Block 2:

Analysis of seroprevalence data and their application...

Practical notes

Introduction to Infectious Disease Modelling and its Applications – 2018

Session 8: Estimating forces of infection by fitting catalytic models to seroprevalence data

Practical

Introduction and Objectives

Few statistical packages have been designed to fit catalytic and other (non-linear) models to data. This practical illustrates how you might adapt existing functions available in Excel to fit simple models to data and thereby calculate useful epidemiological parameters, such as the force of infection of a given infection.

By the end of this session, you should:

- be familiar with the basic methods for fitting catalytic models to seroprevalence data.
- be able to apply such methods to estimate the force of infection and basic reproduction number of a given infection.

Mechanics of calculating forces of infection from seroprevalence data

1. Open the spreadsheet "rubcrude.xls".

You should see:

a) **Yellow cells** containing data on the age-specific numbers of individuals (males and females combined) positive for rubella antibodies in the UK (sheet UK) and in China (sheet China) in different periods.
b) **Pink cells** in which you will set up equations for the age-specific proportion of individuals who have ever been infected.
c) **Blue cells** containing a value for the force of infection in your population. This value has been given the name "foi_c" or "foi_uk".
d) **A graph** plotting the observed proportion seropositive in your populations.

We will first analyse the data from the UK.

Q1 Ignoring the contribution of maternal antibodies for now, what is the Excel formula for the proportion of 0.5 year olds who have ever been infected in terms of foi_uk?

Side note: The Excel expression for a function of the form e^{-c} is

=exp(-c)

2. In the column labelled "Expected proportion ever infected", set up this expression for 0.5 year olds and copy it down for all the age groups in the data set.

Q2 Do you think the true value for the force infection in the UK was greater or smaller than that currently assumed?

We will now find the best-fitting value for the force of infection for the UK by finding the lowest value for the "goodness of fit" statistic.

3. Select rows 5 and 10, click with the right mouse button and select the unhide option.

You should see some grey cells containing an expression for the goodness of fit of the model to the data, technically known as the "loglikelihood deviance". In brief, the deviance calculates how far predictions from your catalytic model **deviate** from those of the "best possible" model (known as the "saturated" model). **Do not worry about the theory underlying this expression for now – some of it is discussed in a later session.** It turns out that the loglikelihood deviance has some convenient properties for calculating confidence limits and is often used for fitting non-linear models. To see how the deviance is calculated, select columns F and J, click with the right mouse button and select the unhide option. For further information about the deviance, see the Appendix. (Ignore the contents of column I for now.)

Q3 What is the current value for the deviance?

We will now find the force of infection which leads to the smallest possible deviance between the observed proportion seropositive and model predictions of the age-specific proportion of individuals who have ever been infected.

5. Select the "Solver" option from the Analysis tab (located under the Data option in the main menu). If it is not available, click on the File option in the menu, and then click on "Options". Then click on "Add-Ins", and, in the "Manage" box, select "Excel Add-ins", before clicking on "Go". In the "Add-Ins available" box, check the "Solver Add-in" box, and then click OK.

To run Solver, we also need to enable some macros which have built into Excel.

6. If you see a security warning below the ribbon stating "Macros have been disabled" click on the "Options" button next to this warning and then select the "Enable this content" option, before clicking on OK.

The "Solver" option is a powerful utility provided by Excel for identifying solutions to a given expression. It requires you just to specify:

1. the location of the cell whose value you want to maximize, minimize etc (specified under the "Set objective" option) and
2. the cell(s) which are allowed to change so that this maximum, minumum etc is attained (under the "By changing variable cells" option).

In our case, we want to identify the value for the force of infection (in cell D4) which leads to the minimum deviance (cell D6).

7. Set up the "Set objective" and the "By changing variable cells" options to refer to the appropriate cells. Select the "Min" option under the "To" option and click on the "Solve" button.

Q4 What is the best-fitting value for the force of infection? Is this consistent with your answer to question Q2 above?

Q5 For which age groups does the model underestimate the proportion of individuals who are sero-positive? For which age groups does it overestimate it?

Q6 According to the formula you saw in the lecture, what is the average age at infection in the UK? (Assume that the force of infection is independent of age)

Q7 Assuming that the average life expectancy (L) is 60 years, what is the R_0 for this population according to the expression $R_0=L/A$? What is the herd immunity threshold?

8. Click on the China worksheet and follow the steps you carried out using the UK data to calculate:

i) the best-fitting force of infection,
ii) the average age at infection,
iii) the R_0 (assuming that the life expectancy is the same as that in the UK) and
iv) herd immunity threshold for China.

Q8 How do the values for the force of infection, average age at infection, R_0 and herd immunity threshold in China compare against those for the UK? Suggest possible reasons for these differences.

Q9 How should your estimate of the force of infection change if you were to assume that individuals are immune for the first 6 months of life as a result of maternal antibodies?

9. Modify your expression for the prevalence of previous infection in each age group to deal with maternal antibodies (assume that individuals are immune for the first 6 months of life and are then susceptible), refit the model and check if the new estimate for the force of infection consistent with your answer to the last question.

Optional technical note: you should notice that, when you change the expression for the prevalence of previous infection to account for maternal immunity for all age groups, the deviance becomes negative, which is statistically unacceptable. This negative deviance results from the fact that, for 0.5 years olds, the contribution to the loglikelihood from the catalytic model is zero. To overcome this problem, we can adjust the expression for the deviance so that it only uses the data and estimates for individuals aged over 0.5 years. However, you should find that the best-fitting value for the force of infection is identical to the value obtained when data for all age groups were used when fitting the model.

Assessing an age-dependency in the force of infection

We will now assess whether our assumption that the force of infection is independent of age is justified in these settings.

1. If you have not already done so, unhide column I (by selecting columns F and J together, clicking with the right mouse button and choosing the unhide option). Enter the appropriate formula into the lilac cells in column I and repeat the same for the UK.

Q10 According to Figure 2 in the sheets for China and the UK, is the assumption that the force of infection is independent of age in these populations justified? At what age does it look as though the force of infection changes in these populations?

The following contrasts the age-specific forces of infection calculated for the UK against those for China.

	Force of infection (% per year) (95% CI)	
Population	<15 yr olds	≥15 yr olds
UK	**13.29** (12.87-13.72)	**4.17** (3.24-5.16)
China	**24.72** (24.32-25.1)	**"0"** (0- 0.00071)

Q11 What do you notice about these values? Suggest reasons for the differences in the force of infection between China and the UK.

In the next session, we will be exploring the effects of vaccination on the age-specific prevalence and incidence of infection.

Further exercises

If you have finished the practical early or if you wish to consolidate your understanding of the concepts covered in this session, please try the following exercises:

1. Supplementary exercises (see the supplementary questions folder on Moodle or in the network folder containing the model files), which show how you can estimate an age-dependent force of infection in Excel.

2. The paper and pen exercises 5.1-5.8 at the end of chapter 5 of the recommended course text[1]. Solutions are available from the book's website.

3. Exercises accompanying models 5.1-5.4 of the recommended course text[1] (see www.anintroductiontoinfectiousdiseasemodelling.com).

References

1. Vynnycky E, White RG. An Introduction to Infectious Disease Modelling". Oxford University Press, Oxford 2010

Appendix

1: The definition of the deviance

The deviance is defined formally as:

$$2\times\{\text{Loglikelihood of the saturated model} - \text{Loglikelihood of observing the data set if “your” model was correct }\}$$

Columns G and H contain expressions for the contribution from each data point to the loglikelihood of the “saturated” model and the contribution from each data point to the log of the likelihood of observing the data set if “your” model was correct. The deviance is calculated by subtracting the sum of the contributions from each data point from your model (given by (SUM(H25:H35) for the China data set) from the sum of the contributions from the saturated model (given by SUM(G25:G35).

To change the data points used to fit the model, you need to modify the expression for the deviance so that it points to the appropriate cells. For example, for the China data set, if you wanted to base your estimate of the force of infection just on the data for 0-18 year olds, your expression for the deviance would need to be:

```
=2*(SUM(G25:G32)-SUM(H25:H32))
```

The deviance follows the chi-square distribution with degrees of freedom given by number of data points used to fit the model-number of parameters. This can be used to assess whether the fit of the model is adequate: the p value obtained by referring the optimal deviance to the chi-square distribution with the appropriate degrees of freedom gives the probability of observing the data set if your model was correct.

2. Calculating 95% Confidence Intervals

Maxlhood01 is a specially written macro (which hasn’t been built into Excel, but which has been provided with this spreadsheet) which calls up Solver three times to calculate the optimal and the upper and lower confidence intervals (see suggestions below if the macro does not run). To run the macro, select the Macro button which you can see after clicking on the “View” option from the main menu, then select “View macros” and click on “Run”. Clicking on “Edit” will allow you to look at or edit the code for the macro.

The lower and upper 95% CI are calculated by identifying the force of infection for which the deviance differs by 3.84 from the optimal deviance (refer to a stats book for the theory!). To check this, select the cells in the range A8:F9, change the font to be black, and look at the value in cell D9 as you run the macro.

If you come up with an error message about not finding the project or library when running the macro, try the following steps before running it again:

<u>Excel 2010</u>

a) Click on OK to stop the macro.
b) Select the tools option from the main menu and select the References option.

c) Unclick the button next to Missing:Solver.XLA, and click on the box next to "SOLVER". After exiting the dialogue box, return to the main spreadsheet and run the macro.

Versions of Excel predating 2010

a) Close the dialogue box and click on the reset button in the window in which the macro has paused to stop the macro. This button resembles a blue box on a grey background.
b) Select the tools option from the main menu and select the Available references option.
c) Unclick the button next to Missing:Solver.XLA, and click on the box next to "SOLVER". After exiting the dialogue box, return to the main spreadsheet and run the macro.

Introduction to Infectious Disease Modelling and its Applications – 2018

Session 10: Contrasting the effects of rubella vaccination between high and low transmission settings

Practical

Overview and Objectives

In this practical, you will be applying the crude forces of infection calculated in the last practical to contrast the transmission dynamics of rubella between China and the UK and to assess how different vaccination strategies will affect the overall serological profile in the population and the average age at infection. For simplicity, we will assume that individuals mix randomly in the population.

By the end of this practical you should understand:

1. The principles of setting up age-structured models of the transmission dynamics of an infection
2. The effect of vaccination on the force of infection, age-specific prevalence of infection and the number of new infections
3. The differences between the impact of a universal as compared with a selective vaccination strategy on the transmission dynamics of rubella.

Table: Summary of the key parameters describing the transmission dynamics of rubella for China and the UK which you obtained in the last session.

Population	Force of infection (% pa)	Average age at infection (yrs)	R_0	Herd immunity threshold
UK	11.59	8.6	6.95	86%
China	20.32	4.9	12.19	92%

Background

For most individuals, rubella is a mild immunising infection, which is associated with a fever and a rash. However, women who are infected during the first 16 weeks of pregnancy are at an increased risk of their child being born with Congenital Rubella Syndrome (CRS). The defects asspciated with this condition include cataracts, deafness and mental retardation.

In countries in which the force of rubella infection is high, most women have already been infected and are immune by the time they reach child-bearing age. This means that in such settings, few women are first infected during child-bearing age and therefore the burden of Congenital Rubella Syndrome is likely to be very low.

The introduction of rubella-containing vaccine (such as the measles-mumps-rubella vaccine) among young children has the potential to lead to increases in the burden of CRS. For example, the introduction of vaccination leads to a reduction in the prevalence of infectious

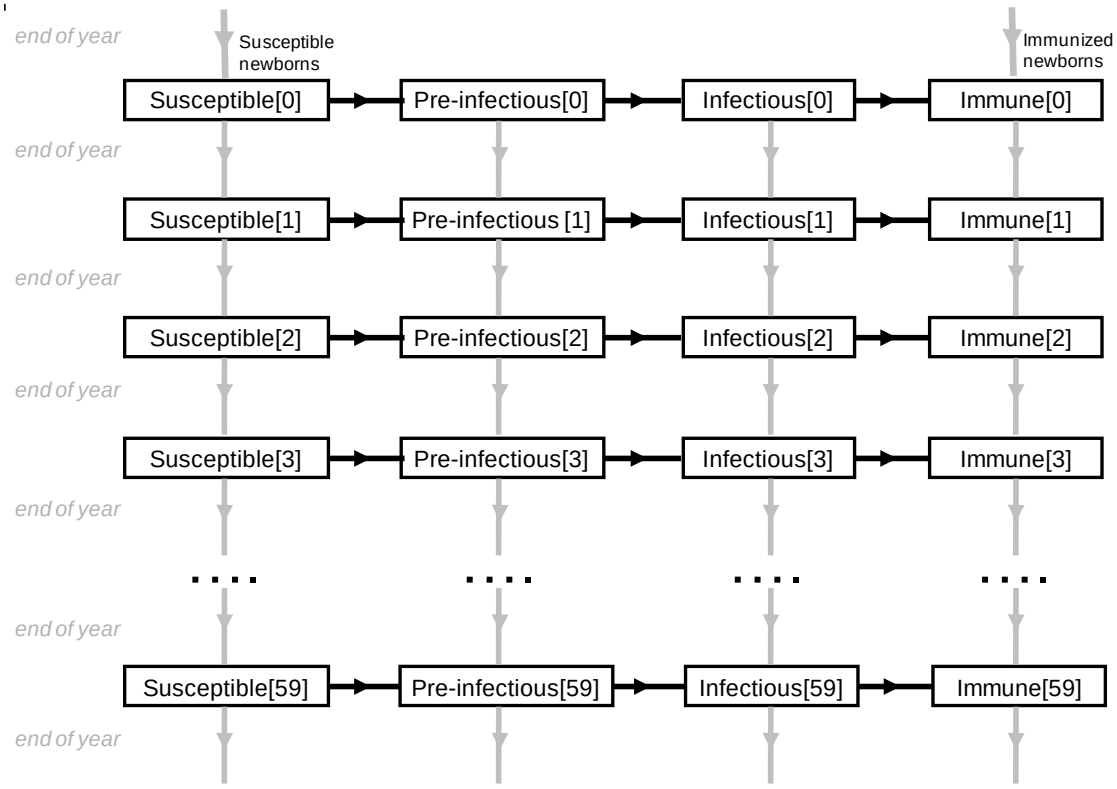
persons, and therefore in the opportunity for exposure to infection. This may mean that a large proportion of those who have not been vaccinated will reach child-bearing age still susceptible to infection. If the force of infection is sufficiently high, this means that the number of new infections among women of child-bearing age, and therefore the burden of Congenital Rubella Syndrome, may be higher after the introduction of vaccination than that in the absence of vaccination.

In this session, we use a model to illustrate how vaccination among young children leads to changes in the proportion of individuals who are susceptible at different age groups and the number of new infections in different age groups.

Part I: Modelling the impact of infant MMR vaccination in China and the UK

Approaches for setting up age-structured models

As mentioned above, the introduction of vaccination into a population can lead to changes in the age distribution of individuals who are susceptible to infection. To explore these effects, it is helpful to have a model which explicitly describes the age of individuals. In this practical we will use a model of the transmission dynamics of rubella with the general structure shown below.



It is very closely related to the models of the transmission dynamics of measles which you worked with during the practicals in block 1, except that it is age-structured. Individuals are stratified into annual age strata, and move to the subsequent age stratum at the end of each

year. The age of individuals is denoted by the number in the square brackets. This method for incorporating age in a model is now standard and was first devised by Schenzle[1].

The equations in this model can be written using either difference or differential equations. However, since the model is easier to set up in Berkeley Madonna using difference equations than using differential equations, we will use difference equations. The equations for the number of individuals in each compartment depend on whether or not they relate to the end of the year.

For example, considering individuals aged 20 years *at any time t apart from the end of year*, the difference equations are analogous to those which you saw in the first session on difference equations, namely:

$$S[20]_{t+1} = S[20]_t - \lambda_t S[20]_t$$

$$E[20]_{t+1} = E[20]_t + \lambda_t S[20]_t - fE[20]_t$$

$$I[20]_{t+1} = I[20]_t + fE[20]_t - r\, I[20]_t$$

$$R[20]_{t+1} = R[20]_t + r\, I[20]_t$$

where

$S[20]_t$ is the number of susceptible individuals of age 20 years at time t;
$E[20]_t$ is the number of individuals of age 20 years in the pre-infectious category at time t
$I[20]_t$ is the number of infectious individuals of age 20 years at time t;
$R[20]_t$ is the number of immune individuals of age 20 years at time t;
λ_t is the force of infection between t and t+1;
f is the rate at which individuals become infectious;
r is the rate at which infectious individuals recover and become immune.

The equations considering susceptible and pre-infectious individuals aged 20 years *at a time t at the end of year*, are as follows:

$$S[20]_{t+1} = S[19]_t - \lambda_t\, S[19]_t$$

$$E[20]_{t+1} = E[19]_t + \lambda_t\, S[19]_t - fE[19]_t$$

1. Write down the difference equations for the number of infectious and immune individuals of age 20 years at time t+1, where t is the end of a given year, assuming that r is the rate at which individuals become infectious:

$I[20]_{t+1}$ =

$R[20]_{t+1}$ =

The equations considering any other age category (including those for individuals in their first year of life) are analogous to these equations.

The above model can be set up in Excel, though this is practical only if there are few age groups in the model. It can be set up in Berkeley Madonna using the equation editor; at present it slightly cumbersome to do this using the flowchart editor.

Setting up age-structured models using Berkeley Madonna

1. Open up the Berkeley Madonna file rubvacc_newborns.mmd, where you will see the equations for the above model set up.

Before exploring the impact of infant MMR vaccination in the model population, we will first familiarize ourselves with the model's key features. **Do not worry about understanding every detail of the model – the main purpose of this session is to interpret model output and for this, you just need to have a general understanding of the model structure.**

1. Individuals are stratified into annual age strata between the ages 0 and 59 years and are assumed to exit the model at the end of their 59th year of life. This stratification is reflected in the notation used by Berkeley Madonna to write the equations for each age class. For example, the notation Sus[0..59] reflects the fact that the susceptible compartment is made up of 60 strata, called Sus[0], Sus[1], Sus[2],… Sus[59]. The absence of equations for the 60th age stratum indicates that this age group is not present in the model.

2. Individuals in each age group move to the subsequent age group at the end of each year. The equations used by Berkeley Madonna depend on whether or not it is considering the end of the year, as specified by the value of the variable year_end (which equals 1 if the end of the year has been reached and 0 otherwise). These equations are analogous to the ones you wrote down earlier in this practical.

   To see the effect of this, run the model and click on page 1 of the figures window, where you will see how the number of Susceptible 5, 20 and 30 year olds changes over time. Zoom in on the time period 80-90 years to see these changes in greater detail. For example, you will see that at the start of the year, the number of susceptible 5 year olds is high, it decreases during the course of the year as this cohort becomes infected and immune, and increases at the start of the next year when this cohort moves to the next age category and the 5 year age group is replaced those who were aged 4 years during the previous year.

3. The population has a rectangular age distribution with 1000 individuals in each age group (and hence 60,000 individuals in the whole population). To see this, click on page 2 of the figures window. This plots the value of the variables tot_pop[0], tot_pop[1], tot_pop[2], …tot_pop[59] where tot_pop[0] equals the total number of individuals who are in their first year of life in the model, tot_pop[1] reflects the total number of individuals who are aged 1 year etc.

   The age group of the individuals is on the x-axis of this figure. Tot_pop[0], tot_pop[1] etc are defined in the "Useful summary variables" section at the end of the equations window. This section also includes other useful summary statistics which we will be

using, such as the proportion of 5, 10, 15 etc year olds who are susceptible, the daily number of new infections per 100,000 in various age groups.

4. Vaccination of newborns is introduced 100 years after the start of the simulations at a level specified by the parameters yr_start_vacc, birth_cov and prop_vacc. These parameters are defined in the "Infection and vaccination-related parameters and variables" section in the equations window.

   Newborns who are not protected by vaccination are added to the Sus[0] compartment at the end of each year; *immunized* newborn individuals are added to the Imm[0] compartment at the end of each year.

5. The force of infection in the population is defined in the "Infection and vaccination-related parameters and variables" section in the equations window and is given by the expression:

   *beta*ARRAYSUM(Infous[*])*

   where *ARRAYSUM(Infous[*])* is the total number of infectious individuals in the population. The asterisk in this expression simply denotes the fact that we are taking the sum of all the age strata of the Infectious compartment, i.e. Infous[0]+Infous[1]+Infous[2]+ ..+ Infous[59].

The model is currently set up to describe the transmission dynamics of rubella for China, as determined by the size of R_0 (=12.19 for China).

1. Run the model and look at the graph on page 3 of the figures window.

Q1.1 What is the long-term average daily force of infection in the model? Is it consistent with the overall (annual) force of infection which you estimated for China (20.32%) during the last practical?

Note: for the purposes of this practical, it is sufficient to obtain the average value by reading off the value for the force of infection midway between the highest and the lowest point for the year that you're interested in. More "sophisticated" ways of obtaining this average are provided in the Appendix, which you can investigate in your spare time or at the end of this practical.

To see the number of individuals who are susceptible or immune in different age groups at the end of the simulations, click on page 4 of the figures window – the lines shown here should be consistent with the corresponding values which you saw during the last practical for the population in China.

We will now explore the effect of different levels of infant MMR vaccination coverage in China on the age-specific prevalence of infection and the age-specific daily number of new infections per 100,000.

Simulating the impact of different levels of infant MMR vaccination coverage on the transmission dynamics of rubella

1. Change the vaccination coverage to be 40% and run the model.

Q1.2 How does the introduction of infant MMR vaccination affect the long-term average force of infection? According to the formula A=1/λ, what is the long-term average age at infection following the introduction of infant MMR vaccination?

2. Click on page 5 of the figures window, where you should see a graph showing the proportion of 5, 20, 30 and 40 year olds who are susceptible to infection in the population.

Q1.3 Why does the average proportion of 5, 20, 30 and 40 year olds who are susceptible to infection increase in the short-term? How soon after the introduction of MMR vaccination does the proportion of 5, 20, 30 and 40 year olds who are susceptible peak? Is this what you would expect and why?

Q1.4 How does infant MMR vaccination affect the long-term average proportion of 5, 20, 30 and 40 year olds who are susceptible to infection? Why does this occur?

3. Add "prop_sus_all" (i.e. the overall proportion of the population which is susceptible) to the components being plotted.

Q1.5 How does the introduction of infant MMR vaccination affect the overall average proportion of individuals who are susceptible to infection? Is this what you would expect? Why?

4. Click on page 6 of the figures window, where you will see a figure showing the daily number of new infections per 100,000 population among 5, 20, 30 and 40 year olds.

Q1.6 How does the introduction of infant MMR vaccination affect the daily number of new infections per 100,000 among 5 year olds? How does it affect the daily number of new infections per 100,000 among 20, 30 and 40 year olds? Why might this occur?

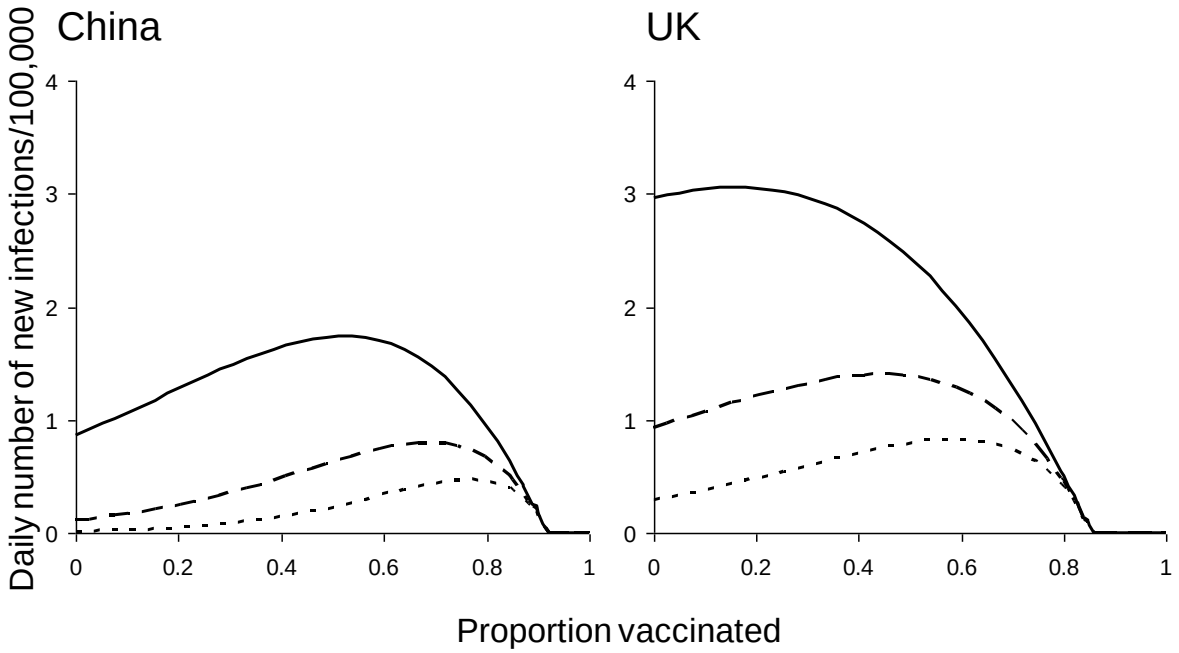
Q1.7 How do these age patterns in the dailynumber of new infections change if you increase the level of vaccination coverage to 50%, 60%, 70%, 80%?

A more reliable indication of the likely impact of the introduction of infant MMR vaccination can obtained by plotting the long-term daily number of new infections per 100,000 among adults against the vaccination coverage, using Berkeley Madonna's parameter plot facility as follows.

5. Select the "Parameter plot" option from the "Parameters" option in the menu. Specify that you would like to run the model 6 times, with prop_vacc as the parameter that you'd like to vary, ranging between 0 and 1.00. Specify that for each model run, you'd like to plot the final values of "new_infns_20", "new_infns_30", "new_infns_40" on the y-axis. Click on the run button to see the plot.

Q1.8 What do you conclude about the likely impact of the introduction of infant MMR vaccination on the daily number of new rubella infections/100,000 among adults in China?

The following contrasts model predictions of the long-term average age-specific daily number of new infections per 100,000 predicted for different levels of vaccination coverage among newborns between China and the UK. In your spare time, you can re-run the parameter plot using the R_0 for the UK to check that you get similar results.



Q1.10 Should you be most cautious about introducing infant MMR vaccination in China or in the UK? Why? How might you amend your vaccination strategy to limit the number of adverse effects?

Optional questions:

6. Run the model for China, with a vaccination coverage of 91% (i.e. very close to the herd immunity threshold and look at the figure of the age-specific daily number of new infections per 100,000 or of the force of infection (page 6 of the figures window)

Q1.11 What do you notice about the time interval between the third and fourth epidemics after the introduction of infant MMR vaccination, as compared with that between the first and second and second and third epidemics? Why might this occur?

7. Check your hypothesis by looking at the ages of individuals which are most affected in each of these epidemics.

If you have time, try the questions in part II of this practical, which explore the effect of selective vaccination strategies against rubella.

Part II – Identifying the impact of infant MMR vaccination on rubella infection trends in specific age groups (optional)

1. Open up the Berkeley Madonna file "rubvacc_cb.mmd".

The model is similar to the one which you were using in the first part of the practical, except that it allows you to explore the effect of vaccinating individuals in different age groups. The basic reproduction number for rubella in this population is taken to be that for the UK.

The equations are set up in an analogous way to those for the model in part I. The main difference is that vaccination is introduced 150 years after the start of the simulations, as specified by the value of yr_start_vacc and individuals are vaccinated at the end of each year, with the effective vaccination coverage among those of a given age group being determined by vacc[0..59]. Vacc[0..59] is defined in the section on "Vaccination and infection-related parameters and variables".

At present only 13 year olds are vaccinated, as reflected by the fact that vacc[13] is set to equal the parameter prop_vacc_13 and vacc[0], vacc[1] etc are all set to equal zero.

2. Set the vaccination coverage among 13 year olds to be 50% by changing the value for prop_vacc_13 accordingly. Look at the figures of the force of infection, the age-specific proportion of individuals who are susceptible and the age-specific daily number of new infections per 100,000 which are on pages 3, 5 and 6 of the figures window.

Q2.1 How does vaccination among 13 year olds affect
a) the force of infection in the population?
b) the age-specific proportion of individuals who are susceptible?
c) the daily number of new infections per 100,000 in different age groups?
Why does this occur?

Q2.2 How does your answer to the last question change if the level of coverage is 75%? 100%?

Q2.3 What are the relative benefits of a partial vaccination strategy as compared with the strategy of vaccinating all individuals in their first year of life?

In the next session, we will continue with this theme, but we will consider the effect of age-dependent mixing between individuals.

Further exercises

If you have finished the practical early or if you wish to consolidate your understanding of the concepts covered in this session, please try the following exercises:

1. The paper and pen exercises 5.9 and 5.10 at the end of chapter 5 of the recommended course text[1]. Solutions are available from the book's website.

2. Exercises accompanying models 5.5 and 5.6 of the recommended course text[2] (see www.anintroductiontoinfectiousdiseasemodelling.com)

3. Supplementary exercises (see the supplementary questions folder on Moodle or in the folder on the network drive with the models).

Further reading

Vynnycky E and White RG (2010) An introduction to infectious disease modelling. Oxford University Press. Chapter 5, sections 5.3 and 5.4.

References

1. Schenzle D. An age-structured model of pre- and post-vaccination measles transmission. IMA J Math Appl Med Biol 1984;1:169–91.

2. Vynnycky E, White RG. An Introduction to Infectious Disease Modelling". Oxford University Press, Oxford 2010

APPENDIX

Using Berkeley Madonna to calculate average values

There are several ways of obtaining the average value of a given output e.g. the force of infection over a given time period.

The most straightforward way is to convert the graph of the force of infection over time to a table (by clicking on the table button on the graph toolbar), saving the table to a file, copying and pasting the output from that table to Excel where you can work out the average value for the interval that you're interested in.

Alternatively, you could set up variables in Berkeley Madonna which calculate the average values automatically. The following shows the lines which you could incorporate into your model (in the globals window for models set up using the flowchart editor and in the equations window otherwise) if you wanted to work out the average value for the force of infection between the 80th and 90th years:

```
INIT cum_foi = 0
INIT cum_dt = 0
next cum_foi = if (year>=80) AND (year<90) THEN cum_foi+force_of_infn ELSE 0
next cum_dt = if (year>=80) AND (year<90) THEN cum_dt+1 ELSE 0
ave_foi = if (year>80) AND (year<90) THEN cum_foi/(cum_dt) ELSE 0
```

According to these lines, we set up a variable called cum_foi, which is the cumulative sum of the force of infection between the 80th and 90th year. The variable cum_dt sums up the number of time steps which occur between the 80th and 90th year (or equivalently, the number of times that force_of_infn is added to the variable). ave_foi is then the average force of infection at a given time calculated between the 80th year and that time point.

Introduction to Infectious Disease Modelling and its Applications – 2018

Session 11: Simulating the effect of non-random mixing on rubella transmission and control

Practical

Overview and Objectives

This practical is designed to consolidate some of the methodological issues covered during the last lecture. It is divided in two parts.

In part I, you will calculate the WAIFW matrix for different assumptions about mixing patterns, using values of the age-specific force of infection for rubella for the UK. In part II, you will explore the implications of different mixing patterns on the impact of MMR vaccination on the transmission dynamics of rubella.

By the end of this session you should:

- be able to define a WAIFW matrix;
- be able to calculate the WAIFW matrix for different assumptions about mixing between individuals, given data on the force of infection and the prevalence of infectious individuals;
- understand the effect of heterogeneous mixing patterns on the impact of e.g. a vaccination strategy.

PART I: Calculating WAIFW matrices

Introduction

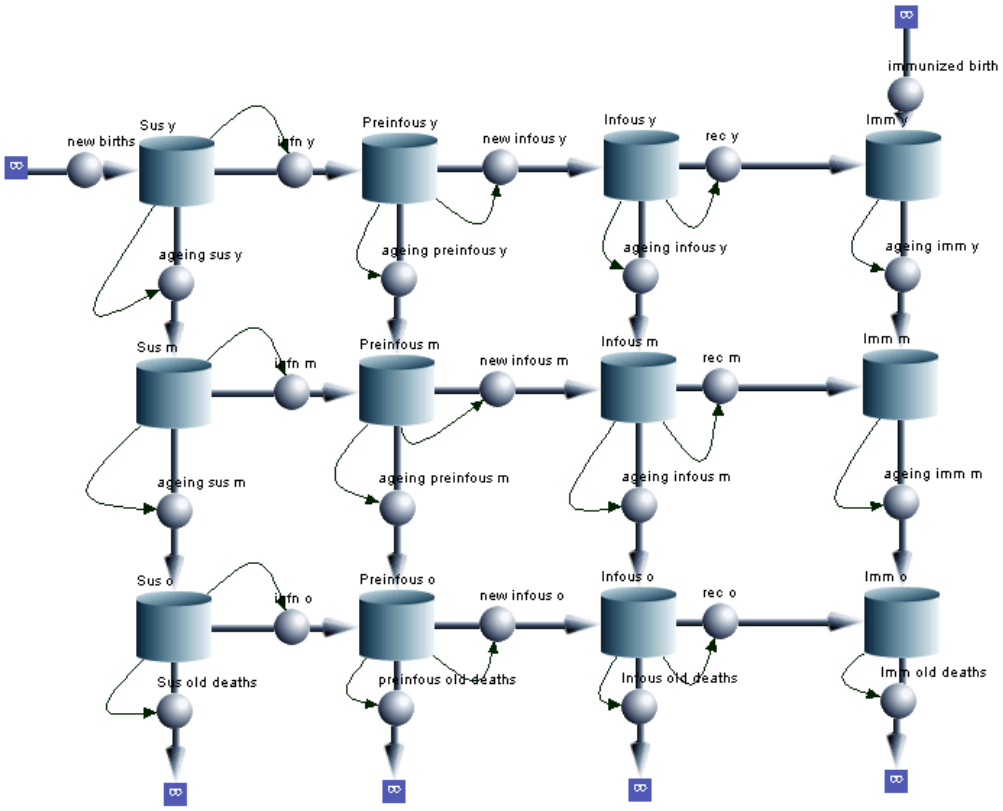
During the practical on analysing seroprevalence data, you estimated the force of rubella infection for the UK assuming that it was the same for all age groups. The following table summarizes estimates of the force of infection assuming that it differs between those aged <15 and ≥15 years. For the purposes of this practical, those aged ≥15 years have been stratified into the 15-29 and ≥30 year age groups.

Table 1: Summary of the estimates for the age-specific force of infection for rubella for the UK

Age group (years)	Average annual force of infection	Average daily force of infection
0-14	0.13286	3.64×10^{-4}
15-29	0.0417	1.14×10^{-4}
≥30	0.0417	1.14×10^{-4}

One explanation for this age-dependency in the force of infection is that mixing between individuals is age-dependent, i.e. that the β parameters are age-dependent. To describe the

transmission dynamics of rubella in the UK, accounting for this age-dependency, we will use a model with the following structure.



In this model, the population is stratified into three broad age classes, namely the young, middle(-aged) and the old.

The demography of the population is simpler than that in the model used in the rubella practical, since individuals move between the different age categories at a constant rate. For example, young individuals age (i.e. enter the middle-aged category) at a constant rate, middle-aged individuals become old at a constant rate, and old people die (or exit the model) at a constant rate. The differential equations for this model are provided in the Appendix for reference after the practical.

Q1.1 How would you calculate the rate at which young and middle-aged individuals age, assuming that they spend an average of 15 years in the young and middle age groups?

Technical note about the method used to describe ageing (optional)

The method used in the above model is a greatly simplified way of dealing with ageing in a model and is included here for illustrative purposes. It is not recommended for practical purposes, since the same ageing rate is applied, for example, to a newborn individual and to someone who was born 14 years previously. Thus paradoxically a newborn could end up in the old category within the first few hours of life, which, of course (!), is unrealistic.

Setting up a model dealing with heterogeneous mixing in Berkeley Madonna

1. Open up the Berkeley Madonna file "rubdyn02 – flowchart.mmd", where the above model has been set up. Recall that to see the parameters at any stage during this practical, you just need to click on the globals button in the flowchart editor.

If you prefer to work without the flowchart, open up the file "rubdyn02 – equations.mmd".

The key features of the model are as follows:

a) Young and middle-aged individuals spend an average of 15 years in the young and middle-aged compartments; old individuals spend an average of 30 years in the old compartment. Deaths only affect individuals in the old compartment. This is specified in the "Demographic parameters and variables" section of the global window or the equations window.

b) The total population size remains constant over time with 60,000 individuals, and 15,000, 15,000 and 30,000 young, middle-aged and old individuals respectively. You can check this by running the model and looking at page 1 of the figures window, which plots the numbers of young, middle-aged and old individuals over time (tot_young, tot_mid, tot_old etc).

   Tot_young, tot_mid and tot_old are defined in the "Demographic parameters and variables" section of the globals or the equations window. To ensure that the population remains the same size over time, the variable for the number of births per unit time in the model ("births") has been set to equal the total number of deaths.

c) Vaccination of newborns is introduced 100 years after the start of the simulations (specified by the parameter yr_start_vacc) at a level specified by the parameters birth_cov and prop_vacc. These are defined in the "Vaccination-related parameters" section of the globals or equations window.

d) Separate variables for the force of infection among the young, middle-aged and old have been set up (i.e. force_of_infn_y, force_of_infn_m and force_of_infn_o). These are defined in the "Infection-related parameters" section of the globals or equations window. At present, these age-specific forces of infection have been set to equal the values estimated for 0-14, 15-29 and ≥30 year olds for the UK shown in Table 1 on page 1.

e) The parameters defining mixing between individuals in the different age categories are set up as b_yy, b_ym, b_yo etc. These are defined in the "Infection-related parameters" section of the globals or equations window and are currently set to be equal to zero – we will calculate appropriate values for them later. b_yy is defined as the rate at which a specific young individual comes into effective contact with another specific young individual per unit time, b_ym is defined as the rate at which a specific young (susceptible) individual comes into effective contact with a specific infectious "middle-aged" individual per unit time etc.

f) Summary variables, such as the proportion of young, middle-aged and old individuals who are susceptible and the age-specific daily number of new infections per 100,000 have been set up in the "Useful summary variables" section of the globals or equations window. These are plotted on pages 2 and 3 of the figures window. You should notice that these are constant over time – this is due to the fact that the force of infection is currently set to be constant over time.

2. Run the model and check that the corresponding long-term age-specific values for the proportion of individuals who are susceptible and the daily number of new infections per 100,000 are consistent with the values in the table below:

Age category	**Average % susceptible**	**Average daily number of new infections/100,000**	**Average daily force of infection**
Young	33.41	12.16	3.64×10^{-4}
Middle-aged	20.56	2.35	1.14×10^{-4}
Old	9.13	1.04	1.14×10^{-4}

We will now adapt the model to incorporate age-dependent mixing between individuals.

As you saw in the lecture, in populations in which individuals are stratified into the young and the old, the force of infection among young and old individuals ($\lambda_y(t)$ and $\lambda_o(t)$ respectively) can be expressed as:

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

where

$I_y(t)$ and $I_o(t)$ are the numbers of young and old infectious individuals at time t.
β_{yy} is the rate at which 2 specific young individuals come into effective contact per unit time,
β_{yo} is the rate at which a specific young susceptible person and an old infectious individual come into effective contact per unit time,
etc

3. Change the current expression in the model for the force of infection for young individuals to be in terms of *b_yy, b_ym, b_yo, Infous_y, Infous_m* and *Infous_o*.

4. In a similar way, change the current expression in the model for the force of infection for middle-aged and old individuals.

We will now obtain values for *b_yy, b_ym* etc which are consistent with the values for the age-specific force of rubella infection which has been estimated for the UK, assuming that mixing between individuals is age-dependent.

Calculating b_yy etc for a non-randomly mixing population

As you saw in the lecture, *b_yy, b_ym etc* are calculated using estimates of
a) the number of infectious individuals and
b) the force of infection
in each age category.

The first of these components (the average number of infectious individuals in each age category) can be calculated using the expression:

(force of infection among individuals in that age category)
×
(Number of individuals in that age category who are susceptible)
×
(average duration of infectiousness)

We will first calculate the number of infectious individuals in each age category.

1. Using the above expression, complete the following table to calculate the number of infectious individuals in each age category for the population in the mode (note that the infectious period for rubella is 11 days):

Age category	Average annual force of infection	Average daily force of infection	Number susceptible[1]	Number infectious
Young	0.13286	3.64×10^{-4}	5012	
Middle-aged	0.0417	1.14×10^{-4}	3083	
Old	0.0417	1.14×10^{-4}	2739	

[1.] The number of susceptible individuals in each age category have been calculated using the expressions in the Appendix; you should find that you get exactly the same values by reading off the number of susceptible individuals in each age group from your Berkeley Madonna model at this stage, or by multiplying the population size of young, middle-aged and old individuals by the corresponding proportion of individuals in these age groups who are susceptible.

Extending the ideas covered in the lecture, the age-specific forces of infection λ_y, λ_m and λ_o are related to the WAIFW matrix and to the number of young, "middle-aged" and old infectious cases in the population through the following equation:

$$\begin{pmatrix} \lambda_y \\ \lambda_m \\ \lambda_o \end{pmatrix} = \begin{pmatrix} \beta_{yy} & \beta_{ym} & \beta_{yo} \\ \beta_{my} & \beta_{mm} & \beta_{mo} \\ \beta_{oy} & \beta_{om} & \beta_{oo} \end{pmatrix} \begin{pmatrix} I_y \\ I_m \\ I_o \end{pmatrix}$$

2. Calculate appropriate contact parameters b_yy, b_ym etc for the following WAIFW matrix (A):

$$\begin{pmatrix} \beta_1 & 0 & 0 \\ 0 & \beta_2 & 0 \\ 0 & 0 & \beta_3 \end{pmatrix}$$

(Hint: first write out the full equations relating the daily force of infection to each of the beta parameters and the number of infectious individuals; by rearranging the equations, you should then be able to calculate all the beta values)

3. If you wish, calculate appropriate contact parameters b_yy, b_ym etc for the following WAIFW matrix (B); alternatively, if you are short of time, use the values provided in the footnote[1]:

$$\begin{pmatrix} \beta_1 & \beta_2 & \beta_3 \\ \beta_2 & \beta_2 & \beta_3 \\ \beta_3 & \beta_3 & \beta_3 \end{pmatrix},$$

(Hint: to calculate the beta values, follow the hint for the preceding step; you should then be able to calculate β_3; substitute the value for β_3 into your second equation and you should be able to calculate β_2; substitute the values for β_2 and β_3 into the first equation and you should be able to calculate β_1.)

Q1.2 Which WAIFW structure – A or B - is the most realistic in a given population?

Q1.3 In which of the following populations should it be easiest to control rubella transmission using childhood MMR vaccination:

i) a population with mixing patterns described by WAIFW A

ii) a population with mixing patterns described by WAIFW B?

Why?

We will now analyse the different effects that childhood MMR vaccination might have in populations with the mixing patterns described by the above WAIFW matrices.

PART II: The implications of heterogeneous mixing

1. Incorporate the values for the contact parameters *b_yy, b_ym, b_yo* etc for WAIFW A into your model and run the model assuming that no individuals in the population receive MMR vaccination. *(Note: to incorporate numbers such as 2.3×10^{-5} type in 2.3e-5).*

Q2.1 How do the long-term values for

i) the proportion of individuals who are susceptible

ii) the age-specific daily number of new infections per 100,000 population

compare against that those which you wrote down from the original model in step 2 (page 3 - 4)? Is this what you would expect? Why?

2. Save your model as "WAIFWA". Incorporate the contact parameters for WAIFW B into your model. Save the model as "WAIFWB" and re-run the model.

Q2.2 How do the long-term values for

i) the proportion of individuals who are susceptible

ii) the age-specific daily number of new infections per 100,000 population compare against that those predicted by the model using the mixing patterns of WAIFWA? Is this what you would expect? Why?

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[1] Step 3: You should find that the values for β_1, β_2 and β_3 for WAIFW B are 1.66×10^{-5} , 4.16×10^{-6} , and 4.16×10^{-6} per day respectively.

2. Check your answer by setting up a figure plotting the daily force of infection among young, middle-aged and old individuals and comparing the force of infection predicted by the two models.
Reminder: To set up a new figure with the force of infection, click on the "New Page" button  *on the toolbar. If buttons for the force of infection are not available at the bottom of this window, double click in the middle of this new figure. This will open up a "Choose variables" window. Double click on the variables that you'd like to plot from the list in the left hand side of this window so that they appear in the list under the "Y Axes" section. Click on OK to continue and re-run the model.*

You can check your models against those in the files "WAIFWAfin.mmd" and "WAIFWBfin.mmd" if you think you are getting unexpected results.

In previous practicals, you calculated that the herd immunity threshold for rubella in the UK, assuming that individuals mixed randomly, was about 86% and that the basic reproduction number was 6.95.

3. Return to the file "WAIFWB" and run the model using the critical levels of vaccination coverage (86%) calculated for the UK.

Q2.3 What happens to the age-specific proportion of individuals who are susceptible and the daily number of new infections per 100,000 population in the model? Why?

Q2.4 What happens to the age-specific proportion of individuals who are susceptible and the daily number of new infections per 100,000 population if you introduce 86% effective vaccination coverage into a population mixing according to WAIFW A? Why?

As you shall see in the next practical, the R_0 for populations with mixing patterns described by WAIFW A and B are about 10.9 and 3.6 respectively.

Q2.5 Is this consistent with your answer to the previous question?

4. Use these values of the basic reproduction number to calculate the critical levels of vaccination coverage for these populations and check that vaccination at these levels in the model population results in patterns in the age-specific daily number of new infections per 100,000 population that you would expect.

Q2.6 What do you conclude from this exercise...?!

In the next practical, you will see how the basic reproduction number can be estimated for different assumptions about mixing between individuals.

Further exercises

If you have finished the practical early or if you wish to consolidate your understanding of the concepts covered in this session, please try the following exercises:

1. Exercises accompanying models 7.1 and 7.2 of the recommended course text[1] (see www.anintroductiontoinfectiousdiseasemodelling.com).

2. The paper and pen exercises 7.1, 7.2, 7.3 at the end of chapter 7 of the recommended course text[1]. Solutions are available from the book's website.

References

1. Vynnycky E, White RG. An Introduction to Infectious Disease Modelling". Oxford University Press, Oxford 2010

Appendix

Summary of the differential equations in the model

The differential equations are as follows::

$$\frac{dS_y(t)}{dt} = B(1-v) - \lambda_y(t)S_y(t) - a_y S_y(t)$$
$$\frac{dS_m}{dt} = a_y S_y(t) - \lambda_m(t)S_m(t) - a_m S_m(t)$$
$$\frac{dS_o}{dt} = a_m S_m(t) - \lambda_o(t)S_o(t) - m_o S_o(t)$$

$$\frac{dE_y(t)}{dt} = \lambda_y(t)S_y(t) - a_y E_y(t) - fE_y(t)$$
$$\frac{dE_m(t)}{dt} = a_y E_y(t) + \lambda_m(t)S_m(t) - a_m E_m(t) - fE_m(t)$$
$$\frac{dE_o(t)}{dt} = a_m E_m(t) + \lambda_o(t)S_o(t) - m_o E_o(t) - fE_o(t)$$

$$\frac{dI_y(t)}{dt} = fE_y(t) - a_y I_y(t) - rI_y(t)$$
$$\frac{dI_m(t)}{dt} = a_y I_y(t) + fE_m(t) - a_m I_m(t) - rI_m(t)$$
$$\frac{dI_o(t)}{dt} = a_m I_m(t) + fE_o(t) - m_o I_o(t) - rI_o(t)$$

$$\frac{dR_y(t)}{dt} = Bv + rI_y(t) - a_y R_y(t)$$
$$\frac{dR_m(t)}{dt} = a_y R_y(t) + rI_m(t) - a_m R_m(t)$$
$$\frac{dR_o(t)}{dt} = a_m R_m(t) + rI_o(t) - m_o R_o(t)$$

where

$S_j(t)$, $E_j(t)$, $I_j(t)$ and $R_j(t)$ are the numbers of susceptible, pre-infectious, infectious and immune individuals in the j^{th} category (where j reflects the young, middle-aged or old category);

$\lambda_y(t)$, $\lambda_m(t)$ and $\lambda_o(t)$ are the forces of infection in the young, middle-aged and old respectively;

a_y and a_m are the rates at which young and middle-aged individuals age into the middle-aged and old compartments respectively;

m_o is the mortality rate among old individuals;

B is the total number of births into the population per unit time;

v is the proportion of newborn individuals who are effectively vaccinated;

f is the rate at which individuals become infectious following infection;

r is the rate at which infectious individuals recover from being infectious.

Expressions for the number of young and old individuals susceptible in the population

Using the notation defined above, the number of young, "middle-aged" and "older" individuals who are susceptible to infection (S_y(t), $S_m(t)$ and $S_o(t)$ respectively) at a given time *t* in the population described in the model satisfy the differential equations:

$$\frac{dS_y(t)}{dt} = -(\lambda_y(t) + a_y)S_y(t) + B$$

$$\frac{dS_m(t)}{dt} = a_y S_y(t) - (\lambda_m(t) + a_m)S_m(t)$$

$$\frac{dS_o(t)}{dt} = S_m(t)a_m - (\lambda_o(t) + m_o)S_o(t)$$

assuming that no individuals are vaccinated. The long-term (equilibrium) average number of young individuals who are susceptible to infection is then obtained by equating these expressions to zero. This gives:

$$S_y = \frac{B}{\lambda_y + a_y}$$

$$S_m = \frac{Ba_y}{(\lambda_y + a_y)(\lambda_m + a_m)}$$

$$S_o = \frac{Ba_y a_m}{(\lambda_o + m_o)(\lambda_y + a_y)(\lambda_m + a_m)}$$

Note that these expressions are specific to the population with the age distribution used in this model. See Anderson and May (1991) [p178] for expressions for the number of individuals susceptible to infection in a population with other more realistic mortality patterns.

Introduction to Infectious Disease Modelling and its Applications – 2018

Sessions 12-13: Groupwork

In these sessions, you are asked to work in your allocated groups to address the problem that you have been assigned.

Introduction to Infectious Disease Modelling and its Applications – 2018

Session 14: Calculating basic reproduction numbers for non-randomly mixing populations

Practical

Objectives

By the end of this session you should:

- Be able to write down the "Next Generation Matrix" for given mixing assumptions.
- Understand the relationship between the basic reproduction number and the Next Generation Matrix.

Introduction

In the last practical, we explored the impact of different levels of vaccination coverage in populations in which young, middle-aged and old individuals contacted each other according to the following WAIFW matrices:

WAIFW A

$$\begin{pmatrix} 1.81\times10^{-5} & 0 & 0 \\ 0 & 2.92\times10^{-5} & 0 \\ 0 & 0 & 3.35\times10^{-5} \end{pmatrix}$$

WAIFW B

$$\begin{pmatrix} 1.66\times10^{-5} & 4.16\times10^{-6} & 4.16\times10^{-6} \\ 4.16\times10^{-6} & 4.16\times10^{-6} & 4.16\times10^{-6} \\ 4.16\times10^{-6} & 4.16\times10^{-6} & 4.16\times10^{-6} \end{pmatrix}$$

In both populations, the age-specific proportion of individuals who were susceptible in the absence of vaccination were identical. However, in population A, the vaccine coverage needed to be at least 91% in order to control transmission, whereas that required for population B was about 73%. These differences reflect differences between the R_0 in these two populations, and you were told that the R_0 in population A was 10.9 and that in population B was 3.6.

This practical is structured into two parts. The first part of this practical illustrates how you would calculate the next generation matrix and part II illustrates an "indirect" method for calculating R_0. If you have time, try the supplementary questions for this session, which illustrate a "direct" method for calculating R_0.

PART I: Calculating the "Next Generation Matrix"

We first focus on how you can calculate the Next Generation Matrix for populations mixing according to WAIFW B.

Calculating the Next Generation Matrix for populations mixing according to WAIFWB

1. Open up the file R0waifb.xls. Otherwise, if you struggled with the last practical, you may prefer to work with the finished version of this file, R0wbfin.xls, in which all the expressions have already been set up.

You should see some blue cells (rows 2-20) which contain the parameters required to calculate the basic reproduction number, namely:

i) The average duration of infectiousness (assigned the name "ave_infous").

ii) The total number of individuals in the young, middle-aged and old categories (assigned the names N_y, N_m and N_o respectively).

iii) The proportion immune (currently set to be 0).

iv) The number of young, middle-aged and old susceptible individuals (assigned the names S_y, S_m and S_o respectively).

iv) The daily rate at which specific infectious and susceptible individuals in different age categories come into effective contact (assigned the names b_yy, b_ym, b_yo, b_my, b_mm, b_mo, b_oy, b_om and b_oo, and located in cells F17:H20), (*Note that you can see the name of a given cell by moving to that cell and looking in the box in the top left hand corner of your sheet, just below the menu bar*).

The orange cells in rows 22-29 will contain the entries for Next Generation Matrix, and have been assigned the names R_yy, R_ym, R_yo, R_my, R_mm, R_mo, R_oy, R_om and R_oo.

Q1.1 How many secondary infectious persons among young individuals will occur as a result of the introduction of i) 1 infectious young person ii) 1 infectious middle-aged person and iii) 1 infectious old person?

2. In cells F26, G26 and H26 set up appropriate expressions for the number of secondary infectious persons which would occur among **middle-aged** susceptible individuals as a result of the introduction of: i) 1 young infectious person ii) 1 middle-aged infectious person and iii) 1 old infectious person.

3. Similarly, in cells F27, G27 and H27 set up appropriate expressions for the number of secondary infectious persons which would occur among **old** susceptible individuals as a result of the introduction of: i) 1 young infectious person ii) 1 middle-aged infectious person and iii) 1 old infectious person.

Q1.2 How many secondary infectious persons does each young, middle-aged and old infectious person generate in a totally susceptible population?

We will calculate the basic reproduction number corresponding to this next generation matrix.

PART II: "Indirect" methods for calculating the basic reproduction number

As mentioned in the lecture, there is a mathematical proof (which is beyond the scope of this course – see reference list) which shows that, by repeatedly applying the Next Generation Matrix to some vector representing an initial infectious person introduced into a totally susceptible population, in which there is an "infinite supply of susceptible individuals", then

a) the number of secondary infectious persons resulting from each infectious person in each generation converges to the basic reproduction number and

b) the distribution of the infectious persons in each generation converges to a certain distribution, which is defined to be that of the "typical" infectious person.

We will now illustrate this feature and how it leads to a relatively straightforward method for calculating the basic reproduction number for different mixing patterns.

1. Select rows 43 and 58 together, click with the right mouse button and choose the unhide option.

You should now see some pink cells which contain the statistics relating to the number of infectious persons which result over time as a result of the introduction of one infectious person. At present, this person has been specified to be young.

Q2.1 According to cell B48, how many young infectious persons will occur in the first generation as a result of the introduction of this infectious individual?

2. Set up appropriate expressions for the numbers of

i) middle-aged infectious persons (in cell C48)

ii) old infectious persons (in cell D48), and

iiii) total number of infectious persons (in cell E48)

which will occur in the first generation as a result of the introduction of this infectious person.

Q2.2 According to cells G48-I48, what proportion of infectious persons in the first generation are young, middle-aged and old?

Q2.3 According to cell K48, how many secondary infectious persons resulted directly from the initial infectious person introduced into the population?

3. Copy down all the expressions for the first generation down until the 10^{th} generation.

4. Select columns N and Y together, click with the right mouse button and select the unhide option. You should now see graphs showing the age distribution of the infectious persons in each generation and the average number of secondary infectious persons resulting from each infectious person.

Q2.4 What happens to the age distribution of the new infectious persons in each generation after a few generations have occurred?

Q2.5 What is the average number of secondary infectious persons resulting from each infectious person after a few generations have occurred?

5. Calculate the level of coverage required to control transmission in a population which mixed according to WAIFW B assuming that the basic reproduction number equalled the value in the last question.

6. Use the Berkeley Madonna file "WAIFWB R0.mmd" to check if this level of coverage is above the herd immunity threshold for this population. The model in this file is identical to the one which you used in the last practical, but in which all the β parameters for WAIFW B have already been set up.

7. Return to the spreadsheet and change the numbers of infectious persons introduced into the population at the start to take the following values:

i) 20, 50, 30 young, middle-aged and old infectious persons respectively.
ii) 30, 20 and 2 young middle-aged and old infectious persons respectively.
iii) 0.5, 0.2 and 0.3 young, middle-aged and old infectious persons respectively.

Q2.6 How does changing the values for the numbers of infectious persons introduced into the population at the start alter your answer to the questions 2.4 and 2.5?

The above method can also be used to calculate the net reproduction number if, for example, a proportion of the population is immunized.

8. Change the value for the parameter prop_imm to see what happens to the average number of secondary infectious persons resulting from each infectious person after a few generations have occurred if the following proportions of the population are immune:

i) 25%
ii) 50%
iii) 72.5%
iii) 75%

In your spare time, you may like to repeat the above exercise using the transmission parameters relating to WAIFW A; you should find that the basic reproduction number corresponding to this matrix is about 11 (depending on the number of decimal places that you use for your β parameters in the calculations).

Further exercises

If you have finished the practical early or if you wish to consolidate your understanding of the concepts covered in this session, please try the following exercises:

1. Supplementary exercises (see the supplementary questions folder on Moodle or in the network folder with the model files), which illustrate how you can calculate the basic reproduction number by using "direct" methods.

2. Exercises accompanying models 7.3, 7.4 and 7.5 of the recommended course text[1] (see www.anintroductiontoinfectiousdiseasemodelling.com)

3. The paper and pen exercises 7.4 and 7.5 at the end of chapter 7 of the recommended course text[1]. Solutions are available from the book's website.

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1. Vynnycky E, White RG. An Introduction to Infectious Disease Modelling". Oxford University Press, Oxford 2010

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Diekmann O, Heesterbeek JAP. Mathematical epidemiology of infectious diseases. Model building, analysis and interpretation. 2000. Wiley, UK