11: Methods for incorporating non-random mixing into models

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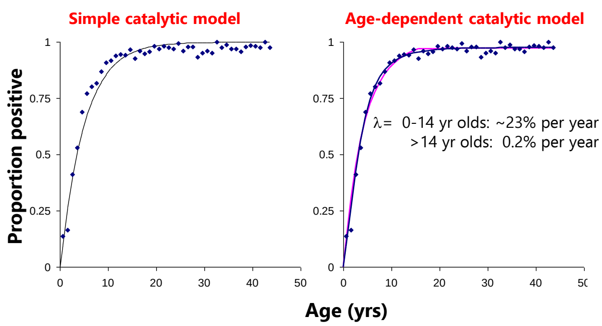
20 June 2018

Objectives

By the end of this session, you should:

- Be able to define and set up "Who Acquires Infection from Whom" (WAIFW) matrices
- Be able to use force of infection estimates to calculate WAIFW matrices
- Understand the impact of non-random (heterogeneous) mixing patterns between individuals on the transmission dynamics and control of infectious diseases (practical session)

Comparison between model fits to seroprevalence data of rubella in the UK (1980s)



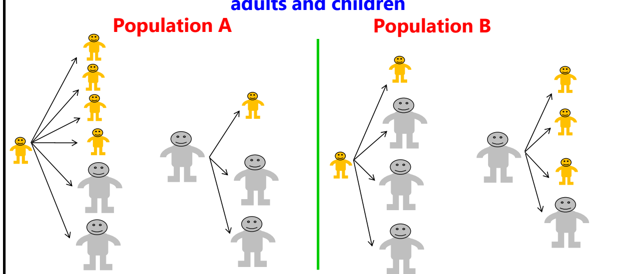
Possible explanations for heterogeneity in the force of infection

- Age-dependent mixing patterns
- Age-dependent differences in susceptibility
- Genetic differences in susceptibility/exposure
- High/low risk groups
- Different area / countries / towns
- In zoonoses: different species
- ...

In this lecture, we will focus on age-dependent mixing, but all the methods apply generally

Heterogeneity has important implications for designing control strategies, as we shall see.

Example: two hypothetical contact patterns between adults and children

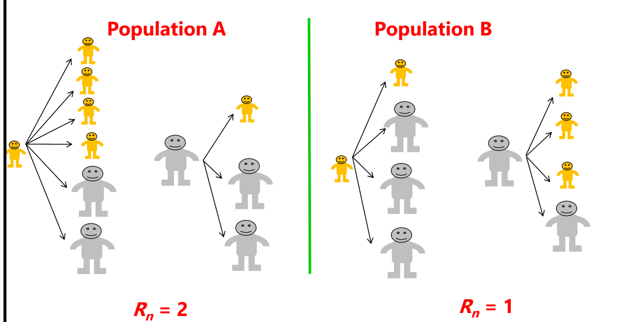


Suppose the same proportion of children are vaccinated against a new strain of pandemic influenza in both populations, no adults vaccinated.

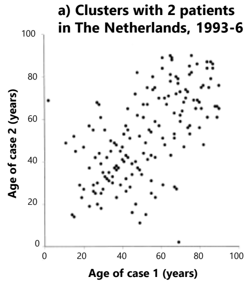
Q: In which population will the vaccine have a stronger effect?

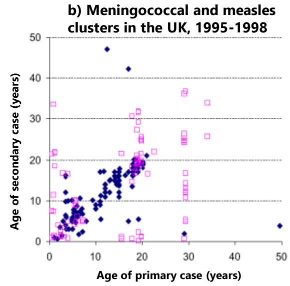
Answer: childhood vaccination most effective in population B

Think about what the net reproduction number would be if all children were to be vaccinated with a vaccine with 100% efficacy.



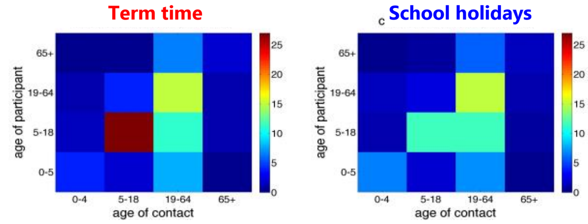
Evidence for an age-dependency in contact patterns: age of first and second cases in clusters





Source: Borgdorff et al (1999) and Edmunds et al (2006)

Evidence for an age-dependency in contact patterns: numbers of individuals contacted per day, UK



Source: Eames et al PLoS Comp Bio (2008)

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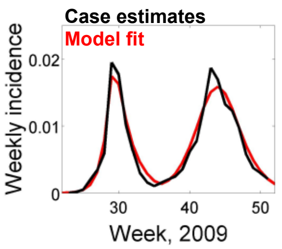
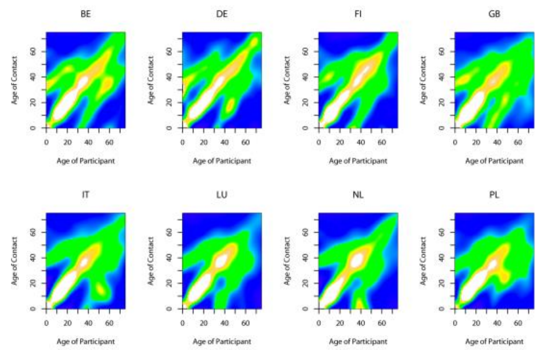
Evidence for an age-dependency in contact patterns: numbers of individuals contacted per day, UK



Source: Eames et al PLoS Comp Bio (2008)



Source: Mossong et al (2008)

The relationship between the force of infection, β, and the number of infectious persons for randomly-mixing populations (revision)

The force of infection at time t, $\lambda(t)$ is given by the equation:

$$\lambda(t) = \beta I(t)$$

- β is the rate at which 2 specific individuals come into effective contact per unit time;
- $I(t)$ is the number of infectious individuals at time t.

Calculating β for heterogeneously mixing populations

Example: population in which contact patterns of young individuals differ from those of the old

Split the force of infection in young individuals, $\overline{\lambda_y(t)}$, into two parts:

force of infection **attributable to contact with other young individuals** $\lambda_{yy}(t)$

+

force of infection **attributable to contact with old individuals** $\lambda_{yo}(t)$

i.e.

$$\overline{\lambda_y(t)} = \lambda_{yy}(t) + \lambda_{yo}(t)$$

Similarly, stratify the force of infection in old individuals, $\overline{\lambda_o(t)}$ into:

force of infection **attributable to contact with the young** $\lambda_{oy}(t)$

+

force of infection **attributable to contact with old individuals** $\lambda_{oo}(t)$

i.e. $$\overline{\lambda_o(t)} = \lambda_{oy}(t) + \lambda_{oo}(t)$$

Can be expressed in terms of the number of young and old infectious people

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Deriving expressions for λ_{yy}, λ_{yo}, λ_{oy}, λ_{oo}

Recall that for **randomly-mixing populations** $\lambda(t)=\beta I(t)$

Using the same reasoning, $\lambda_{yy}(t)=\beta_{yy}I_y(t)$ where

β_{yy} = rate at which a specific young individual comes into effective contact with a specific young individual per unit time

$I_y(t)$ = number of infectious young individuals in the population

Similarly $\lambda_{yo}(t)=\beta_{yo}I_o(t)$ where

β_{yo} = rate at which a specific young individual comes into effective with a specific old individual per unit time

$I_o(t)$ = number of infectious old individuals in the population

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A note on notation

β_{yo}

Denotes category of the susceptible person (or the recipient of the infection)

Denotes category of the infectious person

Therefore:

β_{yo} = rate at which a specific young (susceptible) individual comes into effective with a specific old (infectious) individual per unit time

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Deriving expressions for force of infection

We return to the expression $\overline{\lambda_y(t)} = \lambda_{yy}(t) + \lambda_{yo}(t)$

and substitute in $\lambda_{yy}(t)=\beta_{yy}I_y(t)$ and $\lambda_{yo}(t)=\beta_{yo}I_o(t)$ to get

$$\overline{\lambda_y(t)} = \beta_{yy}I_y(t) + \beta_{yo}I_o(t)$$

Similar reasoning gives:

$$\overline{\lambda_o(t)} = \beta_{oy}I_y(t) + \beta_{oo}I_o(t)$$

We can summarize these two equations using matrix notation

What are matrices?

- Matrices are useful ways to arrange sets of numbers.
- They let us summarise systems of equations that have to be satisfied simultaneously:

$5x+3y=6$

$3x+4y=3$

is equivalent to $$\begin{pmatrix} 5 & 3 \\ 3 & 4 \end{pmatrix}\begin{pmatrix} x \\ y \end{pmatrix} = \begin{pmatrix} 6 \\ 3 \end{pmatrix}$$

Coefficients of x and y in the equations

$4x+8y+3z=18$

$2x+y+5z=12$

$x+3y+8z=4$

is equivalent to $$\begin{pmatrix} 4 & 8 & 3 \\ 2 & 1 & 5 \\ 1 & 3 & 8 \end{pmatrix}\begin{pmatrix} x \\ y \\ z \end{pmatrix} = \begin{pmatrix} 8 \\ 12 \\ 4 \end{pmatrix}$$

Examples: converting sets of equations into matrices

i) $3x+2y = 6$

$5x+5y = 3$

$$\begin{pmatrix} 3 & 2 \\ 5 & 5 \end{pmatrix}\begin{pmatrix} x \\ y \end{pmatrix} = \begin{pmatrix} 6 \\ 3 \end{pmatrix}$$

ii) $2x+6y = 5$

$3x+4y = 3$

$$\begin{pmatrix} 2 & 6 \\ 3 & 4 \end{pmatrix}\begin{pmatrix} x \\ y \end{pmatrix} = \begin{pmatrix} 5 \\ 3 \end{pmatrix}$$

Examples: matrices into converting sets of equations

i) $\begin{pmatrix} 1 & 5 \\ 3 & 8 \end{pmatrix}\begin{pmatrix} x \\ y \end{pmatrix} = \begin{pmatrix} 1 \\ 4 \end{pmatrix}$ x +5y = 1, 3x+8y = 4

ii) $\begin{pmatrix} 8 & 1 \\ 2 & 5 \end{pmatrix}\begin{pmatrix} x \\ y \end{pmatrix} = \begin{pmatrix} 6 \\ 2 \end{pmatrix}$ 8x +y = 6, 2x+5y =2

Expressions for the force of infection using matrix notation

The equations:

$$\lambda_y(t) = \beta_{yy} I_y(t) + \beta_{yo} I_o(t)$$
$$\lambda_o(t) = \beta_{oy} I_y(t) + \beta_{oo} I_o(t)$$

can be summarized using the following matrix equation:

$$\begin{pmatrix} \lambda_y(t) \\ \lambda_o(t) \end{pmatrix} = \begin{pmatrix} \beta_{yy} & \beta_{yo} \\ \beta_{oy} & \beta_{oo} \end{pmatrix}\begin{pmatrix} I_y(t) \\ I_o(t) \end{pmatrix}$$

Matrix of "**Who Acquires Infection From Whom**" (WAIFW)

Calculating the number of infectious individuals

The average number of infectious individuals in a population can be estimated using the following approximation:

Prevalence ≈ Incidence × duration of infectiousness

(assuming that people become infectious shortly after infection)

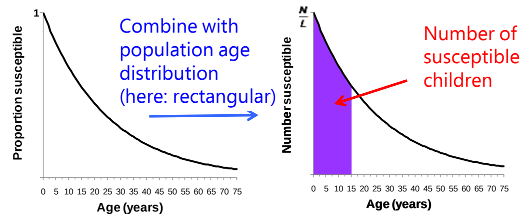
Average number of infectious individuals ≈ Average incidence × D

All ages: λS
Children: $\lambda_y S_y$
Adults: $\lambda_o S_o$

Calculating the average number of susceptible individuals

S_y, S_o, and S can be calculated by summing the area under the curve of the age specific number susceptible for the age group of interest

From the session on analysing seroprevalence data:



See maths refresher for methods for integration (i.e for calculating areas under curves).

Calculating β values for WAIFW matrices

$$\lambda_y(t) = \beta_{yy} I_y(t) + \beta_{yo} I_o(t)$$
$$\lambda_o(t) = \beta_{oy} I_y(t) + \beta_{oo} I_o(t)$$

We have **2 equations** with **4 unknowns** i.e. β_{yy}, β_{yo}, β_{oy} and β_{oo}

=> impossible to calculate unique values for each of these

=> Need to reduce the equations to **2 equations** in **2 unknowns**

Unless we can measure effective contacts directly (which we usually can't), we need to impose constraints on the WAIFW matrix

Possible constraints for WAIFW matrices

1. Symmetrical contact: rate at which a child contacts and infects an adult = rate at which an adult contacts and infects a child

i.e. $\beta_{yo} = \beta_{oy}$

2. Rate at which an adult contacts and infects a child = rate at which an adult contacts and infects an adult $\begin{pmatrix} \beta_1 & \beta_2 \\ \beta_2 & \beta_2 \end{pmatrix}$

$\begin{pmatrix} \beta_1 & \beta_1 \\ \beta_1 & \beta_2 \end{pmatrix}$ $\begin{pmatrix} \beta_1 & \beta_2 \\ \beta_2 & \beta_1 \end{pmatrix}$ $\begin{pmatrix} \beta_1 & 0 \\ 0 & \beta_2 \end{pmatrix}$ Symmetrical

$\begin{pmatrix} 0 & \beta_2 \\ \beta_1 & 0 \end{pmatrix}$ $\begin{pmatrix} \beta_1 & \beta_2 \\ \beta_1 & \beta_2 \end{pmatrix}$ $\begin{pmatrix} \beta_1 & \beta_1 \\ \beta_2 & \beta_2 \end{pmatrix}$ Asymmetrical

Calculating β parameters

If β_{yy}, β_{yo}, β_{oy} and β_{oo} are assumed to be constant over time, they can be estimated from the following equations (assuming a given WAIFW structure) if the values for $I_y(t)$, $I_o(t)$, $\lambda_y(t)$ and $\lambda_o(t)$ are known at some time t.

$$\lambda_y(t) = \beta_{yy} I_y(t) + \beta_{yo} I_o(t)$$
$$\lambda_o(t) = \beta_{oy} I_y(t) + \beta_{oo} I_o(t)$$

In practice, the values for $I_y(t)$, $I_o(t)$, $\lambda_y(t)$ and $\lambda_o(t)$ are usually taken to be those calculated at equilibrium (e.g. from cross-seroprevalence data).

Example 1: Calculating β parameters

Suppose λ_y = 0.12/year, λ_o = 0.05/year and I_y=29 , I_o=6 then we need to solve the following equations,

$$\begin{pmatrix} 0.12 \\ 0.05 \end{pmatrix} = \begin{pmatrix} \beta_{yy} & \beta_{yo} \\ \beta_{oy} & \beta_{oo} \end{pmatrix} \begin{pmatrix} 29 \\ 6 \end{pmatrix}$$

If the WAIFW matrix has the following structure: $\begin{pmatrix} \beta_1 & 0 \\ 0 & \beta_2 \end{pmatrix}$

then we would need to solve the following equations:

$$\begin{pmatrix} 0.12 \\ 0.05 \end{pmatrix} = \begin{pmatrix} \beta_1 & 0 \\ 0 & \beta_2 \end{pmatrix} \begin{pmatrix} 29 \\ 6 \end{pmatrix}$$

Example 1: Calculating β parameters (cont)

The equations: $\begin{pmatrix} 0.12 \\ 0.05 \end{pmatrix} = \begin{pmatrix} \beta_1 & 0 \\ 0 & \beta_2 \end{pmatrix} \begin{pmatrix} 29 \\ 6 \end{pmatrix}$

can be rewritten as:

$0.12 = 29\beta_1$

$0.05 = 6\beta_2$

=> β_1 = 0.12/29 = 0.00413/year

β_2 = 0.05/6 = 0.008/year

Example 2: Calculating β parameters

Suppose λ_y = 0.12/year, λ_o = 0.05/year and I_y=29 , I_o=6 (as before)

If the WAIFW matrix has the following structure: $\begin{pmatrix} \beta_1 & \beta_2 \\ \beta_2 & \beta_2 \end{pmatrix}$

then we would need to solve the following equations:

$$\begin{pmatrix} 0.12 \\ 0.05 \end{pmatrix} = \begin{pmatrix} \beta_1 & \beta_2 \\ \beta_2 & \beta_2 \end{pmatrix} \begin{pmatrix} 29 \\ 6 \end{pmatrix}$$

These can be written as:

$0.12 = 29\beta_1 + 6\beta_2$ *eqn 1*

$0.05 = (29 + 6)\ \beta_2$ *eqn 2*

Eqn 2 can be solved to give β_2=0.0014/year.

Substituting for β_2 into eqn 1 gives β_1=0.0038/year

Summary: calculating WAIFW matrices

- If we're lucky, we can measure effective contacts (semi-)directly, and use this matrix of β values.
- If not, we usually have to make assumptions about the structure of the WAIFW matrix.
- Having settled on a matrix structure, we can use estimates of the force of infection and number of infectious individuals in each group to calculate the matrix.
- If we haven't measured the number of infectious individuals, we can estimate it using the force of infection, the duration of infectiousness, and the number of susceptibles in each group.

Practical: How do different assumptions about mixing patterns influence the effectiveness of vaccination?