Imperial College London

Modelling heterogeneities in risk

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Heterogeneity in transmission

Transmission of infectious agents can be influenced by many types of heterogeneity:

- Demographic (e.g. age structure)
- Behavioural
- Genetic
- Spatial

Why is it important to include heterogeneity in a model?

- Heterogeneity in risk alters the chances of invasion and persistence of an infection.
- Altered risks of disease on infection (e.g. rubella).
- Can be considered in design of interventions i.e. *targeting* specific groups.

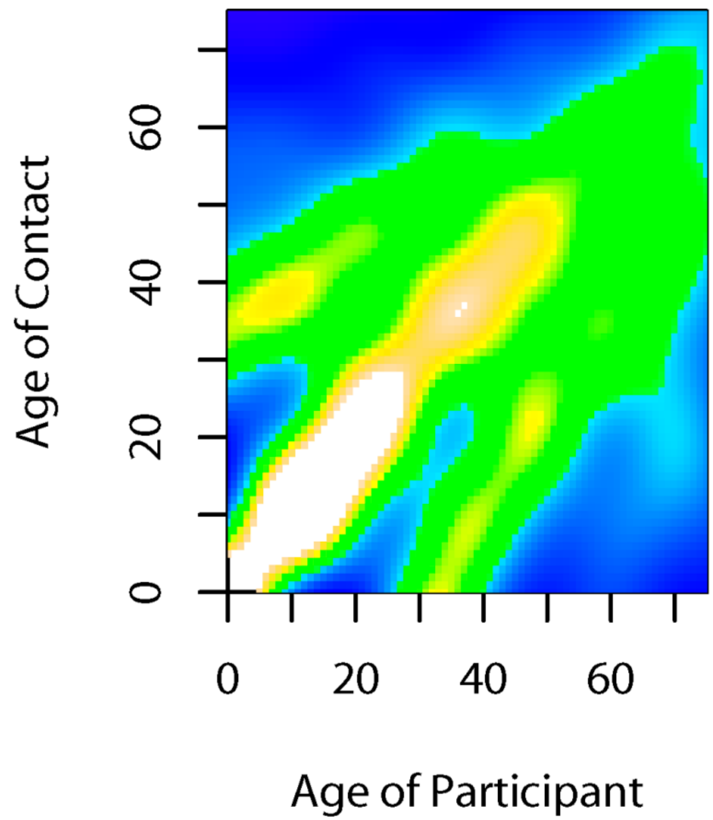
Lecture outline

- Age structure for childhood infections
- Behavioural risk structure for sexually transmitted infections
  - Heterogeneity in behaviour
  - Mixing matrices
  - Influence on transmission
  - Implications for interventions
- A framework for representing heterogeneity in risk behaviour and mixing in an STI model

Age structure

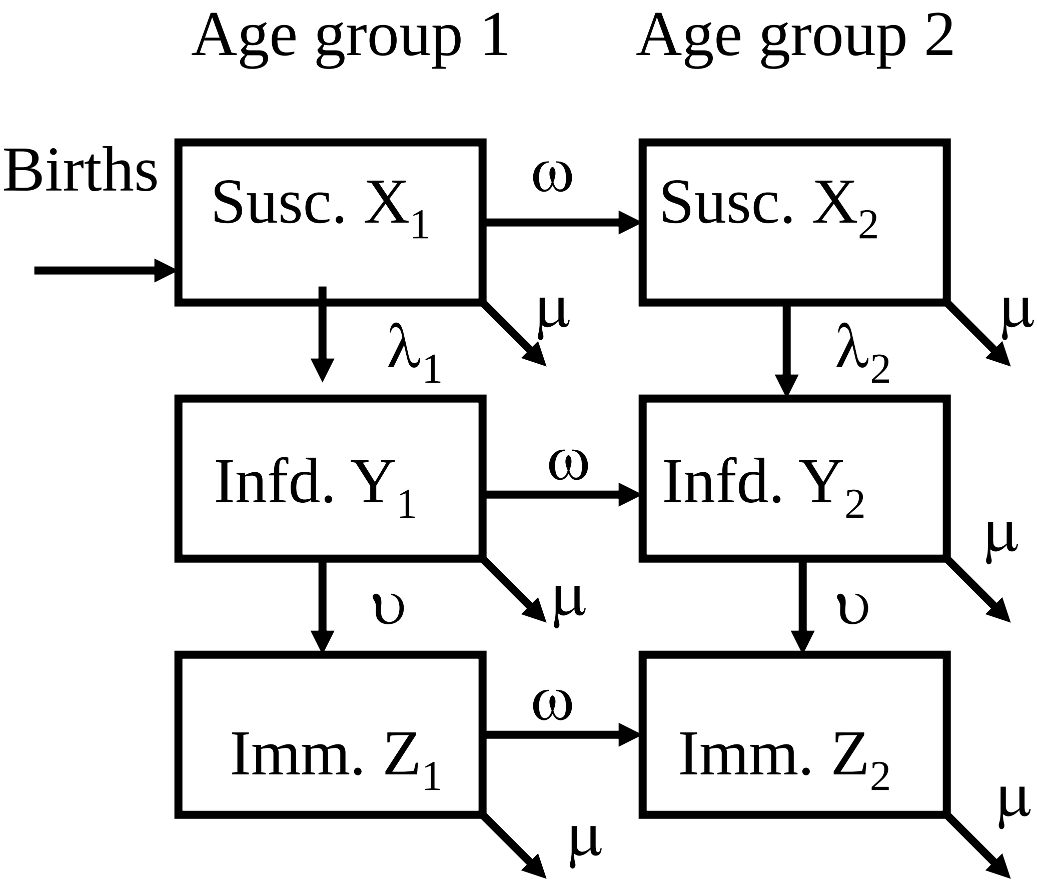
Why include age structure?

- Diseases with long-lasting immunity (e.g. measles, mumps, chickenpox) are often classically concentrated in childhood
- Assumption that people mix randomly is unrealistic
- Heterogeneity in symptom severity with age (e.g. whooping cough, influenza)
- Often interested in targeting interventions by age



Mossong J, Hens N, Jit M, Beutels P, et al. (2008) Social Contacts and Mixing Patterns Relevant to the Spread of Infectious Diseases. PLoS Med 5(3): e74. doi:10.1371/journal.pmed.0050074

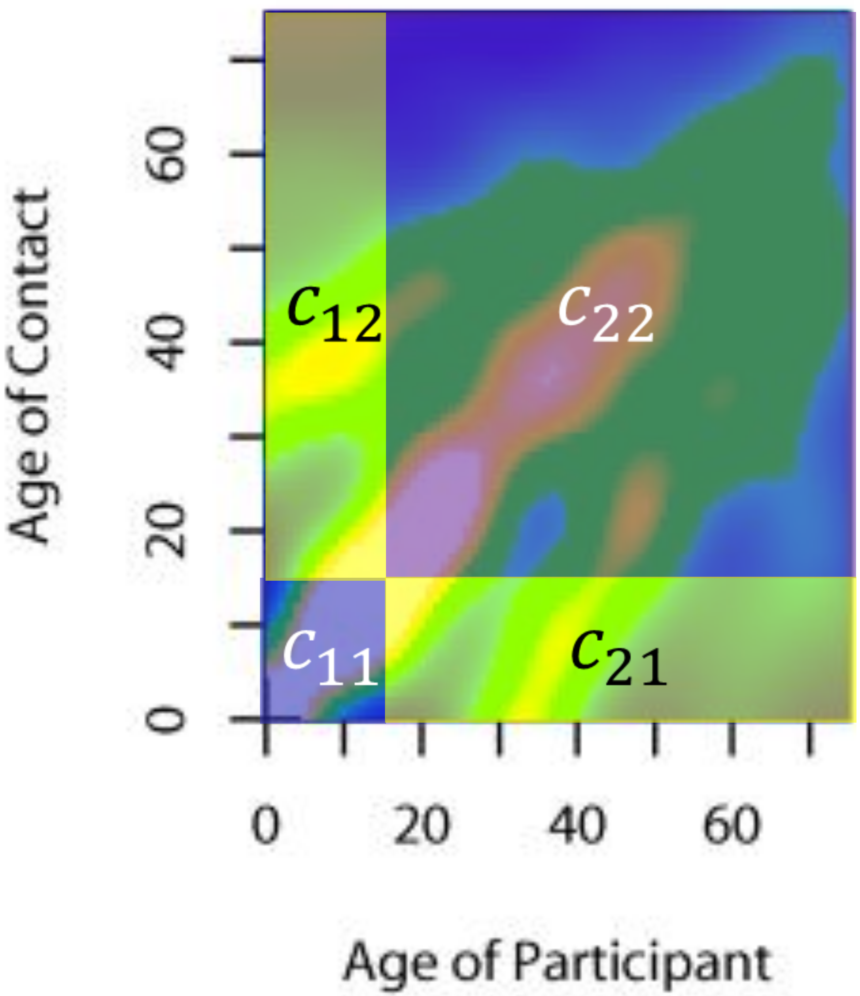
The Most Simple Way of Modelling Age-structure



$$\lambda_1 = \beta_{11} Y_1 + \beta_{12} Y_2$$
$$\lambda_2 = \beta_{21} Y_1 + \beta_{22} Y_2$$

β_{ij} = rate susceptible individual in age group i infected by infectious individual in age group j

Parameterising age-structure



β_{ij} will depend upon underlying contact structure c_{ij} within the population.

If all contacts have same risk of transmission:

$$\lambda_1 = \beta c_{11} Y_1 + \beta c_{12} Y_2$$

$$\lambda_2 = \beta c_{21} Y_1 + \beta c_{22} Y_2$$

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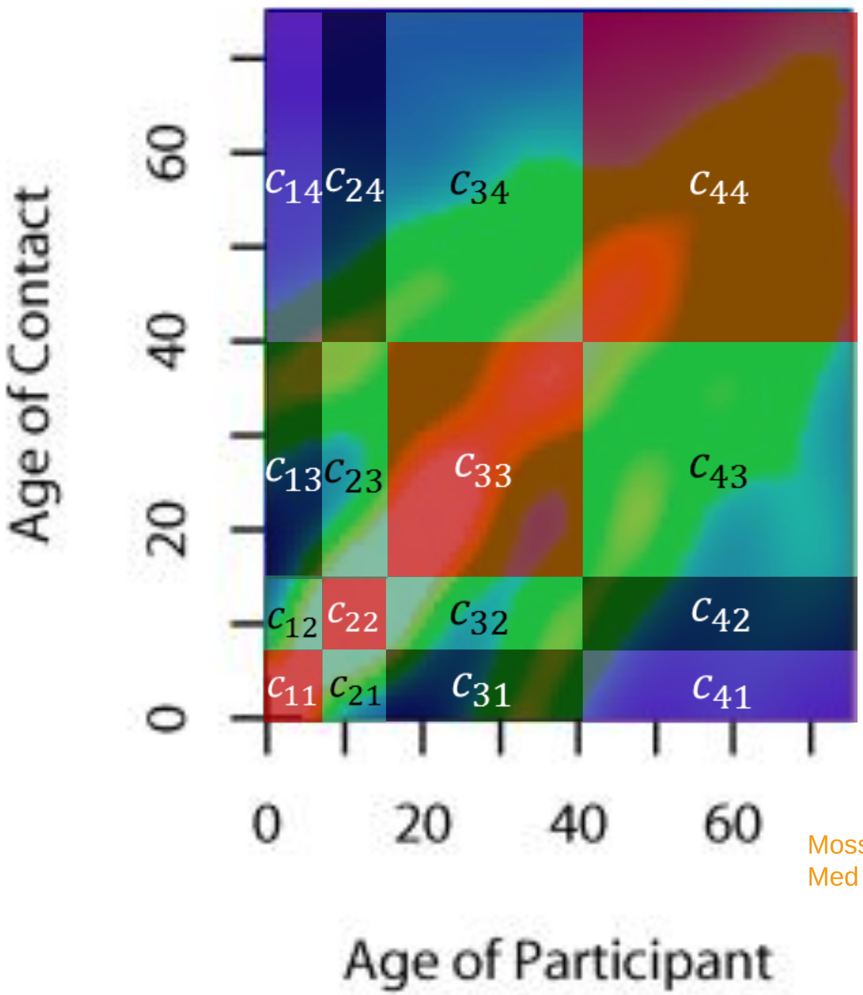

$$\lambda_i = \sum_{j=1}^{n} \beta c_{ij} Y_j$$

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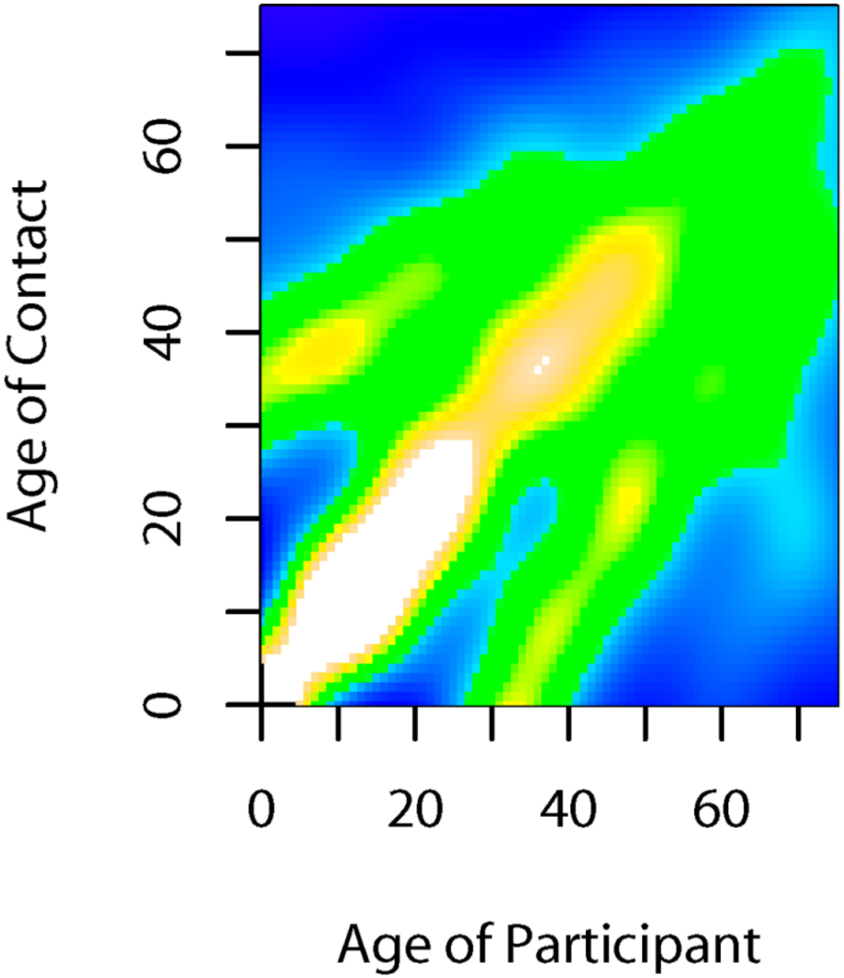
Choice of age categories should depend on underlying contact structure and epidemiology of the disease but often a function of data availability

Simulating age-structure



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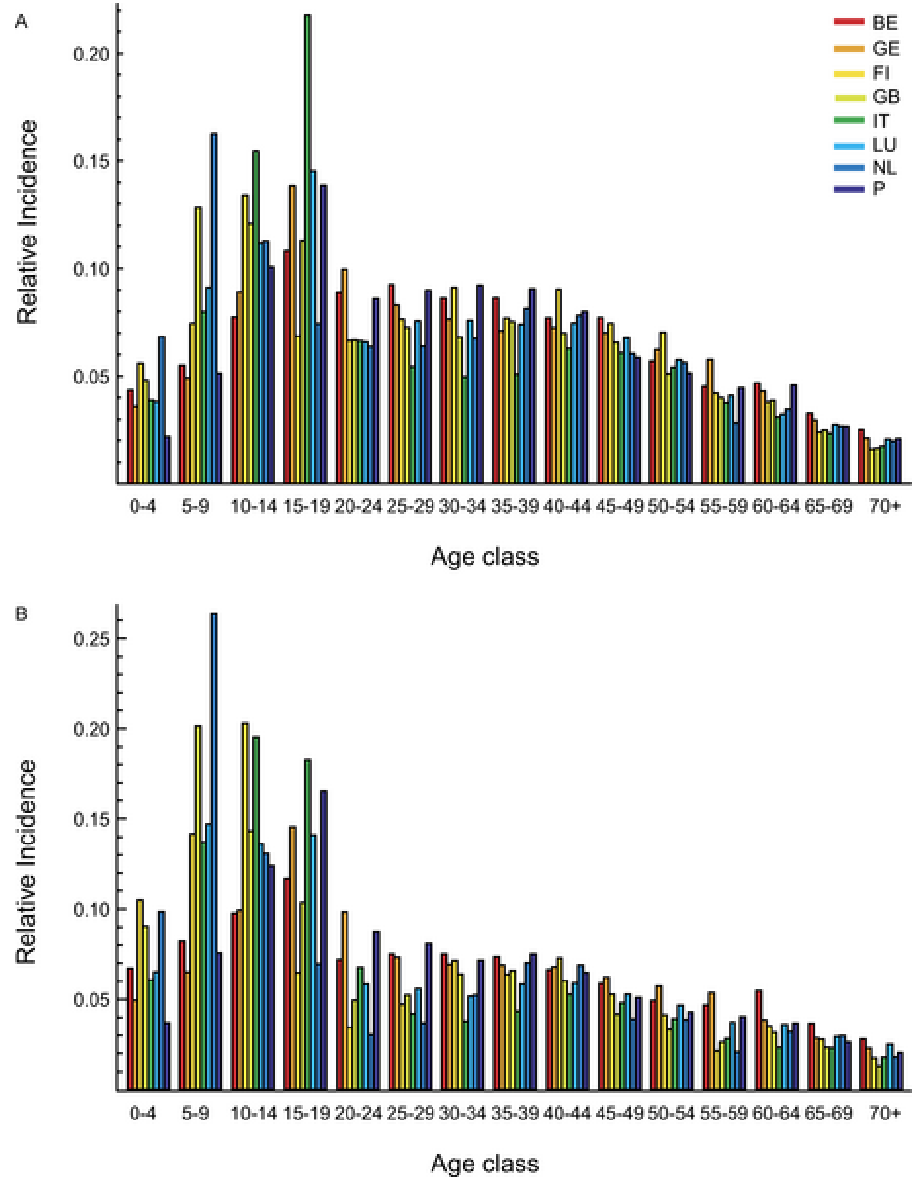
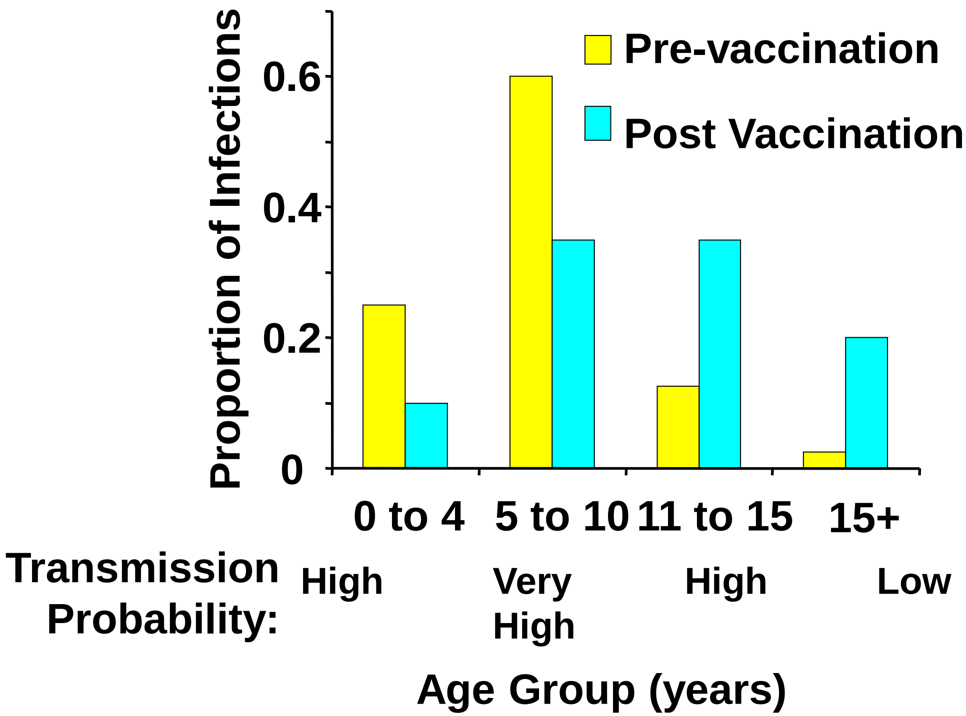
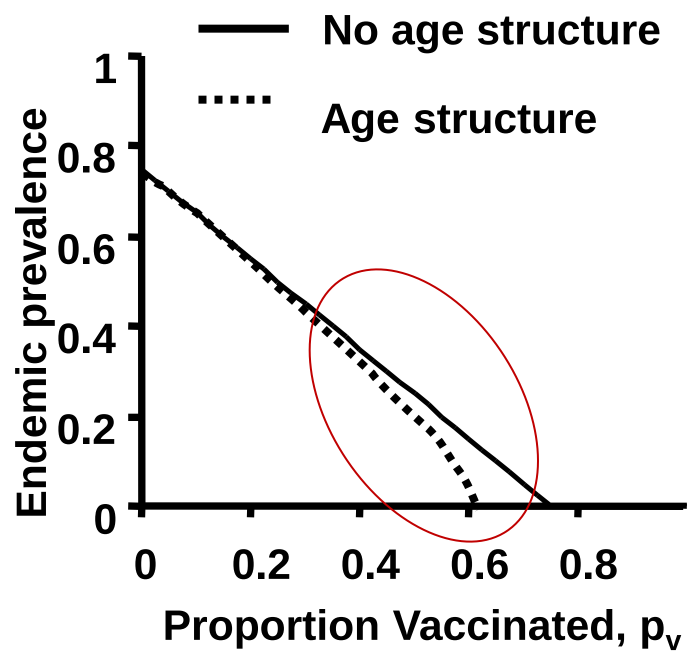


Results of an age structured model of a childhood infection

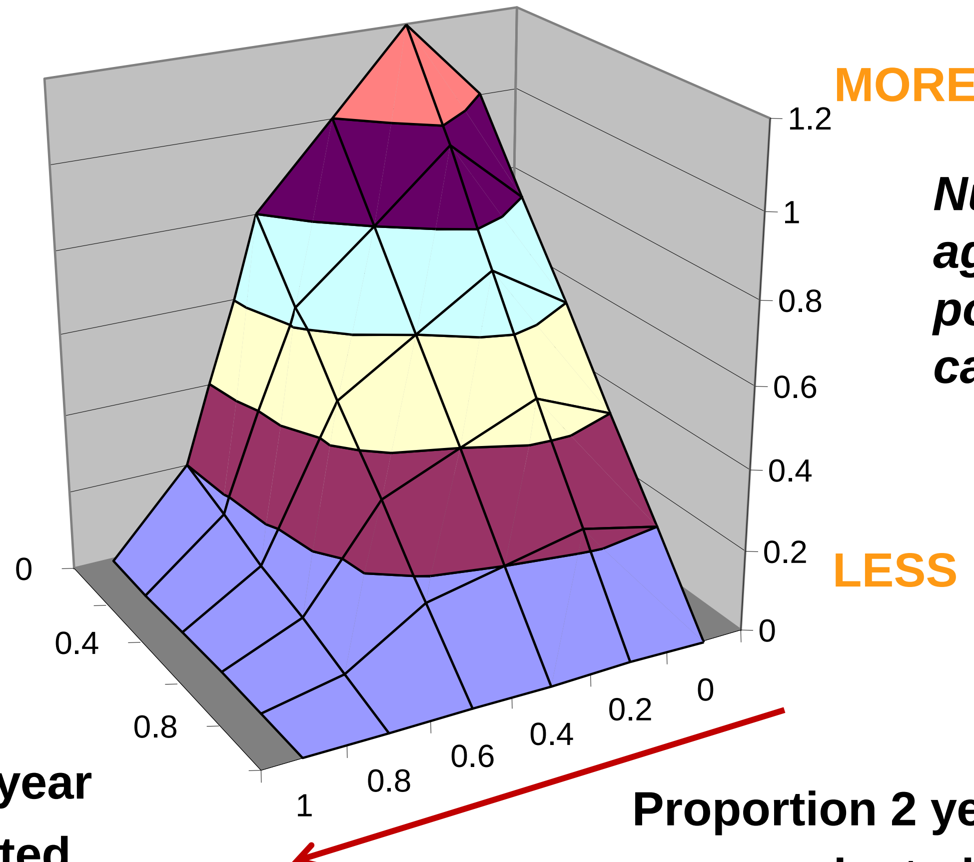
- **Vaccination increases the average age of newly infected people (lower rate of infection -> takes longer to get infected following birth)**
- **Age-structure captures the fact children are more infectious (will come into contact with more susceptible children than adults)**
- **Childhood vaccination at a given prevalence will be more effective in a model with age-structure.**





Rubella Vaccination:

Congenital rubella syndrome -- risk of severe birth abnormalities.



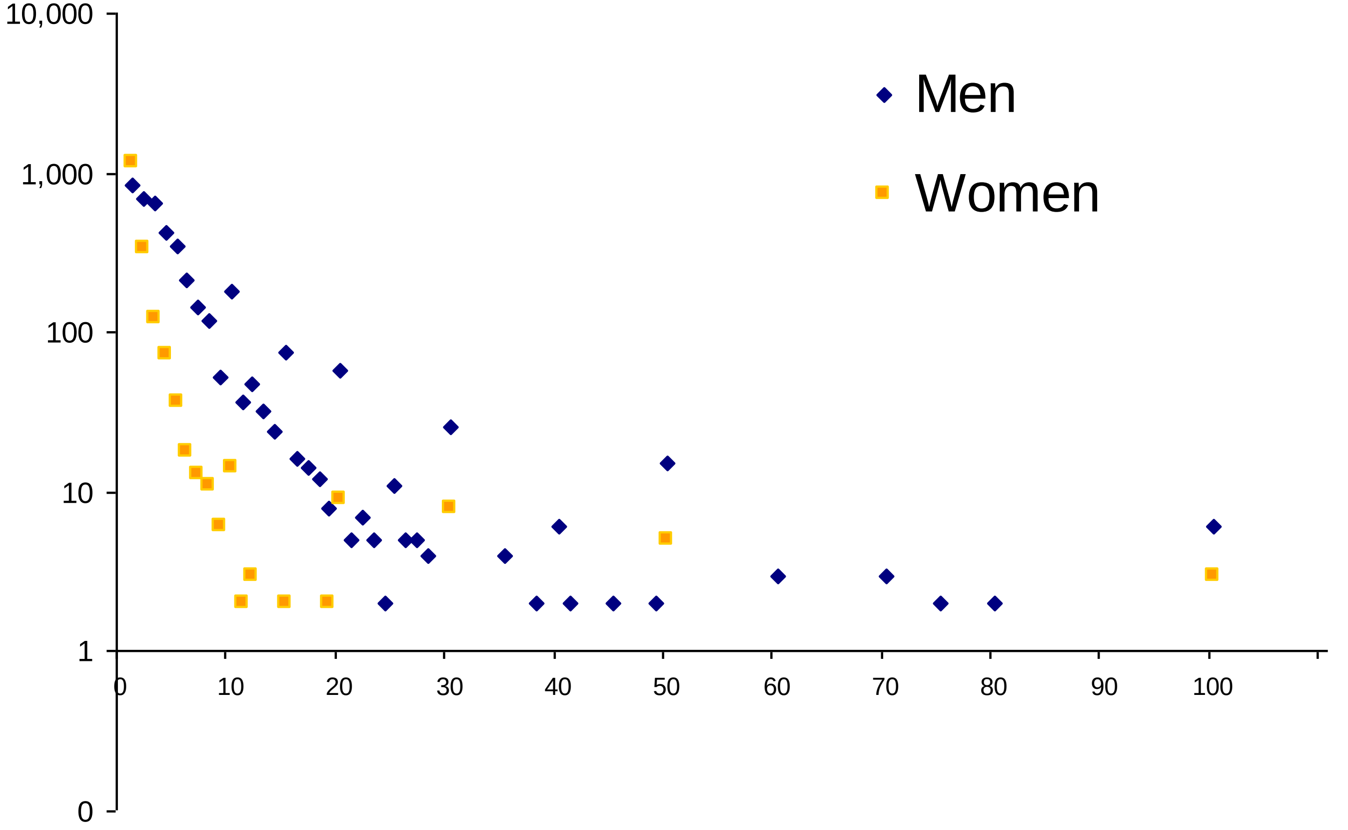
Number of cases in ages 16 to 40 years post vaccination: cases pre vaccination

Proportion 12 year girls vaccinated

Proportion 2 year olds vaccinated

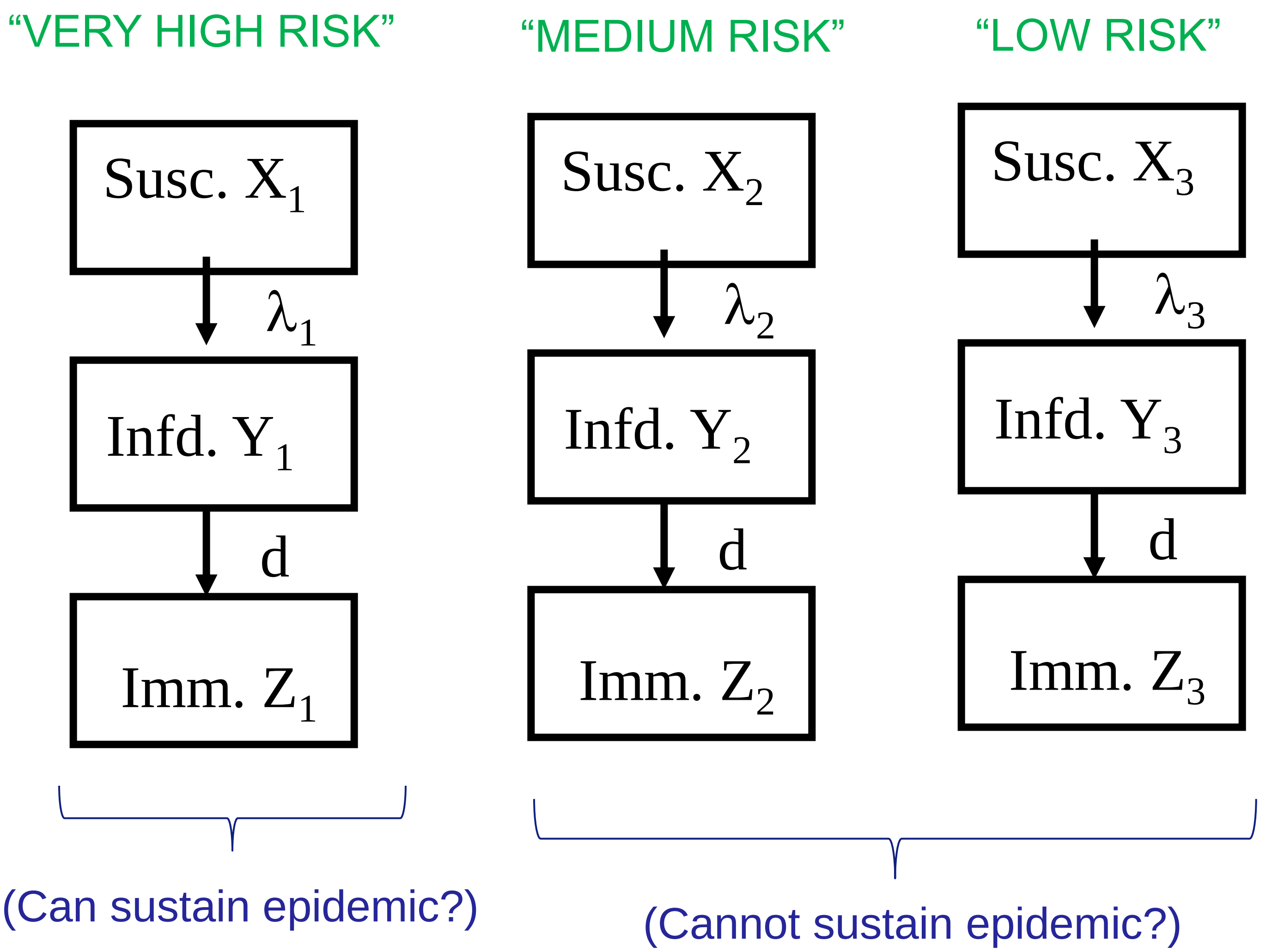
Sexual risk structure

Behavioural heterogeneity



Lifetime **non-regular** partners, Manicaland, Zimbabwe 2003/05

Stratification according to risk group



Mixing between different risk groups

- Unstructured models: single contact rate
- Structured models: matrix of contact rates
  “mixing matrix”

Mixing matrix

- Cross tabulate of contact rates $c_{i,j}$ according to characteristic of a respondent and their partners

Partner types (columns); Respondent types (rows)

	1	…	n	Total
1	$c_{1,1}$	$c_{1,\ldots}$	$c_{1,n}$	C_1
…	$c_{\ldots,1}$	$c_{\ldots,\ldots}$	$c_{\ldots,n}$	$C_{\ldots}$
n	$c_{n,1}$	$c_{n,\ldots}$	$c_{n,n}$	C_n

$$\lambda_i = \sum_{j=1}^{n} \beta c_{ij} Y_j$$

- Often easier to “normalise” these rates to give table of probabilities: $\rho_{i,j} = c_{i,j}/C_i$

Partner types (columns); Respondent types (rows)

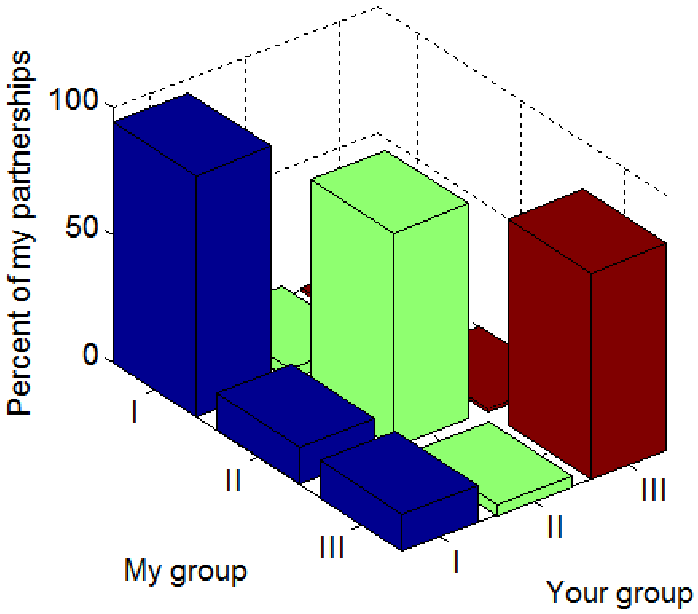
	1	…	n	Total
1	$\rho_{1,1}$	$\rho_{1,\ldots}$	$\rho_{1,n}$	C_1
…	$\rho_{\ldots,1}$	$\rho_{\ldots,\ldots}$	$\rho_{\ldots,n}$	$C_{\ldots}$
n	$\rho_{n,1}$	$\rho_{n,\ldots}$	$\rho_{n,n}$	C_n

$$\lambda_i = \sum_{j=1}^{n} \beta C_i \rho_{ij} Y_j$$

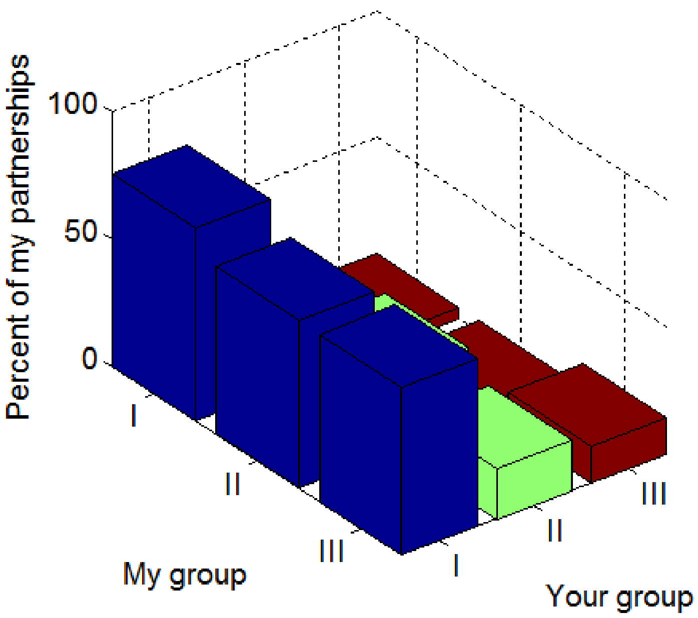
Mixing patterns

- Random
- Assortative ("like-with-like")
- Dissassortative (opposites attract!)

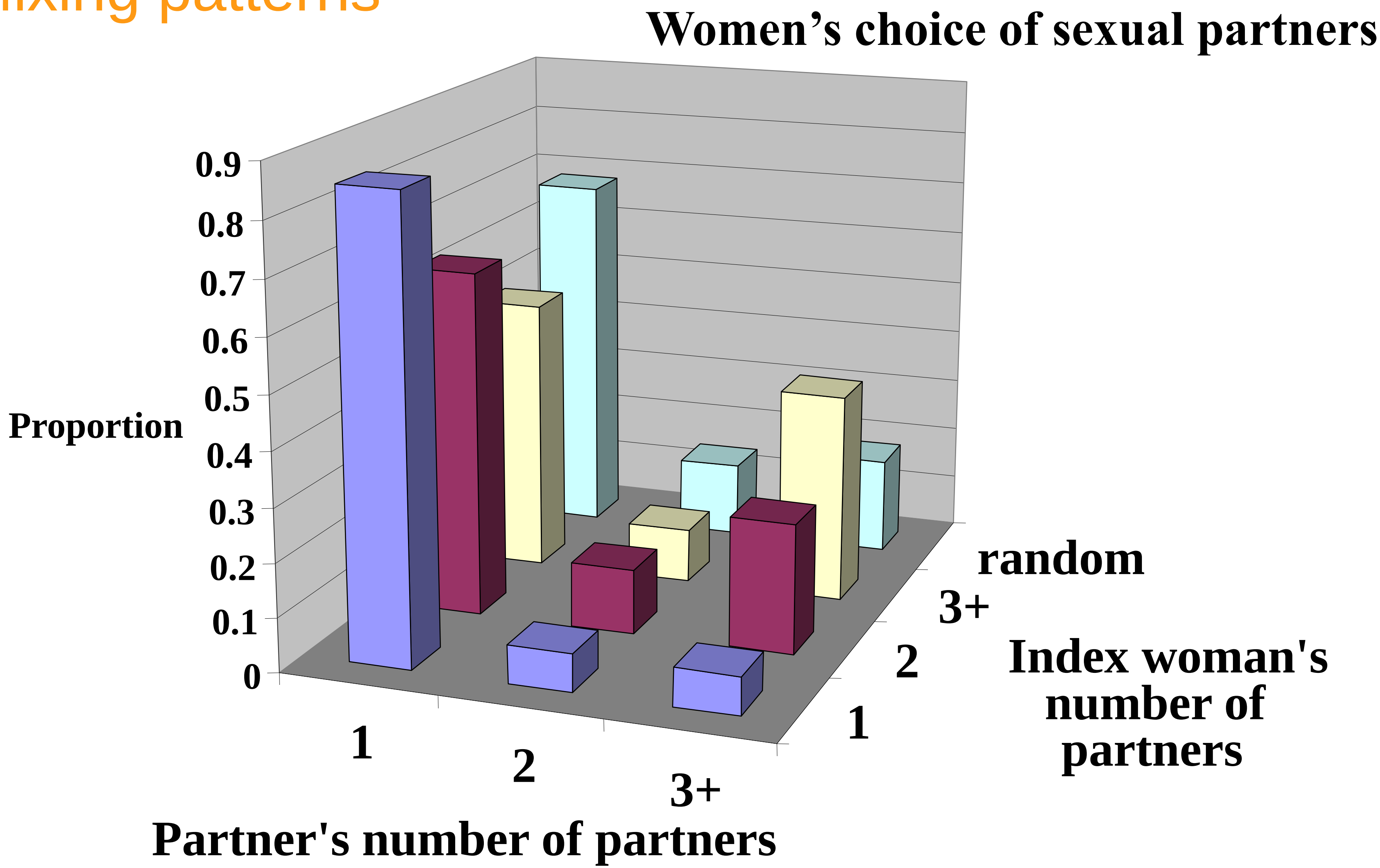
More Assortative



More Random

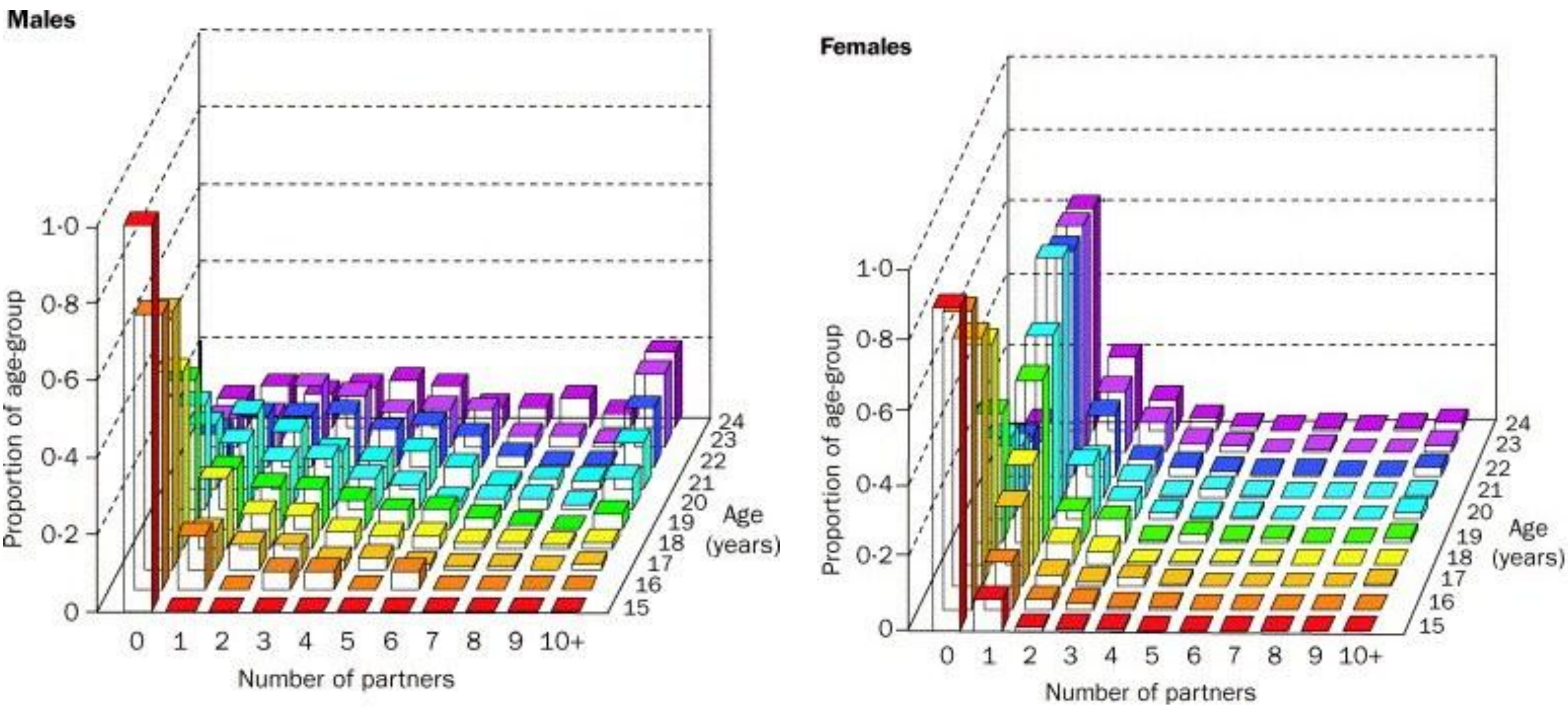


Mixing patterns



Harborview STD Clinic Seattle
Garnett et al. 1996

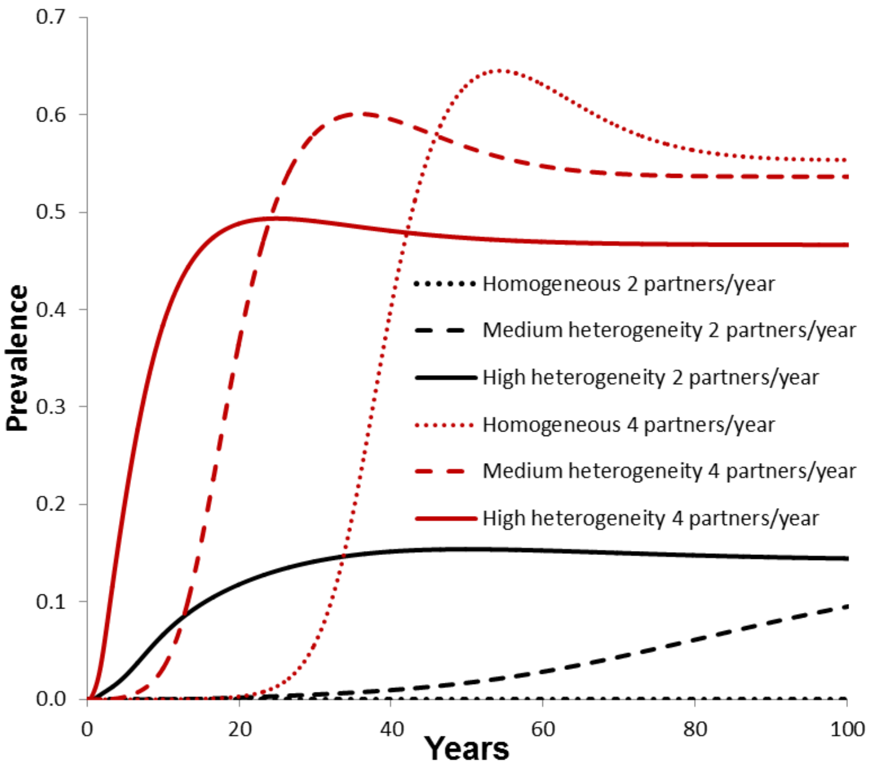
Mixing patterns (sex, risk and age)

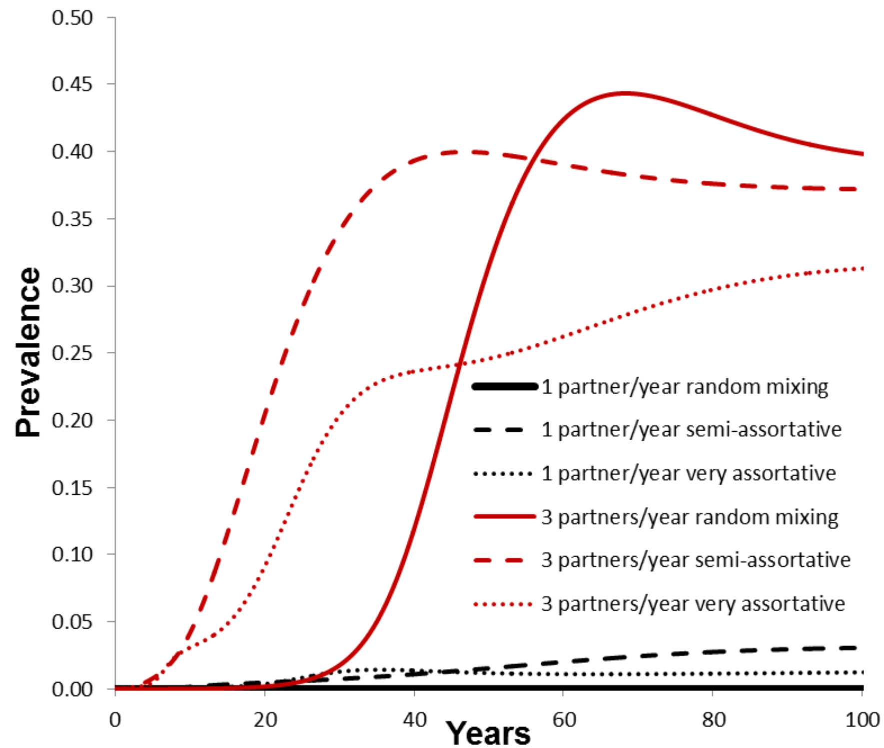


Manicaland population-based cohort study, Zimbabwe
Gregson et. al., Lancet, 2002

Impact of heterogeneity upon transmission dynamics

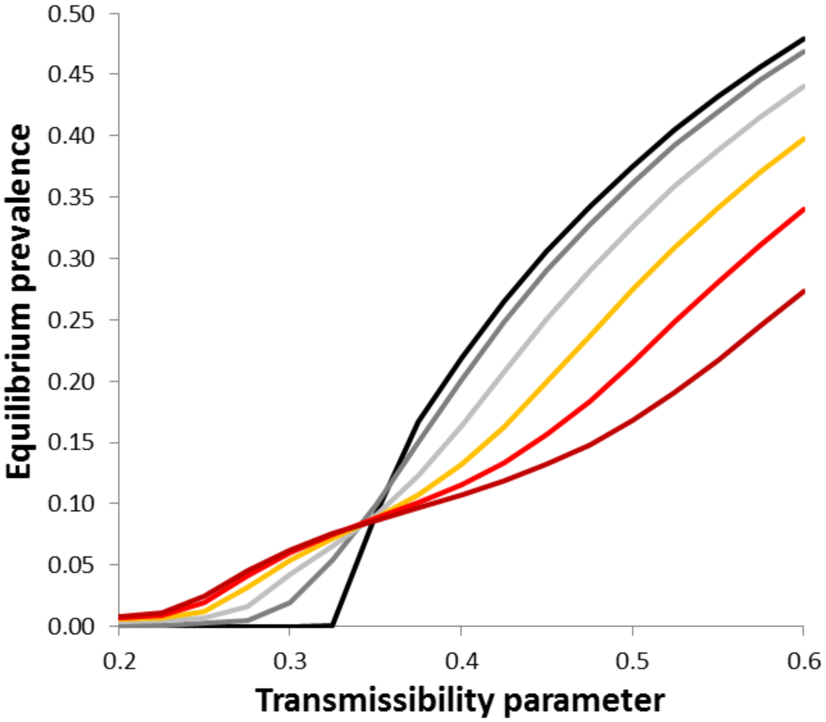
Heterogeneity in transmission influences natural dynamics of an epidemic





Influence of heterogeneity on transmission

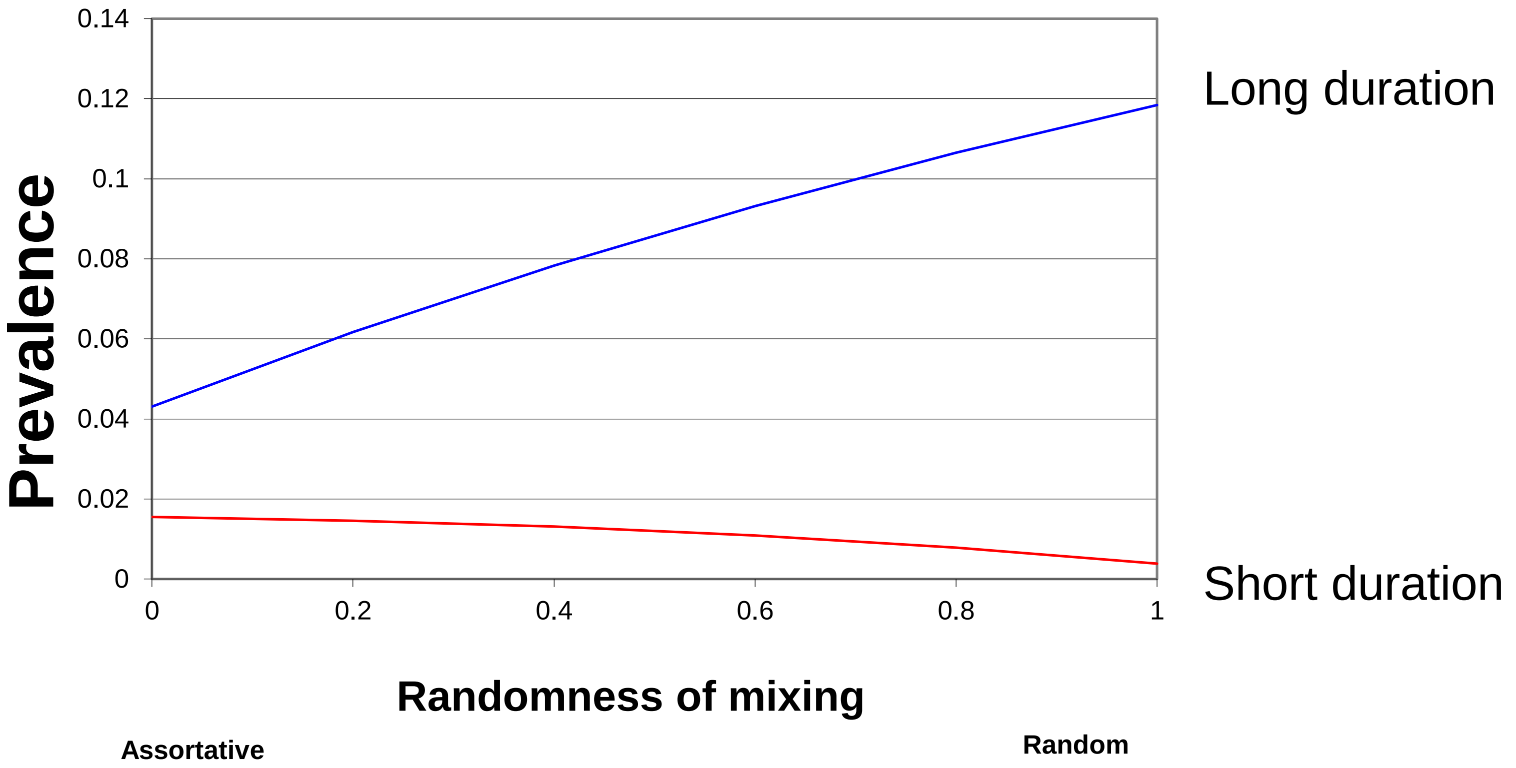
The impact of mixing and biology on endemic prevalence
(<u>mean rate of partner change = 2</u>)



No Variation

Lots of Heterogeneity

Influence of heterogeneity on transmission



Implications for interventions

Interventions in Different Contexts

A simple example: “Universal Test and Treat intervention” in two populations:

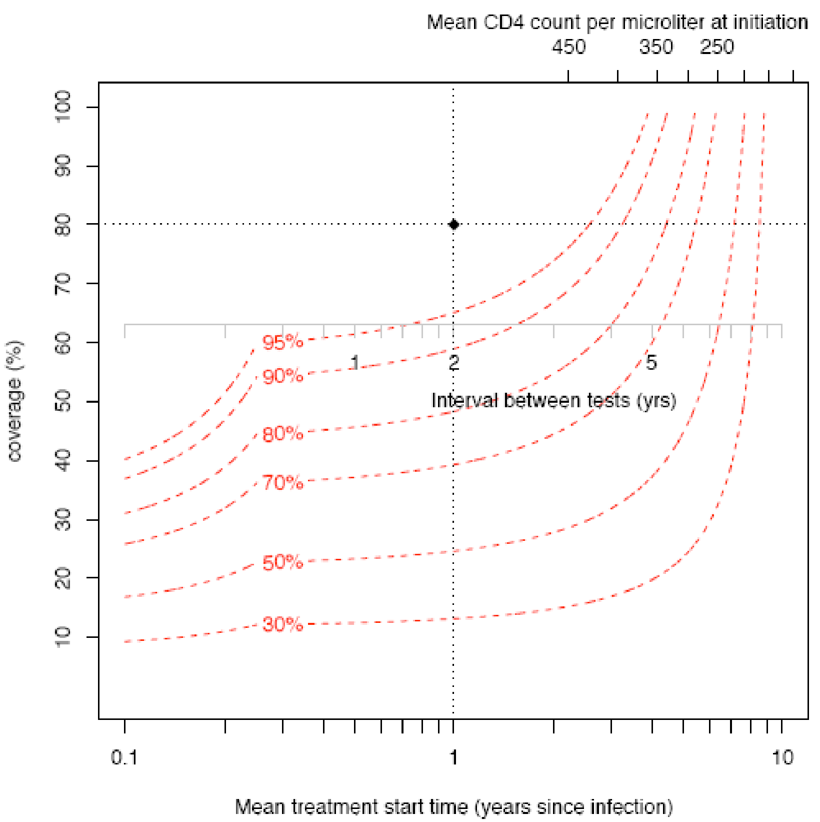
1. Population with little variation in risk and random mixing.

2. Population with strong variation in risk and partly restricted mixing

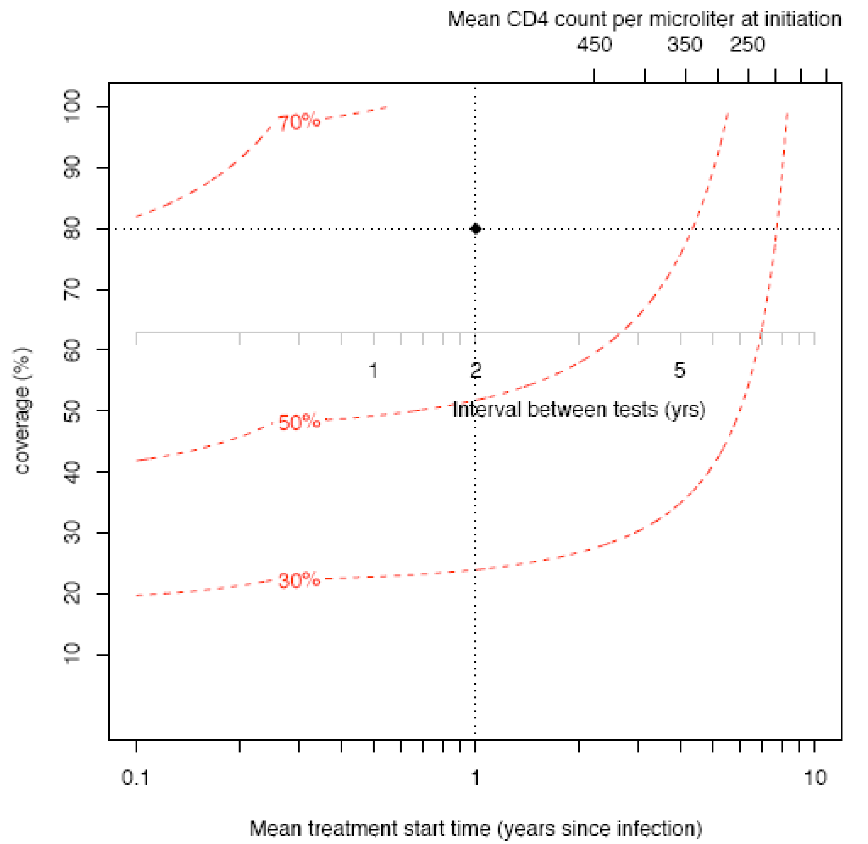
Universal test and treat intervention:

1. Population with little variation in risk and random mixing.

2. Population with strong variation in risk and partly restricted mixing



(a)

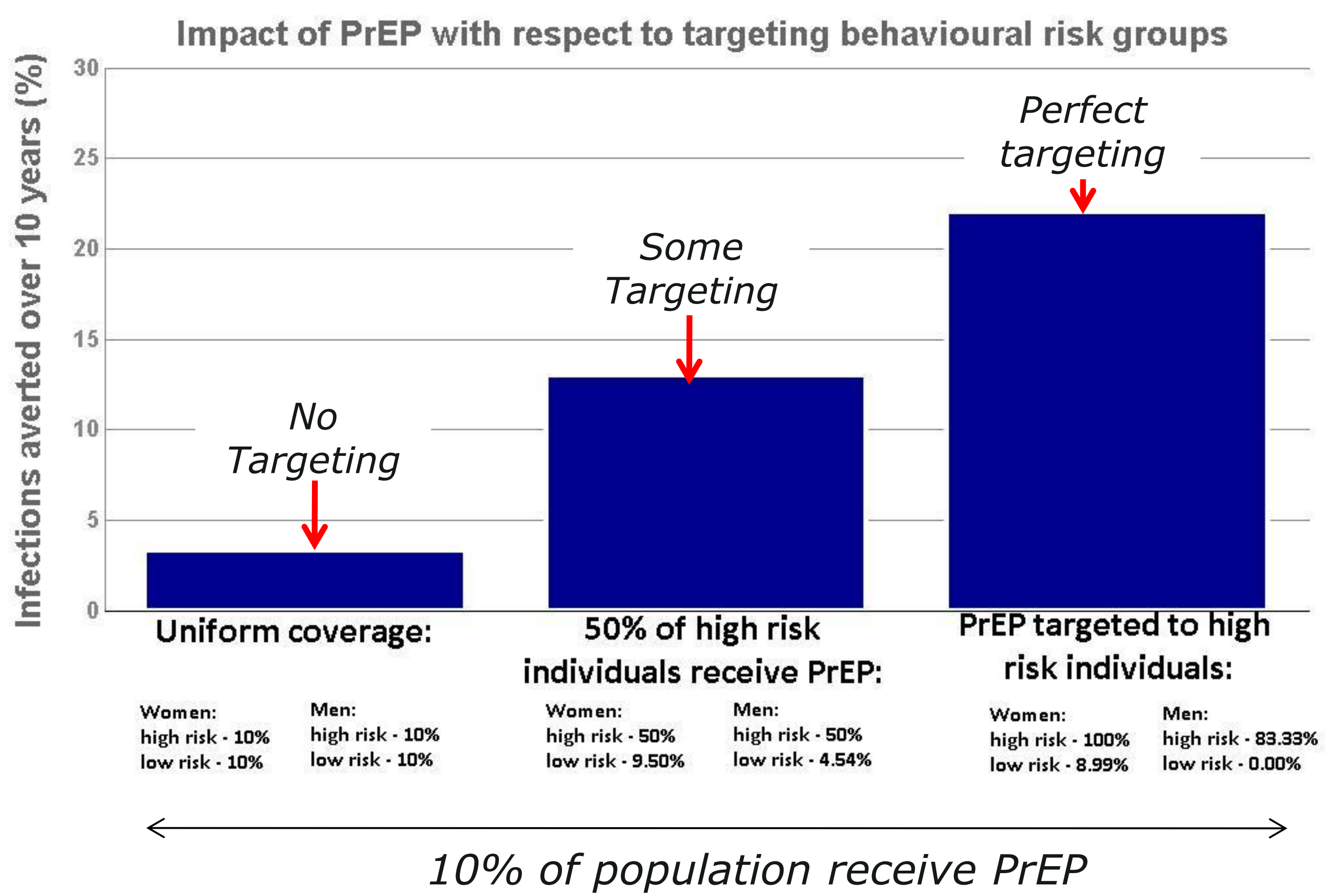


(c)

(dots shows same intervention – 80% coverage of ART initiation within 1 year of infection)
Lines show iso-clines in reduction in incidence in these populations.

Pre-Exposure Prophylaxis: effective targeting within a population

For the <u>same</u> number of pills, effective targeting to those at most risk can substantially amplify impact.



Conclusions

- Heterogeneities in transmission can be efficiently incorporated into mathematical models by stratification using different indices of risk and defining a mixing (or who acquires infection from whom –WAIFW) matrix.

- Allow us to capture important aspects of transmission and to investigate targeted interventions.

- Age-dependence is particularly important for:
  - Highly transmissible diseases leading to immunity
  - Planning childhood vaccination campaigns
  - When symptoms depend on age

- Heterogeneity in STI dynamics often described by defining compartments with different partner rates and the degree of assortative mixing between compartments

- In general heterogeneity can limit spread to general population but also makes diseases difficult to eradicate.

One Framework For Representing Heterogeneity in Risk Behaviour and Mixing in an STI model

M_{HIGH}

$N_{M\text{-}HIGH}$ 25% of men

$C_{M\text{-}HIGH}$ average 3 partners/year

M_{LOW}

$N_{M\text{-}LOW}$ 75% of men

$C_{M\text{-}LOW}$ Average 1 partners/year

W_{HIGH}

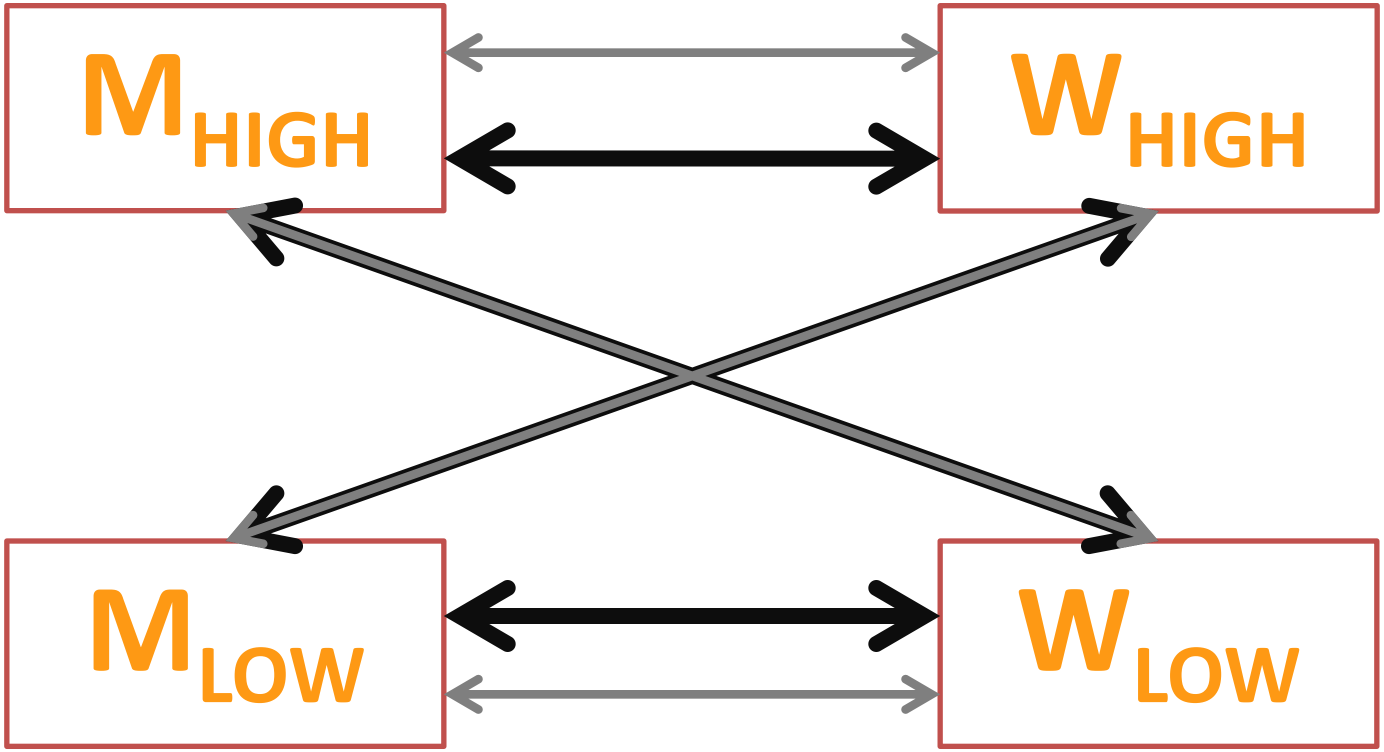
$N_{W\text{-}HIGH}$ 5% of women

$C_{W\text{-}HIGH}$ average 20 partners/year

W_{LOW}

$N_{W\text{-}LOW}$ 95% of women

$C_{W\text{-}LOW}$ Average 0.53 partners/year



1. Only W-HIGH (“assortative”)

2. Only W-LOW   (“disassortative”)

3. Mixture
   - Random mixture
   - <u>*A bit random and a bit assortative.*</u>

$$\rho^{MEN}{}_{i,j}$$

“Proportion of high risk male partnerships that are with high risk women”	***Potential partners***	
	“j=1” W_{HIGH}	“j=2” W_{LOW}
(M_{HIGH}) “i=1”	$\rho_{1,1}$	$\rho_{1,2}$
(M_{LOW}) “i=2”	$\rho_{2,1}$	$\rho_{2,2}$

$\rho_{1,1} + \rho_{1,2} = 1$

$\rho_{2,1} + \rho_{2.2} = 1$

IF RANDOM...

	Potential partners	
	W_{HIGH}	W_{LOW}
M_{HIGH}	% of partnerships offered by W_{HIGH}	% of partnerships offered by W_{LOW}

$$\frac{\text{Partnerships offered by } W_{HIGH}}{\text{All available partnerships}} = \frac{c_{W\text{-}H}.N_{W\text{-}H}}{c_{W\text{-}H}.\ N_{W\text{-}H} + c_{W\text{-}L}.\ N_{W\text{-}L}}$$

$$\frac{\text{Partnerships offered by } W_{LOW}}{\text{All available partnerships}} = \frac{c_{W\text{-}L}.N_{W\text{-}L}}{c_{W\text{-}H}.\ N_{W\text{-}H} + c_{W\text{-}L}.\ N_{W\text{-}L}}$$

IF RANDOM...

	Potential partners	
	W_{HIGH}	W_{LOW}
M_{LOW}	% of partnerships offered by W_{HIGH}	% of partnerships offered by W_{LOW}

$$\frac{c_j N_j}{\sum_{\text{all j}} c_j N_j}$$

"j=1"

"j=2"

IF ASSORTATIVE...

	Potential partners	
	W_{HIGH} "j=1"	W_{LOW} "j=2"
(M_{HIGH}) "i=1"	1	0
(M_{low}) "i=2"	0	1

$$\delta_{i,j}$$

$$\delta_{i,j} = 1 \text{ if } i = j$$

$$\delta_{i,j} = 0 \text{ otherwise}$$

A MIXTURE...

ε is randomness
(ε = 1 for random; ε = 0 for assortative)

	Potential partners	
	W_{HIGH}	W_{LOW}
(M_{HIGH})	(1-ε)+ε.(% if random)	ε.(% if random)
(M_{LOW})	ε.(% if random)	(1-ε)+ε.(% if random)

Mathematical representation in model

$$\rho^{MEN}{}_{i,j} = (1-\varepsilon)\delta_{i,j} + \varepsilon\left(\frac{c_j N_j}{\sum_{\text{all j}} c_j N_j}\right)$$

$$\delta_{i,j} = 1 \text{ if } \mathrm{i} = \mathrm{j}$$

$$\delta_{i,j} = 0 \text{ otherwise}$$

Balancing sexual partnerships

Each partnership has to include exactly one man and one woman.

Number of partnerships by a particular type of man with each type of woman MUST equal the number of partnerships that those types of woman form with that particular type of man.

EXAMPLE: High-risk man and low-risk woman

Number of partnerships formed by men: $N_{M-HIGH}\, c_{M-HIGH}\, \rho^{MEN}{}_{1,2}$

Number of partnerships formed by women: $N_{W-LOW}\, c_{W-LOW}\, \rho^{WOMEN}{}_{2,1}$

Balancing sexual partnerships

$$N_{W-LOW} c_{W-LOW} \rho^{WOMEN}{}_{2,1} = N_{M-HIGH} c_{M-HIGH} \rho^{MEN}{}_{1,2}$$

$$\rho^{WOMEN}{}_{2,1} = \rho^{MEN}{}_{1,2} \left(\frac{c_{M-HIGH} N_{M-HIGH}}{c_{W-LOW} N_{W-LOW}} \right)$$

There are other ways…...

Recommended reading

- Heterogeneities in the transmission of infectious agents: Implications for the design of control programs. M.E.J. Woolhouse et. al. PNAS (1997) 94, 338-342.
- Chapter 3: Host heterogeneities. In “Modeling Infectious Diseases in Humans and Animals”. M.J. Keeling and P. Rohani. Princeton University Press (2008).
- Factors controlling the spread of HIV in heterosexual communities in developing countries: patterns of mixing between different age and sexual activity classes. G.P. Garnett and R.M. Anderson. Phil. Trans. R. Soc. Lond. B (1993) 342, 137-159.