How much complexity is needed to describe the fluctuations observed in dengue hemorrhagic fever incidence data?

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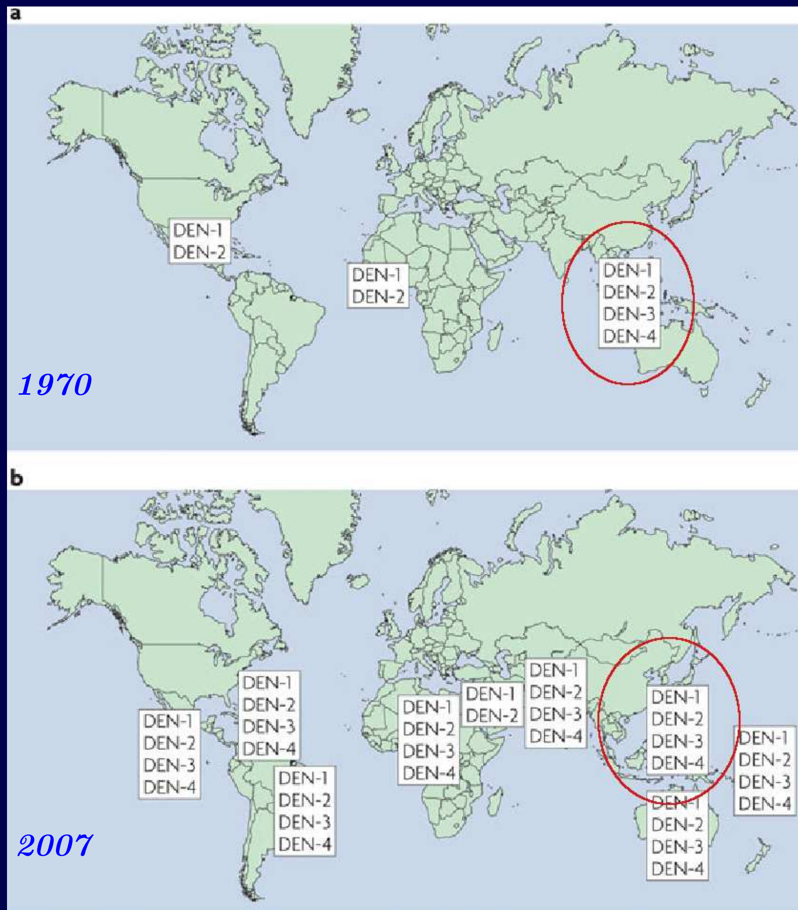
Dengue Fever Epidemiology

- *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.*

Worldwide dengue distribution 2008 - ©Biogents AG
Source: WHO (2007) & CDC (2008)

Dengue Fever Epidemiology



Guzmán, M. G. et al. (2010)

Nature Reviews | Microbiology

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

Dengue Fever Epidemiology

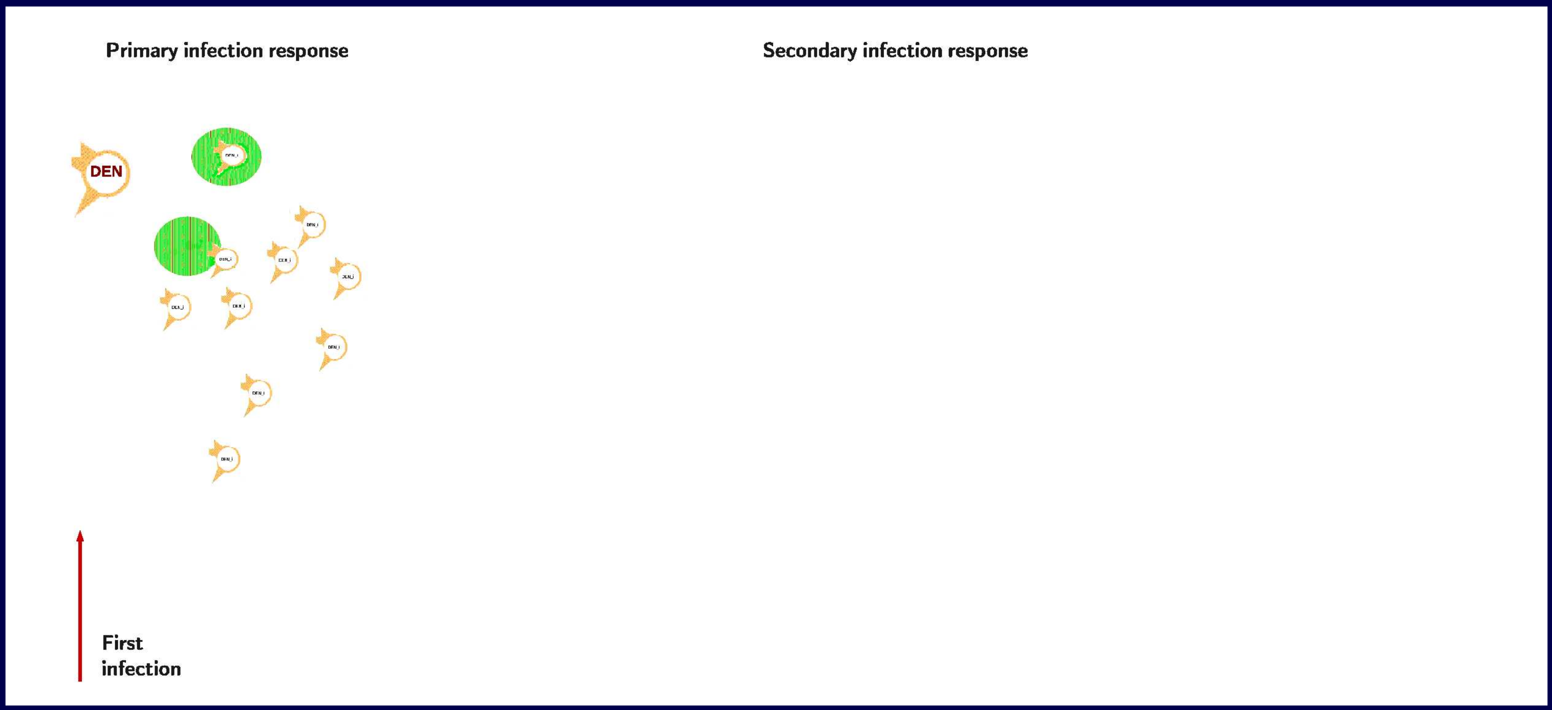
- *Infection by one serotype confers life-long immunity to that serotype and a short period of temporary cross-immunity to other serotypes (3-9 months).*

- *Two forms of the disease exist: dengue fever (DF), and dengue hemorrhagic fever (DHF).*

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

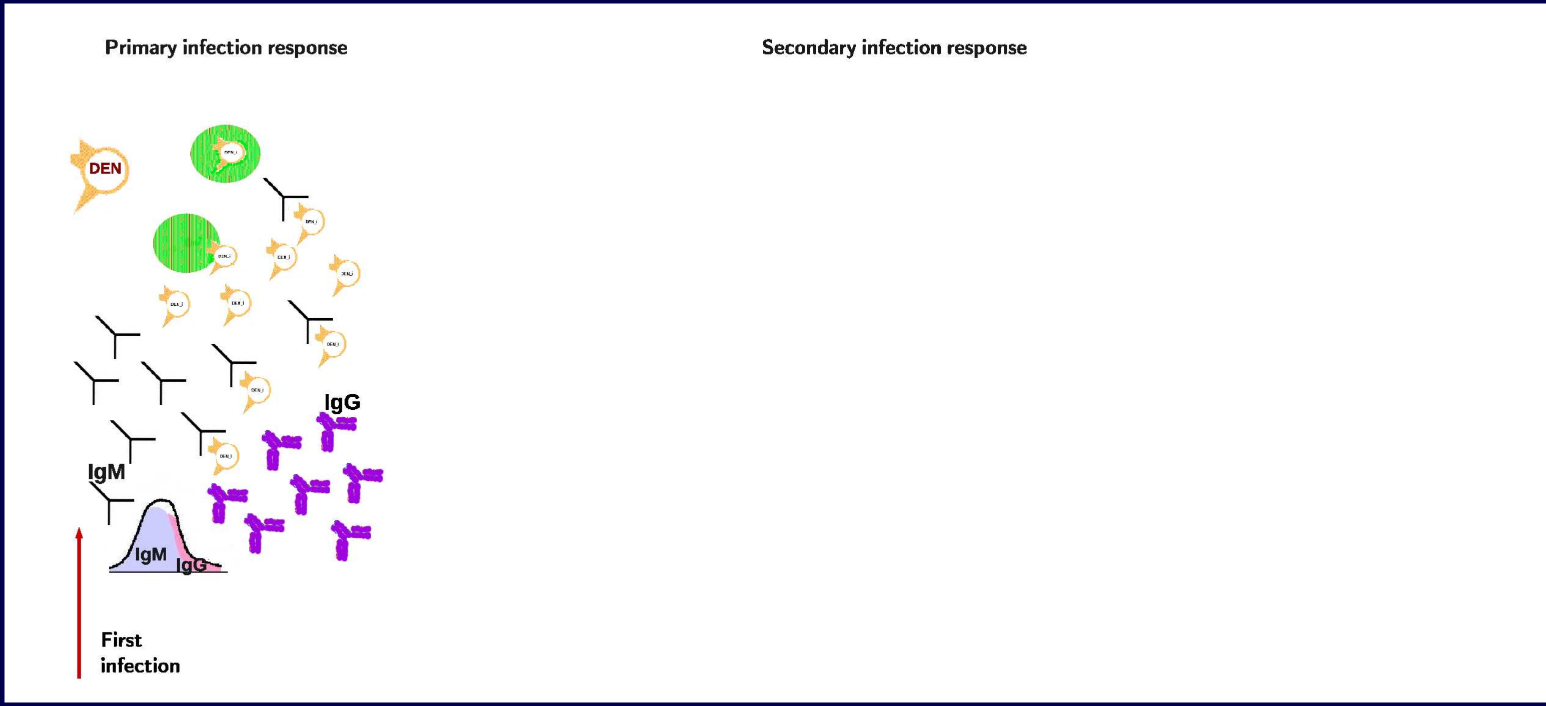
Dengue Fever Epidemiology

ADE in recurrent infections



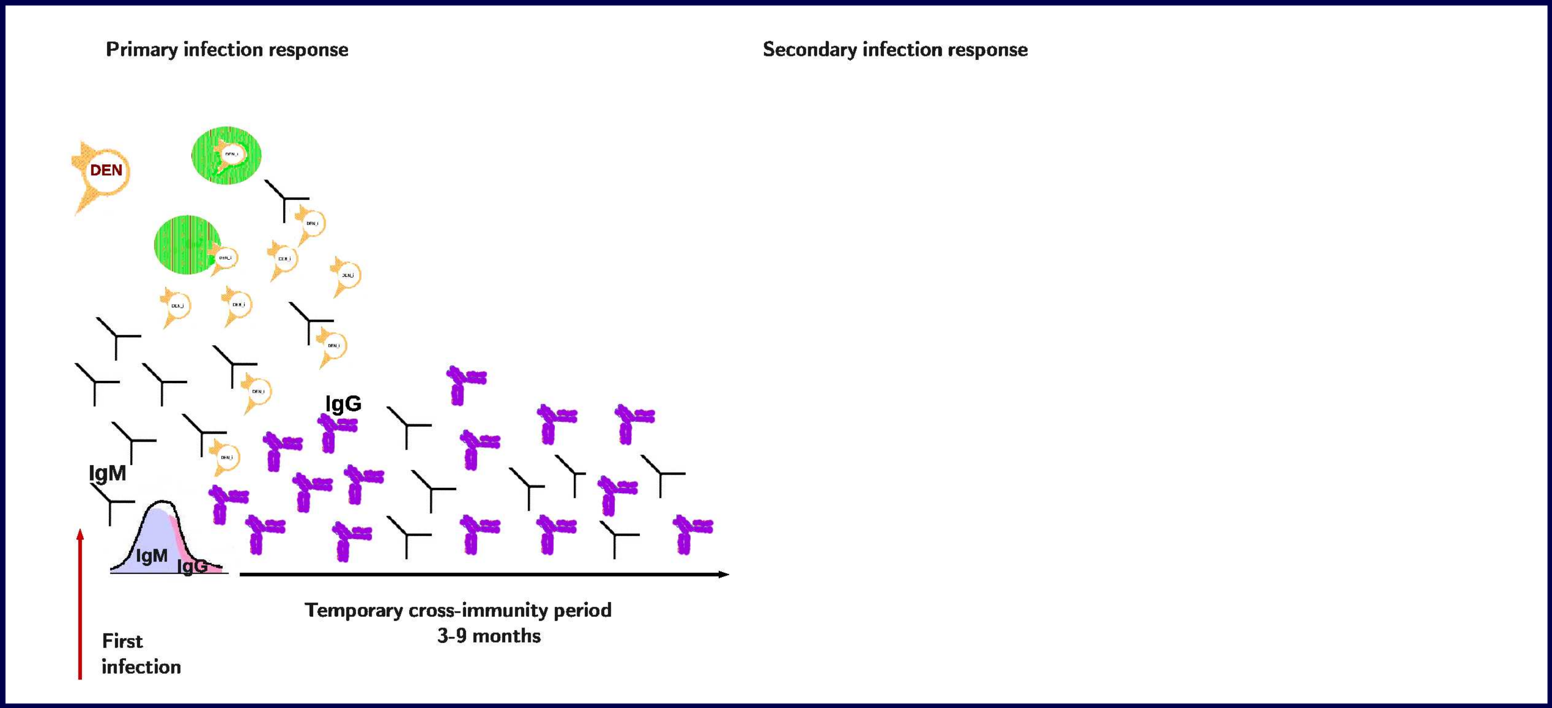
Dengue Fever Epidemiology

ADE in recurrent infections



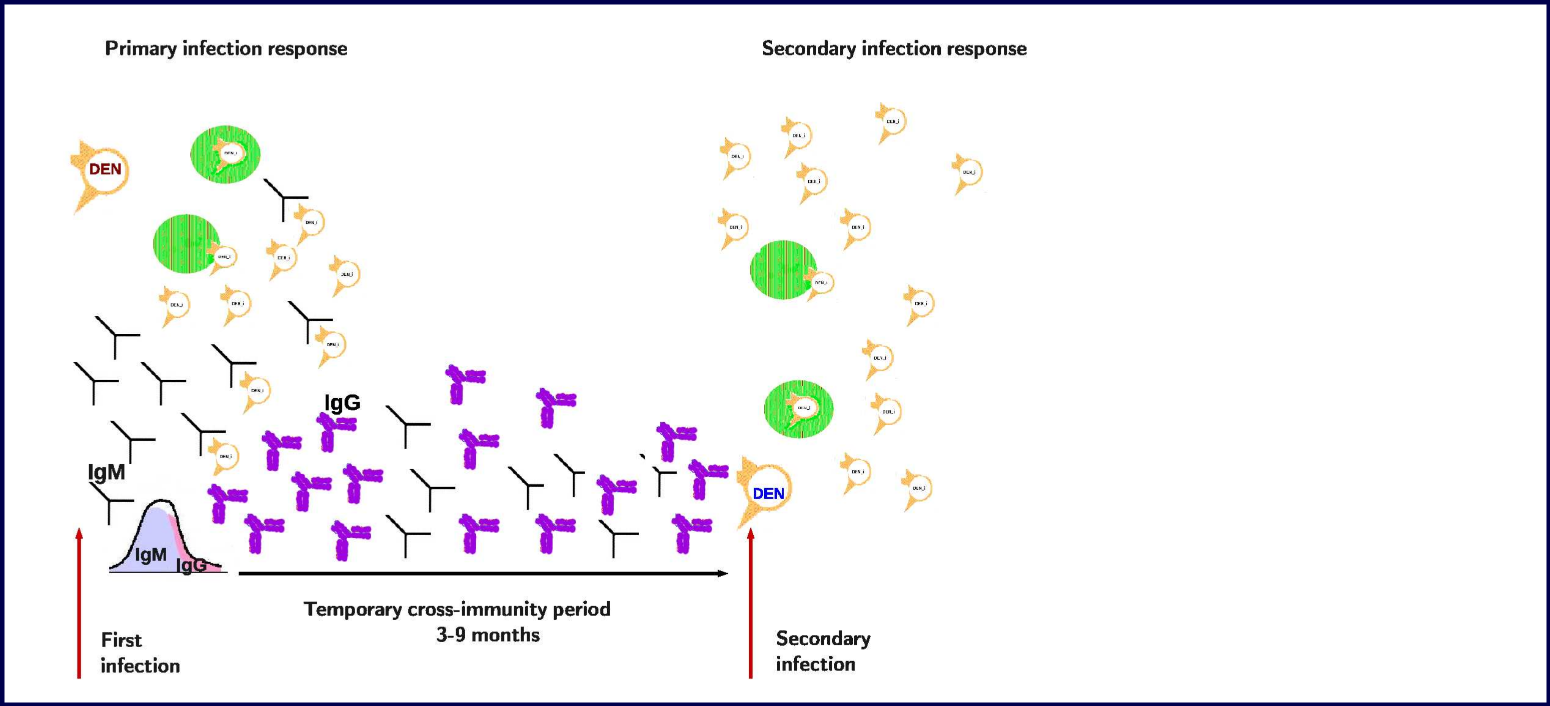
Dengue Fever Epidemiology

ADE in recurrent infections



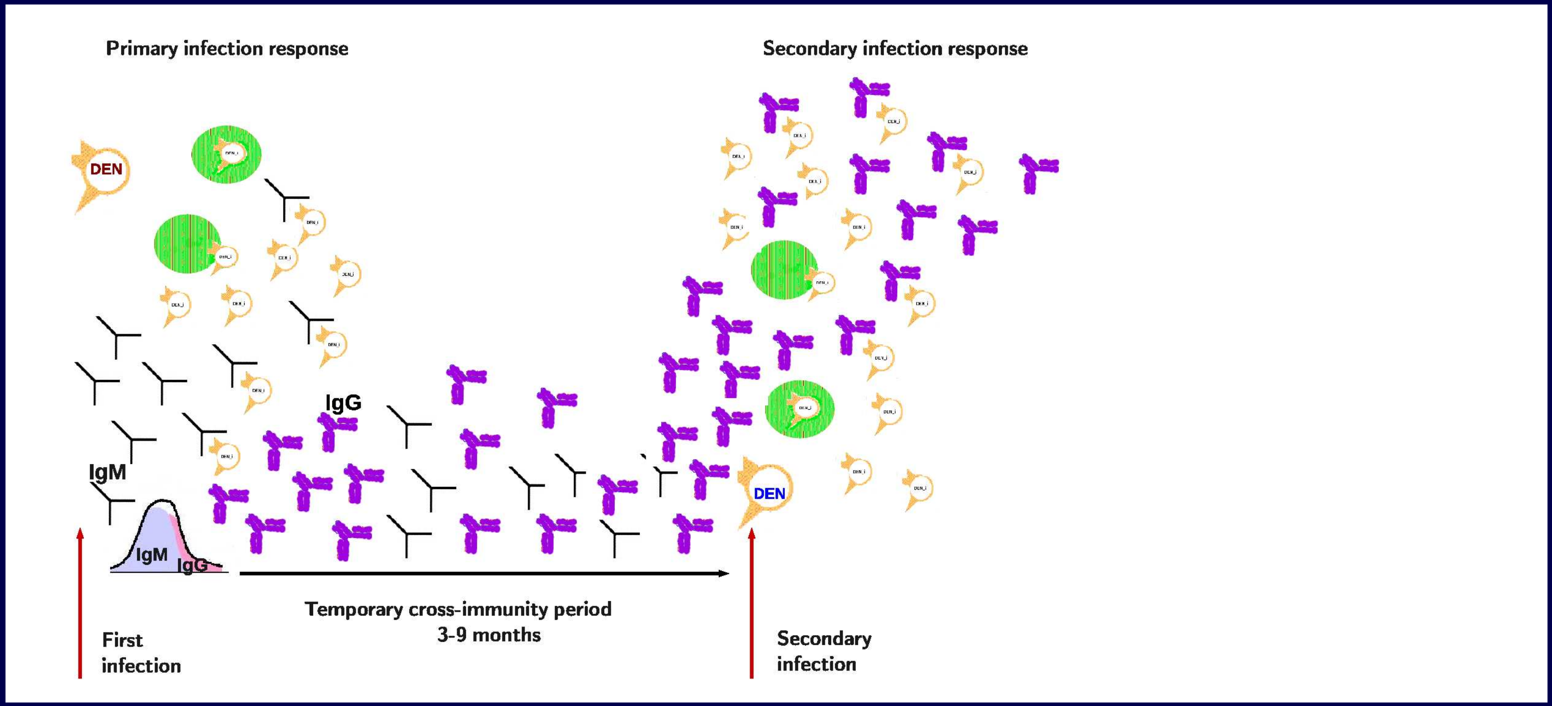
Dengue Fever Epidemiology

ADE in recurrent infections



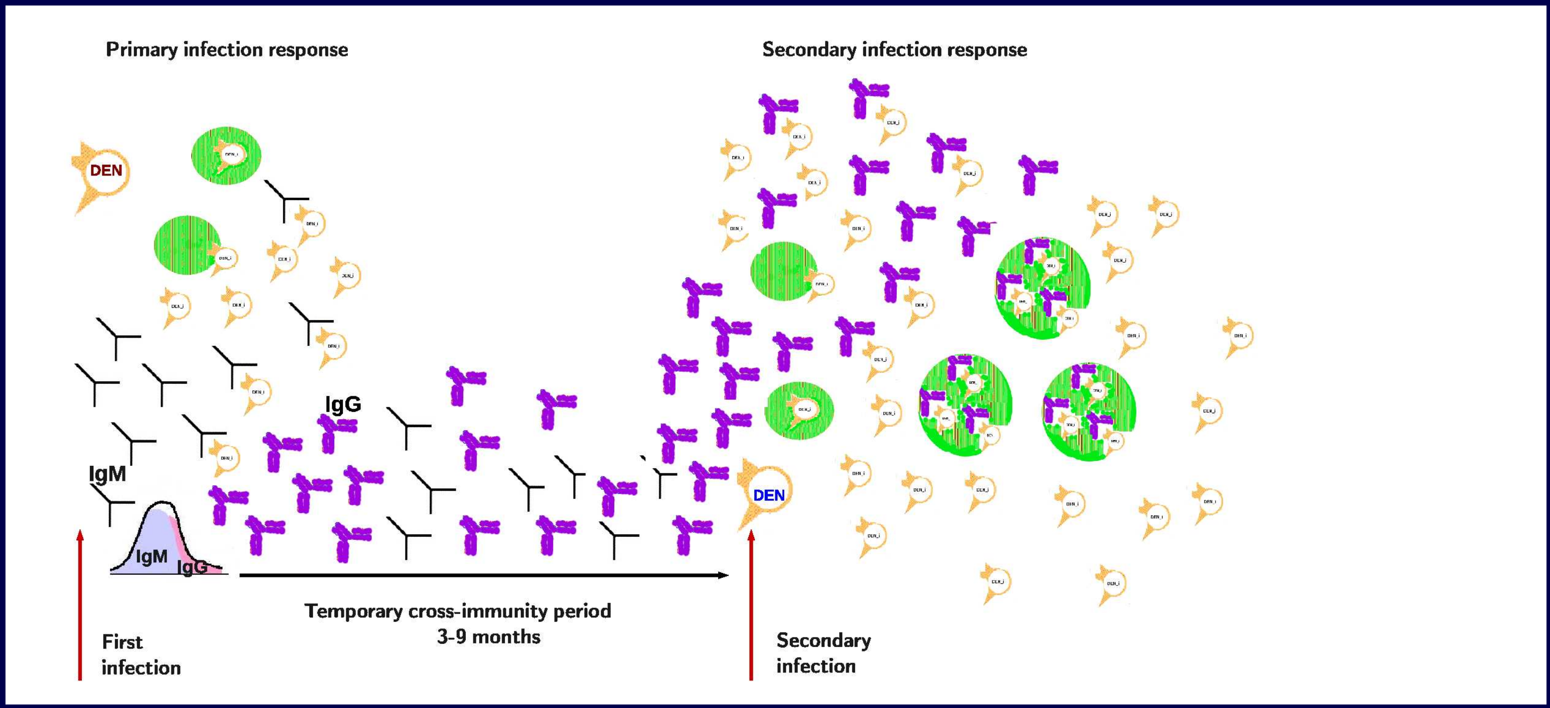
Dengue Fever Epidemiology

ADE in recurrent infections



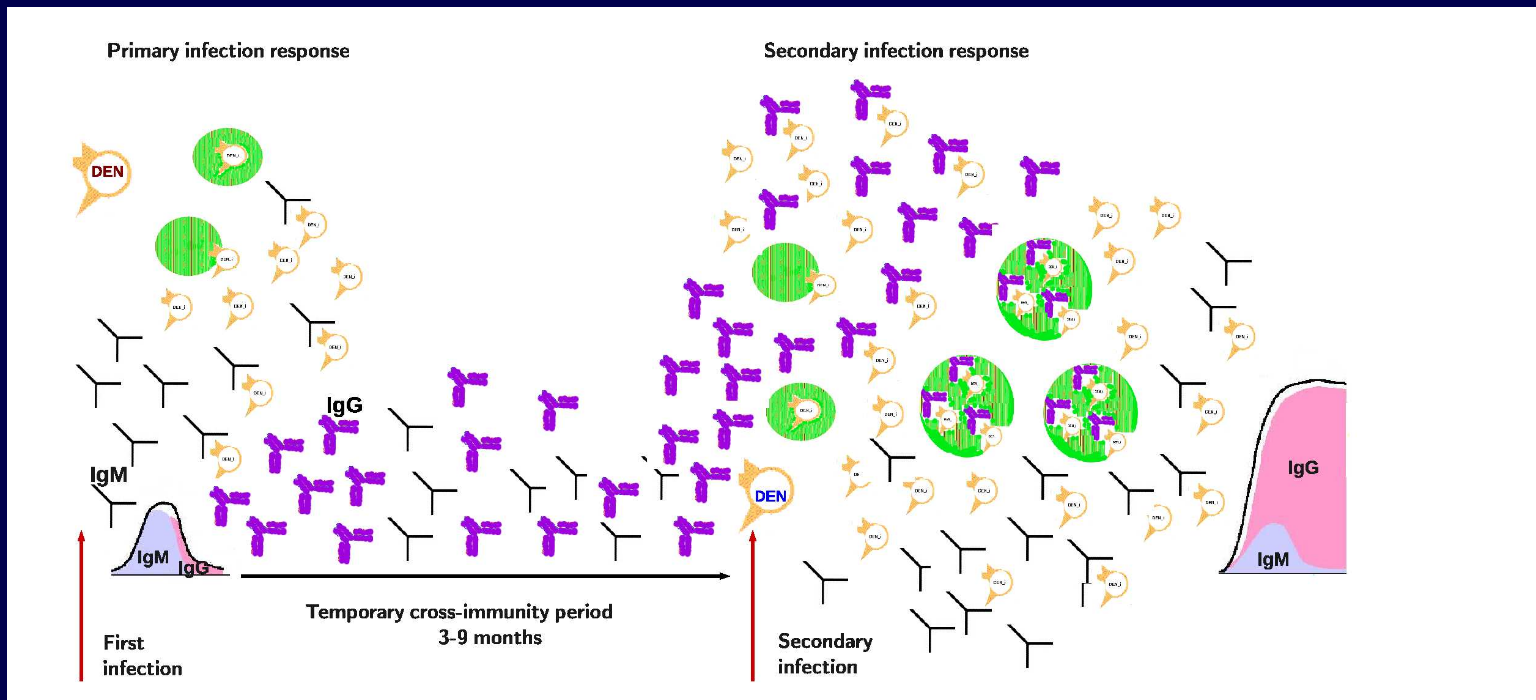
Dengue Fever Epidemiology

ADE in recurrent infections



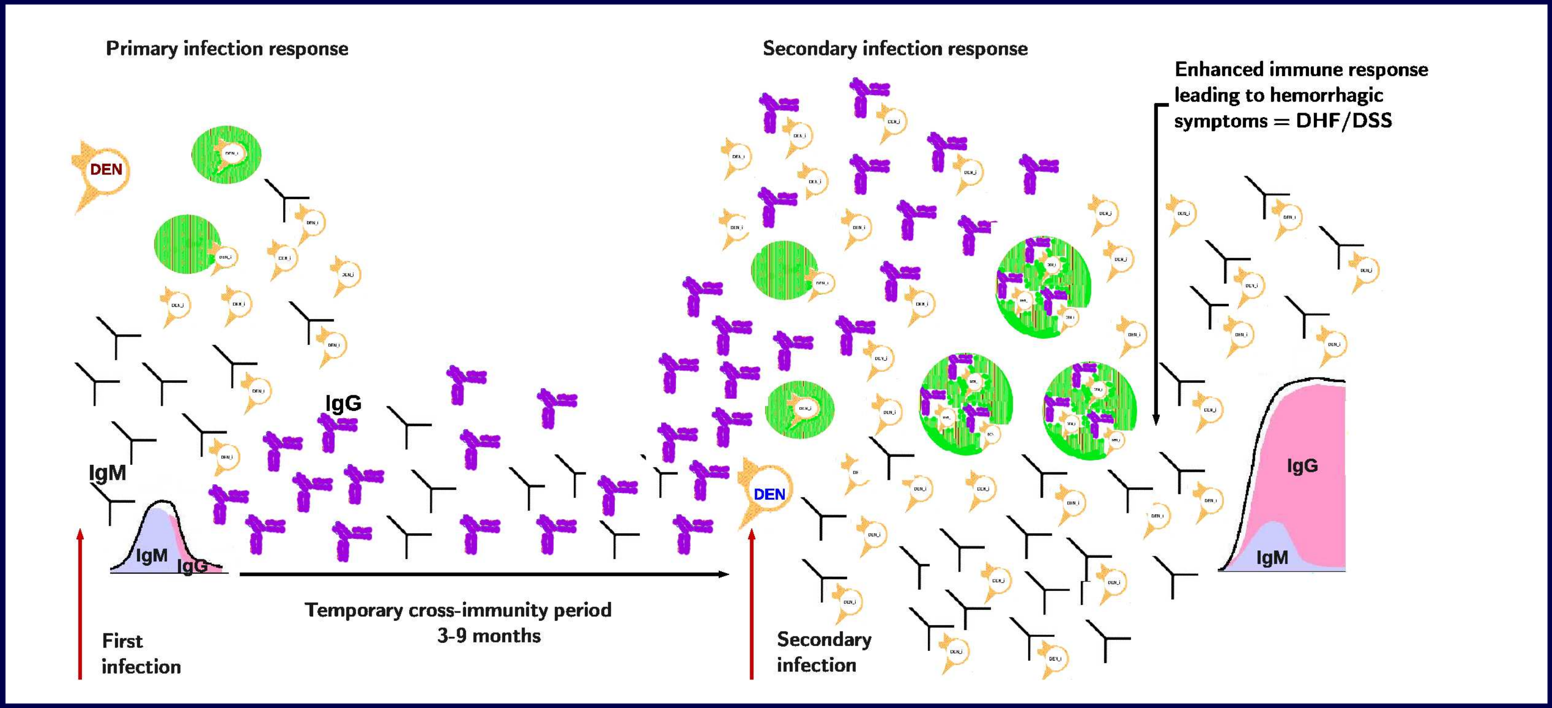
Dengue Fever Epidemiology

ADE in recurrent infections



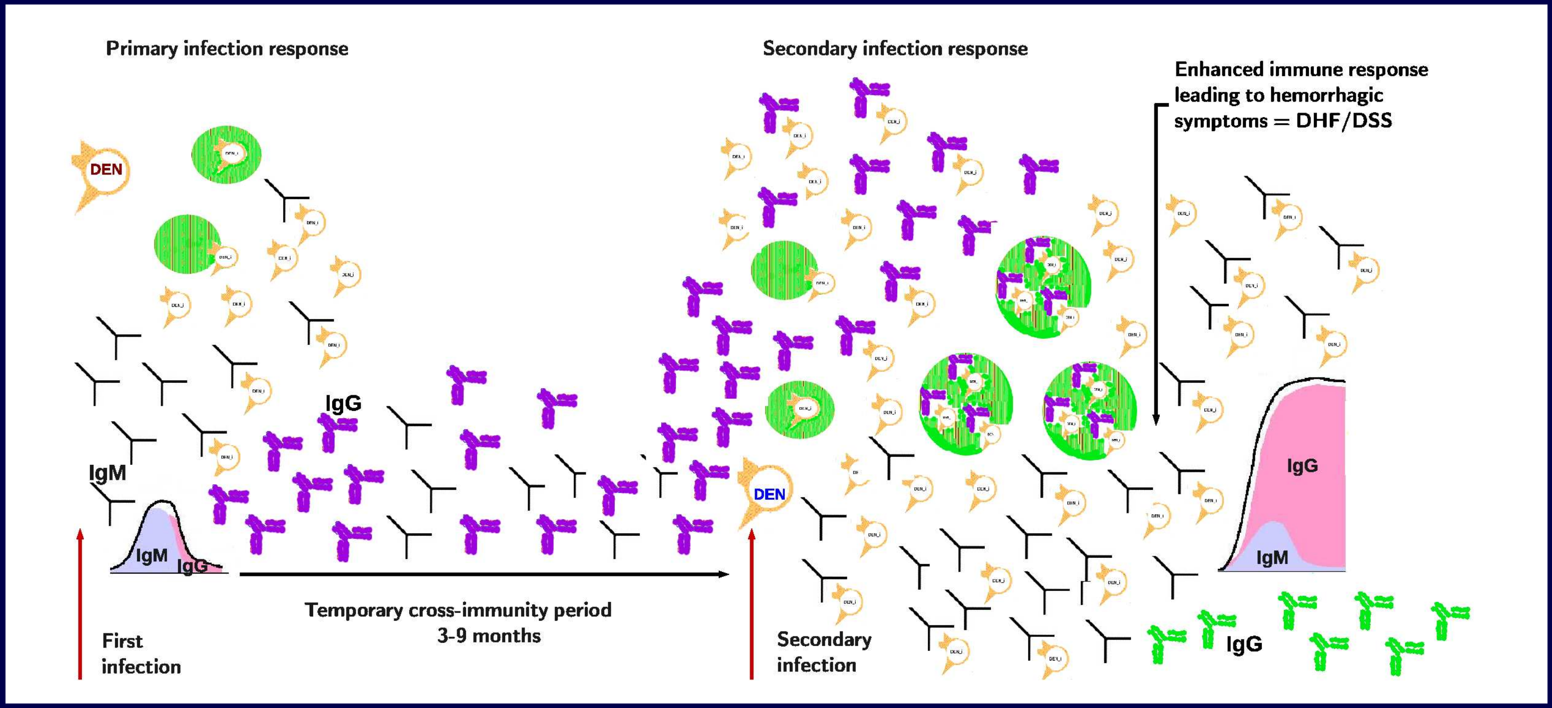
Dengue Fever Epidemiology

ADE in recurrent infections



Dengue Fever Epidemiology

ADE in recurrent infections



Dengue Fever Epidemiology

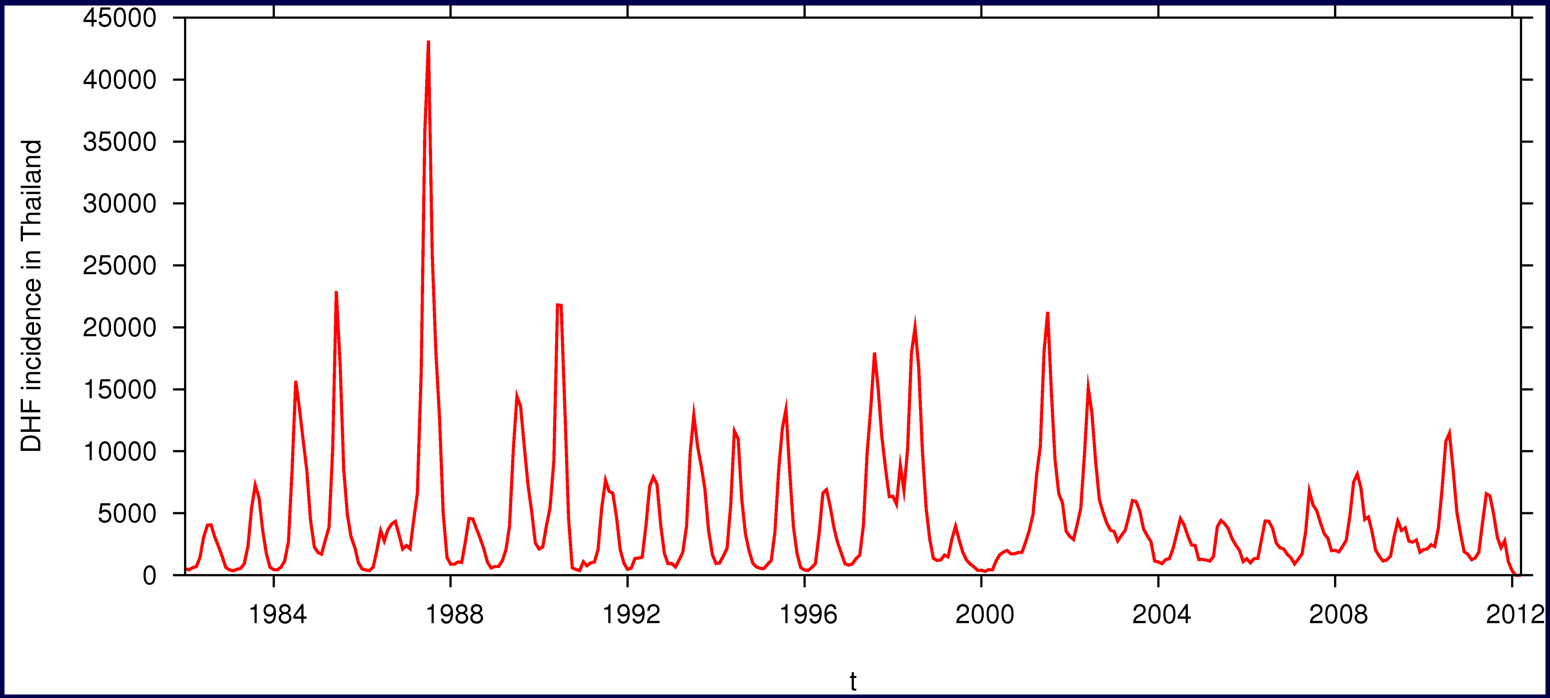
- *It is suggested that the majority of second dengue infections occur at a spacing of more than 6 months, however, the reasoning behind it (temporary cross-immunity period) is still an open question.*

- *There is no specific treatment for DF, and DHF cases require hospitalization.*

- *A vaccine is not yet available. So far, prevention of exposure and vector control remain the only alternatives to prevent dengue transmission.*

Dengue Fever Epidemiology

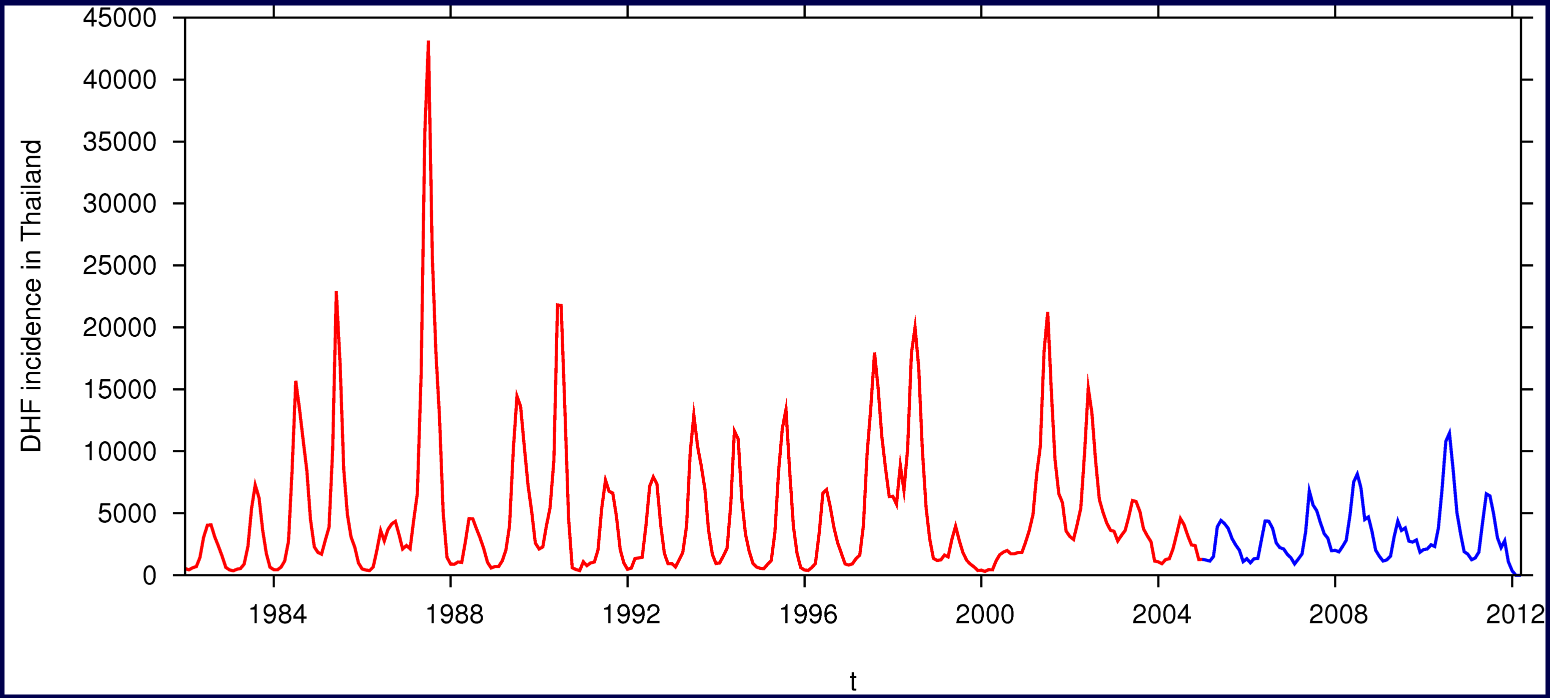
Source: Ministry of Public Health, Thailand. Bureau of Epidemiology (2012)



Note the yearly fluctuations

Dengue Fever Epidemiology

Source: Ministry of Public Health, Thailand. Bureau of Epidemiology (2012)



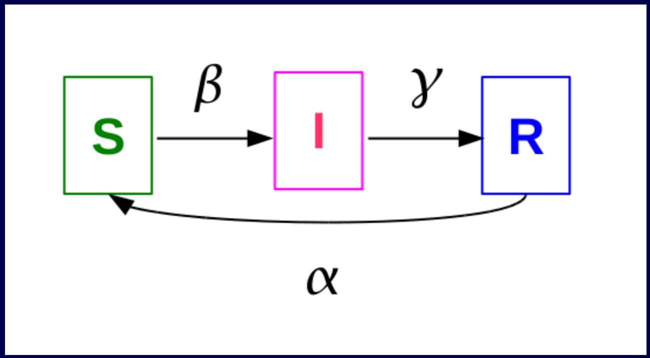
DENFREE EU project under FP7:
Dengue Research Framework for Resisting Epidemics in Europe

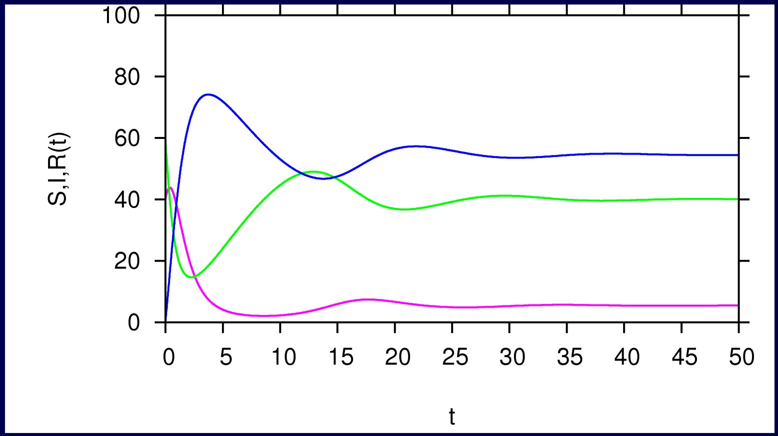
Mathematical modeling

The understanding of infectious disease epidemiology and control has been greatly increased through mathematical modeling.

Epidemic models describe the transition of the individuals in a population through a sequence of disease-related stages:

susceptible (S), infected (I), recovered (R).





The n-strain epidemiological model

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

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

$$\dot{I}_i = \frac{\beta}{N} \left(I_i + \rho \cdot N + \phi \left(\sum_{j=1, j\neq i}^{n} I_{ji} \right) \right) - \left(\gamma + \mu\right) I_i \quad (2)$$

$$\dot{R}_i = \gamma I_i - \left(\alpha + \mu\right) R_i \quad (3)$$

$$\dot{S}_i = \alpha R_i - \sum_{j=1, j\neq i}^{n} \frac{\beta}{N} S_i \left(I_j + \rho \cdot N + \phi \left(\sum_{k=1, k\neq j}^{n} I_{kj} \right) \right) - \mu S_i \quad (4)$$

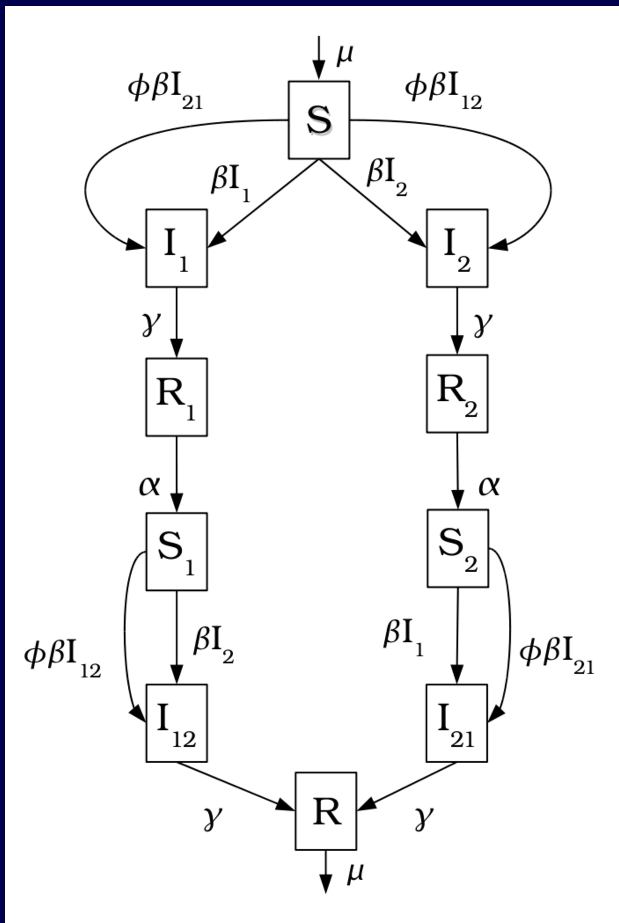
and for $i = 1, ..., n$ and $j = 1, ..., n$ with $j \neq i$

$$\dot{I}_{ij} = \frac{\beta}{N} S_i \left(I_j + \rho \cdot N + \phi \left(\sum_{k=1, k\neq j}^{n} I_{kj} \right) \right) - \left(\gamma + \mu\right) I_{ij} \quad (5)$$

and finally

$$\dot{R} = \gamma \left(\sum_{i=1}^{n} \sum_{j=1, j\neq i}^{n} I_{ij} \right) - \mu R \quad (6)$$

Modeling dengue fever epidemiology



$$\dot{S} = -\frac{\beta}{N}S(I_1 + \phi_1 I_{21}) - \frac{\beta}{N}S(I_2 + \phi_2 I_{12}) + \mu(N - S)$$

$$\dot{I}_1 = \frac{\beta}{N}S(I_1 + \phi_1 I_{21}) - (\gamma + \mu)I_1$$

$$\dot{I}_2 = \frac{\beta}{N}S(I_2 + \phi_2 I_{12}) - (\gamma + \mu)I_2$$

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

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

$$\dot{S}_1 = -\frac{\beta}{N}S_1(I_2 + \phi_2 I_{12}) + \alpha R_1 - \mu S_1$$

$$\dot{S}_2 = -\frac{\beta}{N}S_2(I_1 + \phi_1 I_{21}) + \alpha R_2 - \mu S_2$$

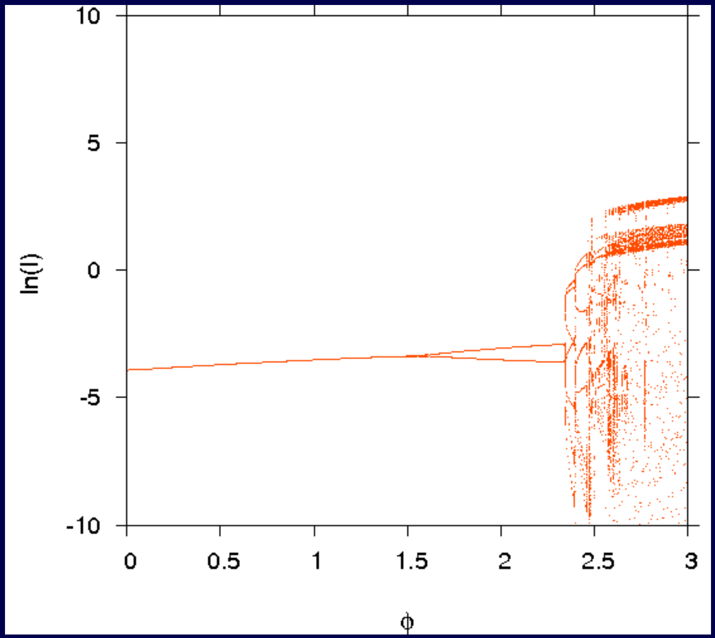
$$\dot{I}_{12} = \frac{\beta}{N}S_1(I_2 + \phi_2 I_{12}) - (\gamma + \mu)I_{12}$$

$$\dot{I}_{21} = \frac{\beta}{N}S_2(I_1 + \phi_1 I_{21}) - (\gamma + \mu)I_{21}$$

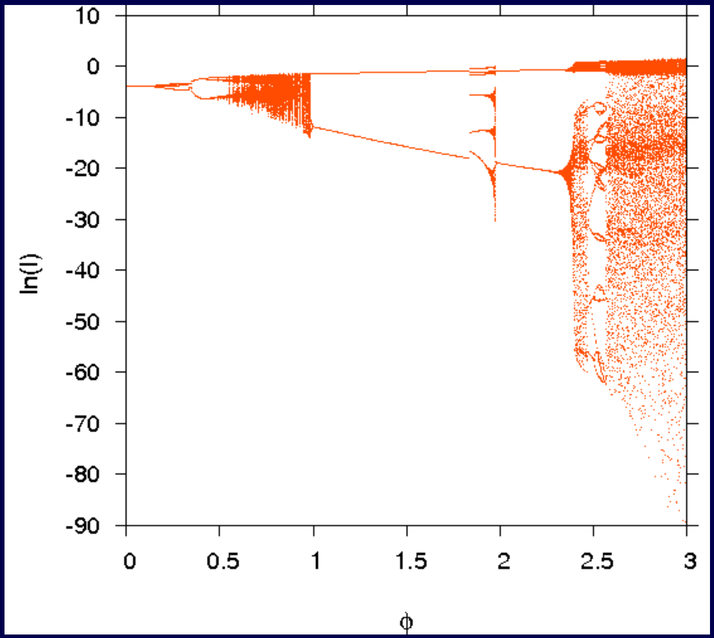
$$\dot{R} = \gamma(I_{12} + I_{21}) - \mu R$$

Non-seasonal 2-strain dengue model

No Temporary Cross-Immunity versus Temporary Cross-Immunity

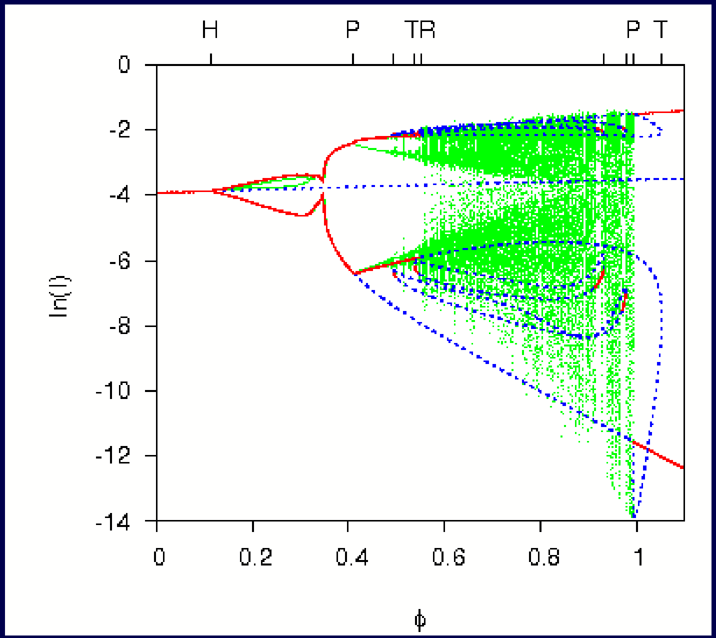


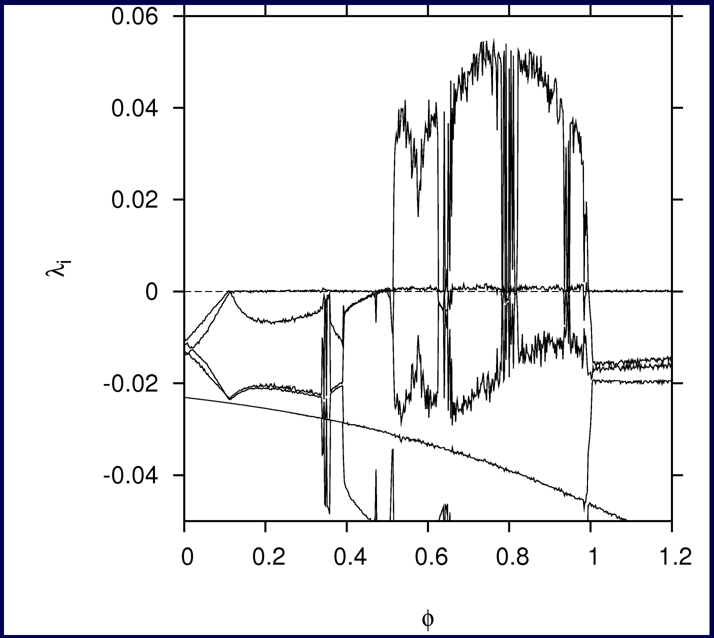
$\alpha = 52$ *(one week)*



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

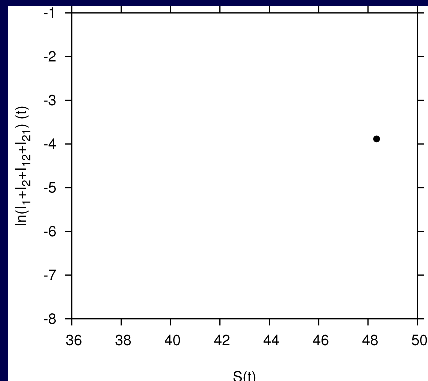
Non-seasonal 2-strain dengue model with temporary cross-immunity



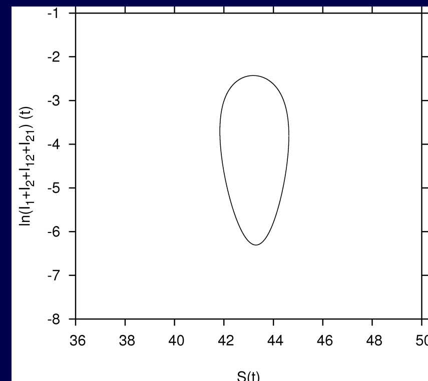


Rich dynamic structure (Hopf, pitchfork, torus and tangent bifurcations) including deterministic chaos in a wider and more biologically realistic parameter regions, than previously expected.

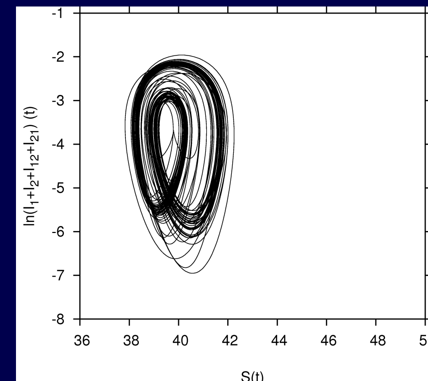
Non-seasonal 2-strain dengue model with temporary cross-immunity



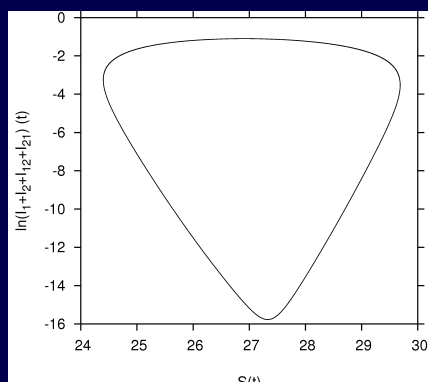
$\phi = 0.1$



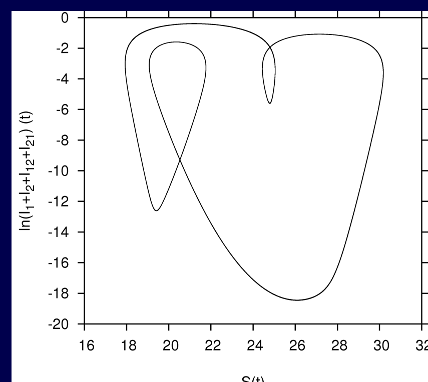
$\phi = 0.4$



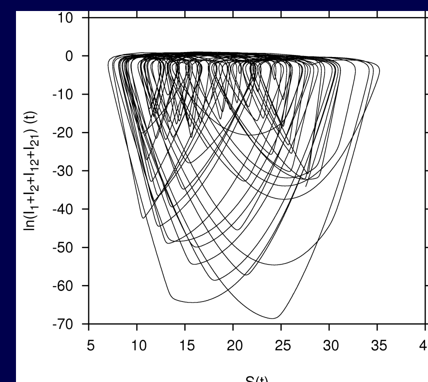
$\phi = 0.6$



$\phi = 1.5$

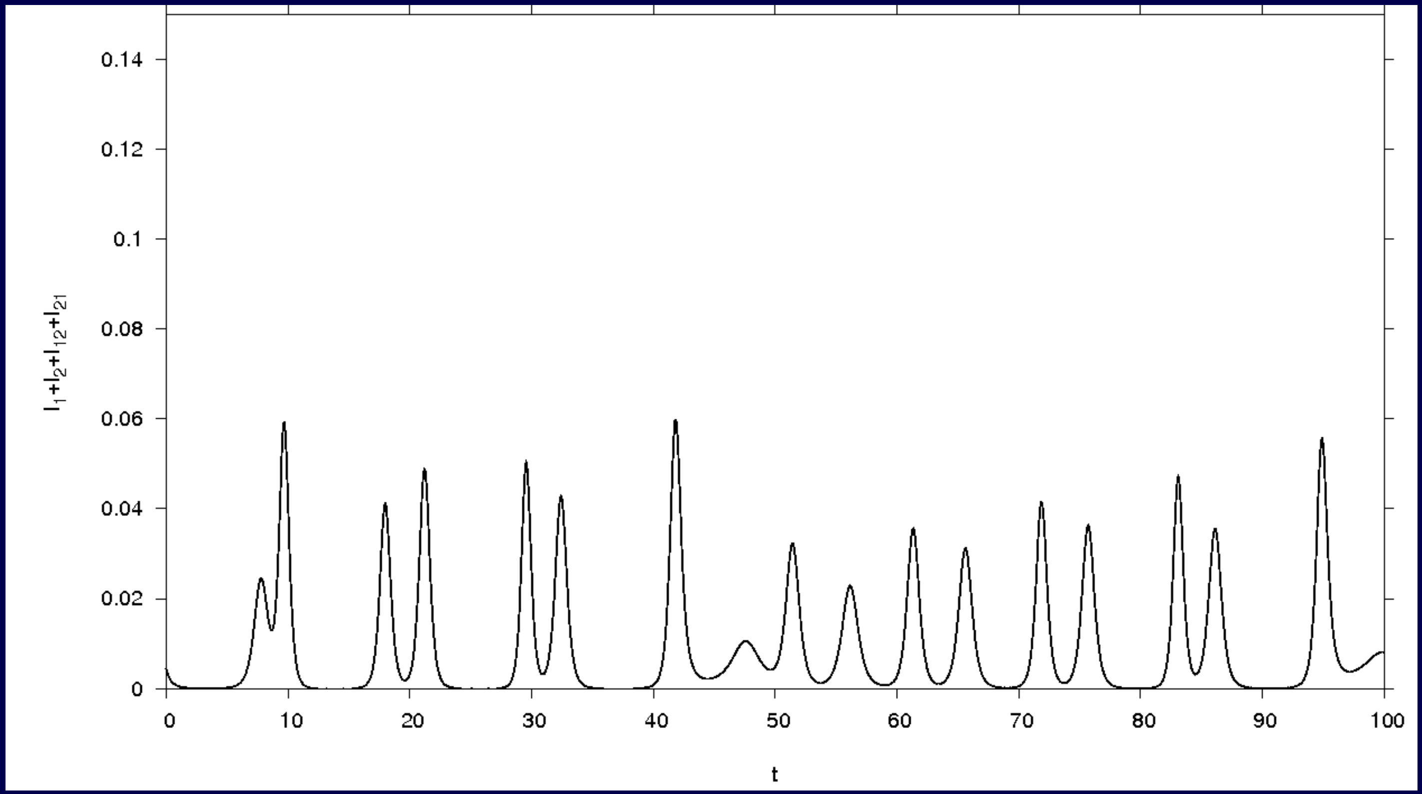


$\phi = 1.9$



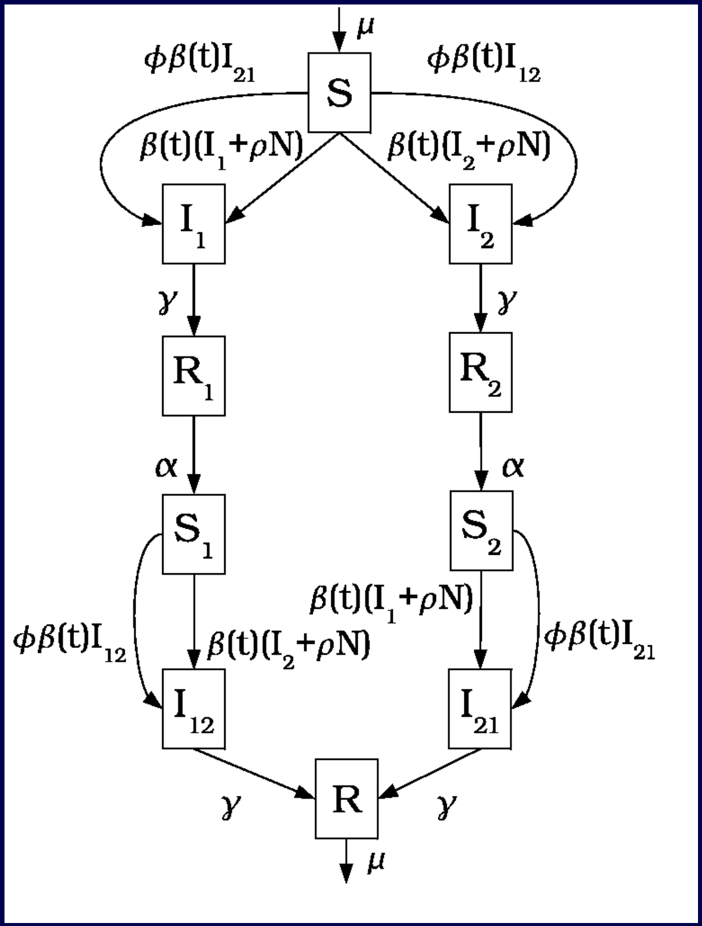
$\phi = 2.7$

Non-seasonal 2-strain dengue model with temporary cross-immunity



Irregular pattern every 5 years

Seasonal 2-strain dengue model with temporary cross-immunity



$$\beta(t) = \beta_0(1 + \eta \cdot \cos(\omega t))$$

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

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

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

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

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

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

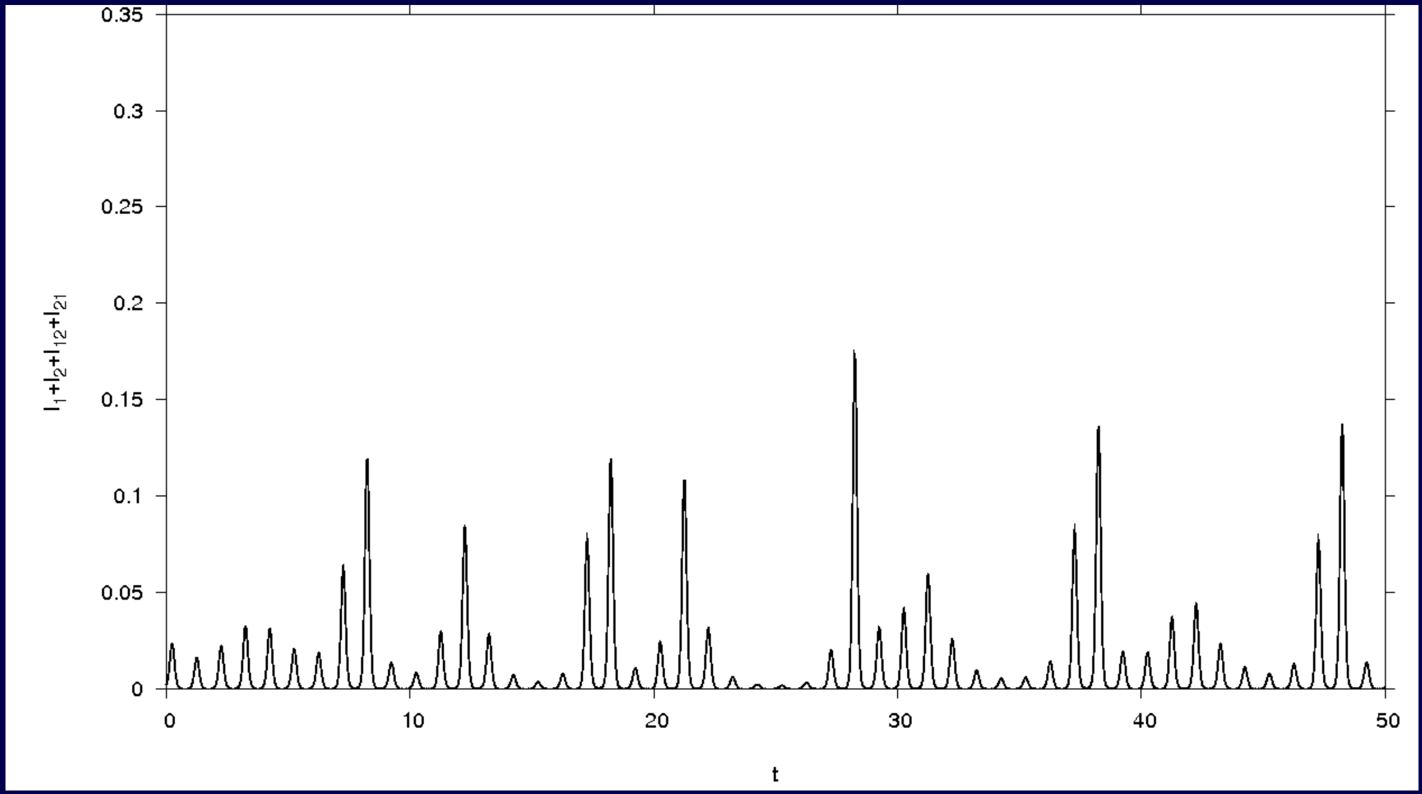
$$\dot{S}_2 = -\frac{\beta(t)}{N} S_2(I_1 + \rho \cdot N + \phi I_{21}) + \alpha R_2 - \mu S_2$$

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

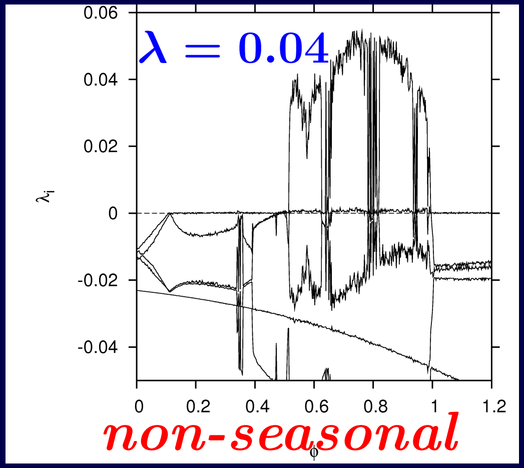
$$\dot{I}_{21} = \frac{\beta(t)}{N} S_2(I_1 + \rho \cdot N + \phi I_{21}) - (\gamma + \mu) I_{21}$$

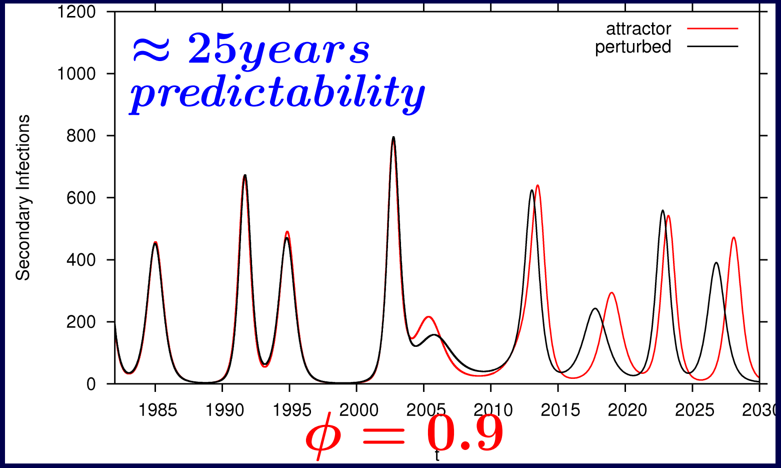
$$\dot{R} = \gamma(I_{12} + I_{21}) - \mu R$$

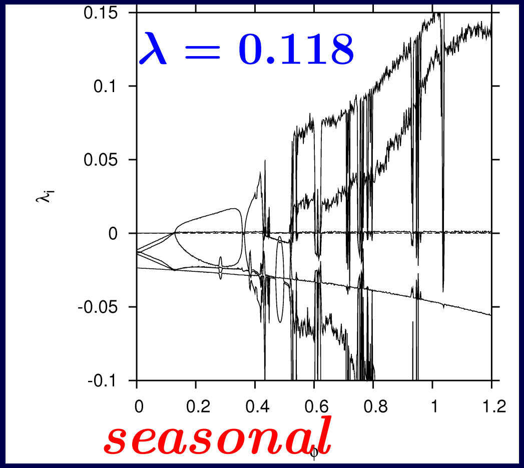
2-strain dengue model: seasonality and import

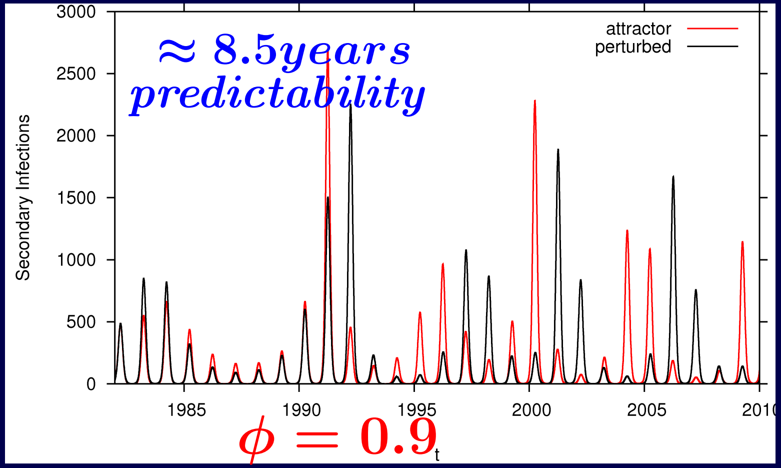


Lyapunov exponents and predictability

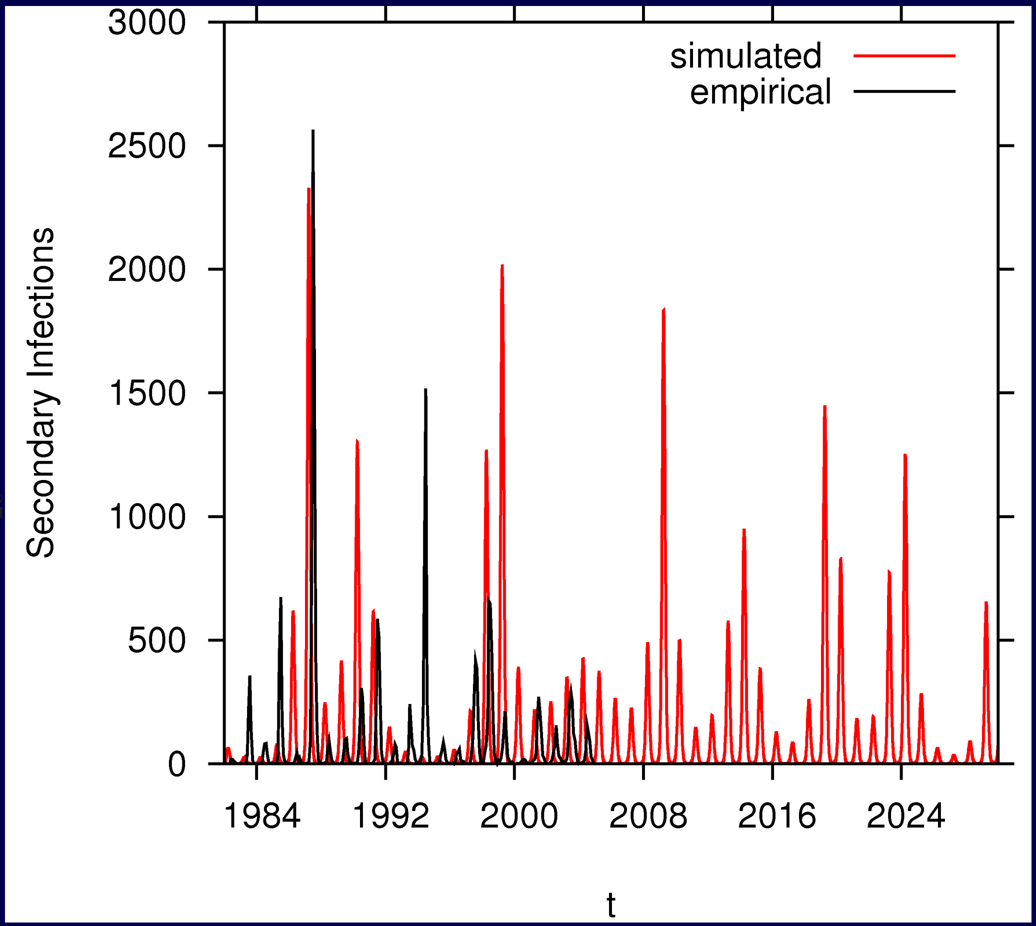






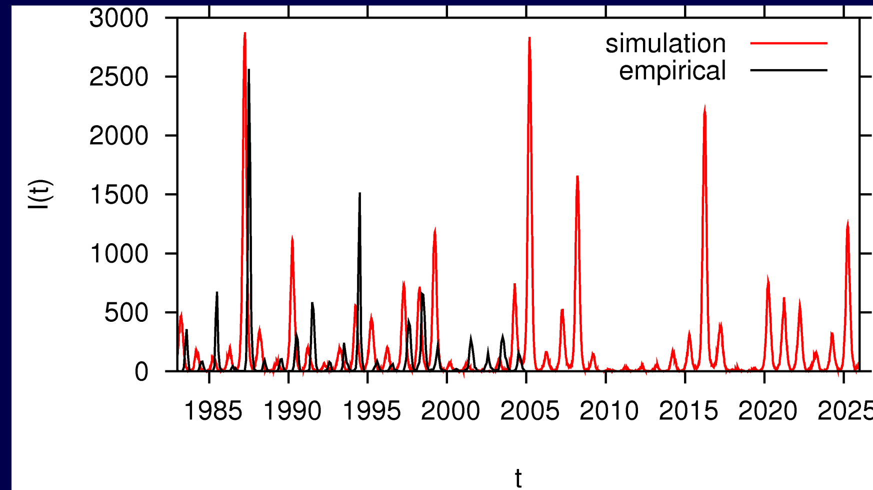


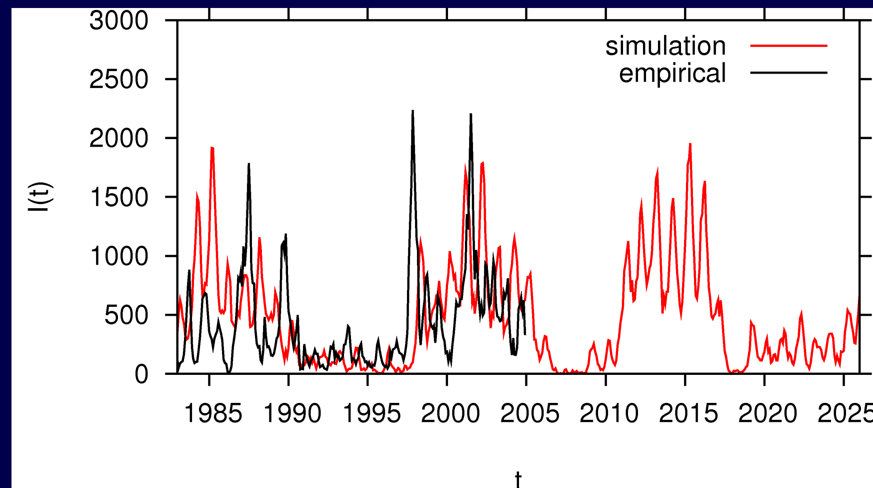
Implications for data analysis



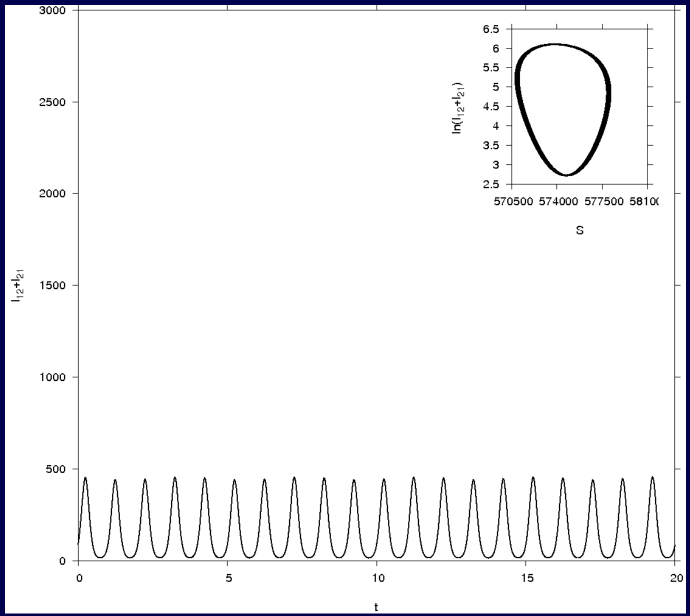
A qualitatively a very good agreement between empirical data and model simulation, suggesting that this parameter set could be the starting set for a more detailed parameter estimation procedure.

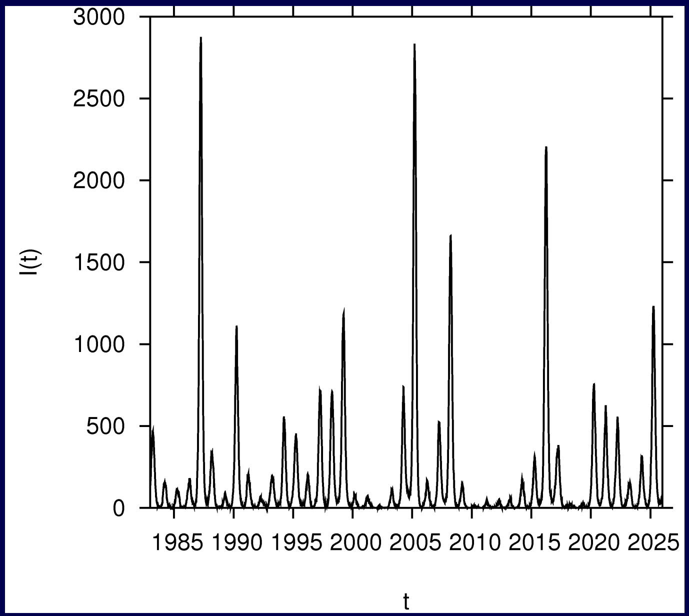
The stochastic approach is able to describe both types of the dynamics, the smooth data with a well defined maximum each year of irregular hight, found in the high endemic regions of Thailand and also the noisy data found mainly in low endemic regions of Thailand.





Small population size: deterministic vs stochastic

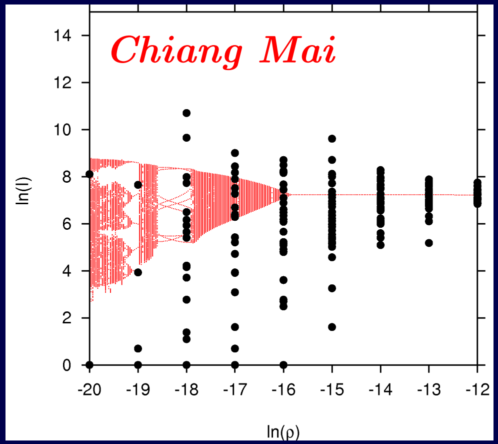


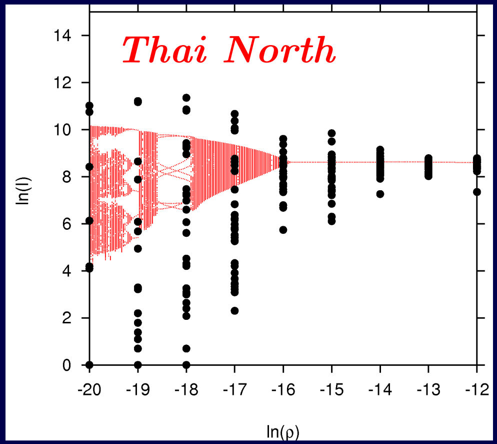


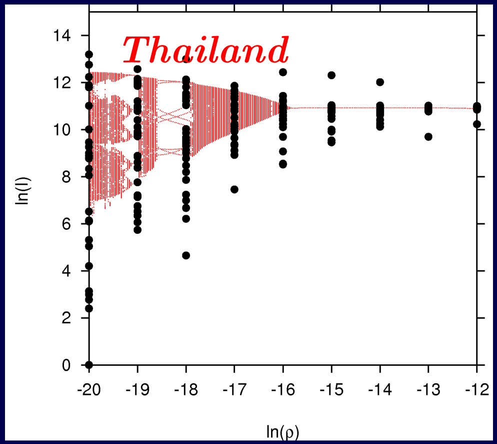
The quasi-periodicity becomes more irregular resembling a chaotic behaviour in the stochastic modelling.

Scaling of stochasticity

Stochastic simulations, using a finite size population, involve extinction phenomena operating through demographic stochasticity which acts drastically on small populations.

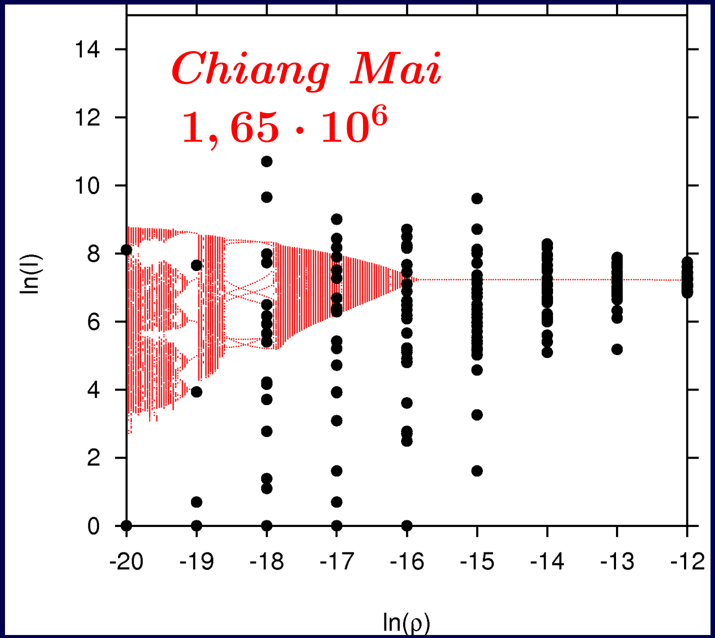


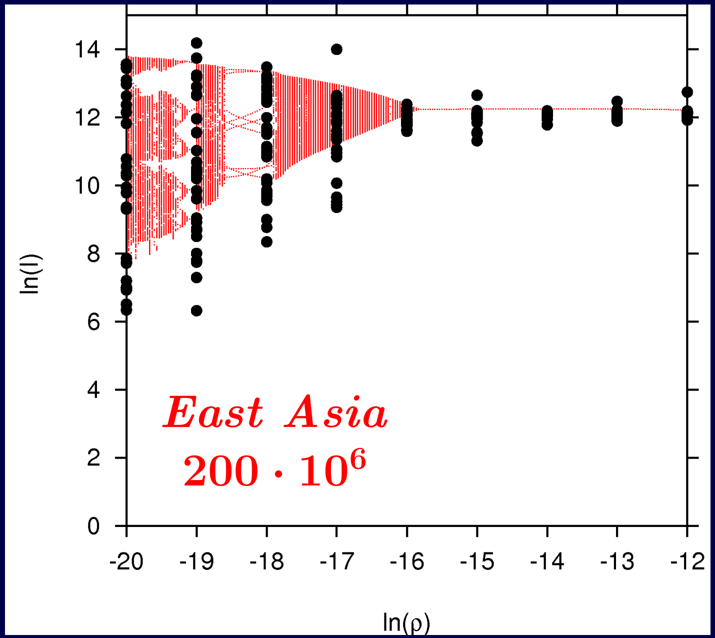




Scaling of stochasticity

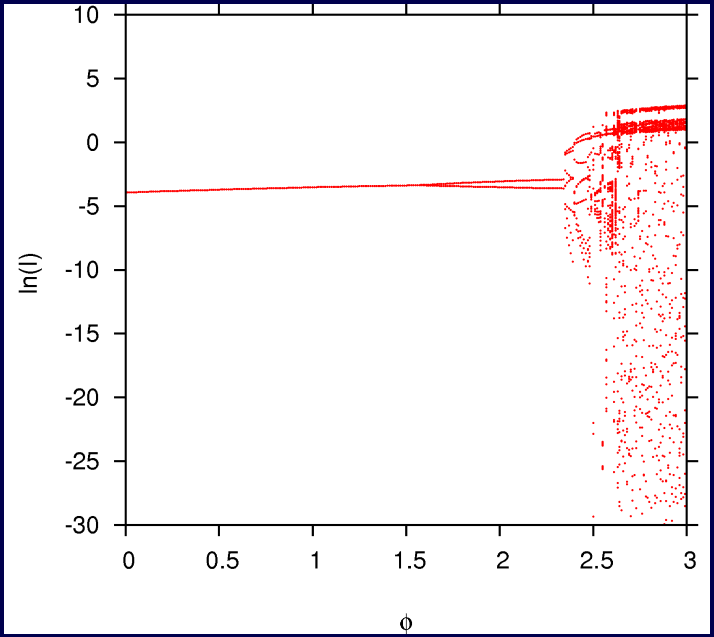
For large enough population size, the stochastic system can be well described by the deterministic skeleton, where the essential dynamics are captured.

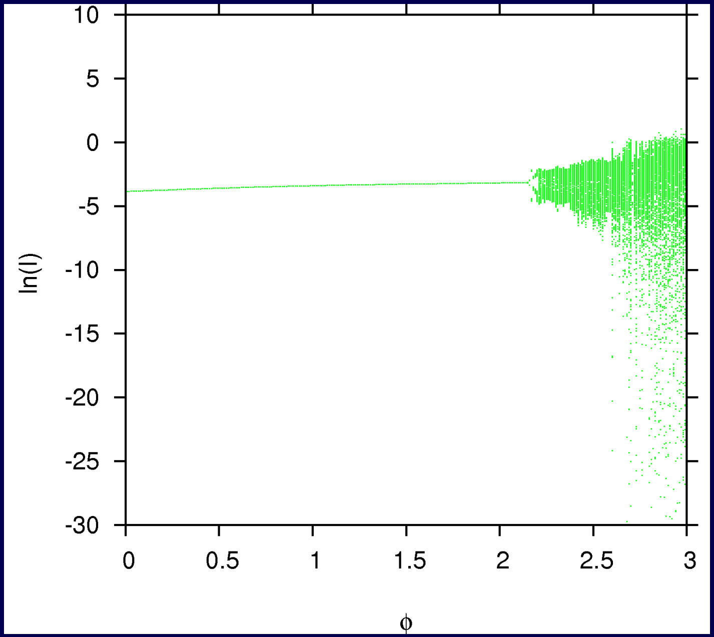




The detailed number of strains: a dimensional problem

two-strains (10 ODEs) *vs four-strains* (26 ODEs)

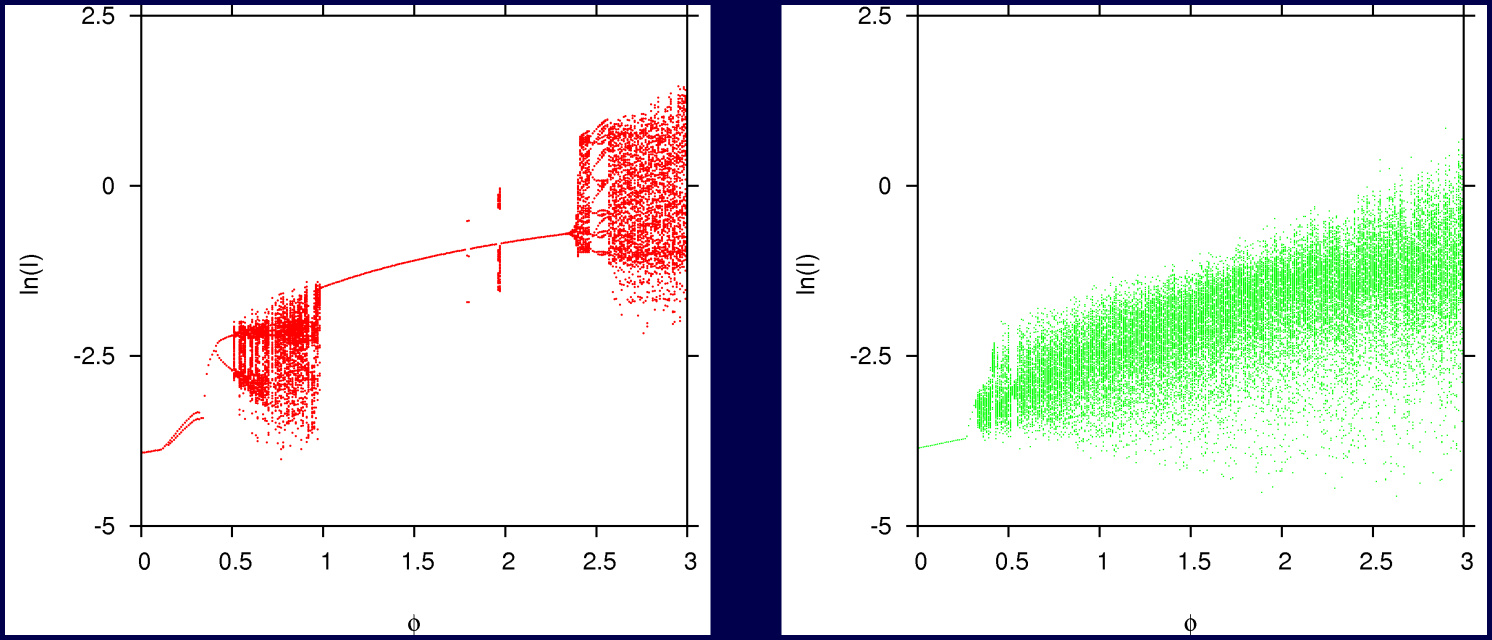




no cross-immunity

The detailed number of strains: a dimensional problem

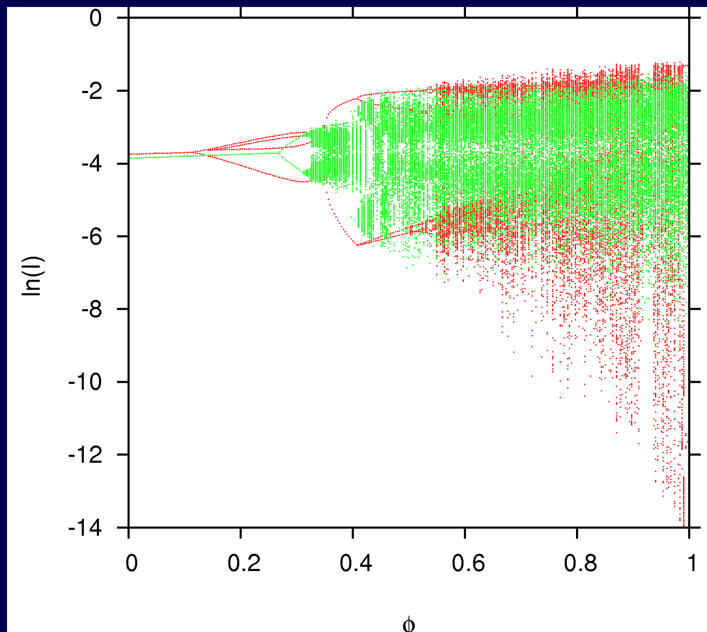
two-strains (10 ODEs) vs four-strains (26 ODEs)

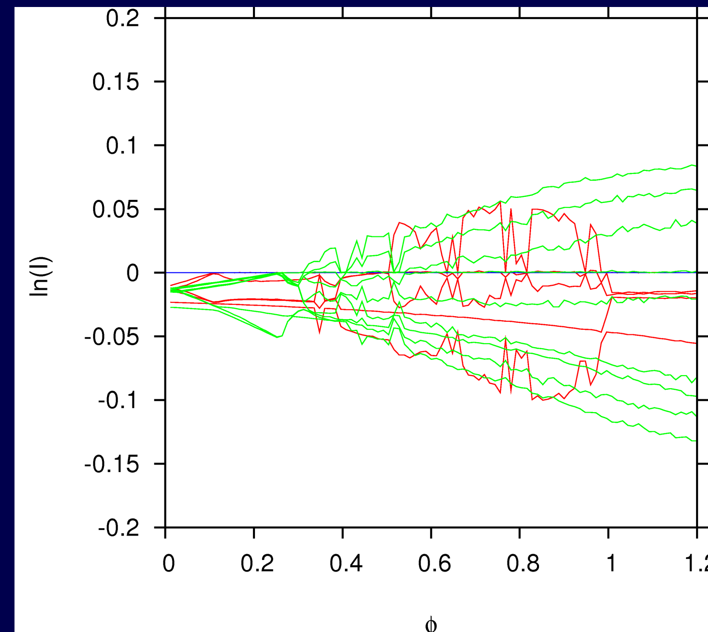


with cross-immunity

The detailed number of strains: a dimensional problem

two-strains (10 ODEs) vs four-strains (26 ODEs)





For both models we observe the same order of magnitude of the DLE and also similar structure.

Final Conclusions and remarks (1)

- Basic n-strain SIR-type model for the host population, capturing differences between primary and secondary infections.

- Consideration of temporary cross-immunity gives bifurcations up to chaotic attractors in much wider and also unexpected parameter regions.

- Adding seasonality gives qualitatively a very good result when comparing empirical DHF data and simulation.

- Introduction of stochasticity is needed to get even better agreement for some of the available data set (noisy data).

Final Conclusions and remarks (2)

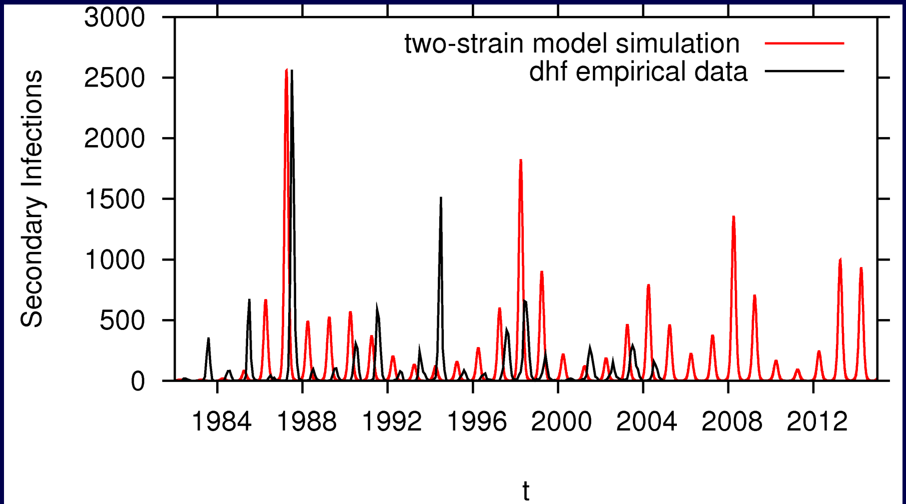
- *For large enough population size, the stochastic system can be well described by the deterministic skeleton gaining insight on the relevant parameter values purely on topological information of the dynamics.*

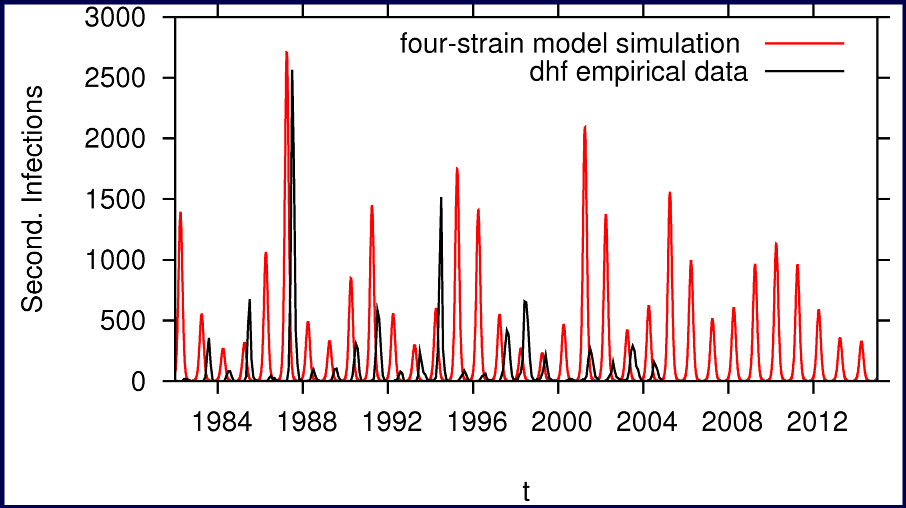
- *The difference between first and secondary infection combined with the temporary cross-immunity period is driving more the complex dynamics than the detailed number of strains to be considered in the model assumptions.*

- *The practical predictability of the system do not change significantly when considering two or four strains in the model.*

Final Conclusions and remarks (3)

⋇ *The two-strain model in its simplicity is a good model to be analyzed, giving the expected complex behavior to explain the fluctuations observed in empirical data.*





Final Conclusions and remarks (4)

- *For future parameter estimation only the two-strain model could attempt to estimate all initial conditions as well as the few model parameters.*

Thank you for your attention