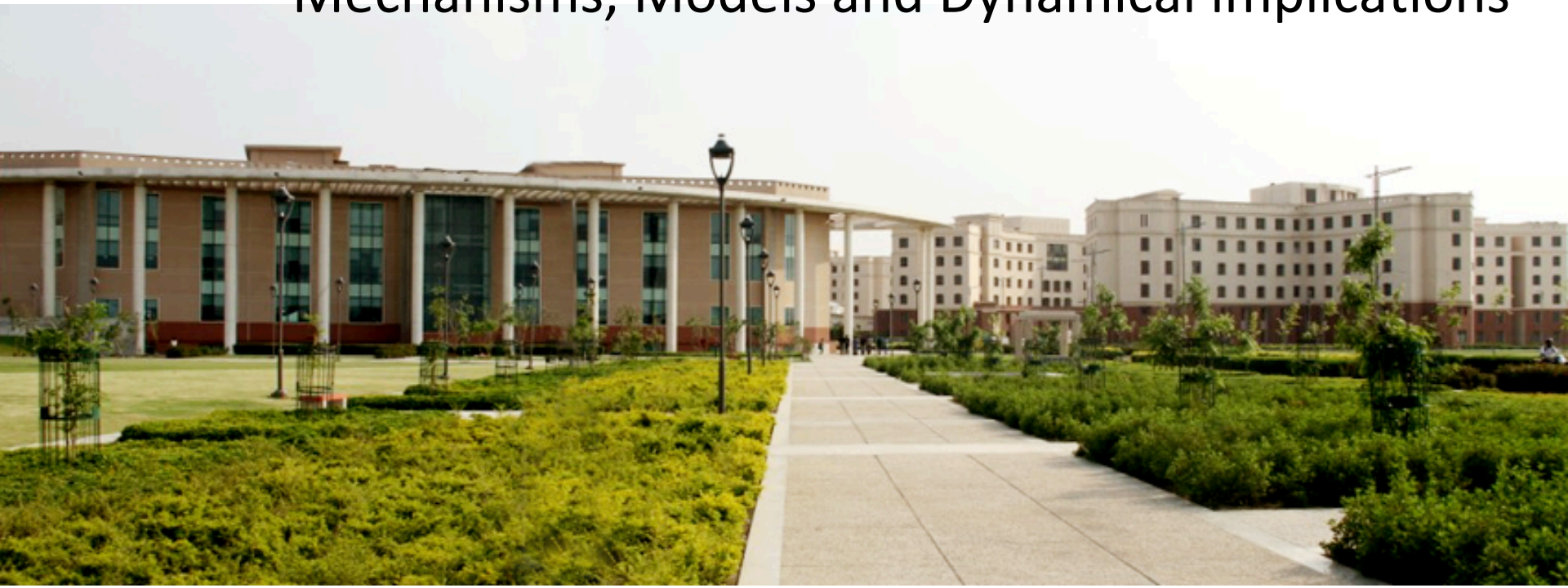
Pathogens Cross-talks

- Mechanisms, Models and Dynamical implications



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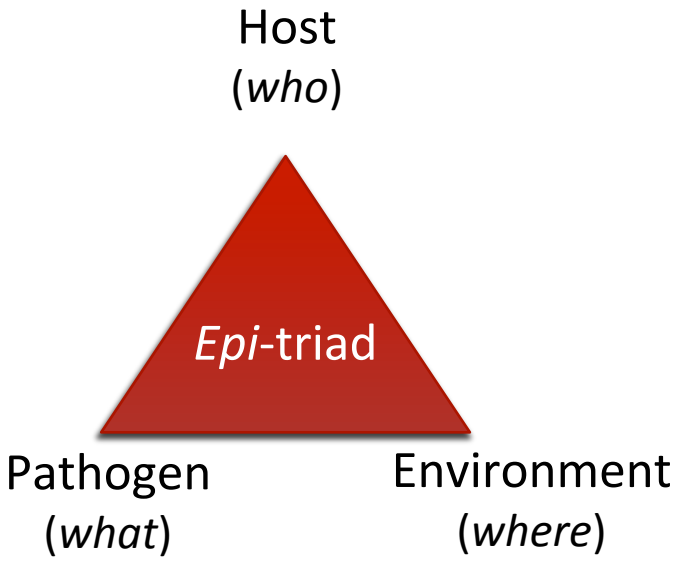


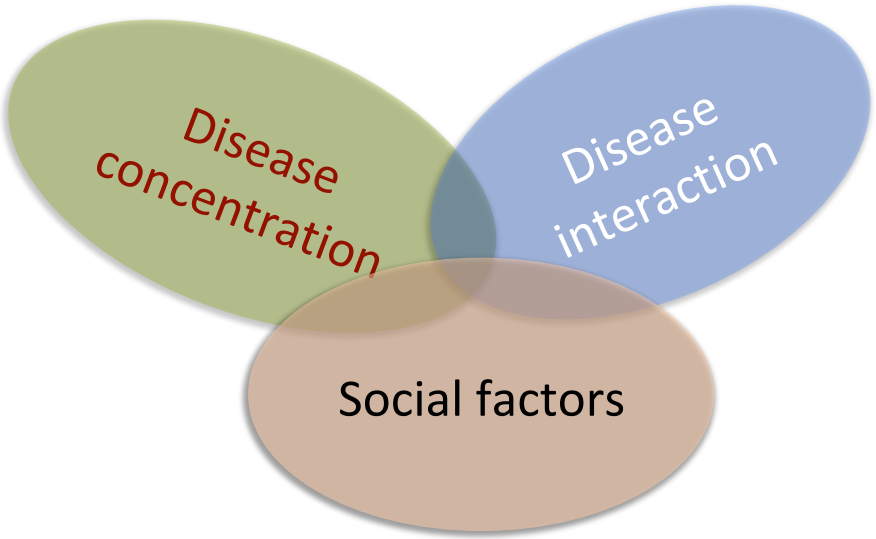
— Epidemic –

Complex interactions among *Host-Pathogen-environment*

Traditionally, each disease were assumed **a distinct entity** that existed in nature separate from other diseases and **independent of the bio-social contexts** in which it occurs.

The biomedical and public health strategy has been to **diagnostically isolate**, narrowly study, and treat **individual cases of disease**.

A syndemic approach



Disease concentration – multiple epidemics co-occur in particular temporal or geographical contexts

Disease interactions - co-occurring epidemics interact at the level of populations and individuals, with mutually enhancing deleterious consequences for health

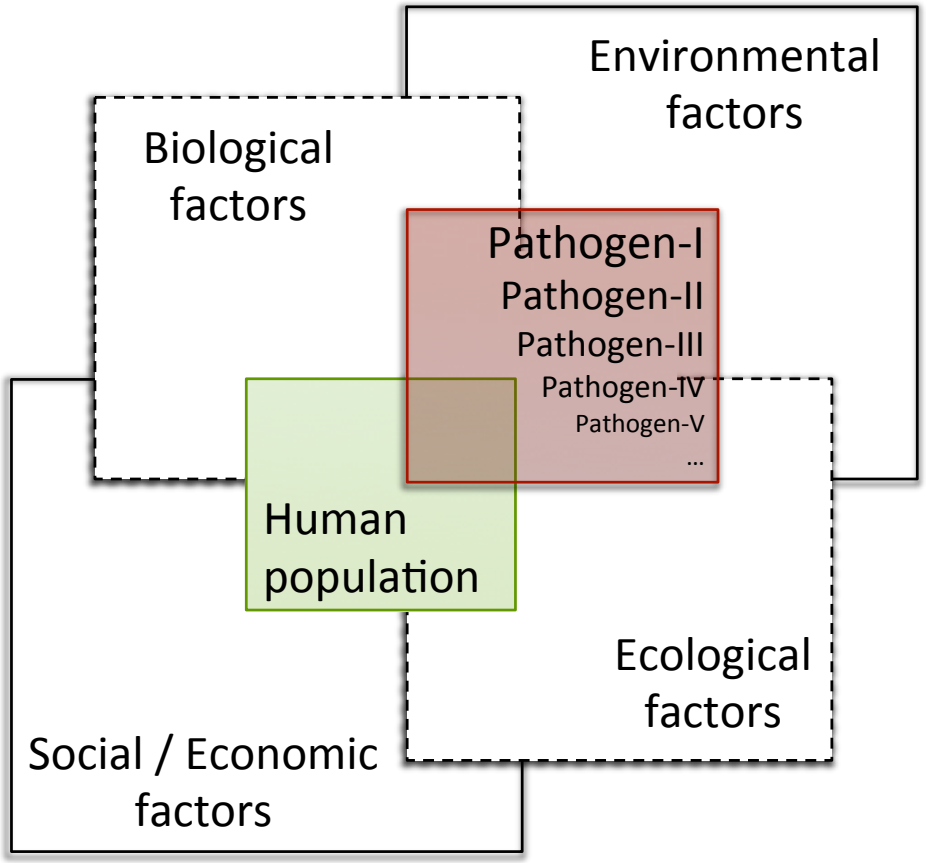
Social factors – economic opportunity, gender-inequitable norms, human behavior, etc.

A syndemic is the aggregation of two or more concurrent or sequential epidemics or **disease clusters** in a population with **biological interactions**, which exacerbate the prognosis and burden of disease.

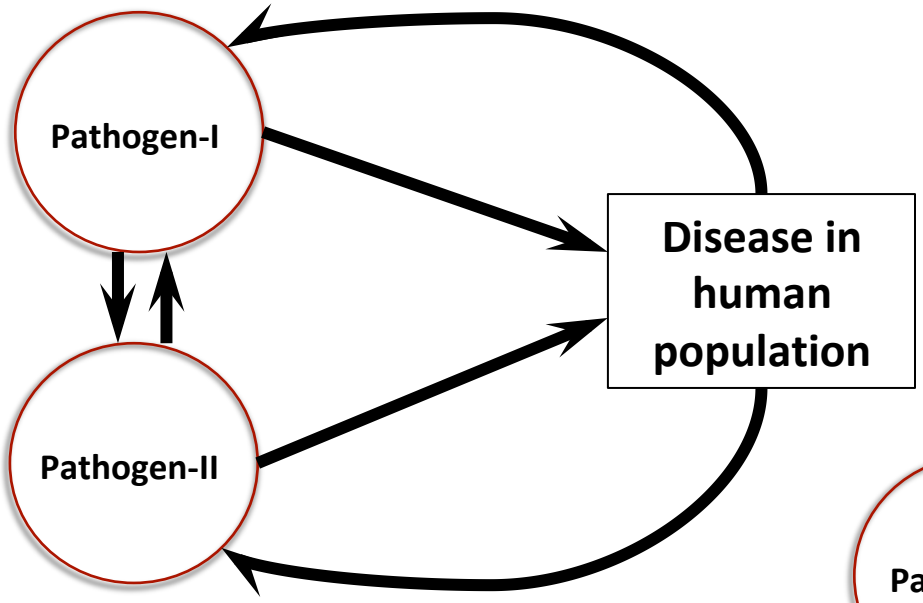
A syndemic approach

Multi-level models - that bridge between ecological study designs and cohort or case-control study designs to show how epidemics and large-scale social forces interact at both the population and individual levels to worsen the burden of disease.

The study of **Pathogen-Pathogen Interaction**, a form of epidemiological synergism, is emerging as an important arena of new research and new understanding in community health and clinical care.

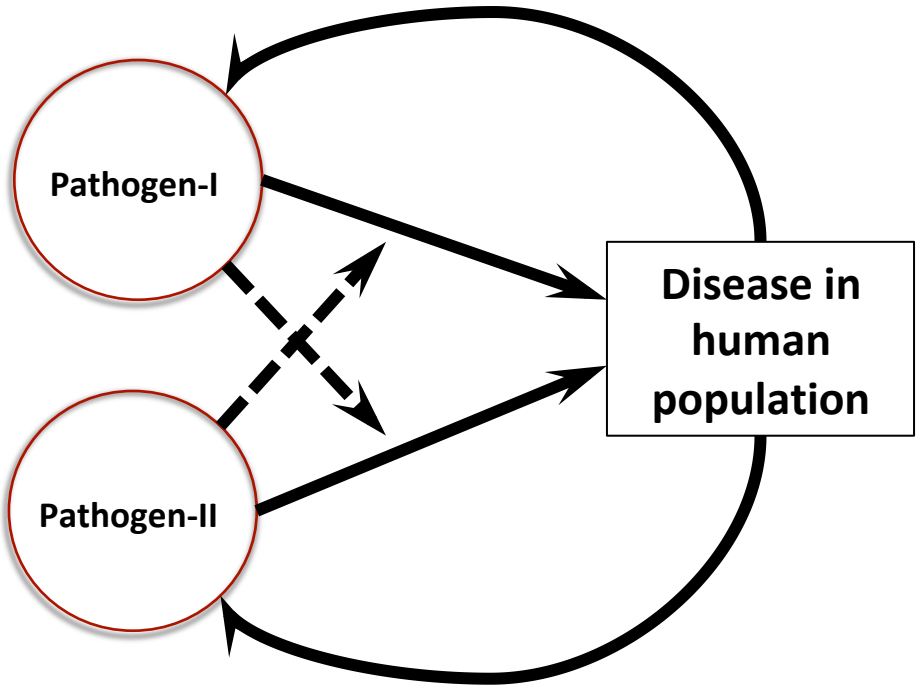


Disease interactions

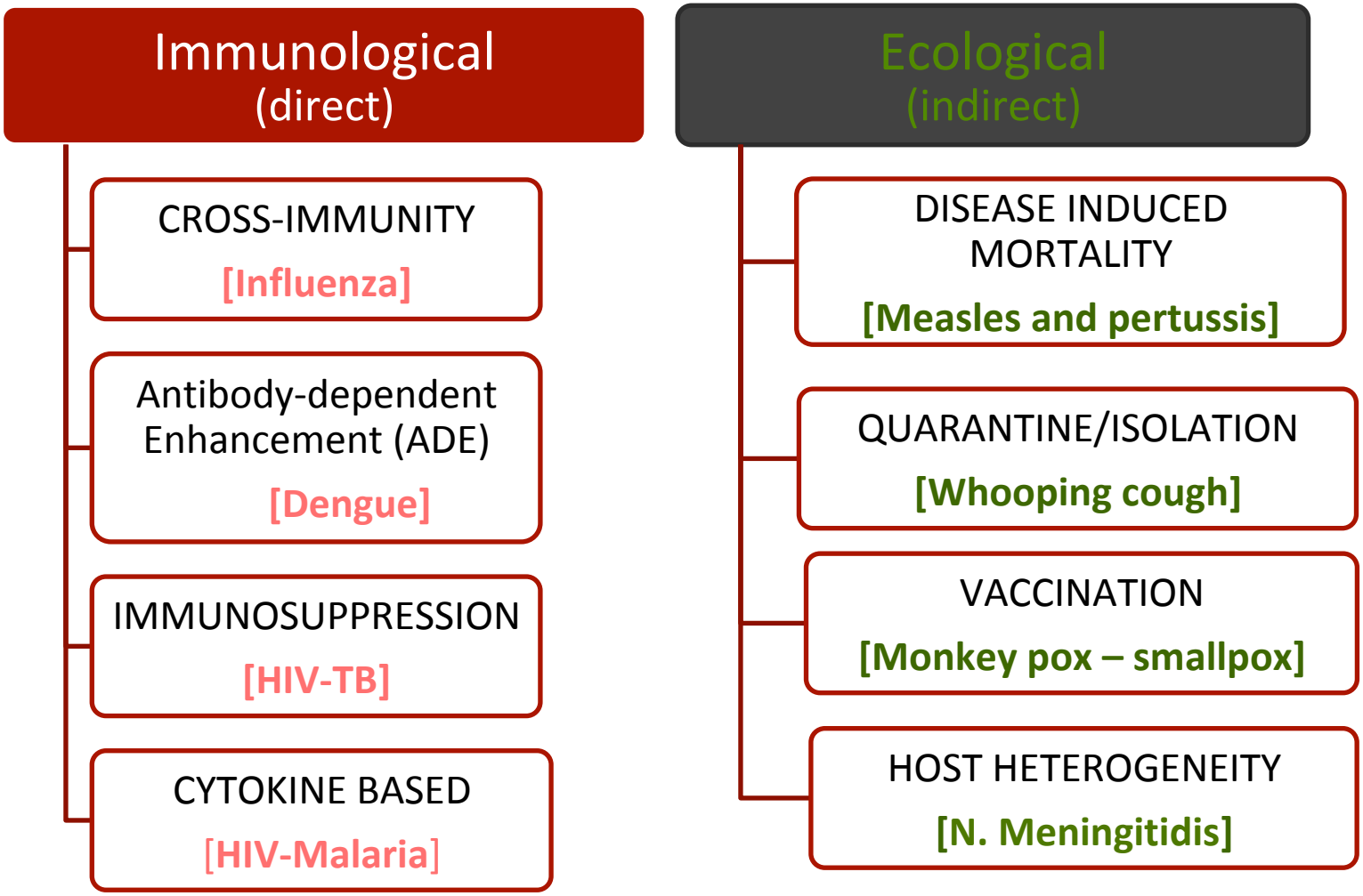


Direct – Pathogens directly interfere with each other via host immune system

Indirect – causal influence due to other activities



Disease interactions



Disease Interactions

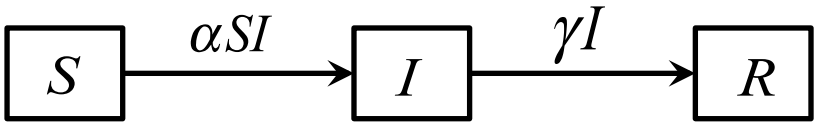
Disease Interactions

Immunological interaction occurs through host-immunity system.

Cross-protective immunity is a mechanism that infection by one pathogen reduces the chance of getting infected by antigenically similar pathogen.

Ecological competition arises via temporary or permanent removal of host individuals from the chain of circulation.

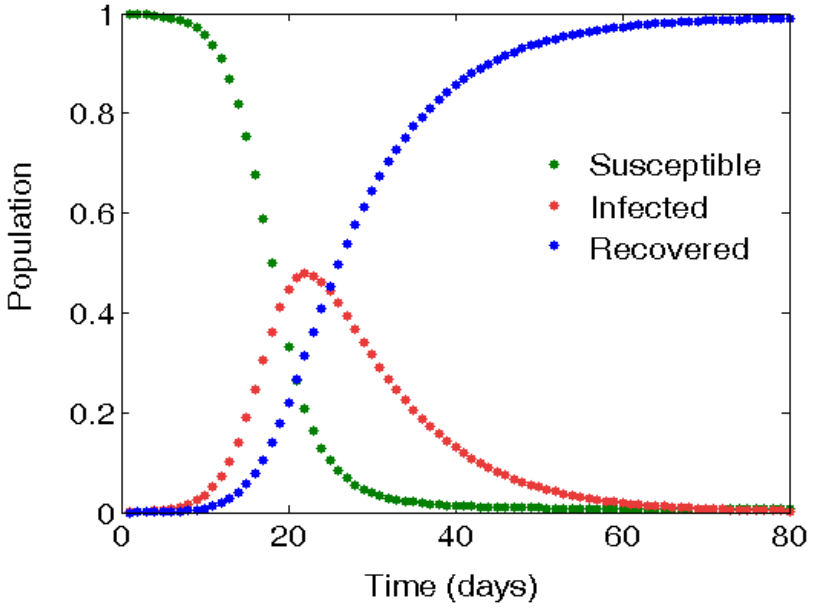
SIR model of an epidemic



Susceptible $\frac{dS}{dt} = -\alpha SI$

Infected $\frac{dI}{dt} = \alpha SI - \gamma I$

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



R_0 : average number secondary infections from a single infected individual

$$\left.\frac{dI}{dt}\right|_{t=0} = \left(\frac{\alpha}{\gamma}S(0) - 1\right)\gamma I(0) \equiv (R_0 - 1)\gamma I(0)$$

(Kermack–McKendrick theory (1927))

SIR model and Seasonality

SIR model with Birth-Death

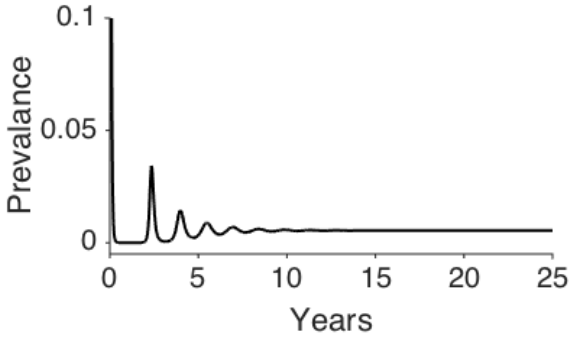
$$\frac{dS}{dt} = \mu - \alpha SI - \mu S$$

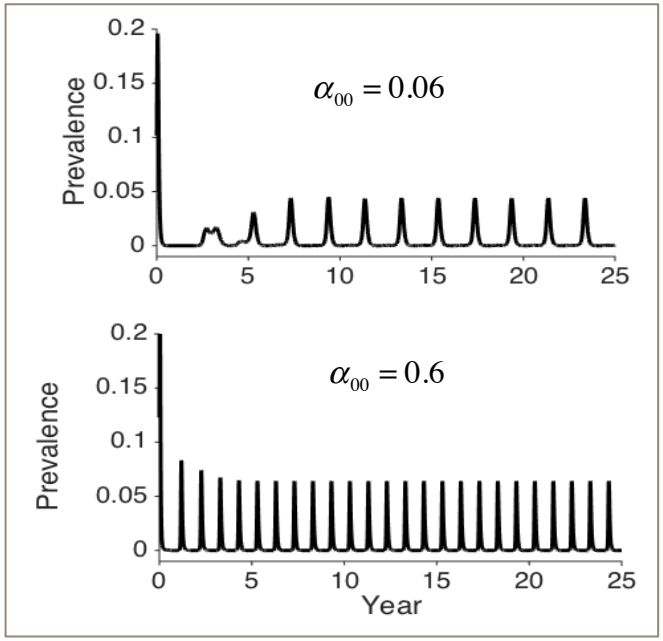
$$\frac{dI}{dt} = \alpha SI - (\gamma + \mu) I$$

$$\frac{dR}{dt} = \gamma I + \mu R$$

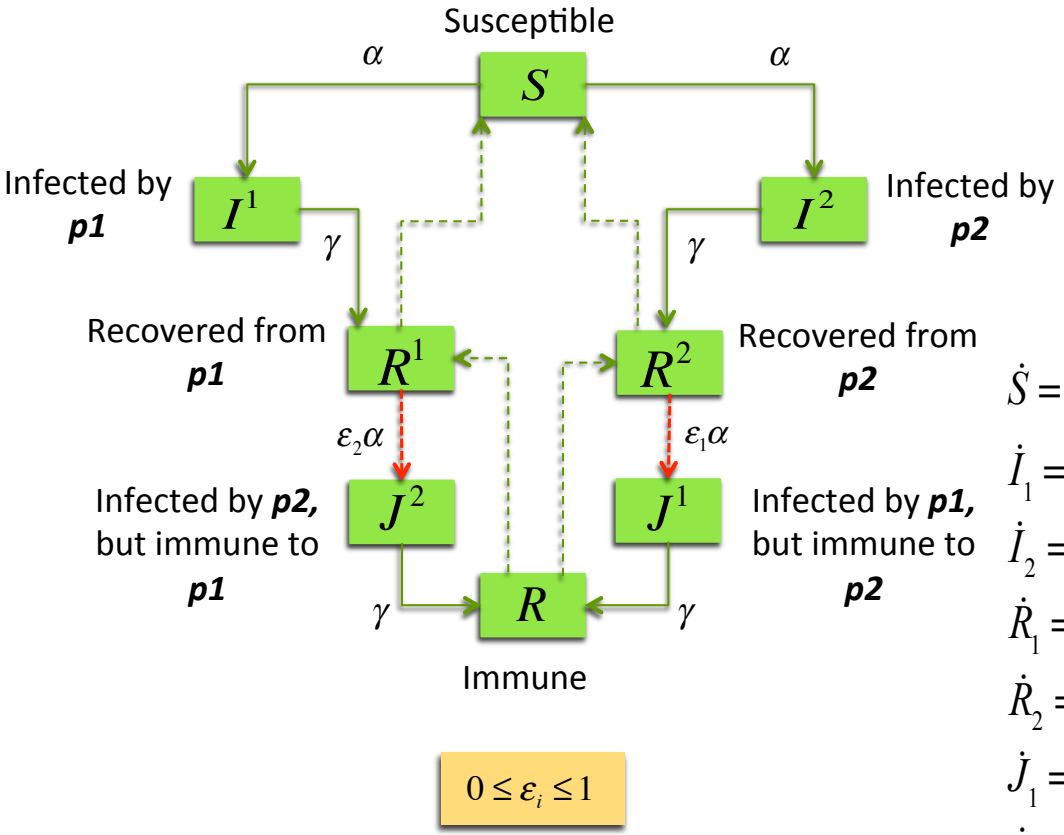
Seasonally forcing

$$\alpha = \alpha_0 [1 + \alpha_{00} \sin(2\pi(t - \phi)/T)] \qquad T = 1 \text{ year}$$





Cross-immunity



$0 \le \varepsilon_i \le 1$

Seasonally forcing

$$\alpha = \alpha_0[1+\alpha_{00}\sin(2\pi(t-\phi)/T)]$$

Cross-immunity by one pathogen reduces the rate of infection by other pathogen

$$\dot{S} = \mu - \alpha S\{q_2[I_2+J_2]+q_1[I_1+J_1]\} + \rho_1 R_1 + \rho_2 R_2 - \mu S$$

$$\dot{I}_1 = \alpha S q_1[I_1+J_1] - \gamma_1 I_1 - \mu I_1$$

$$\dot{I}_2 = \alpha S q_2[I_2+J_2] - \gamma_2 I_2 - \mu I_2$$

$$\dot{R}_1 = \gamma_1 I_1 - \alpha q_2 \varepsilon_2 R_1[I_2+J_2] - \rho_1 R_1 + \rho_2 R - \mu R_1$$

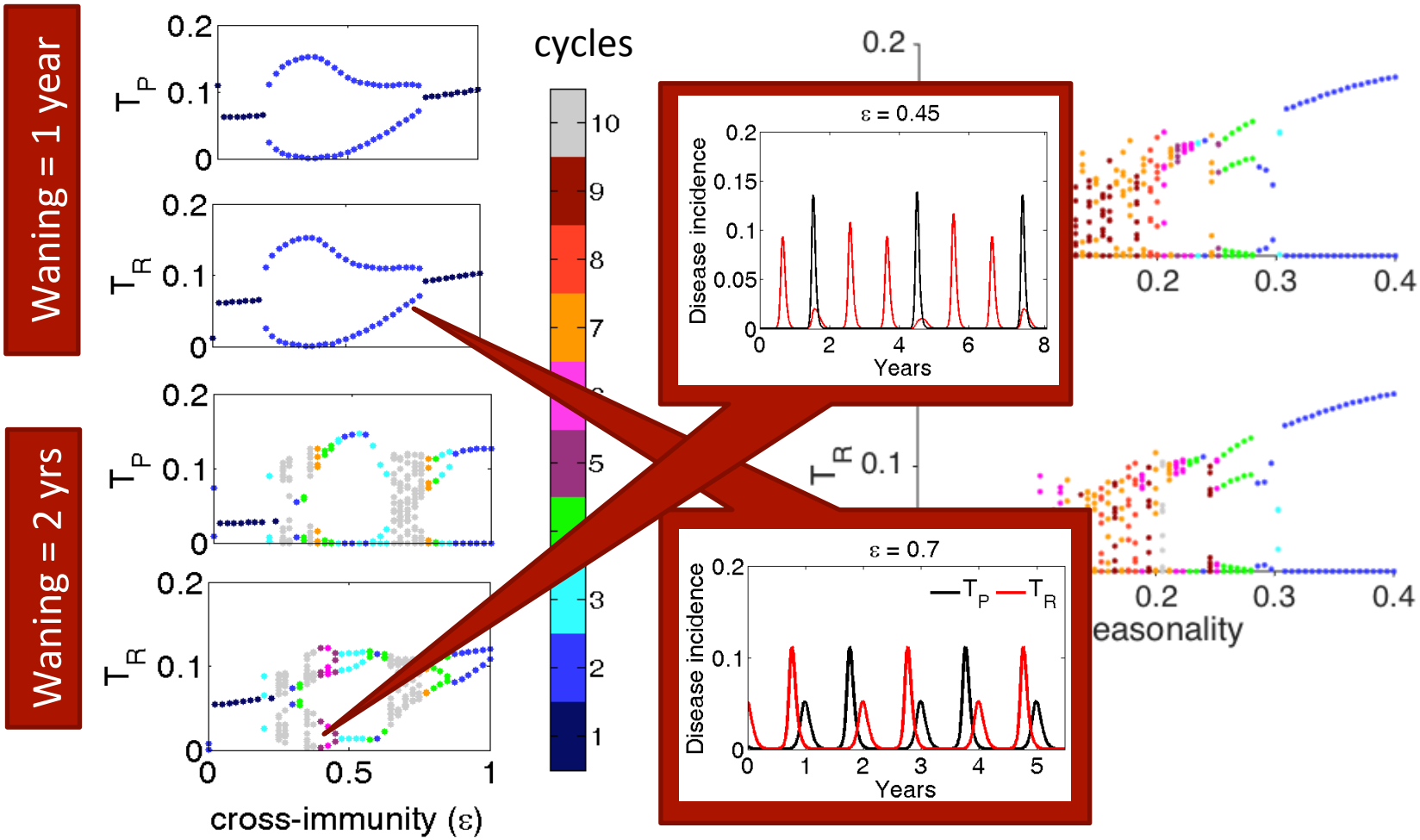
$$\dot{R}_2 = \gamma_2 I_2 - \alpha q_1 \varepsilon_1 R_2[I_1+J_1] - \rho_2 R_2 + \rho_1 R - \mu R_2$$

$$\dot{J}_1 = \alpha q_1 \varepsilon_1 R_2[I_1+J_1] - \gamma_1 J_1 - \mu J_1$$

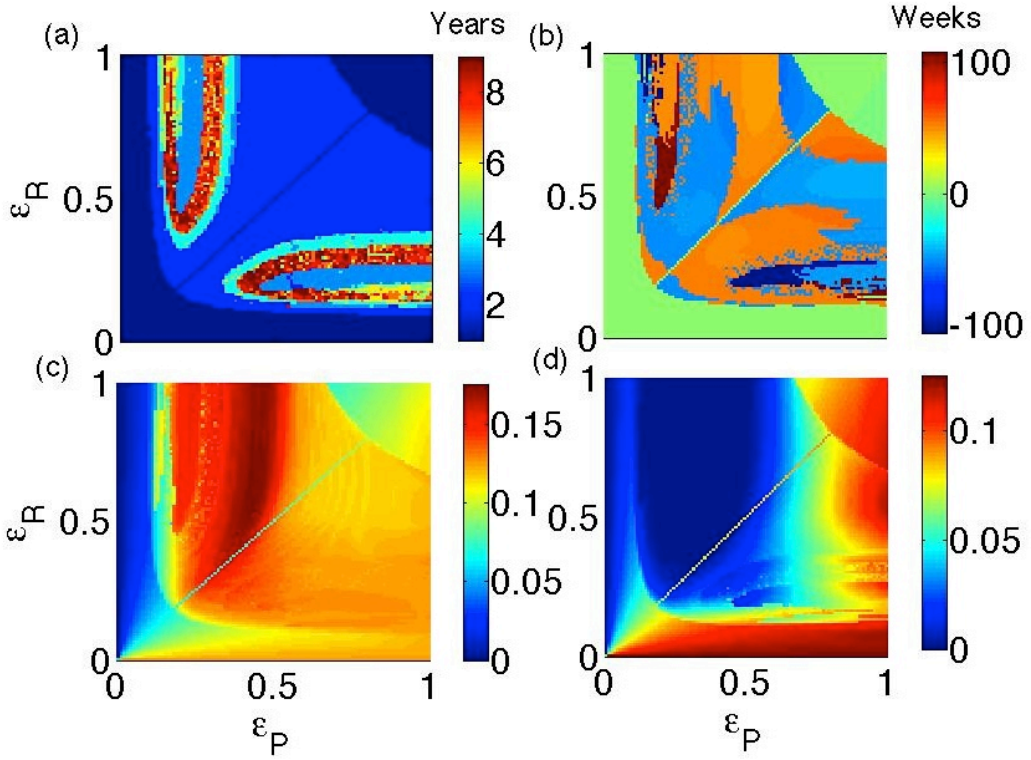
$$\dot{J}_2 = \alpha q_2 \varepsilon_2 R_1[I_2+J_2] - \gamma_2 J_2 - \mu J_2$$

$$\dot{R} = \gamma_1 J_1 + \gamma_2 J_2 - \rho_2 R - \rho_1 R - \mu R$$

Seasonality and Cross-immunity



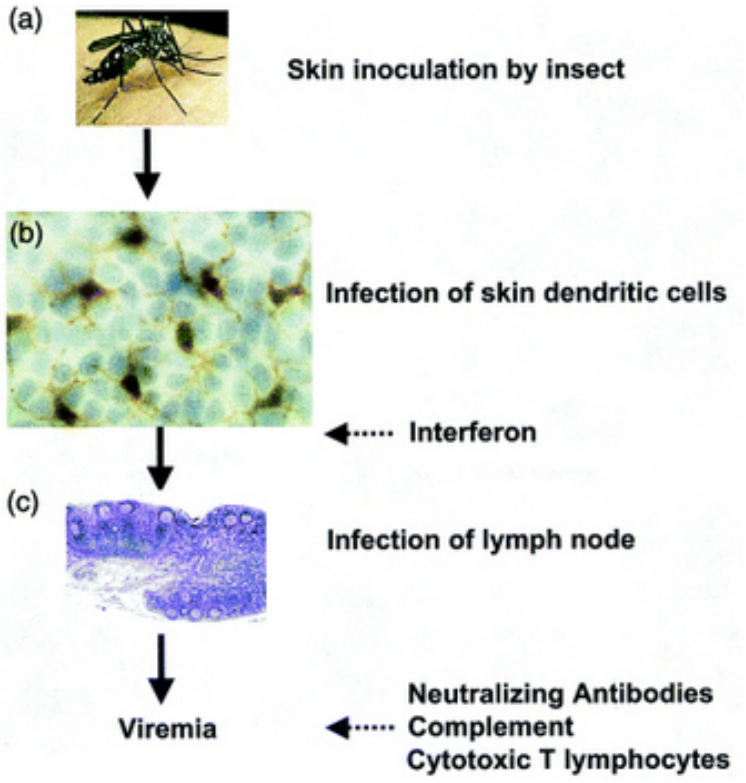
Asymmetric cross-immunity



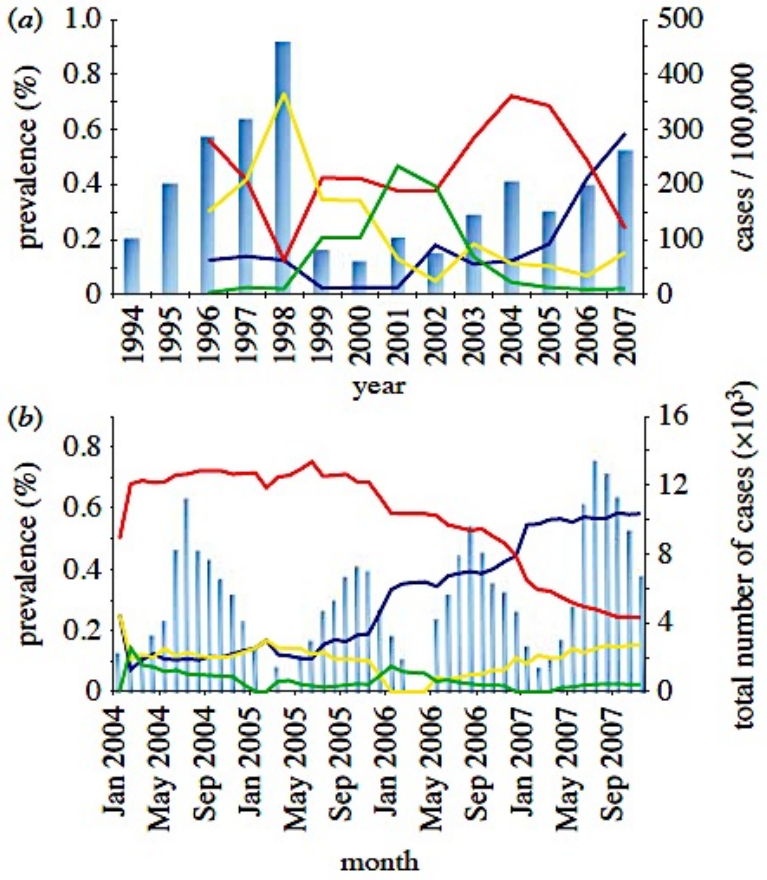
Analysis of this model showed that the **magnitude of seasonal variation in transmission** and the **degree of cross-immunity** between the two strains strongly influence the **period and existence of resonant solutions**

Dengue viral infection

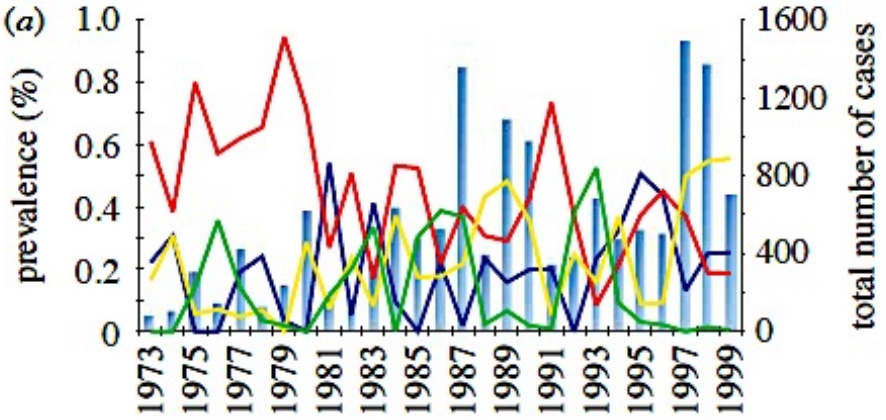
- A person is infected with the dengue virus when an infected mosquito bites the person's skin.
- The dengue virus infects the Langerhans cells, a type of dendritic cell in the skin.
- Infected Langerhans cells travel to the lymph nodes and infect more cells and it spreads all over the body.
- This results in **viremia**, which is a high level of the virus in the bloodstream.



Dengue Outbreaks



Dengue outbreak in South Viet Nam (1994 - 2007)



Dengue outbreak in Thailand (1973-1999):

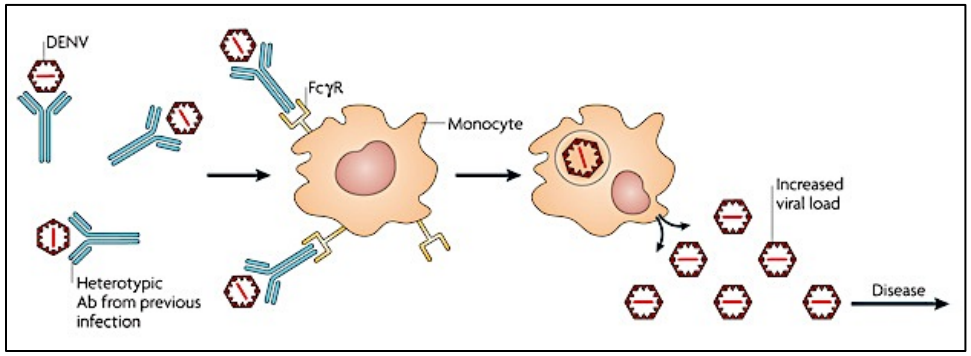
Total disease incidence (**Blue bar**).

Serotypes prevalence: **DENV-1**, **DENV-2**, **DENV-3**, **DENV-4**

Nisalak (2003), AMJTMH

Antibody-dependent enhancement

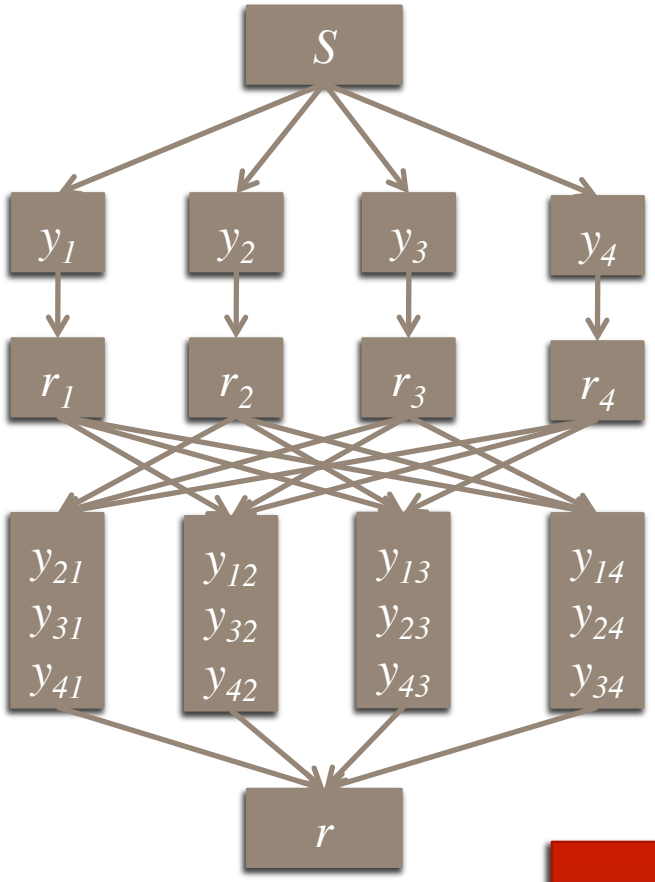
- ADE occurs when preexisting antibodies are present in the body from a primary dengue infection.
- It binds to an infecting DENV particle during a subsequent infection
- Instead of neutralize the virus, the Ab–virus complex attaches to receptors on circulating monocytes.



Model of ADE of dengue infection

The outcome is an increase in the overall replication of the virus and a higher risk of severe dengue.

Model



Susceptible

$$\frac{dS}{dt} = \mu - S\sum_{i=1}^{4}\lambda_i - \mu S$$

Primary infection

$$\frac{dy_i}{dt} = S\lambda_i - (\sigma + \mu)y_i$$

Primary recovery

$$\frac{dr_i}{dt} = \sigma y_i - r_i\left(\mu + \sum_{j\neq i}\gamma_{ij}\lambda_j\right)$$

Secondary infection

$$\frac{dy_{ij}}{dt} = r\gamma_{ij}\lambda_j - (\sigma + \mu)y_{ij} \qquad i \neq j$$

Recovered

$$\frac{dr}{dt} = \sigma\sum_{i=1}^{4}\sum_{j\neq i} y_{ij} - \mu r \qquad i, j = 1\ldots4$$

FOI $\lambda_i = \beta_i\left(y_i + \sum_{j\neq i}\phi_{ji}y_{ji}\right)$

γ_{ij} : Enhancement of susceptibility

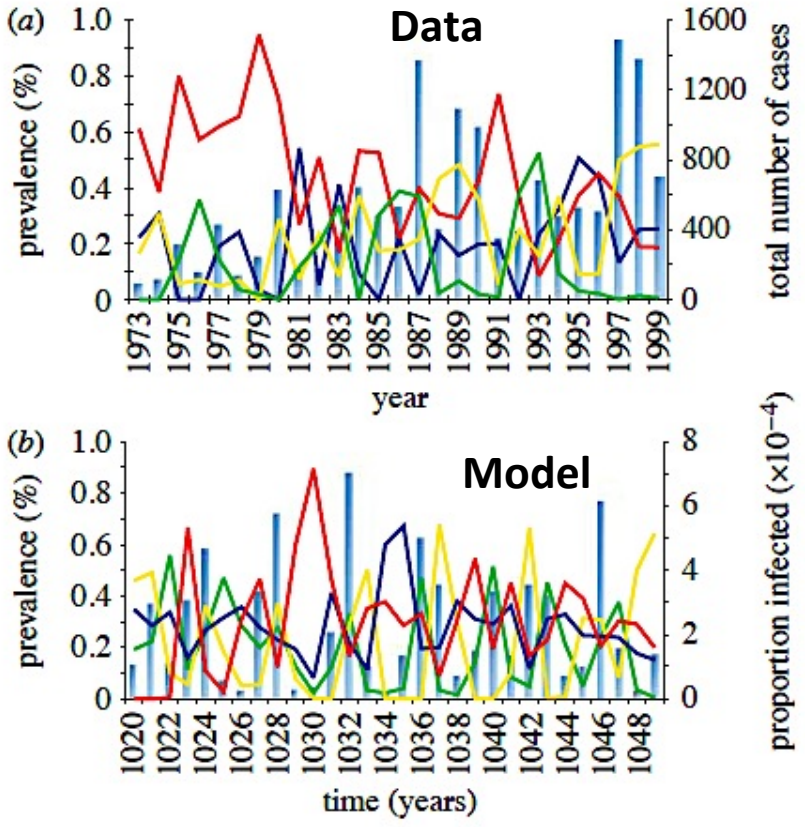
ϕ_{ij} : Enhancement of transmissibility

Recker et al. (2010), Proc. B

Data and model

There is a good qualitative agreement between the data and model output in both overall serotype dynamics and disease incidence:

- Multi-annual cycles (~ 3–5 year) in disease prevalence
- The sequential replacement of prevailing serotypes.



DENV-1, DENV-2, DENV-3, DENV-4

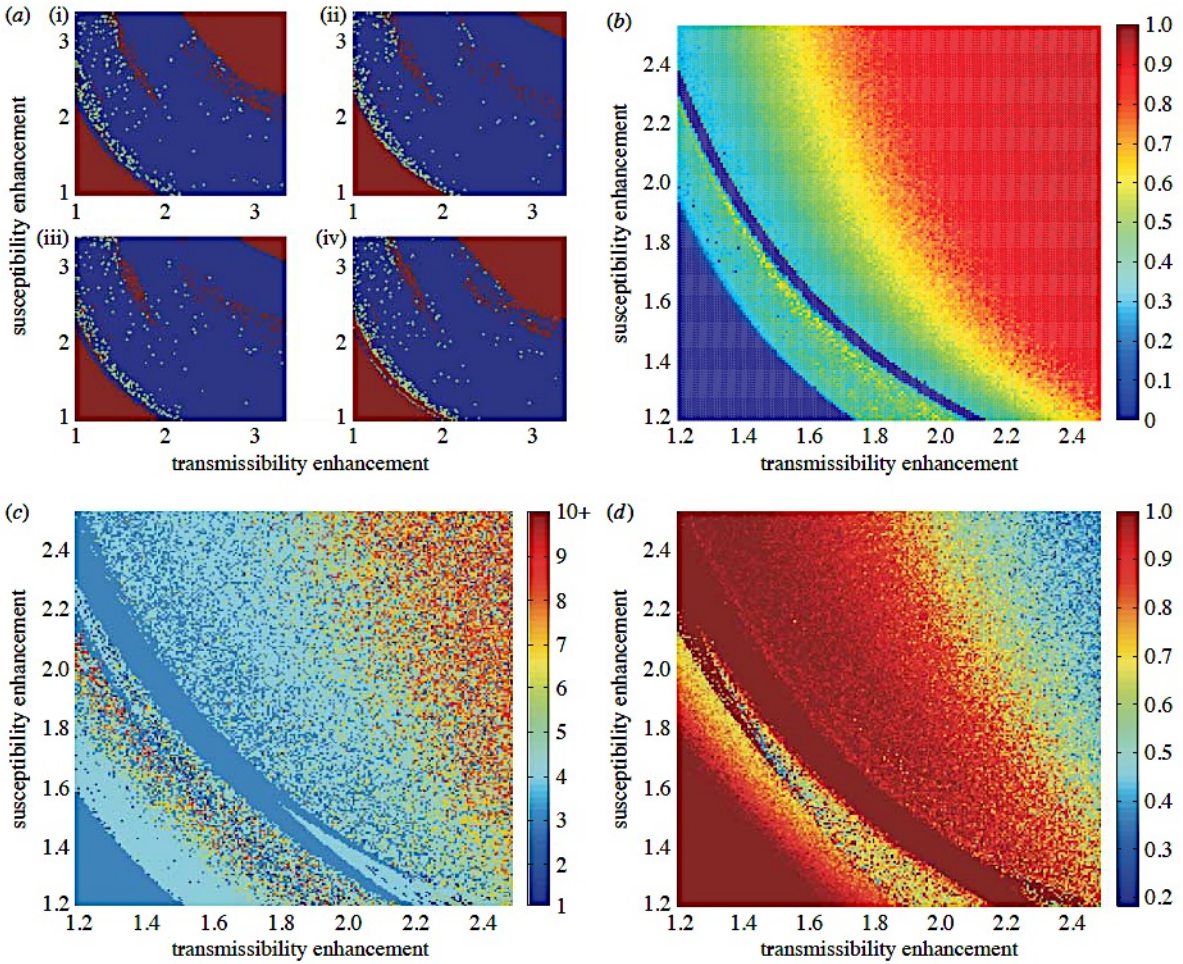
Effect of ADE

(*a*) **Synchronization pattern** [desynchronized, complete synchronized, partial]: (i) 1-2, (ii) 1-3, (iii) 2-3, (iv) 3-4

(*b*) **Serotype dominance:** 0 – at least two types are dominant

(*c*) **Inter-epidemic period**

(*d*) **Serotype persistence:** proportion of time a serotype persists above a persistence-threshold level of 10^{-8}



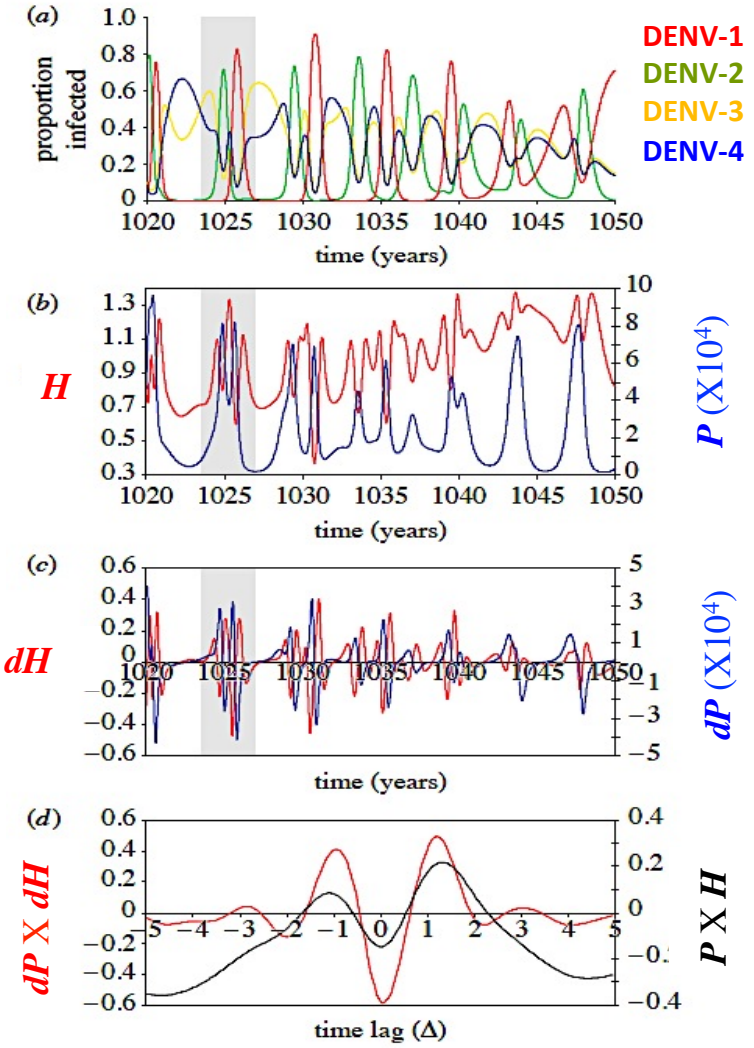
Serotype diversity

Shannon index & correlation

$$H(t) = -\sum_{i=1\ldots4} p_i(t)\log(p_i(t)) \qquad P(t) = \sum y_i(t) + y_{ij}(t)$$

$$r(\Delta) = (P \otimes H)(\Delta) = \frac{\sum_t (P_t - \mu_P)(H_{t+\Delta} - \mu_H)}{\sigma_P \sigma_H}$$

- The cross-correlations over a 100-year period shows a bimodal distribution, which indicates negative correlation between prevalence and diversity at lag 0.
- The bimodal shape of the cross-correlation between the rates of change also reveals the negative feedback between prevalence and diversity.

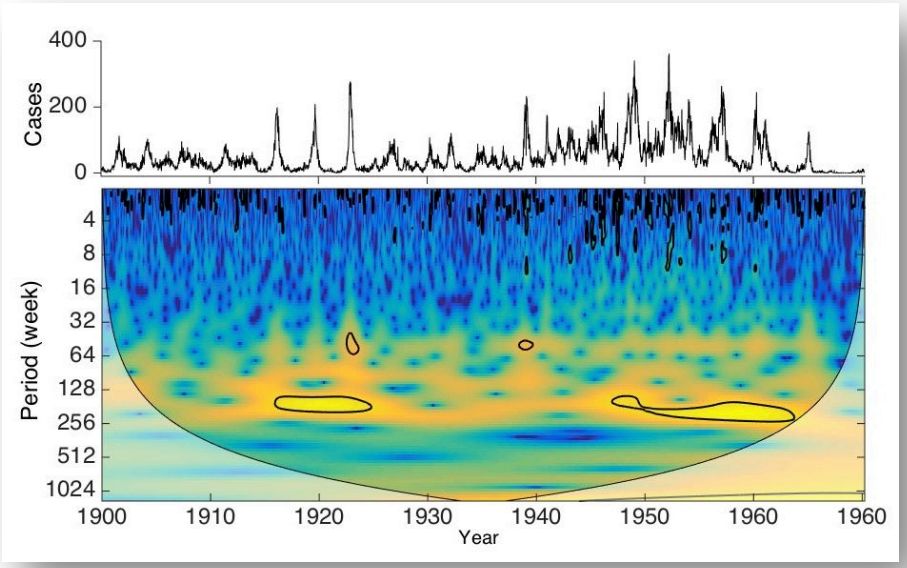


Whooping Cough

- Whooping cough is a highly contagious respiratory tract infection.
- Bacterial disease
- Disease starts with cold-like symptoms. Within 2 weeks severe coughing begins that continues for several weeks with series of coughing fits (sounds like “Whoop”).
- It can cause serious illness in infants, children and adults.

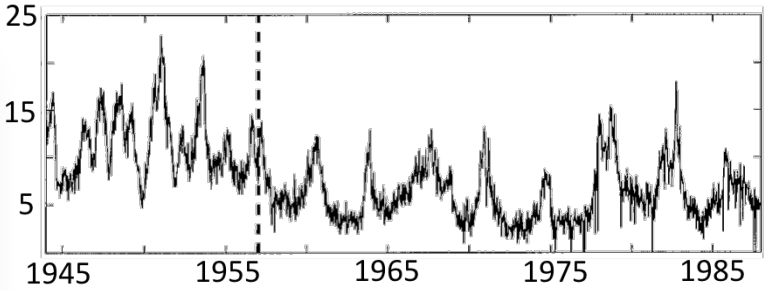
Time series and periodicity

Cases in Copenhagen (1900-60)

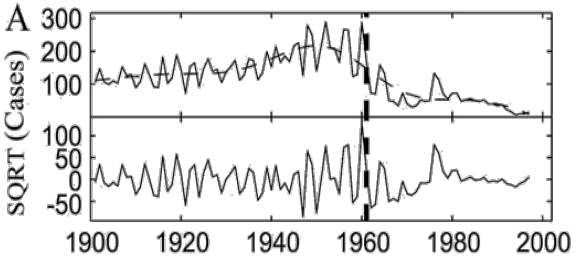


Whooping cough incidence exhibit erratic periodicity across space and time

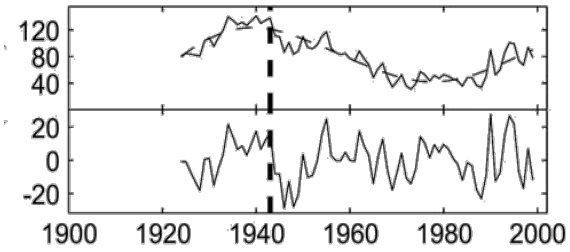
Cases in England and Wales (1944-94)



Denmark (1900-98)



Canada (1920 - 98)



Hypotheses

- ✓ Noise in transmission *(Rohani et al. 1999, 2002)*
- ✓ Immunization *(Rohani et al. 2000)*
- ✓ Demographics: birth rate *(Bauch & Earn 2003)*
- ✓ Gamma distributed latent and infectious period *(Rohani et al. 2008)*
- ✓ Immune boosting *(Lavine et al. 2011, 2013)*

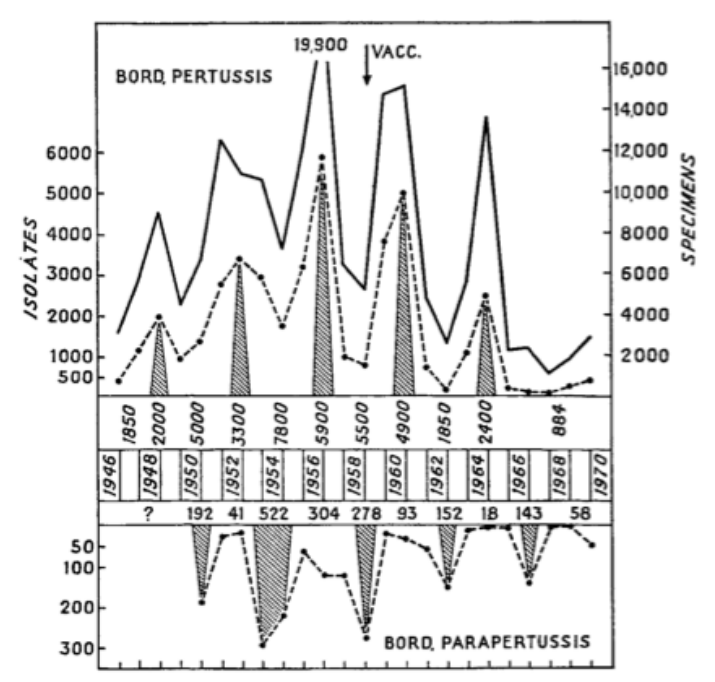
Proposed hypothesis

Some of these observed dynamics may be the consequence of interaction between two strains of whooping cough:

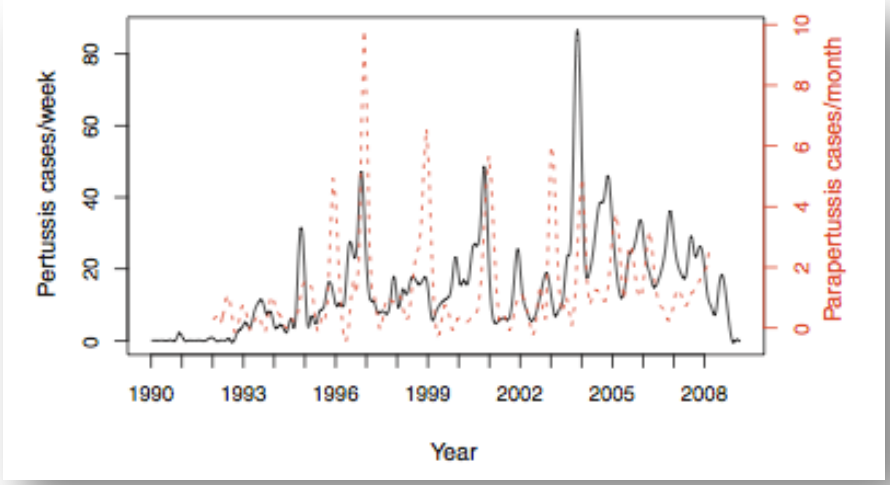
B. pertussis and B. parapertussis

Pertussis and Parapertussis

Denmark (1946-70)



Massachusetts (1990-2009)



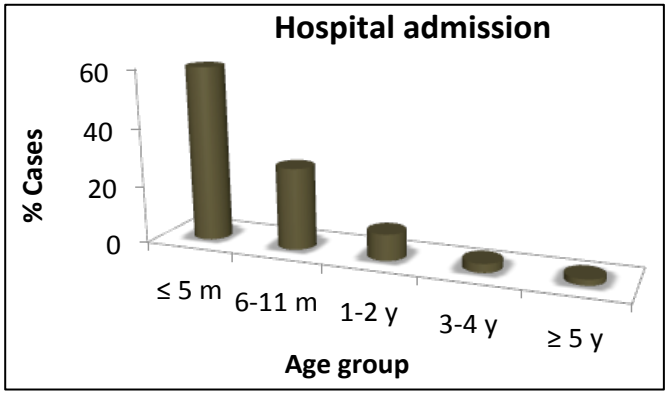
Both outbreaks exhibit **out-of-phase cycle** of Pertussis and Parapertussis

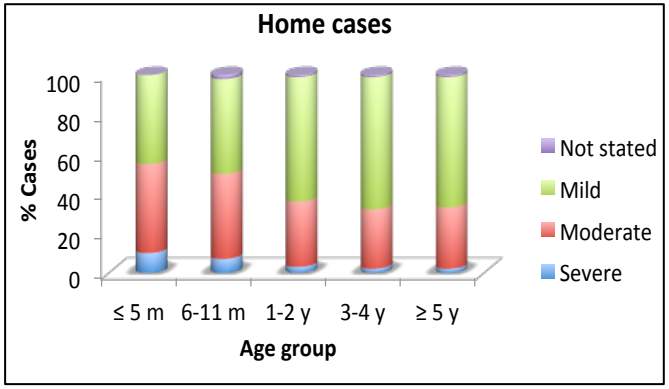
Mechanism of interaction

- Disease severity and quarantine that declines over age
- Relatively higher severity from pertussis than parapertussis

Whooping cough disease severity

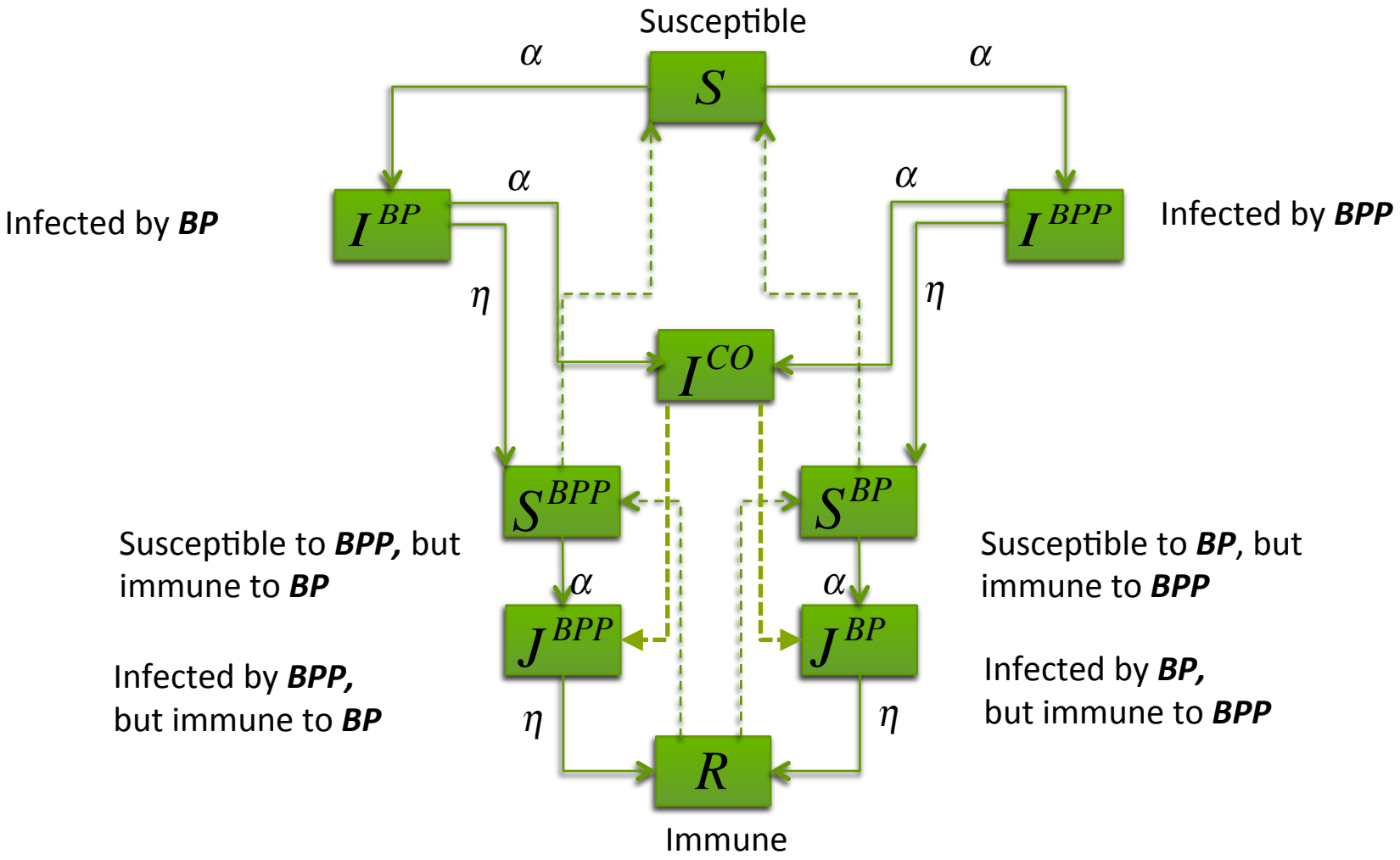
- ✓ London
- ✓ Oct 1974 - Mar 1975
- ✓ ~ 10% of total cases admitted in hospital



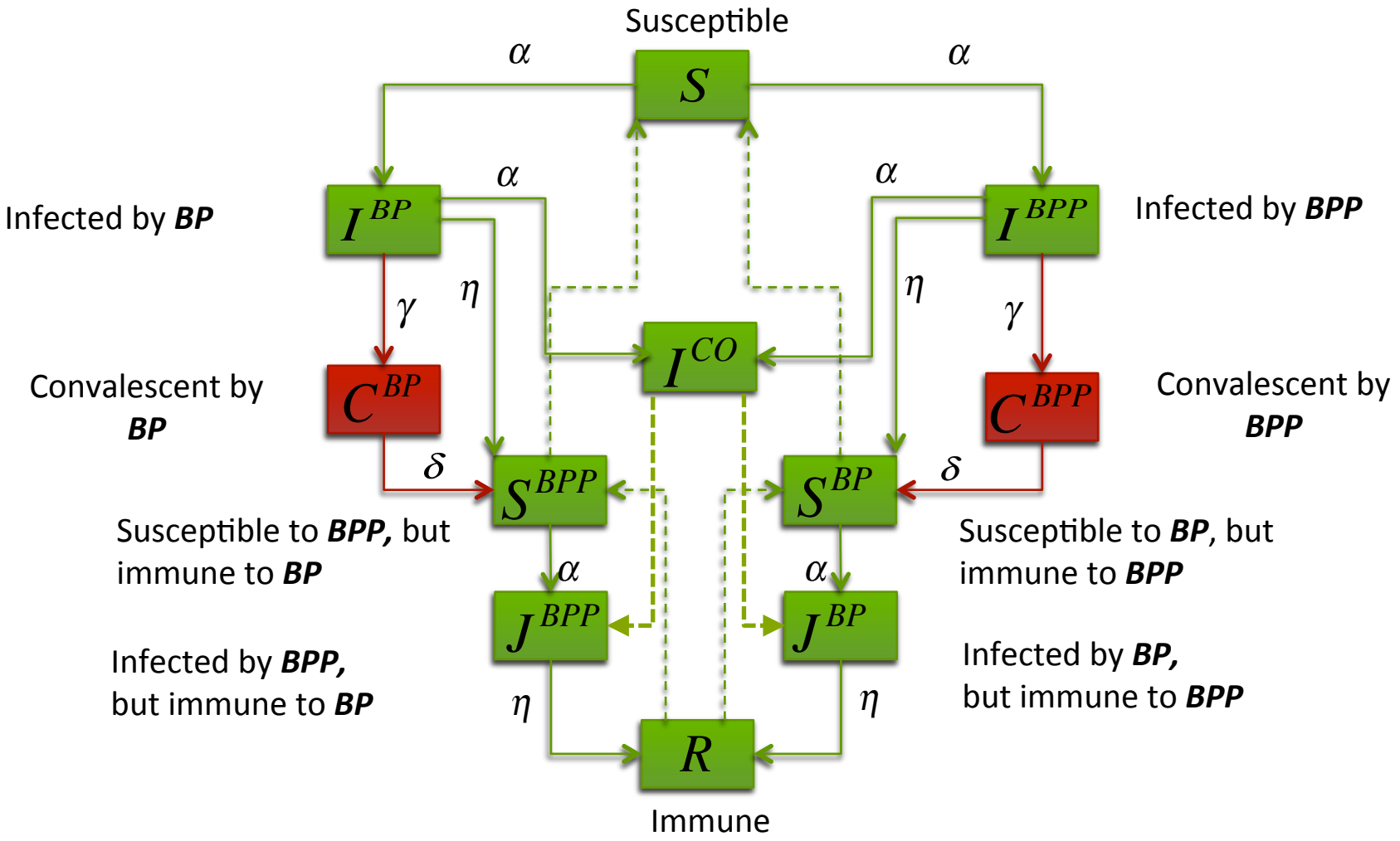


(Miller & Fletcher, BMJ, 1976)

Model Schematic



Model Schematic



Model

$$\left\{\frac{\partial}{\partial t}+\frac{\partial}{\partial a}\right\}S(t,a)=-(\lambda_1(t,a)+\lambda_2(t,a)+\mu)S+\rho_1 S_1+\rho_2 S_2$$

$$\left\{\frac{\partial}{\partial t}+\frac{\partial}{\partial a}\right\}I_1(t,a)=\lambda_1(t,a)S-\lambda_2(t,a)I_1-(\gamma_1(a)+\eta_1+\mu)I_1$$

$$\left\{\frac{\partial}{\partial t}+\frac{\partial}{\partial a}\right\}I_2(t,a)=\lambda_2(t,a)S-\lambda_1(t,a)I_2-(\gamma_2(a)+\eta_2+\mu)I_2$$

$$\left\{\frac{\partial}{\partial t}+\frac{\partial}{\partial a}\right\}I_{CO}(t,a)=\lambda_2(t,a)I_1+\lambda_1(t,a)I_2-(\eta_1+\eta_2+\mu)I_{CO}$$

$$\left\{\frac{\partial}{\partial t}+\frac{\partial}{\partial a}\right\}C_1(t,a)=\gamma_1(a)I_1-(\delta_1+\mu)C_1$$

$$\left\{\frac{\partial}{\partial t}+\frac{\partial}{\partial a}\right\}C_2(t,a)=\gamma_2(a)I_2-(\delta_2+\mu)C_2$$

$$\left\{\frac{\partial}{\partial t}+\frac{\partial}{\partial a}\right\}S_1(t,a)=\eta_2 I_2+\delta_2 C_2-(\lambda_1(t,a)+\mu)S_1-\rho_1 S_1+\rho_2 R$$

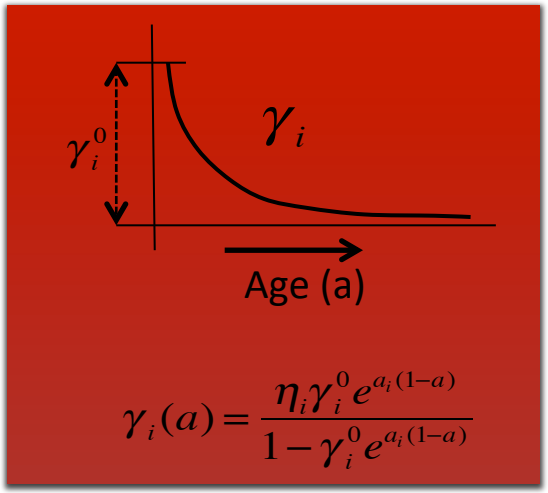
$$\left\{\frac{\partial}{\partial t}+\frac{\partial}{\partial a}\right\}S_2(t,a)=\eta_1 I_1+\delta_1 C_1-(\lambda_2(t,a)+\mu)S_2-\rho_2 S_2+\rho_1 R$$

$$\left\{\frac{\partial}{\partial t}+\frac{\partial}{\partial a}\right\}J_1(t,a)=\lambda_1(t,a)S_1-(\eta_1+\mu)J_1$$

$$\left\{\frac{\partial}{\partial t}+\frac{\partial}{\partial a}\right\}J_2(t,a)=\lambda_2(t,a)S_2-(\eta_2+\mu)J_2$$

$$\left\{\frac{\partial}{\partial t}+\frac{\partial}{\partial a}\right\}R(t,a)=\eta_1 I_1+\eta_2 I_2+\eta I_{CO}-(\rho_2+\rho_1+\mu)R$$

Age-dependent severity



Force of infection

$$\lambda_i(t,a)=\int_0^\infty \beta(t,a,\alpha)(I_i(t,a)+J_i(t,a)+I_{CO}(t,a))d\alpha,\quad i=1,2$$

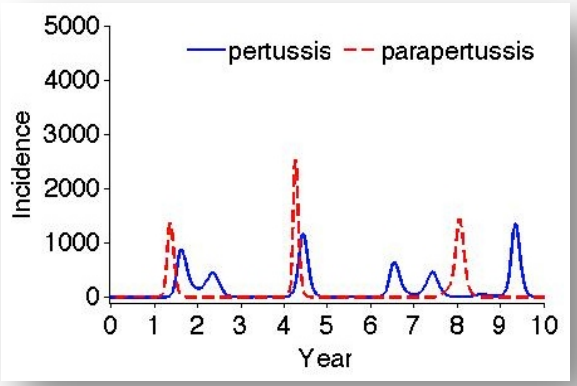
Boundary conditions

$$S(t,0)=\mu N$$

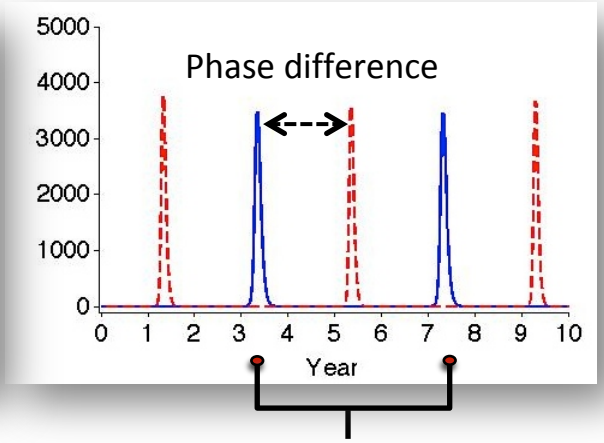
$\beta(t,..)$ = Seasonally-forced (sinusoidal)

How *competition* works

No Interactions



Interactions



Interepidemic period

Interaction between strains induces stable out-of-phase oscillation in the dynamics

Baseline parameters

Life expectancy = 75 y

Infectious period BP = 14 d

Infectious period BPP = 10 d

convalescence period BP = 30 d

convalescence period BPP = 10 d

Waning of immunity BP = 40y

Waning of immunity BPP = 35y

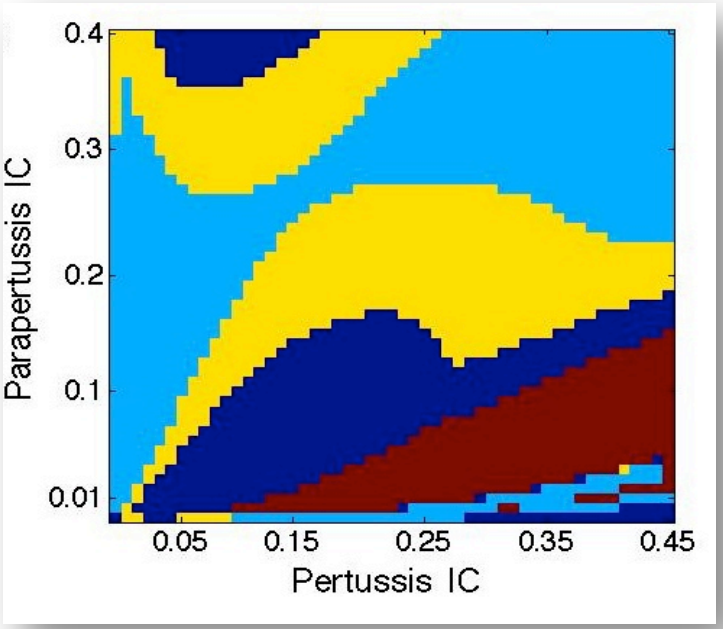
Fraction of severity

$$\gamma_1^0 = 0.5$$

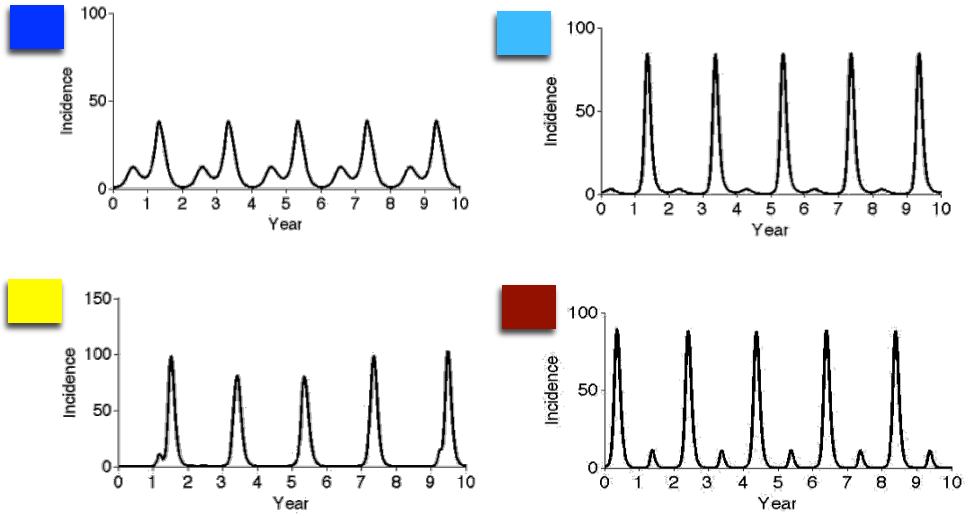
$$\gamma_2^0 = 0.1$$

Basin of attraction

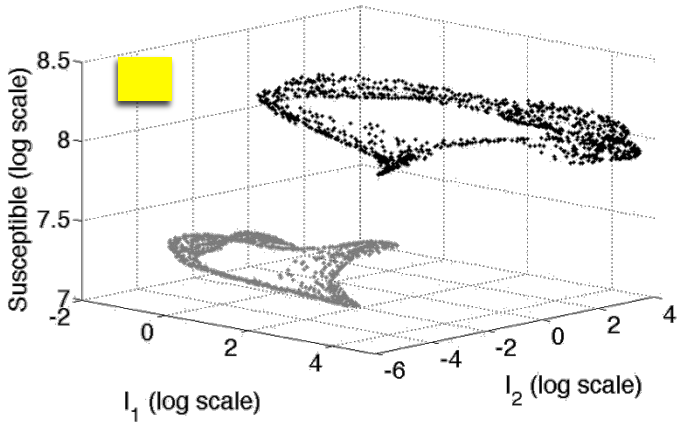
High R_0



Severe disease from either of strains

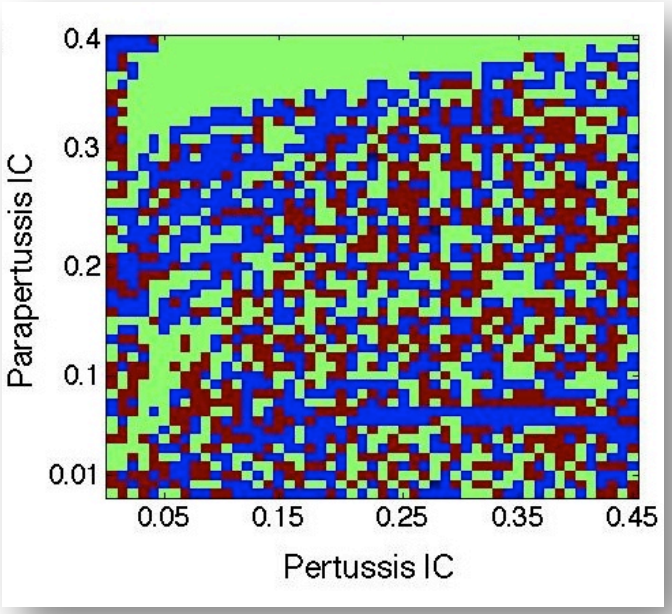


Four different attractors coexist in a nicely intertwined basin of attraction

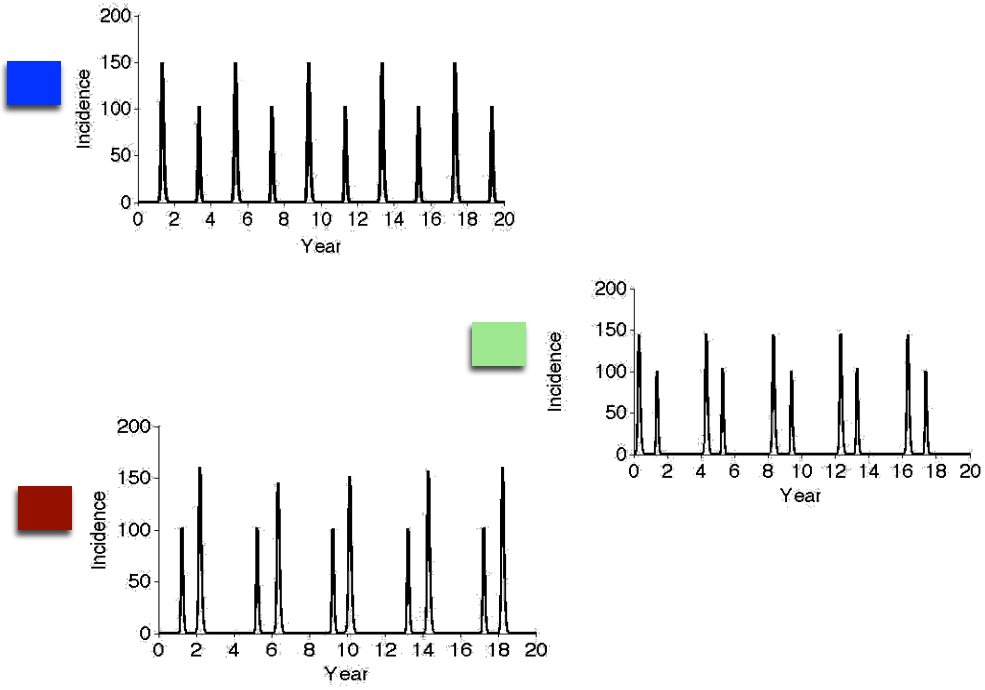


Basin of attraction

Low R_0

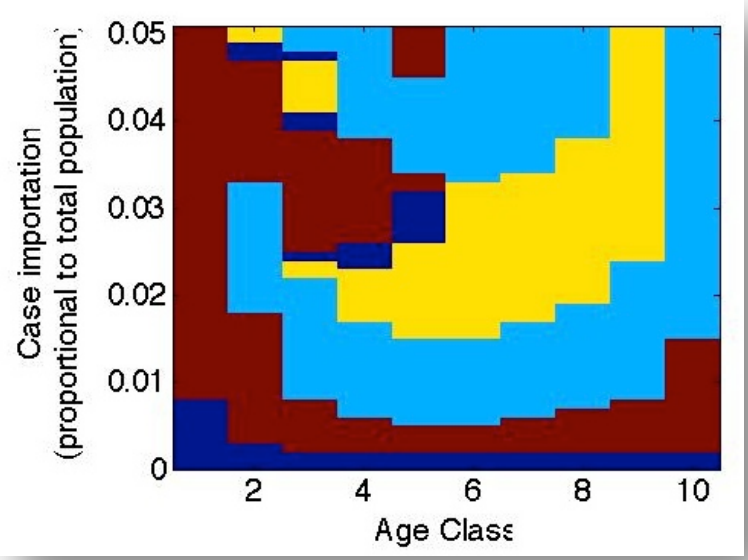


Severe disease from either of strains

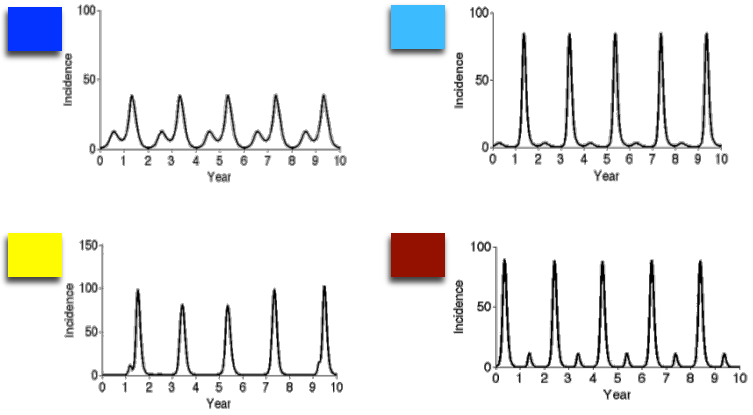


Multiple coexisting attractors of different periods is an emergent property of this interacting system

Case-importation



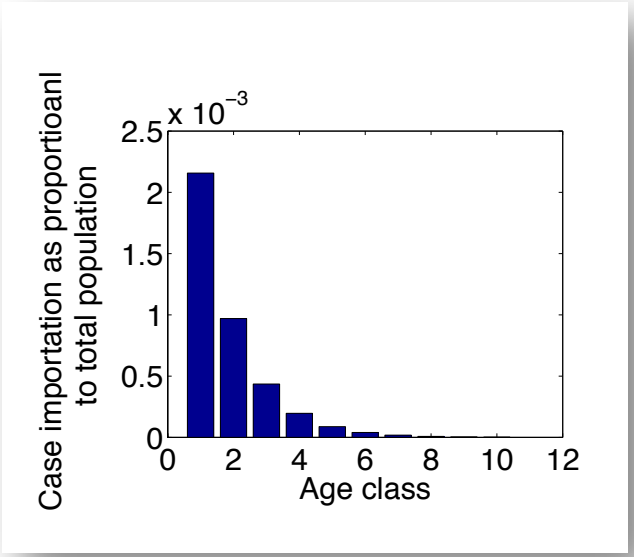
Only pertussis cases of specific age are imported once at a time.



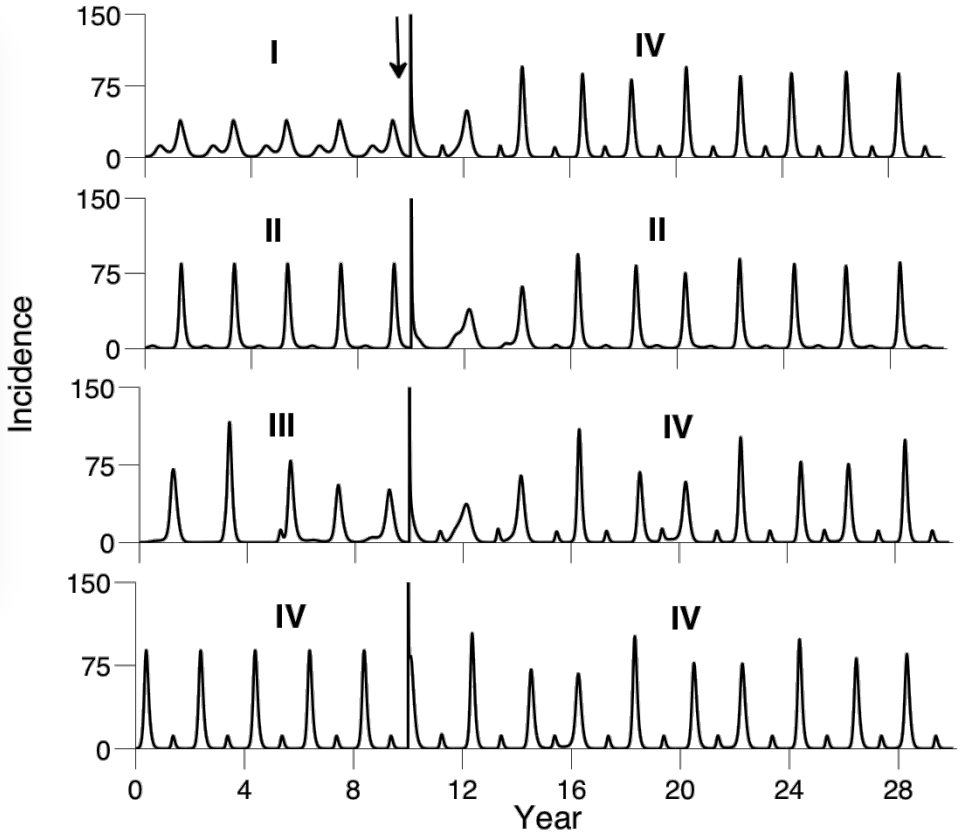
The *age-structure* complexity continues to play itself out.
Migration at different age classes have different impacts on the dynamics.

Immigrants of distributed age

- Exponential distribution (i.e. more infants and younger children)

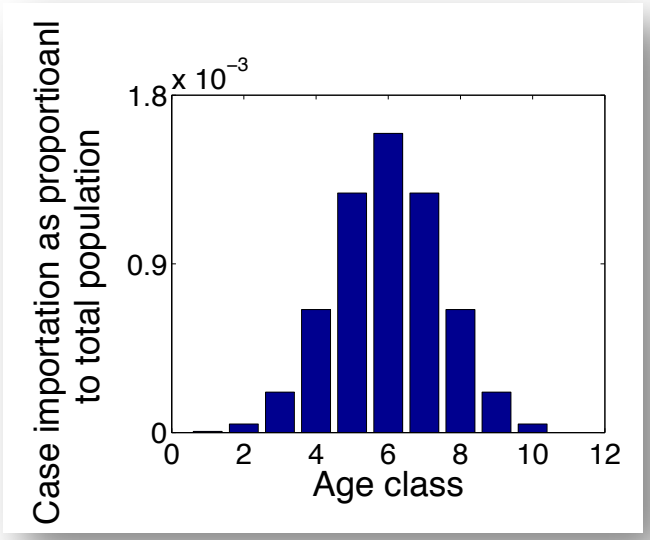


Attractor- I and III shifts to attractor- IV

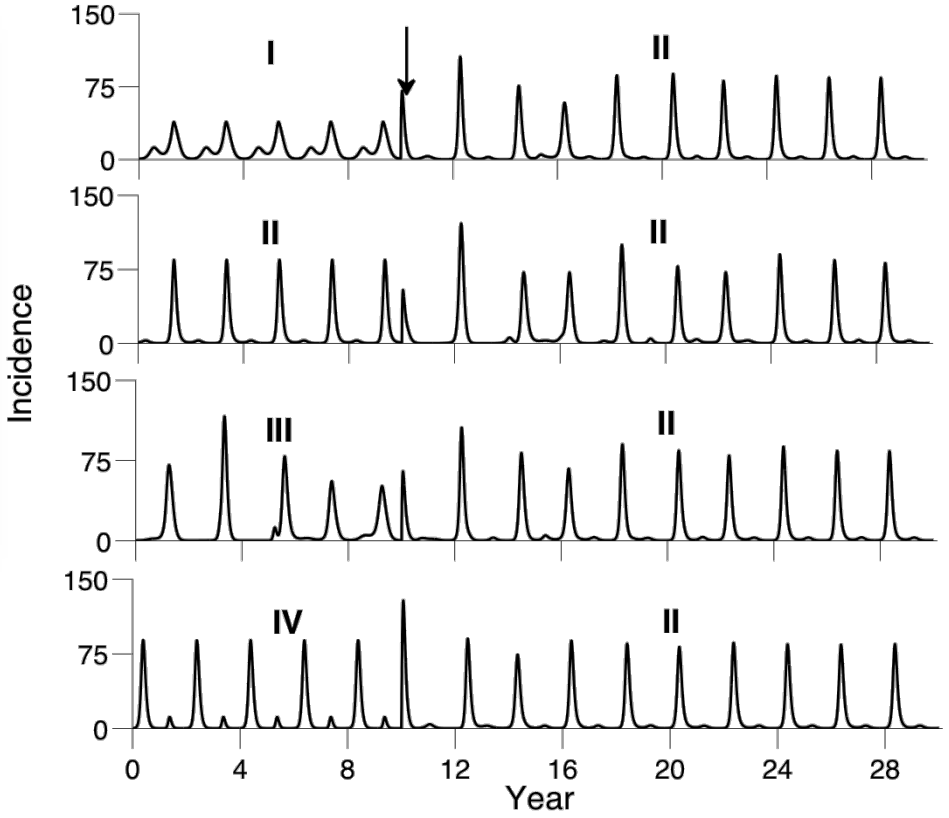


Immigrants of distributed age

- Normal distribution (i.e. more adults)



Attractor- I, III and IV shifts to attractor- II



Summary

- ✓ Combining two processes – **species interactions** and **perturbation of attractors** – to explain the multiannual complex time series of childhood disease.
- ✓ Our results provide an additional hypothesis for complex dynamics of whooping cough.
- ✓ Competition between etiological agents play important role in shaping epidemiological data, and species-specific surveillance may help improve our understanding of the interaction of these pathogens.

Bhattacharyya et al. (2017), *Epidemics,* AIP

RSV & HPIV

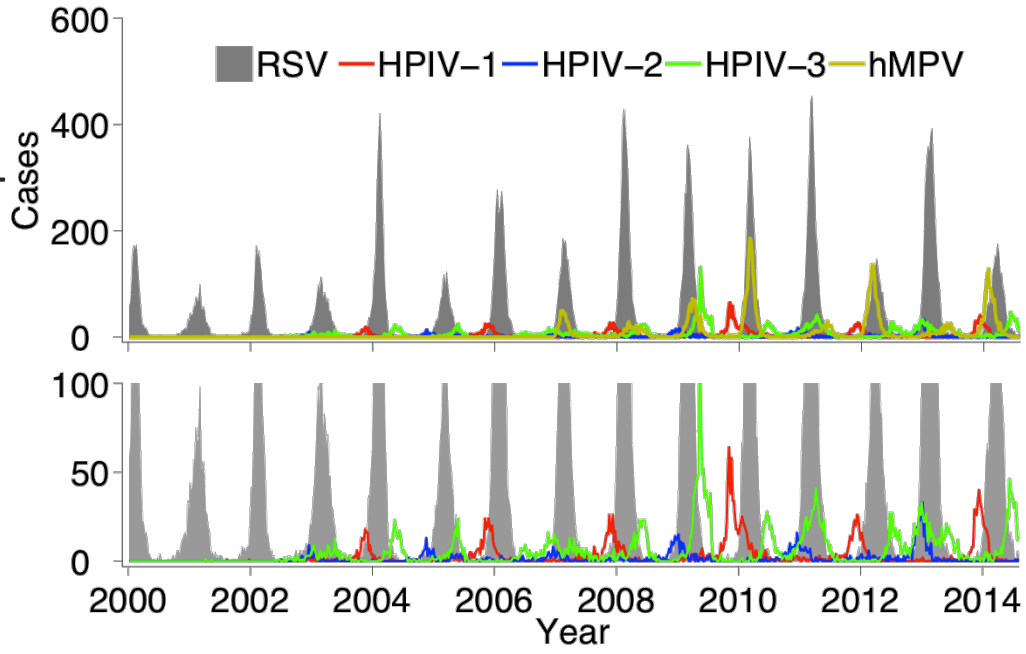
Respiratory syncytial virus (**RSV**) –

- Annual outbreak from **late fall through early spring**

Human parainfluenza virus (**HPIV**) –

- HPIV-1 & HPIV-2 – **Biennial fall outbreaks in alternate year**
- HPIV-3 – **spring and early summer months each year**

(6 week, 2000– 52 week, 2014)



(Source: Intermountain Health Care, Utah)

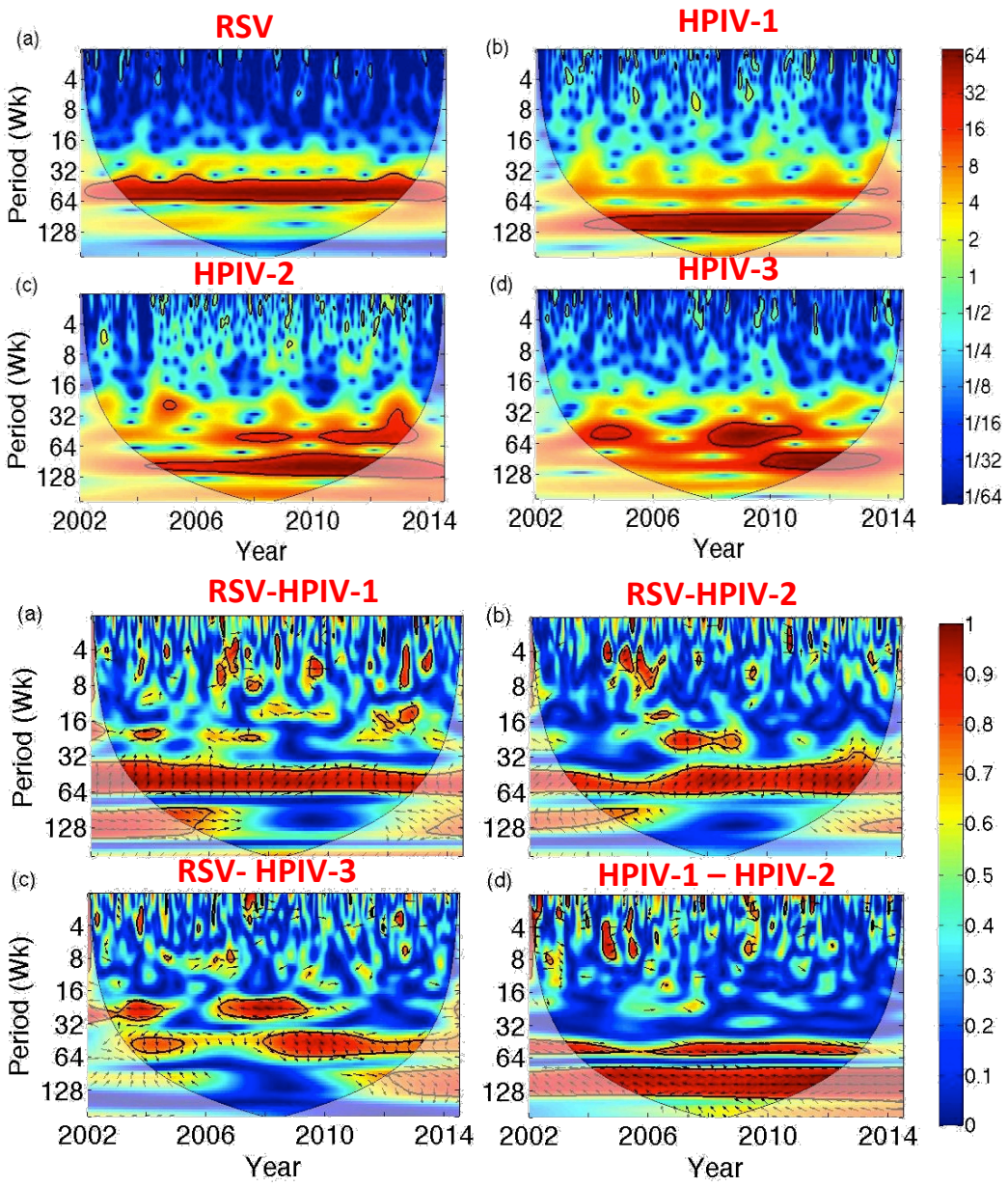
RSV & HPIV, being members of the same *Paramyxovirus* family, exhibit out-of-phase outbreaks in the same host population

Wavelet decomposition

- RSV periodicity in 52 weeks
- HPIV-1 and HPIV-2 periodicity in 104 weeks
- HPIV-3 does not exhibit any consistent period

Wavelet coherence

- HPIV-1 and HPIV-2 are strongly correlated with RSV in 52 weeks and they lead RSV
- HPIV-3 only shows significant spots of correlation with RSV
- HPIV-1 and HPIV-2 shows consistent anti-phase relation

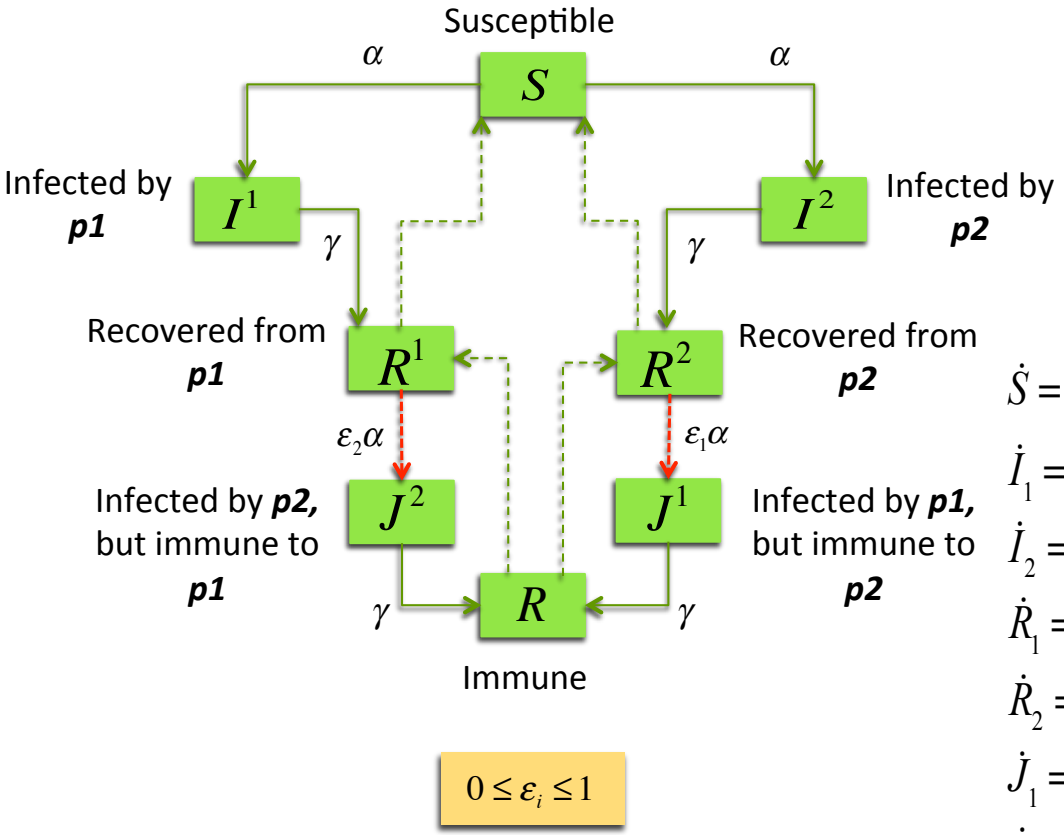


Limitations

- ✓ Wavelet analysis of incidence data is the strongest preliminary evidence of interactions between strains and so there are changes in the dynamical pattern of incidence.

- ✓ **Modelling approach** requires to investigate what type of interactions, and what strength those pathogens do interact.

Cross-immunity



$0 \le \varepsilon_i \le 1$

Seasonally forcing

$$\alpha = \alpha_0[1+\alpha_{00}\sin(2\pi(t-\phi)/T)]$$

Cross-immunity by one pathogen reduces the rate of infection by other pathogen

$$\dot{S} = \mu - \alpha S\{q_2[I_2+J_2]+q_1[I_1+J_1]\} + \rho_1 R_1 + \rho_2 R_2 - \mu S$$

$$\dot{I}_1 = \alpha S q_1[I_1+J_1] - \gamma_1 I_1 - \mu I_1$$

$$\dot{I}_2 = \alpha S q_2[I_2+J_2] - \gamma_2 I_2 - \mu I_2$$

$$\dot{R}_1 = \gamma_1 I_1 - \alpha q_2 \varepsilon_2 R_1[I_2+J_2] - \rho_1 R_1 + \rho_2 R - \mu R_1$$

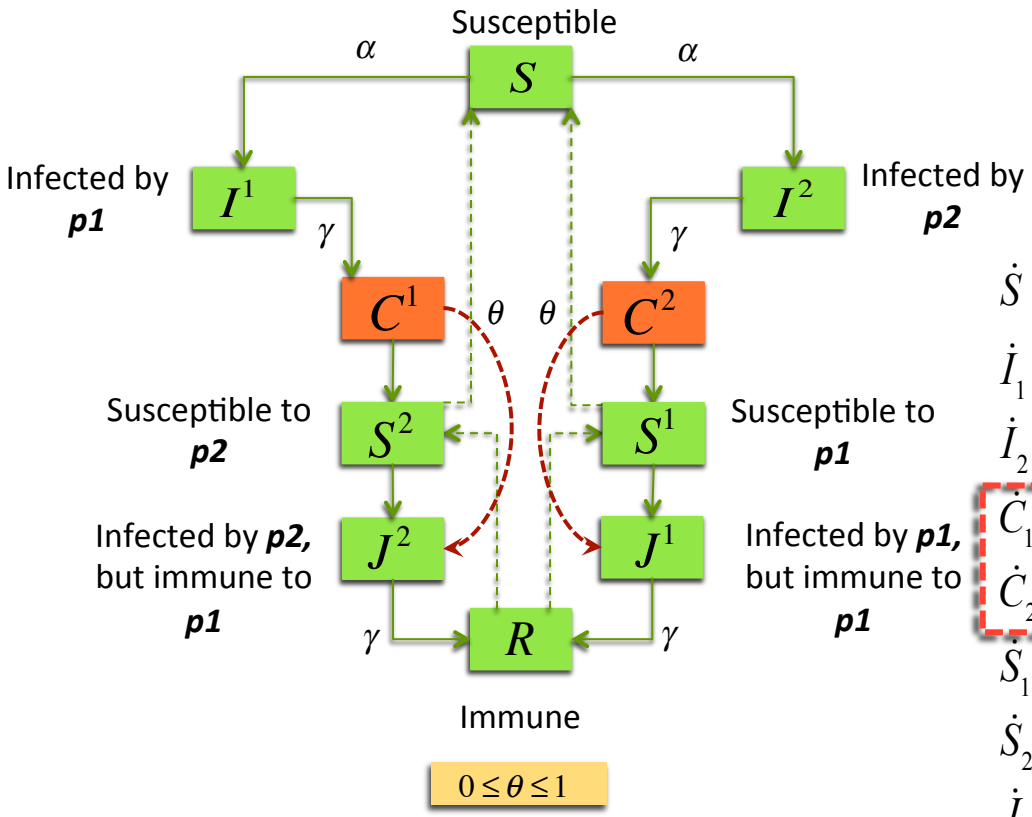
$$\dot{R}_2 = \gamma_2 I_2 - \alpha q_1 \varepsilon_1 R_2[I_1+J_1] - \rho_2 R_2 + \rho_1 R - \mu R_2$$

$$\dot{J}_1 = \alpha q_1 \varepsilon_1 R_2[I_1+J_1] - \gamma_1 J_1 - \mu J_1$$

$$\dot{J}_2 = \alpha q_2 \varepsilon_2 R_1[I_2+J_2] - \gamma_2 J_2 - \mu J_2$$

$$\dot{R} = \gamma_1 J_1 + \gamma_2 J_2 - \rho_2 R - \rho_1 R - \mu R$$

Competition



Seasonally forcing

$$\alpha = \alpha_0[1+\alpha_{00}\sin(2\pi(t-\phi)/T)]$$

Competition occurs by *short-term isolation* of individuals after infection due to illness

$$\dot{S} = \mu - \alpha S\{q_2[I_2+J_2]+q_1[I_1+J_1]\} + \rho_1 S_1 + \rho_2 S_2 - \mu S$$

$$\dot{I}_1 = \alpha S q_1[I_1+J_1] - (\gamma_1+\mu)I_1$$

$$\dot{I}_2 = \alpha S q_2[I_2+J_2] - (\gamma_2+\mu)I_2$$

$$\dot{C}_1 = \gamma_1 I_1 - \delta_1 C_1 - \alpha\{\theta C_1\}q_2[I_2+J_2] - \mu C_1$$

$$\dot{C}_2 = \gamma_2 I_2 - \delta_2 C_2 - \alpha\{\theta C_2\}q_1[I_1+J_1] - \mu C_2$$

$$\dot{S}_1 = \delta_2 C_2 - \alpha q_1 S_1[I_1+J_1] - \rho_1 S_1 + \rho_1 R - \mu S_1$$

$$\dot{S}_2 = \delta_1 C_1 - \alpha q_2 S_2[I_2+J_2] - \rho_2 S_2 + \rho_2 R - \mu S_2$$

$$\dot{J}_1 = \alpha q_1 S_1[I_1+J_1] + \alpha\{\theta C_2\}q_1[I_1+J_1] - \gamma_1 J_1 - \mu J_1$$

$$\dot{J}_2 = \alpha q_2 S_2[I_2+J_2] + \alpha\{\theta C_1\}q_2[I_2+J_2] - \gamma_2 J_2 - \mu J_2$$

$$\dot{R} = \gamma_1 J_1 + \gamma_2 J_2 - \rho_2 R - \rho_1 R - \mu R$$

Parameter estimation

- Transmission rate – α_0
- Seasonal forcing – α_{00}
- Strength of Interactions – ε_i, θ
- Detection probability – $f_{i,\ i=1,\ 2}$

Observational model

If $T_{i,t}$ is total number of newly infected in week t for pathogen i, and f_i is the reporting probability, then weekly case notification is drawn from a Poisson distribution with mean $f_i T_{i,t}$.

Measure of Parsimony

Aikaike Information Criterion (AIC): $AIC = -2\log M + 2l$

Log likelihood $\log M(\Theta) = \sum_{j=1}^{n} \log M_{t_j}(\Theta)$

$$\log M_{t_j}(\Theta) = \log M_{t_j}(y(t_j) \mid \hat{y}_\Theta(t_j)) = y(t_j)\log \hat{y}_\Theta(t_j) - \log(y(t_j)!) - \hat{y}_\Theta(t_j)$$

Where

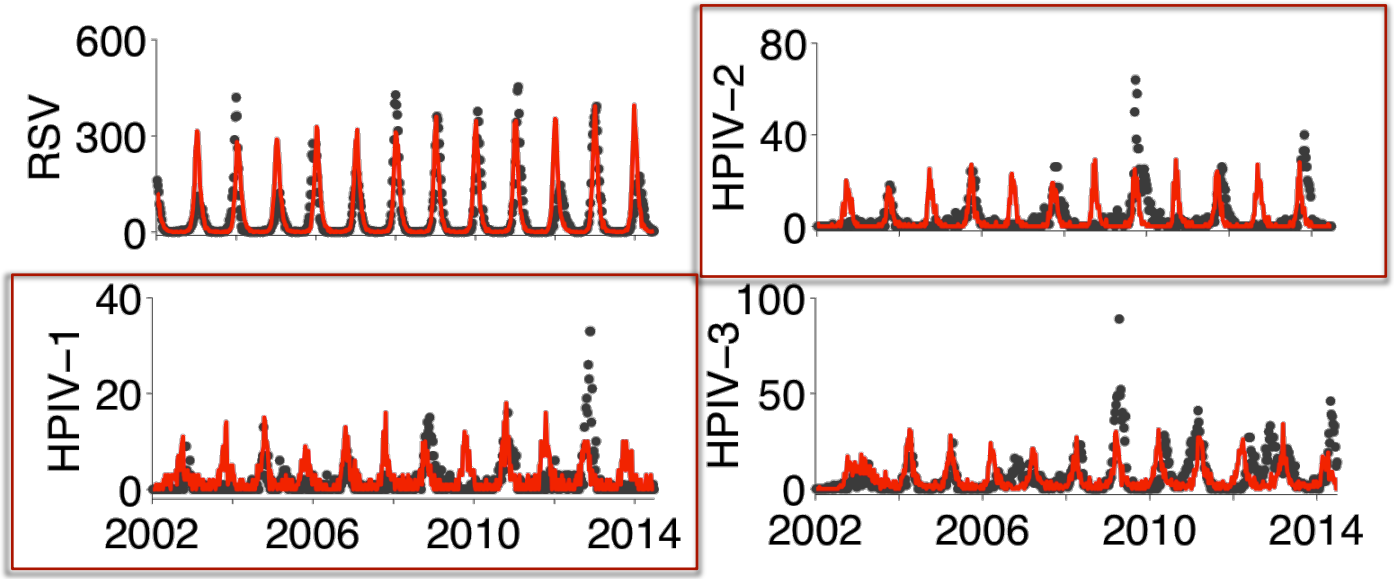
$\hat{y}_\Theta(t_j)$ - observed new infections on day t_j

n - number of points

l - number of fitted parameters

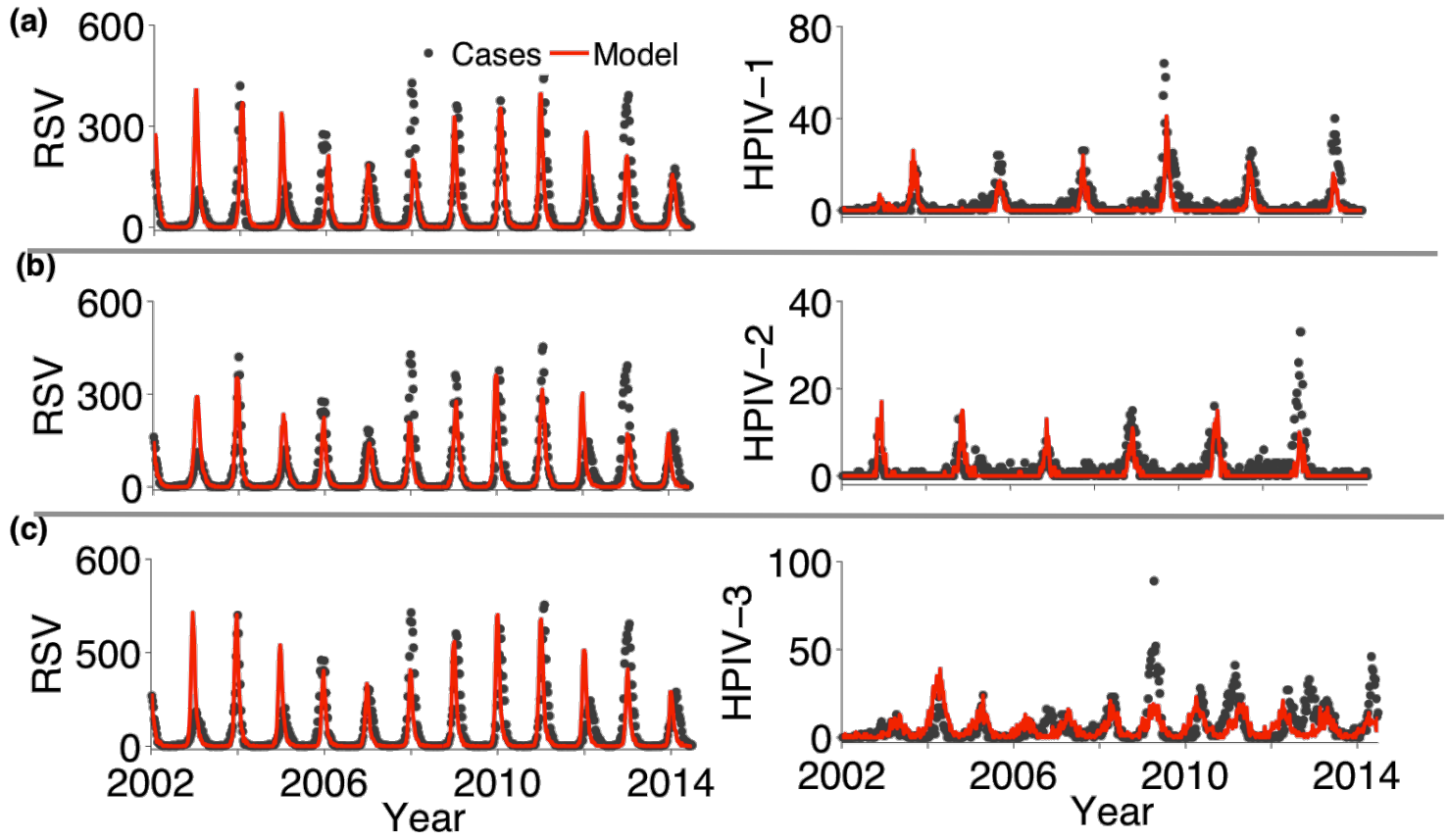
Model with LOWEST AIC is considered the most parsimonious

No interaction



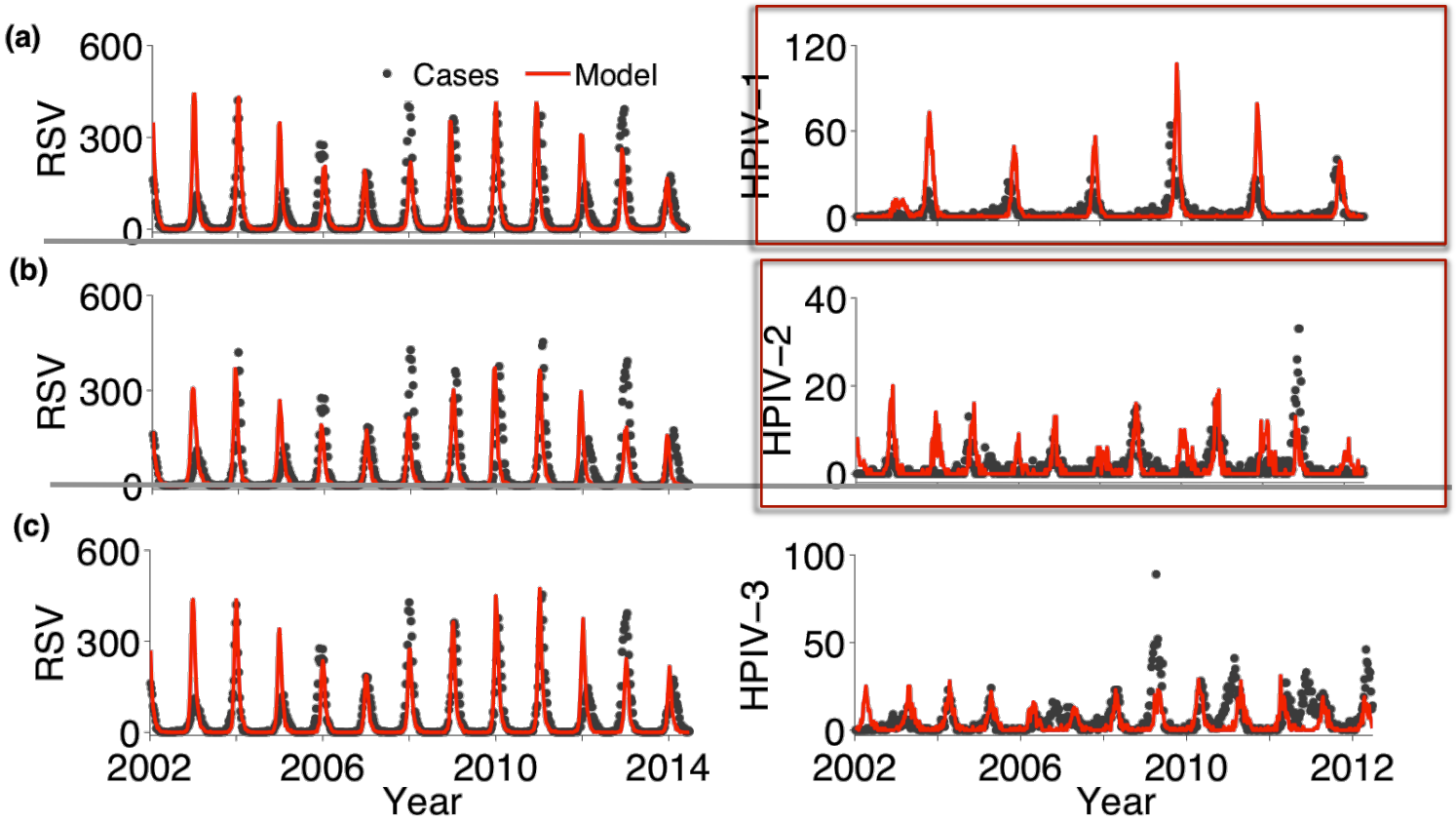
Single SIR model **can't** explain the biennial structure of HPIV-1 and HPIV-2

Cross-immunity



Cross-immunity model captures the peak *timing* as well as *size* of all epidemic trajectories

Competition



Competition model **can't** explain the biennial dynamics of HPIV-2

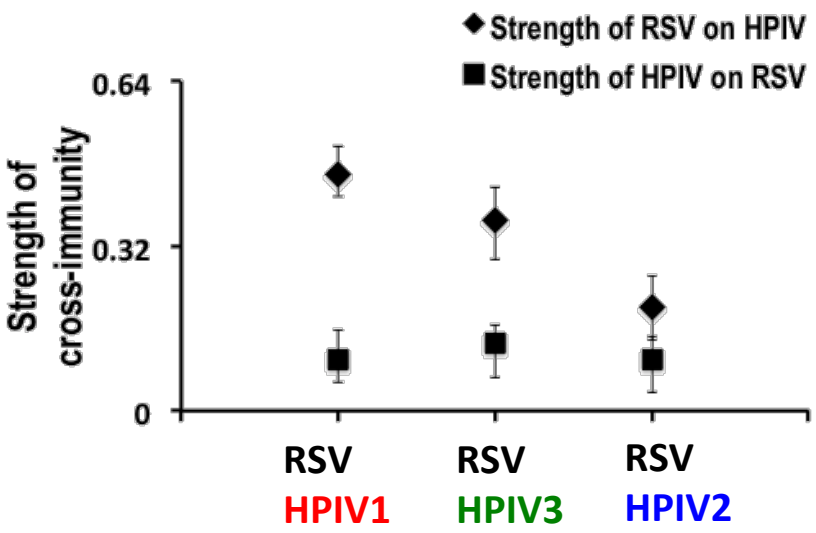
AIC analysis

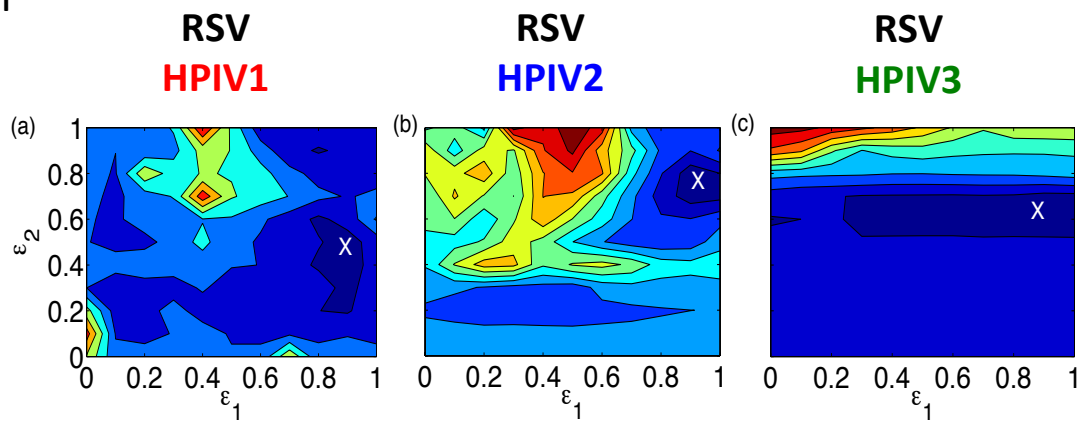
Single SIR model		Cross-immunity		Competition	
RSV	5.4×10^4	RSV-HPIV-1	2.36×10^4	RSV-HPIV-1	2.41×10^4
HPIV-1	3.9×10^4	RSV-HPIV-2	2.08×10^4	RSV-HPIV-2	2.2×10^4
HPIV-2	2.3×10^4	RSV-HPIV-3	2.21×10^4	RSV-HPIV-3	2.5×10^4
HPIV-3	3.2×10^4				

Cross-immunity model shows lowest AIC for all combinations

Likelihood surface

Estimated strength of cross-protection by RSV on other pathogens



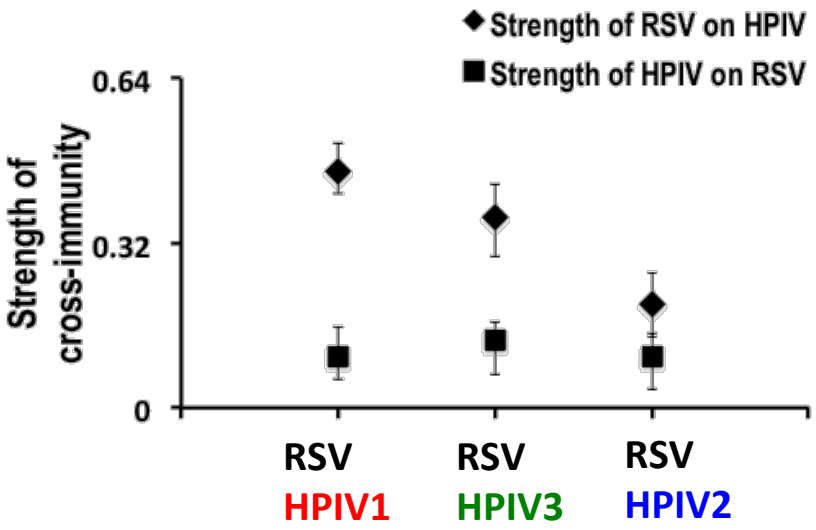


Likelihood surface describes how likely the parameter combination can explain the observed data.

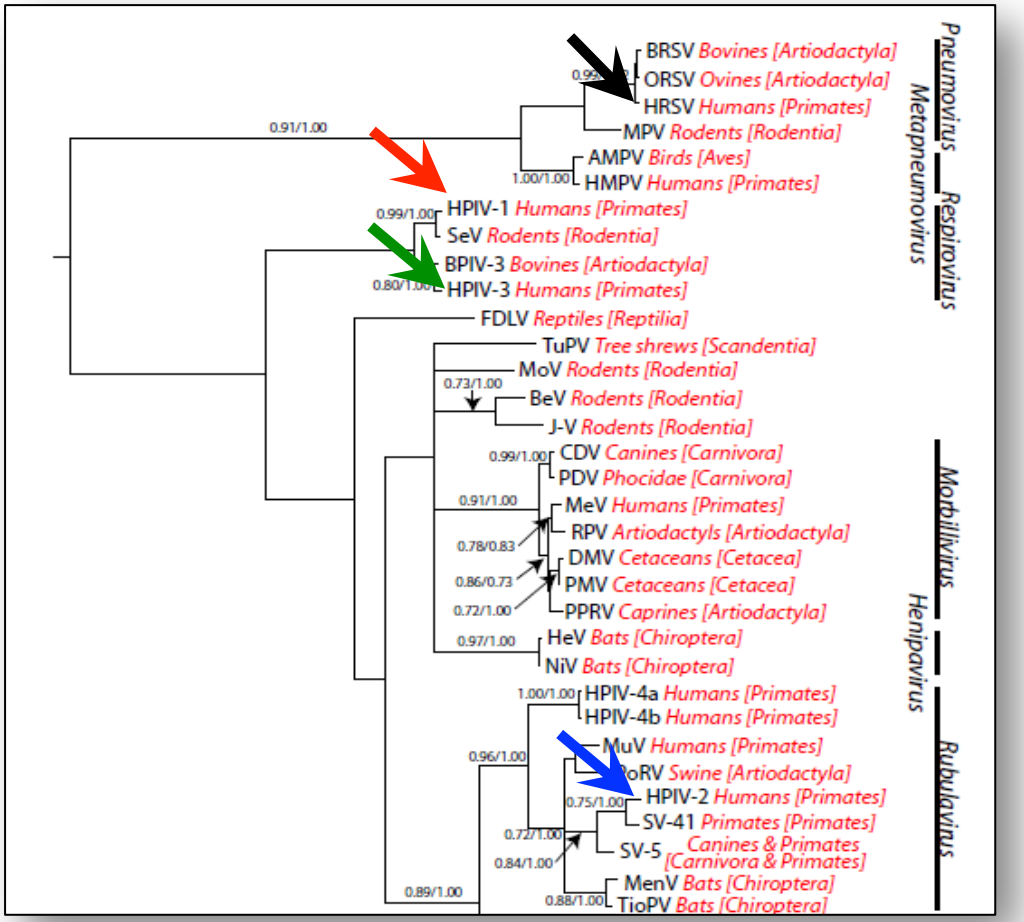
X — best parameter combination obtained in the model fitting process

Linking biology

Estimated strength of cross-protection by RSV on other pathogens



Strength of cross-protection are inversely proportional to genetic distance



Phylogenetic tree of the family Paramyxoviridae *(kitchen et al. 2011)*

Summary

- ✓ **Seasonality is necessary to explain intra-annual variation** in these weekly incidence, but **cross-protection immunity is essential for explaining inter-annual dynamics**.

- ✓ **Maximum likelihood** approach and **model-selection** methodology may be an useful technique to identify mechanism of the process.

- ✓ This work could aid in designing vaccination strategies that make optimal use of interference.

Bhattacharyya et al. (2015), *PNAS USA, 112 (43), 13396-13400*

Thank you