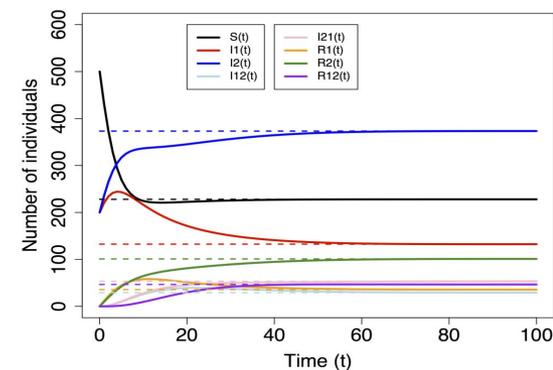


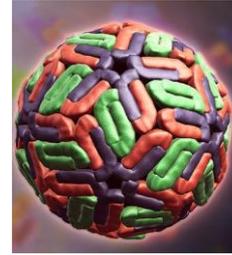
Mechanistic modelling of dengue transmission in Singapore

Ryan Chisholm

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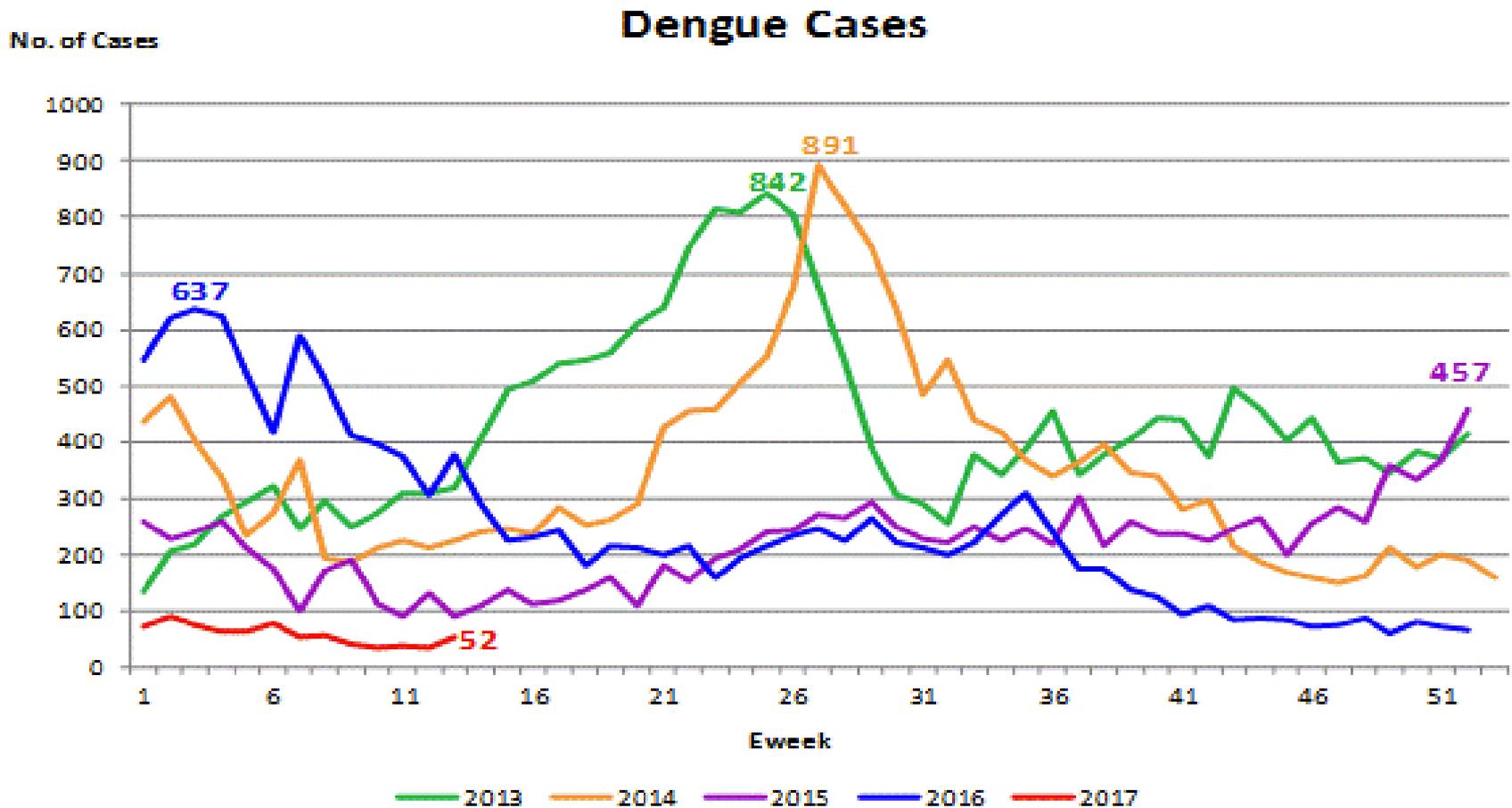
Dengue



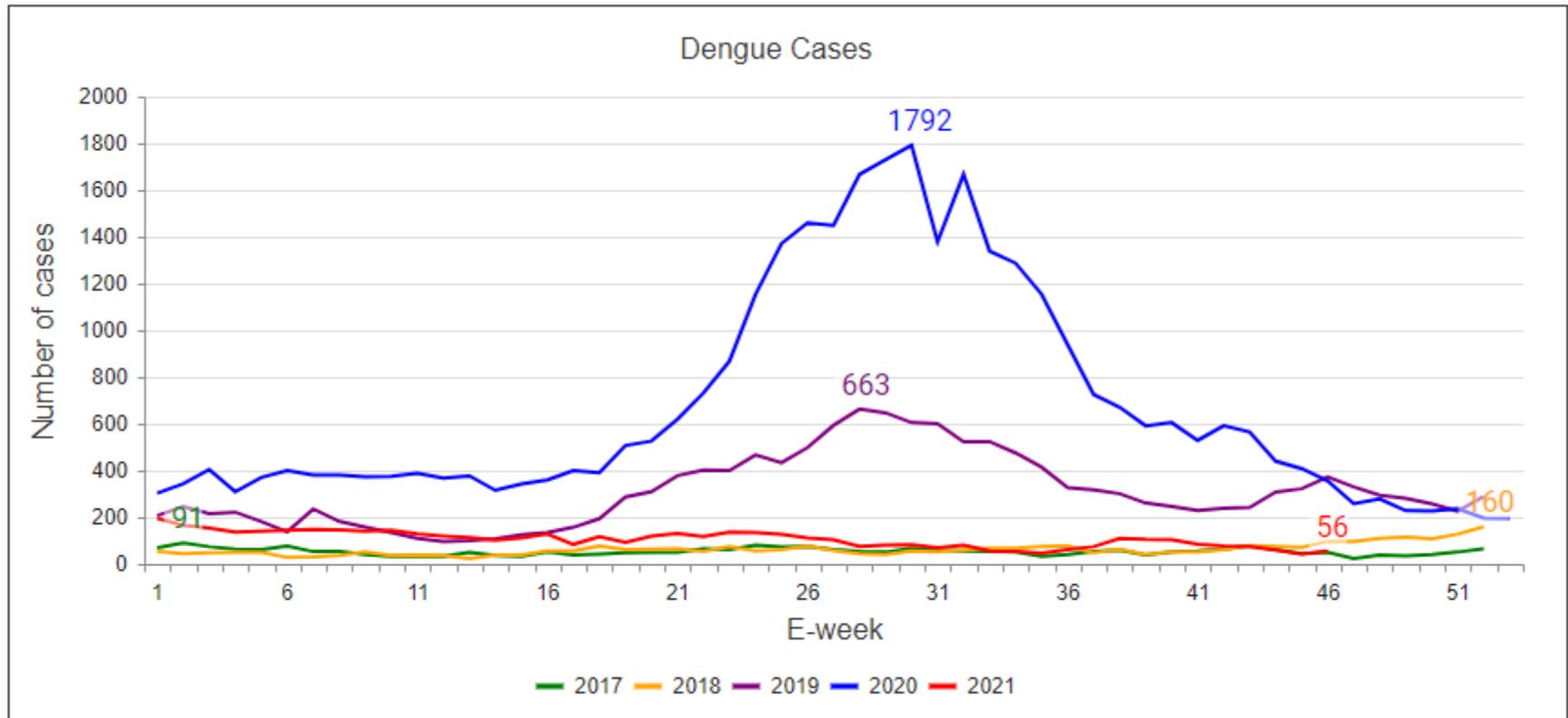
Aedes aegypti

- Member of the Flaviviridae virus family
- World's most prevalent mosquito-borne disease: over 100 million cases globally per year
- Four serotypes: infection with a second serotype can lead to more severe illness
- Historically serotypes DENV-1 and DENV-2 dominant in Singapore
- Over 35,000 cases and 32 deaths in Singapore in 2020 (mostly DENV-2 and DENV-3)

Dengue in Singapore



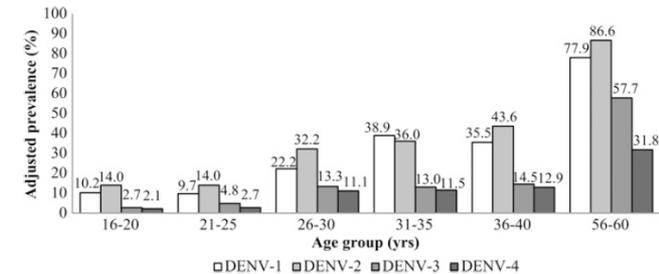
Dengue in Singapore



Dengue in Singapore

What drove the big 2020 outbreak?

- Lack of herd immunity to DENV-3?
- New strains?
- Work-from-home policies (due to COVID)?



Dengue in Singapore

1. What drives overall case numbers?
2. What drives the multi-serotype dynamics?

Dengue in Singapore

Grant under NUS Reimagine
Research Initiative



Department of Biological Sciences
Faculty of Science



Ryan Chisholm



Duane Loh



Saw Swee Hock
School of Public Health



Hannah Clapham



Natasha Howard

Modelling dengue in Singapore

Mechanistic models:

- Mathematical descriptions from first principles of the processes of infection, recovery, vaccination, quarantine, etc.

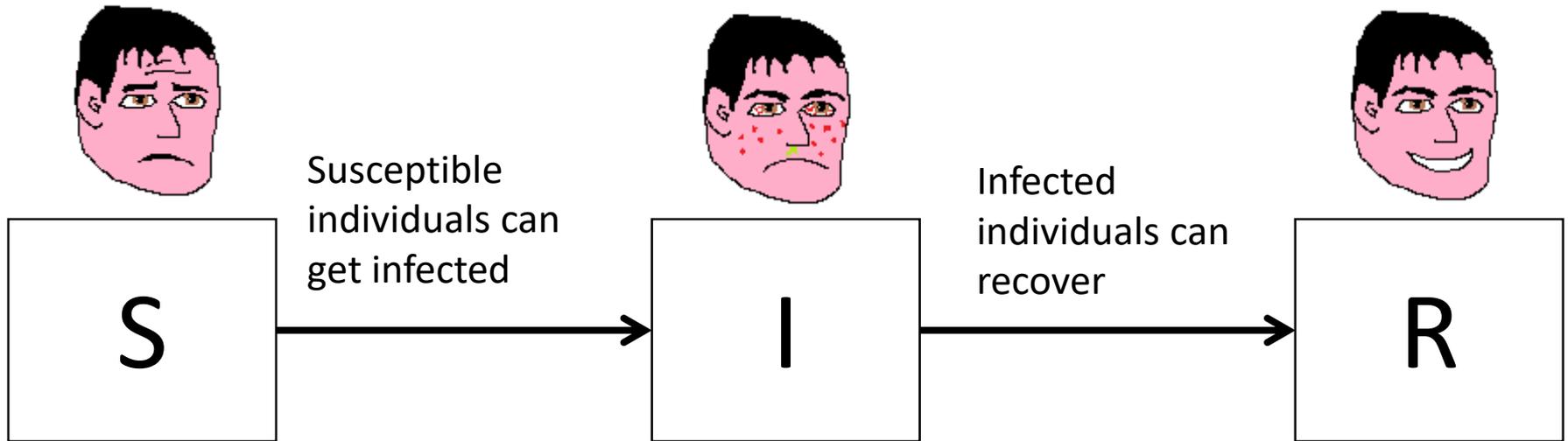
Can give more insight into the actual drivers of epidemics and, in principle, give predictions under novel conditions

Statistical models:

- Identification of statistical patterns in data

Can be good at short-term prediction under conditions similar to past

SIR models



SIR model



$$\frac{dS}{dt} = -\frac{\beta SI}{N}$$



$$\frac{dI}{dt} = \frac{\beta SI}{N} - \gamma I$$

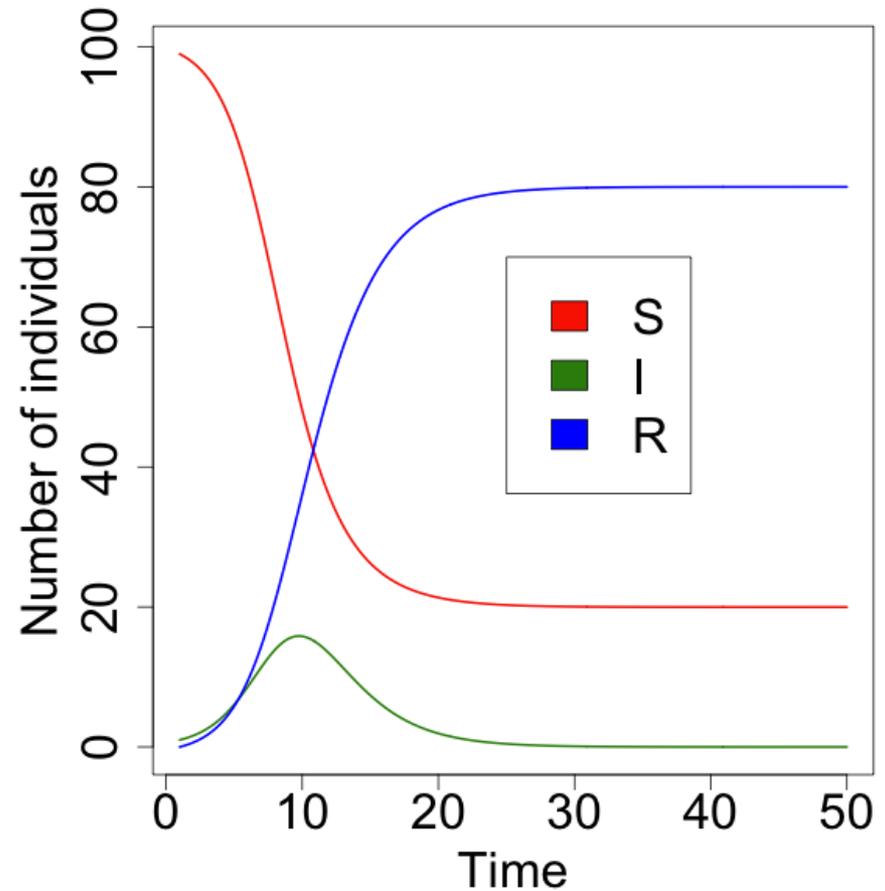


$$\frac{dR}{dt} = \gamma I$$

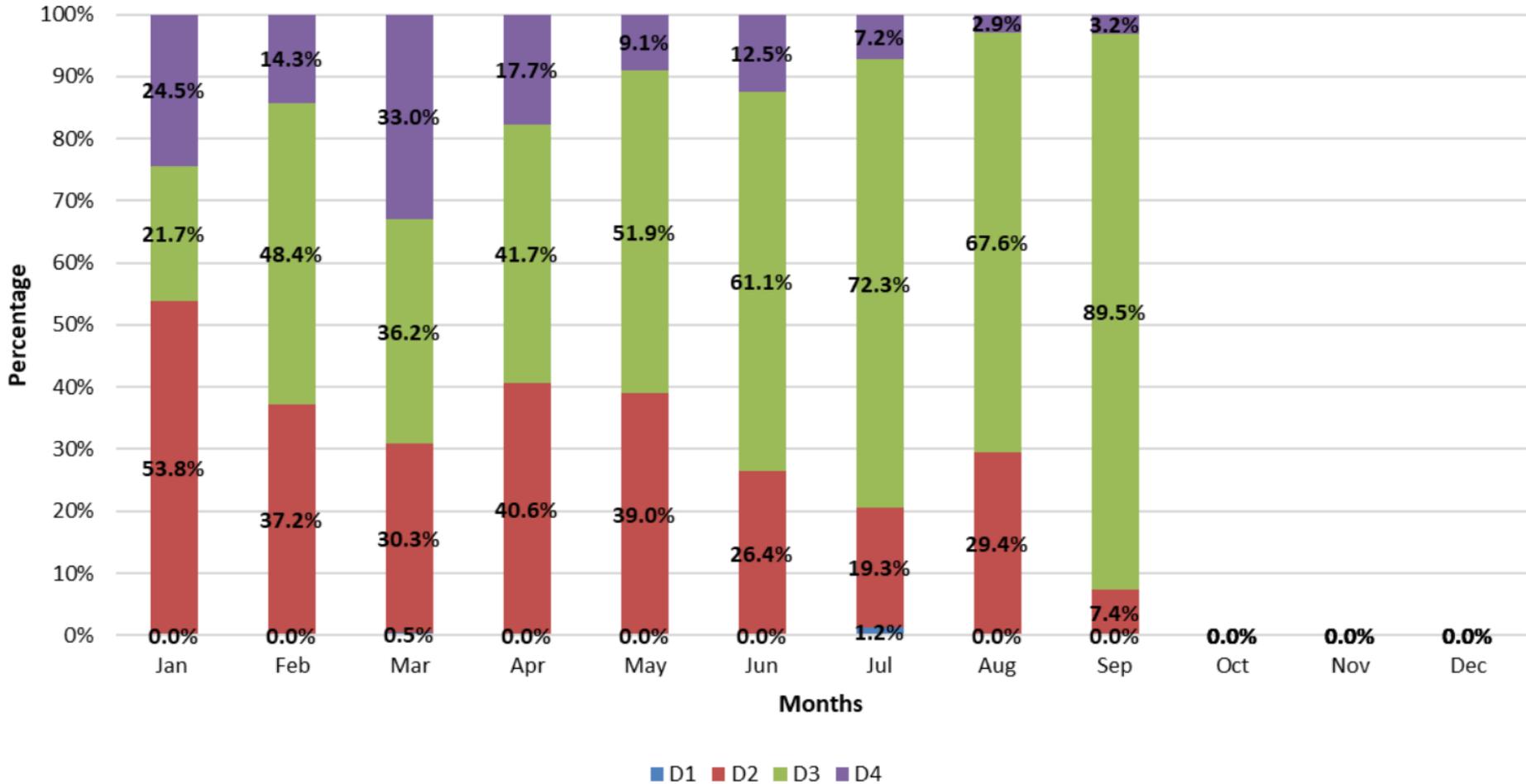
β is the transmission rate

γ is the recovery rate

$N = S + I + R$ is the population size



Surveillance of Dengue Virus Serotypes 2021

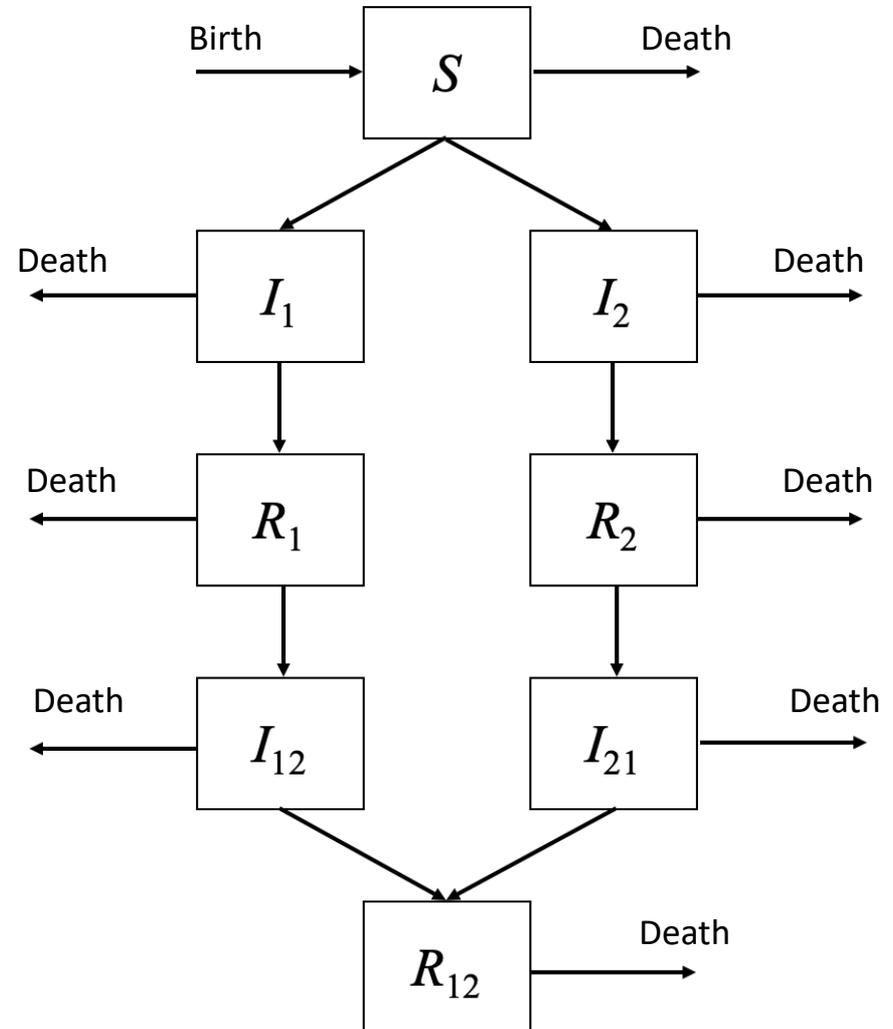


Multi-serotype SIR model

Model with two serotypes,
partial cross-immunity, natural
births and deaths, disease-
induced deaths

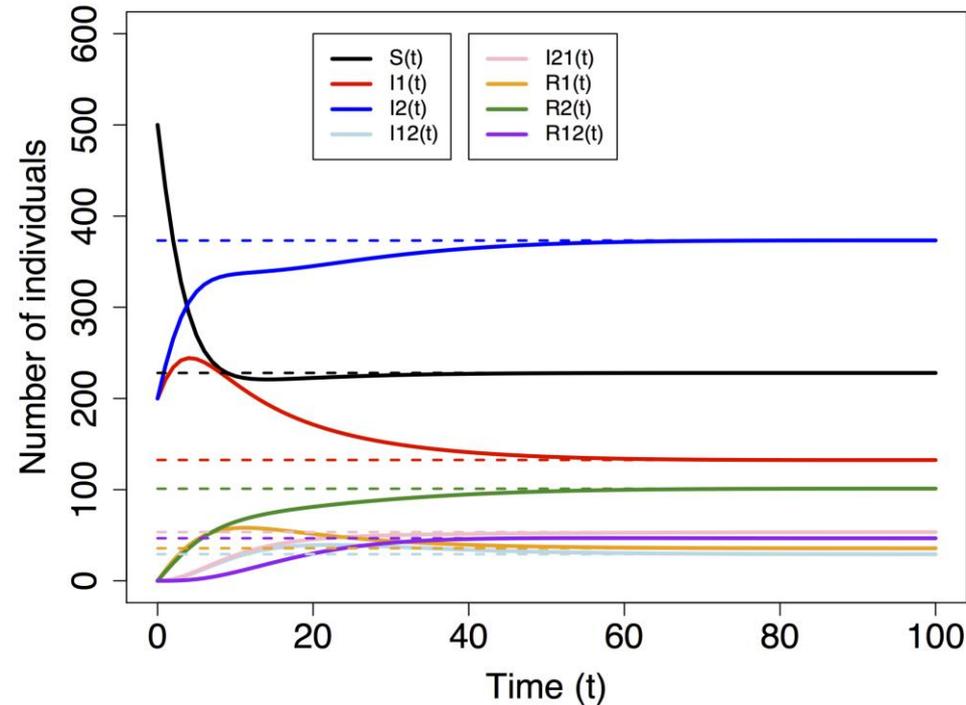


Tak Fung



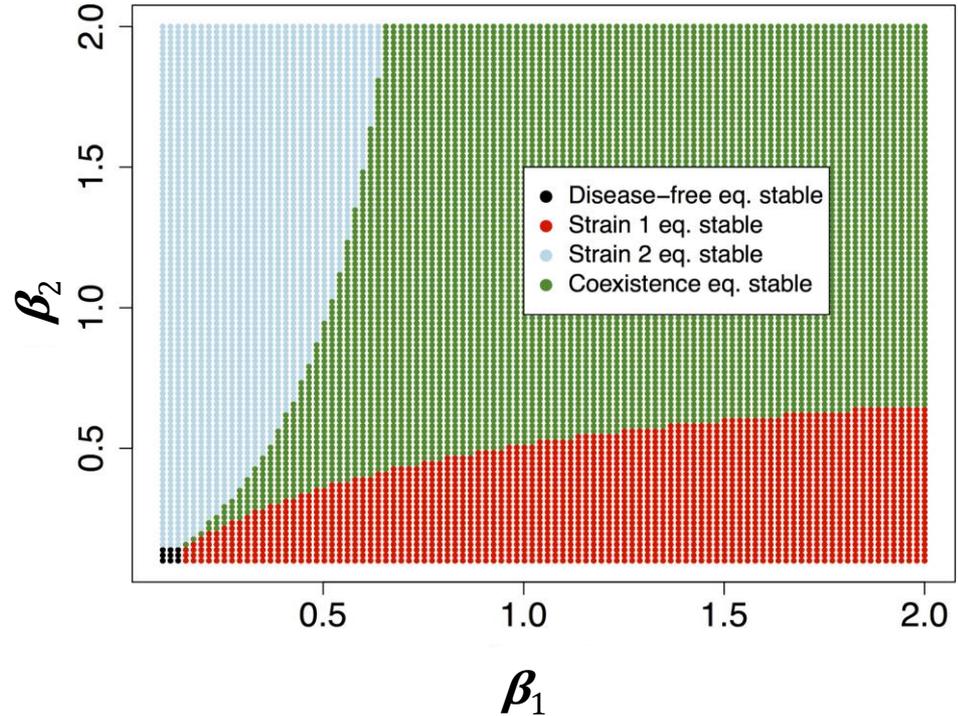
Multi-serotype SIR model

$$\begin{aligned} \frac{dS}{dt} &= \Lambda - \beta_1 \frac{S(I_1 + I_{21})}{N} - \beta_2 \frac{S(I_2 + I_{12})}{N} - \mu S \\ \frac{dI_1}{dt} &= \beta_1 \frac{S(I_1 + I_{21})}{N} - (\mu + \alpha_1) I_1 \\ \frac{dI_2}{dt} &= \beta_2 \frac{S(I_2 + I_{12})}{N} - (\mu + \alpha_2) I_2 \\ \frac{dI_{12}}{dt} &= \sigma_1 \beta_2 \frac{R_1(I_2 + I_{12})}{N} - (\mu + \alpha_2) I_{12} \\ \frac{dI_{21}}{dt} &= \sigma_2 \beta_1 \frac{R_2(I_1 + I_{21})}{N} - (\mu + \alpha_1) I_{21} \\ \frac{dR_1}{dt} &= \alpha_1 I_1 - \sigma_1 \beta_2 \frac{R_1(I_2 + I_{12})}{N} - \mu R_1 \\ \frac{dR_2}{dt} &= \alpha_2 I_2 - \sigma_2 \beta_1 \frac{R_2(I_1 + I_{21})}{N} - \mu R_2 \\ \frac{dR_{12}}{dt} &= \alpha_1 I_{21} + \alpha_2 I_{12} - \mu R_{12} \end{aligned}$$



Multi-serotype SIR model

$$\begin{aligned} \frac{dS}{dt} &= \Lambda - \beta_1 \frac{S(I_1 + I_{21})}{N} - \beta_2 \frac{S(I_2 + I_{12})}{N} - \mu S \\ \frac{dI_1}{dt} &= \beta_1 \frac{S(I_1 + I_{21})}{N} - (\mu + \alpha_1)I_1 \\ \frac{dI_2}{dt} &= \beta_2 \frac{S(I_2 + I_{12})}{N} - (\mu + \alpha_2)I_2 \\ \frac{dI_{12}}{dt} &= \sigma_1 \beta_2 \frac{R_1(I_2 + I_{12})}{N} - (\mu + \alpha_2)I_{12} \\ \frac{dI_{21}}{dt} &= \sigma_2 \beta_1 \frac{R_2(I_1 + I_{21})}{N} - (\mu + \alpha_1)I_{21} \\ \frac{dR_1}{dt} &= \alpha_1 I_1 - \sigma_1 \beta_2 \frac{R_1(I_2 + I_{12})}{N} - \mu R_1 \\ \frac{dR_2}{dt} &= \alpha_2 I_2 - \sigma_2 \beta_1 \frac{R_2(I_1 + I_{21})}{N} - \mu R_2 \\ \frac{dR_{12}}{dt} &= \alpha_1 I_{21} + \alpha_2 I_{12} - \mu R_{12} \end{aligned}$$



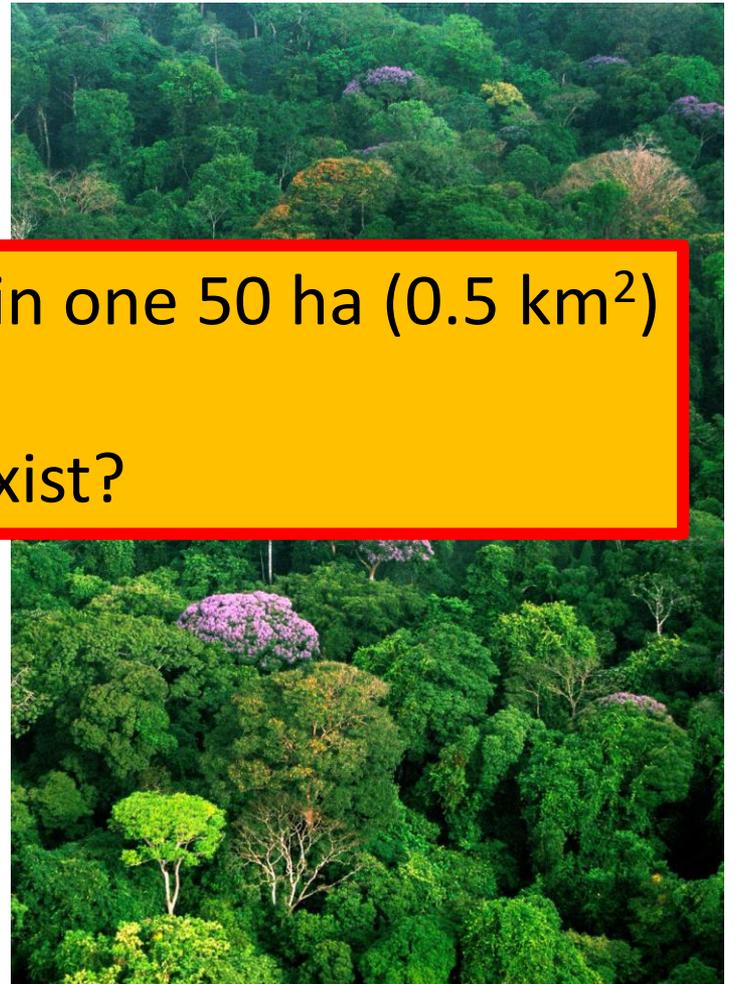
Dengue in Singapore

- What drives overall case numbers?

Tropical tree diversity



Over 300 tree species found in one 50 ha (0.5 km²) forest plot!
How do all these species coexist?



Tropical tree diversity

How do hundreds of tree species coexist in 50 ha?

Hypothesis 1: Local processes—each species has its own niche

Hypothesis 2: Continued dispersal from the wider landscape

Dengue in Singapore

What drives dengue case numbers in Singapore?

Hypothesis 1: Local processes—level of herd immunity to each serotype, control efforts, etc.

Hypothesis 2: Dispersal from surrounding countries

Dengue in Singapore

Force of infection* ≈ 0.01

\Rightarrow Total cases per year $\approx 57,000$

\Rightarrow **Cases per day ≈ 150**

Number of international visitors per year $\approx 18.5\text{m}$

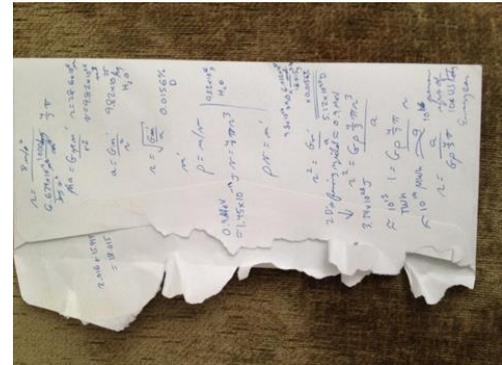
Suppose force of infection also ≈ 0.01 internationally

Infectious period[†] ≈ 5 days

\Rightarrow Infected visitors per day $\approx 18.5\text{m} \times 0.01/365 \times 5/365 =$ **7 infected visitors per day**

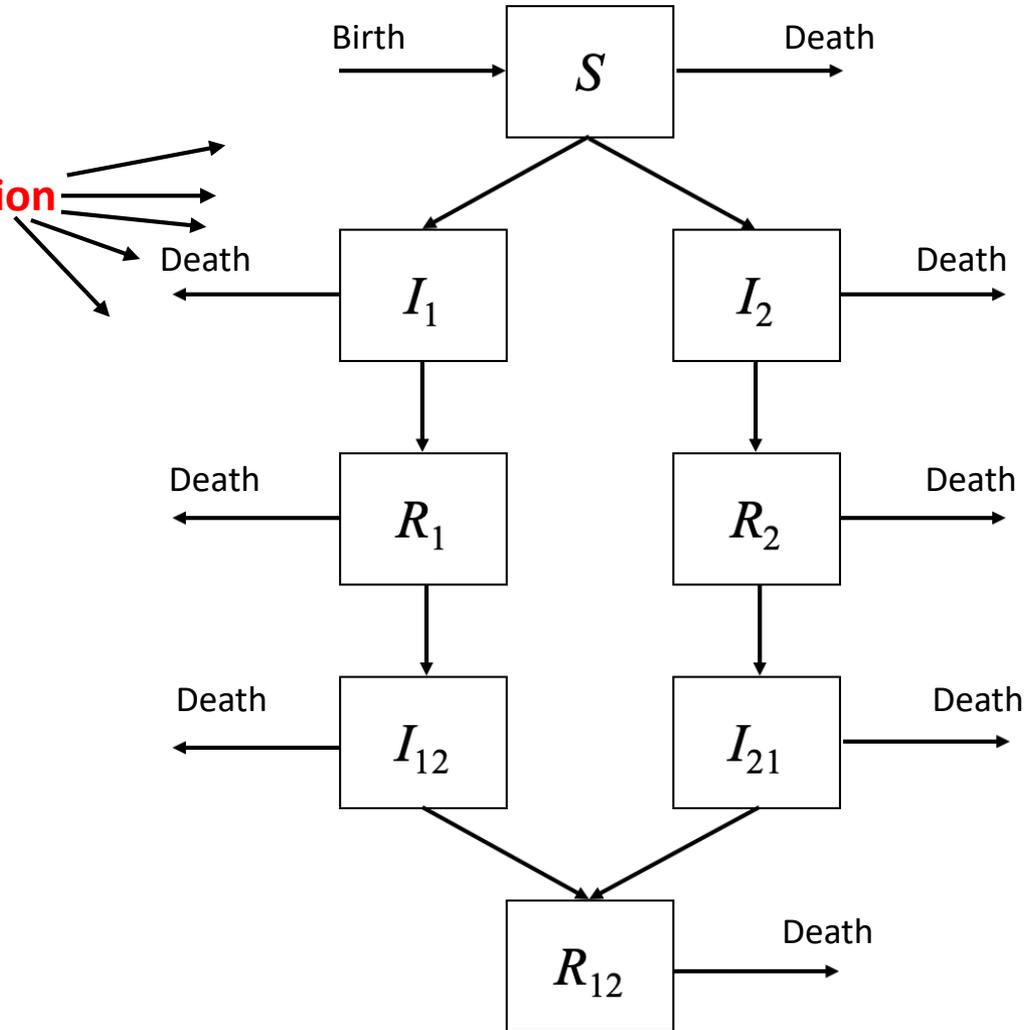
Immigration not a huge source of cases, but could potentially spark outbreaks during periods of low local transmission.

Could we perhaps get away with modelling immigration as just a small input that prevents local dengue extinction?



Multi-serotype SIR model

Model with two serotypes,
partial cross-immunity, natural
births and deaths, disease-
induced deaths, and **immigration**

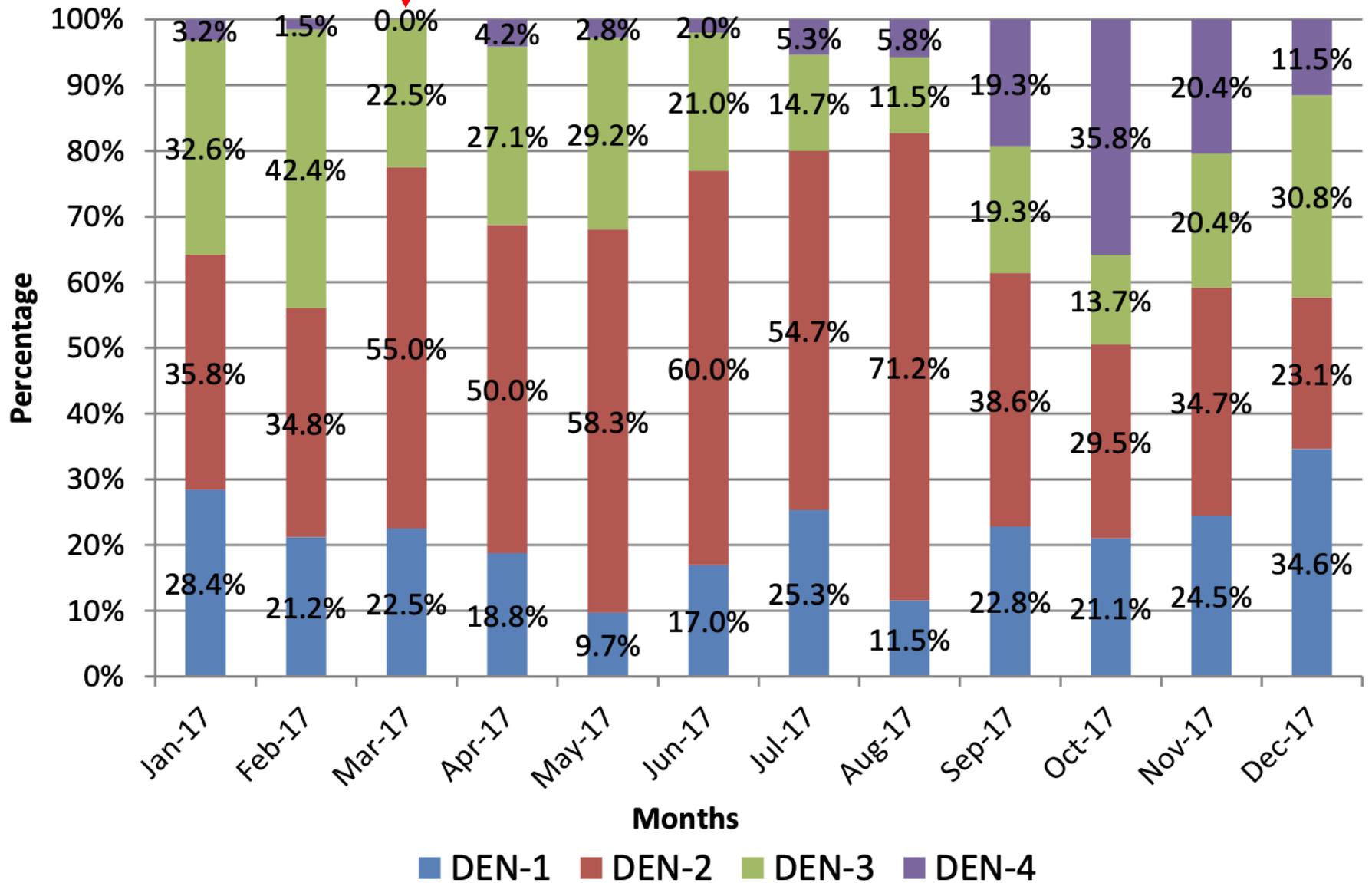


Dengue in Singapore

1. What drives overall case numbers?
2. What drives the multi-serotype dynamics?

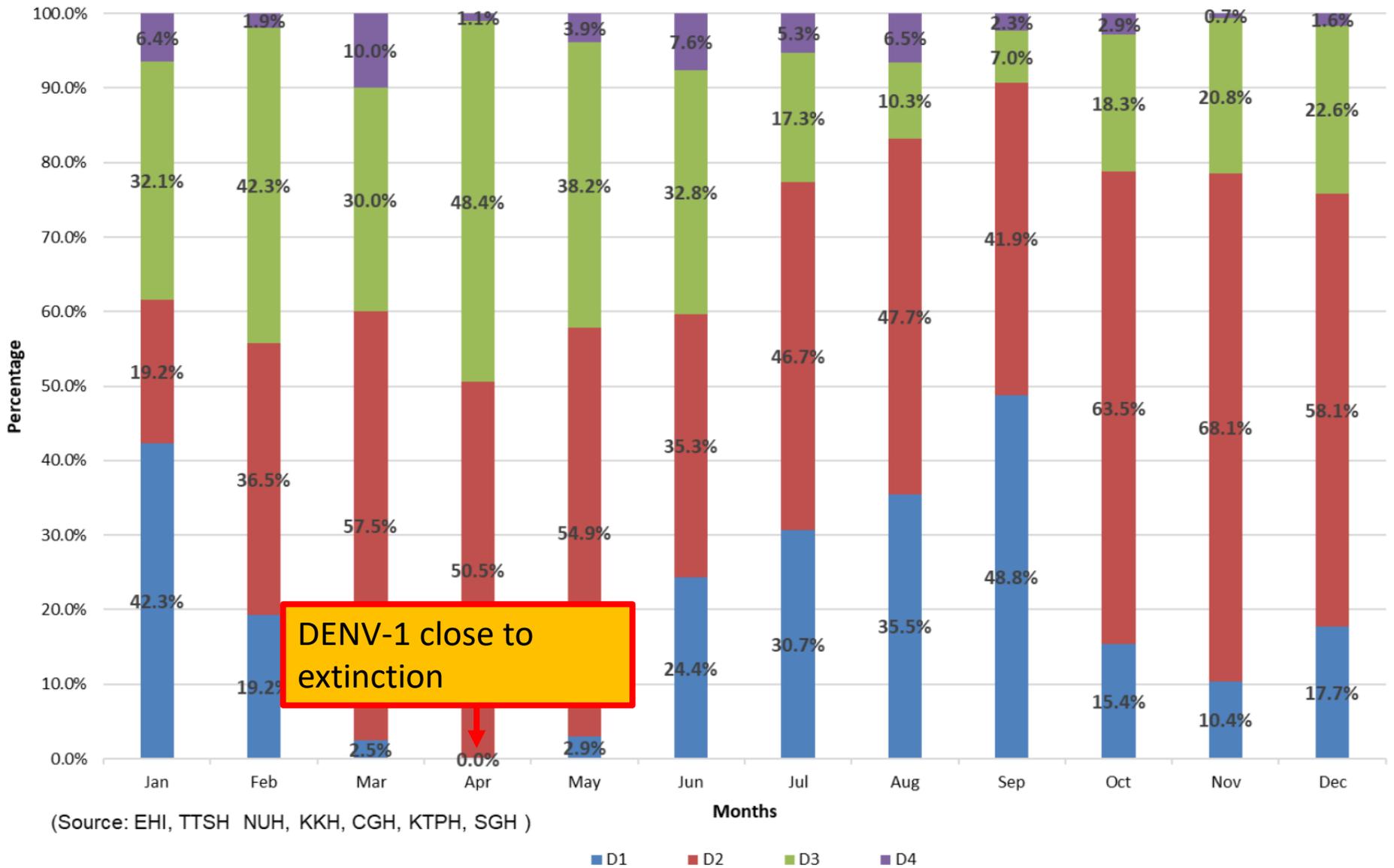
Summertime dengue virus serotypes 2017

DENV-4 close to extinction

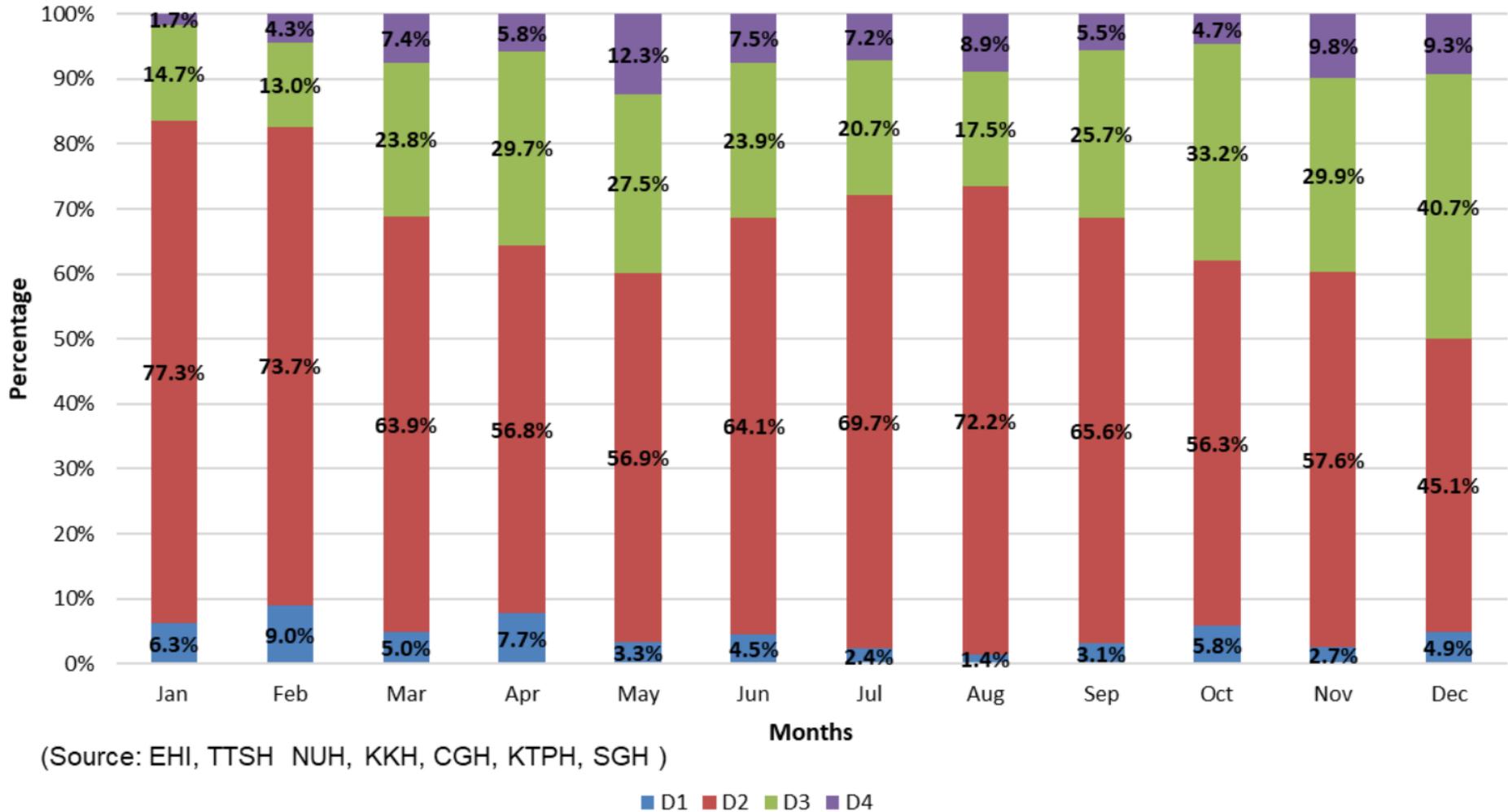


(Source: EHI, TTSH NUH, KKH, CGH, KTPH, SGH)

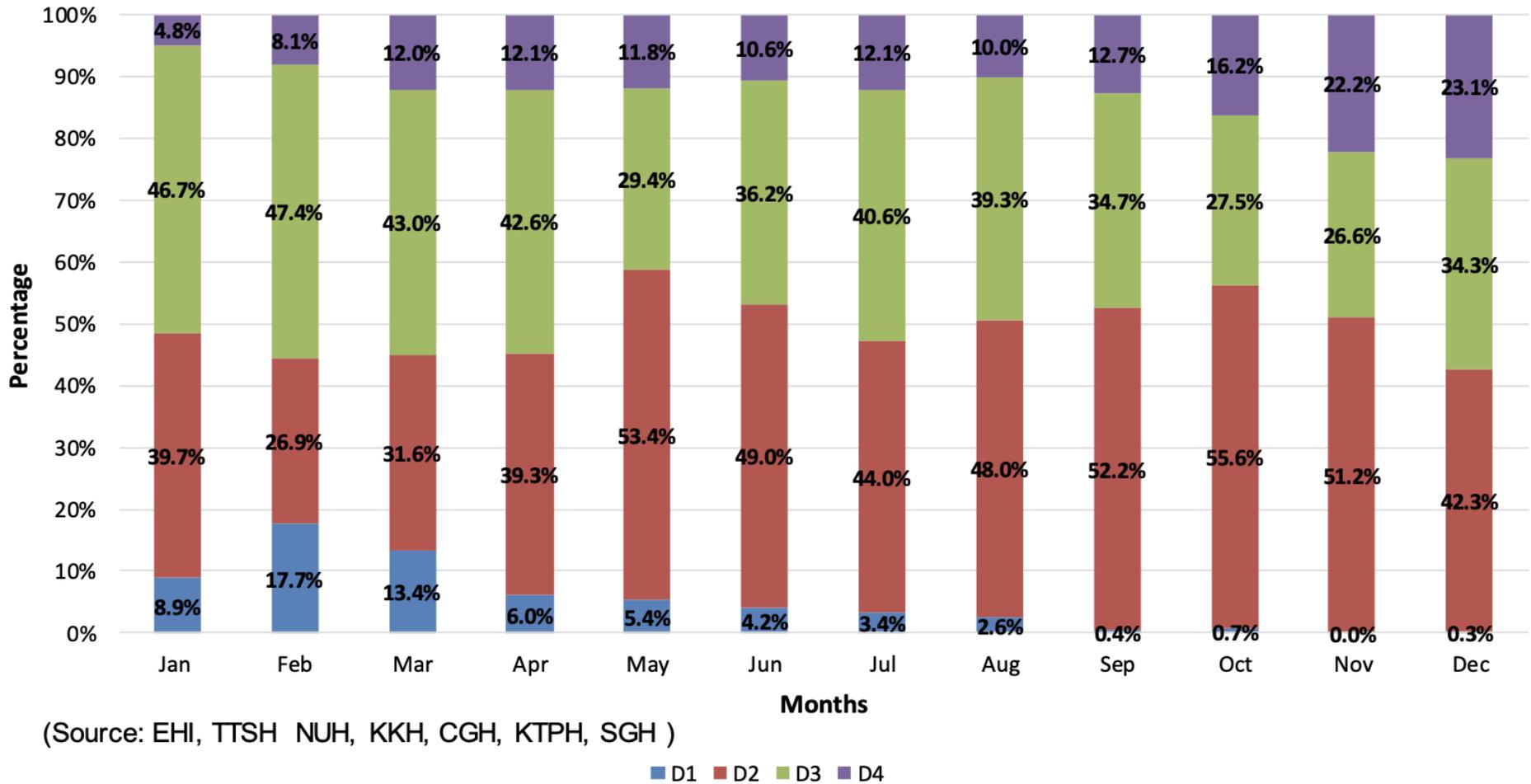
Surveillance of Dengue Virus Serotypes 2018



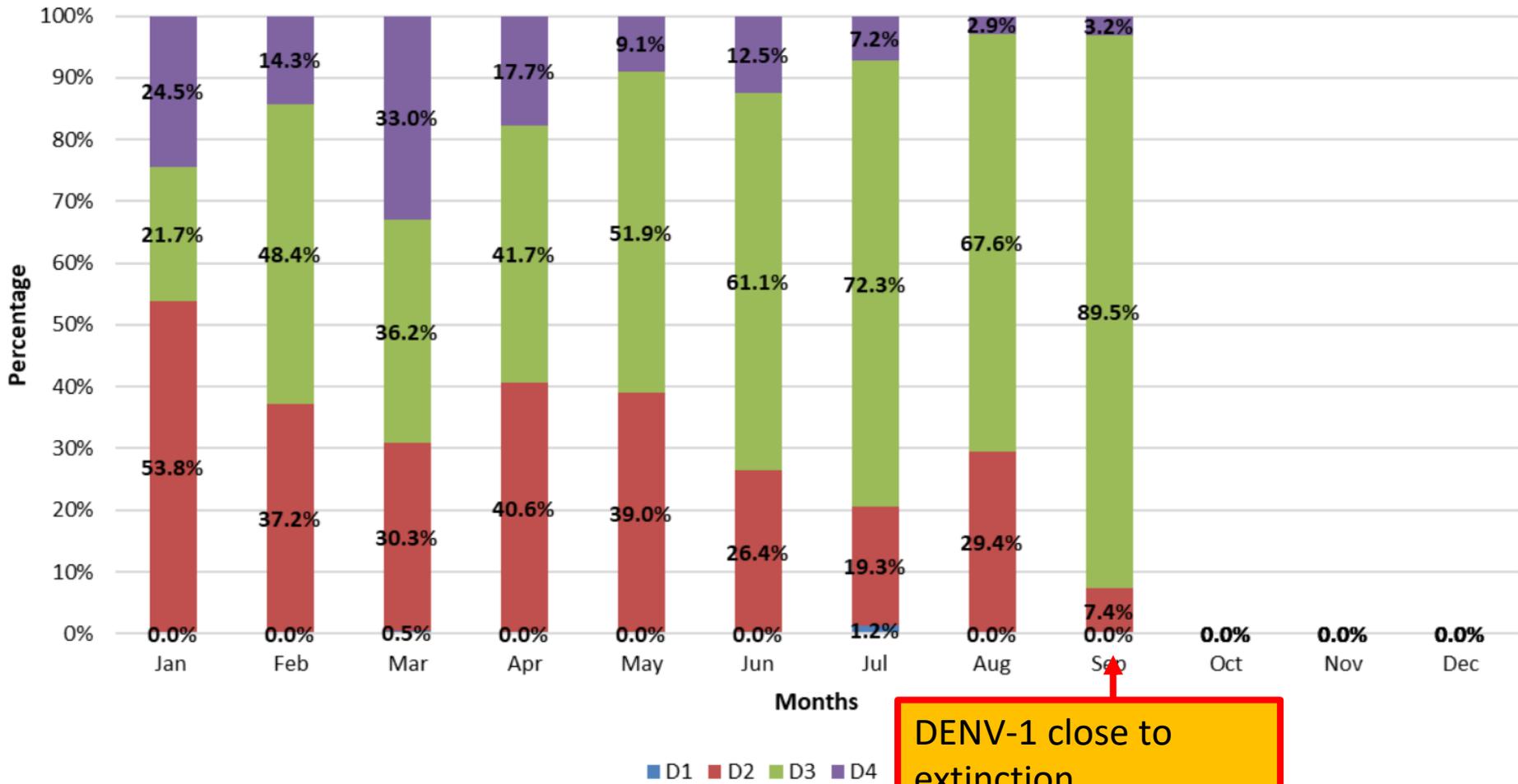
Surveillance of Dengue Virus Serotypes 2019



Surveillance of Dengue Virus Serotypes 2020



Surveillance of Dengue Virus Serotypes 2021



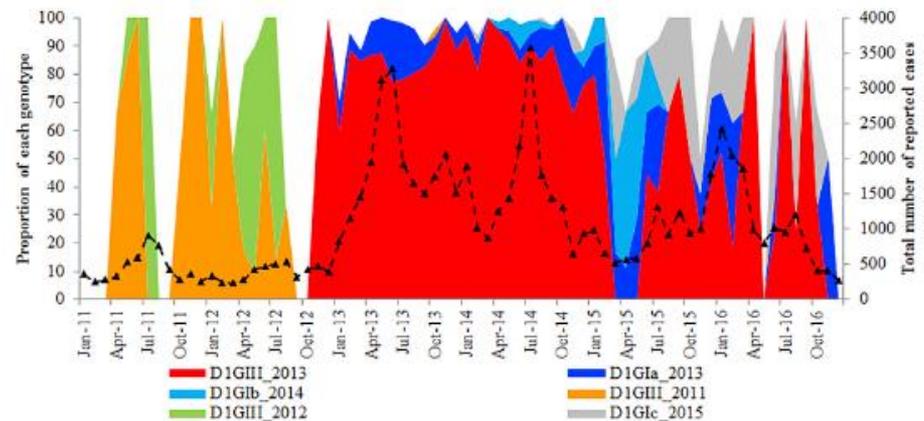
Dengue in Singapore

Likely need immigration in model to prevent extinction of each serotype.
But do we need even greater model complexity?

Koo *et al.* 2018 Highly Selective Transmission Success of Dengue Virus Type 1 Lineages in a Dynamic Virus Population: An Evolutionary and Fitness Perspective. *iScience* 6:38–51

“Given the relatively short time gap of emergence between each lineage, limited number of genotype III strains detected during 2009–12, and lack of intermediate sequences, we postulated that DENV-1 genotype III lineages observed since 2011 have been introduced rather than emerging through an in situ evolutionary process.”

“Each ‘established’ lineage shared a common regional ancestor, indicating the cross-border virus sharing.”



Dengue in Singapore

1. What drives overall case numbers?
2. What drives the multi-serotype dynamics?

Dengue in Singapore

Conclusions:

- Deterministic models with partial cross-immunity predict possible coexistence of multiple serotypes
- Immigration clearly important to dengue dynamics: prevents local extinction of serotypes and brings in new strains with different adaptations
- Beyond this, still unclear what the most important drivers of local outbreaks are:
 - Local factors?: herd immunity, control efforts, other policy changes (work-from-home)
 - Regional factors?: new strains

