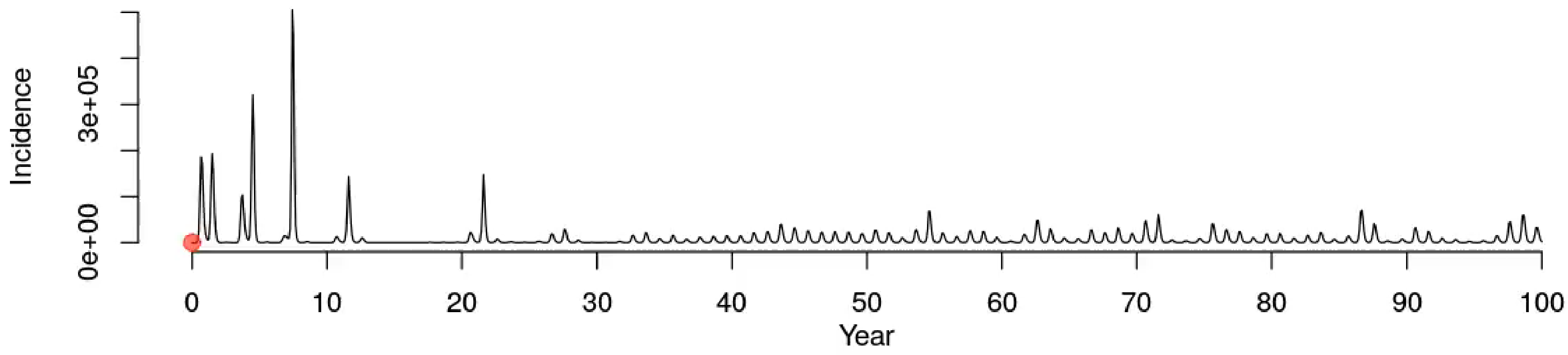
- Vaccine effectiveness depends on
  - Force of infection of each serotype
  - Mix of serotypes circulating
  - Level of immunity in the population
  - Age structure of the population
    - Change immunity patterns
    - Level of exposure
- Vector control
  - Need to establish the relationship between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

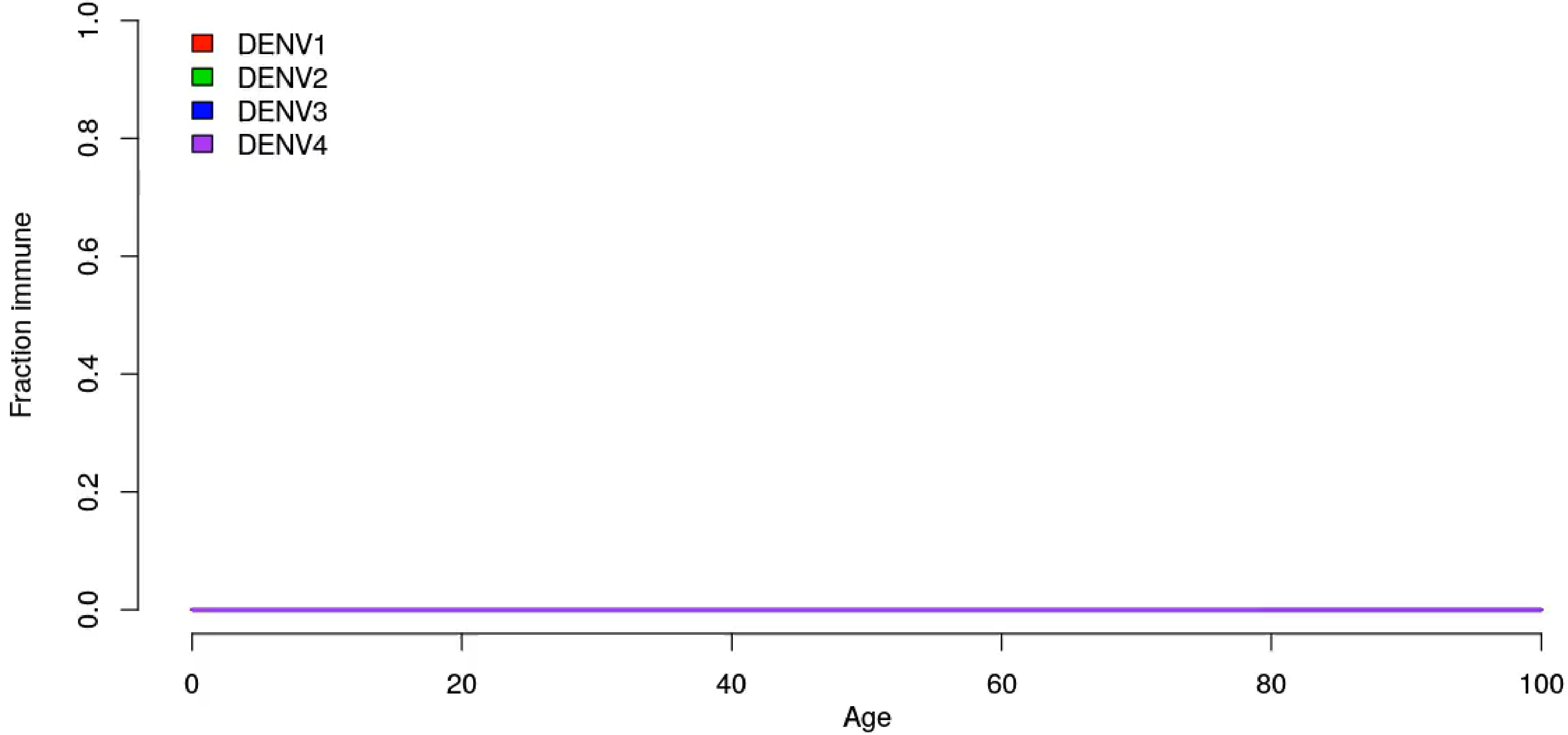
Dengue in Yucatan, 1979-2015



Data from Hladish *et al*. PLOS NTDs (2018)

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]

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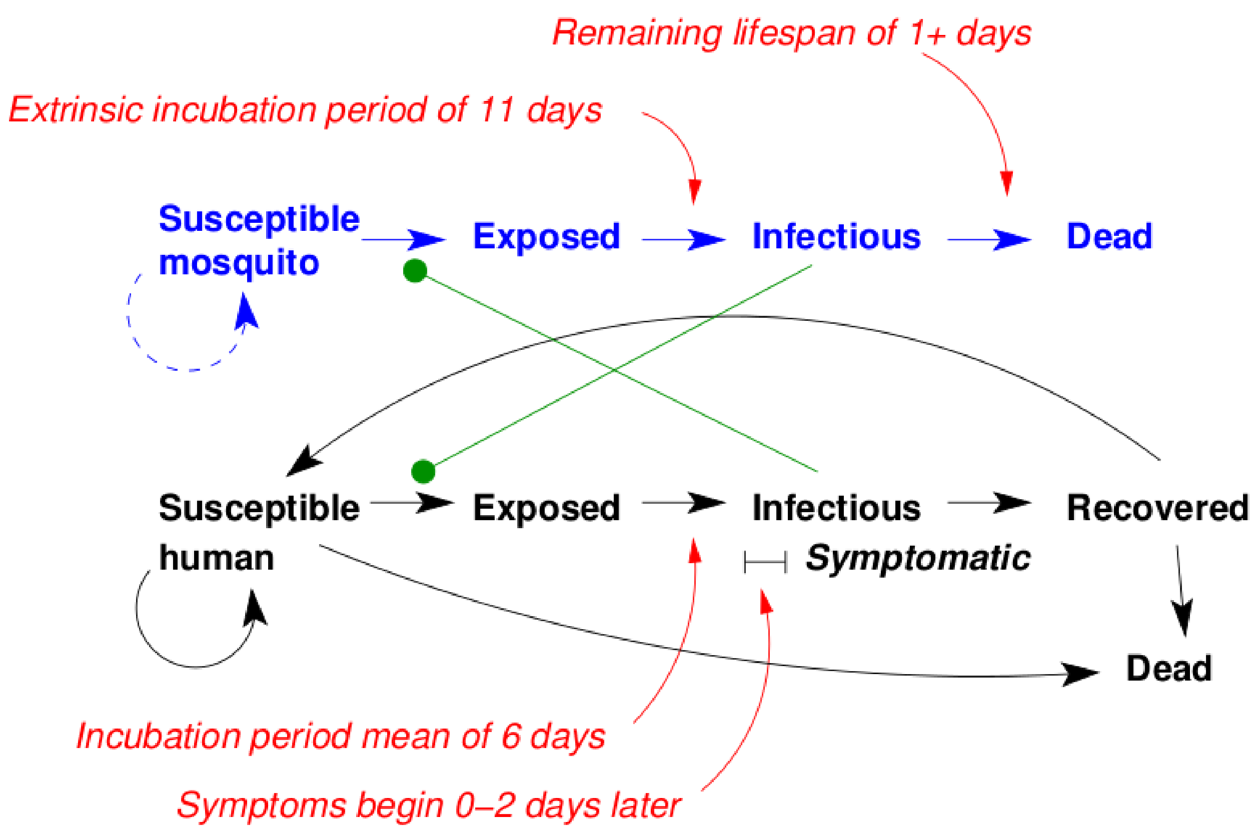
Citation: Hladish TJ, Pearson CAB, Chao DL, Rojas DP, Recchia GL, Gómez-Dantés H, et al. (2016) Projected Impact of Dengue Vaccination in Yucatán, Mexico. PLoS Negl Trop Dis 10(5): e0004661. doi:10.1371/journal.pntd.0004661

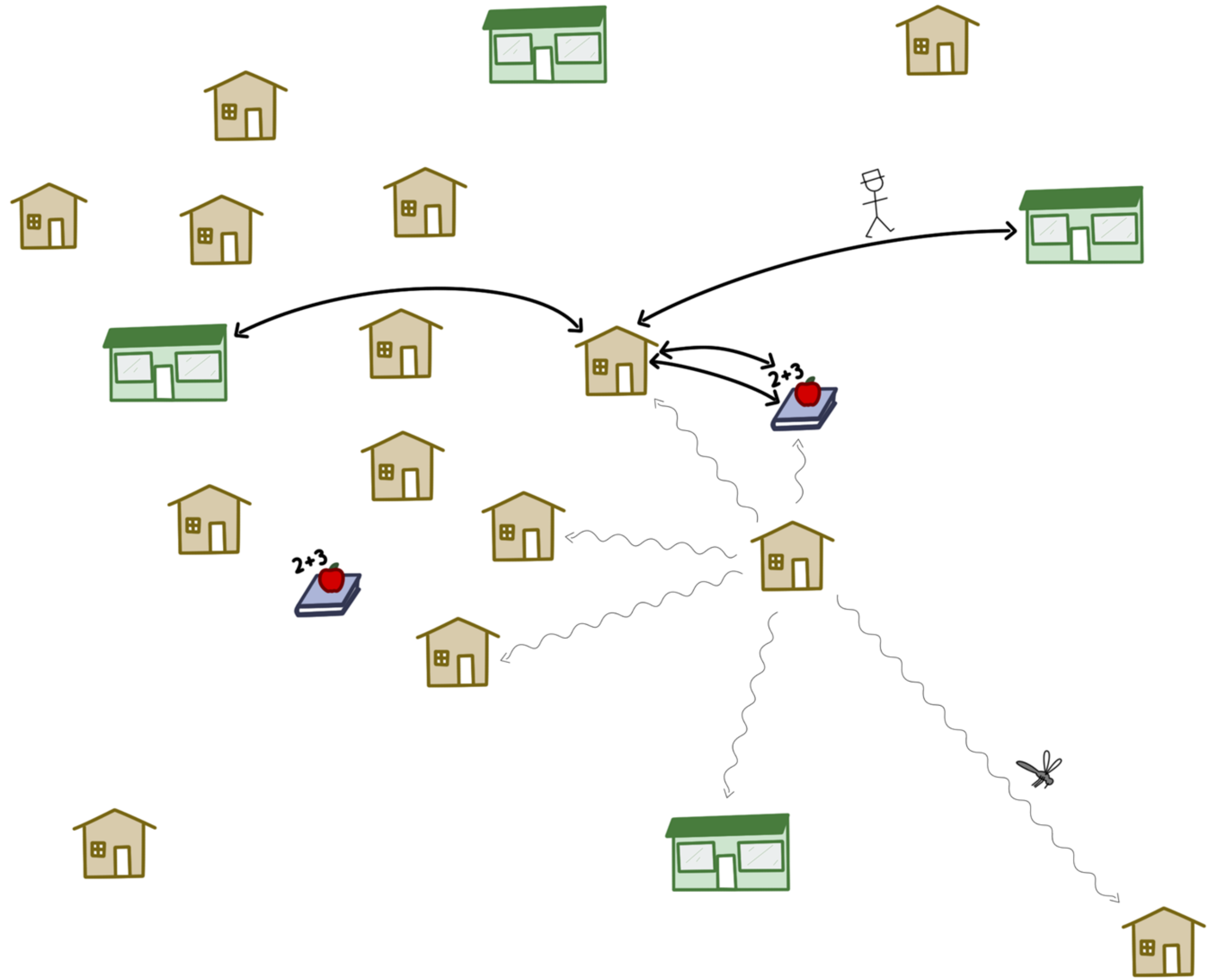
Abstract

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

Dengue model overview



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

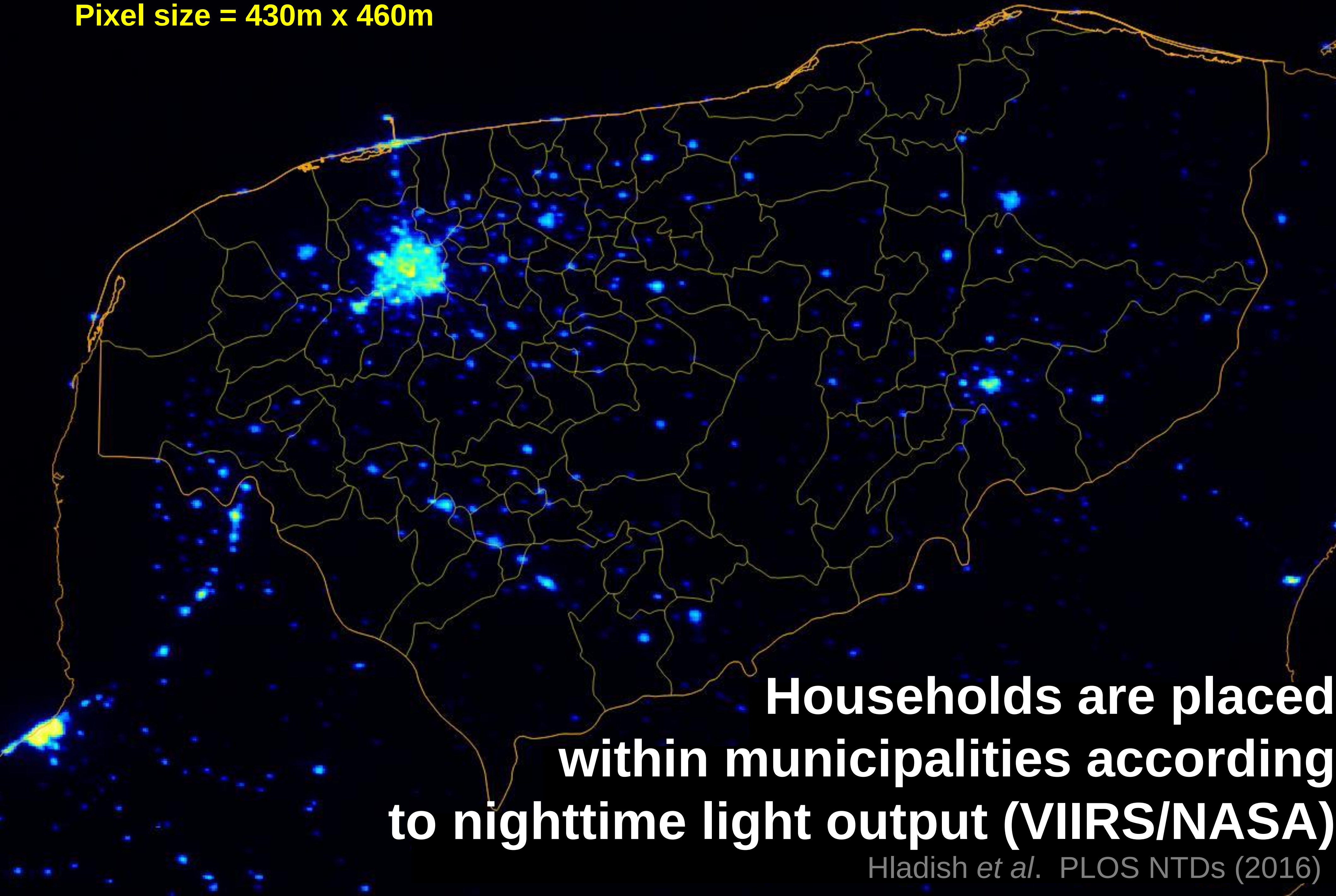
– 376k Households (5% sample, municipality)

– 96k Workplaces (size, postal code)

– 3.4k Schools (postal code)

Hladish *et al*. PLOS NTDs (2016)

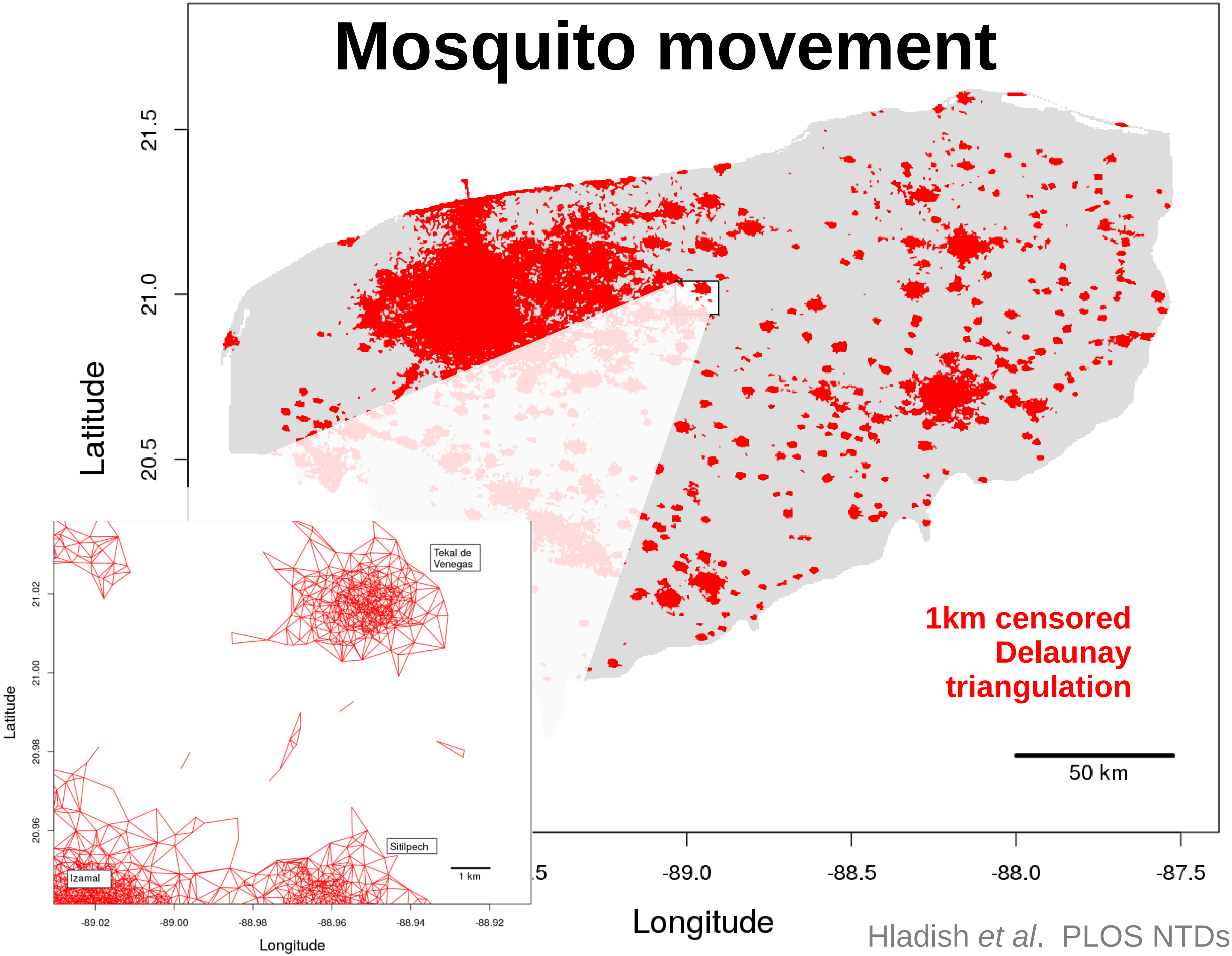
Pixel size = 430m x 460m



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

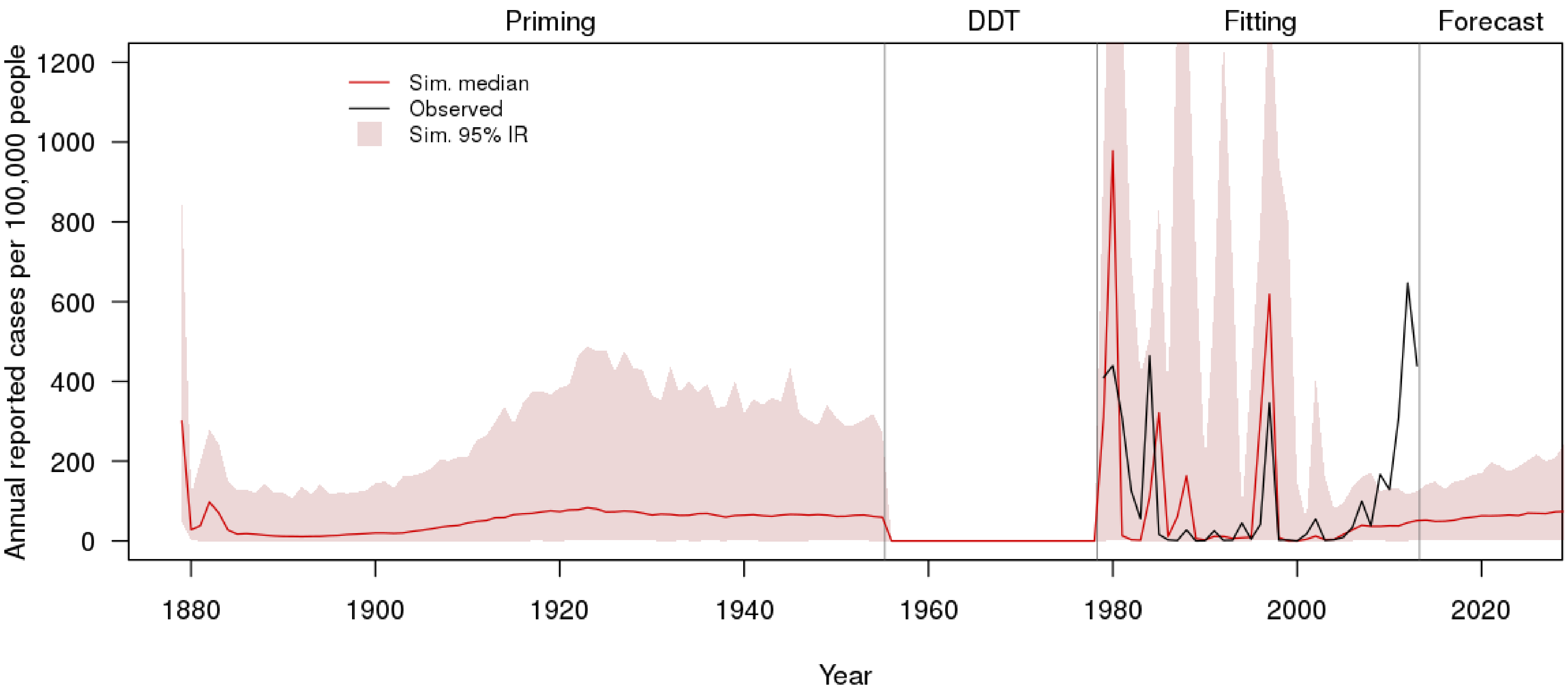
Hladish *et al*. PLOS NTDs (2016)

Mosquito movement



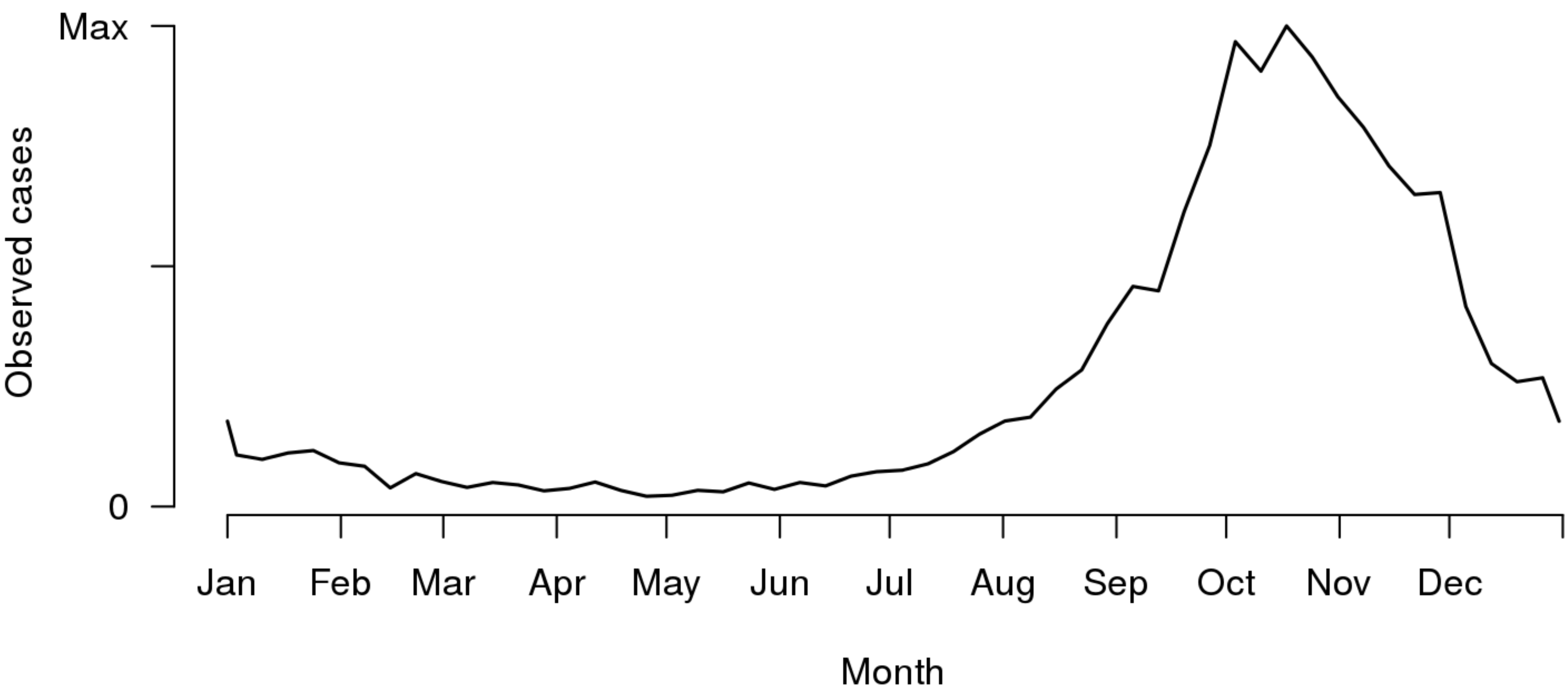
Hladish *et al*. PLOS NTDs (2016)

Reconstruct the past, forecast the future



Hladish *et al*. PLOS NTDs (2016)

Observed seasonality (1995-2011)



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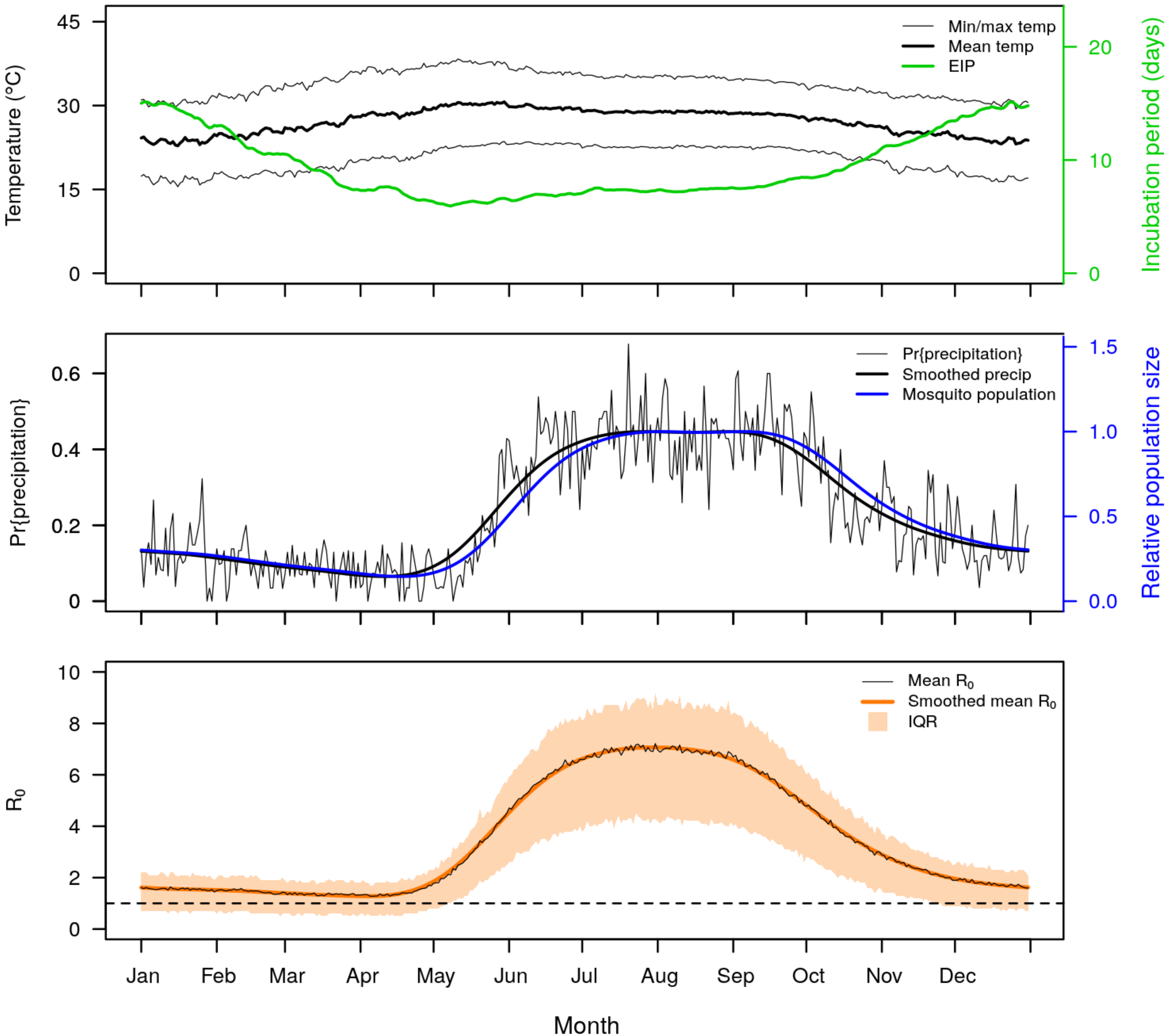
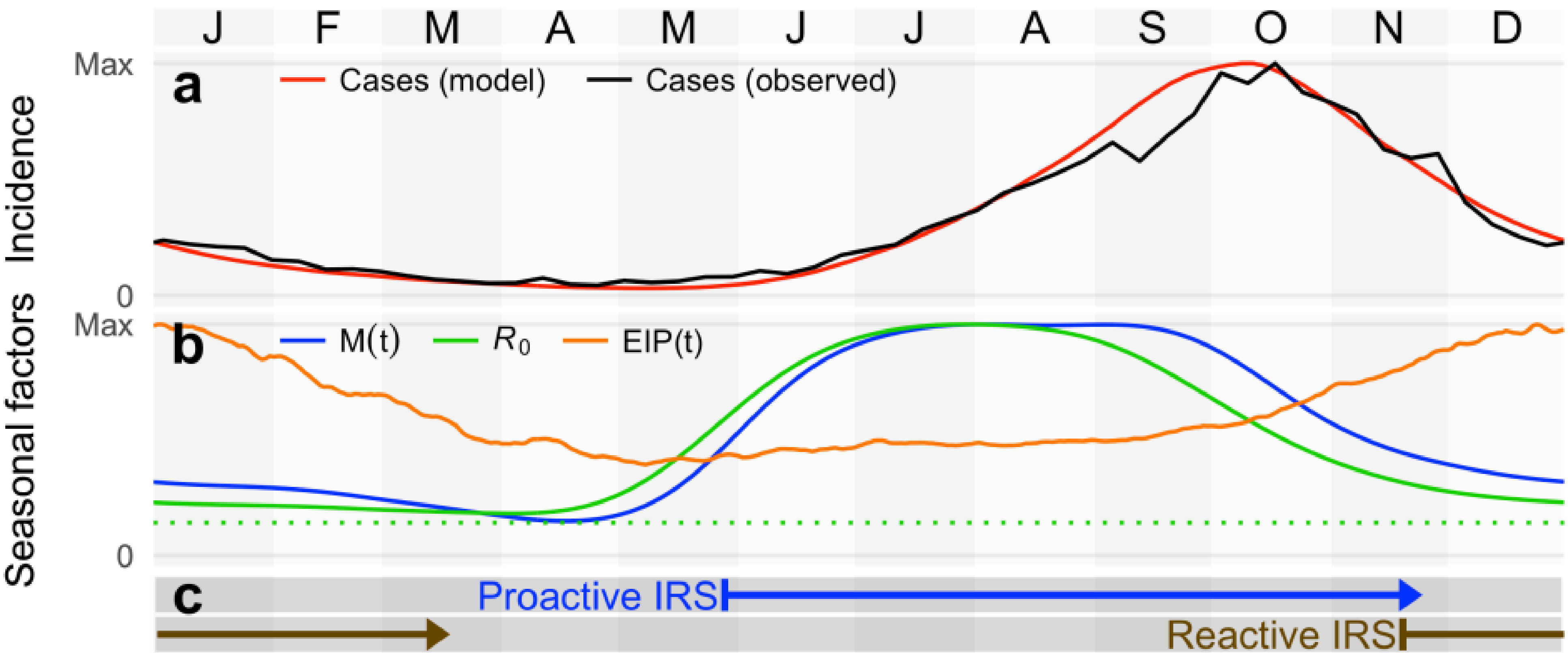


45
30
15
0
Temperature (°C)
Min/max temp
Mean temp
EIP
20
10
0
Incubation period (days)
0.6
0.4
0.2
0
Pr{precipitation}
Pr{precipitation}
Smoothed precip
Mosquito population
1.5
1.0
0.5
0.0
Relative population size
10
8
6
4
2
0
R_0
Mean R_0
Smoothed mean R_0
IQR
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
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: Forecasting the effectiveness of indoor residual spraying for reducing dengue burden. *PLoS Neglected Tropical Diseases* Published: June 25, 2018 https://doi.org/10.1371/journal.pntd.0006570 PMCID: PMC6042783

Indoor residual spraying*

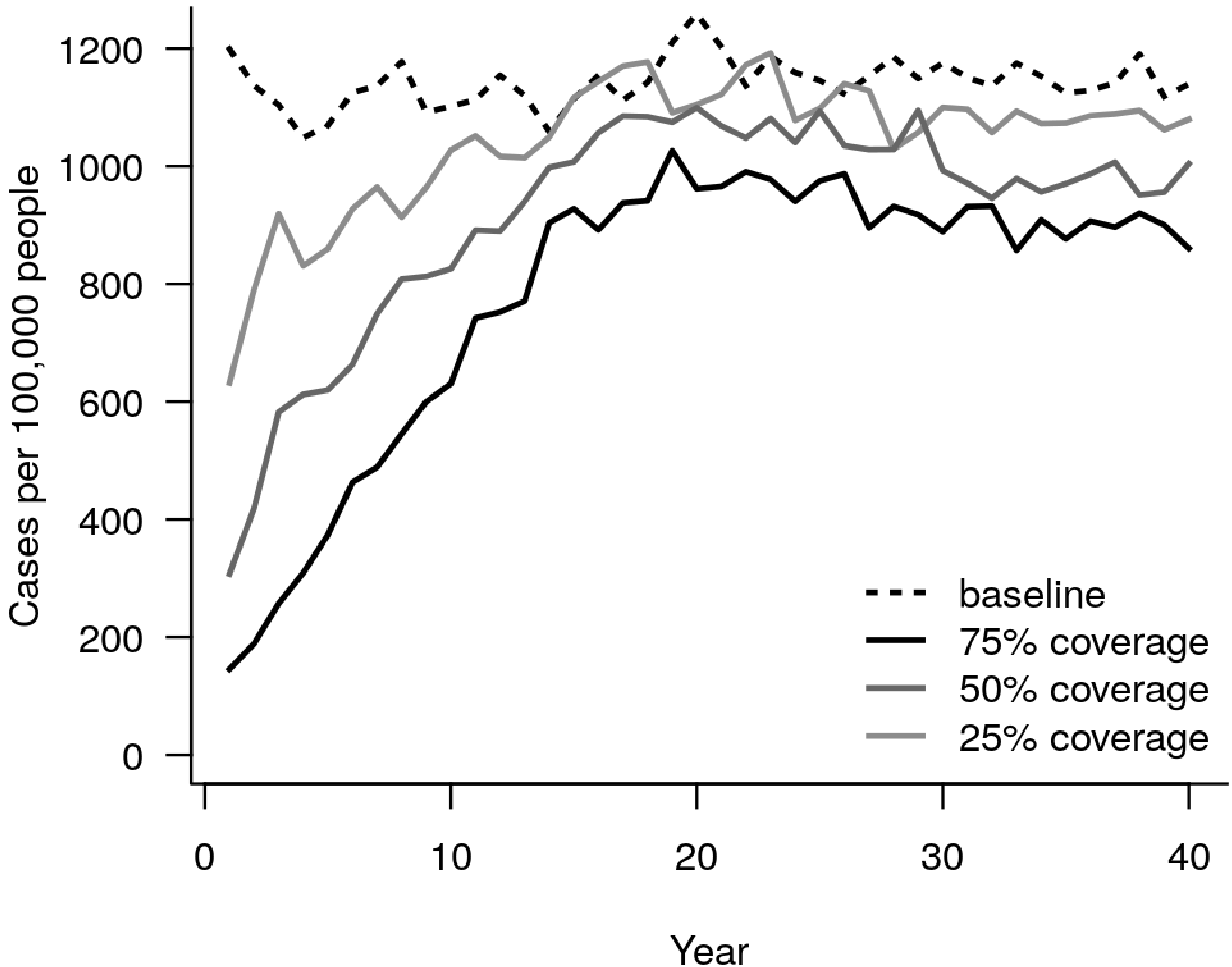
- Coverage: Treat 25/50/75% of houses per year
- Efficacy: 80% reduction in equilibrium pop size in treated houses
    - Corresponds to 13% daily mortality due to IRS
- Treatment lasts 90 days

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)

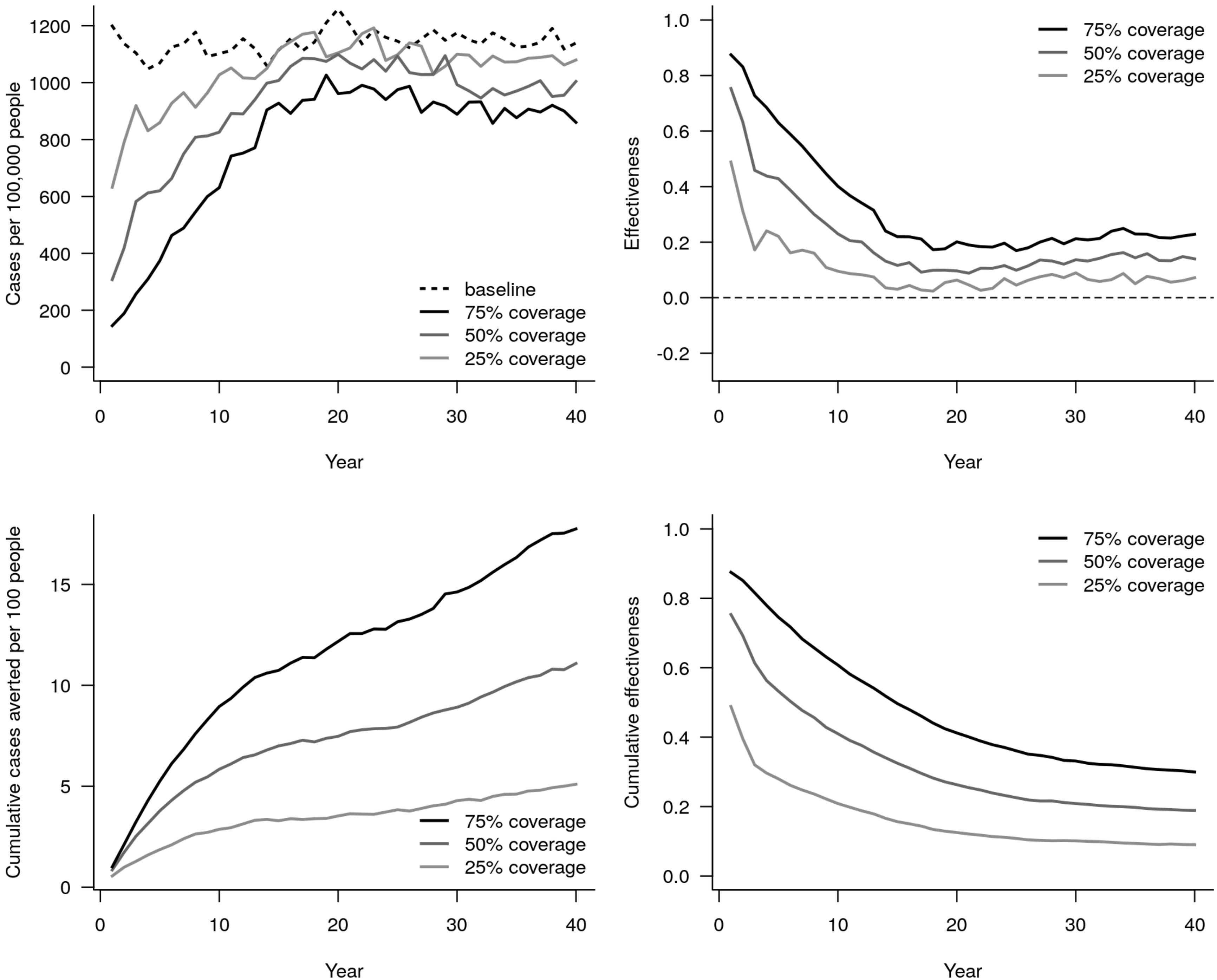
Simulated impact of IRS (90-day campaign, 90-day durability, late May start)



Overall Effectiveness

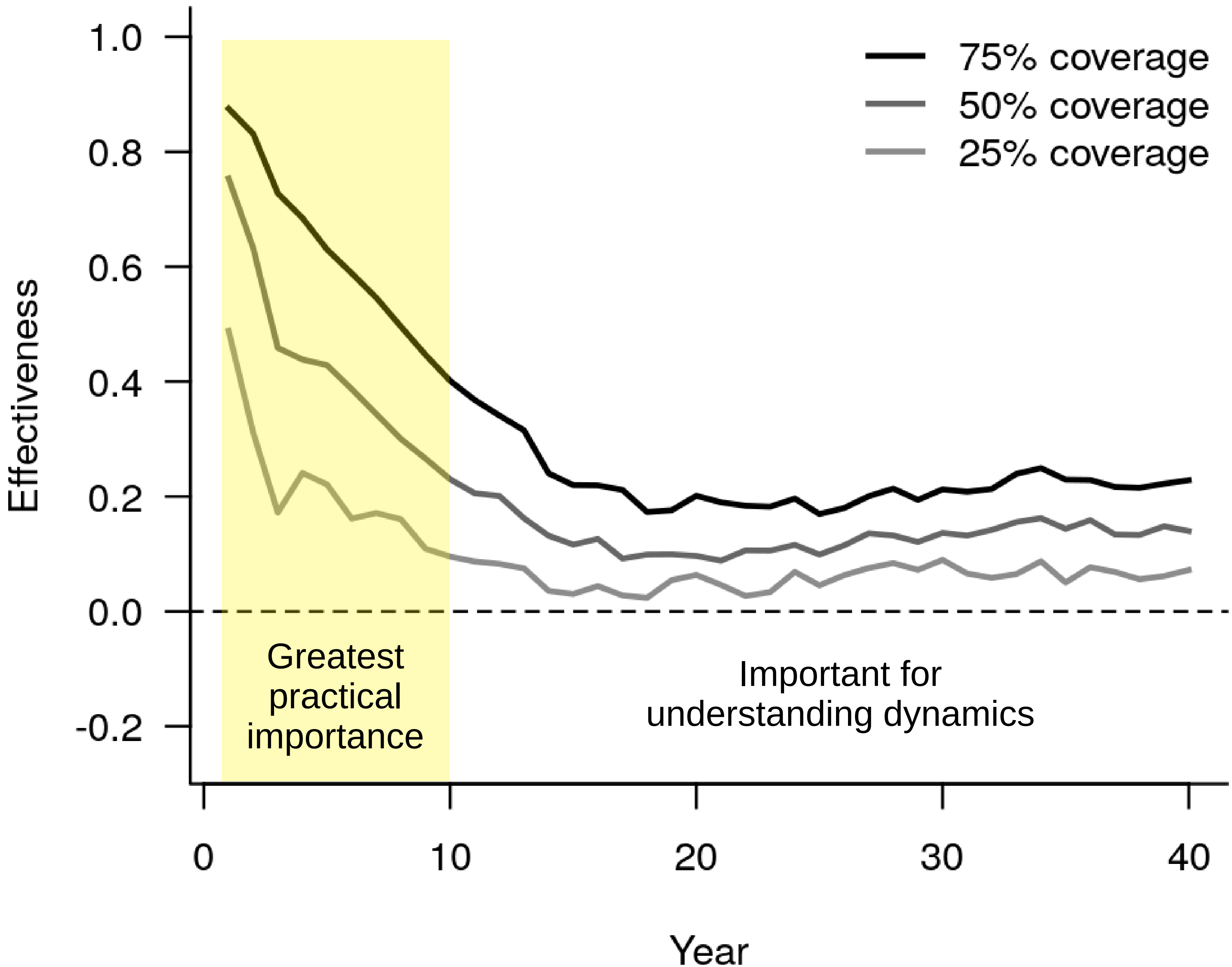
- Overall effectiveness based on incidence
  - Effectiveness = 1 - $\frac{\lambda_1}{\lambda_0}$
  - $\lambda_0 =$ dengue incidence with no intervention
  - $\lambda_1 =$ dengue incidence with intervention
- Overall effectiveness can also be based on cumulative incidence

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

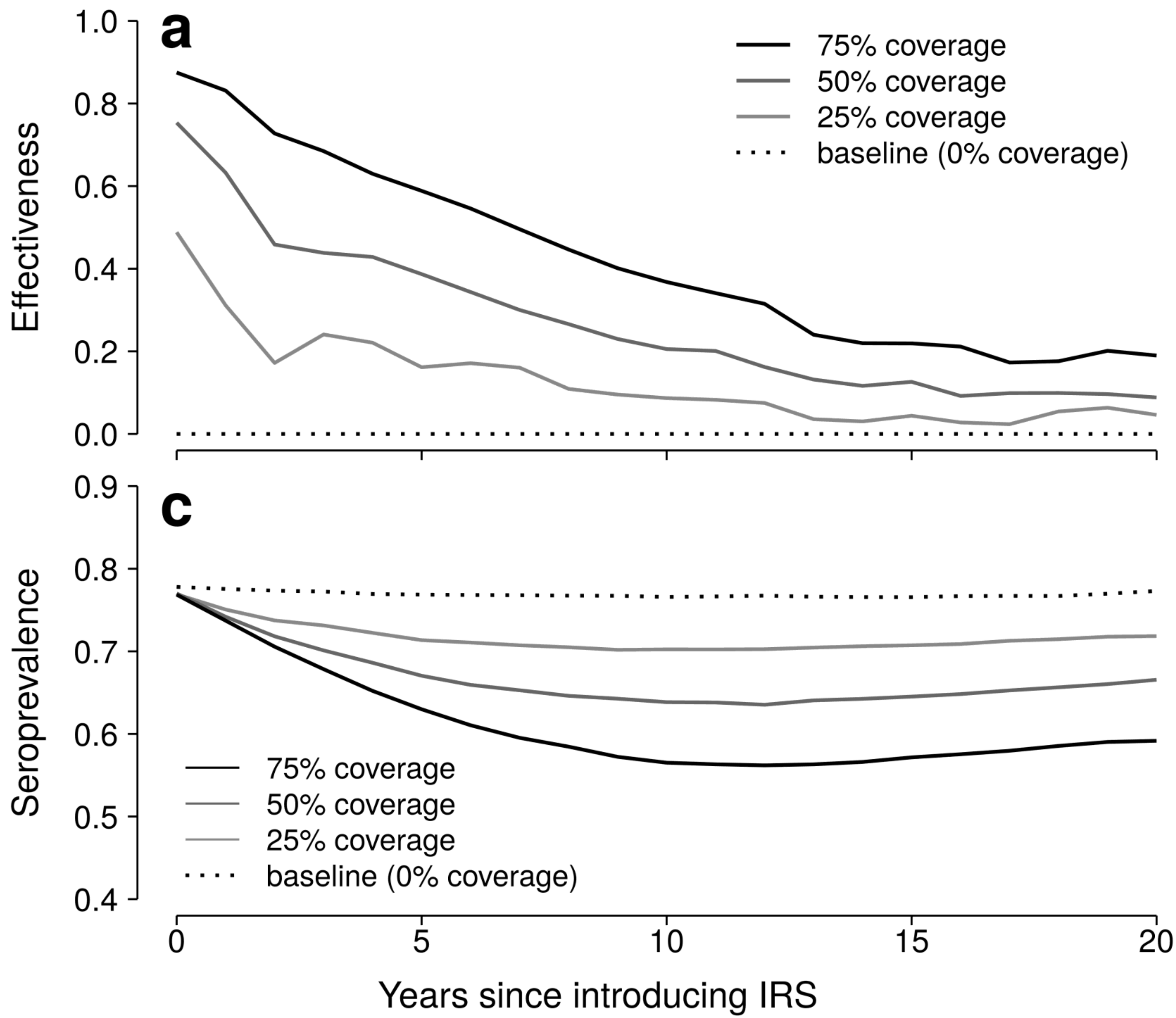


Effectiveness decreases for 15 years, then levels out. Why?

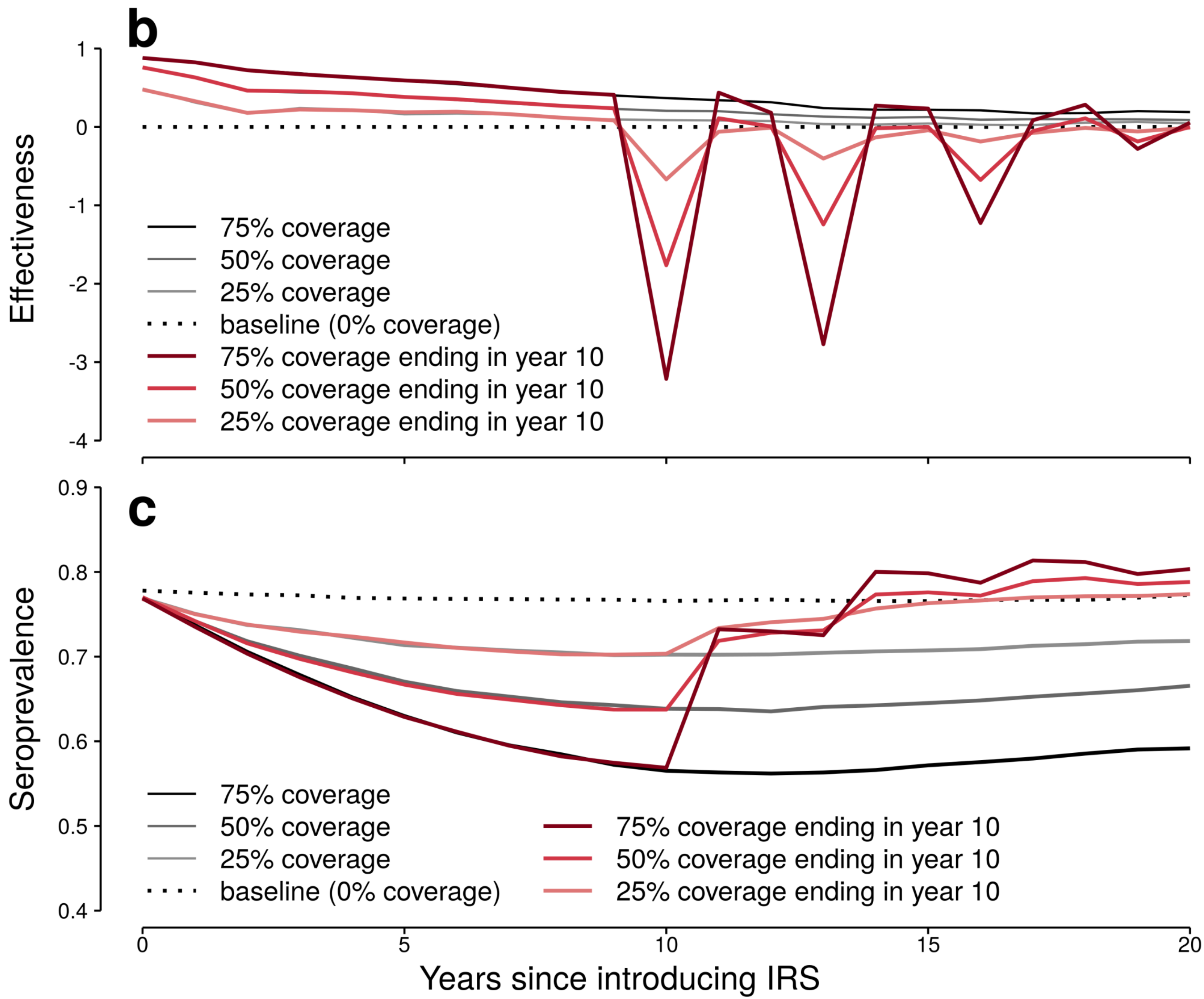
(90-day campaign, 90-day durability, optimal timing: late May start)



Population immunity drives long-term IRS effectiveness



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


b
Effectiveness
1
0
-1
-2
-3
-4
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
c
Seroprevalence
0.9
0.8
0.7
0.6
0.5
0.4
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
0
5
10
15
20
Years since introducing IRS

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

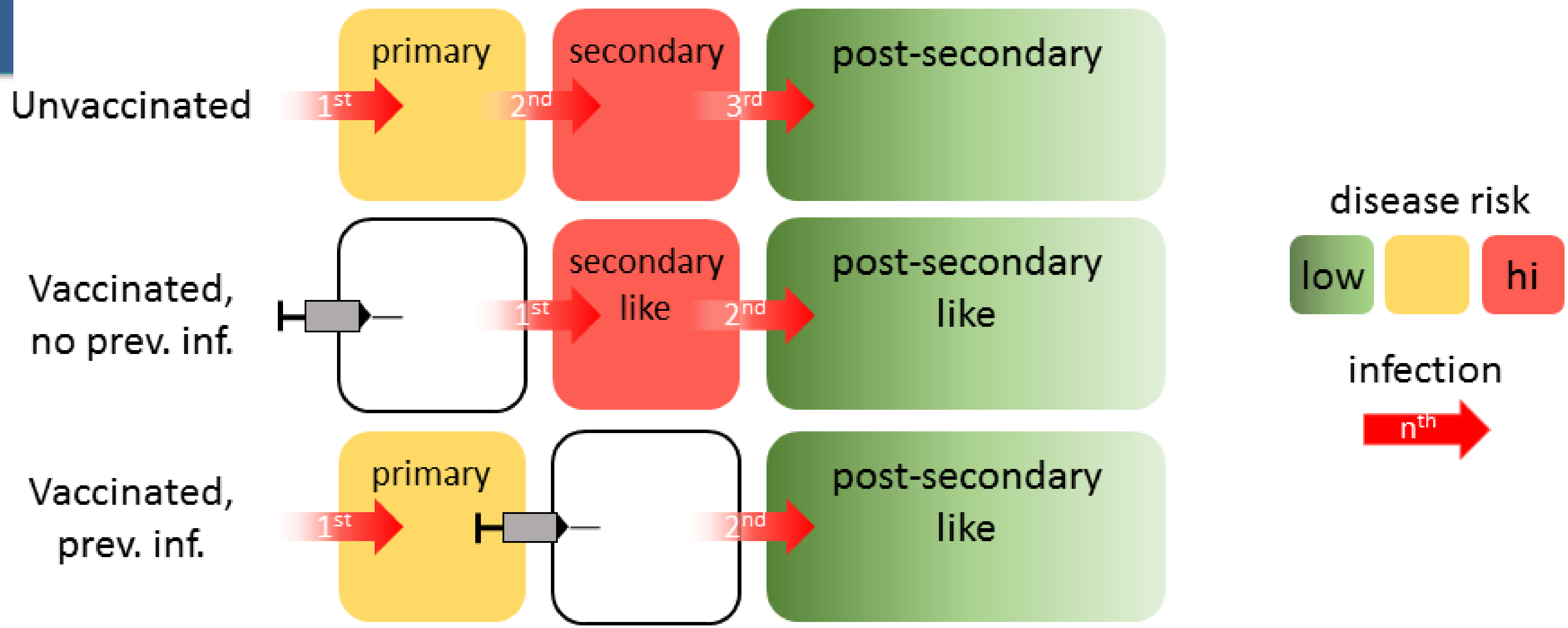
Dengvaxia assumptions:

- 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

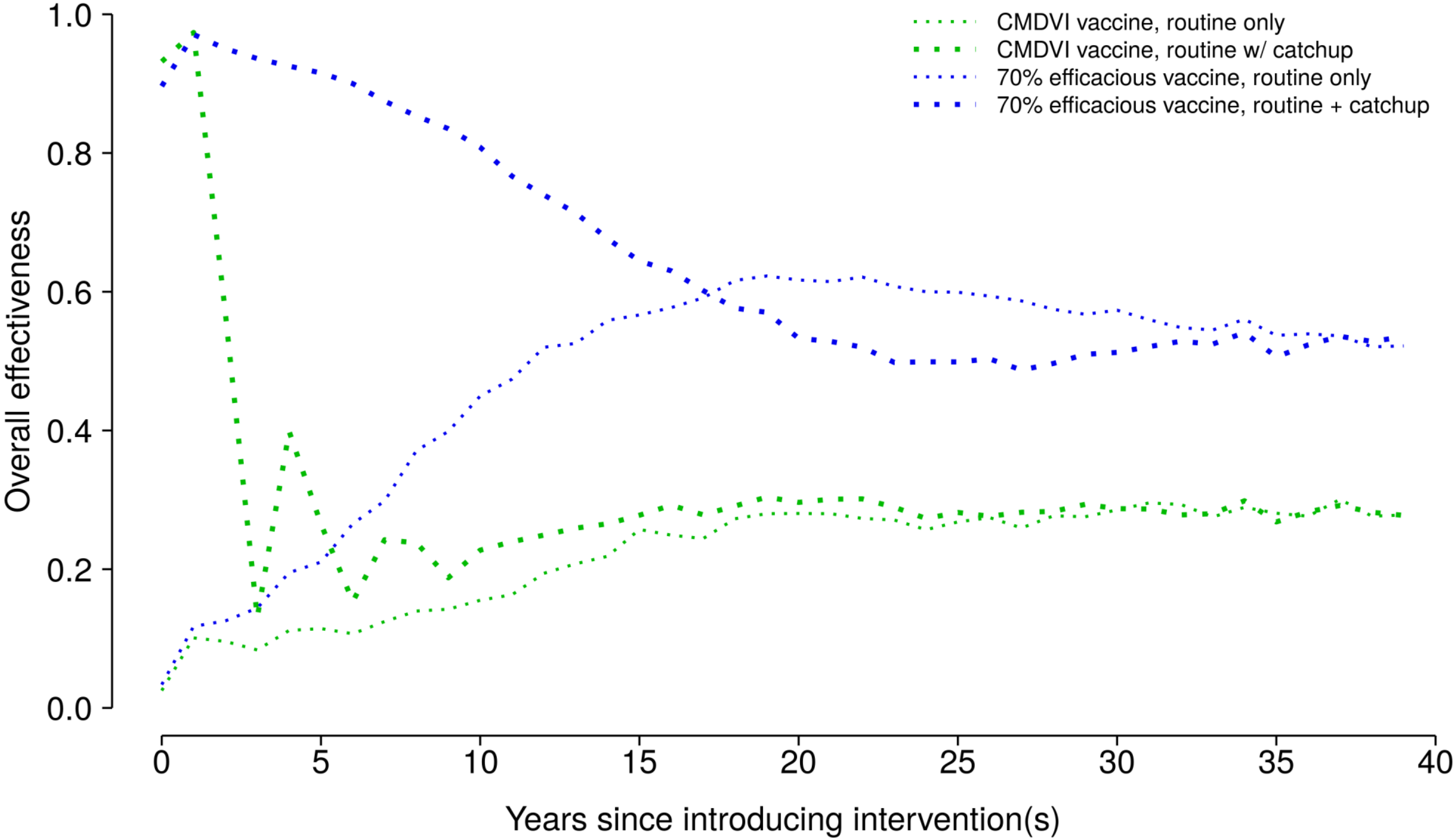
Explanatory hypothesis about vaccine action for Dengvaxia (CYD-TDV) by Sanofi Pasteur



Assumes that vaccination primes the immune system similarly to infection:

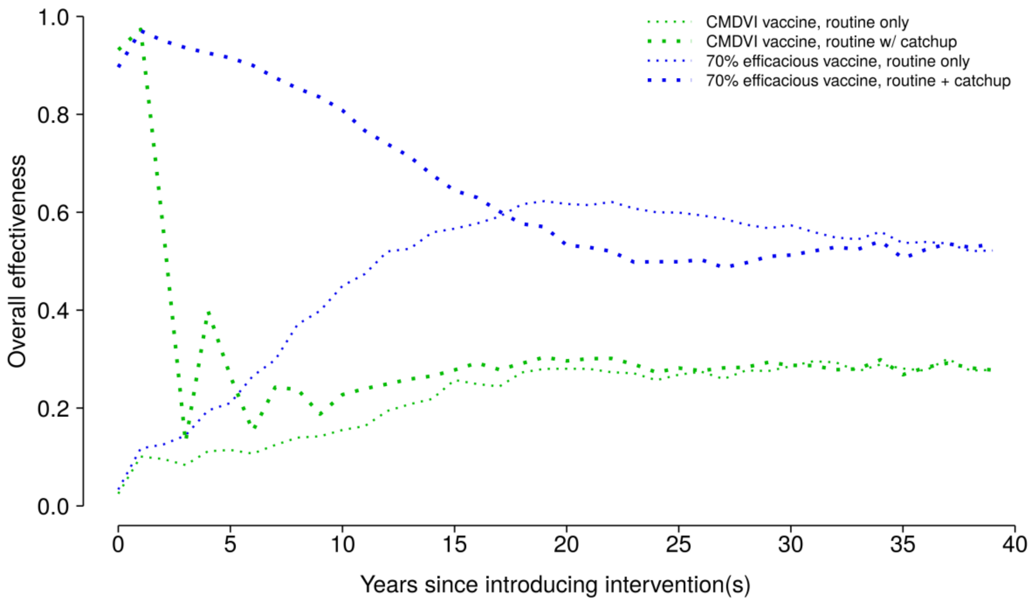
- Temporary high degree of cross-immunity in at least seronegative recipients
- Seronegatives primed to secondary-like (more severe) infection once cross-immunity wanes
- Seropositives boosted so that future infections are tertiary-like (less severe)

Vaccination only

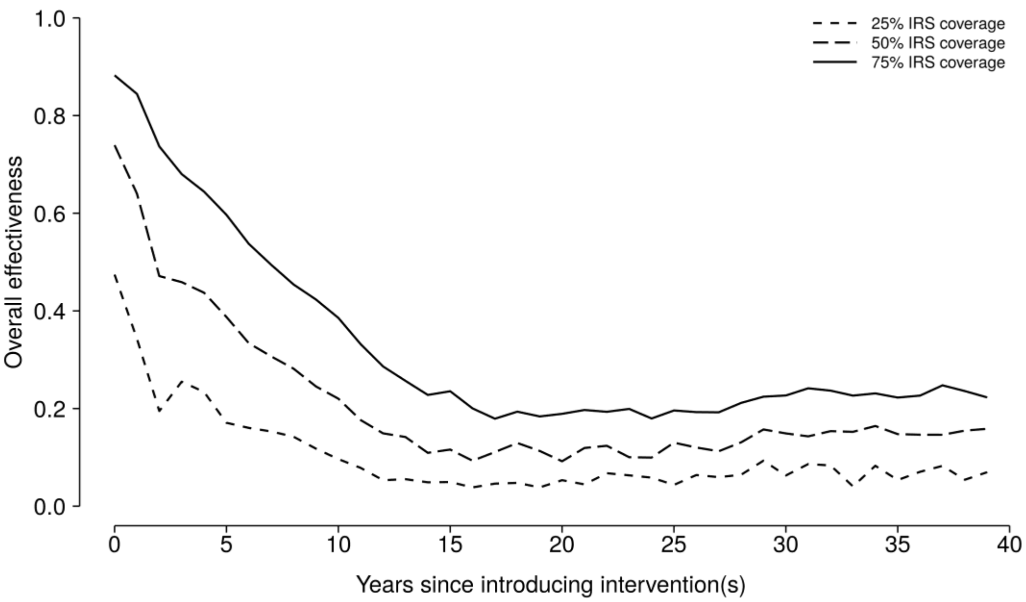


CMDVI – Comparative modeling of dengue vaccine impact (Dengvaxia)

Vaccine only



Vector control only

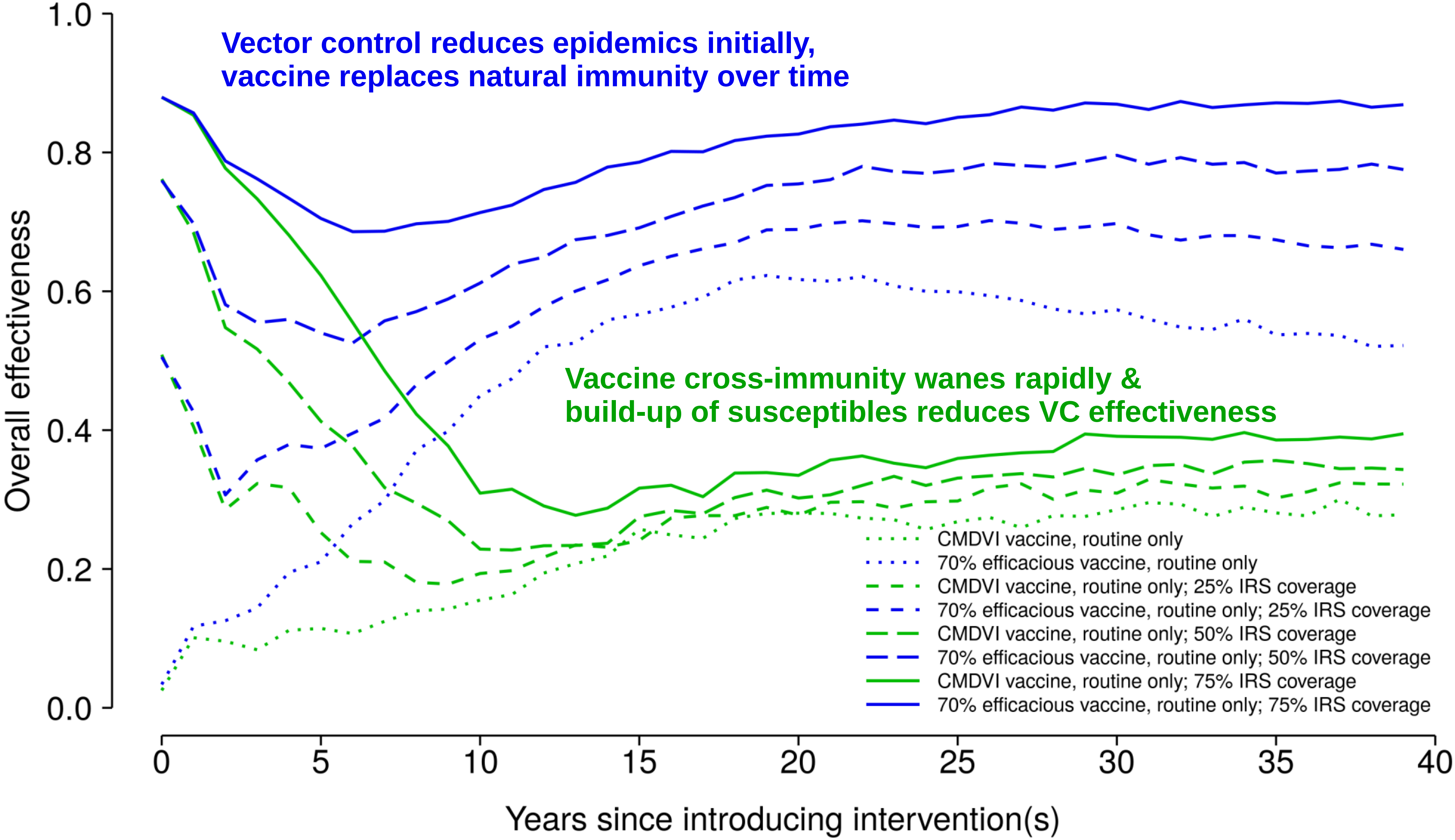


- Catchup vaccination and vector control both provide early effectiveness that decreases as susceptible population increases
- Effectiveness of routine vaccination by itself builds over ~20 years, but plateaus before reaching high effectiveness

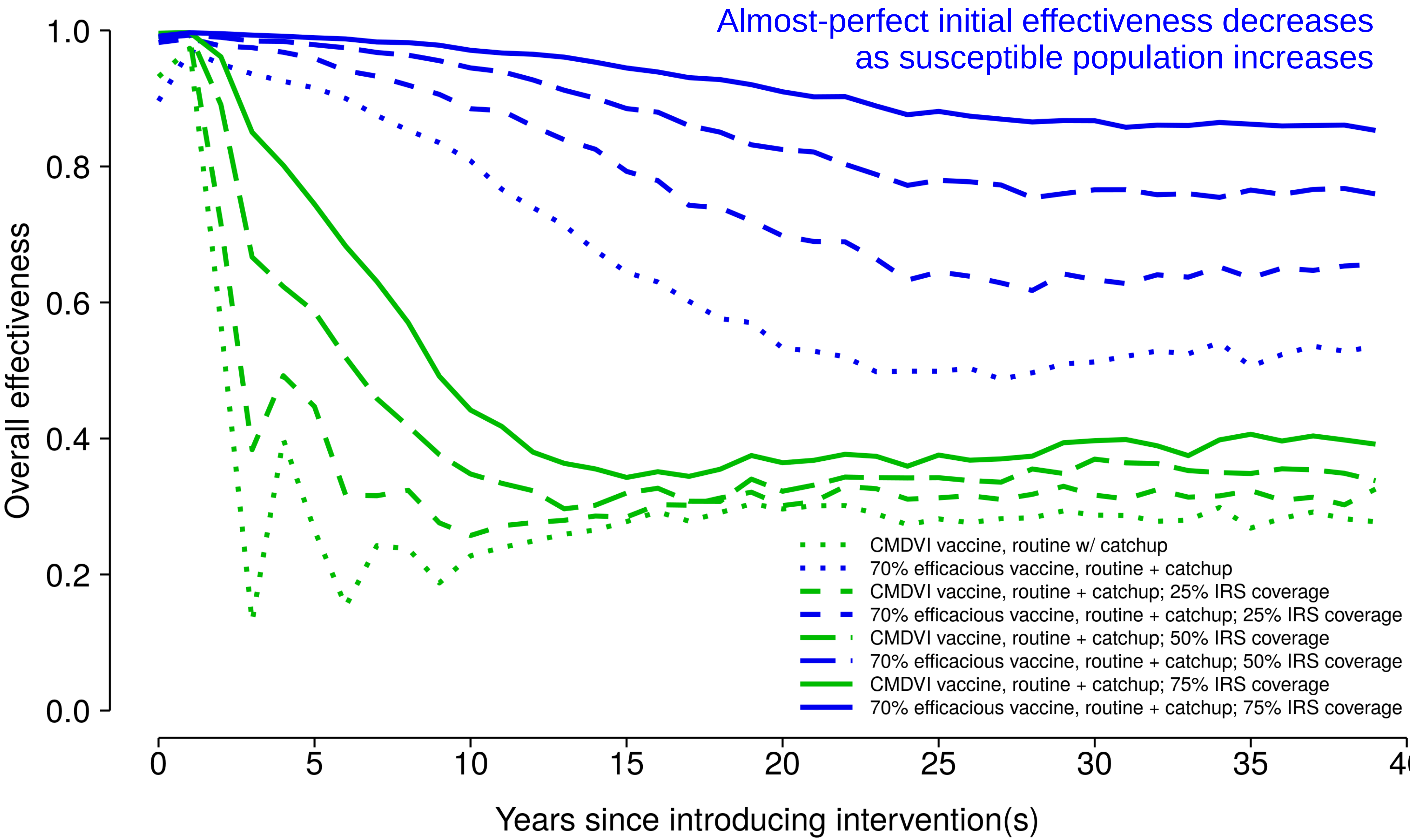
Vaccination + Vector control

Hladish TJ, Pearson CAB, Toh BK, Rojas DP, Manrique-Saide P, Gomez-Dantes H, Vazquez-Prokopec GM, Halloran ME, Longini IM: Designing effective control of dengue with combined interventions. Under review

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

Thank You