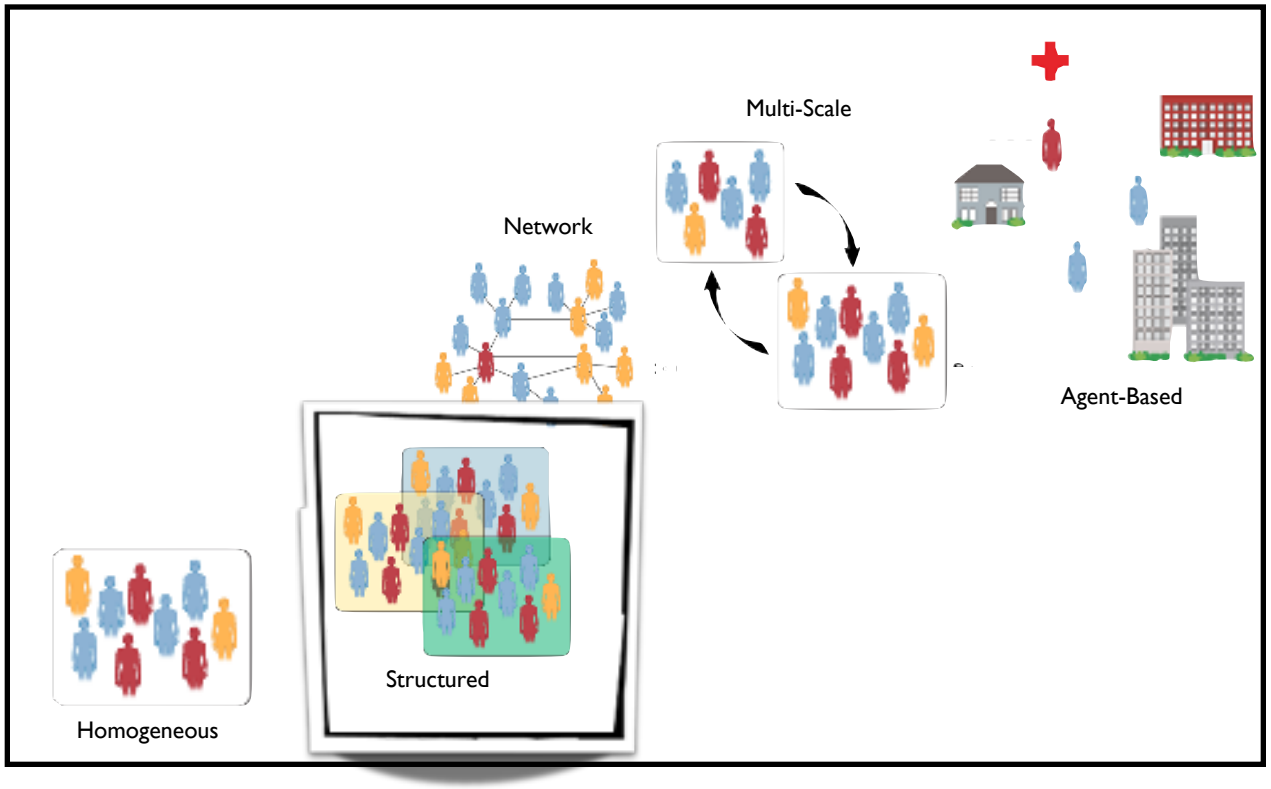
Heterogeneity in Contacts

Behaviour & Age

Realism Vs Transparency



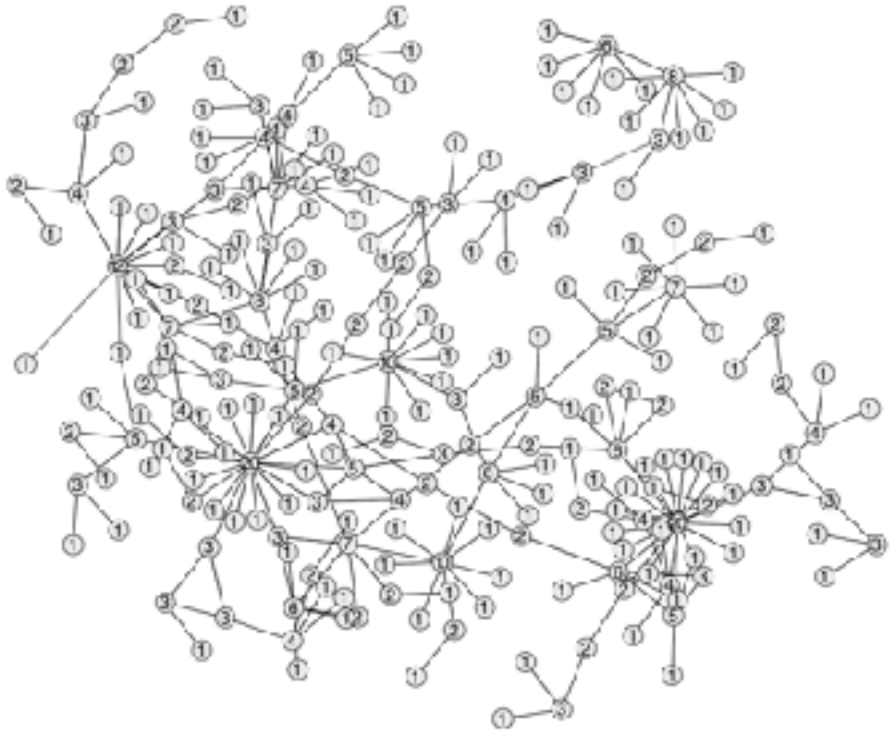
Sources of Heterogeneity in Contacts

Individual exposure and infection hazard may be heterogeneous for a number reasons:

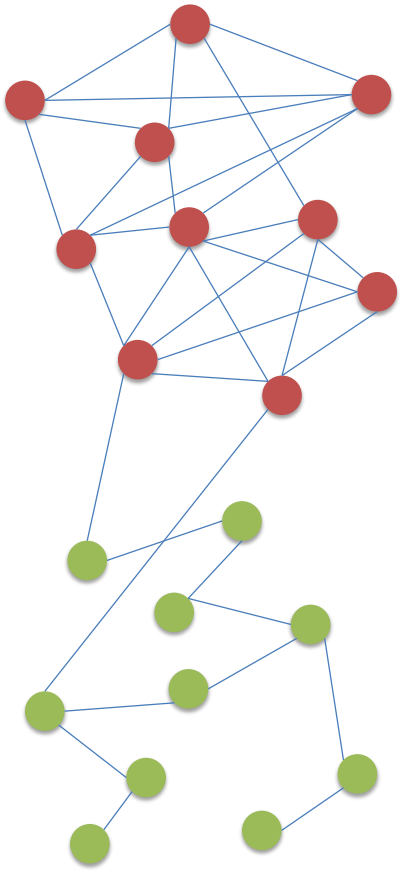
1. Risk structure
   - Determined by behavioural patterns
   - Or related to occupation
2. Age-determined contacts
   - Childhood diseases
3. Seasonality
   - Time-dependent contact rates result in sustained oscillations

Simple contact heterogeneities

- Contact tracing to examine HIV transmission network in Colorado Springs:



More Generally

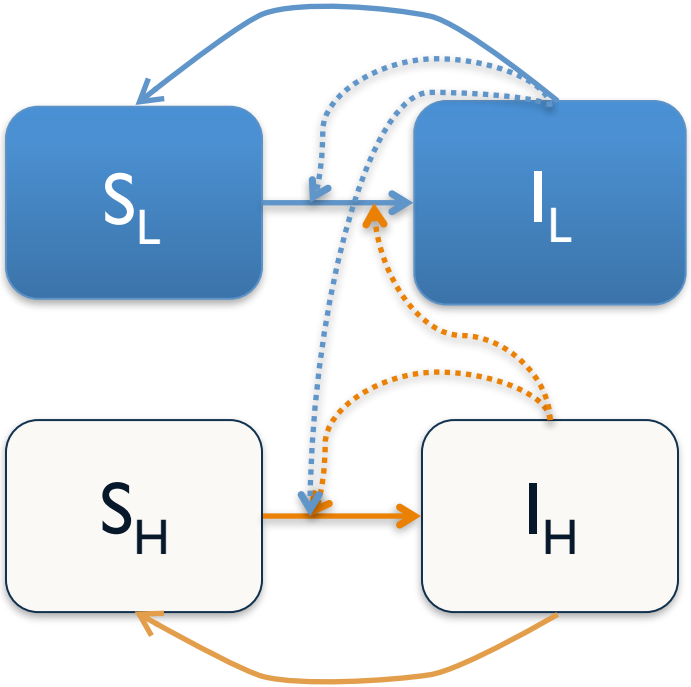


High risk group

Low risk group

Modeling Risk Structure

Introduce a model consisting of individuals whose behaviour/work places them in one of two *kinds* of groups: Low risk and High risk



Use an extension of simple SIS model

$$\frac{dS_L}{dt} = \gamma_L I_L - \beta_{LL} S_L I_L \; -\beta_{LH} S_L I_H$$

$$\frac{dI_L}{dt} = -\gamma_L I_L + \beta_{LL} S_L I_L \; +\beta_{LH} S_L I_H$$

$$\frac{dS_H}{dt} = \gamma_H I_H - \beta_{HH} S_H I_H \; -\beta_{HL} S_H I_L$$

$$\frac{dI_H}{dt} = -\gamma_H I_H + \beta_{HH} S_H I_H \; +\beta_{HL} S_H I_L$$

What's R_0?

- Instead of a single transmission rate (β), we now have a matrix of transmission parameters (β)

$$\begin{pmatrix} \beta_{HH} & \beta_{HL} \\ \beta_{LH} & \beta_{LL} \end{pmatrix}$$

- This is called WAIFW (Who Acquires Infection From Whom) matrix
- Typically, it's assumed $\beta_{LH} = \beta_{HL}$
- And high assortativity, such that $\beta_{HH} > \beta_{LL} > \beta_{HL}$

What's R_0?

- At disease-free equilibrium

$$(S_H^*, I_H^*, S_L^*, I_L^*) = (1, 0, 1, 0)$$

- $\mathcal{F}$ = new infections
- $\mathcal{F}_H = \beta_{HH} S_H I_H + \beta_{HL} S_H I_L$
- $\mathcal{F}_L = \beta_{LL} S_L I_L + \beta_{LH} S_L I_H$
- $\mathcal{V}$ = pathogen progression
- $\mathcal{V}_H = \gamma_H I_H$
- $\mathcal{V}_L = \gamma_L I_L$

$$F = \begin{pmatrix} \beta_{HH} S_1^* & \beta_{HL} S_1^* \\ \beta_{HL} S_2^* & \beta_{LL} S_2^* \end{pmatrix} = \begin{pmatrix} \beta_{HH} & \beta_{HL} \\ \beta_{HL} & \beta_{LL} \end{pmatrix} \qquad V = \begin{pmatrix} \gamma_H & 0 \\ 0 & \gamma_L \end{pmatrix}$$

Diekmann *et al.* (1990; *J Math Biol.*)

What's R_0?

- Next generation operator, K, given by

$$FV^{-1} = \begin{pmatrix} \beta_{HH} & \beta_{HL} \\ \beta_{HL} & \beta_{LL} \end{pmatrix} \begin{pmatrix} \frac{1}{\gamma_H} & 0 \\ 0 & \frac{1}{\gamma_L} \end{pmatrix}$$

$$K = FV^{-1} = \begin{pmatrix} \frac{\beta_{HH}}{\gamma_H} & \frac{\beta_{HL}}{\gamma_L} \\ \frac{\beta_{LH}}{\gamma_H} & \frac{\beta_{LL}}{\gamma_L} \end{pmatrix}$$

$$\det(K - \Lambda I) = \begin{vmatrix} \frac{\beta_{HH}}{\gamma_H} - \Lambda & \frac{\beta_{HL}}{\gamma_L} \\ \frac{\beta_{LH}}{\gamma_H} & \frac{\beta_{LL}}{\gamma_L} - \Lambda \end{vmatrix} = 0$$

- Solve for largest Λ

Worked example

- Let $\gamma_H=\gamma_L = 50$,
- with WAIFW matrix give by $\beta = \begin{pmatrix} 45 & 20 \\ 20 & 35 \end{pmatrix}$

$$K = FV^{-1} = \begin{pmatrix} 45 & 20 \\ 20 & 35 \end{pmatrix} \begin{pmatrix} \frac{1}{50} & 0 \\ 0 & \frac{1}{50} \end{pmatrix}$$

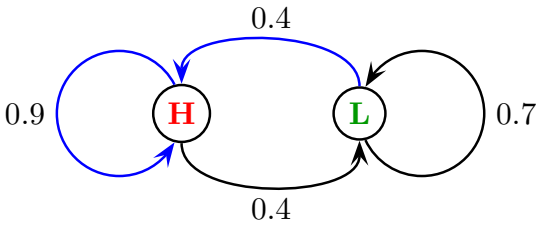
$$= \begin{pmatrix} .9 & .4 \\ .4 & .7 \end{pmatrix}$$

$$\det(K = \Lambda I) = \begin{vmatrix} .9-\Lambda & .4 \\ .4 & .7-\Lambda \end{vmatrix} = \Lambda^2 - 1.6\Lambda + 0.47$$

- So Λ = 1.21 or .39 $\Rightarrow R_0$ = 1.21

Limitations

- R_0 quantifies overall transmission — useful for control measures that ignore epidemiological "type"
- Not target specific
- What if interested in focusing on high risk group?



- Control measures could be aimed at, for example, paths leading to High risk group

Type Reproduction Number

- If a control strategy is aimed at particular host types only, (vectors, wildlife reservoir, vaccination of domestic animals), then so-called "type reproduction number", $\mathcal{T}$, takes over role of R_0
- Its value determines control effort needed

Roberts & Heesterbeek (2003; *Proc B*)

Type Reproduction Number

- **Type reproduction Number, T_i**
  - All paths leading to *i* targeted

    $1 \rightarrow i, 2 \rightarrow i, \ldots, p \rightarrow i.$

- Then
  - $x_1=\{i\}$, $x_2=\{1, \ldots, n\}$ and $T_i = \mathcal{T}_{1\rightarrow i,\ 2\rightarrow i,\ \ldots,\ n\rightarrow i}$.

- **Basic reproduction Number, R_0:** all possible paths are targeted
  - $x_1=\{1,2, \ldots, n\}$, $x_2=\{1, \ldots, n\}$

Roberts & Heesterbeek (2003; *Proc B*)

Target Reproduction Number

- Suppose we target q paths of transmission

  $j_1 \rightarrow i_1, j_2 \rightarrow i_2, \ldots, j_q \rightarrow i_q$

  - Let X be set of all targeted paths

'recipient' classes → $x_1 = \{i_1, i_2, \ldots, i_q\}$, $x_2 = \{j_1, j_2, \ldots, j_q\}$ ← 'donour' classes

  - The Target Reproduction Number is

$$\mathcal{T}_X = \rho(P_{x_1} K P_{x_2} (1 - K + P_{x_1} K P_{x_2})^{-1})) \text{ if } \rho(K - P_{x_1} K P_{x_2}) < 1$$

- where P_{xi} is a projection matrix ($P_{k,k} = 1$ if $k \in x_i$, zero otherwise).

Shuai *et al.* (2012; *J Math Biol*)

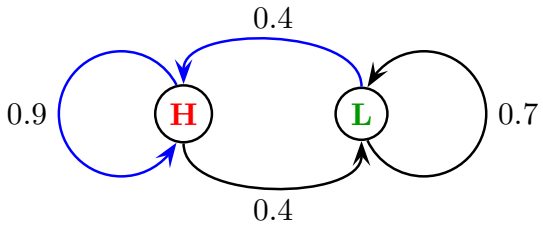
Target Reproduction Number

$$\text{if } \rho(K - P_{x_1} K P_{x_2}) > 1$$

then $\mathcal{T}_X$ is not defined since disease cannot be eradicated by targeting only X

Shuai *et al.* (2012; *J Math Biol*)

Targeting S_H



- Target paths: H → H, L → H.
- x_1={H}, x_2={H, L}
- Target reproduction number:

$$T_H = \mathcal{T}_{H\to H,\ L\to H}$$
$$= \rho(P_{x_1} K P_{x_2} (1 - K + P_{x_1} K P_{x_2})^{-1})), \text{if } \rho(K - P_{x_1} K P_{x_2}) < 1$$

$$K = \begin{pmatrix} 0.9 & 0.4 \\ 0.4 & 0.7 \end{pmatrix} \quad P_{x_1} = \begin{pmatrix} 1 & 0 \\ 0 & 0 \end{pmatrix} \quad P_{x_2} = \begin{pmatrix} 1 & 0 \\ 0 & 1 \end{pmatrix}$$

Targeting S_H

$$P_{x_1} K P_{x_2} = \begin{pmatrix} 1 & 0 \\ 0 & 0 \end{pmatrix} \begin{pmatrix} 0.9 & 0.4 \\ 0.4 & 0.7 \end{pmatrix} \begin{pmatrix} 1 & 0 \\ 0 & 1 \end{pmatrix} = \begin{pmatrix} 0.9 & 0.4 \\ 0 & 0 \end{pmatrix}$$

- Check: $\rho(K - P_{x_1} K P_{x_2}) = 0.7$ ✓

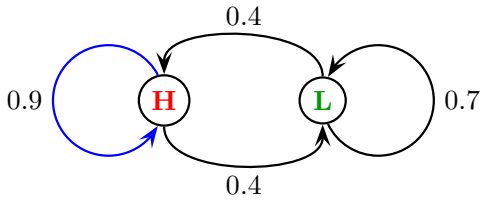
$$(P_{x_1} K P_{x_2}) \Big(I - K + (P_{x_1} K P_{x_2}) \Big)^{-1}$$

$$= \begin{pmatrix} 0.9 & 0.4 \\ 0 & 0 \end{pmatrix} \left[\begin{pmatrix} 1 & 0 \\ 0 & 1 \end{pmatrix} - \begin{pmatrix} 0.9 & 0.4 \\ 0.4 & 0.7 \end{pmatrix} + \begin{pmatrix} 0.9 & 0.4 \\ 0 & 0 \end{pmatrix} \right]^{-1}$$

$$= \begin{pmatrix} 1.43 & 1.33 \\ 0 & 0 \end{pmatrix}$$

- Hence, $T_H = \mathcal{T}_{H \to H,\, L \to H} = 1.43$
- Need to vaccinate *H* susceptibles: $1 - 1/T_H = 1 - 1/1.43 = 0.3$

Lowering H➛H transmission



- Target paths: H → H.
- x_1={H}, x_2={H}
- Target reproduction number: $T_H = \mathcal{T}_{H \to H}$

$$= \rho(P_{x_1} K P_{x_2} (1 - K + P_{x_1} K P_{x_2})^{-1})), \text{if } \rho(K - P_{x_1} K P_{x_2}) < 1$$

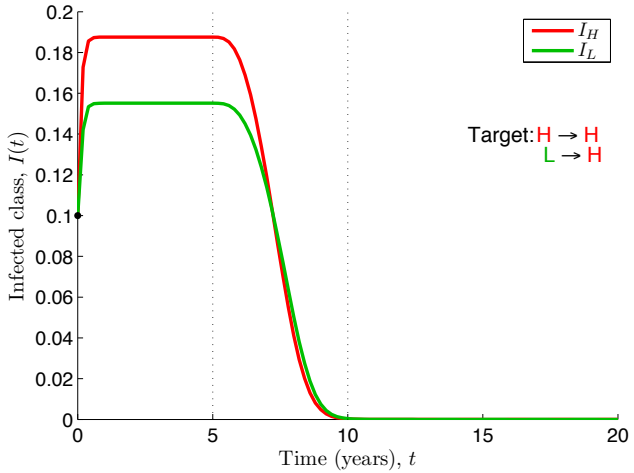
$$K = \begin{pmatrix} 0.9 & 0.4 \\ 0.4 & 0.7 \end{pmatrix} \quad P_{x_1} = \begin{pmatrix} 1 & 0 \\ 0 & 0 \end{pmatrix} \quad P_{x_2} = \begin{pmatrix} 1 & 0 \\ 0 & 0 \end{pmatrix}$$

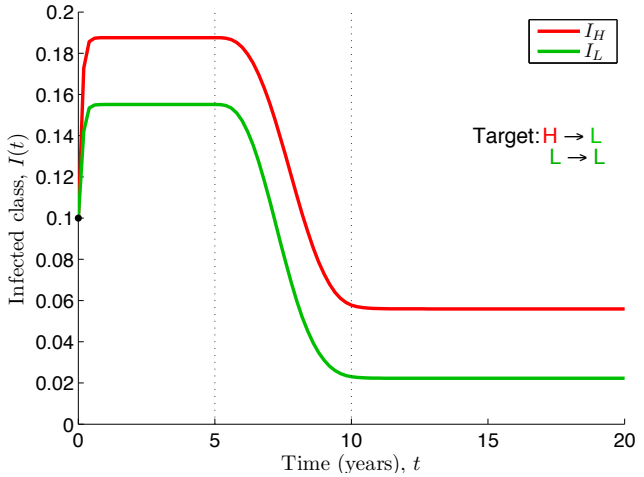
- Hence, $T_H = \mathcal{T}_{H \to H} = 1.93$
- Need to reduce contact by $1\text{-}1/T_H = 1\text{-}1/1.93 = 0.48$

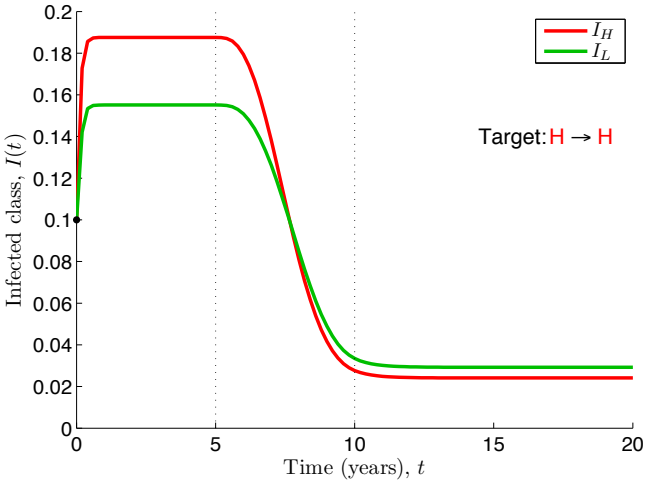
More Generally

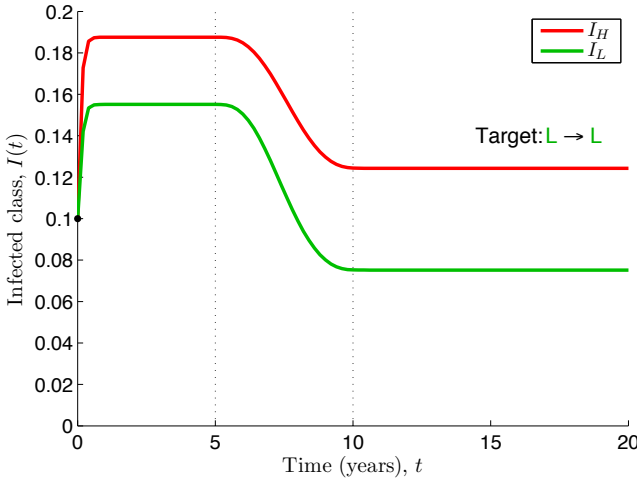
Target Paths	x_1	x_2	Target Reproduction	Reduction	Vaccination
All	H, L	H, L	$R_0 = 1.21$	0.17	17% H 17% L
H → H L → H	H	H, L	$T_H = 1.43$	0.3	30% H 0% L
H → L L → L	L	H, L	$T_L = 2.30$	0.57	0% H 57% L
H → H	H	H	1.93	0.48	-
L → L	L	L	Not Defined	-	-
L → H	H	L	5.33	0.81	-
H → L	L	H	5.33	0.81	-

Reduce targeted transmission by 40%

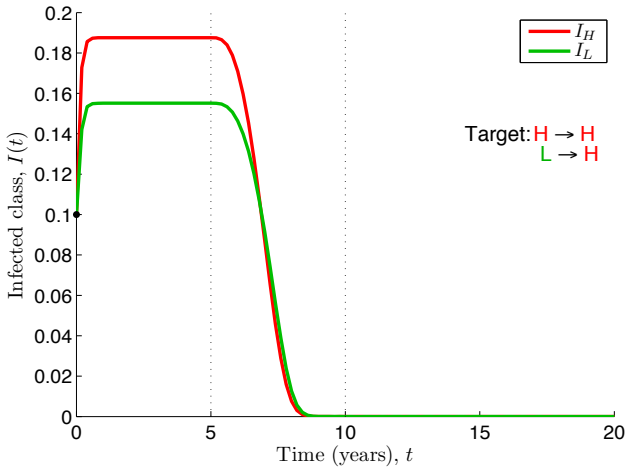


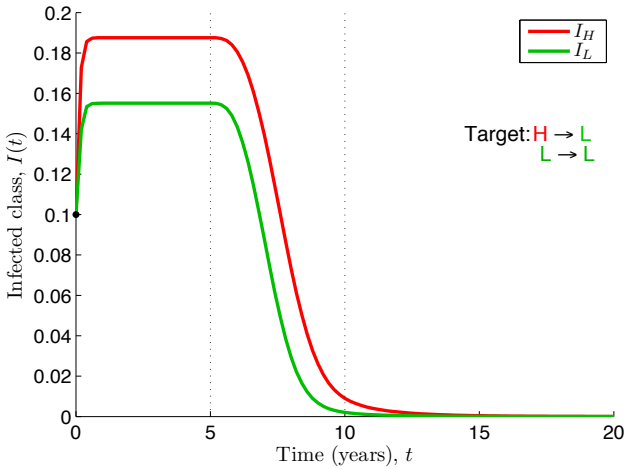


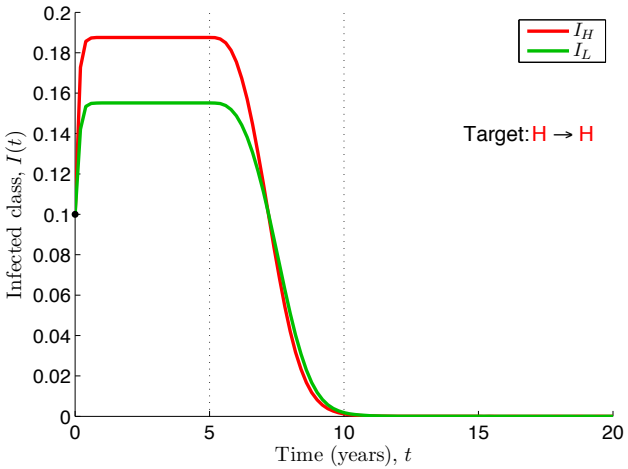


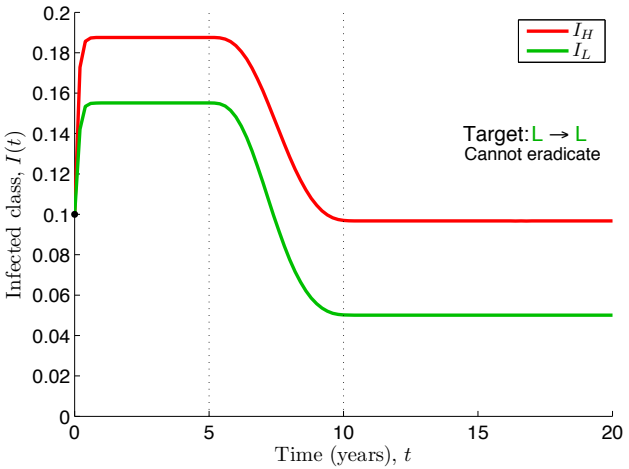


Reduce targeted transmission by 60%









Summary

- Target reproduction number informative for heterogeneous populations
- Behavioural risk (core groups)
- Vectors & Hosts
- Age structure
- Spatial structure

Modeling Age Structure

- So far, looked at heterogeneity arising in contacts, due to behavioural differences (risk structure)
- Now, we consider changing risk due to age structure, motivated by childhood diseases (ie SIR)
- Initially, assume only two age groups: Low risk (Adults) and High risk (Children)
- Differences from previous model: (i) SIR not SIS, (ii) individuals eventually move from class *C* to class *A* in SIR model

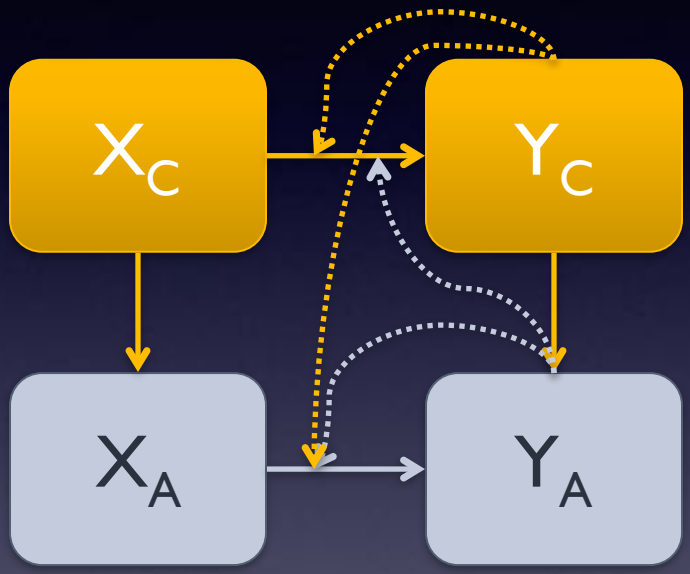
Modeling Risk Structure

$$\frac{dX_C}{dt} = \nu - (\beta_{CC}Y_C + \beta_{CA}Y_A)X_C - \mu_C X_C - \tau_C X_C$$

$$\frac{dY_C}{dt} = (\beta_{CC}Y_C + \beta_{CA}Y_A)X_C - \gamma Y_C - \mu_C Y_C - \tau_C Y_C$$

$$\frac{dX_A}{dt} = \tau_C X_C - (\beta_{AC}Y_C + \beta_{AA}Y_A)X_A - \mu_A X_A$$

$$\frac{dY_A}{dt} = \tau_C Y_C + (\beta_{AC}Y_C + \beta_{AA}Y_A)X_A - \gamma Y_A - \mu_A Y_A$$



$$N = N_C + N_A = (X_C + Y_C + Z_C) + (X_A + Y_A + Z_A)$$

Initial Dynamics

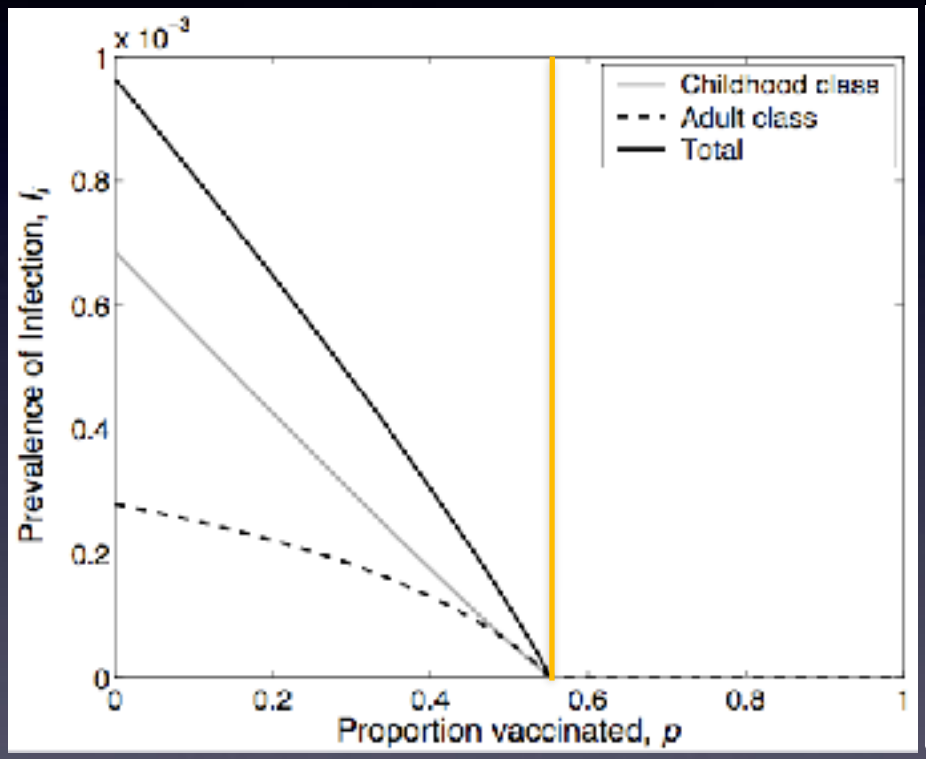
- Again, key thing is WAIFW matrix, which we'll assume to take following form

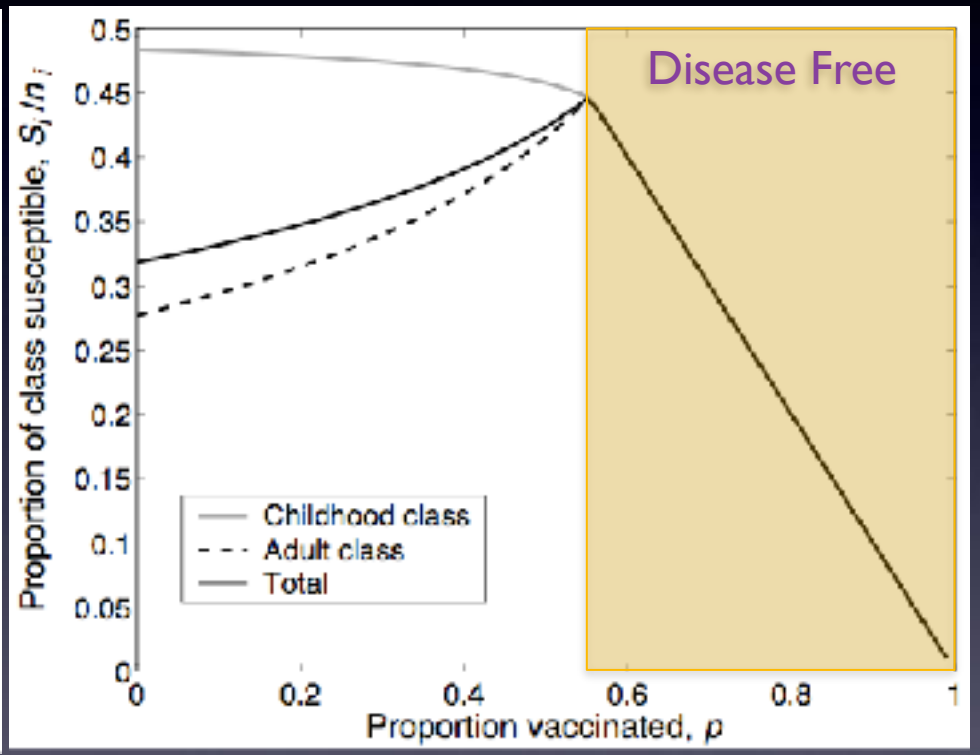
$$\beta = \begin{pmatrix} 100 & 10 \\ 10 & 20 \end{pmatrix}$$

- Let's assume $1/\tau_C$ = 15 years & $1/\tau_A$ = 60 years
- So, $N_C/N = 0.2$ and $N_A/N = 0.8$
- Using same spectral radius approach as before, we get R_0 ~2.2

Paediatric Vaccination

$P_c \sim 0.55$





- Prevalence much higher in *C* class than *A* class
- Vaccination threshold same as in unstructured model (!!)
- Low levels of immunization *increase* fraction of population

Which WAIFW?

- So far, we have used hypothetical WAIFW matrices
- In reality, we may have data on disease prevalence in *C* and *A* classes, but our matrix β has 4 entries we need to estimate!
- Pragmatic assumption has been to simplify WAIFW along intuitive/sensible lines, eg

$$\beta = \begin{pmatrix} \beta_1 & \beta_2 \\ \beta_2 & \beta_2 \end{pmatrix}$$

- Often, reasonably obvious what's not a plausible WAIFW matrix

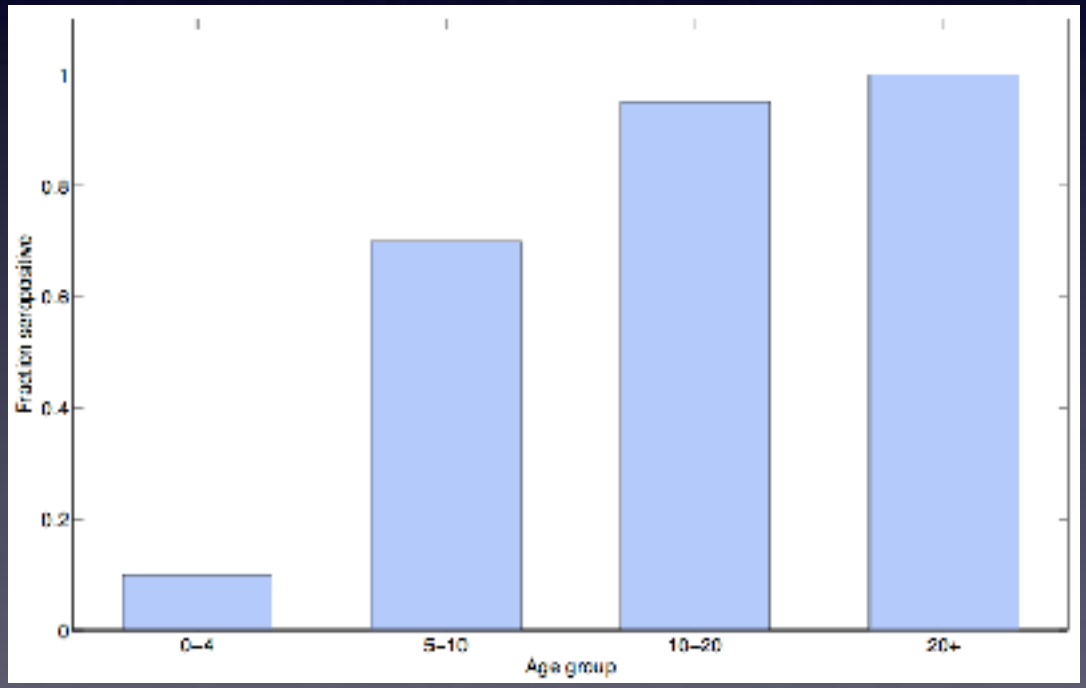
$$\beta_{\text{unlikely}} = \begin{pmatrix} \beta_1 & \beta_2 \\ \beta_2 & \beta_1 \end{pmatrix}, \begin{pmatrix} \beta_1 & 0 \\ 0 & \beta_1 \end{pmatrix}, \begin{pmatrix} \beta_1 & 0 \\ \beta_2 & 0 \end{pmatrix}, \cdots$$

Application to Childhood Diseases

- Some of earliest discrete age-class (RAS) models developed for measles (Schenzle 1984)
- Make pragmatic assumption: transmission, especially in pre-vaccine era, primarily driven by school dynamics
- Need four age groups
  - Pre-school (0-4 years)
  - Primary school (5-10 years)
  - Secondary school (11-16 years)
  - Adults (16+)
- We're now faced with old problem of which WAIFW?

Typical age-specific data

Given n age classes, age-specific transmission matrix has n^2 elements … correcting for reciprocity, we still have $n(n-1)/2$ term



Often, only have information on age-specific prevalence or serology

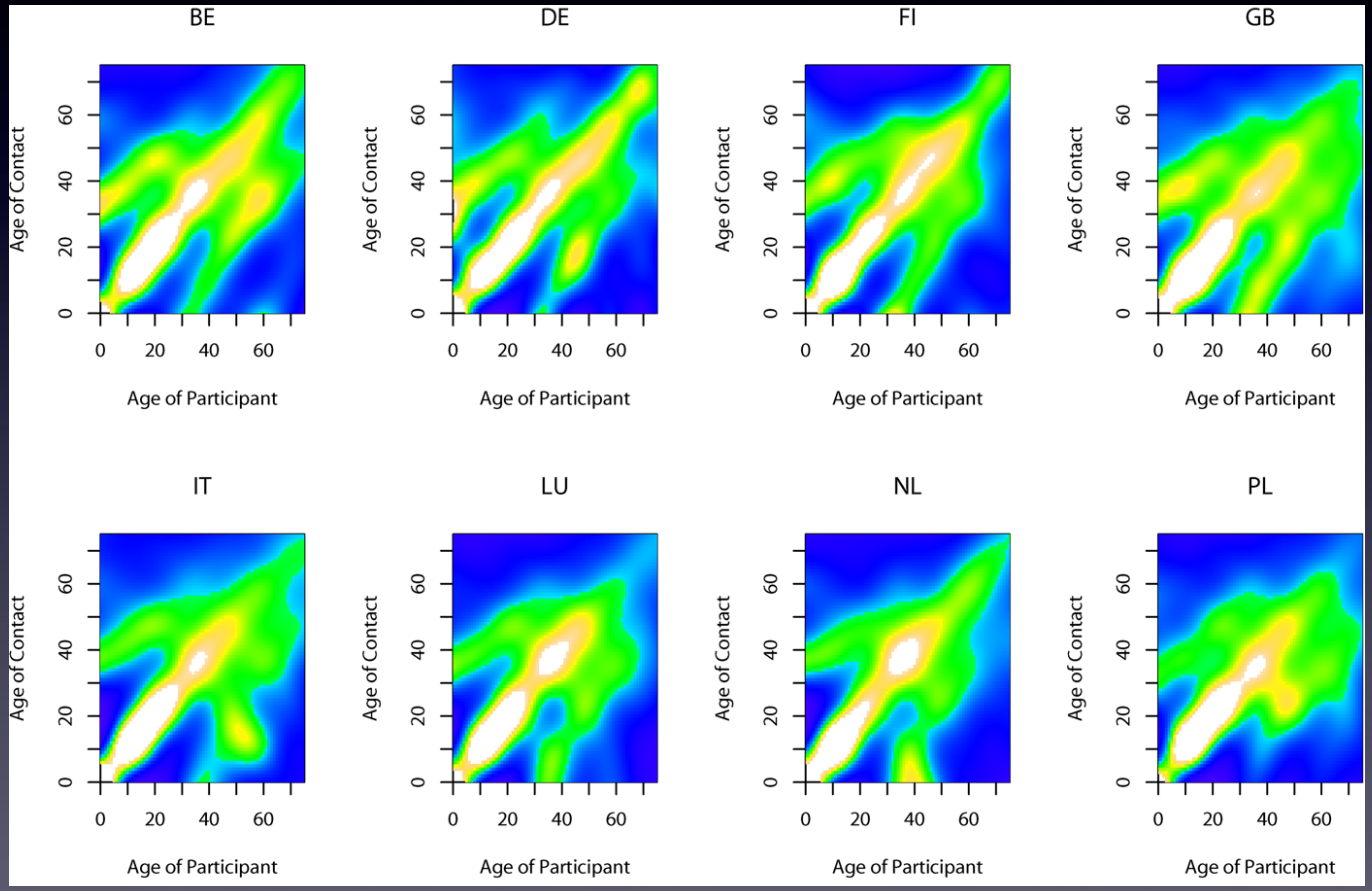
Which WAIFW?

- Two seemingly sensible WAIFW matrices are

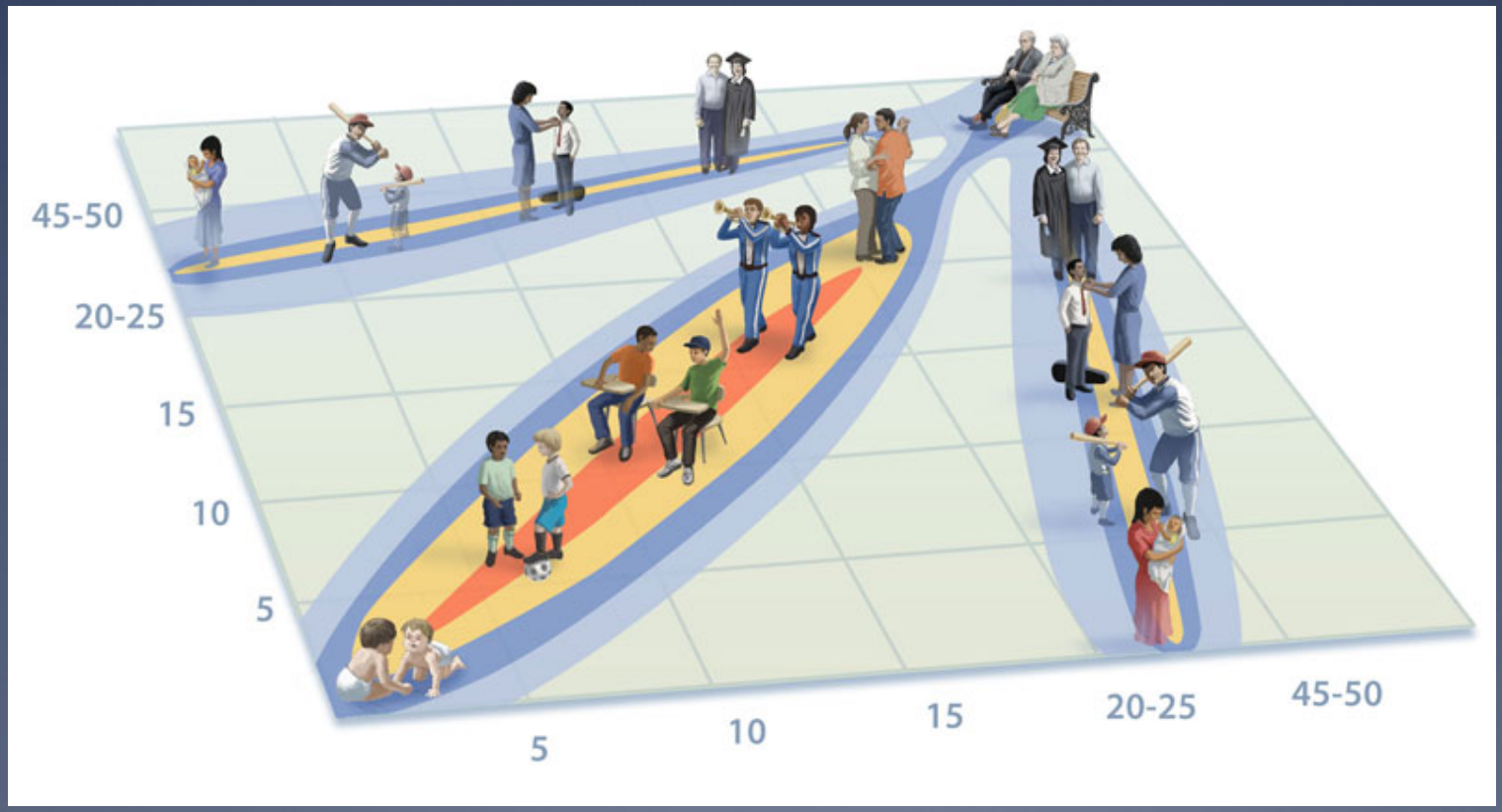
$$\beta = \begin{pmatrix} \beta_2 & \beta_2 & \beta_3 & \beta_4 \\ \beta_2 & \beta_1 & \beta_3 & \beta_4 \\ \beta_3 & \beta_3 & \beta_3 & \beta_4 \\ \beta_4 & \beta_4 & \beta_4 & \beta_4 \end{pmatrix} \quad \beta = \begin{pmatrix} \beta_2 & \beta_4 & \beta_4 & \beta_4 \\ \beta_4 & \beta_1 & \beta_4 & \beta_4 \\ \beta_4 & \beta_4 & \beta_3 & \beta_4 \\ \beta_4 & \beta_4 & \beta_4 & \beta_3 \end{pmatrix}$$

With $\beta_1 > \beta_2 > \beta_3 > \beta_4$

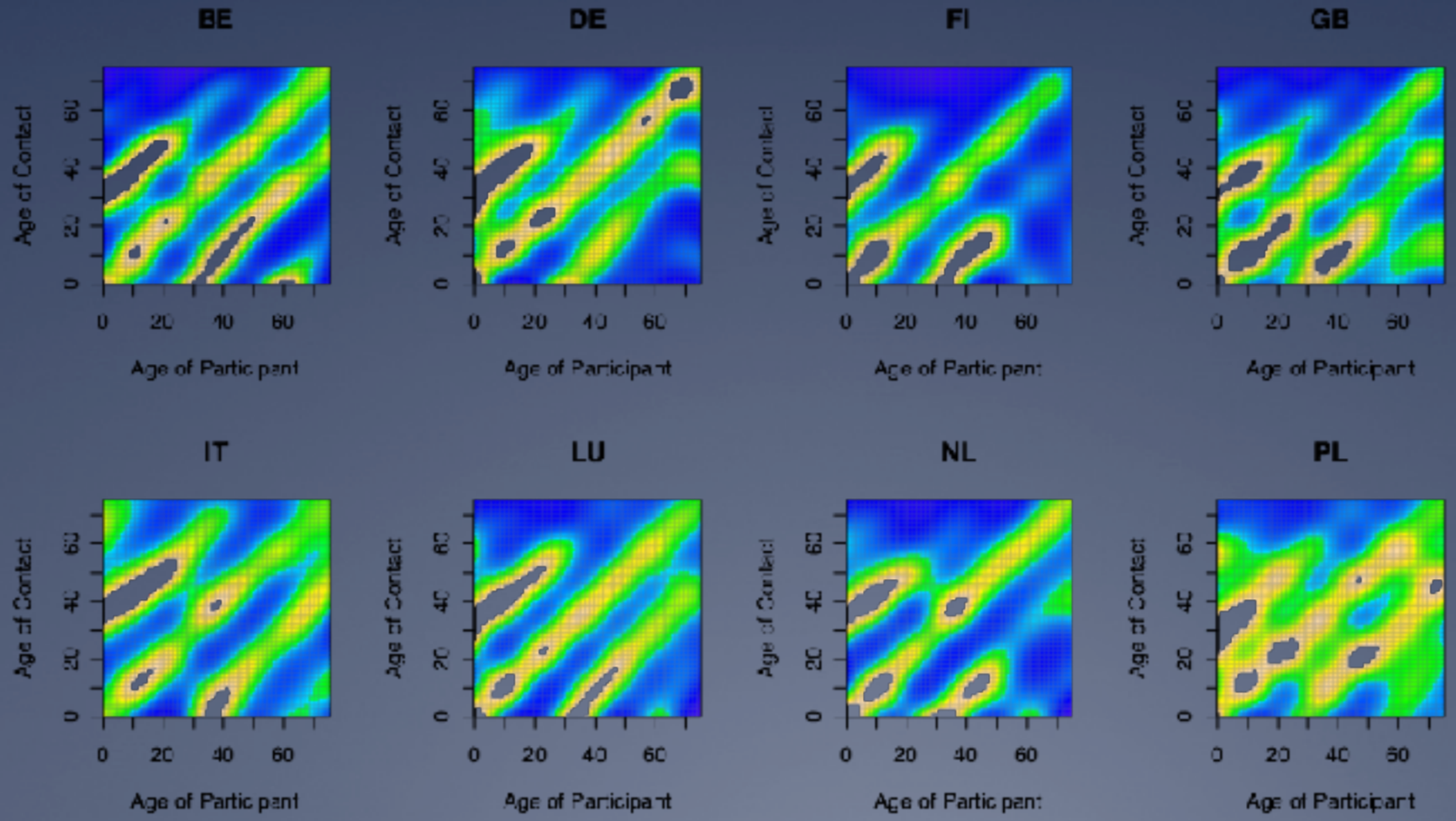
Mossong *et al.* (2008)



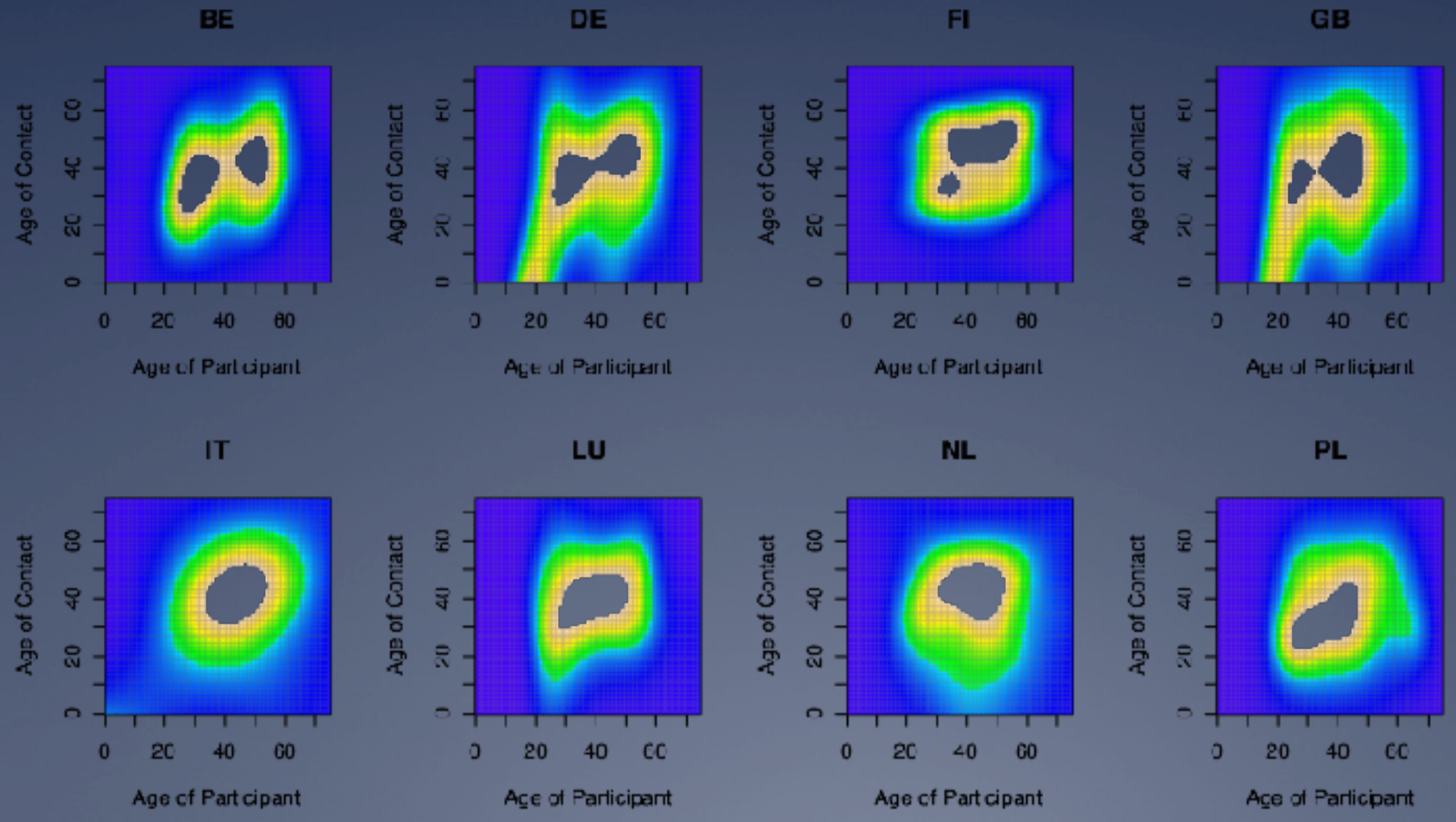
Age-specific contacts



Contacts at home

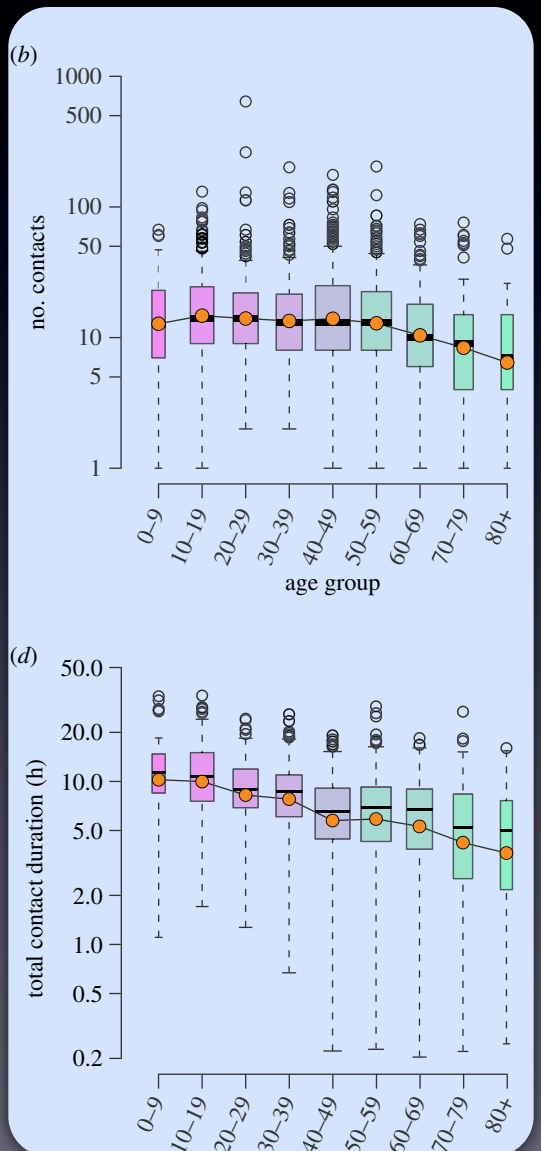


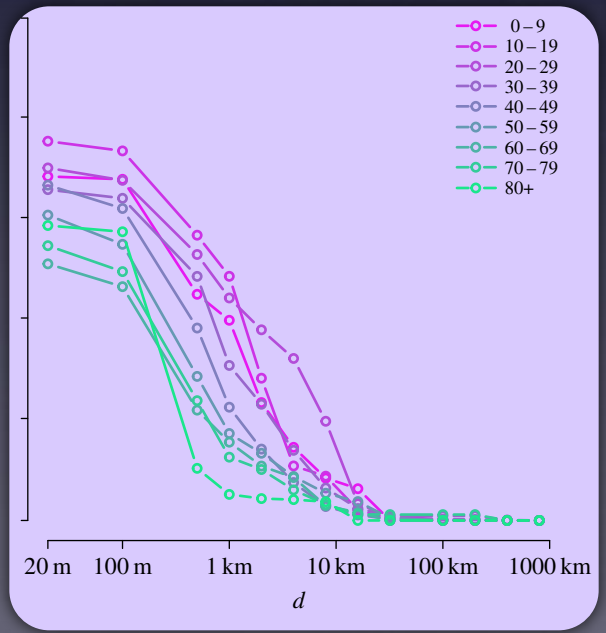
Contacts at work

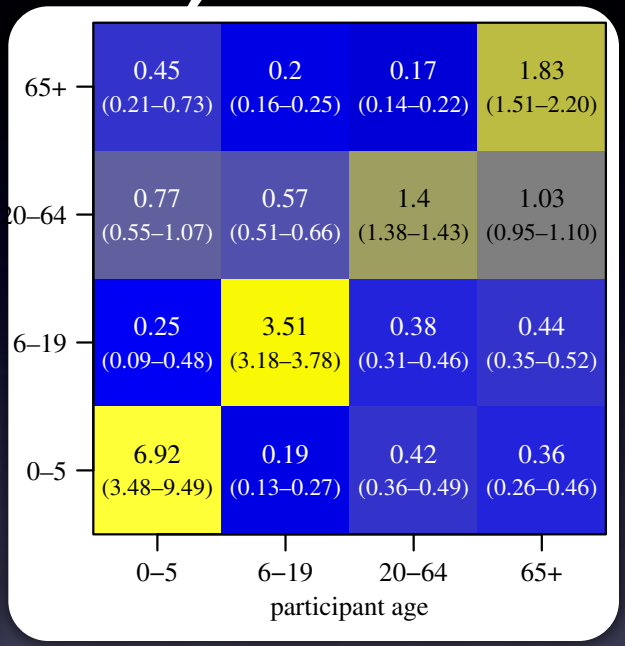


Read et al. (2014)

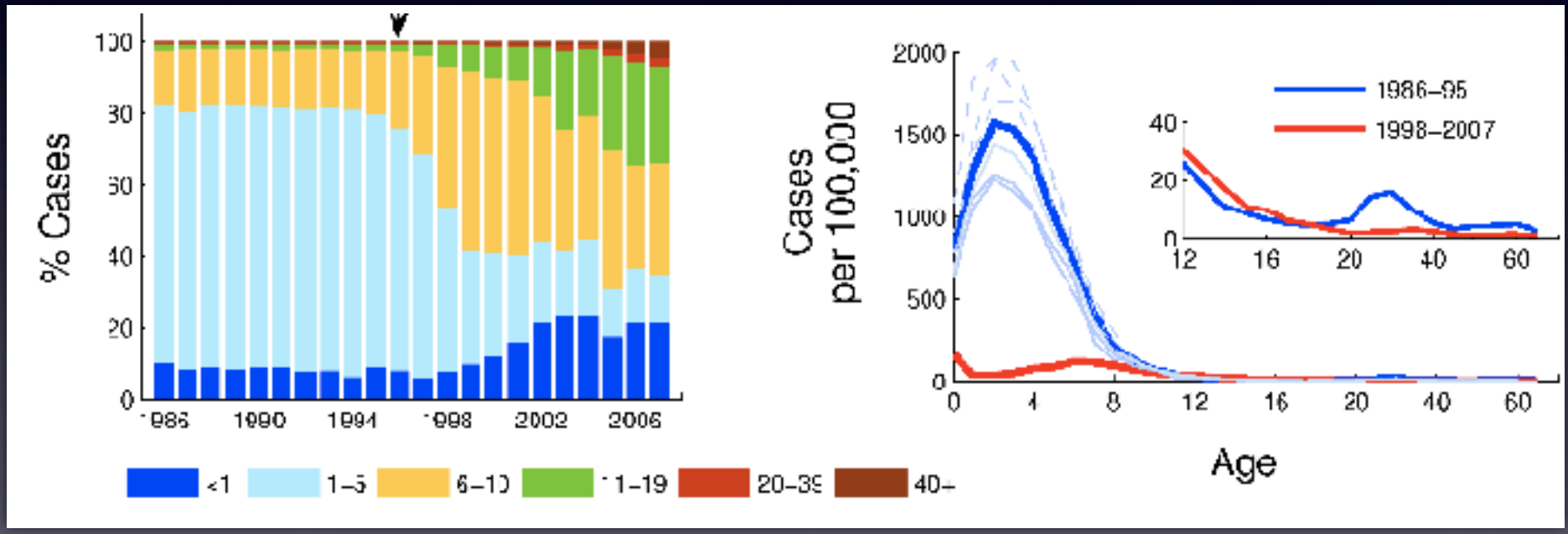
Social mixing data from urban & rural China







Age Structured Dynamics



Rohani, Zhong & King (2010) *Science*

Age-structured SEIR model

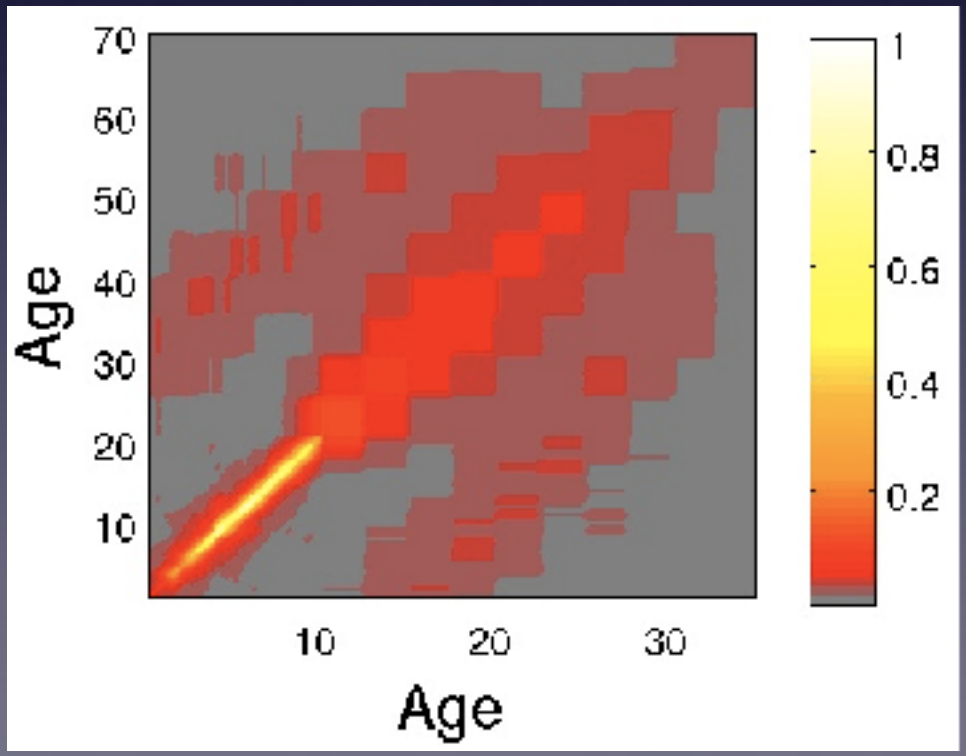
Model, simulated as time varying Markov Chain
Updating of age-classes occurs annually
0-19 one-year classes, and 20+

Age-specific transmission rate

Force of infection determine by:

- Contact structure ($c_{i\,j}$) -- from Mossong study
- Probability that contact is with infectious -- I_j/N_j
- Transmission probability, given contact -- q_i

$$\lambda_i = q_i \sum_j c_{ij} \frac{I_j}{N_j}$$



Age-Structured transmission: from data

- From age-specific incidence data, calculate age-specific force of infection
- That is, probability of infection while in age class i
- P(infection in age *i*) = 1 – exp(-$\lambda_i \Delta a_i$)

$$\lambda_i^d = -\frac{1}{\Delta a_i} \log\left(\frac{\sum_{j=i+1}^{n} D_j}{\sum_{j=i}^{n} D_j}\right)$$

Δa_i is width of class *i*

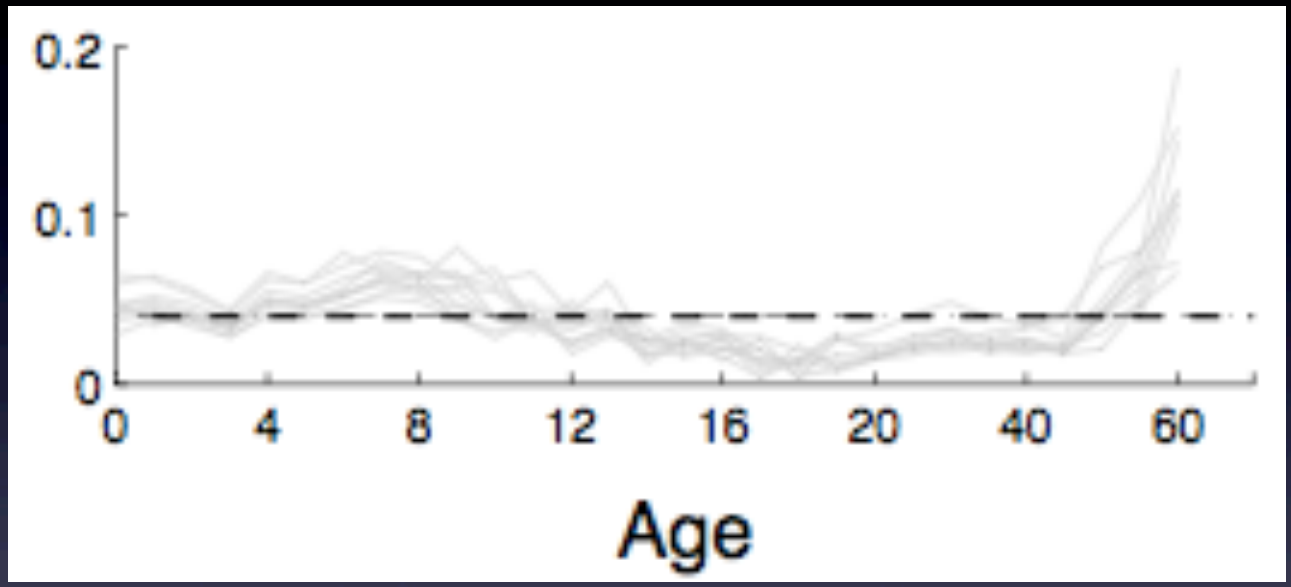
D_j is incidence data in class *j*

Age-Structured transmission: from model

- If we know c_{ij} –rate of contacts between class *i* and class *j*– then
- K_i is risky contacts of class *i* = $\Sigma_j\ c_{ij}\ I_j/N_j$
- Thus, force of infection is
  - $\lambda_i = q\ K_i$

- q is probability of infection given contact
- So, $q = K_i/\lambda^{d_i}$

Estimating *q*



Fluctuations likely due to age-specific biases in contact data and age-specific variation in detectability, susceptibility, and nature of contacts as related to transmission

Assume *q* constant to assay role of age-specific contacts in transmission

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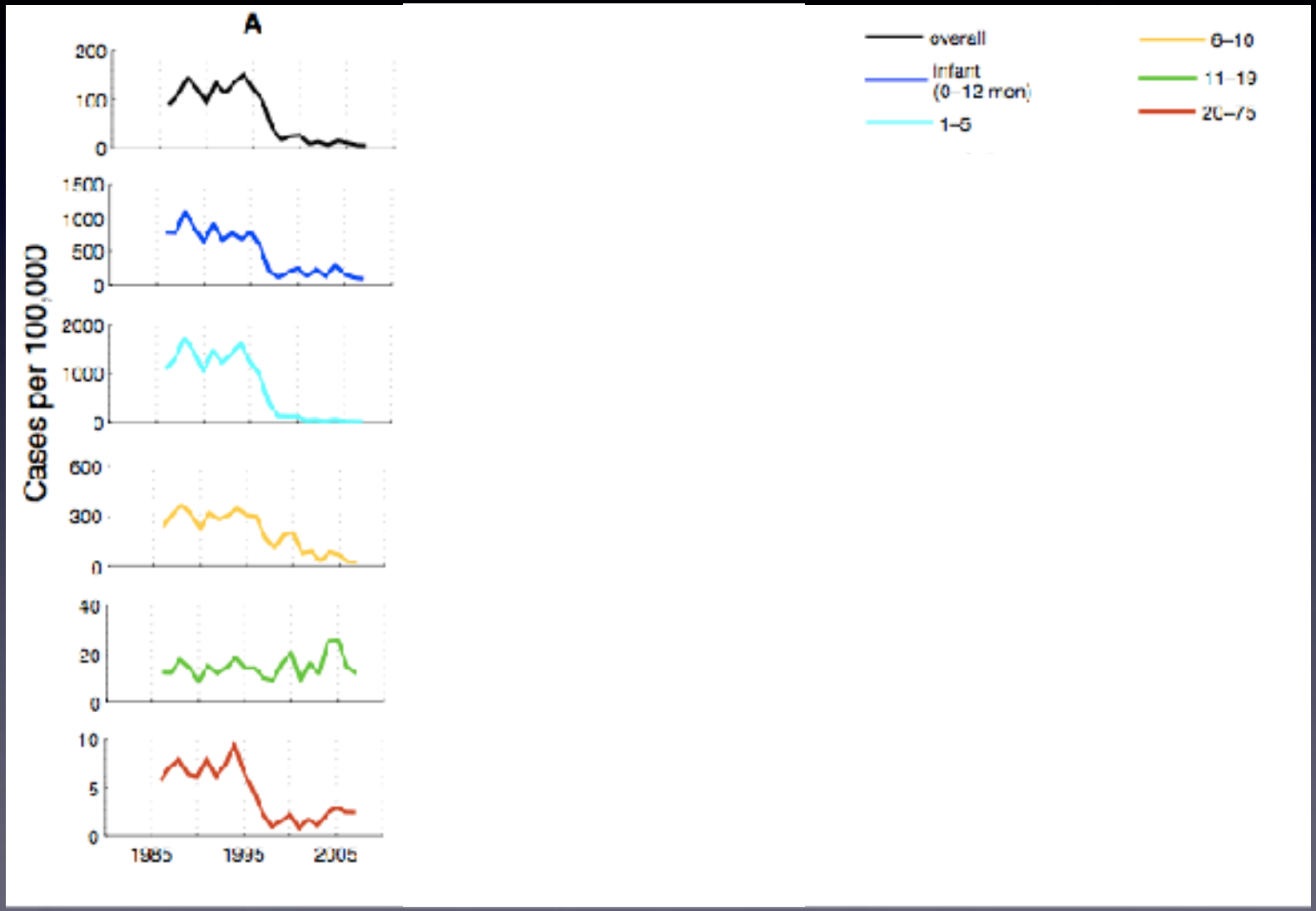
Can use data to

- determine transmission probability, given contact -- q_i
- validate model

Model-data comparison



Does the Contact Matrix Matter?