Session 5: The natural dynamics of infectious diseases

Introduction to Infectious Disease Modelling and its Applications

19th June 2018

Aims and objectives

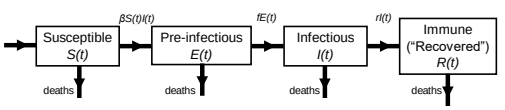
Aim: To discuss the insights into infectious disease epidemiology provided by simple models of immunizing infections

Objectives

By the end of this lecture you should:

- know what determines whether the incidence of an infection increases or decreases in a population
- be aware of methods for calculating R0 for an infection from the growth rate of an outbreak
- be able to explain the theory underlying the cycles in the incidence of immunizing infections
- be able to calculate the inter-epidemic period for an immunizing infection

General structure of the model set up so far:

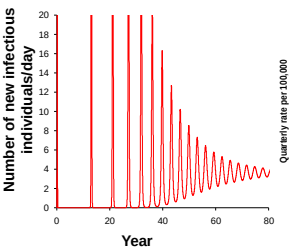


Assumptions:

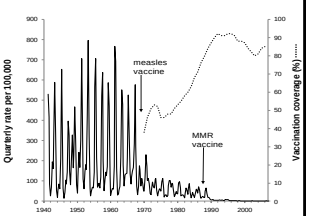
- Random mixing
- Individuals not stratified by age
- Population size constant over time

Comparison between the predictions of the simple model and observed data

Model predictions



Quarterly measles notifications in England and Wales, 1941-2010 (HPA and ONS)



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

1. What determines whether or not the numbers of infectious individuals increases after an infectious person enters a totally susceptible population?

2. How fast might the number of infectious individuals increase 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 the epidemic cycles?

5. What inter-epidemic period might we expect to see?

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

Simple answer:

Reminder (from difference equations lecture)

β is the "the *per capita* rate at which two specific individuals come into effective contact per unit time"

If in a population, of size ***N,*** each person 'effectively contacts' ***ecr*** other people per unit time, then

$$\beta = ecr / N$$

If the duration of the infectious period is ***D***, then:

$$R_0 = ecr \times D$$

So, $\beta = R_0/(N \times D)$

Reminder (from difference equations lecture)

$\beta = R_0/(N \times D)$

This expression can be rearranged to give the following expression for the basic reproduction number:

$$R_0 = \beta ND$$

or, equivalently:

$$R_0 = \frac{\beta N}{r}$$

where *r* is the rate at which infectious individuals recover from being infectious

We will show that βND must be bigger than 1 for the number of infectious individuals to increase following the introduction of an infectious person into a totally susceptible population

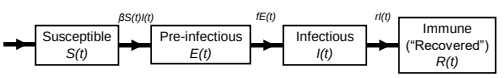
Proof that βND>1 for an epidemic to occur following the introduction of an infectious individual into a totally susceptible population

If the number of infectious individuals increases then:

the ***rate of change*** in the number of ***pre-infectious*** individuals **must be positive**
and
the ***rate of change*** in the number of ***infectious*** individuals over time **must be positive**

$$\frac{dE}{dt} > 0 \quad \text{and} \quad \frac{dI}{dt} > 0$$

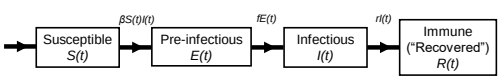
Proof that βND > 1 for an epidemic to occur



$\frac{dE}{dt}$ = + number newly infected per unit time
- number who become infectious per unit time
=

$\frac{dI}{dt}$ = + number who become infectious per unit time
- number who recover/unit time
=

Proof that βND > 1 for an epidemic to occur



$\frac{dE}{dt} > 0$ and $\frac{dE}{dt} = \beta S(t)I(t) - fE(t)$

then $\beta S(t)I(t) - fE(t) > 0$ and ***$\beta S(t)I(t) > fE(t)$***

$\frac{dI}{dt} > 0$ and $\frac{dI}{dt} = fE(t) - rI(t)$

then $fE(t) - rI(t) > 0$ and ***$fE(t) > rI(t)$***

Proof that βND > 1 for an epidemic to occur

If $\beta S(t)I(t) > fE(t)$ and $fE(t) > rI(t)$ then:

$\beta S(t)I(t) > rI(t)$

cancelling $I(t)$ from both sides, we see that:

$\beta S(t) > r$

for the number of infectious individuals to increase

Proof that $\beta ND>1$ for an epidemic to occur

When the population is totally susceptible, $S(t)$ = total population, (N)

Substituting N for $S(t)$ into the expression $\beta S(t) > r$ we get:

$$\beta N > r$$

and, after rearranging (dividing both sides by r), we see that the condition:

$$\frac{\beta N}{r} > 1$$

Since r = 1/(duration of infectiousness) =1/D, we see that $\beta ND>1$ for this to be true.

Since $\beta ND>1$ we obtain the result that $R_0 > 1$ for the number of infectious individuals to increase

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

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

2. How fast might the number of infectious individuals increase after one infectious person enters 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 the epidemic cycles?

5. What inter-epidemic period might we expect to see?

2. How fast should the number of infectious individuals increase and what can we infer from it?

According to theory, the rate of increase (Λ) is given by:

$$\Lambda = \frac{R_0 - 1}{D}$$

where D is the average duration of infectiousness.

Intuitive explanation:
at the end of the infectious period of the initial infectious person, R_0 infections will have occurred in the population and the initial infectious person will have recovered

The rate of increase/unit time =
(No. of infections at end of infectious period - No. of infections at start)
(duration of infectiousness)

What can be inferred from this rate of increase?

The expression $\Lambda = \frac{R_0 - 1}{D}$ can be rearranged to give R_0 :

$$R_0 = \Lambda D + 1$$

e.g. estimates of R_0 ranged from 4-11 for HIV, calculated using data from the early stages of the HIV epidemic in Uganda and Kenya

Note

- There are other variants of this expression (Wearing et al, Lipsitch et al, Anderson and May)
- It is only reasonably reliable during the early stages of an outbreak

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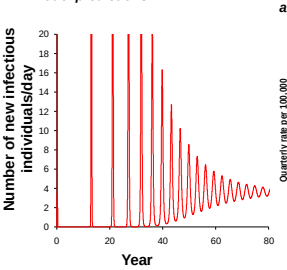
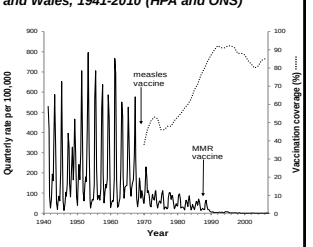
Comparison between the predictions of the simple model and observed data

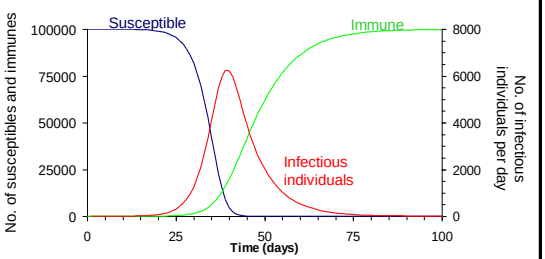
Model predictions



Quarterly measles notifications in England and Wales, 1941-2010 (HPA and ONS)



To understand cycles, let's look at a single outbreak



The answer lies with the relationship between R_0, the proportion of the population that is susceptible and the net reproduction number...

Revision of the relationship between the net and basic reproduction numbers

You may remember that

$$R_n = R_0 s$$

where *s* is the proportion of the population that is susceptible

If the number of new infectious individuals is increasing, $R_n > 1$

So $R_n = R_0 s > 1$

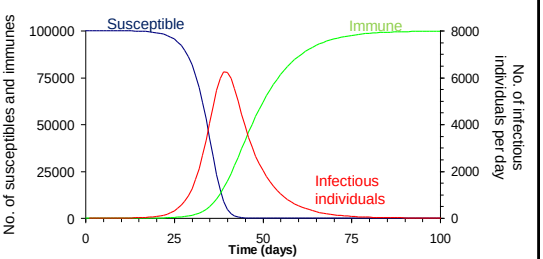
Rearranging this expression implies that when the number of new infectious individuals is increasing:

$$s > 1/R_0$$

Relationship between the net reproduction number and the proportion susceptible

No. of new infectious people	R_n	Proportion susceptible
increasing	>1	$>1/R_0$
decreasing	<1	$<1/R_0$
peaking	1	$1/R_0$

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



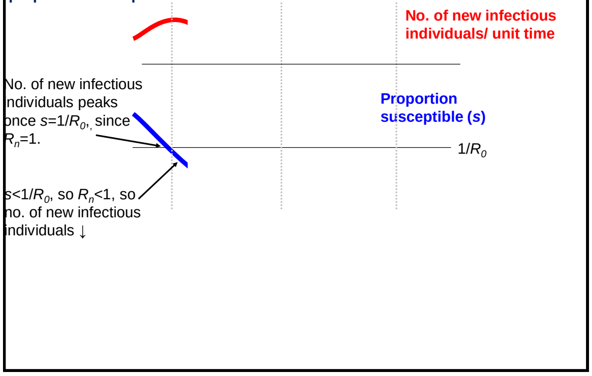
Summary of what happens during an epidemic

- No. of new infectious individuals increases as there are sufficient numbers of susceptibles for each infectious person to lead to > 1 secondary infectious person
- Proportion of susceptible individuals decreases
- Once this proportion is sufficiently low ($<1/R_0$), each infectious person leads to <1 infectious person, and the number of new infectious individuals starts to decrease

Summary of what happens during an epidemic (2)

- **If no new susceptibles are born into the population**, all the susceptibles are eventually depleted, and no new infections occur in the population
- Births provide a supply of new susceptibles into the population, fuelling continued infections.
- Changes in the proportion of the population that is susceptible because of newborns leads to epidemic cycles in immunizing infections

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



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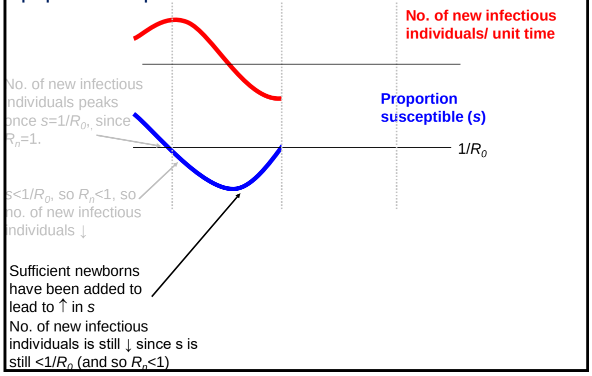

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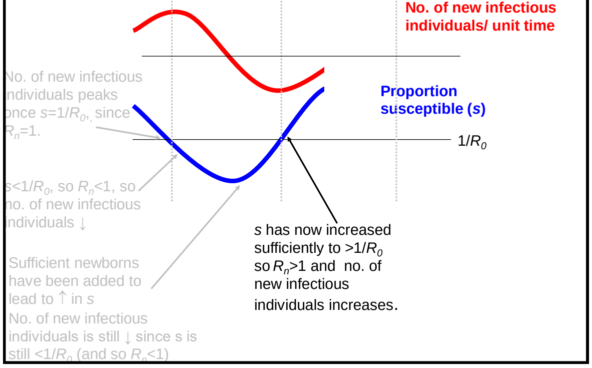

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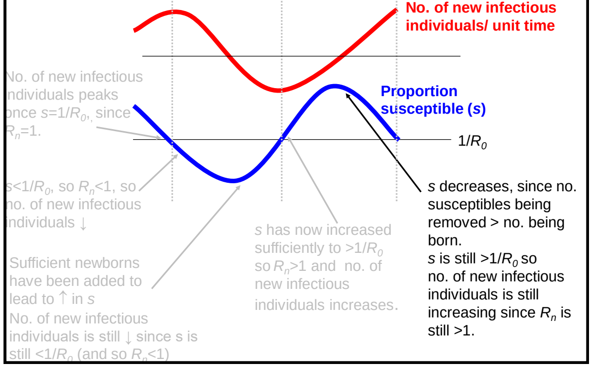

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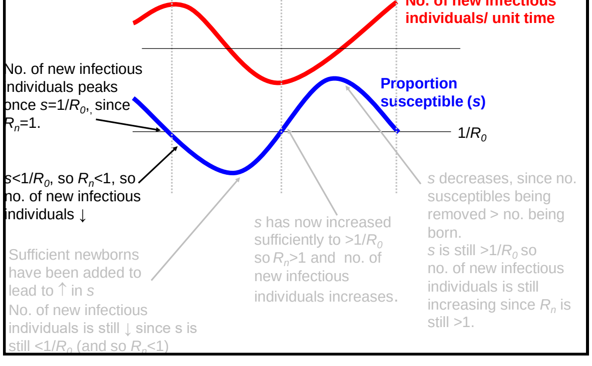

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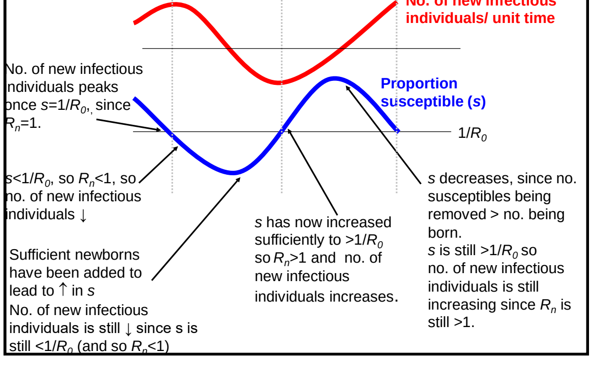
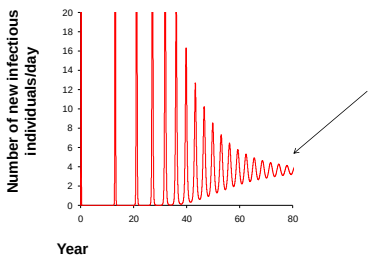


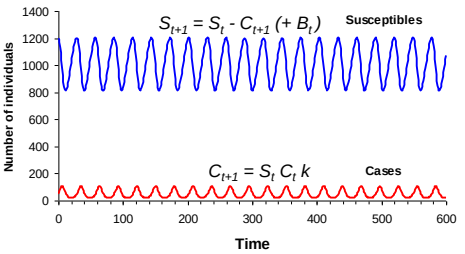
Predicted daily number of new infectious people with measles predicted



Cycles seem to become increasingly weaker ("damp" out)…

Is the model wrong?

NB. A v simple model (Hamer's mass action model) predicts that the cycles are sustained…



k = the proportion of total possible contacts between cases and susceptibles which leads to new infections (nowadays denoted by β)

Dilemma...

Hamer's model - the cycles do not damp out. However, the model is very (too?) simple

Differential/difference equations model - the cycles damp out, but assumptions are more realistic than those of Hamer's model

Which model should we trust?

Conclusion: There must be other factors which help to sustain the cycles:

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

4. What other factors lead to the epidemic cycles?

5. What inter-epidemic period might we expect to see?

4. What other factors lead to the epidemic cycles?

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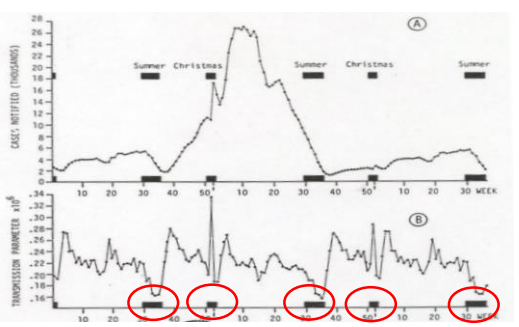
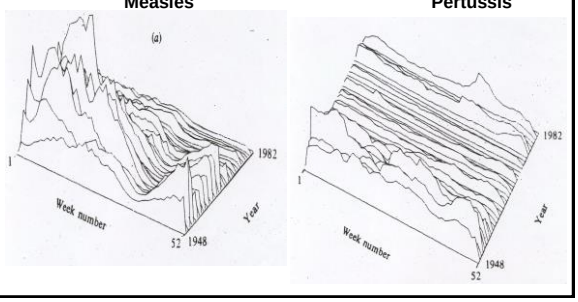
Evidence for "seasonal" transmission: the transmission parameter is lowest during school holidays



Seasonal patterns in measles and pertussis notifications, based on weekly case reports in England and Wales 1948-82 (Anderson et al (1982))

Measles **Pertussis**



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5. What inter-epidemic period might we see?

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

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

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:

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

The effect of R_0 on the inter-epidemic period will be discussed during the practical

Comparison between the observed and predicted inter-epidemic periods (Anderson and May (1991))

Infection	Location	Inter-epidemic period Calculated	Observed
Measles	England and Wales 1948-68	2	2
	Aberdeen, Scotland 1883-1902	2	2
	Baltimore, USA 1900-27	2	2
	Paris, France 1880-1910	2	2
	Yaounde Cameroon, 1968-75	1-2	1
	Ilesha, Nigeria, 1958-61	1-2	1
Rubella	Manchester, UK 1916-83	4-5	3.5
	Glasgow, Scotland, 1929-64	4-5	3.5
Mumps	England and Wales 1948-82	3	3
	Baltimore, USA 1928-73	3-4	2-4
Polio	England and Wales, 1948-65	4-5	3-5
Smallpox	India, 1868-1948	4-5	5
Chickenpox	New York City, USA, 1928-72	3-4	2-4
	Glasgow, Scotland, 1929-64	3-4	2-4
Scarlet fever	England and Wales, 1897-1978	4-5	3-6
Diphtheria	England and Wales, 1897-1979	4-5	4-6
Pertussis	England and Wales, 1970-82	3-4	3-4

Utility of inter-epidemic period calculations:

Quantifying the effect of vaccination

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

vaccination => reduction in prevalence of infectious cases

=> postpones infection until later in life

=> increases average age at infection

=> increases inter-epidemic period

NB for some infections, the inter-epidemic period has been shorter than expected following vaccination => mixing may be age-dependent...

Final conclusions

The above theory relates to simple immunizing infections – pre-infectious and infectious periods are short relative to the lifetime of individuals

The same logic cannot be applied for infections which

- do not confer immunity against re-infection
- have long incubation periods

For TB, the time interval between infection and disease may be as long as a lifetime, and conditions may change during this time...

Summary of Objectives

By the end of this lecture you should:

- know the "conditions" required for an infection to persist in a population
- be aware of methods for calculating R0 for an infection from the growth rate of an outbreak
- be able to explain the theory and factors underlying the cycles in the incidence of immunizing infections
- be able to calculate the inter-epidemic period for an immunizing infection

Summary of key messages

1. For the numbers of infectious individuals to increase for an immunizing infection once an infectious person enters a totally susceptible population, R_0……..

2.During the early stages of an epidemic of a new infection, R_0 can be estimated from the epidemic growth rate *(Λ):* $R_0 \approx 1+\Lambda D$ (and other equations!)

3. For an endemic infection, $R_n = 1$, so $R_n = R_0 \times s = 1$

$\therefore s = 1/R_0$ if the infection is endemic.

For an epidemic to occur, s ……

Summary of key messages

4. Changes in the proportion of the population that is susceptible resulting from the continuous entry of newborns leads to epidemic cycles for an immunizing infection.

5. Further factors, e.g. seasonal contact patterns are required for the cycles to persist.