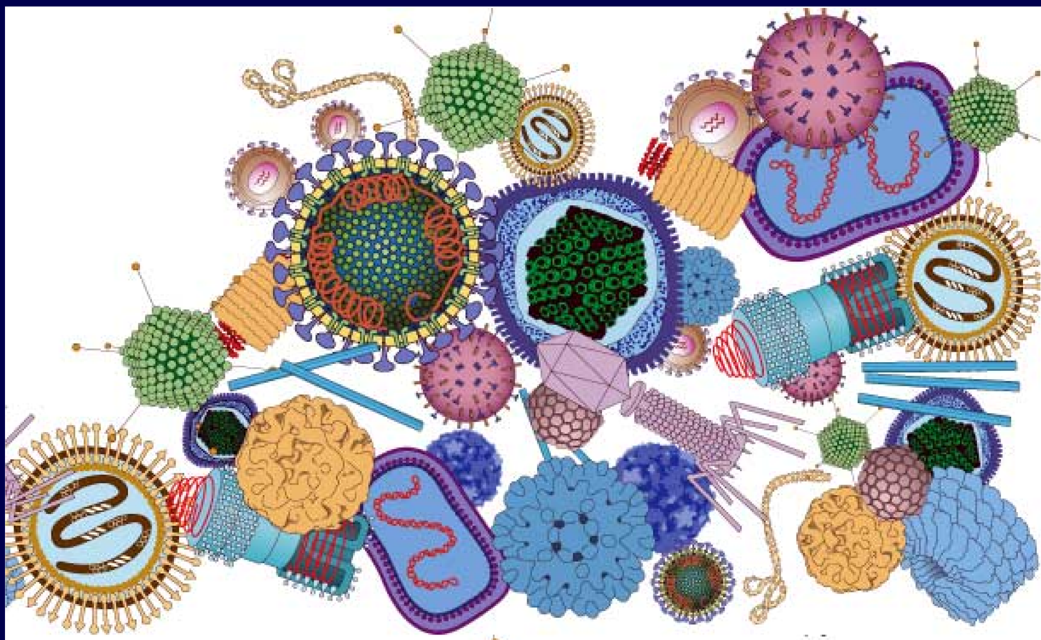
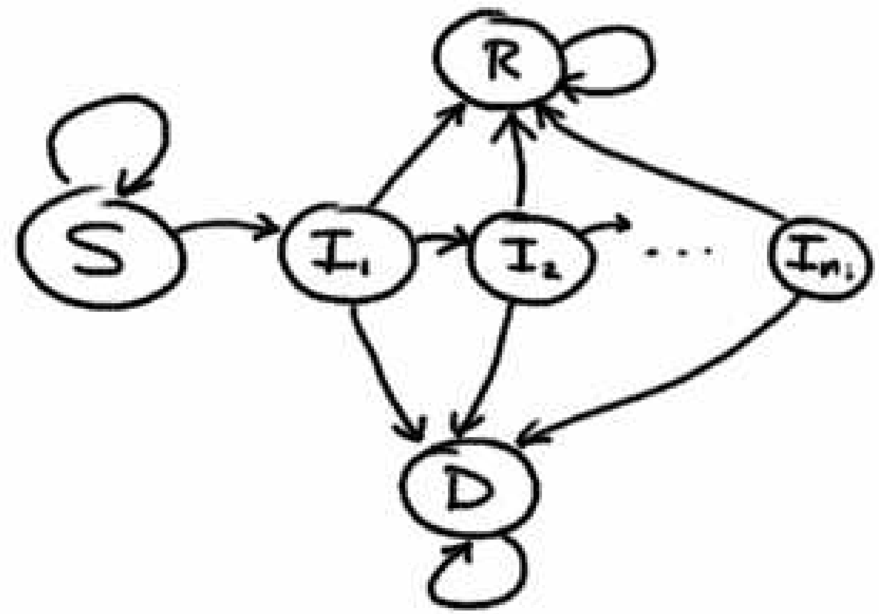
On the origin of complex dynamics in multi-strain dengue models





Maíra Aguiar

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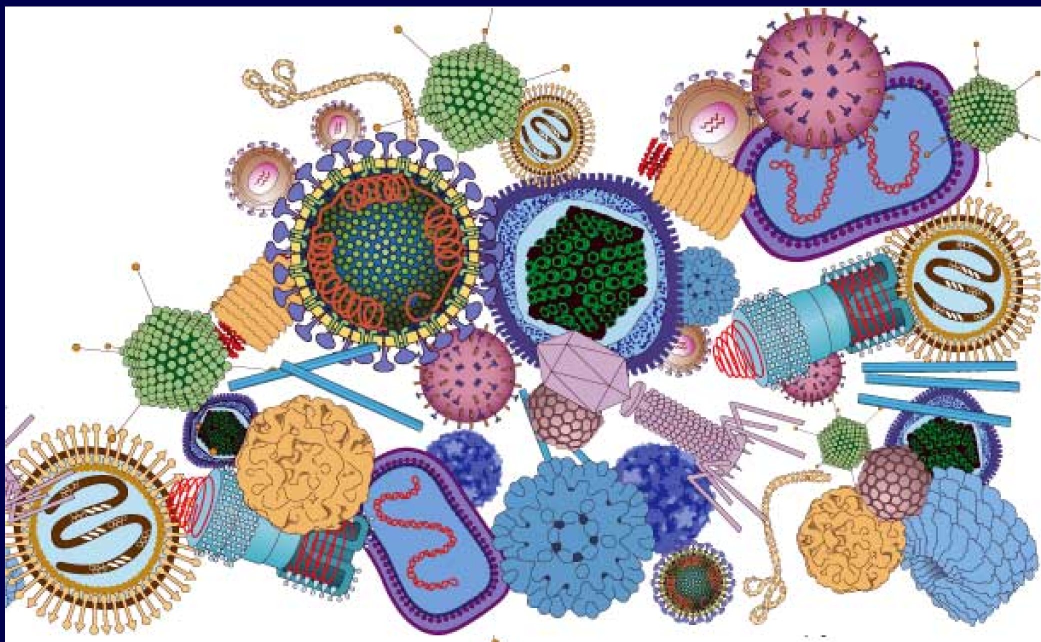
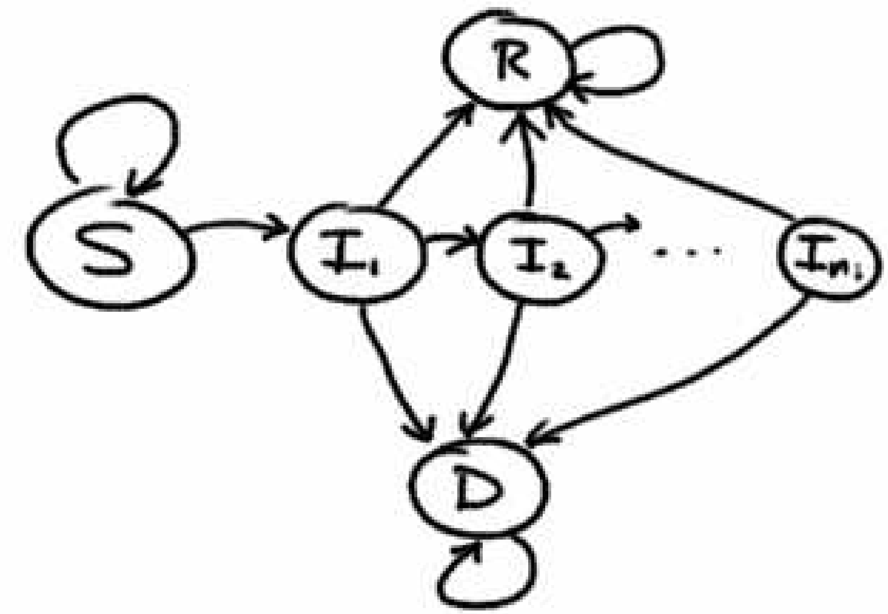
Mathematical and Theoretical Biology Group

On the origin of complex dynamics
in multi-strain dengue models



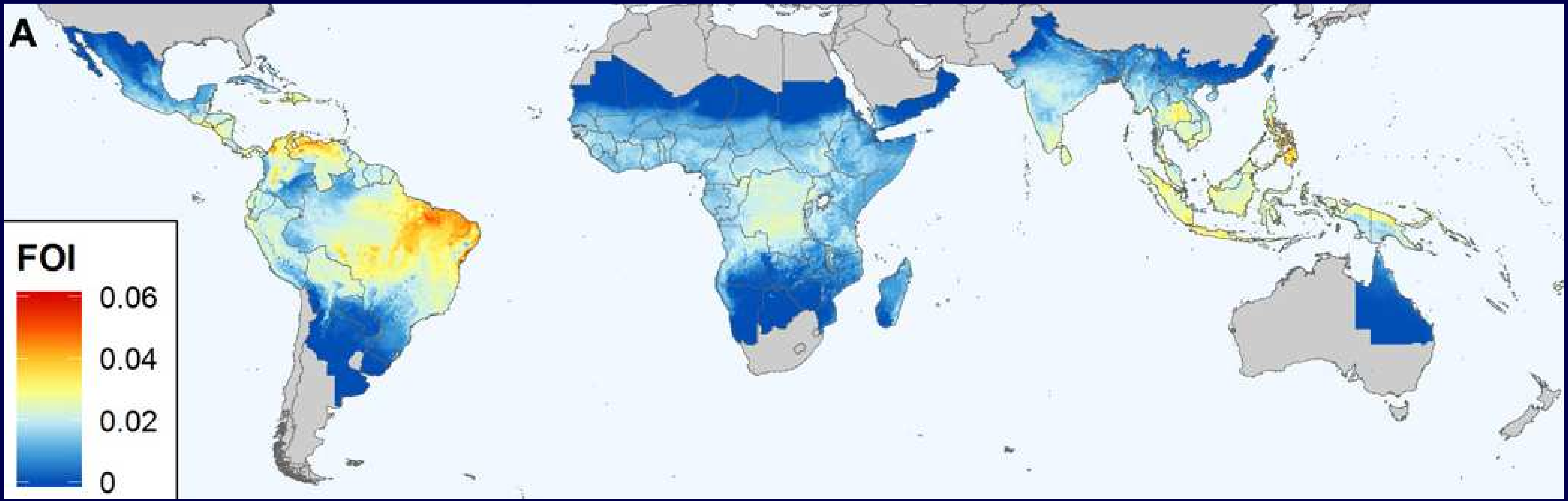


... and its impact on public health interventions
on chaotic epidemiological scenarios

Dengue fever epidemiology and modeling assumptions

- *Dengue is a viral mosquito-borne infection, a leading cause of illness and death in the tropics and subtropics.*

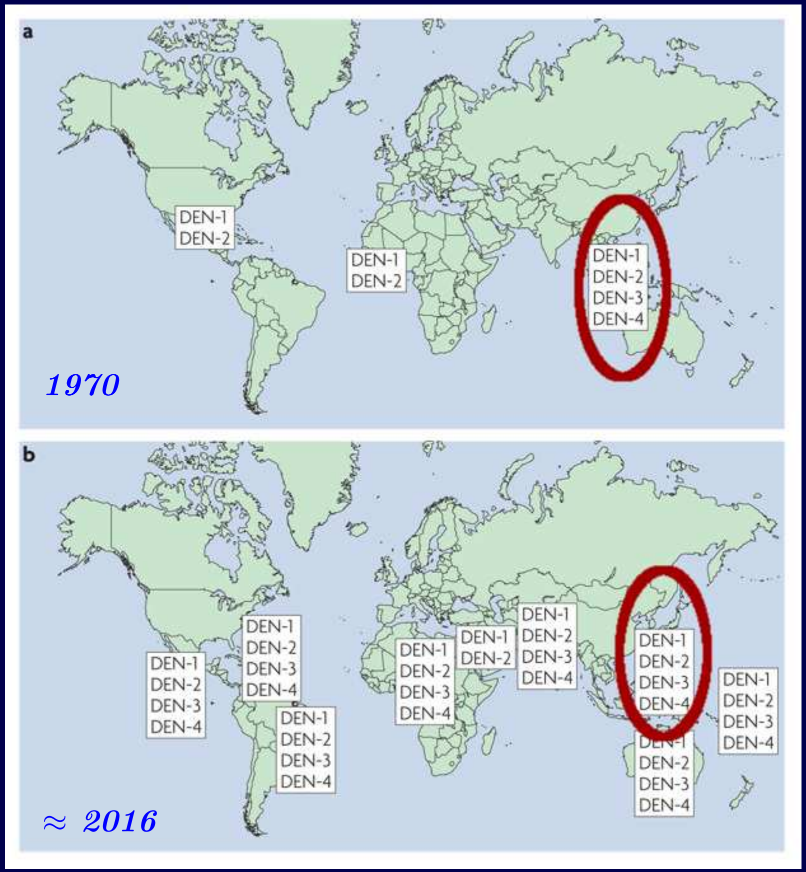
- *More than one-third of the world's population are living in areas at risk of acquiring dengue infection.*



Predicted global dengue risk (update to the estimates from Bhatt et al., Nature, 2013)

Lorenzo Cattarino et al., Science Translational Medicine, 2020

⁎ *Four antigenically distinct but closely related dengue viruses: DEN-1, DEN-2, DEN-3, DEN-4.*



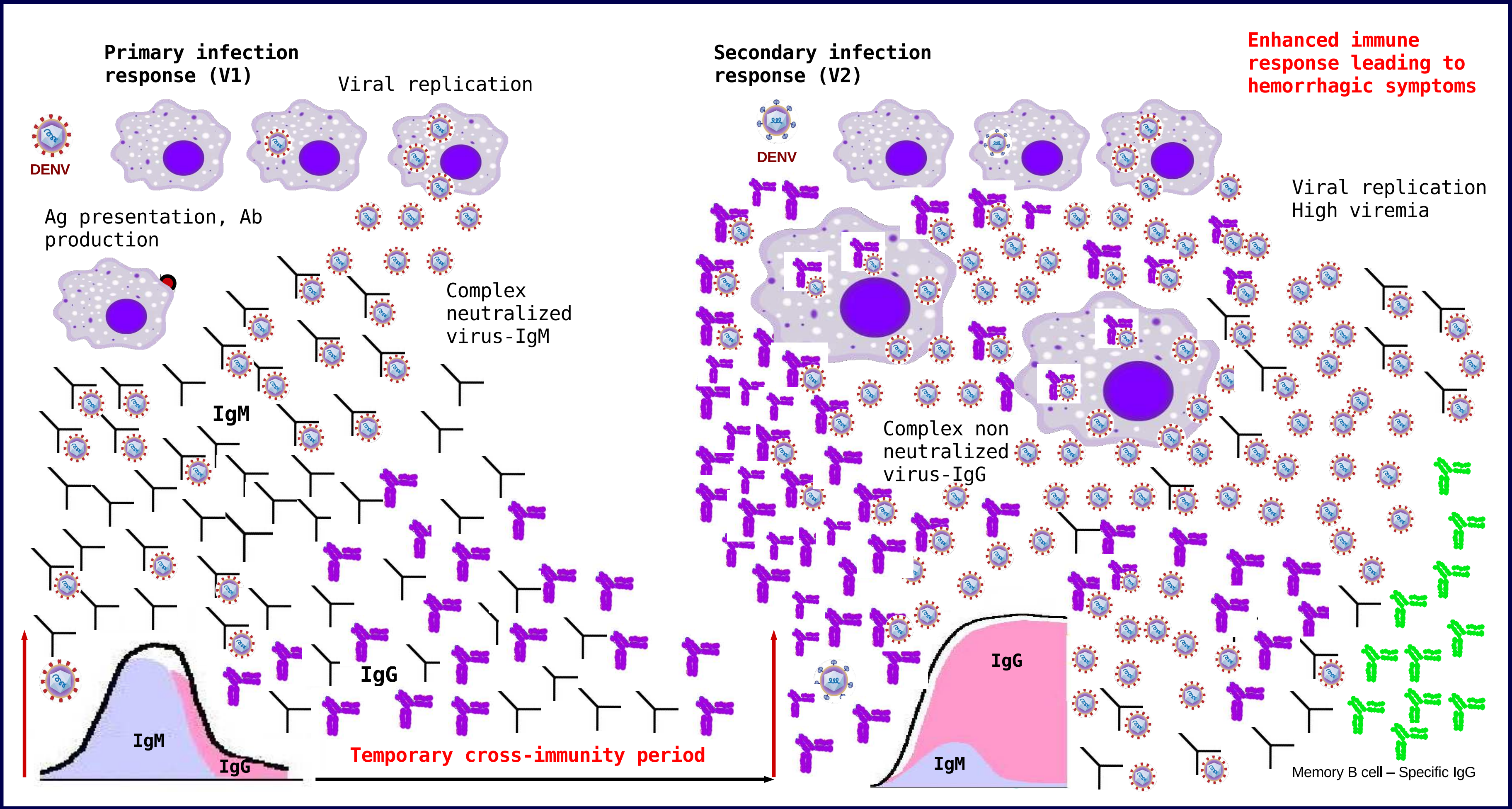
Guzmán et al., Nat. Rev. Microbiol., 2010

- *Infection by one serotype confers life-long immunity to that serotype and a short period of temporary cross-immunity to other serotypes (3-9 months).*

- *Dengue has a wide spectrum of clinical presentations: from asymptomatic to severe cases. Most patients recover following a self-limiting non-severe clinical course, a small proportion progress to severe disease, mostly characterized by plasma leakage with or without haemorrhage.*

- *Epidemiological studies support the association of severe disease with secondary dengue infection, due to the antibody-dependent enhancement (ADE) process.*

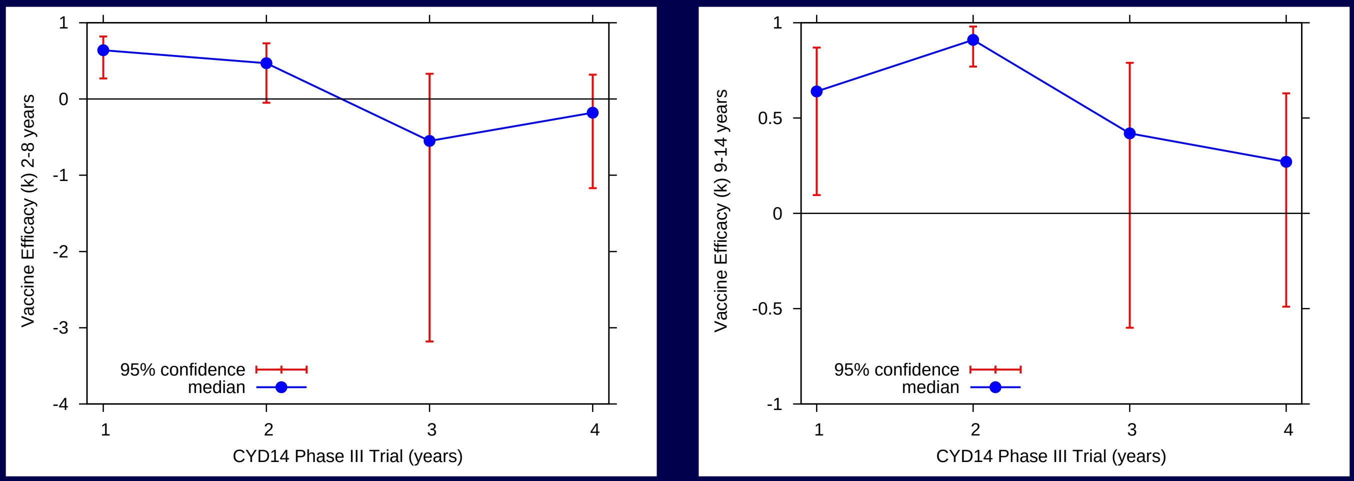
ADE in recurrent dengue infections for modeling purposes



※ The majority of secondary dengue infections occur at a spacing of more than 6 month (seasonality + TCI).

※ There is no specific treatment for dengue, and severe cases require hospitalization.

※ The only licensed dengue vaccine, Dengvaxia, developed by Sanofi Pasteur had its Phase III trials successfully completed in the Asian-Pacific region and in Latin American countries.

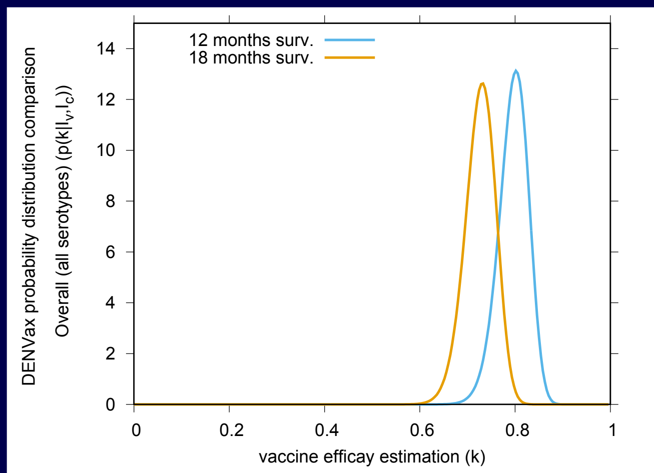


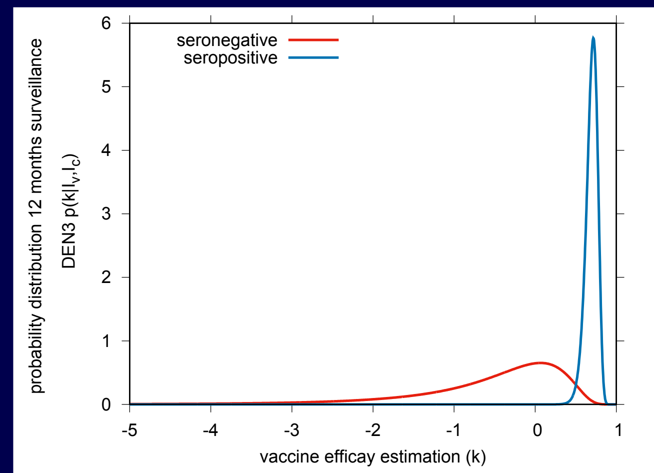
vaccine efficacy estimation by age group

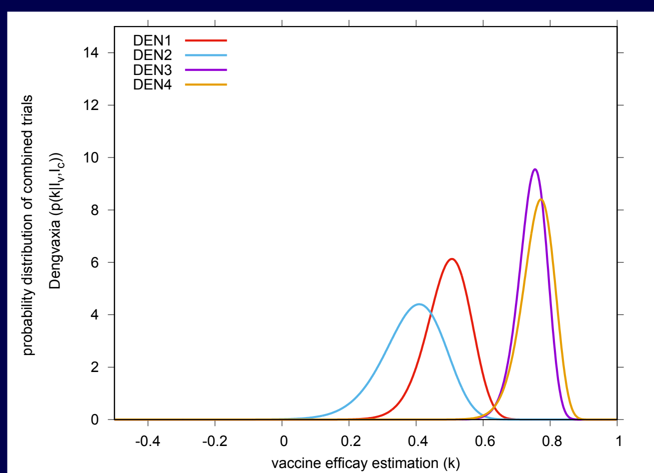
Aguiar et al., Expert Review of Vaccines, 2018

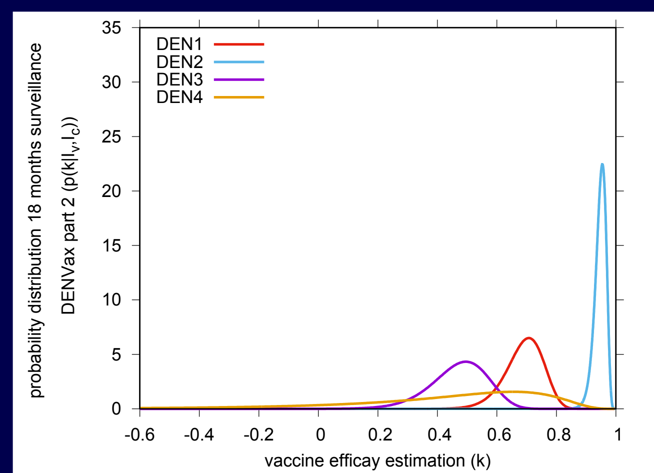
Aguiar et al., Clinical Infectious Disease, 2018

⋇ ***The much expected results of the Takeda's DENVax vaccine trials were recently published.***



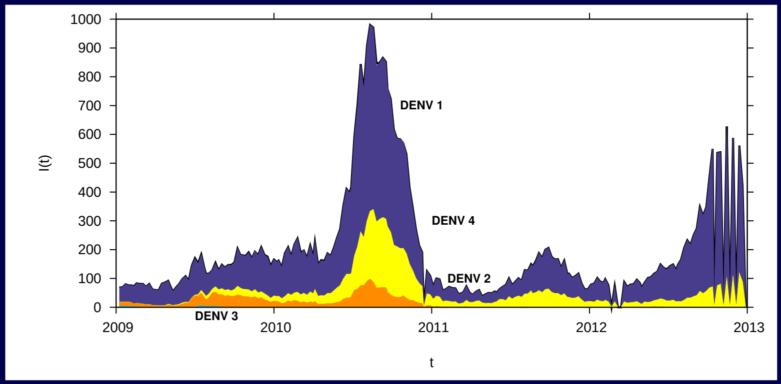


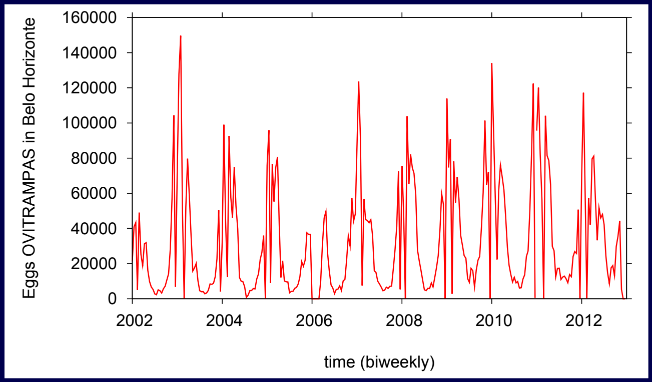


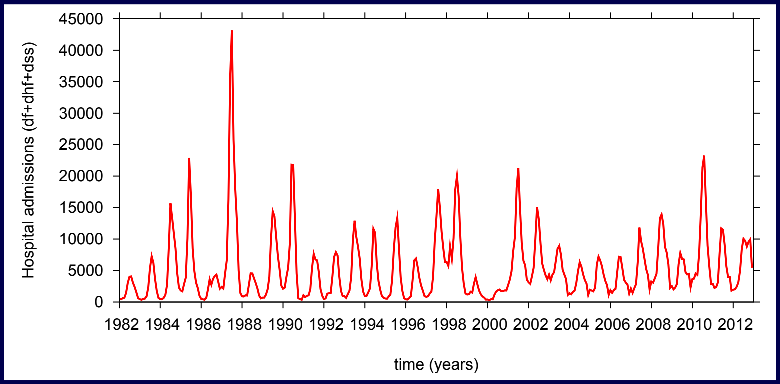


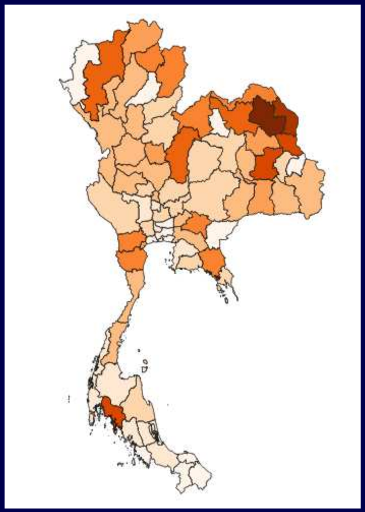
Aguiar et al., Vaccines, 2020

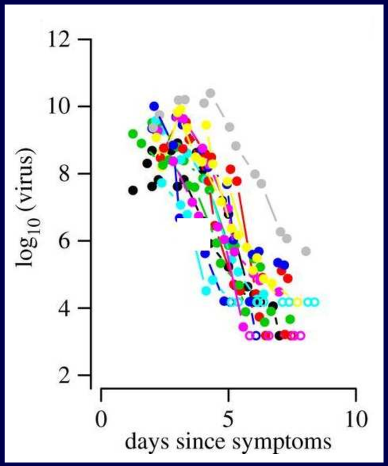
Real world dengue data







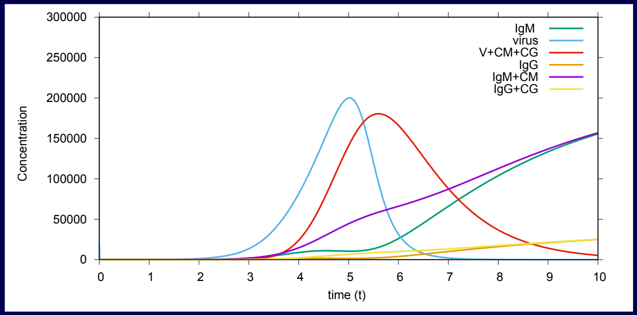


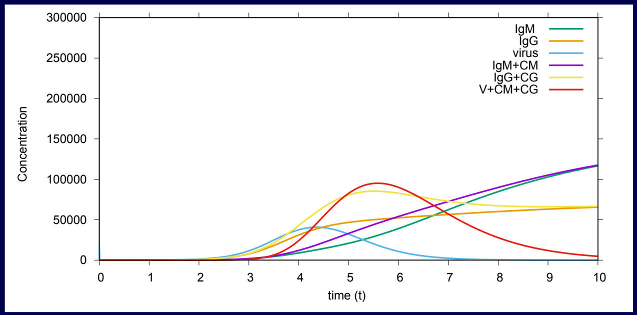


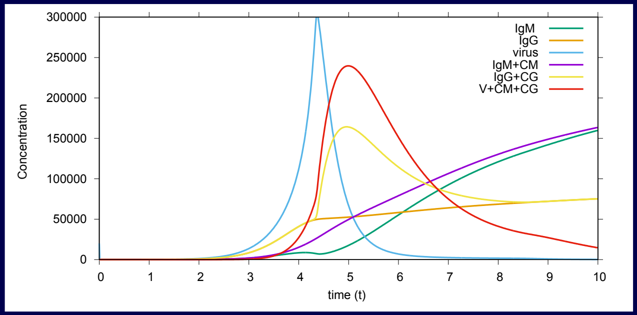
define the model framework!

Can we describe what happens within host using a simple model?

Modeling dengue immune responses mediated by antibodies





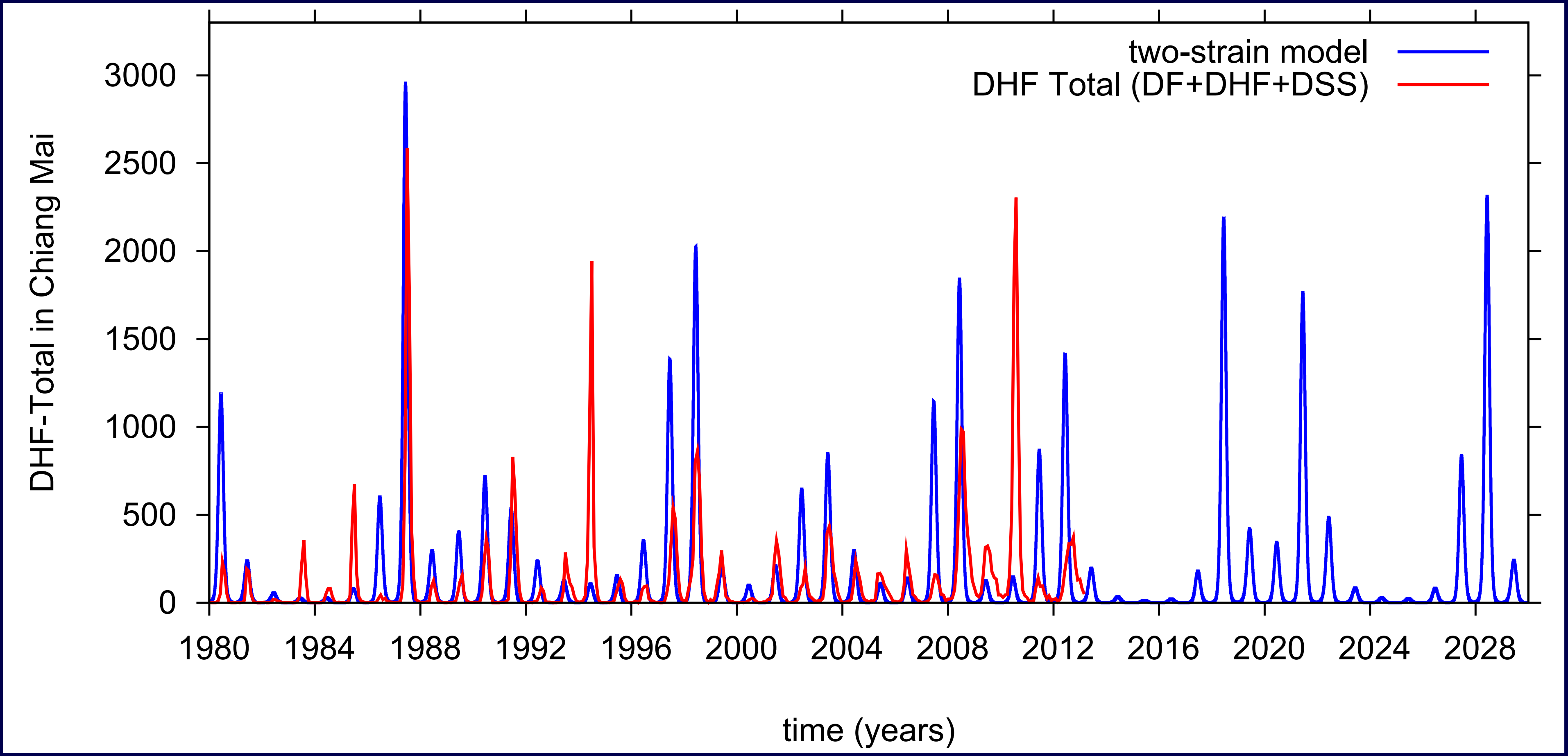


- ※ *Describe antibody depended-enhancement in a secondary dengue infection with a different virus.*
- ※ *Evaluate the role of temporary cross-immunity in the immunopathogenesis of severe disease.*
- ※ *Evaluate the impact of vaccination on disease prevention and control.*

Manuscript submitted

Can we describe disease transmission using a simple SIR model?

Real world data matching



Source: Ministry of Public Health, Thailand. Bureau of Epidemiology.

How much complexity is needed?

Modeling dengue fever epidemiology

β - *Infection rate*

ϕ- *Second. infection contribution*

to the force of infection(ADE ratio)

α - *Cross-immunity period*

γ - *Recovery rate*

μ - *Demographic rate*

The n-strain epidemiological model

$$\dot{S} = \mu\left(N - S\right) - \sum_{i=1}^{n} \frac{\beta}{N} S \left(I_i + \rho \cdot N + \phi \left(\sum_{j=1, j\neq i}^{n} I_{ji} \right) \right)$$

and for $i = 1, ..., n$

$$\dot{I}_i = \frac{\beta}{N} \left(I_i + \rho \cdot N + \phi \left(\sum_{j=1, j\neq i}^{n} I_{ji} \right) \right) - \left(\gamma + \mu\right) I_i$$

$$\dot{R}_i = \gamma I_i - \left(\alpha + \mu\right) R_i$$

$$\dot{S}_i = \alpha R_i - \sum_{j=1, j\neq i}^{n} \frac{\beta}{N} S_i \left(I_j + \rho \cdot N + \phi \left(\sum_{k=1, k\neq j}^{n} I_{kj} \right) \right) - \mu S_i$$

and for $i = 1, ..., n$ *and* $j = 1, ..., n$ *with* $j \neq i$

$$\dot{I}_{ij} = \frac{\beta}{N} S_i \left(I_j + \rho \cdot N + \phi \left(\sum_{k=1, k\neq j}^{n} I_{kj} \right) \right) - \left(\gamma + \mu\right) I_{ij}$$

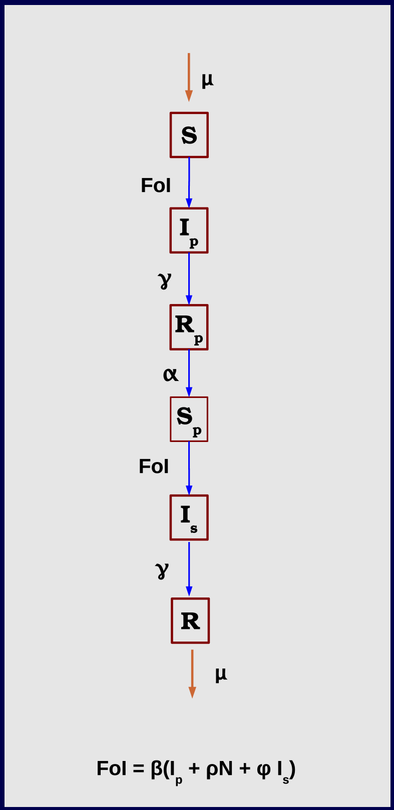
and finally

$$\dot{R} = \gamma \left(\sum_{i=1}^{n} \sum_{j=1, j\neq i}^{n} I_{ij} \right) - \mu R$$

only two possible infections; low frequency of tertiary and quaternary infections

The 2-infections n-strain epidemiological model can be analyzed as follows

One-strain epidemiological, an Eq. system with 6 ODE's



$$\begin{aligned}
\dot{S} &= -\frac{\beta(t)}{N} S(I_P + \rho \cdot N + \phi I_S) + \mu(N - S) \\
\dot{I}_P &= \frac{\beta(t)}{N} S(I_P + \rho \cdot N + \phi I_S) - (\gamma + \mu) I_P \\
\dot{R}_P &= \gamma I_P - (\alpha + \mu) R_P \\
\dot{S}_P &= -\frac{\beta(t)}{N} S_P(I_P + \rho \cdot N + \phi I_S) + R_P \alpha - S_P \mu \\
\dot{I}_S &= \frac{\beta(t)}{N} S_P(I_P + \rho \cdot N + \phi I_S) - (\gamma + \mu) I_S \\
\dot{R} &= \gamma I_S - \mu R
\end{aligned}$$

No vector dynamics explicitly: $\beta(t) = \beta_0(1 + \eta \cdot \cos(\omega t))$

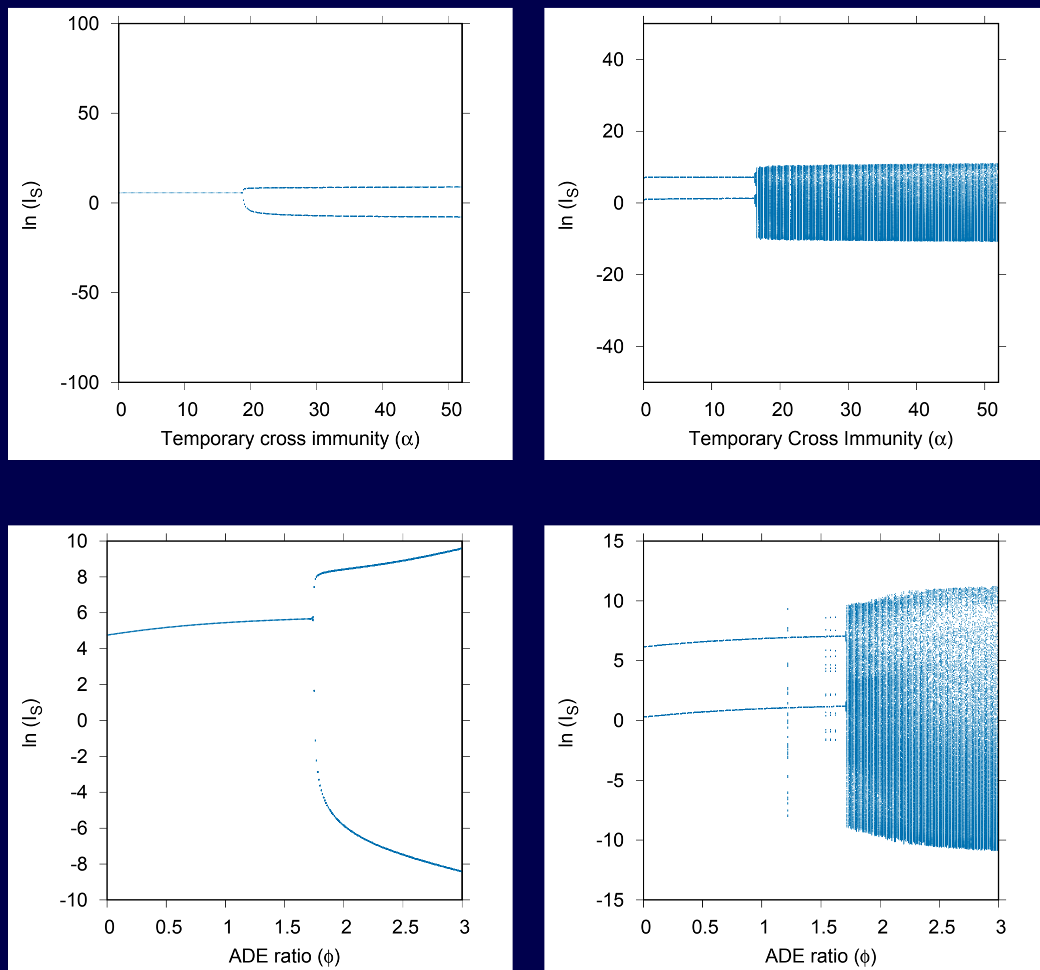
Only two possible infections

(low frequency of tertiary and quaternary infections)

Bifurcation Diagram for ADE and TCI

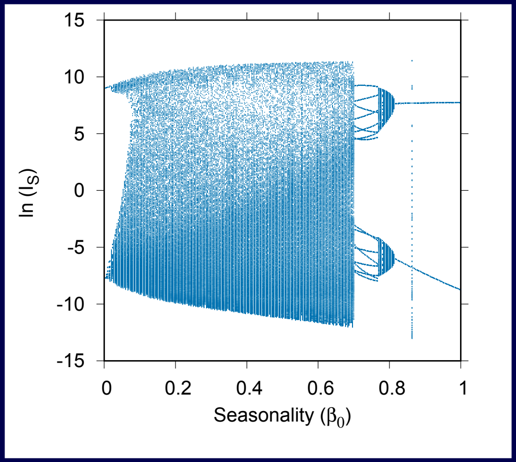
Non-seasonal ***Seasonal***

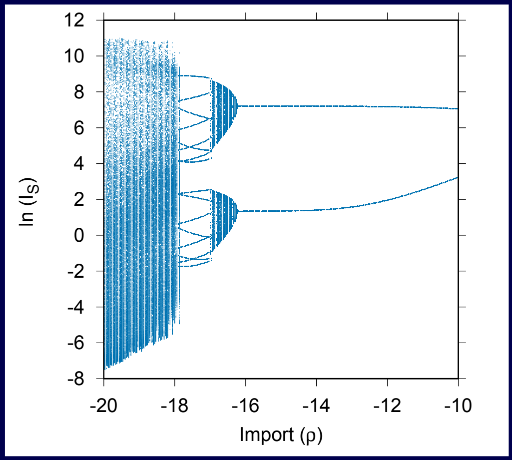
$$\alpha = 52, \; \phi = 2.6$$



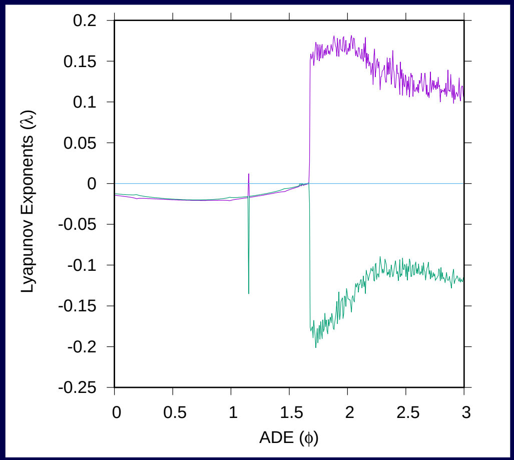
Manuscript in preparation

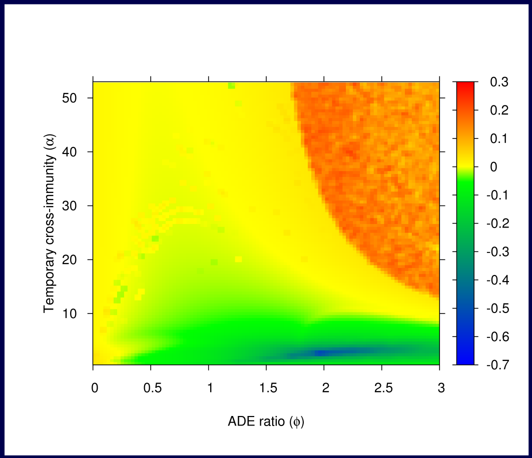
Bifurcation Diagram for Seasonality and Import





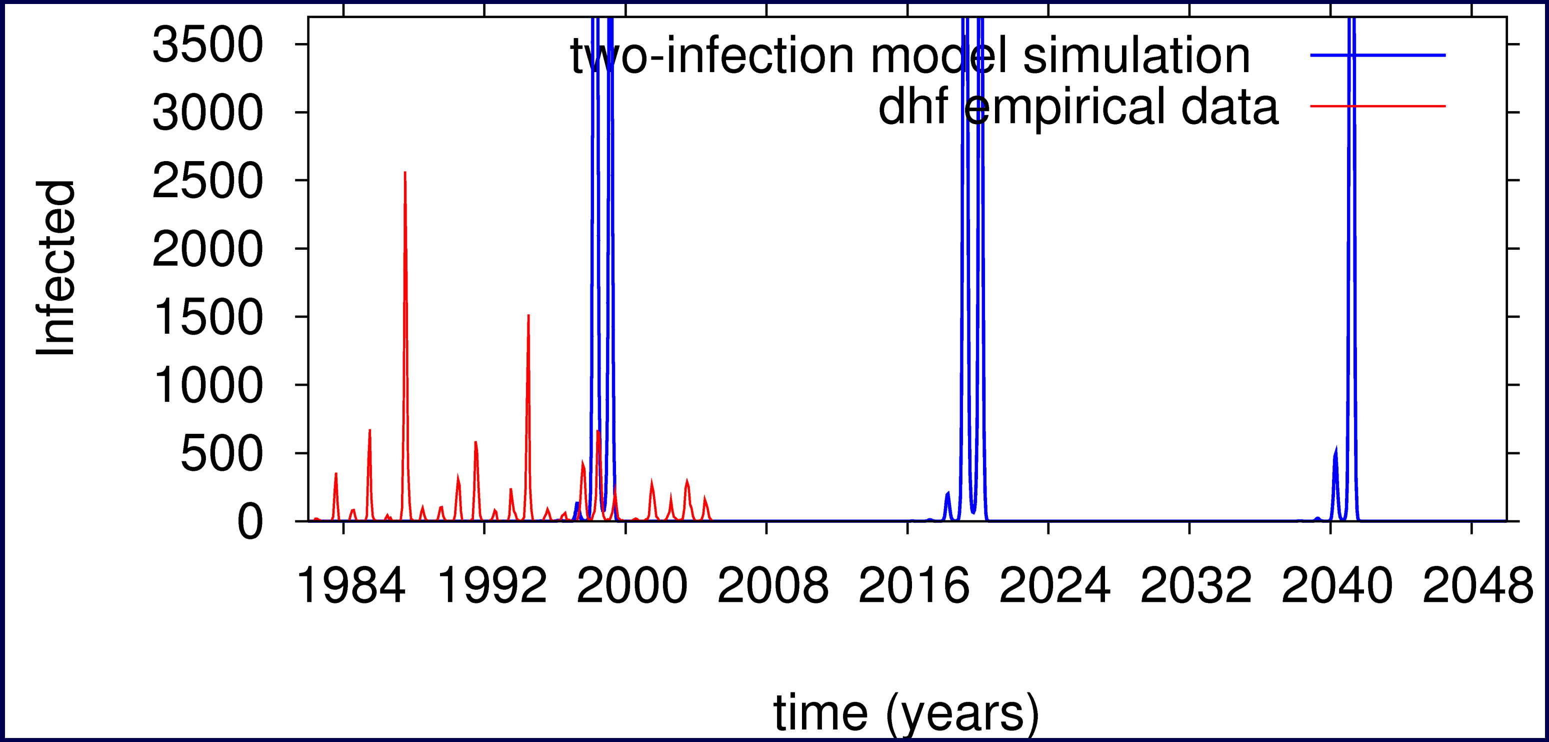
Lyapunov exponents and 2D Lyapunov spectra





$(\lambda_1 < 0)$ fixed point, $(\lambda_1 = 0)$ limit cycle, $(\lambda_1 > 0)$ chaos

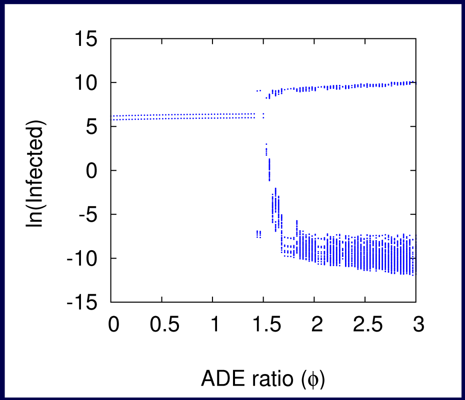
Time Series and Data Matching

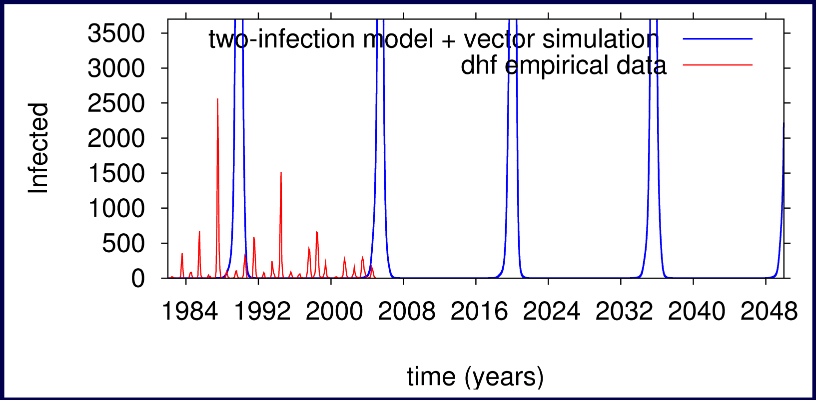


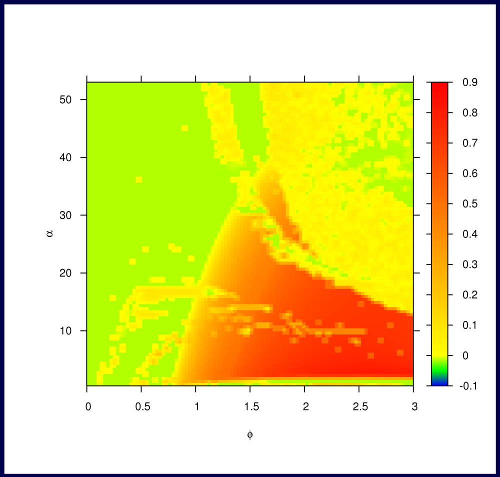
Seasonal model: $\alpha = 52$ *and* $\phi = 2.6$

Irregular outbreaks every 25 years and not data alike

One-strain epidemiological + vector, an Eq. system with 8 ODE's

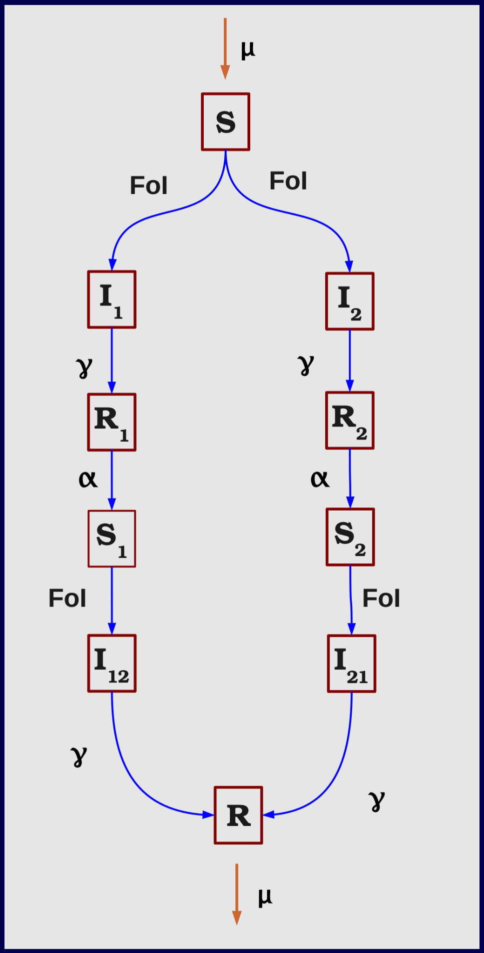






Irregular outbreaks and not data alike

The 2-strain dengue model, JTB, 2011



$$\dot{S} = -\frac{\beta(t)}{N} S(I_1 + \rho \cdot N + \phi I_{21}) - \frac{\beta(t)}{N} S(I_2 + \rho \cdot N + \phi I_{12}) + \mu(N - S)$$

$$\dot{I}_1 = \frac{\beta(t)}{N} S(I_1 + \rho \cdot N + \phi I_{21}) - (\gamma + \mu) I_1$$

$$\dot{I}_2 = \frac{\beta(t)}{N} S(I_2 + \rho \cdot N + \phi I_{12}) - (\gamma + \mu) I_2$$

$$\dot{R}_1 = \gamma I_1 - (\alpha + \mu) R_1$$

$$\dot{R}_2 = \gamma I_2 - (\alpha + \mu) R_2$$

$$\dot{S}_1 = -\frac{\beta(t)}{N} S_1(I_2 + \rho \cdot N + \phi I_{12}) + \alpha R_1 - \mu S_1$$

$$\dot{S}_2 = -\frac{\beta(t)}{N} S_2(I_1 + \rho \cdot N + \phi I_{21}) + \alpha R_2 - \mu S_2$$

$$\dot{I}_{12} = \frac{\beta(t)}{N} S_1(I_2 + \rho \cdot N + \phi I_{12}) - (\gamma + \mu) I_{12}$$

$$\dot{I}_{21} = \frac{\beta(t)}{N} S_2(I_1 + \rho \cdot N + \phi I_{21}) - (\gamma + \mu) I_{21}$$

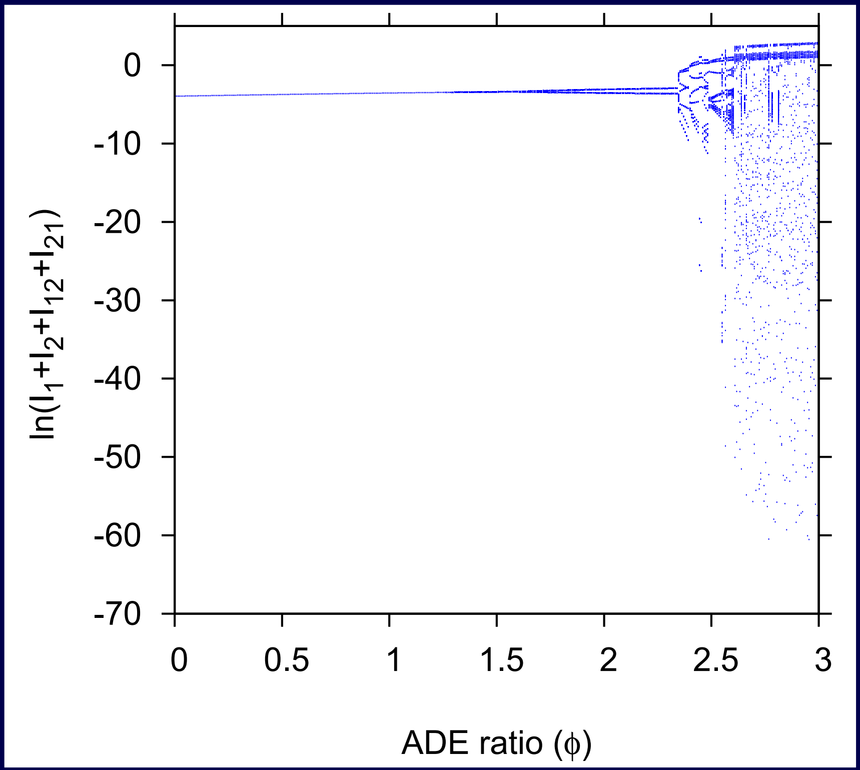
$$\dot{R} = \gamma(I_{12} + I_{21}) - \mu R$$

No vector dynamics explicitly: $\beta(t) = \beta_0(1 + \eta \cdot \cos(\omega t))$

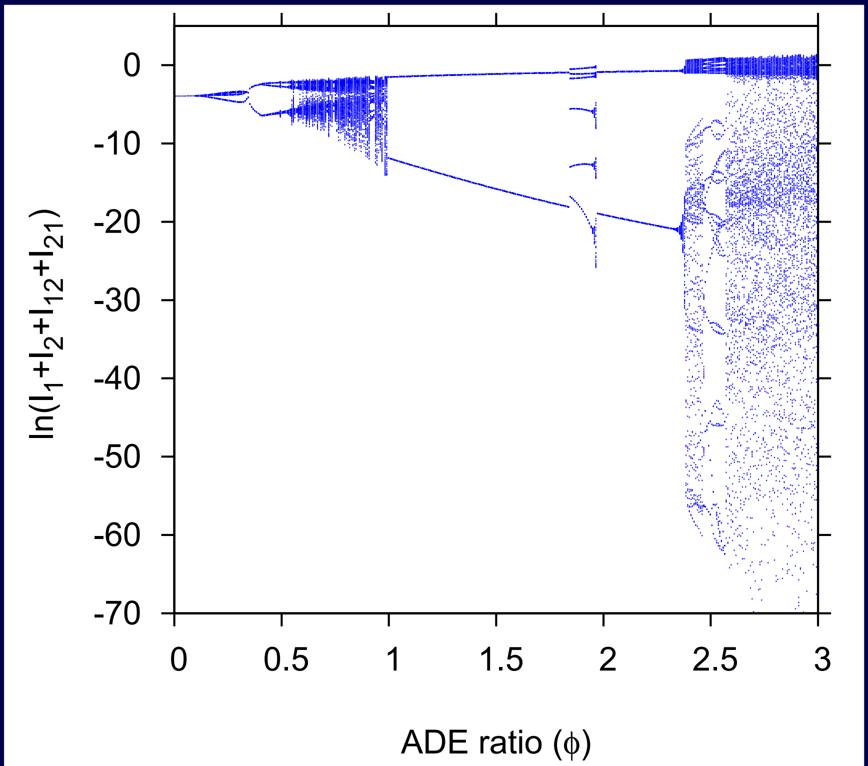
FoI$= \beta(I_1 + I_2 + \phi(I_{12} + I_{21}))$. *Only two possible infections.*

(low frequency of tertiary and quaternary infections)

Bifurcation Diagram for ADE (non-seasonal)



$\alpha = 52$ *(one week)*



$\alpha = 2$ *(six months)*

New chaotic window for $\phi < 1$*!*

More realistic due to hospitalization of the severe cases.

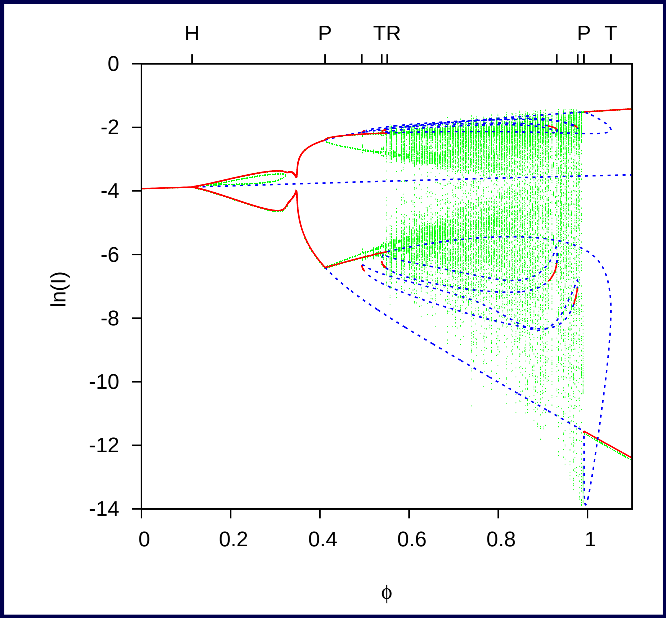
Lyapunov exponents (non-seasonal)

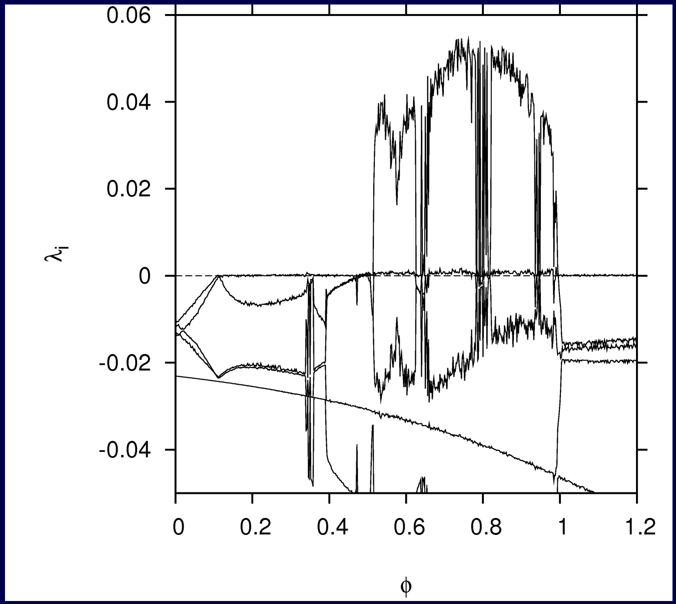
$$\lambda_i = \frac{1}{n \cdot \Delta t} ln \left(\prod_{\nu=0}^{n} |r_{ii}(\nu)| \right)$$

$\lambda < 0$ *fixed point*

$\lambda = 0$ *limit cycle*

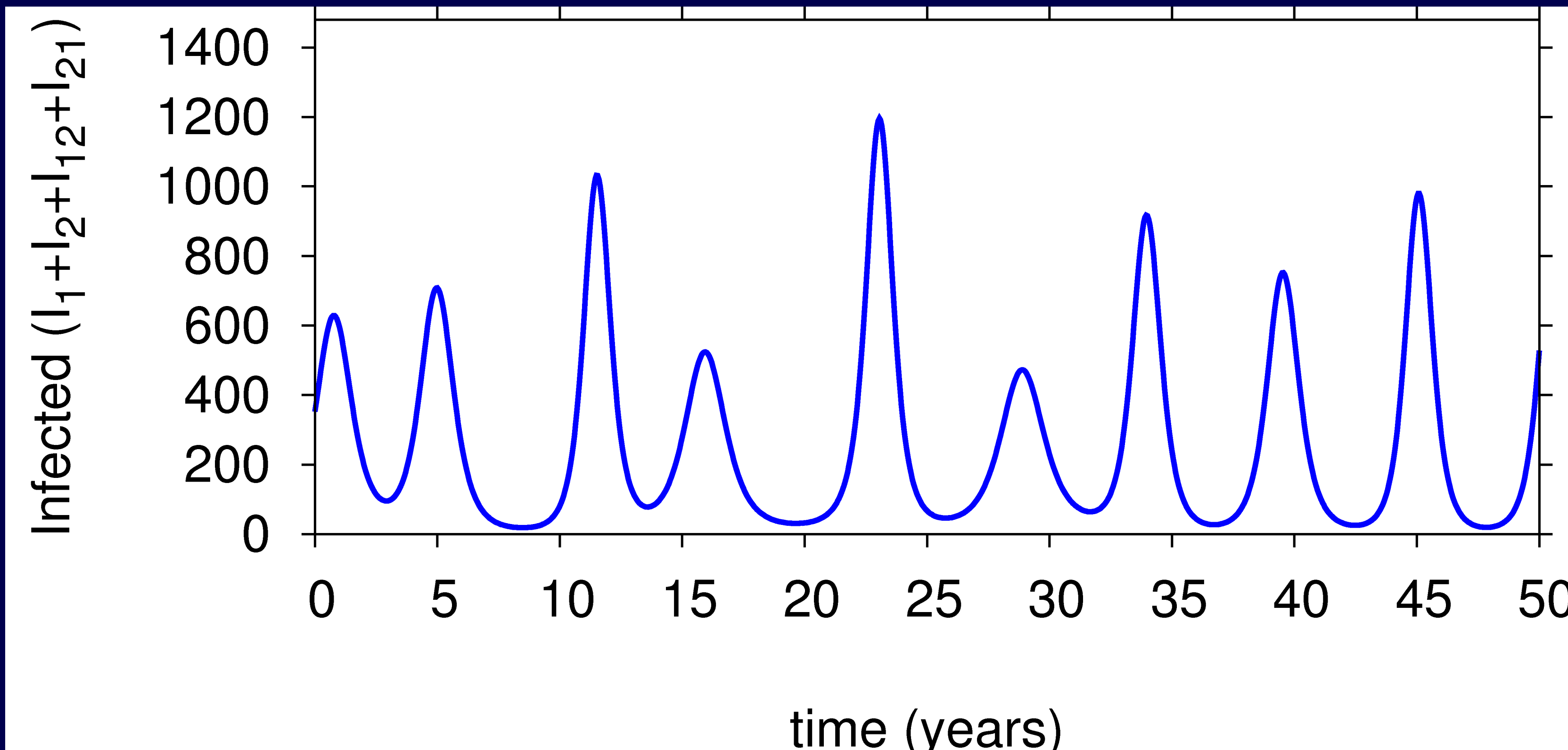
$\lambda > 0$ *chaos*





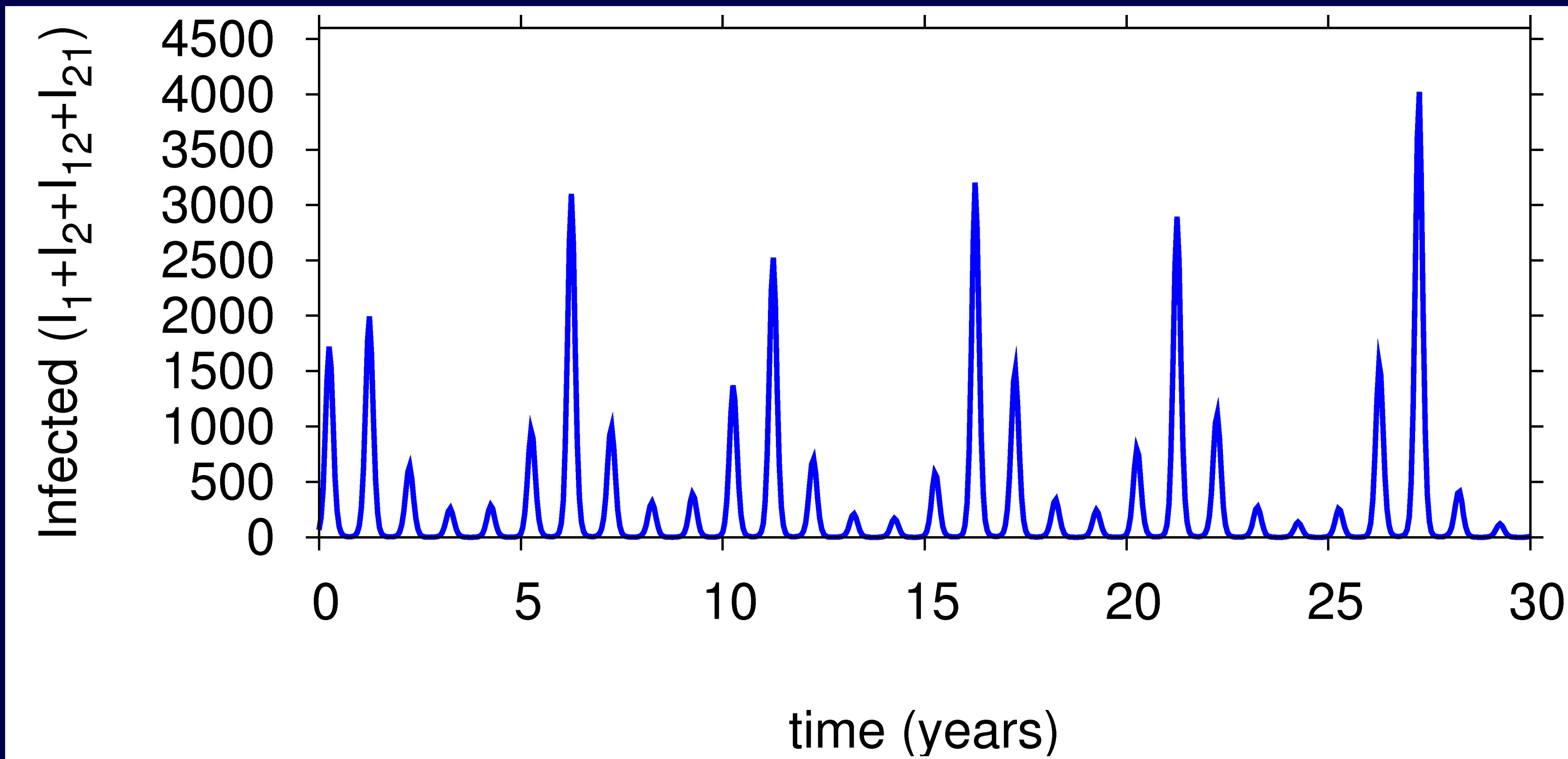
Rich dynamic structure (Hopf, pitchfork, torus and tangent bifurcations) including deterministic chaos in a wider and more biologically realistic parameter regions ($\phi < 1$) , than previously expected.

Time Series (non-seasonal)



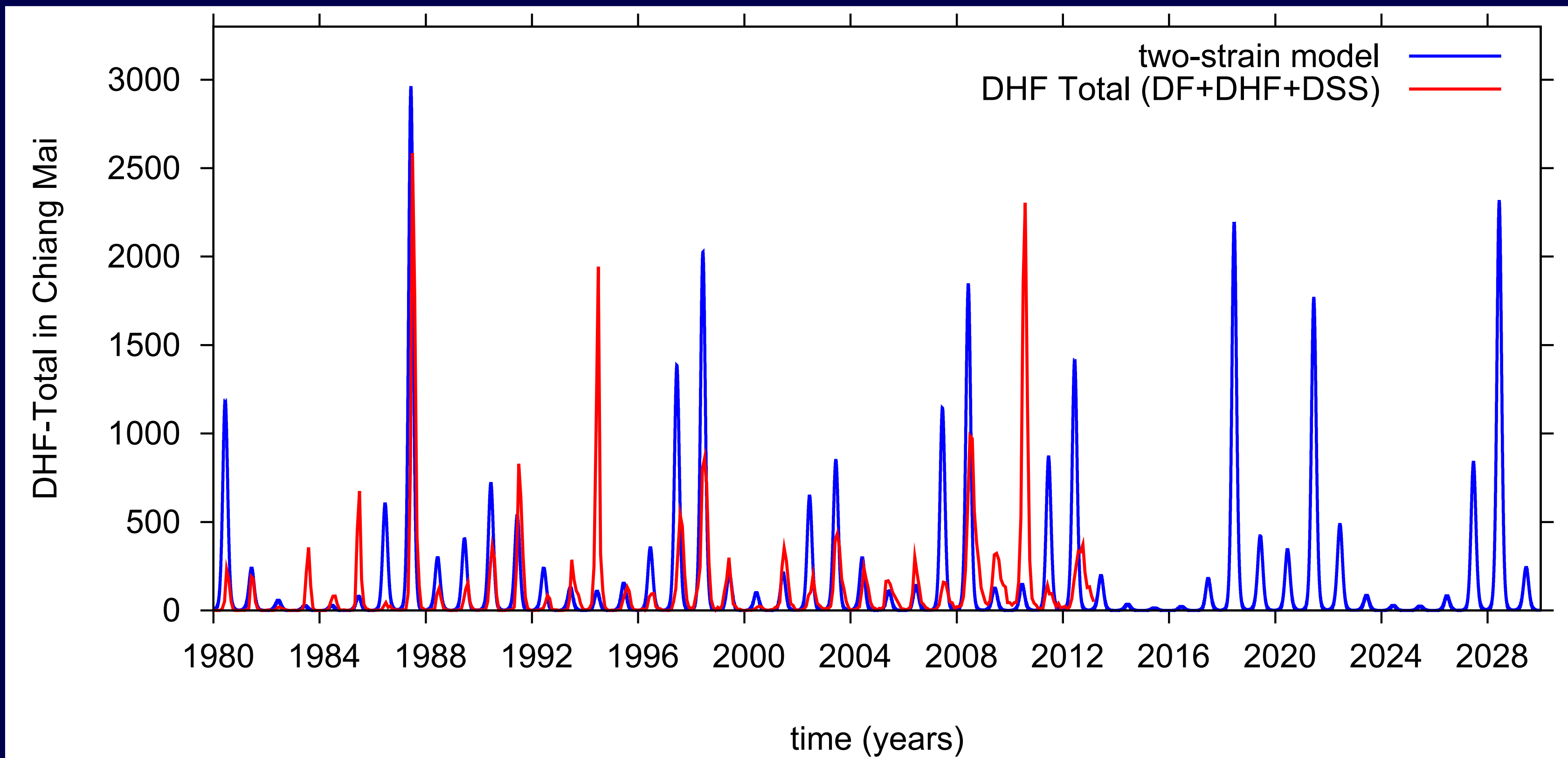
Irregular pattern every 5 years.

Time Series (seasonal)



Realistic pattern with irregular, yearly and smooth outbreaks.

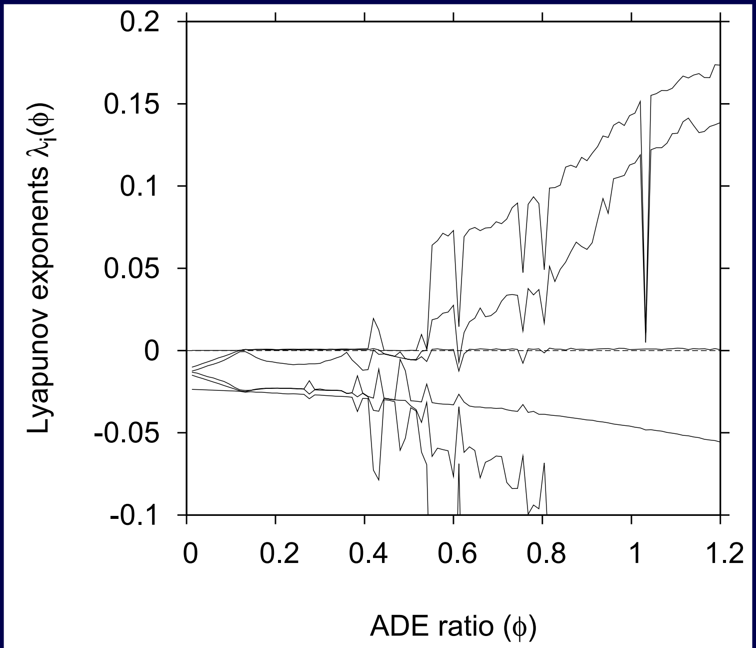
Time Series and Data Matching (seasonal)

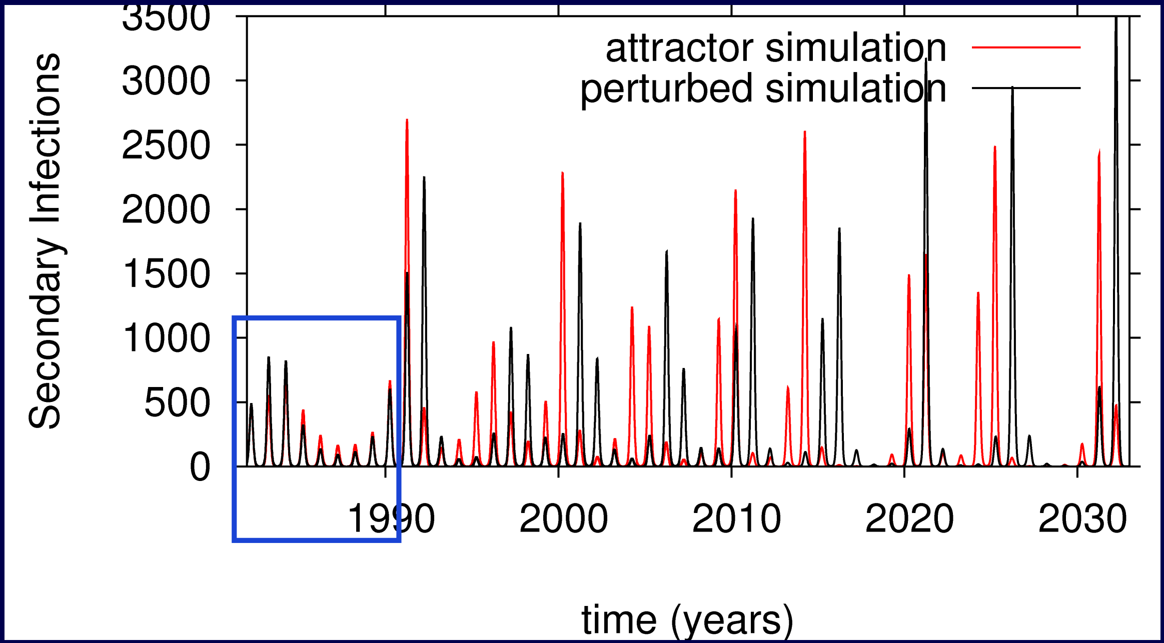


Qualitatively a very good result when comparing empirical empirical data and model simulation.

Aguiar et al. JTB, 2011

Lyapunov exponents and Average Predictability (seasonal)

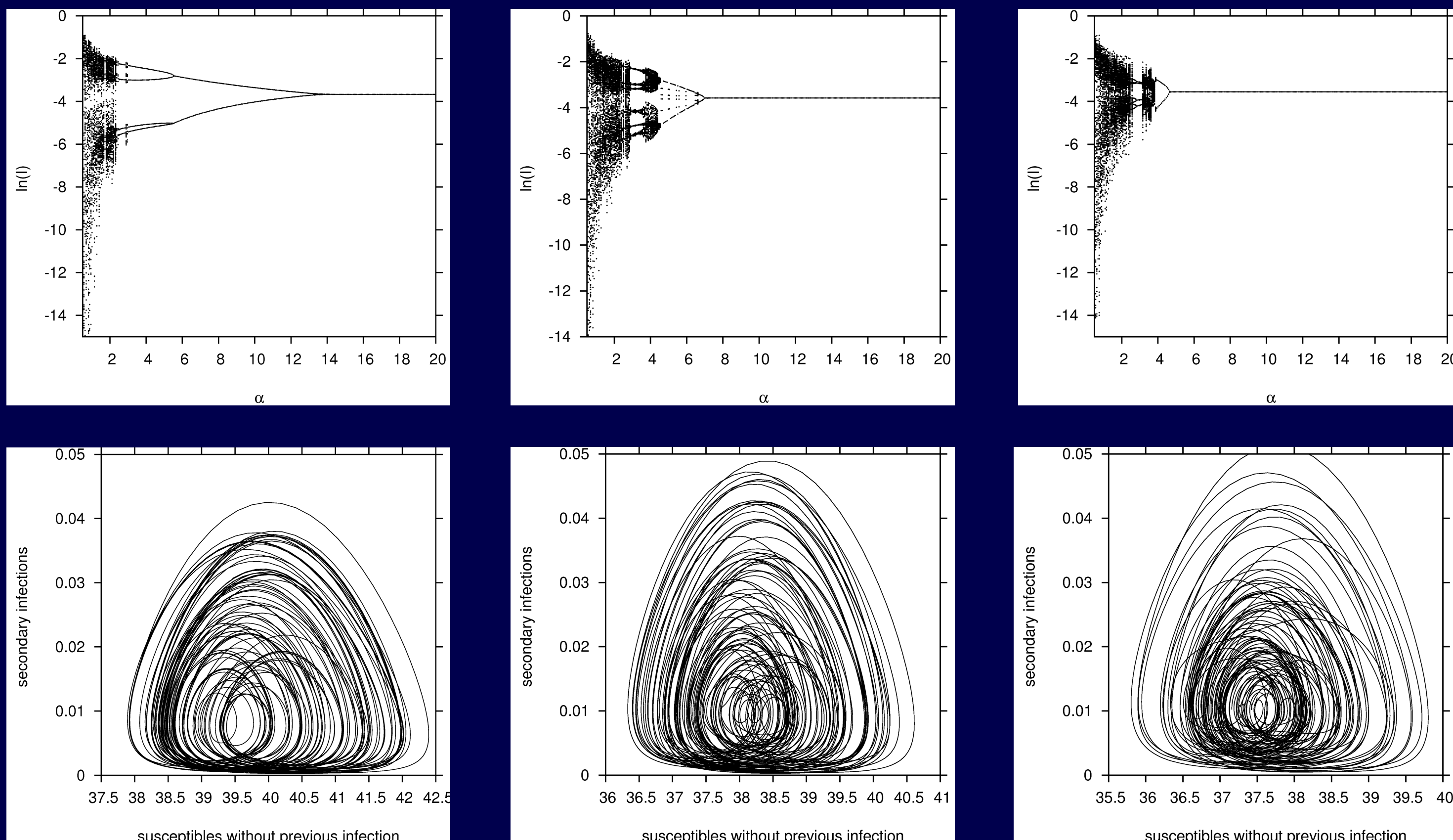




Dominant Lyapunov Exponent (DLE) at $\phi = 0.9$ is $\lambda = 0.118$ giving ≈ 8.5 years of prediction horizon.

Aguiar et al. Ecol. Complex., 2013

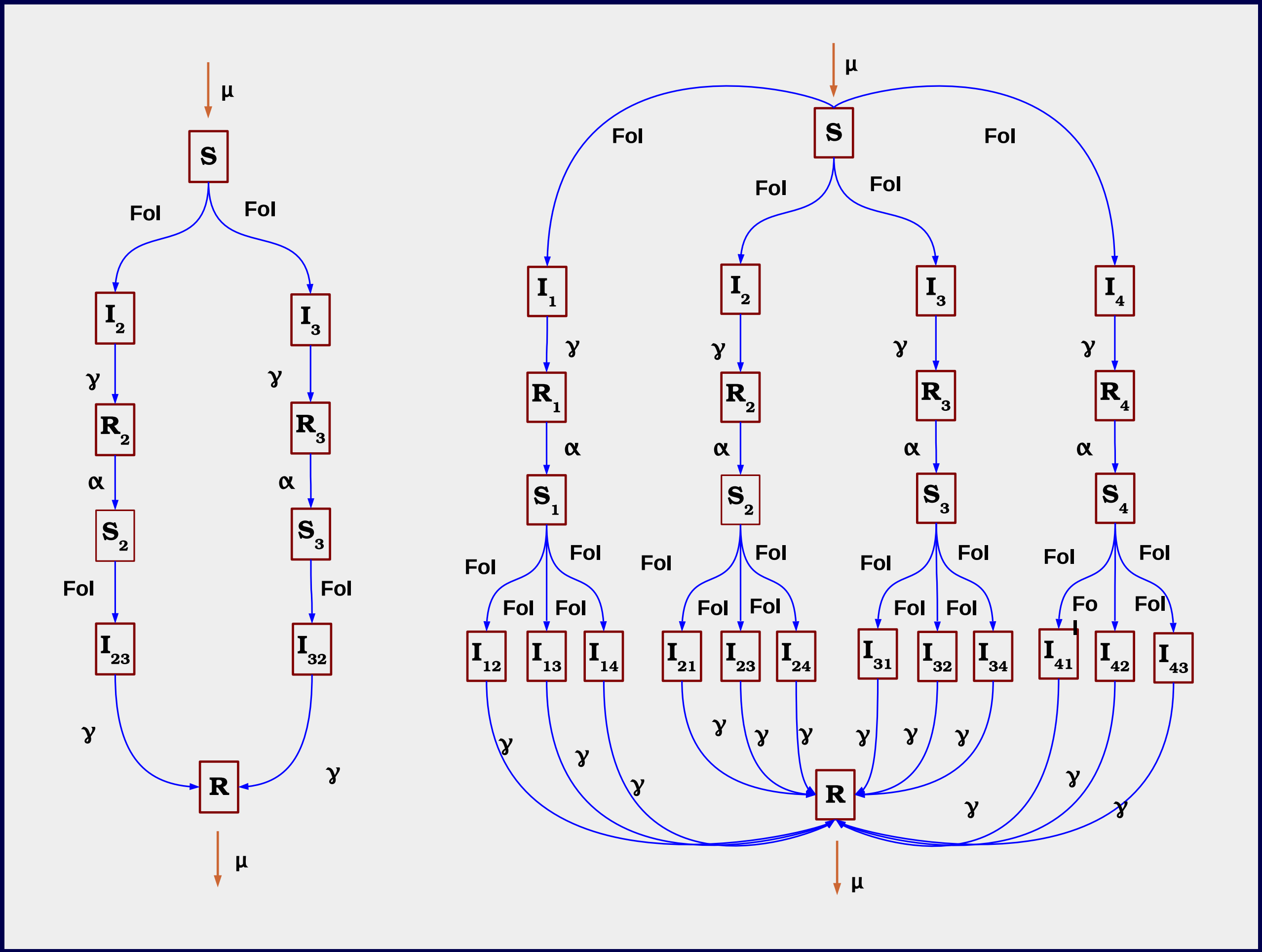
Similarities between the 2-strain (10 ODE's), the 3-strain and the 4-strain (26 ODE's) dengue models



2-strain model *3-strain model* *4-strain model*

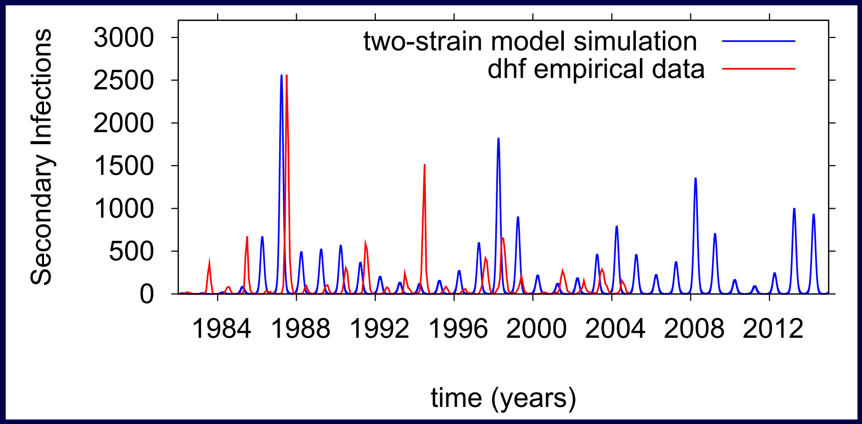
***Strain structure of pathogen shifts the chaotic behaviour to a more realistic parameter region** (In preparation).*

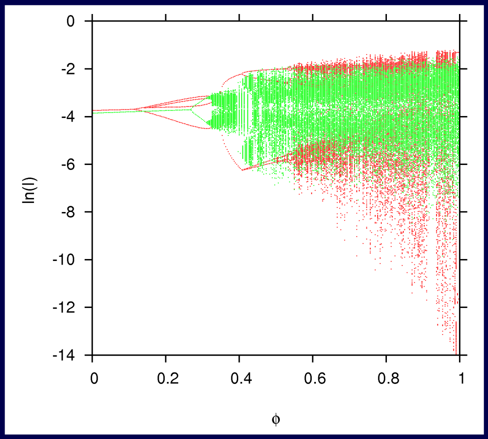
Two-strain and four-strain epidemiological models: a dimensional problem

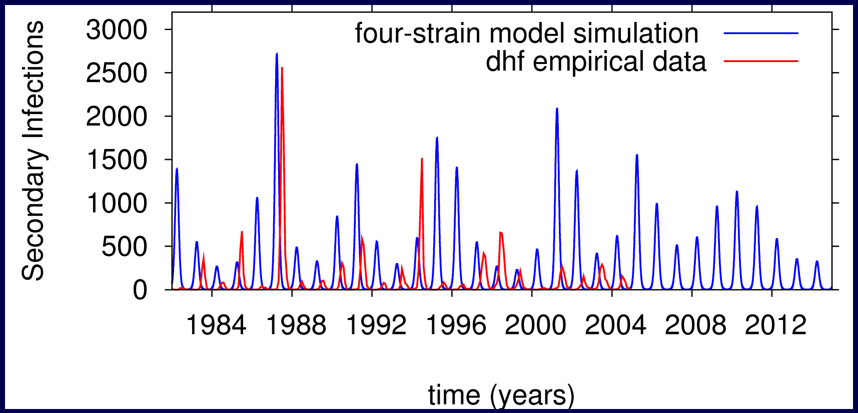


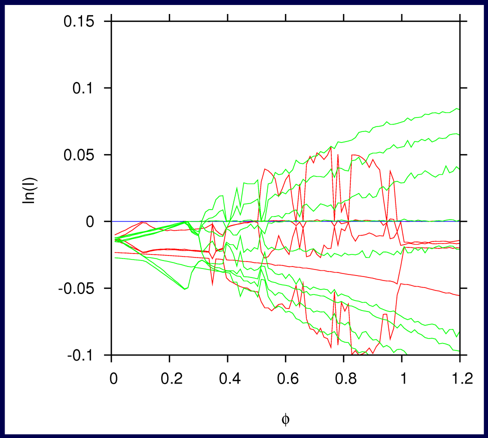
10 versus 25 dimensions!

Two-strains (10 ODE's) and four-strains (26 ODE's)









Similar structure, order of magnitude and same prediction horizon (DLE).

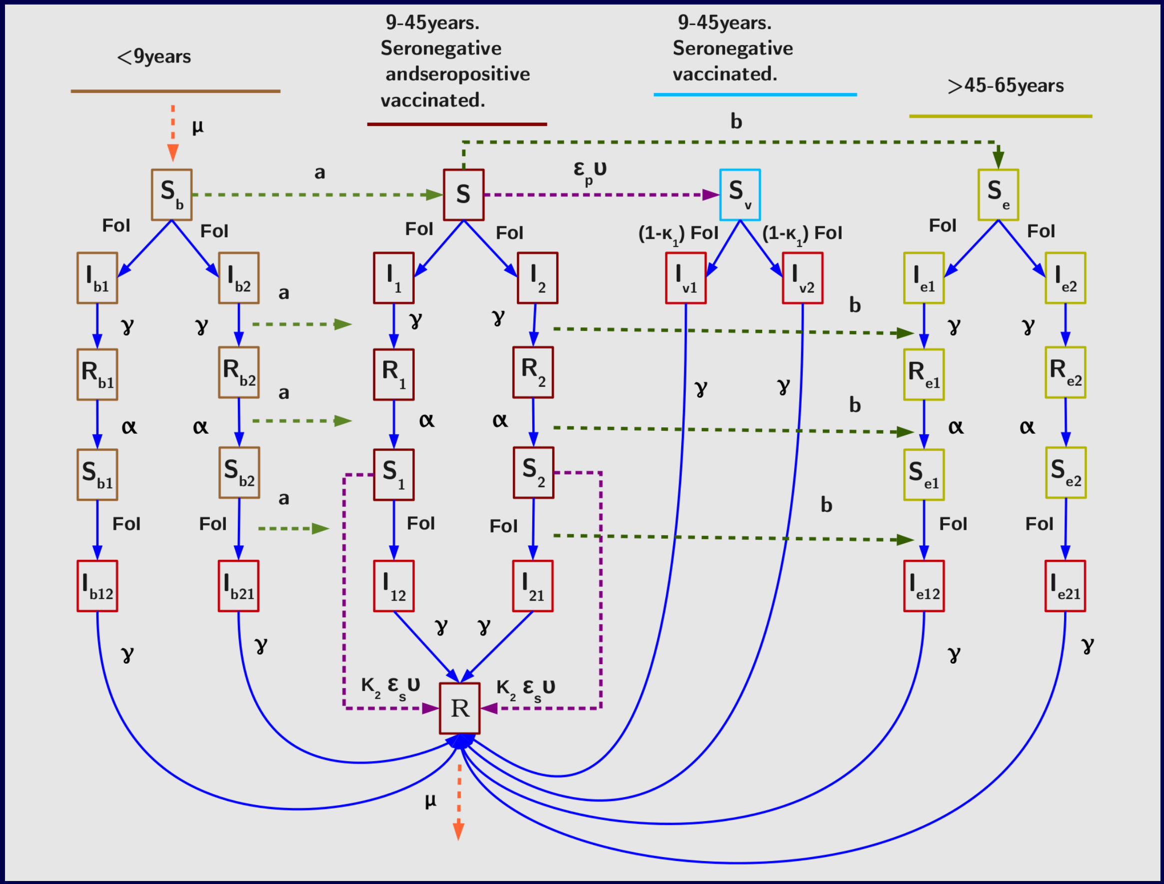
2-strain chosen according to the parsimony law.

Aguiar et al. Ecol. Complex., 2013

Model extension to include vaccination

Modeling vaccine introduction phase

Age-group-structured (2-strain) dengue model



5 years data matching — plus 5 years prediction

Aguiar, Stollenwerk and Halstead. PLoS NTDs, 2016

Age-group-structured dengue model *(extension of our pre-vaccination model)*

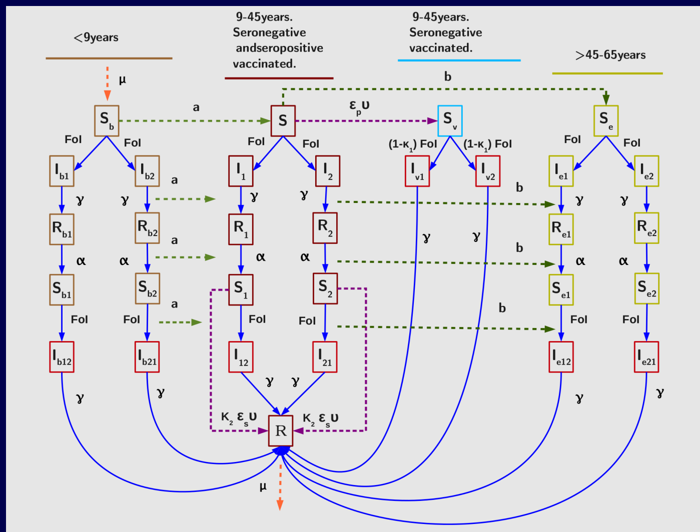
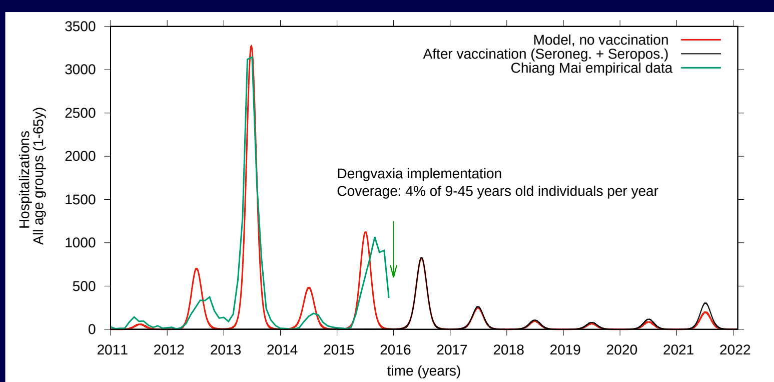
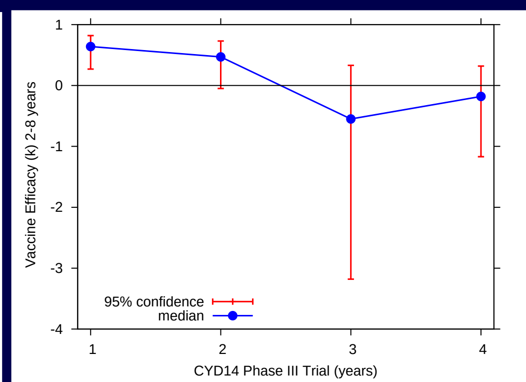


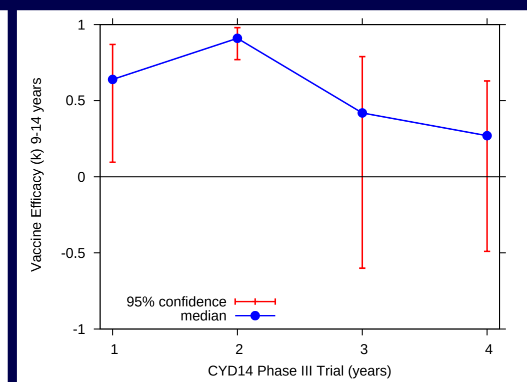
Table 8 Vaccine effect on hospitalized dengue of any severity (ITT population) over time for CYD14, CYD15, and CYD23/57. [32] and provided by manufacturer on request.

		CYD14			CYD15			CYD23/57		
Age Group	Time Period	CYD cases	Control cases	RR (95%CI)	CYD cases	Control cases	RR (95%CI)	CYD cases	Control cases	RR (95%CI)
2-5 Years CYD14 N=2451 CYD23/57 (starting at 4yrs) N=623	Year 1 (Active)	8	6	0.644 (0.20-2.32)				1	2	0.239 (0.00-4.58)
	Year 2 (Active)	9	7	0.641 (0.21-2.02)				3	1	1.413 (0.11-74.17)
	Year 3 (Hospital)	15	1	7.45 (1.15-313.80)				5	1	2.443 (0.27-115.54)
	Year 4 (Hospital)	20	7	1.424 (0.58-3.99)	Not included in trial population			5	3	0.814 (0.16-5.24)
	Year 5 (Hospital/SEP)	6	2	1.495 (0.27-15.15)				4	0	+inf (0.32- +inf)
	Year 6 (Hospital)	NA	NA	NA				11	4	1.344 (0.40-5.76)
	Cumulative to date	**58**	**23**	**1.256 (0.76-2.13)**				**29**	**11**	**1.274 (0.62-2.83)**
6-8 Years CYD14 N=2791 CYD23/57 N=1513	Year 1 (Active)	5	12	0.209 (0.06-0.64)				4	3	0.670 (0.11-4.57)
	Year 2 (Active)	8	9	0.446 (0.15-1.3)				18	13	0.705 (0.33-1.57)
	Year 3 (Hospital)	4	5	0.400 (0.08-1.86)				14	5	1.401 (0.48-4.97)
	Year 4 (Hospital)	18	9	1.000 (0.43-2.53)	Not included in trial population			8	9	0.445 (0.15-1.30)
	Year 5 (Hospital/SEP)	5	3	0.833 (0.16-5.37)				3	1	1.498(0.12-78.66)
	Year 6 (Hospital)	NA	NA	NA				15	4	1.873 (0.60-7.75)
	Cumulative to date	**40**	**37**	**0.541 (0.34-0.87)**				**62**	**35**	**0.890 (.058-1.39)**
9-11 Years CYD14 N=2618 CYD15 N=8436 CYD23/57 N=1311	Year 1 (Active)	5	5	0.502 (0.12-2.18)	2	8	0.125 (0.01-0.63)	3	2	0.759 (0.09-9.08)
	Year 2 (Active)	2	13	0.077 (0.01-0.34)	6	14	0.214 (0.07-0.59)	3	9	0.169 (0.03-0.68)
	Year 3 (Hospital)	6	3	1.009 (0.22-6.23)	10	9	0.554 (0.20-1.54)	3	5	0.308 (0.05-1.58)
	Year 4 (Hospital)	12	3	2.013 (0.54-11.11)	6	5	0.601 (0.15-2.49)	3	5	0.308 (0.05-1.58)
	Year 5 (Hospital/SEP)	3	2	0.755 (0.09-9.04)	1	1	0.498 (0.01-39.12)	1	3	0.171 (0.00-2.13)
	Year 6 (Hospital)	NA	NA	NA	NA	NA	NA	11	5	1.126 (0.36-4.14)
	Cumulative to date	**28**	**26**	**0.542 (0.31-0.96)**	**25**	**37**	**0.337 (0.19-0.58)**	**24**	**29**	**0.422 (0.24-0.75)**
12-16 Years CYD14 N=2309 (up to 14 yrs) CYD15 N=10174	Year 1 (Active)	2	5	0.139 (0.02-1.22)	3	7	0.214 (0.04-0.94)			
	Year 2 (Active)	1	7	0.071 (0.00-0.55)	7	14	0.250 (0.09-0.66)			
	Year 3 (Hospital)	2	4	0.249 (0.02-1.74)	6	6	0.501 (0.13-1.87)	Not included in trial population		
	Year 4 (Hospital)	7	10	0.348 (0.11-1.01)	0	2	0.000 (0.00-2.67)			
	Year 5 (Hospital/SEP)	1	2	0.249 (0.00-4.79)	0	0	NC (NC)			
	Cumulative to date	**13**	**27**	**0.240 (0.11-0.48)**	**16**	**29**	**0.276 (0.14-0.52)**			

N= denominator of evaluable subjects for the RR calculation for the entire study.
SEP=Surveillance expansion phase







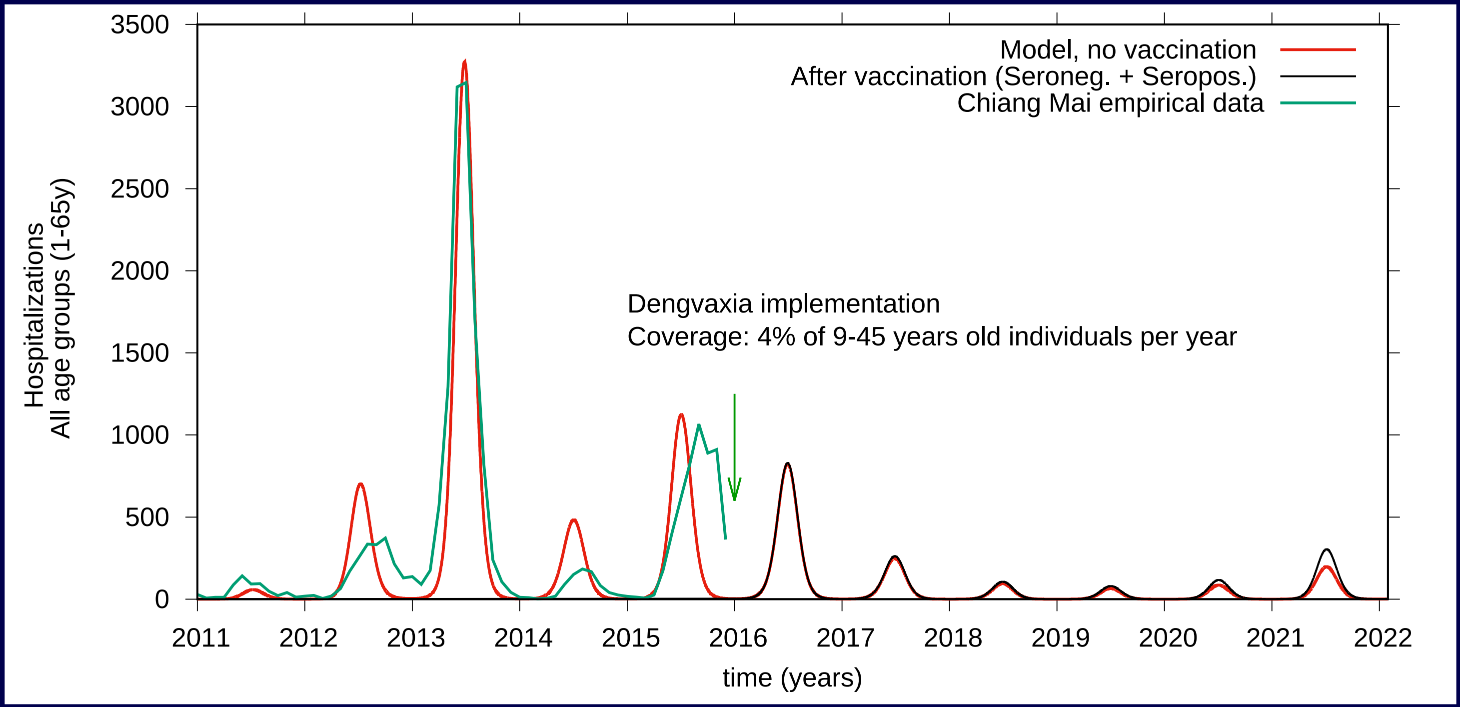
NOT recommended for use in children under 9 years of age. *Recommended for use in individuals 9-45 y, living in high endemic countries. During year 4, RR > 2 for age group 9-11 years!* *Aguiar, Stollenwerk and Halstead, PLoS NTDs, 2016 & ERV, 2017*

Modeling Dengvaxia introduction phase

Dengvaxia WITHOUT immunological screening

Vaccination coverage: 4% per year, seropos. and seroneg. individuals 9-45 years

All hospitalizations (ψ=1)



hospitalizations increase on average by 25% in 5 years

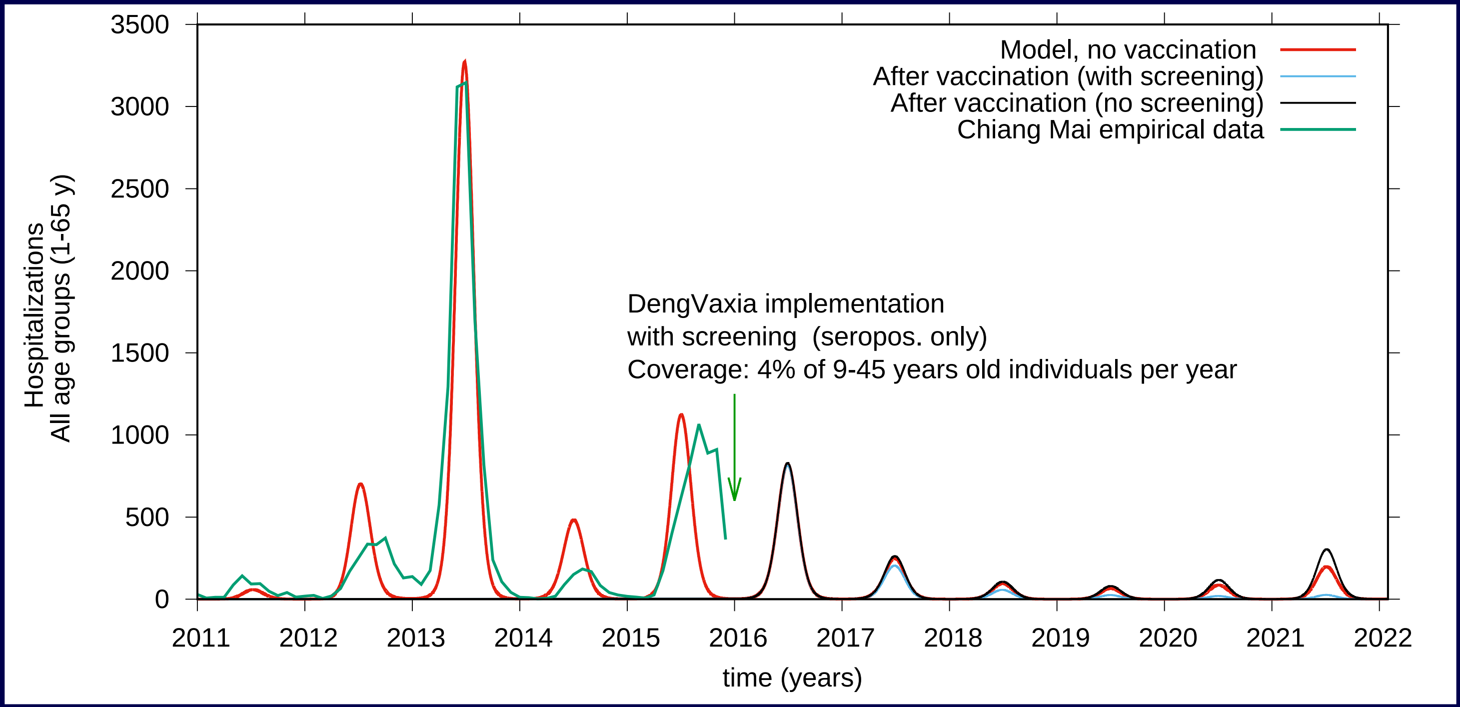
Aguiar, Stollenwerk and Halstead. PLoS NTDs, 2016

Modeling Dengvaxia introduction phase

Dengvaxia WITH prior immunological screening

Vaccination coverage: 4% per year, seropos. individuals 9-45 years

All hospitalizations (ψ=1)

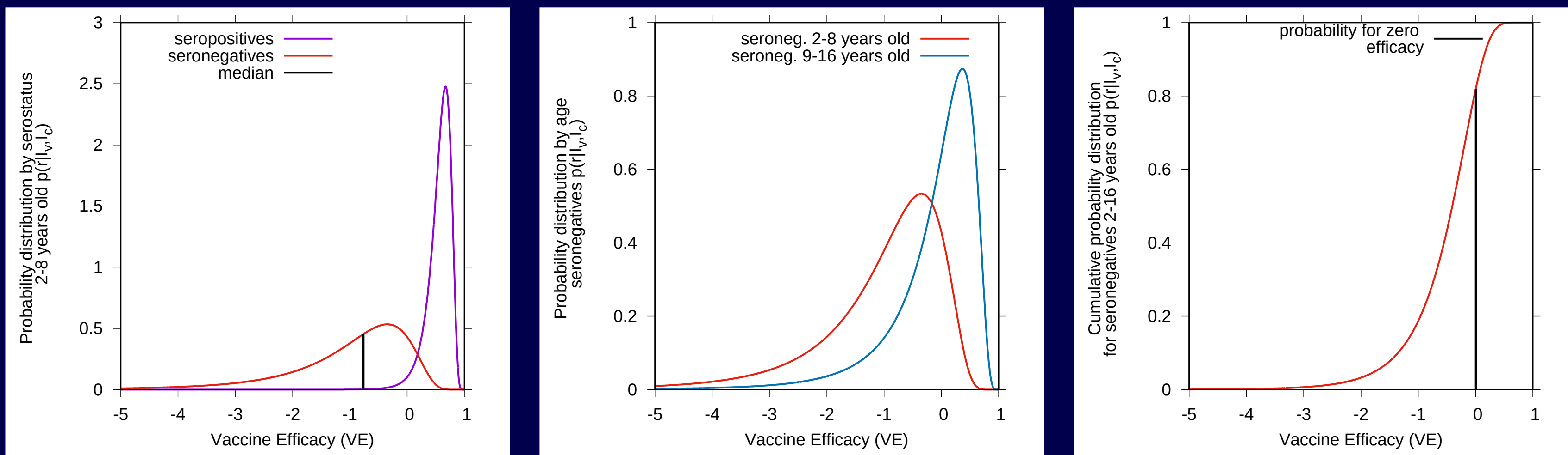


overall reduction of hospitalization of more than 40% in 5 years.

Aguiar, Stollenwerk and Halstead. PLoS NTDs, 2016

Recent data and the concept of vaccine disease enhancement discussion

(Martinez-Vega et al., Vaccine, 2017)



Aguiar, M. & Stollenwerk, N., Clinical Infectious Diseases, 2017

Individual serostatus is the most important feature when implementing this vaccine and that only individuals of any age who have experienced at least one dengue virus infection could benefit from vaccination.

Dengvaxia, from 2016 to 2018

- *April 2016: recommended by the WHO, ignoring the observations (Phase III trial data) of high rate of hospitalizations in vaccinated seronegative children.*

- *end of 2016-2017: implemented in two large vaccination programs, the Phillipines and Brazil, with more than 1 million children and adolescents vaccinated without any pre-vaccination testing.*

- *end of 2017: Results from Sanofi's new test.*
  Dengvaxia mass vaccinationprograms were suspended

- *mid of 2018: WHO new recommendation requiring a pre-testing before vaccination.*

A bomb…

… that could have been avoided since 2 years earlier!

THE LANCET
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Volume 16, Issue 8, August 2016, Pages 882-883

Comment

The risks behind Dengvaxia recommendation

Maira Aguiar [a, b], Nico Stollenwerk [a], Scott B Halstead [c]

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Travel Medicine and Infectious Disease (2016) 14, 178–181

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COMMENTARY

Dengue vaccines: Are they safe for travelers?

Scott B. Halstead [a,*], Maira Aguiar [b]

PLOS | NEGLECTED TROPICAL DISEASES

RESEARCH ARTICLE

The Impact of the Newly Licensed Dengue Vaccine in Endemic Countries

Maíra Aguiar[1]*, Nico Stollenwerk[1], Scott B. Halstead[2]

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Dengue vaccine and the 2016 Olympics

Scott B Halstead, Maira Aguiar

Published: 16 July 2016

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Volume 66, Issue 4
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Dengvaxia Efficacy Dependency on Serostatus: A Closer Look at More Recent Data

Maíra Aguiar, Nico Stollenwerk

Clinical Infectious Diseases, Volume 66, Issue 4, 1 February 2018, Pages 641–642,
https://doi.org/10.1093/cid/cix882
Published: 21 October 2017

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EXPERT REVIEW OF VACCINES, 2016
http://dx.doi.org/10.1080/14760584.2017.1276831

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EDITORIAL

Consider stopping dengvaxia administration without immunological screening

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Dengue vaccination: a more ethical approach is needed

Maíra Aguiar

Published: 05 May 2018

DENVax Takeda Vaccine

Part 1 efficacy data of the TAK-003 phase 3 trial [15]									
section A							section B		
	Seropositive at baseline (82.2%)			Seronegative at baseline (74.9%)			Overall (seropositive and seronegative) vaccine efficacy		
Dengue Serotype	Vaccinated (n= 9167)	Control (n=4589)	Estimated vaccine efficacy and 95% Confidence Interval [17]	Vaccinated (n=3531)	Control (n=1726)	Estimated Vaccine efficacy and 95% Confidence Interval [17]	Vaccinated (n= 12700)	Control (n=6316)	Estimated vaccine efficacy and 95% Confidence Interval [17]
	Dengue cases	Dengue cases		Dengue cases	Dengue cases		Dengue cases	Dengue cases	
ALL	41	110	81.4% [73.6%, 87.1%]	20	39	74.8% [57.4%, 85.4%]	61	149	79.7% [72.8%, 85.1%]
DEN1	7	17	78.9% [51.8%, 91.4%]	9	13	65.9% [22.2%, 85.8%]	16	30	73.2% [52.2%, 85.4%]
DEN2	3	42	96.2% [89.9%, 98.8%]	0	22	100%	3	64	97.5% [93.6%, 99.3%]
DEN3	28	47	70.0% [52.6%, 81.4%]	11	4	**-31.2% [-353.2.7%, 53.8%]**	39	51	61.9% [42.4%, 75.8%]
DEN4	3	4	**61.9% [-63.2%, 91.9%]**	0	0	inconclusive	3	4	**61.9% [-62.4%, 91.9%]**

Part 2 efficacy data of the TAK-003 phase 3 trial [16]									
section A							section B		
	Seropositive at baseline (82.2%)			Seronegative at baseline (74.9%)			Overall (seropositive and seronegative) vaccine efficacy		
Dengue Serotype	Vaccinated (n= 9167)	Control (n=4589)	Estimated vaccine efficacy and 95% Confidence Interval [17]	Vaccinated (n=3531)	Control (n=1726)	Estimated Vaccine efficacy and 95% Confidence Interval [17]	Vaccinated (n= 12700)	Control (n=6316)	Estimated vaccine efficacy and 95% Confidence Interval [17]
	Dengue cases	Dengue cases		Dengue cases	Dengue cases		Dengue cases	Dengue cases	
ALL	75	150	75.8% [67.2%, 81.0%]	39	56	66.1% [48.9%, 77.3%]	114	206	72.5% [65.6%, 78.1%]
DEN1	21	37	71.2% [51.8%, 83.3%]	17	25	66.7% [39.2%, 82.1%]	38	62	69.4% [54.6%, 79.7%]
DEN2	7	54	93.2% [91.1%, 97.1%]	1	26	97.7% [90.7%, 99.7%]	8	80	94.6% [90.3%, 97.7%]
DEN3	43	54	60.3% [40.6%, 73.2%]	20	6	**-59.9% [-328.5%, 31.1%]**	63	60	47.7% [25.4%, 63.1%]
DEN4	4	5	**59.5% [-47.2%, 89.4%]**	1	0	inconclusive	5	5	**50.1% [-72.5%, 85.4%]**

Efficacy and safety conclusions require long-term surveillance.

TCI period; No DEN4 cases observed during the first part of the trial.

Thank you for your attention!

MTB Seminar Series (BCAM)

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