Review of block 1: The basic methods and dynamics of infectious diseases

Emilia Vynnycky

Introduction to Infectious Disease Modelling and its Applications

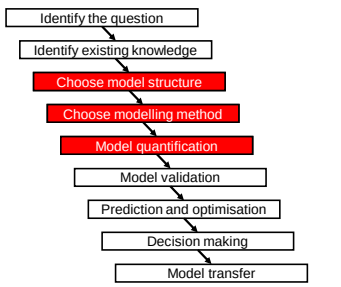
LSHTM

20th June 2018

Aims of the course

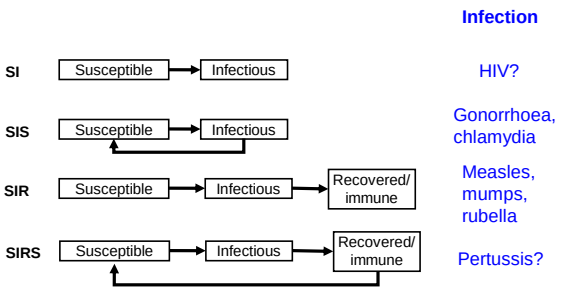
- To introduce you to the basic methods for setting up models
- To illustrate some of the areas of applications of modelling
- To illustrate some of the insights provided into the dynamics of infectious diseases

Model development steps

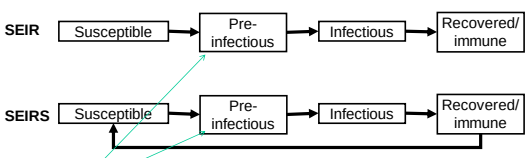


(after Habbema et al, 1996)

Examples of common model structures



Examples of model structures



NB Often referred to as the "Infected" or "Exposed" category in the modelling literature...

BUT....this can be misleading : everyone is "Exposed" and infectious individuals can be considered "infected".

Stage 4: Choose type of modelling method

2 main types:

Stochastic **– to be discussed in Block 3**

- incorporate chance variation
- provide the probability of a given outcome or range in which the outcome is likely to occur eg
  - probability that transmission ceases
  - 95% certain that 10-15 cases will be seen

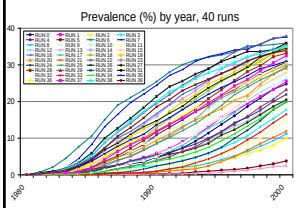
Deterministic models

- describe what will happen on average in a population
- individuals are subdivided into categories ("compartments")
- describe transitions between compartments

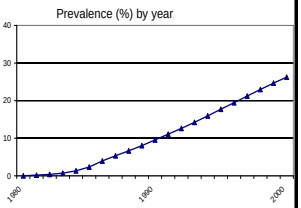
Stage 4: Choose type of modelling method

Examples of output from a deterministic and a stochastic model

Stochastic model



Deterministic model



Stage 4: Choose type of modelling method

Deterministic models are set up using either difference or differential equations

Difference equations calculate the number in each infection category using discrete time steps e.g. 1, 2, 3 days etc

number of cases tomorrow =
number of cases today
+ number of new cases with onset between today and tomorrow
– the number of cases who recover between today and tomorrow

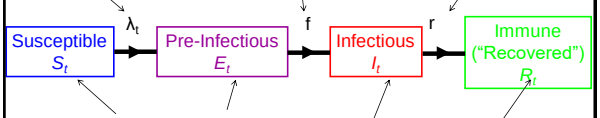
Differential equations calculate the number in each infection category using time steps which are "infinitesimally" small, i.e. in continuous time

Developing the measles model using difference equations – key definitions

Risk of a susceptible person being infected between time t and t+1; also known as the force of infection or the incidence risk

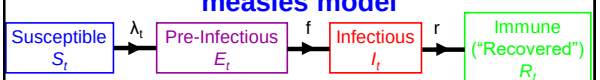
Proportion of pre-infectious individuals who become infectious between time t and t+1

Proportion of infectious individuals who recover to become immune between time t and t+1



Number of susceptible, pre-infectious, infectious and immune individuals at time t

Summary of the difference equations for the measles model



$S_{t+1} = S_t - \lambda_t S_t$

$E_{t+1} = E_t + \lambda_t S_t - f E_t$

$I_{t+1} = I_t + f E_t - r I_t$

$R_{t+1} = R_t + r I_t$

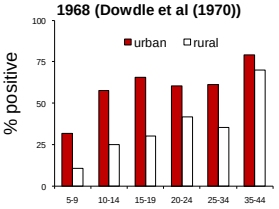
The force (or risk) of infection, λ_t

- Depends on the number of infectious individuals and rate at which susceptible individuals come into **effective contact** with an infectious individual

Defined as contact that is sufficient to lead to infection if it occurs between a susceptible and an infectious person

NB depends on the infection and the setting

Positivity for rubella antibodies in urban and rural Panama, 1968 (Dowdle et al (1970))

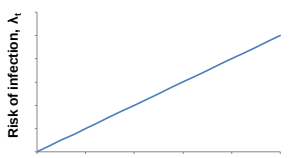


The force (or risk) of infection, λ_t

The simplest assumption: individuals mix randomly or the "mass action principle"

i.e. Risk of infection is proportional to the number of infectious individuals, I_t:

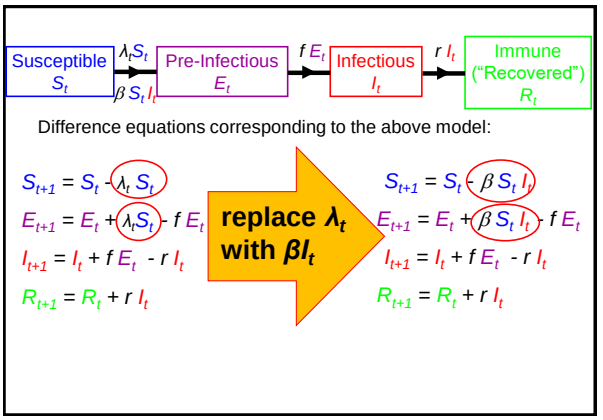
$\lambda_t = \beta I_t$



Precise definition of β:
The per capita (or per person) rate at which two specific individuals come into effective contact per unit time

Also known as "transmission rate", "transmission parameter" , "transmission probability" etc

During the course, it will usually be referred to as the "rate at which two specific individuals come into effective contact per unit time"



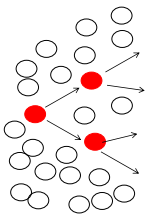
Difference equations corresponding to the above model:

$S_{t+1} = S_t - \lambda_t S_t$
$E_{t+1} = E_t + \lambda_t S_t - f E_t$
$I_{t+1} = I_t + f E_t - r I_t$
$R_{t+1} = R_t + r I_t$

replace λ_t with βI_t

$S_{t+1} = S_t - \beta S_t I_t$
$E_{t+1} = E_t + \beta S_t I_t - f E_t$
$I_{t+1} = I_t + f E_t - r I_t$
$R_{t+1} = R_t + r I_t$

Summary of contact parameters



R_0 - the average number of secondary infectious individuals resulting from one infectious person introduced into a totally susceptible population

Example: $R_0=2$

"ecr" (c_e) - the number of individuals effectively contacted by each person per unit time ("effective contact number" - or "effective contact rate")

"ecr" = R_0/duration of infectiousness (D)

Example: if D = 2days, ecr = 2/2 = 1 per day

β - the (per capita) rate at which 2 specific individuals come into effective contact per unit time

β = "ecr"/Total population size (N)

= R_0/(DN)

Example: $\beta = 2/(2\times25) = 0.04$ (per person) per day

Summary of "contact" parameters (cont)

λ_t - the risk that a susceptible individual is infected per unit time

Assuming random mixing, the risk (or force) of infection is proportional to the number of infectious individuals:

$\lambda_t = \beta I_t$

Input parameters (1)

The parameters which go into difference equations should be risks

e.g. the number of individuals who are infectious at time t+1 =

{number who were infected at time t}

×

{proportion who became infectious between t and t+1

However, under for most situations, the risk ≈ rate

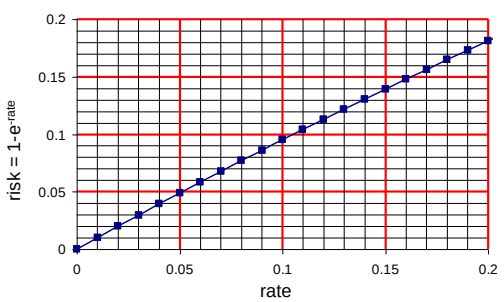
From previous training you may recall:

Risks and rates are related through the following expression:

$risk = 1 - e^{-rate}$

If the rate is small, then $e^{-rate} \approx 1 - rate$, and so risk ≈ rate

An illustration of the relationship between risks and rates

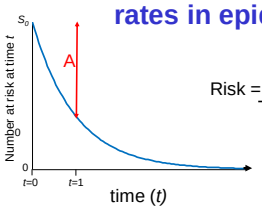


Revision (optional): incidence risks vs rates in epidemiology

Incidence risk = $\frac{\text{Number of new cases in a time period}}{\text{Population at risk at the start}}$

Incidence rate = $\frac{\text{Number of new cases}}{\text{Total person-time at risk}}$

Revision optional: incidence risks vs rates in epidemiology



Risk = number who became cases (A) / number at risk at the start (S_0)

Rate = Number of new cases (A) / Total person-time at risk

Accounts for fact that those who develop disease by point A would have become cases in the meantime

Input parameters (2)

The rate at which something occurs

= 1/{average time to the event}

The rate at which individuals become infectious

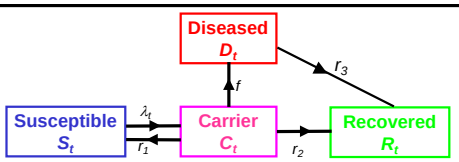
=1/{average pre-infectious period}

The rate at which individuals recover from being infectious

=1/{average duration of infectiousness}

The mortality rate

= 1/{average "duration of life" or the life expectancy}



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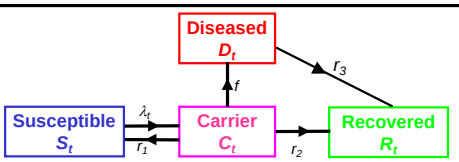
$D_{t+1} = D_t + f C_t - r_3 D_t$

$R_{t+1} = R_t + r_3 D_t + r_2 C_t$

What would you expect to happen to the population size over time?



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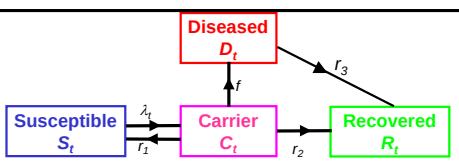
$R_{t+1} = R_t + r_3 D_t + r_2 C_t$

We can check if the equations are probably correct in this model by checking what the model predicts about the population size.

i.e. does $S_{t+1} + C_{t+1} + D_{t+1} + R_{t+1} = S_t + C_t + D_t + R_t$?



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$R_{t+1} = R_t + r_3 D_t + r_2 C_t$

i.e. $S_{t+1} + C_{t+1} + D_{t+1} + R_{t+1} = S_t + C_t + D_t + R_t$

i.e. population is constant over time

Model prediction, time step =1 days, rate at which 2 specific individuals come into effective contact per day (β)= 1.86×10^{-5} **per day**

Day number	Number of individuals who are:		
	Susceptible	Infectious	Newly infected by the end of the current time step ($\beta \times S_t \times I_t$)
50	9.45	24044	4.22
51	9.14	22381	3.80
52	9.26	20735	3.56
53	9.61	19131	3.41
54	10.11	17586	3.30
55	10.72	16114	3.21

Model prediction, time step =5 days, rate at which 2 specific individuals come into effective contact per 5 days (β)= 9.29×10^{-5} per 5 days

Day number	Number of individuals who are:		
	Susceptible	Infectious	Newly infected by the end of the current time step ($\beta \times S_t \times I_t$)
50	50387	11530	53948
55	-3551	24265	-8002

Differential equations describe the transmission dynamics of an infection assuming that individuals move between categories at a continuous rate

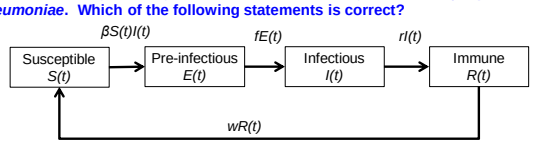
Differential equations describe the dynamics in terms of the rate of change in eg the number of susceptible individuals

NB The rate of change in the number of individuals =

+ the number who enter the category

- the number who exit the category

Q1. The following is a diagram of the transmission dynamics of *Mycoplasma pneumoniae*. Which of the following statements is correct?



a) The model will predict that the total population size will decrease over time

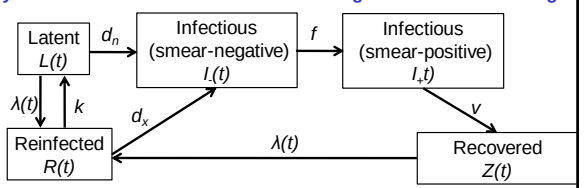
b) The model will predict that the total population size will increase over time.

c) The model will predict that the total population size will remain unchanged over time.

d) The rate of change in the number of Immune individuals is given by the following equation: $\frac{dR(t)}{dt} = r - w$

e) The rate of change in the number of Immune individuals is given by the following equation: $\frac{dR(t)}{dt} = rI(t) - wR(t)$

Q2. The following is a simplified diagram of the transmission dynamics of *M tuberculosis* in a closed high transmission setting.



Smear-negative and smear-positive individuals are both infectious; however, smear-negative individuals are 25% less infectious than are smear-positive individuals.

The *per capita* rate at which smear-positive individuals come into effective contact with others is denoted by the symbol *ß*.

Which of the following statements is correct?

a) The rate of change in the total number of infectious individuals ($I(t) = I_+(t) + I_-(t)$) is given by the following equation:

$$\frac{dI(t)}{dt} = d_n L(t) + d_x R(t) - vI_+(t)$$

b) The rate of change in the total number of infectious individuals ($I(t) = I_+(t) + I_-(t)$) is given by the following equation:

$$\frac{dI(t)}{dt} = d_n L(t) + d_x R(t) - fI_-(t) - vI_+(t)$$

c) There are no errors in the following equation:

$$\frac{dL(t)}{dt} = -\lambda(t)R(t) + kL(t) - d_n L(t)$$

d) The force of infection is given by the following equation:

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

e) The force of infection is given by the following equation:

$$\lambda(t) = \beta I_+(t) + 0.25\beta I_-(t)$$

NB It is often useful to draw the model corresponding to a set of differential equations.

Exercise:

Draw the diagram of the model implicit in the following equations:

$$\frac{dS}{dt} = -\lambda(t)S(t) + r_1 E(t)$$

$$\frac{dE}{dt} = \lambda(t)S(t) - r_1 E(t) - r_2 E(t) + r_3 R(t)$$

$$\frac{dR}{dt} = -r_3 R(t) + r_2 E(t)$$

Notation for difference and differential equations

Difference equations

S_t λ_t

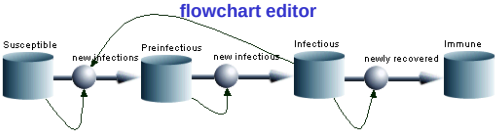
Subscripts to denote dependency on time (or other factors)

Differential equations

$S(t)$ $\lambda(t)$

"t" is enclosed in parentheses to denote events occurring continuously

Summary of setting up models using Berkeley Madonna's flowchart editor



Flow arrows contain the equations for the number of individuals who move from one category to the next per unit time

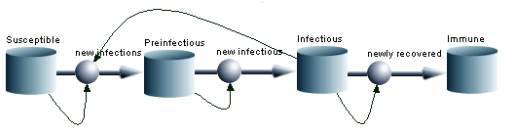
e.g. new infections = beta*Susceptible*Infectious

Arc arrows tell Berkeley Madonna which components depend on each other

e.g. the number of new infections/unit time depends on the number of Susceptibles

=> arc arrow from *Susceptible* compartment to new infections flow arrow

Summary of the relationship between flow diagrams and differential



$\frac{dS(t)}{dt} = -\beta S(t)I(t)$ =new infections

$\frac{dE(t)}{dt} = \beta S(t)I(t) - fE(t)$ =new infectious

$\frac{dI(t)}{dt} = fE(t) - rI(t)$ =newly recovered

$\frac{dR(t)}{dt} = rI(t)$

Approaches for setting up models in Berkeley Madonna

•Flowcharts provide a quick way of setting up models without worrying too much about differential equations

•However, the differential equations cannot be edited directly in the model; you can edit equations in the flow arrows and global windows.

•If you prefer to work with exclusively with equations, you can either:

- discard your flowchart completely
- set up your model using the equations editor

BOTH APPROACHES ARE EQUIVALENT AND GIVE IDENTICAL RESULTS!

Further practice with setting up models is provided in the practical at the end of this block.

Session 5: Insights into the epidemiology of infections which are derivable from the simple model

1. What determines whether or not the number of infectious individuals increases following the introduction of an infectious person into a totally susceptible population?

2. How fast might we expect the number of infectious individuals to increase following the introduction of an infectious person into a totally susceptible population and what can we infer from it?

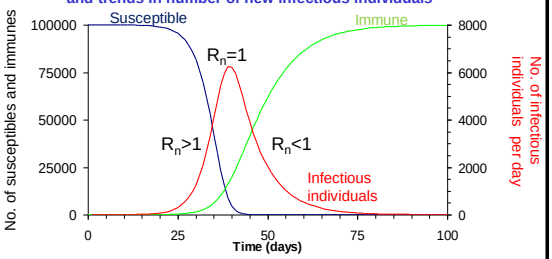
3. Why does the incidence of an immunizing infection cycle over time?

4. What other factors lead to cycles in incidence?

5. What value might we expect for the inter-epidemic period?

Why do we see cycles in the incidence of immunizing infections?

Relationship between the net reproduction number, proportion susceptible and trends in number of new infectious individuals



no. of new infectious individuals/day	↑	peaking	↓
R_n	>1	=1	<1
Proportion susceptible (s):	>1/R_0	=1/R_0	<1/R_0

Revision of the relationship between the net and basic reproduction numbers and the proportion susceptible and trend in incidence

Note that

$$R_n = R_0\, s$$

where s is the proportion of the population that is susceptible

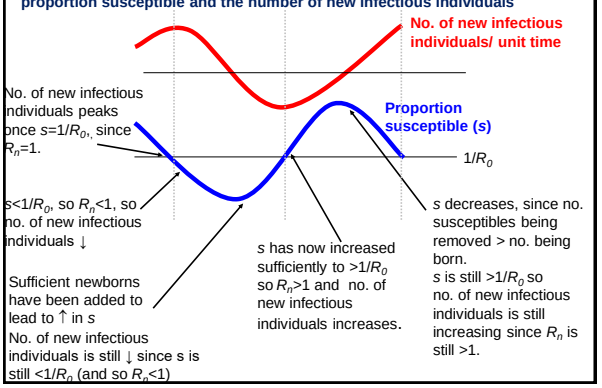
If the incidence is increasing, $R_n > 1$

So $R_n = R_0\, s > 1$

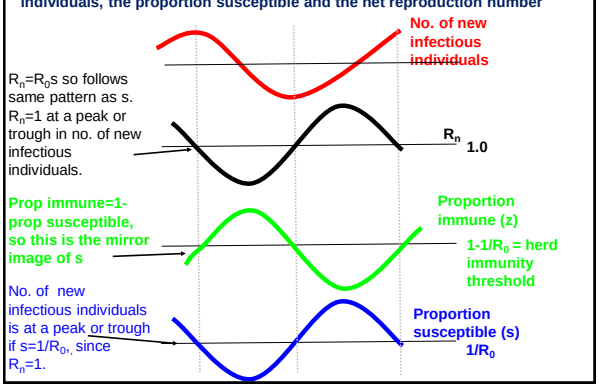
Rearranging this expression implies that when the incidence is increasing:

$$s > 1/R_0$$

Explanation for the epidemic cycles for measles – the relationship between the proportion susceptible and the number of new infectious individuals



The relationship between the cycles in the number of new infectious individuals, the proportion susceptible and the net reproduction number



5. What should be the inter-epidemic period for an immunizing infection?

"It can be shown that" the inter-epidemic period (T) is given by:

$$T = 2\pi\sqrt{A(D+D')}$$

where: A is the average age at infection

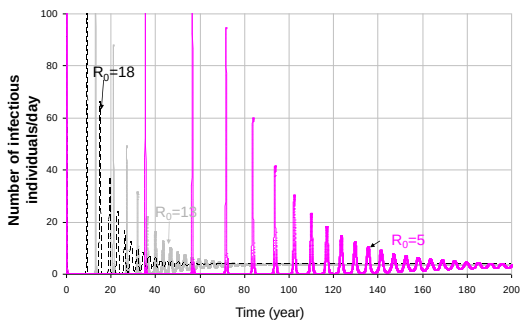
D' is the average pre-infectious period

D is the average duration of infectiousness

Using the expression R_0 = 1+L/A, this expression can be rearranged to give:

$$T = 2\pi\sqrt{\frac{L(D+D')}{R_0 - 1}}$$

Summary of the effect of the R_0 on the cycles in the number of new infectious individuals (practical revision)



Utility of inter-epidemic period calculations:

Quantifying the effect of vaccination

(vaccination => reduction in prevalence of infectious individuals

=> postpones infection until later in life

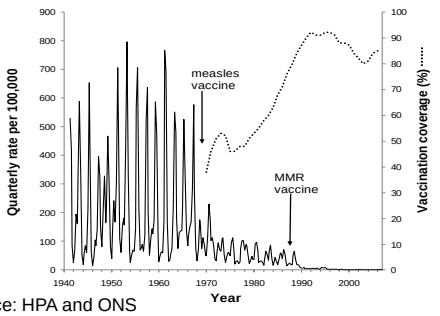
=> ↑ average age at infection

=> ↑ inter-epidemic period

NB for some infections, the inter-epidemic period has been shorter than expected following vaccination

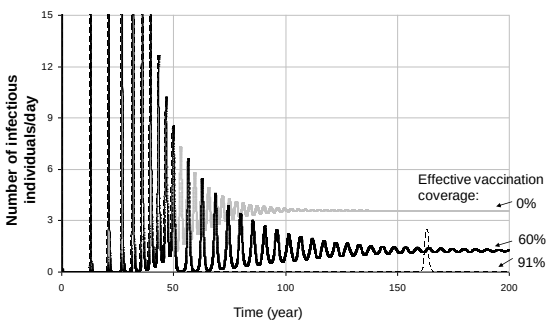
=> Important role of age-dependent contact in determining transmission…

Quarterly measles notifications in England and Wales, 1941-2010



Data source: HPA and ONS

Model predictions of the effect of the vaccination on the inter-epidemic period (practical revision)



Q3. The inter-epidemic period for rubella in some populations was roughly 4 years before the introduction of vaccination. The value for R_0 for rubella was about 7. Which one of the following statements is correct?

a) The introduction of rubella vaccination among newborns was likely to lead to a reduction in the inter-epidemic period.

b) The introduction of rubella vaccination among newborns was likely to lead to an increase in the inter-epidemic period.

c) When the incidence of rubella was at a peak, on average, 25% of the population was likely to be susceptible.

d) When the incidence of rubella was increasing, the proportion of the population that was susceptible was less than 14%

e) The inter-epidemic period of rubella was likely to be less than that for measles, for which the value for R_0 was about 13

Key messages from block 1

1. Deterministic models can be written and set up using difference or differential equations:

$S_{t+1} = S_t - \beta S_t I_t$

$E_{t+1} = E_t + \beta S_t I_t - f E_t$

$I_{t+1} = I_t + f E_t - r I_t$

$R_{t+1} = R_t + r I_t$

$$\frac{dS}{dt} = -\beta S(t)I(t)$$

$$\frac{dE}{dt} = \beta S(t)I(t) - fE(t)$$

$$\frac{dI}{dt} = fE(t) - rI(t)$$

$$\frac{dR}{dt} = rI(t)$$

2. For the incidence of an immunizing infection to increase once an infectious person enters a totally susceptible population, $R_0 = \beta ND > 1$
3. $R_n = R_0 \times$ proportion susceptible
4. For an endemic infection, average $R_n = 1$, so $R_n = R_0 \times s = 1$

   $\therefore s = 1/R_0$ (on average) if the infection is endemic.

   For an epidemic to occur, $s > 1/R_0$