Lecture 9: **Stochastic models for arboviruses**

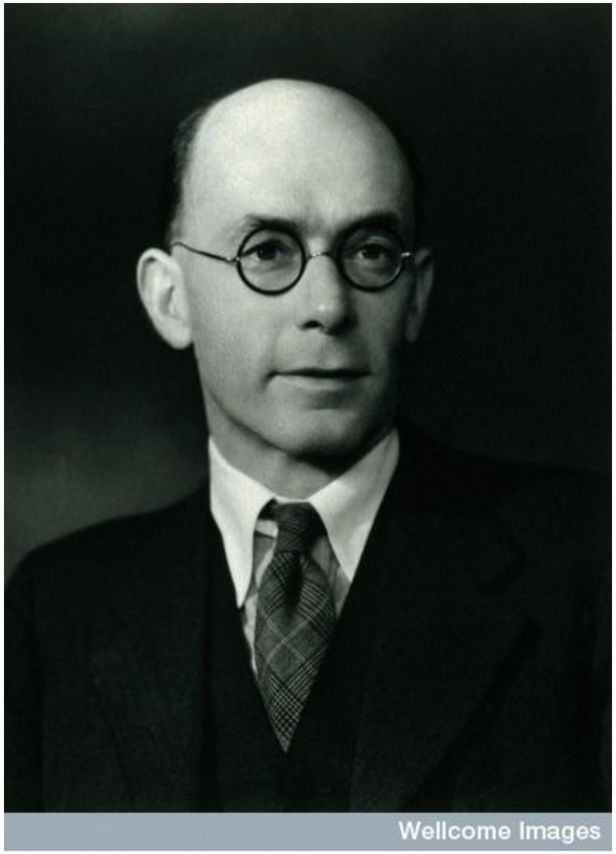
Ira Longini

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

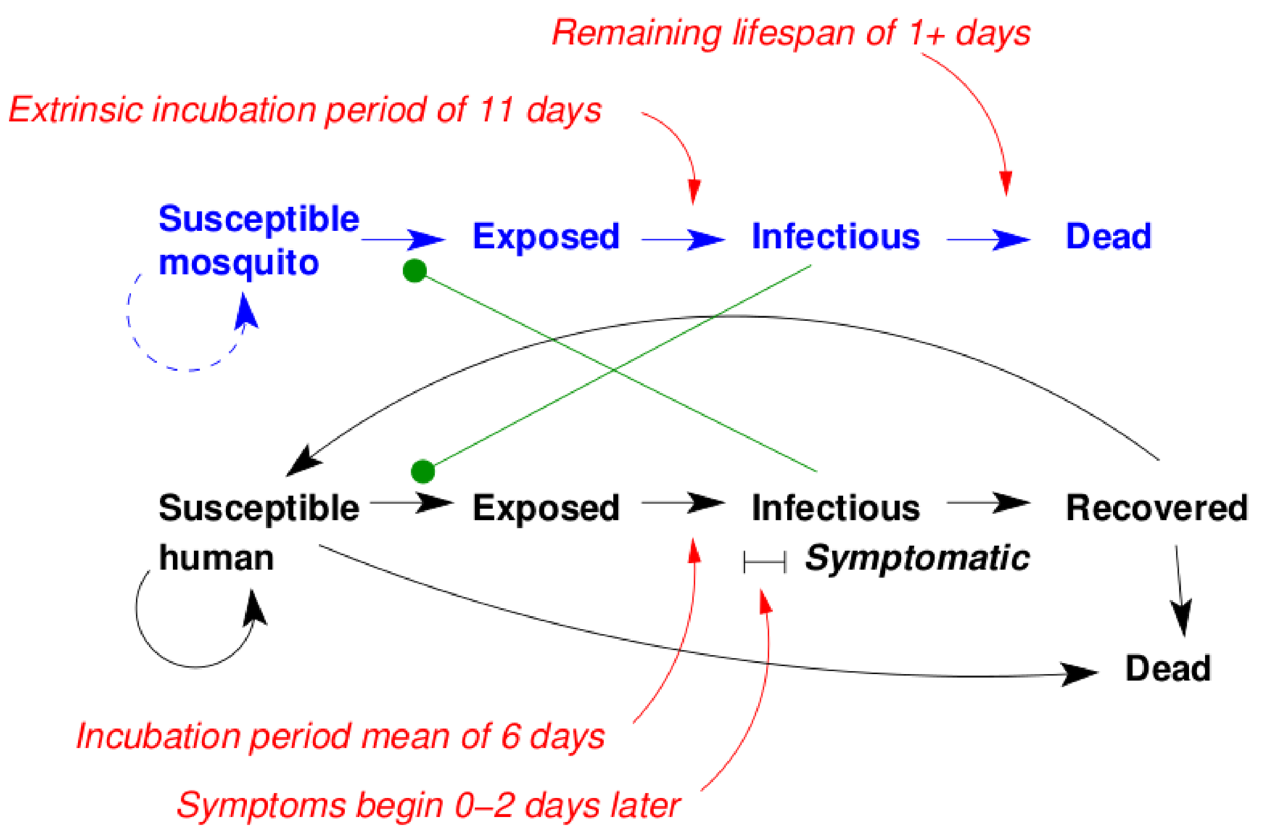
Model Structure

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 $(\frac{R_0-1}{R_0+\frac{ab}{\gamma_2}}, \frac{R_0-1}{R_0+\frac{mab}{\gamma_1}})$ 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 $(0.67, 0.40)$.

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\# hum inf by a mos   \# mosqitoes inf by a hum

Threshold Theorem: Epidemiological Folk Theorem for Host-Vector Systems

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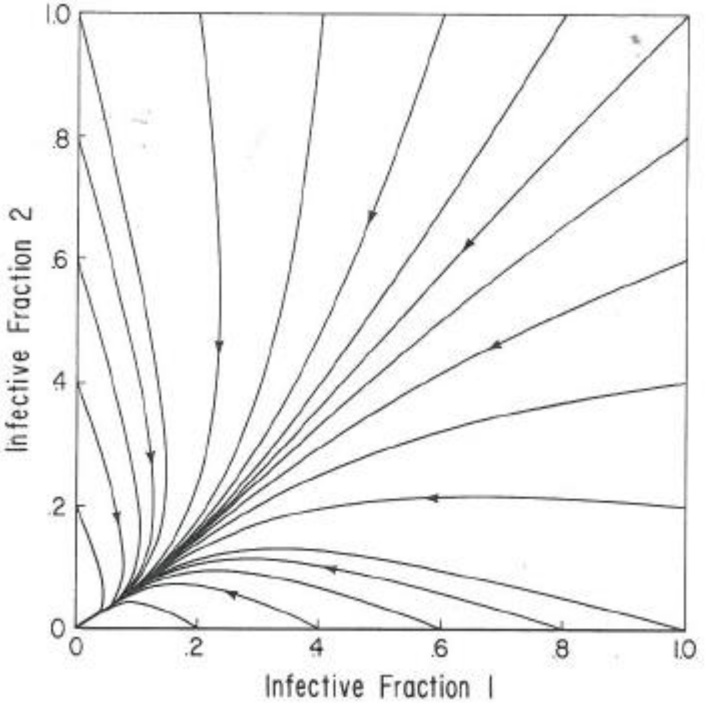
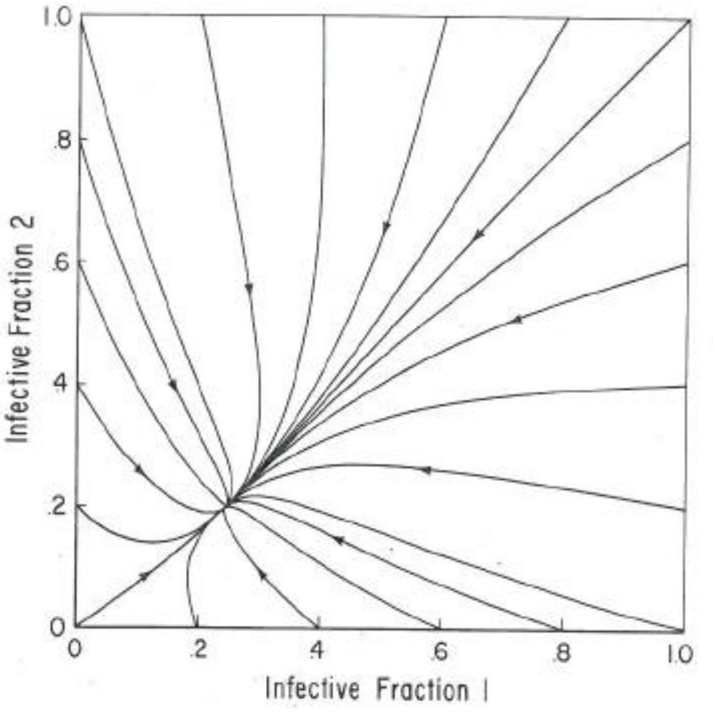
$e.g.$, $m = 5, a = 2, b = c = 0.1, D_1 = 5, D_2 = 5$, then $R_0 = 5.0$,
and the equilibrium infection prevalence is $(0.67, 0.40)$.

Typical I_1I_2 - plane phase portraits*



$R_0 \leq 1$



$R_0 > 1$

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

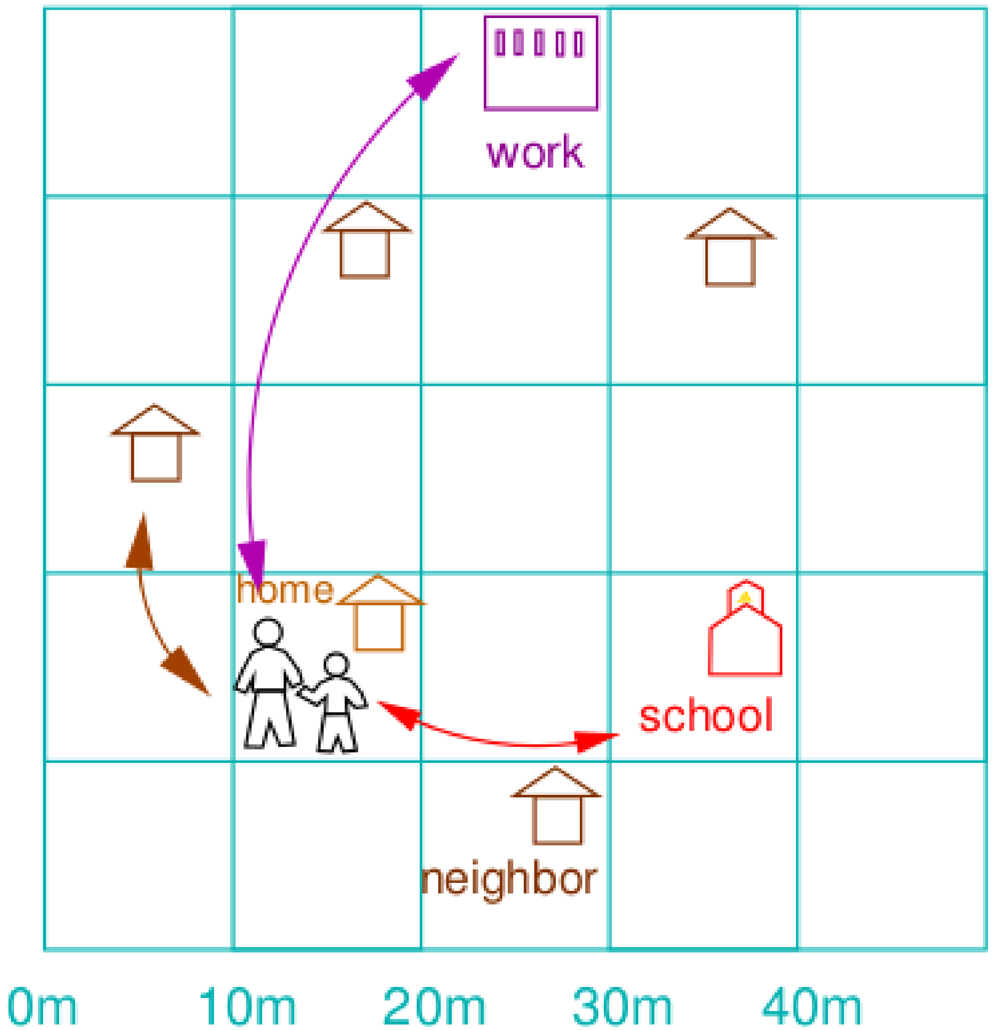
Basic Reproductive Number

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

- 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*.

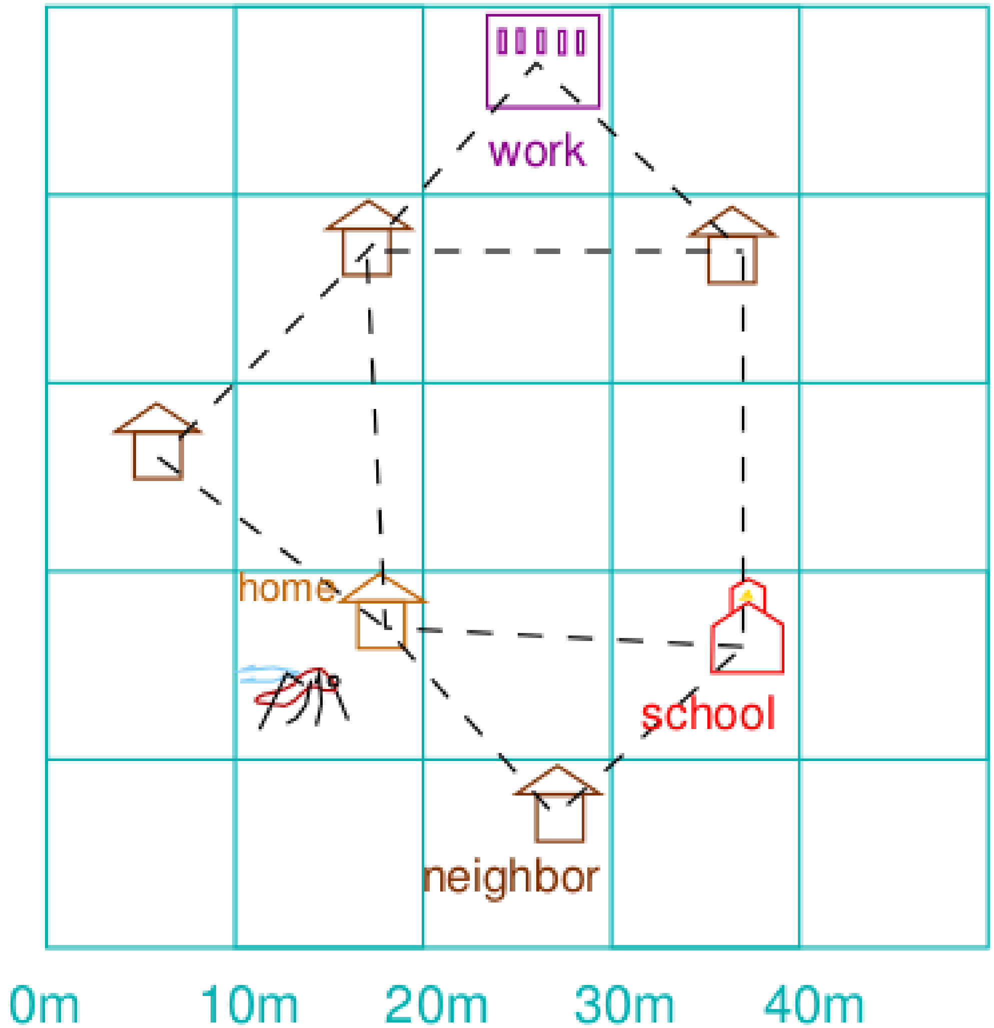
Stochastic models

Model: human movement



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

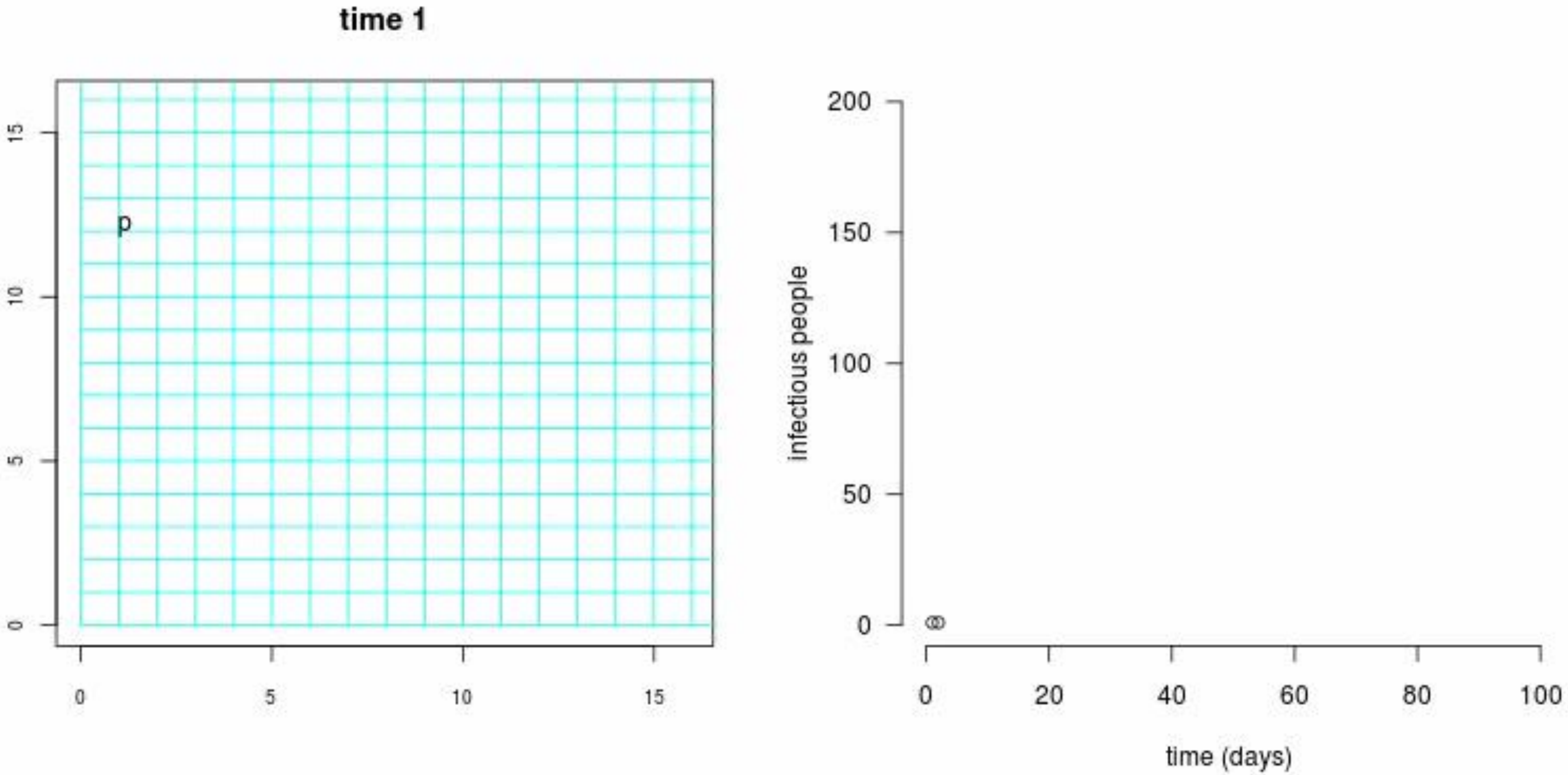
Model: mosquito movement



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

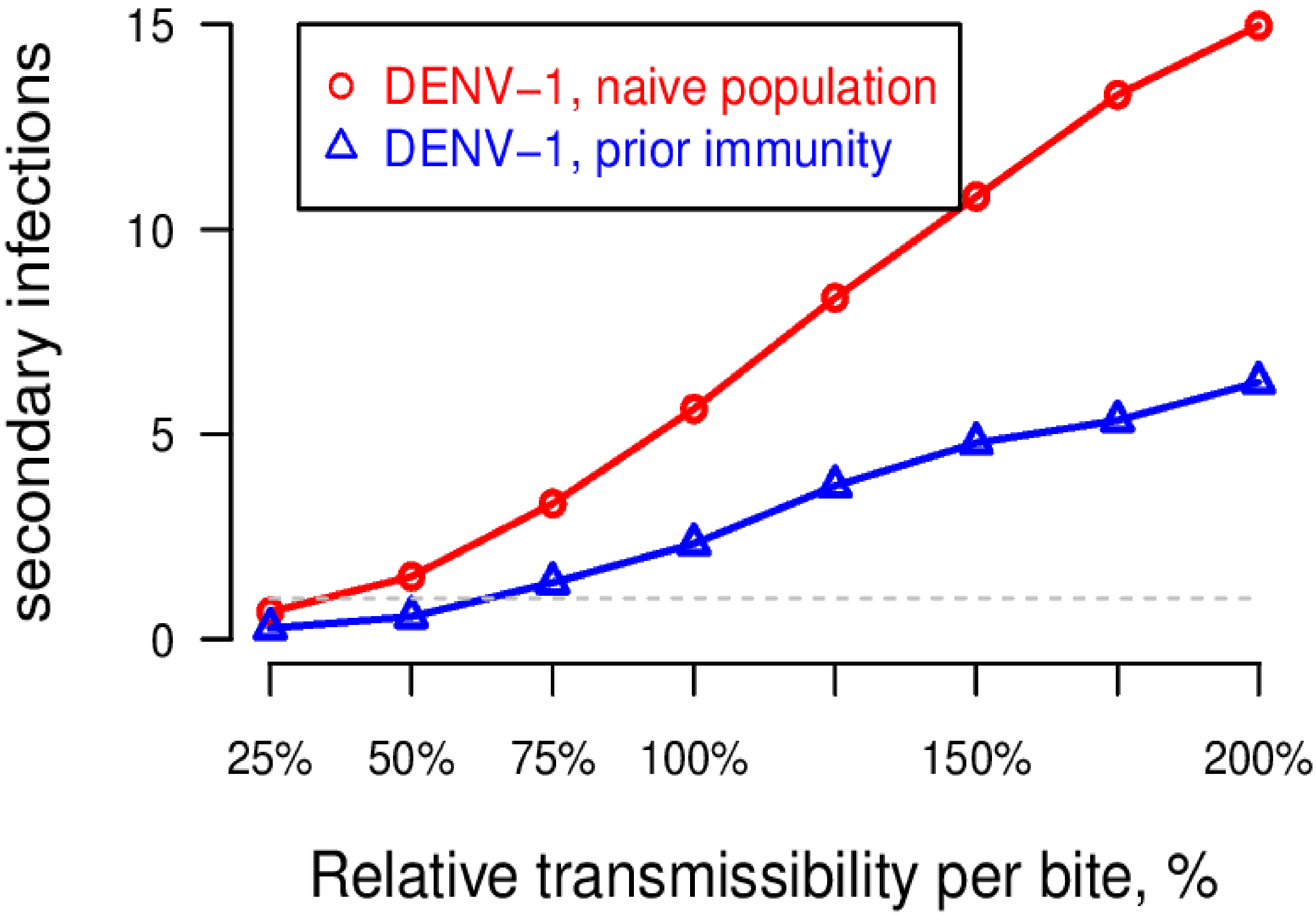
Simplified Model

- 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

Vaccine efficacy and effectiveness

- Direct effects
  - direct protective effects in person who is vaccinated
- Indirect effects
  - effects of widespread vaccination on someone who is not vaccinated
- Total Effects
  - possibly synergistic effect of being vaccinated and widespread vaccination on someone who is vaccinated
- Overall effects
  - overall population effect, say, reduction in incidence, of widespread vaccination.

Measures of Vaccine Efficacy

- VE_S Vaccine Effect on Susceptibility
- VE_P Vaccine Effect on Clinical Disease
  - Classical III vaccine trials

    Many times observe

    $VE_{SP} = 1 - (1 - VE_S)(1 - VE_P)$

- VE_I Vaccine Effect on Infectiousness
- Search for immune correlates (even surrogates for VE)

Overall effectiveness and impact

- Overall effectiveness
  - $VE_{overall} = 1 – (r_{vac}/r_{novac})$
    - r_{vac} overall incidence rate with vaccination campaign
    - r_{novac} overall incidence rate with no vaccination in a comparable population

- $CA_{overall}$ = (#risk) $r_{novac} VE_{overall}$, cases averted

  = (#risk) $(r_{novac} – r_{vac})$

Dengue vaccines pipeline

Vaccine Candidate	Manufacturer	Vaccine Type	Mechanism of attenuation or inactivation	Clinical Phase
CYD	Sanofi Pasteur	Live Attenuated	Yellow Fever vaccine backbone, premembrane and envelope proteins from wildtype dengue virus	III
DENVax	Takeda	Live Attenuated	Wildtype DEN2 strain attenuated in primary dog kidney cells and further attenuated by mutation in NS3 gene	II
TV003/TV005	NIAID and Butantan Institute	Live Attenuated	Wildtype strains with genetic mutations	III
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

Phase IIb and III vaccine trials of Sanofi Pasteur tetravalent dengue vaccine

- Phase I and II in many countries
- Phase IIb completed in Thailand (CYD23)*
- Phase III completed late 2014
  - 5 countries in SE Asia (CYD14)**
  - 5 countries in Latin America (CYD15)***

*Sabchareon, et al. *Lancet* (2012)

**Capeding, et al., *Lancet* (2014)

***Villar, et al., *N Engl J Med* (2014)

Summary: CYD 15 *

- Overall VE_{SP} = 60.8% [CI: 52.0 – 68.0]**
- Overall VE_{Hosp} = 80.3% [CI: 64.7 - 89.5]
- Serotype-specific VE_{SP}
  - ST1: 50.3% [CI: 29.1–65.2]
  - ST2: 42.3% [CI: 14.0–61.1]
  - ST3: 74.0% [CI: 61.9–82.4]
  - ST4: 77.7% [CI: 60.2–88.0]
- Vaccine more efficacious in people with prior immunity compared to those who are naïve, 2 to 1 ratio, accounts for age differences in VE

*Villar, et al., *N Engl J Med*. (2014) , **Per-protocol analysis

Sanofi dengue vaccine so far

- Very safe
- Reasonable protection for disease with infection
- No apparent increase in VE with dose number
- Could be waning protection, but to early to tell
- Excellent protect against severe disease
- Heterogeneity in protection
  - Serotypes
  - Prior immunity
  - Other factors?

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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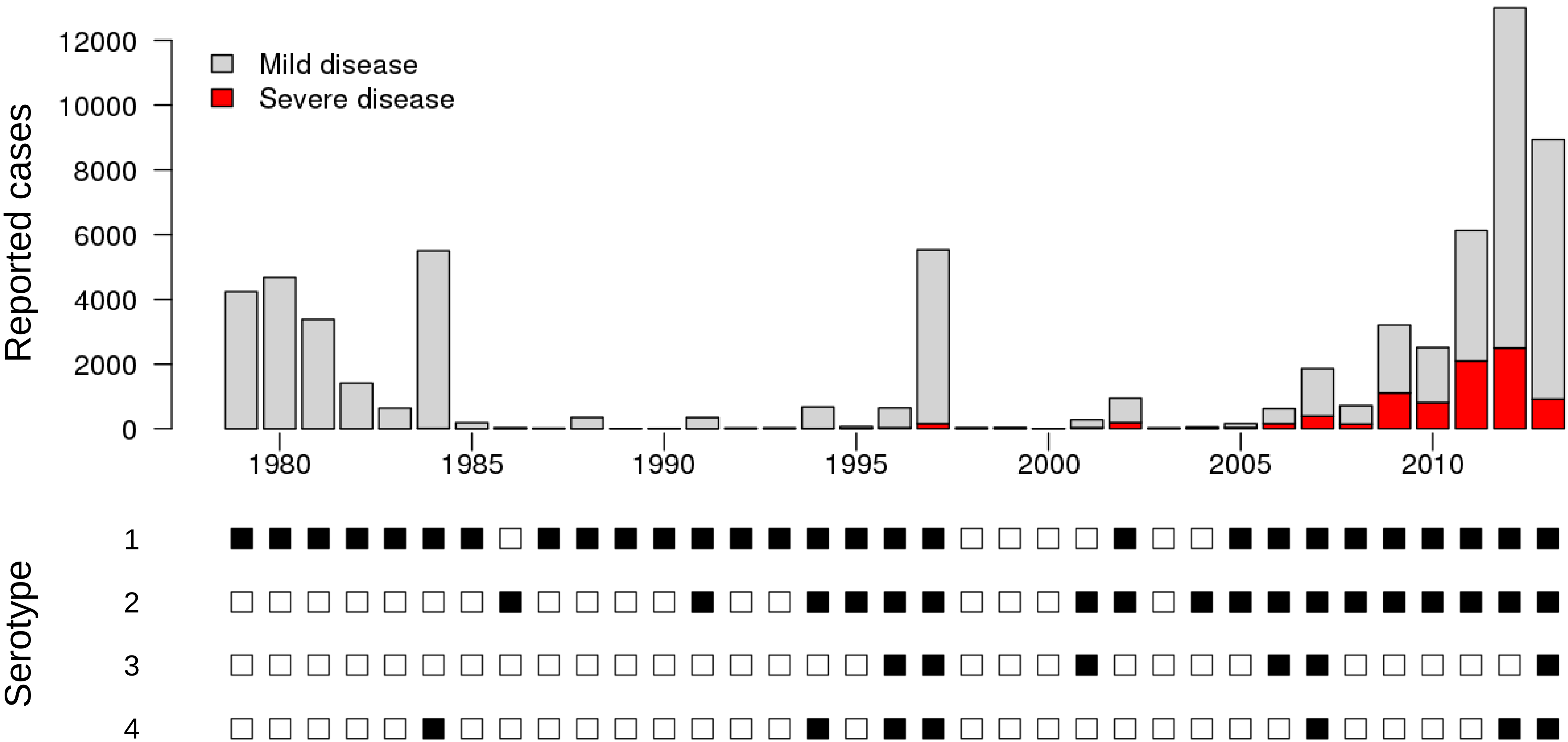
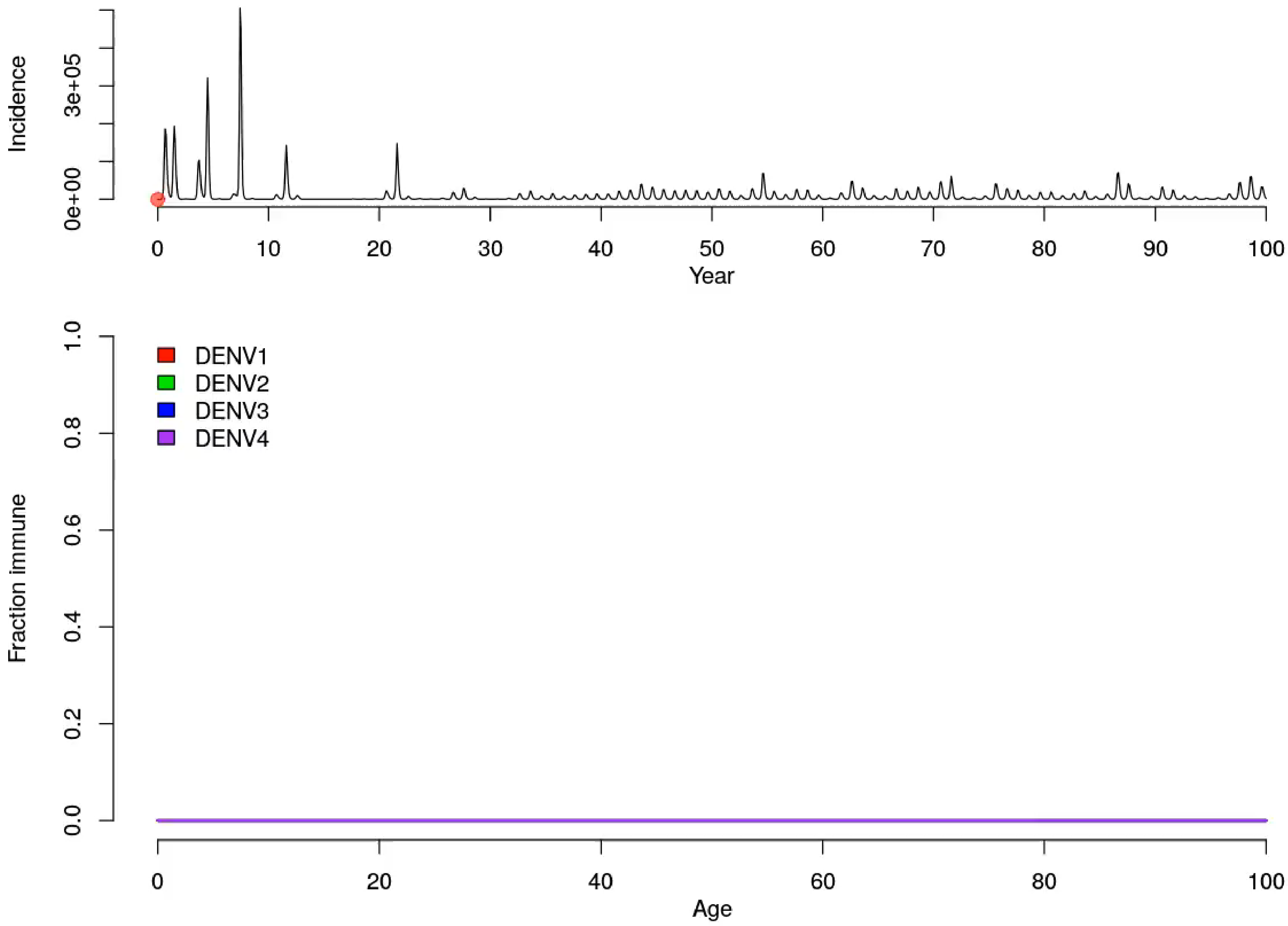
Abstract

Dengue in Yucatan, 1979-2013



Hladish et al (2016), *in review*.

Simulated immune profile



Research questions

- Will vaccination be effective?
  - 1 vaccine licensed, 5 others in dev
- Should we expect vector control to work?
  - It often appears not to
  - Singapore: >$100 mil/year
  - “Revenge against the grandchildren”
- Beneficial synergy?

Agent based model

People

- Home
- Day location
- Age
- Infection state
- Immune state

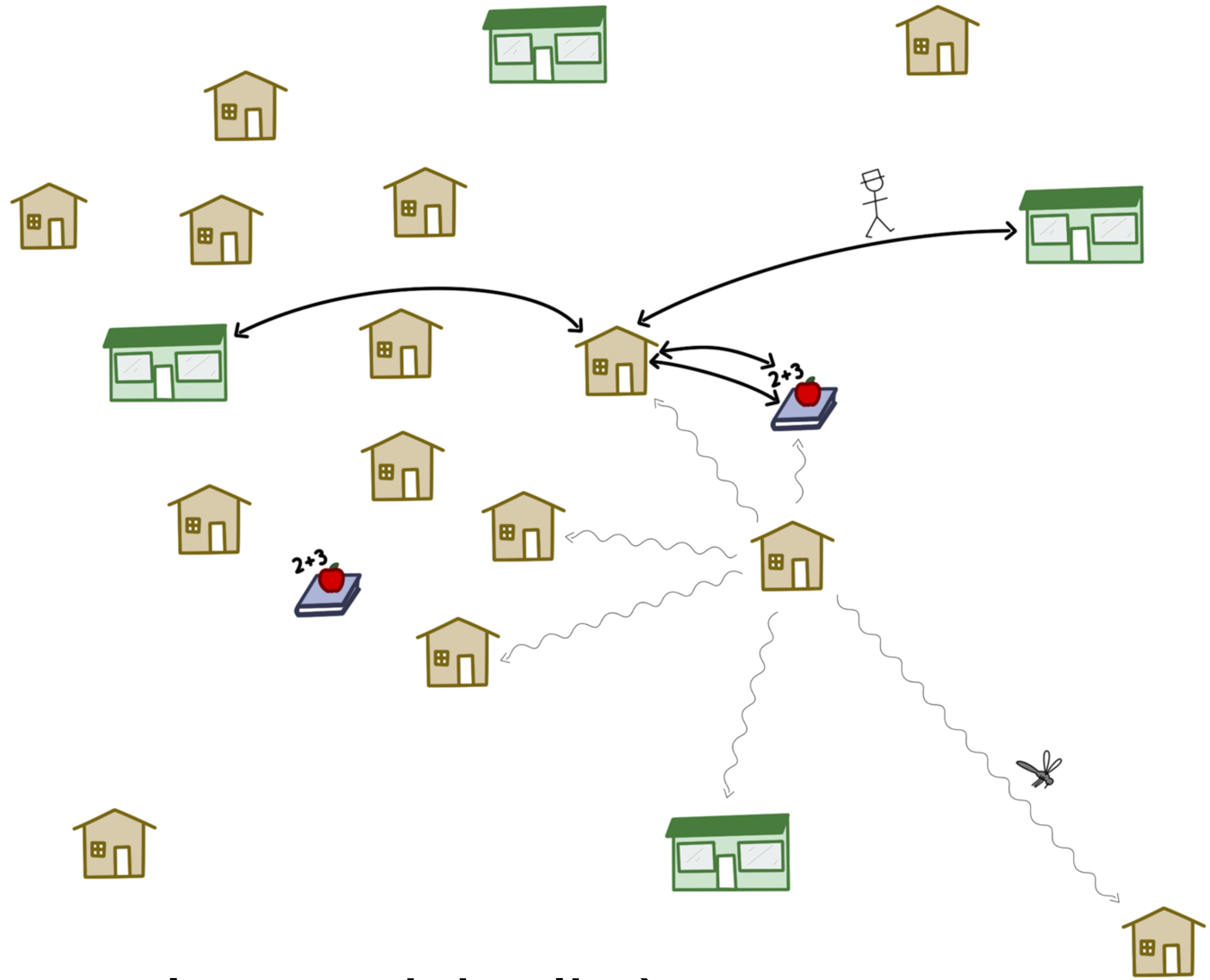
Mosquitoes

- Infection state
- Age
- Location

People age yearly

Mosquitoes age daily

Dengue model overview



1.82 million people

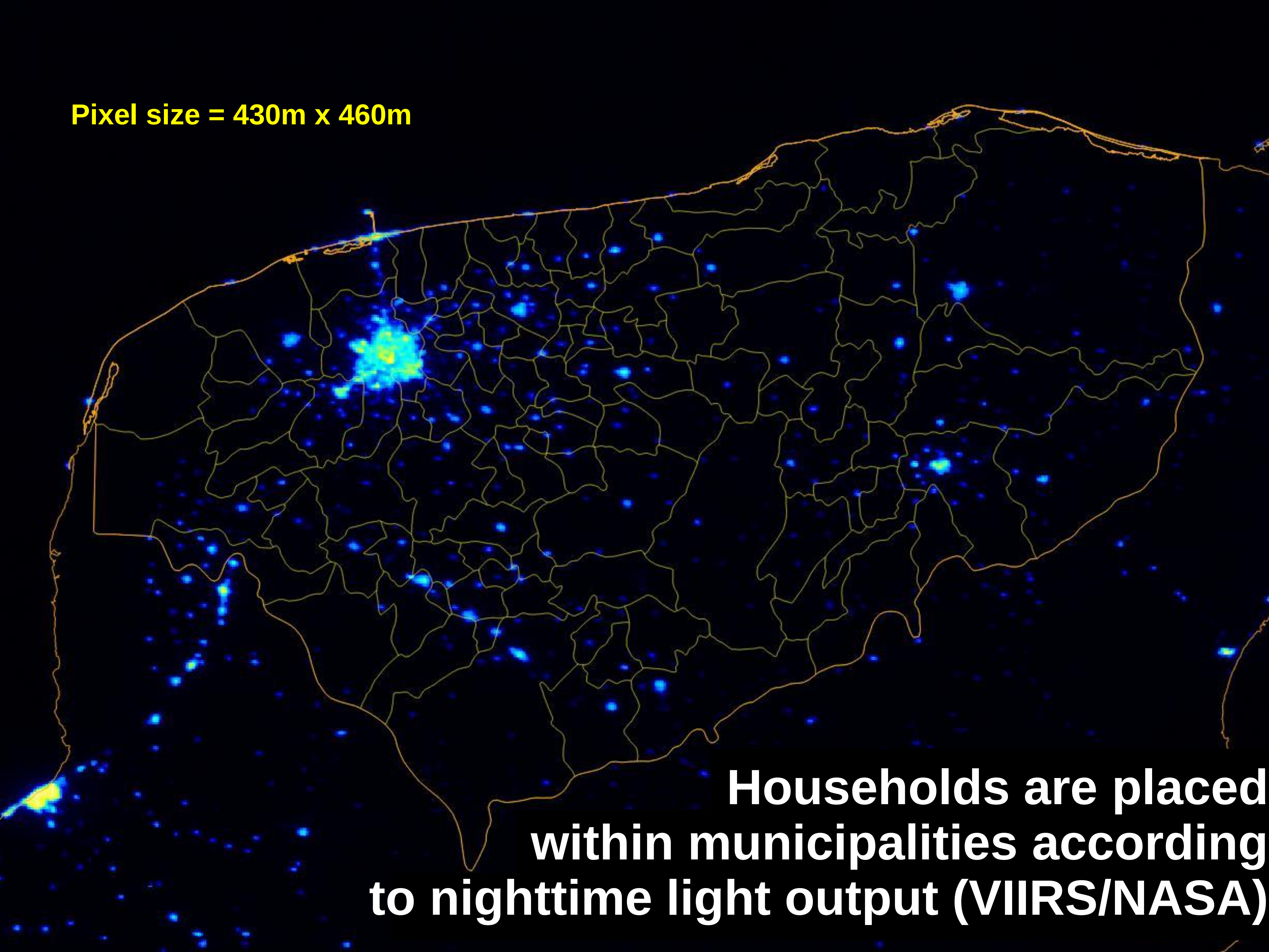
- 38% employed
- 28% in school
- 34% stay at home

376k Households (5% sample, municipality)

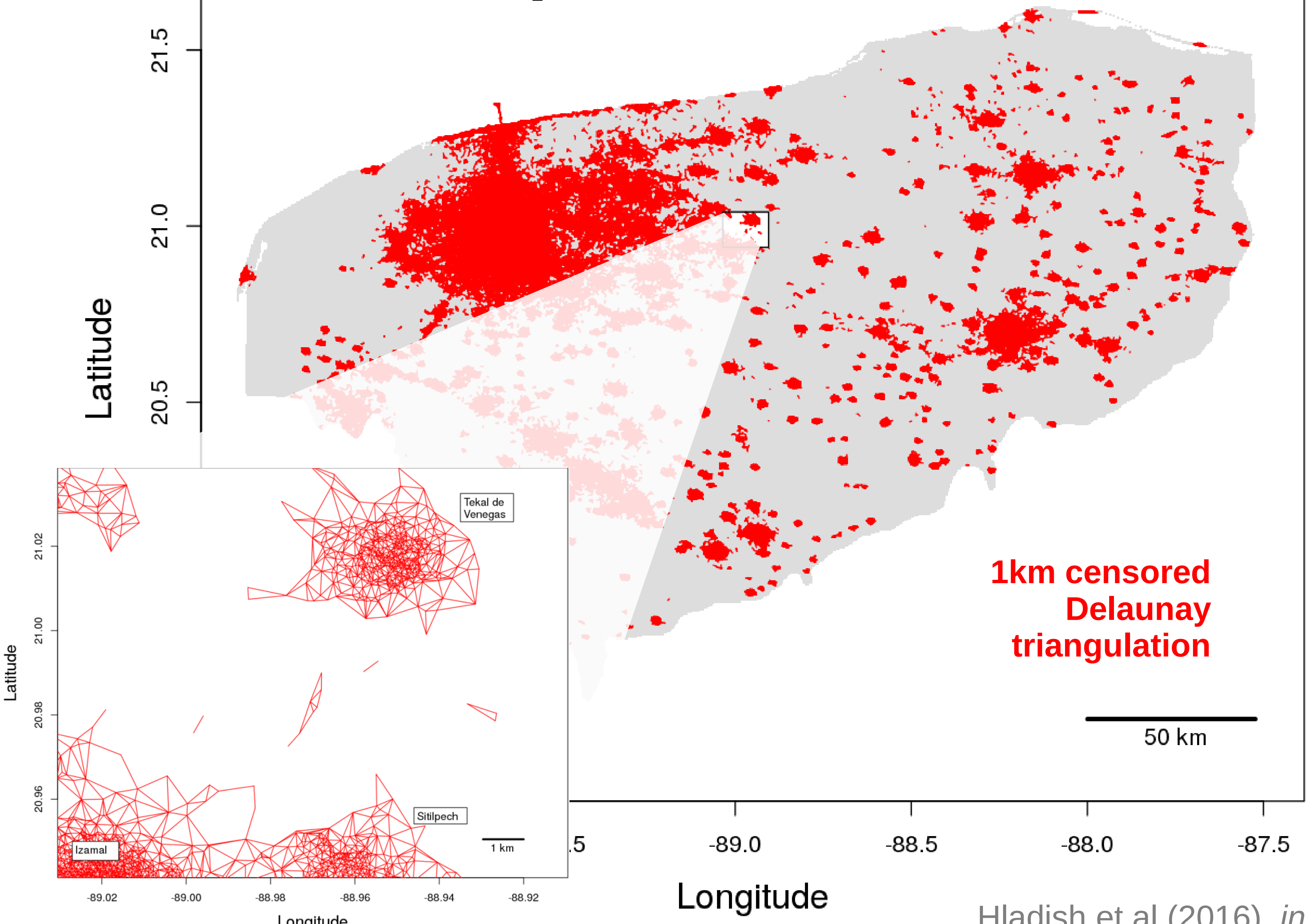
96k Workplaces (size, postal code)

3.4k Schools (postal code)

Model based on Chao et al (2012), *PLOS NTD*

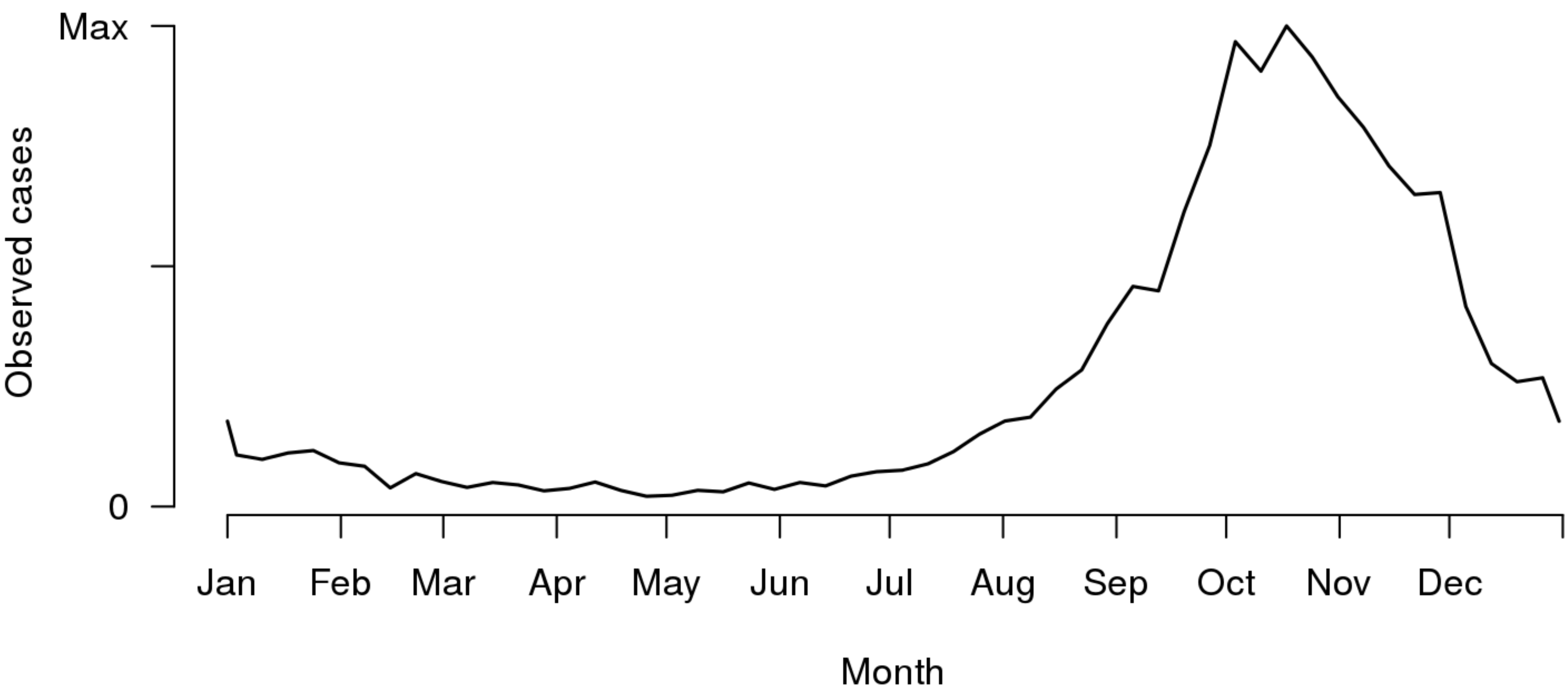

Pixel size = 430m x 460m
Households are placed
within municipalities according
to nighttime light output (VIIRS/NASA)

Mosquito movement



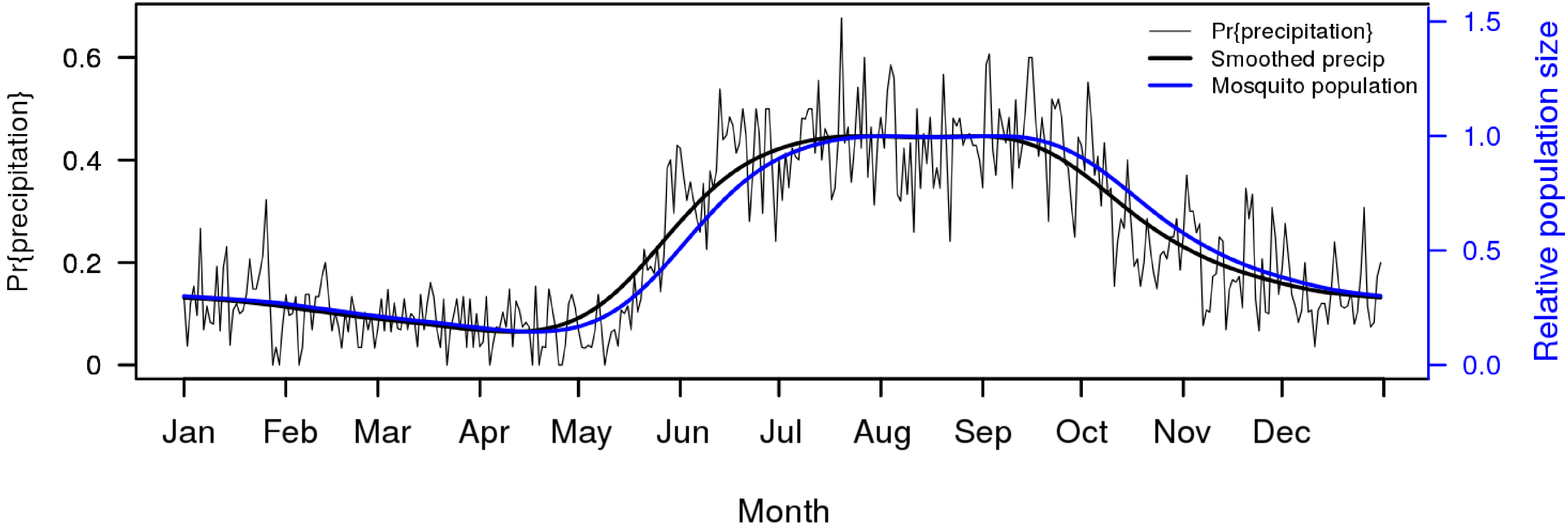
Hladish et al (2016), *in review*.

Observed seasonality (1995-2011)



Hladish et al (2016), *in review*.

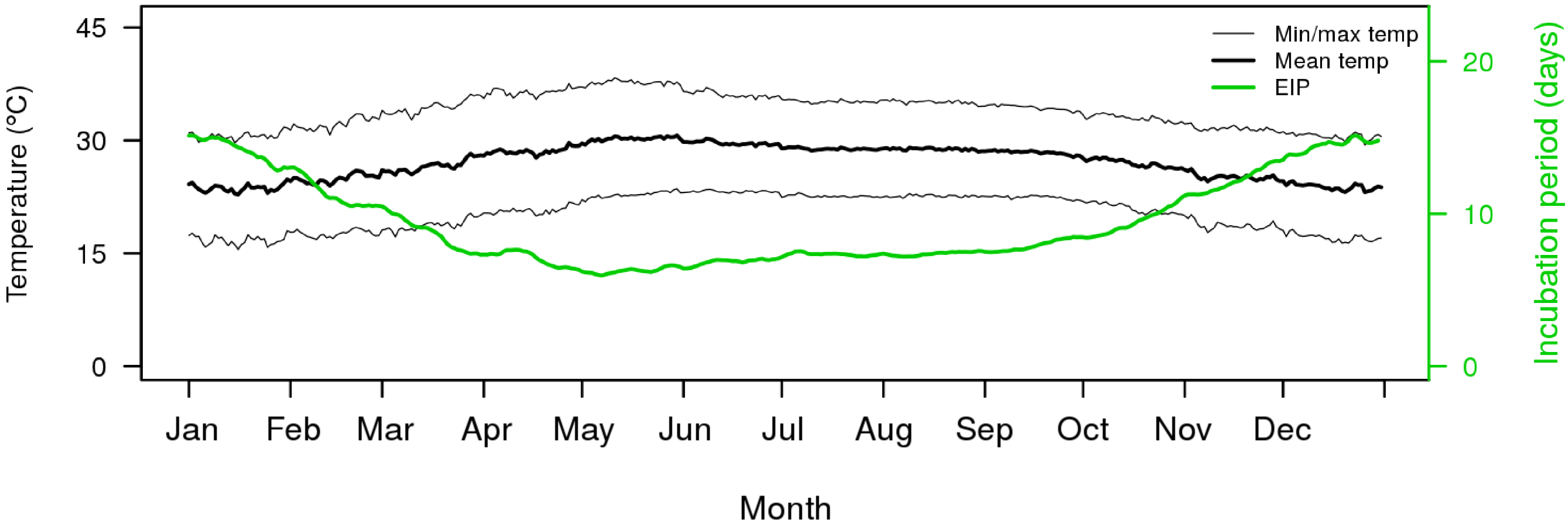
Rainfall → Mosquito population



Precipitation data from NOAA

Hladish et al (2016), *in review*.

Temperature → Incubation Period



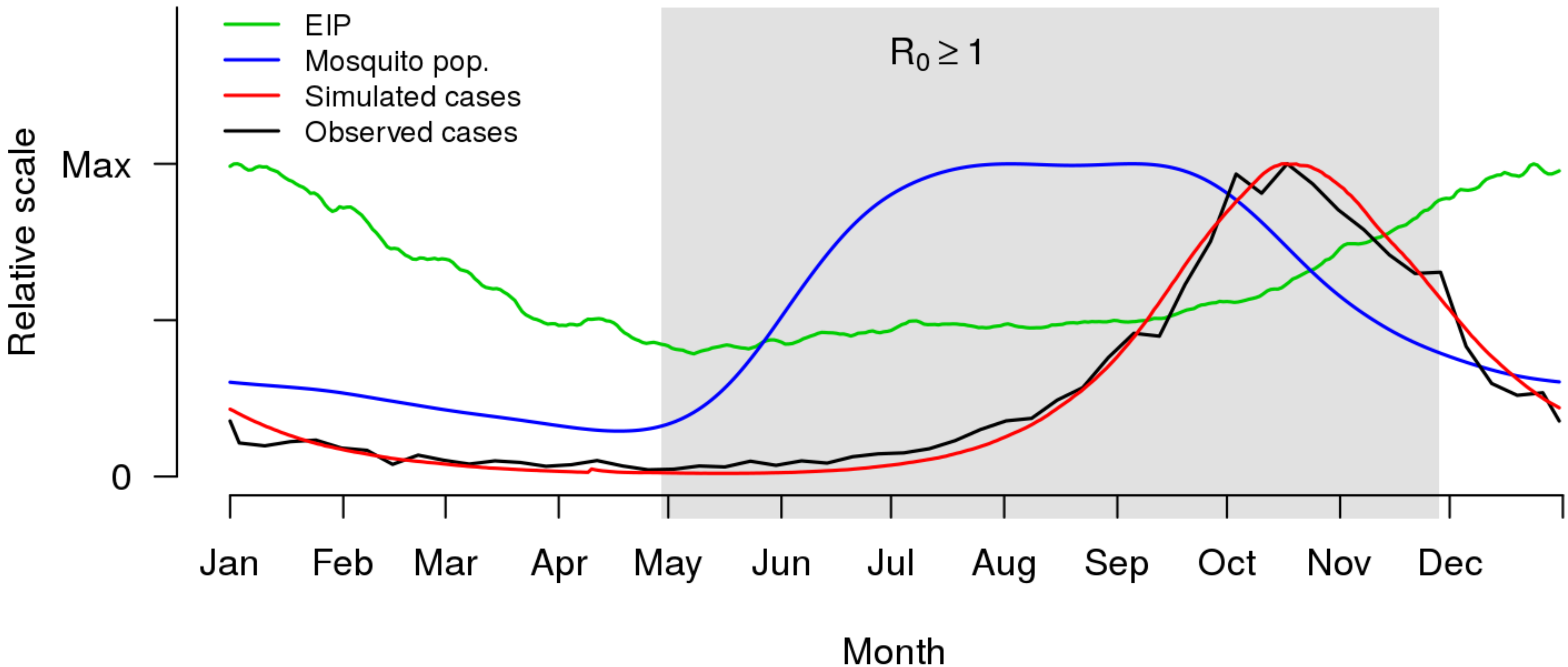
Log-normal EIP distribution based on hourly temperatures in Merida, 1995-2011

$EIP(T) = e^{\left[\left(e^{2.9-0.08T}\right)+0.1\right]}$, after Chan and Johansson (2012)

Temperature data from weatherspark.com

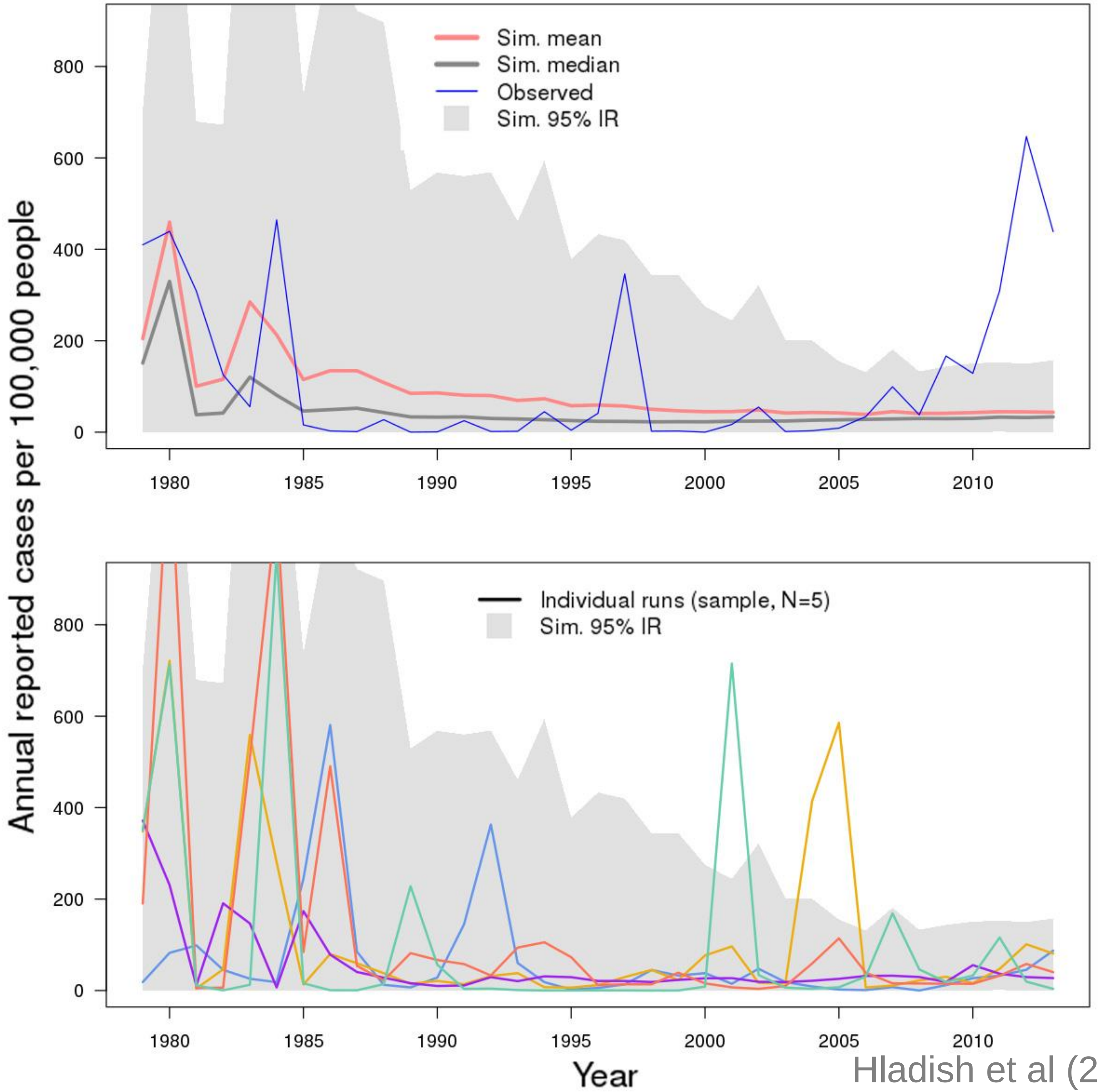
Hladish et al (2016), *in review*.

Emergent seasonality



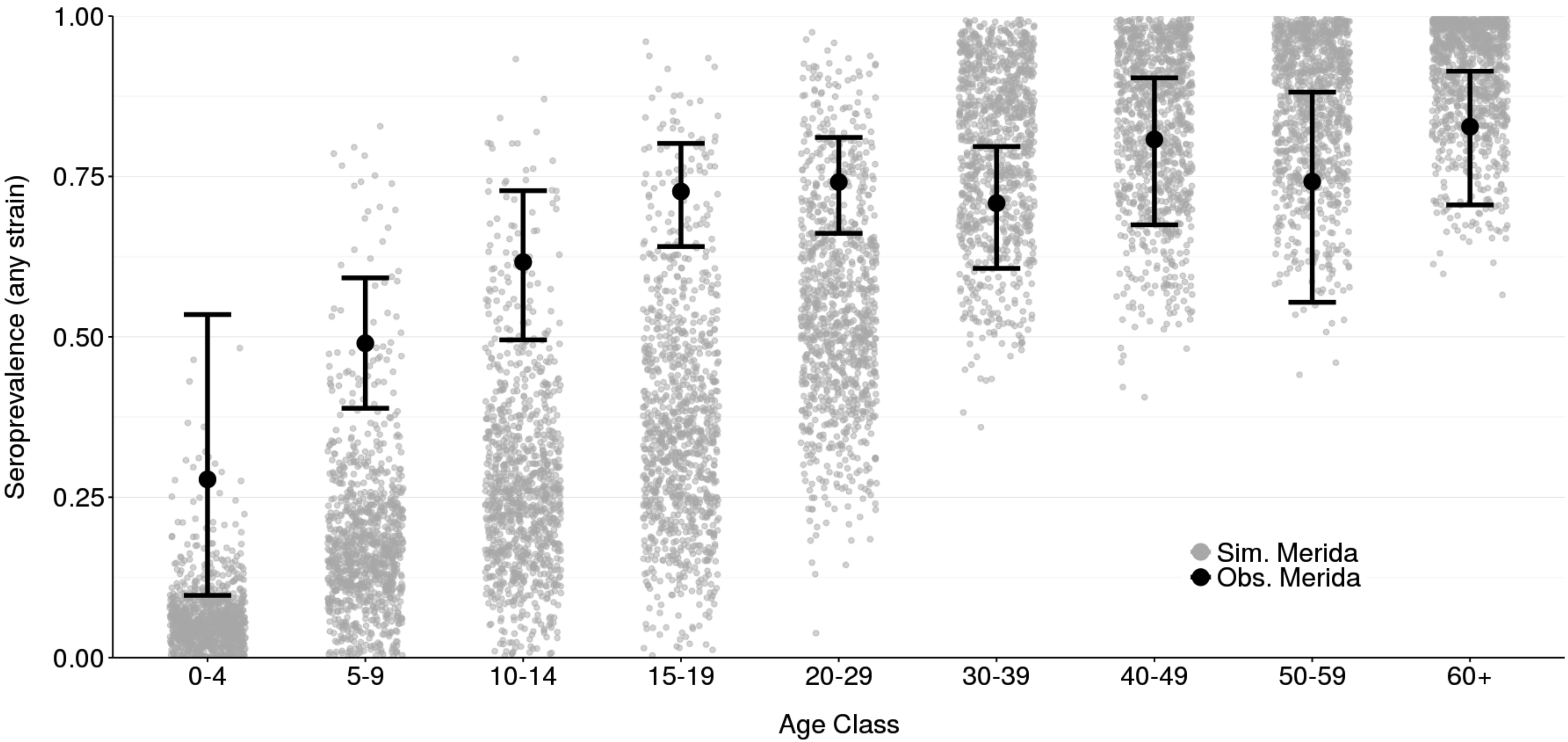
Hladish et al (2016), *in review*.

Reconstruct the past (1979-2013)



Hladish et al (2016), *in review*.

Immune profile validation



95% CI bars on empirical data

Hladish et al (2016), *in review*.

Vaccination strategies

Routine vaccination

- Vaccination of 9 or 16 year-olds every year

Routine vaccination with one-time catchup

- Vaccination of 9 or 16 year-olds every year
- One time catch-up up to 30 in first year

Coverage:

- 80% coverage for 9 year-old routine
- 60% coverage for 10-30 year-old catchup
- Same # vaccines for 16/16-30 scenarios

Vaccine efficacy for simulations

(Efficacy: direct, individual effect)

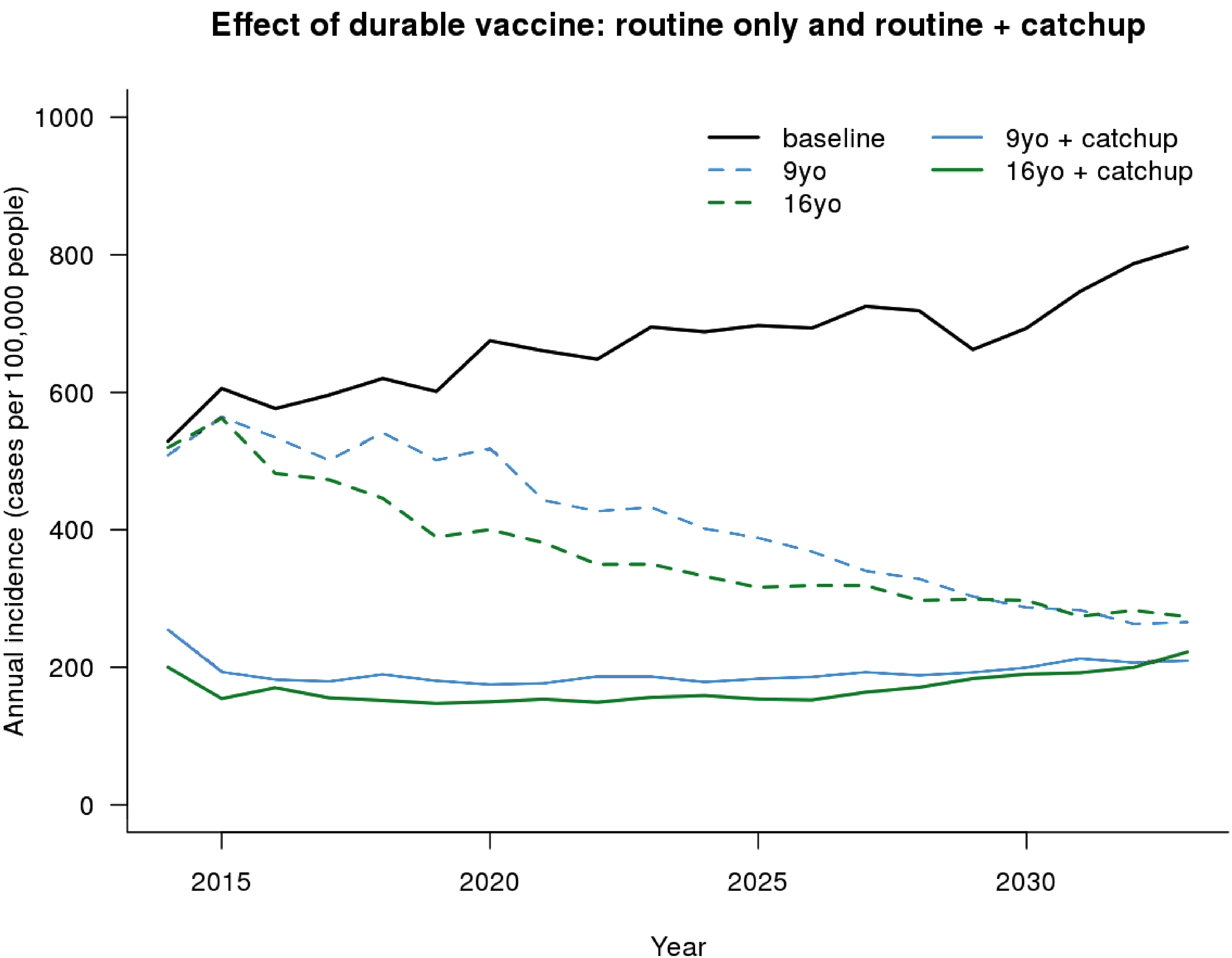
Serotype	Vaccine Efficacy*		
	Antibody positive	Antibody negative	Overall**
1	60	30	50
2	54	27	42
3	90	45	74
4	95	48	78

* Assuming leaky vaccine effect

** Based on 60% antibody positive

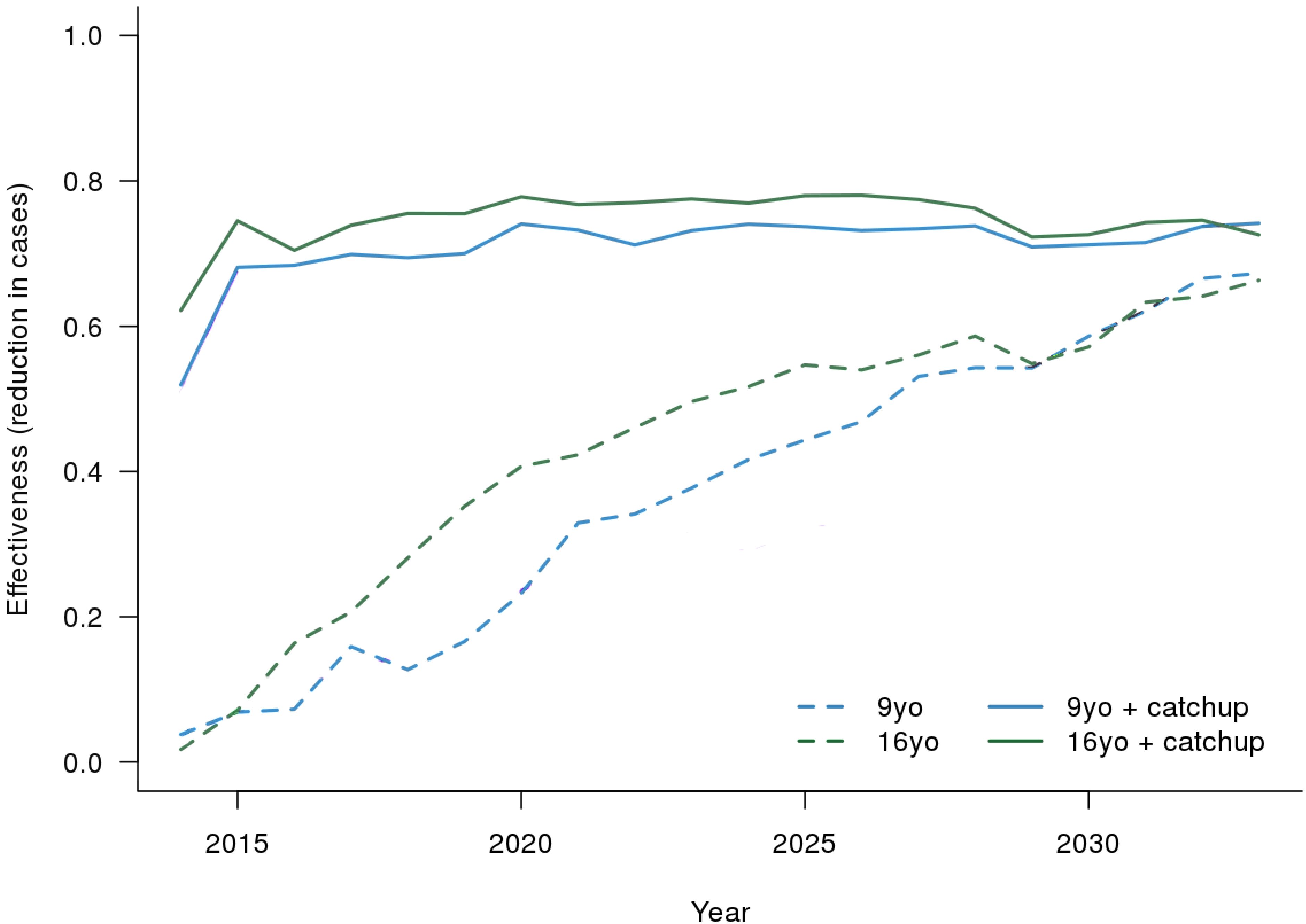
Yucatan Simulation with Vaccination

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



Hladish et al (2016), *in review*.

Effectiveness of durable vaccine: routine only and routine + catchup

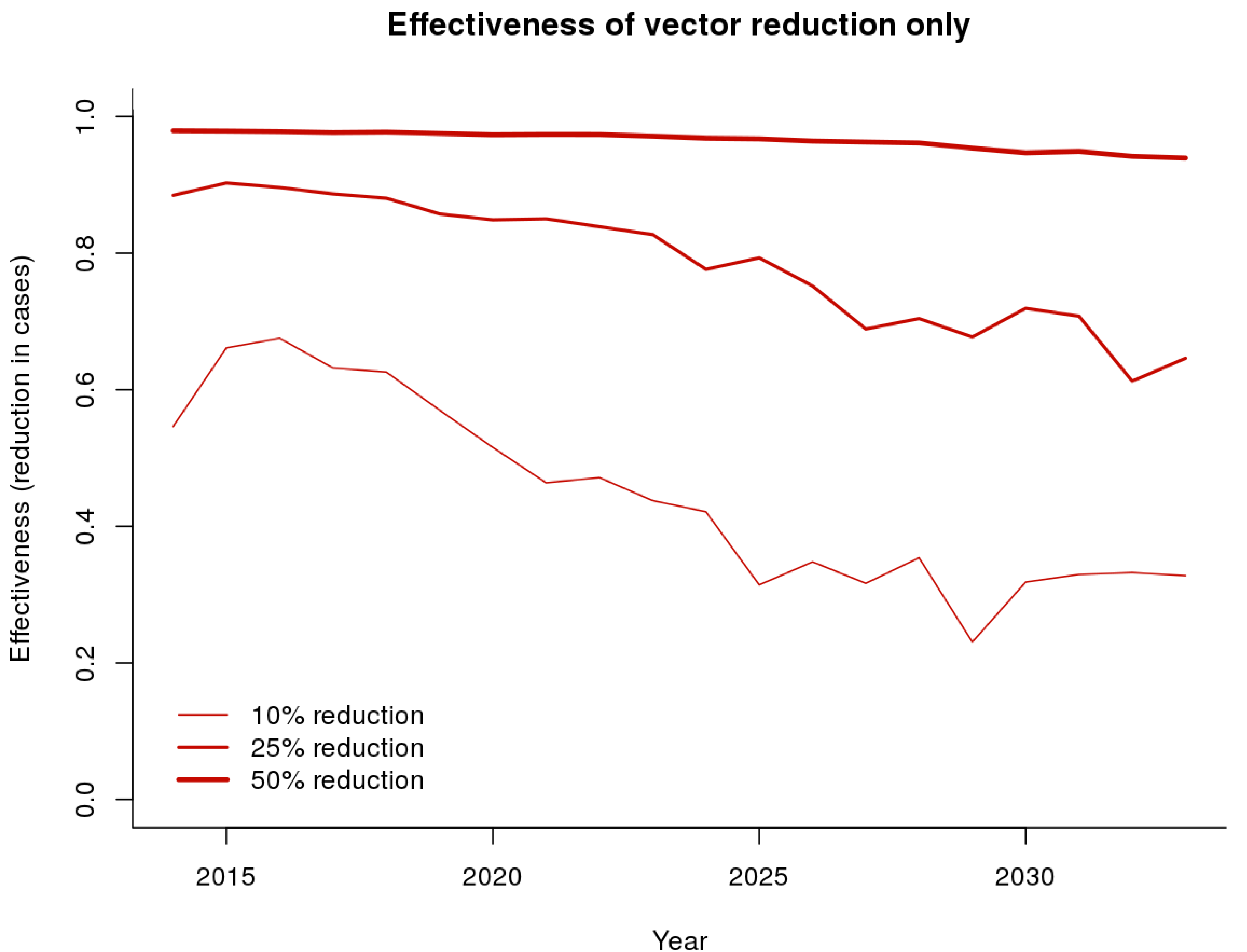


Hladish et al (2016), *in review*.

Vector reduction model

- Simulate past dynamics (1878-2013)
- Reduce mosquito population by 10, 25, or 50% (2014-2033)

Vector reduction ≠ vector control



Hladish et al (2016), *in prep*.

Why does vector reduction lose effectiveness?

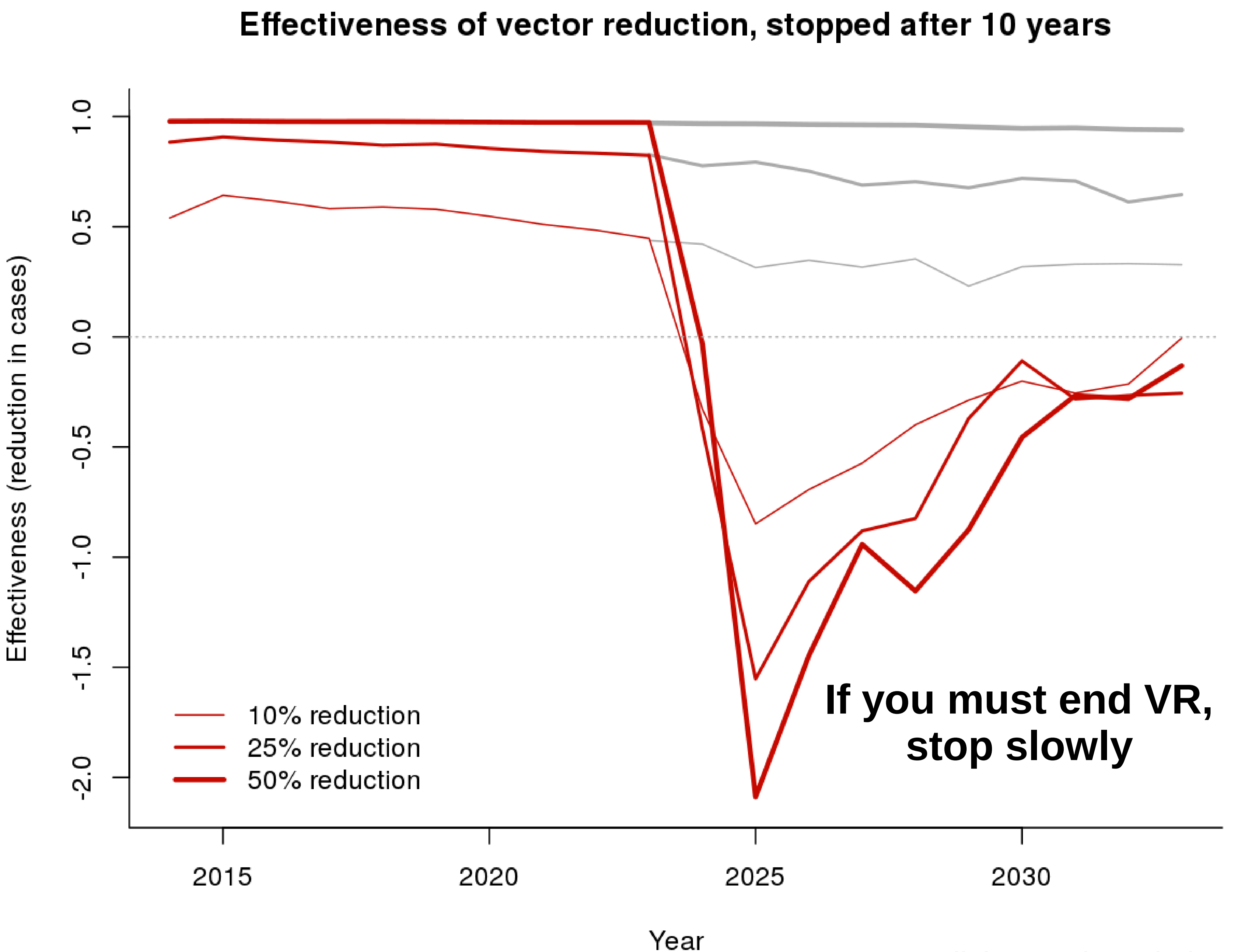
Initially:

High natural immunity + VC = small epidemics

Later:

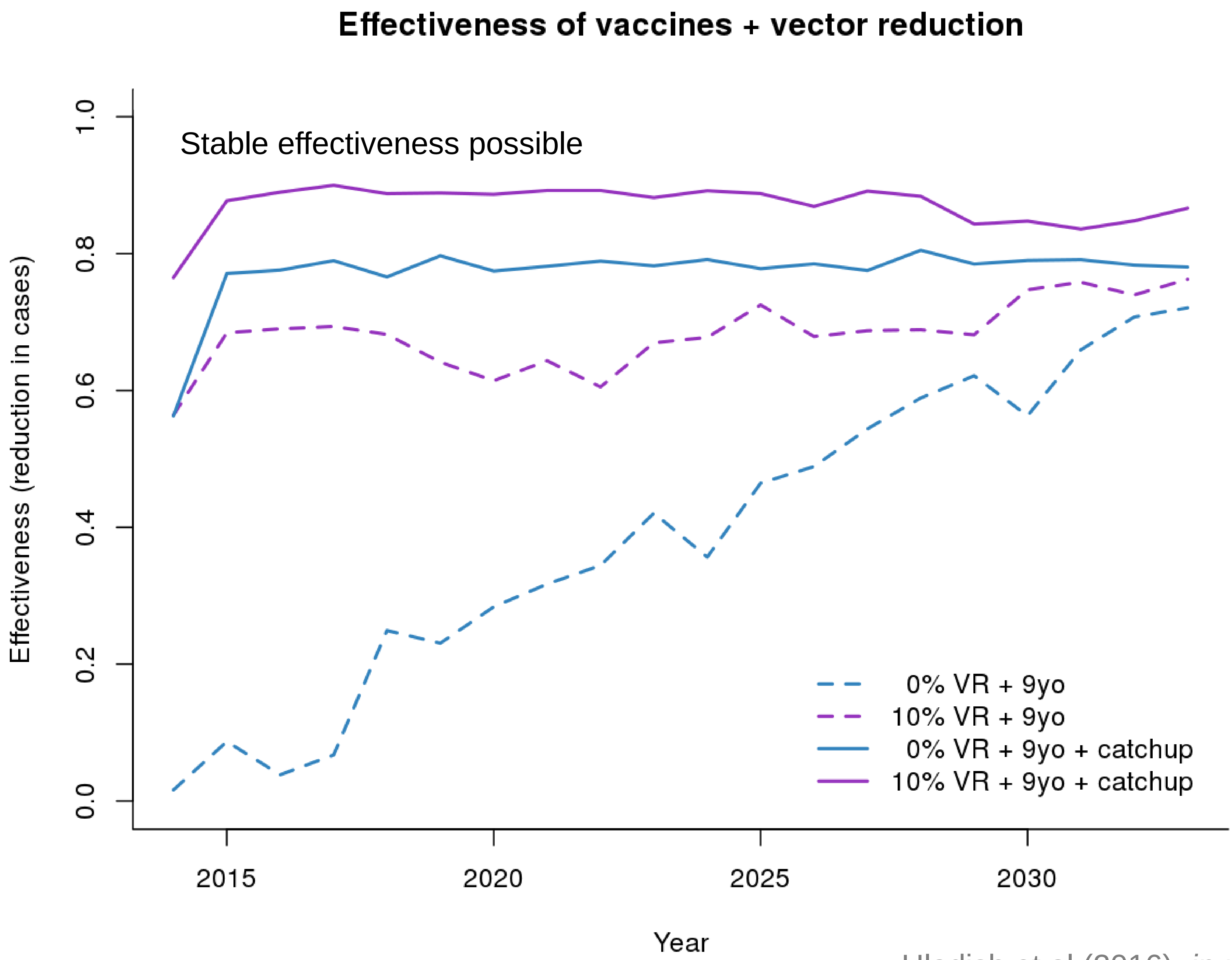
Modest natural immunity + VC = ~normal epidemics

What if we stop?



Hladish et al (2016), *in prep*.

Effects of new vector reduction plus vaccination



Hladish et al (2016), *in prep*.

Overall conclusions

Modest interventions not bad, may be politically untenable

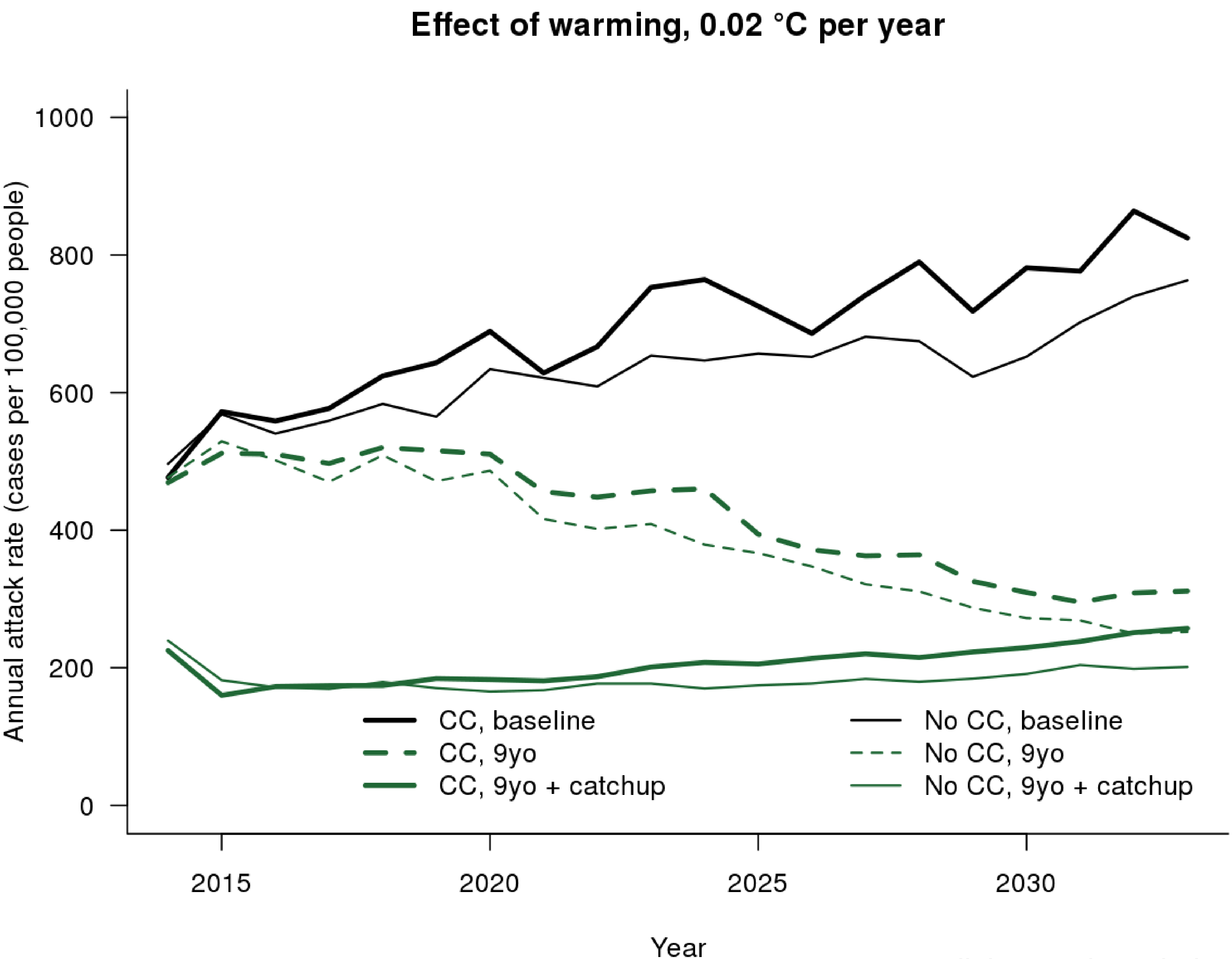
- Vector reduction effectiveness doesn’t persist
- Routine vaccination effectiveness starts low
- Noisy empirical data may obscure effectiveness
- Elimination unlikely

Catchup, Combined modest interventions promising

- Increased, sustained effectiveness
- Ambitious VR and catchup not needed

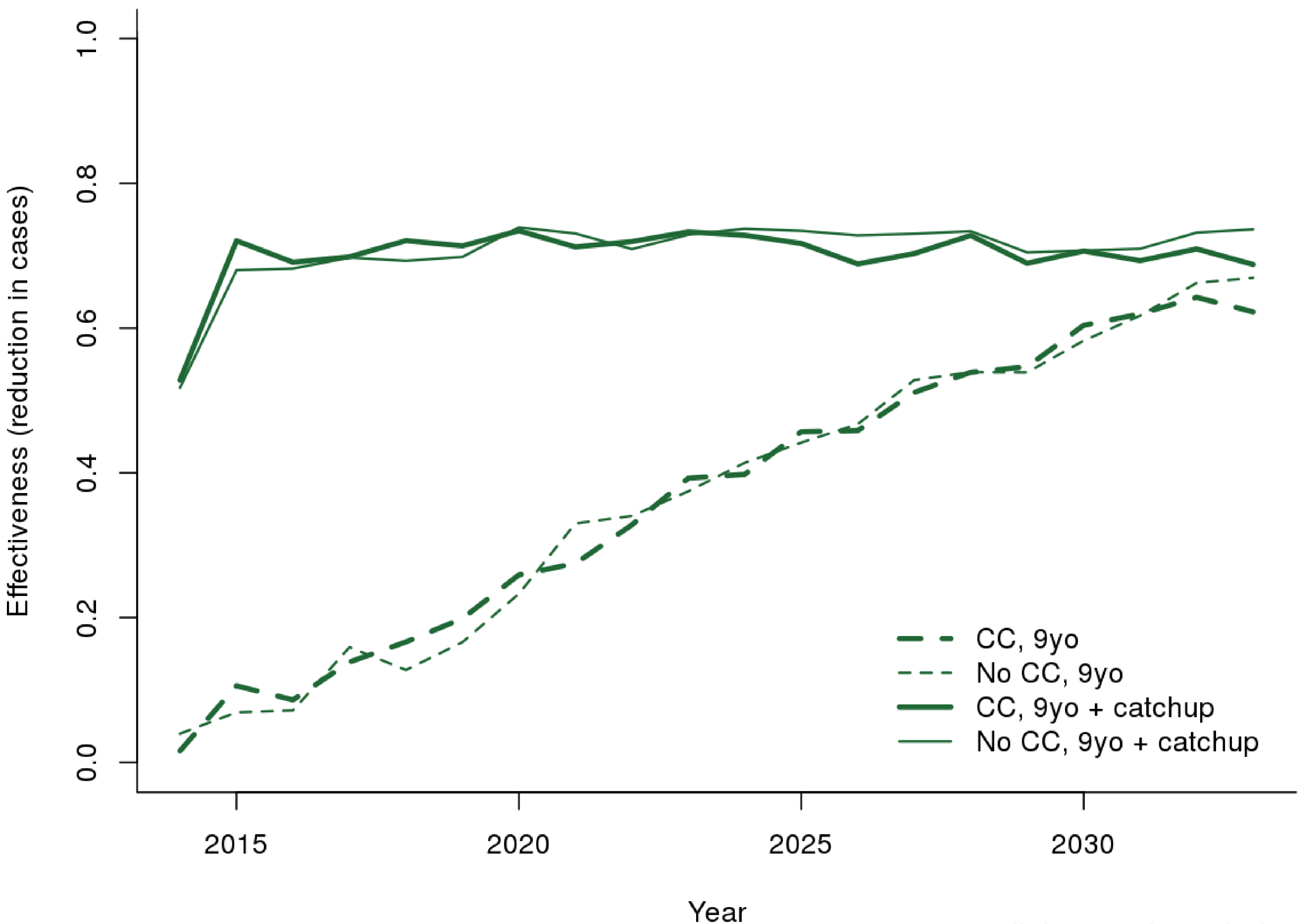
Cost-benefit analysis needed to find balance

Effect of climate change (+0.02 °C per year) on vaccination effectiveness



Hladish et al (2016), *in review*.

Effectiveness of vaccination, given warming, 0.02 °C per year



Hladish et al (2016), *in review*.

Thanks