Pathogens and hosts, epidemiology

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Overview

- Epidemiology
- Micro- and Macroparasites
- SIS model
- Basic reproductive number
- SIR model
- Vaccination
- Measles
- Ebola

Parasitism

- Parasitoids live a large part of their life on a host and cause considerable harm or death
- Parasitism is a lifestyle in which the parasite benefits from its host (+-)
- Parasites are smaller than their host
- It is like a very small predator, although the interaction need not result in death

Epidemiology:

- Is the study of a disease within a population of hosts
- Population biology and ecology of pathogens/parasites, vectors and hosts is important for disease control and management
- Links processes/parameters at the individual level to population level
- Uses mathematical models and statistical techniques

Two groups of parasites:

- Microparasites
  - Have direct and often rapid reproduction within the host
- Macroparasites
  - Do not multiply directly within their host

This difference leads to a convenient dichotomy

Macroparasites

- Do not multiply directly within their host

  - Are larger and often sexual, e.g parasitic helminths and arthropods
  - Disease intensity depends on burden

  As a consequence:

  • The individual *parasite* is a convenient basic unit of study

Microparasites

- Reproduce directly and rapidly within the host

- Are small and often asexual, e.g bacteria, viruses and protozoa
- Burden not very relevant/difficult to measure; host is either infected or not

As a consequence:

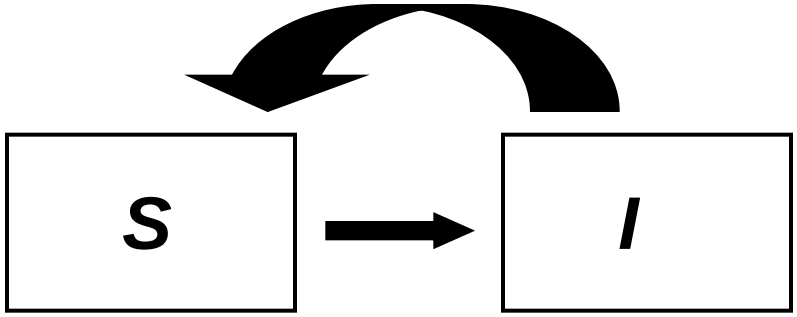
- The *host* individual is the convenient basic unit of study

Microparasites

- I will discuss two standard models (SIS and SIR) to describe the epidemiology of microparasites
- This model describes different classes of hosts
- And the processes of infection, recovery and mortality (+ births and deaths)

Host classes:

- Susceptible hosts can be infected by parasites
- Infected hosts carry the parasite
  - I will assume that all infected hosts transmit the parasite (not doing so leads to a slightly different model which has an extra class)
  - Infected individuals that recover return to the S class
- This is the SIS model



Transmission process

- Susceptible host can become infected
- This turns them into infecteds
- The rate with which susceptibles encounter infected is given by βSI, where β is the transmission parameter

Recovery process

- Infected hosts can recover
- If we assume that the rate of recovery is a constant (which is saying that the time until recovery is exponentially distributed), the per capita recovery rate is γ with $1/\gamma$ the average time until recovery
- We assume that the disease has no lasting effect, and doesnot kill

SIS model

- The SIS model reads

$$\frac{dS}{dt} = \gamma I - \beta SI$$

$$\frac{dI}{dt} = \beta SI - \gamma I$$

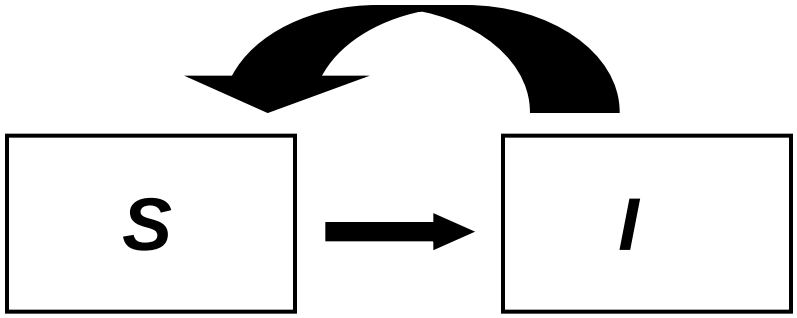
- This is like the Lotka-Volterra pp model, the Susceptibles act as “prey” for the pathogen. They do not disappear after becoming ill though

- In this model $\frac{dS}{dt} + \frac{dI}{dt} = 0$ so that *S+I=N* is constant

SIS model

- We can thus rewrite the model

$$\frac{dI}{dt} = \beta(N - I)I - \gamma I = \beta I(N - \frac{\gamma}{\beta} - I)$$



SIS model

- In the SIS model you return to a susceptible state after you have had the disease
- This is rarely true, but it could be a valid assumption for the common cold, or head lice
- The transmission process assumes that if your population is bigger (more S, more I), that there is more transmission
- This is often not the case, for instance, much of the transmission of head lice as well as the common cold, takes place in schools or in families
- A bigger population does not mean that school classes or families are bigger.

SIS model

- As the number of contacts is independent of population size it is often assumed that the transmission is proportional to the fraction of the population that is infected

SIS model

- The model then reads

$$\frac{dS}{dt} = \gamma I - \beta S \frac{I}{N}$$

$$\frac{dI}{dt} = \beta S \frac{I}{N} - \gamma I$$

- The total population size remains constant, and therefore

$$\frac{dI}{dt} = \beta (N - I) \frac{I}{N} - \gamma I = \beta I (1 - \frac{\gamma}{\beta} - \frac{I}{N})$$

SIS model

- We can rewrite this as the change in the fraction of the population that is infected:

$$\frac{d}{dt}\frac{I}{N} = \frac{1}{N}\beta(N-I)\frac{I}{N} - \gamma\frac{I}{N} = \beta\frac{I}{N}(1-\frac{\gamma}{\beta}-\frac{I}{N})$$

- Does the equation look familiar?

- What is the equilibrium?

SIS model

The equilibrium is

$$\frac{I^*}{N} = 1 - \frac{\gamma}{\beta}$$

$$\frac{S^*}{N} = \frac{\gamma}{\beta}$$

The parameter combination β/γ can be interpreted as the transmission rate times the average duration of the infection.

It is the average number of new infections that an infected individual produces in a completely susceptible population.

This is called the basic reproductive number: R_0.

R_0: The basic reproductive number

- The number of secondary infections caused by a single infected individual in a completely susceptible population
- If $R_0<1$ the disease will disappear
- If $R_0>1$ an epidemic is possible

SIS model

The equilibrium is

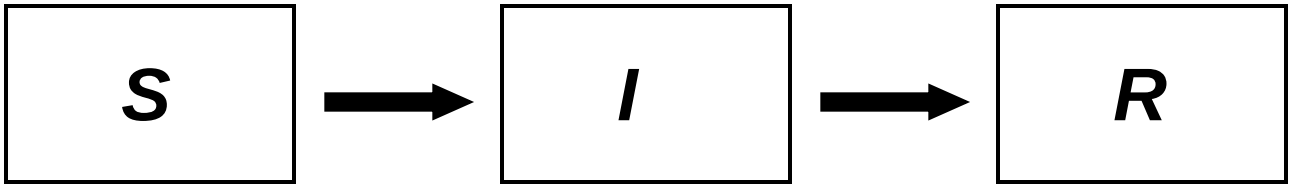
$$\frac{I^*}{N} = 1 - \frac{1}{R_0}$$

$$\frac{S^*}{N} = \frac{1}{R_0}$$

- If $R_0<1$ the disease will disappear
- If $R_0>1$ the disease has a non-trivial equilibrium

More elaborate: the SIR model

- **S**usceptible hosts can be infected by parasites
- **I**nfected hosts carry the parasite
  - I will assume that all infected hosts transmit the parasite (not doing so leads to a SEIR model, E stands for Exposed)
- **R**ecovered (immune) hosts do not transmit the parasite and cannot be infected



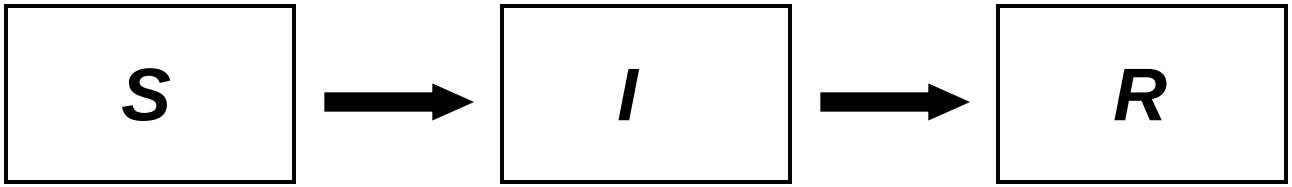
More elaborate: the SIR model

- In its simplest form the SIR model takes the form

$$\frac{dS}{dt} = -\beta S \frac{I}{N}$$

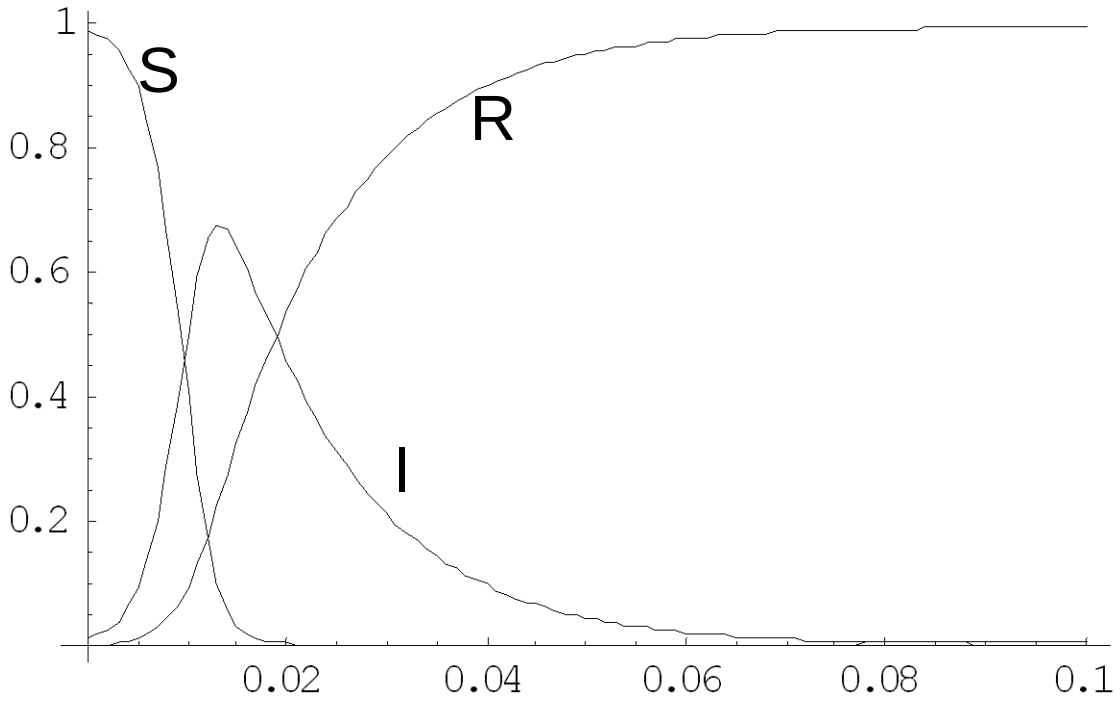
$$\frac{dI}{dt} = \beta S \frac{I}{N} - \gamma I$$

$$\frac{dR}{dt} = \gamma I$$



Solution: an epidemic

Fraction of population

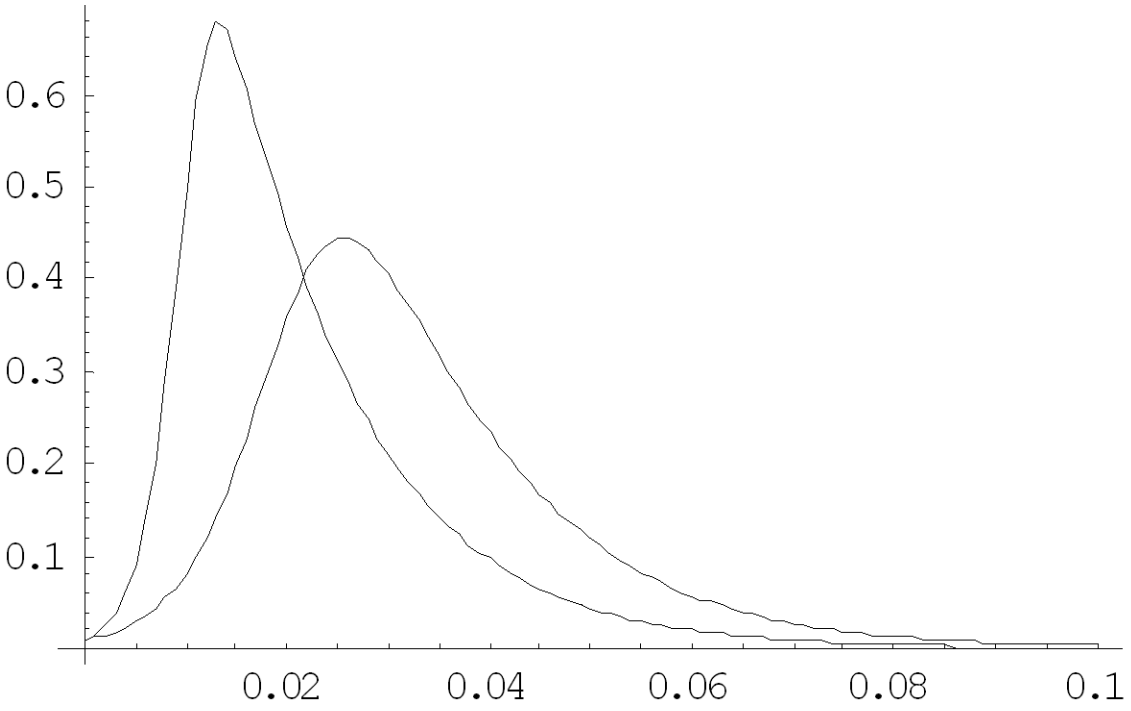


Time (years)

Note: the disease disappears in this case

Effect of decreasing the transmission rate

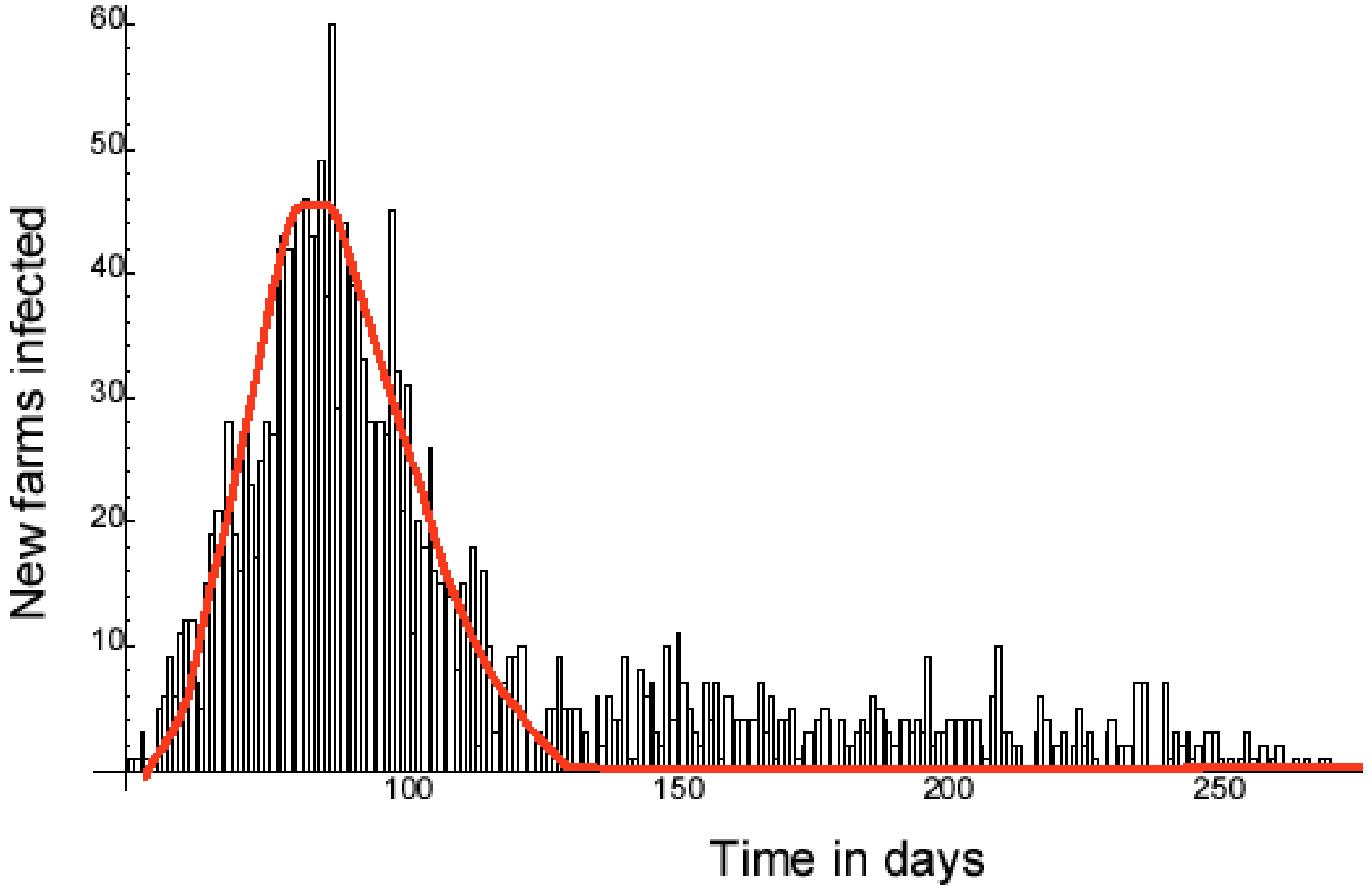
Infecteds as fraction of population



Time (years)

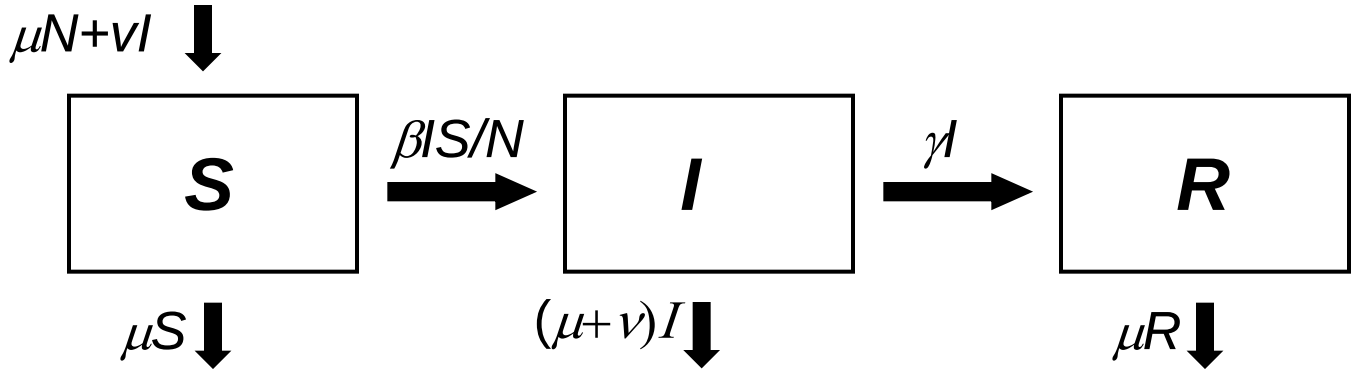
Campaign against AIDS in Vietnam

Outbreak of Foot and Mouth Disease in 2001



A more elaborate SIR model

- The model can easily be extended
- For instance, if we add natural death (with rate μ) and disease induced mortality, ν, we get (if we replace all dead by newborns)



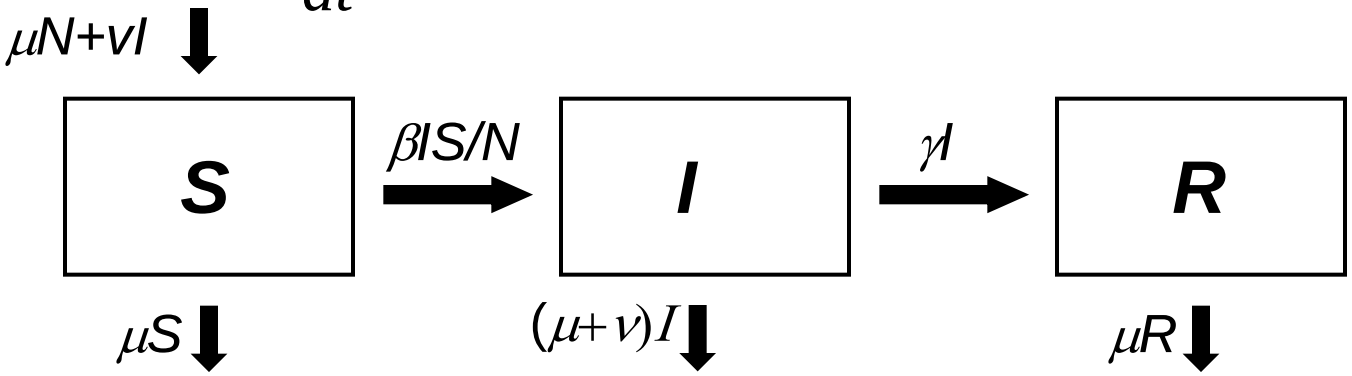
More elaborate: the SIR model

- The model reads:

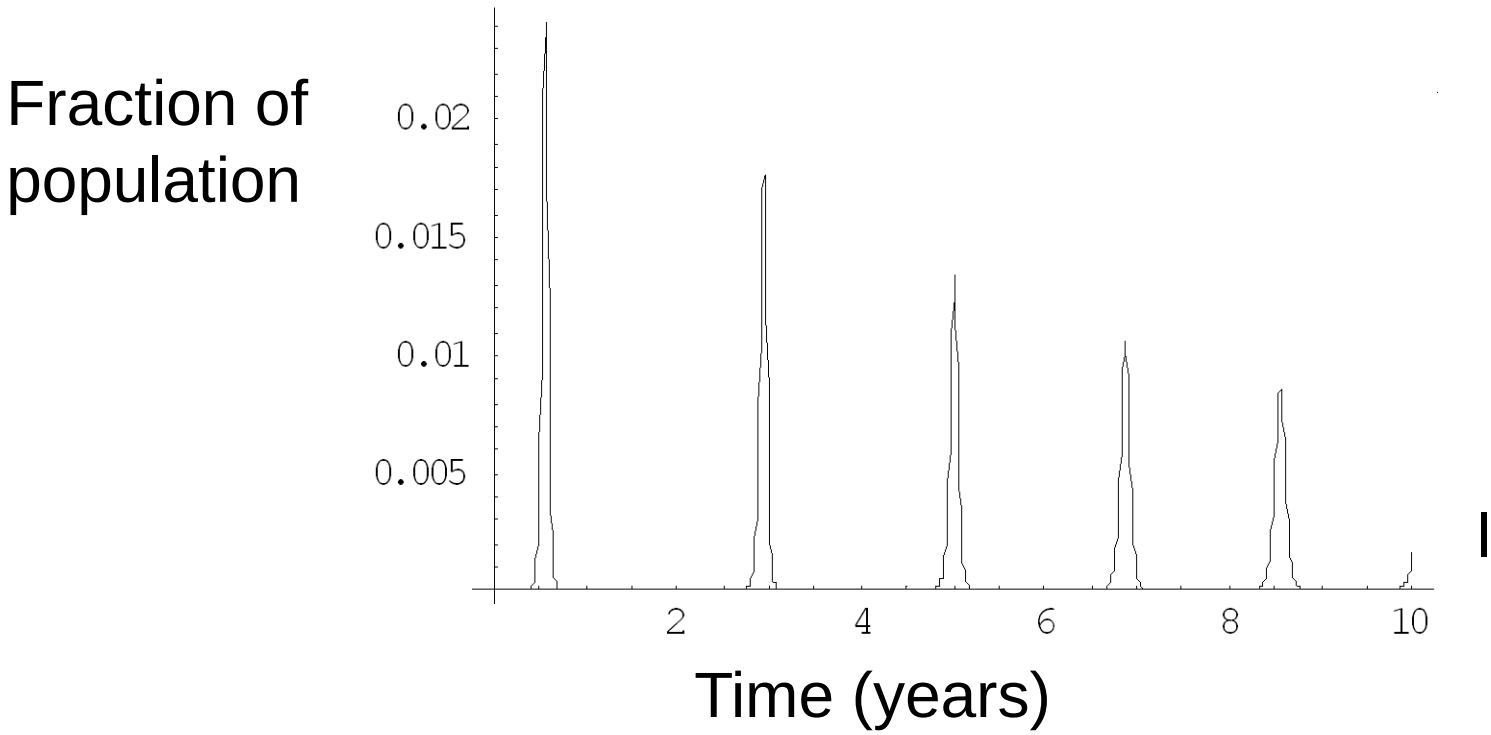
$$\frac{dS}{dt} = \mu N + \nu I - \beta S \frac{I}{N} - \mu S$$

$$\frac{dI}{dt} = \beta S \frac{I}{N} - \gamma I - (\mu + \nu) I$$

$$\frac{dR}{dt} = \gamma I - \mu R$$



Now susceptibles are born into the population the disease can become endemic



If new susceptibles are born into the population the disease can become endemic

- Note the oscillatory behaviour. This is similar to the behaviour of prey-predator models
- This is caused by the slow build up of susceptibles, that then get immunised in an epidemic

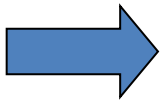
SIR model

- When is an epidemic possible?
- This is asking if the disease-free equilibrium *S=N, I=0, R=0* is unstable.

$$\frac{dS}{dt} = \mu N + vI - \beta S\frac{I}{N} - \mu S$$

$$\frac{dI}{dt} = \beta S\frac{I}{N} - \gamma I - (\mu + v)I$$

$$\frac{dR}{dt} = \gamma I - \mu R$$



$$\frac{dI}{dt} = I(\beta\frac{S}{N} - (\gamma + \mu + v))$$

SIR model

- When is an epidemic possible?

$$\frac{dI}{dt} = I(\beta \frac{S}{N} - (\gamma + \mu + \nu)) > 0$$

$$\Rightarrow \beta \frac{S}{N} > (\gamma + \mu + \nu)$$

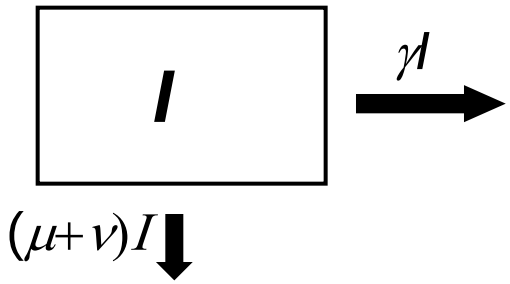
$$\frac{\beta}{\gamma + \mu + \nu} \frac{S}{N} > 1$$

This turns out to be $R_0 > 1$

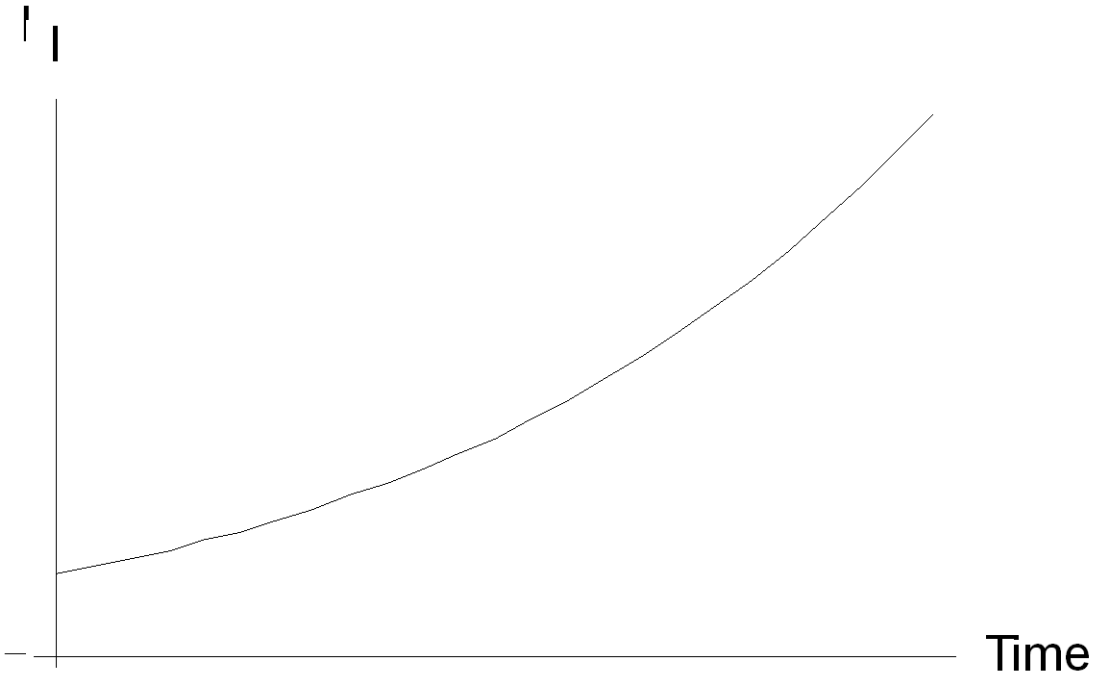
R_0 for the SIR model

$$R_0 = \beta S_0/N \times \frac{1}{\mu+\nu+\gamma} = \frac{\beta S_0/N}{\mu+\nu+\gamma}$$

S_0=The number of susceptibles in population without disease



R_0: The basic reproductive number



If the reproductive number > 1 the nr of infecteds increases, possibly leading to epidemic

To control and eradicate a disease R_0 has to be reduced below 1

$$R_0 = \frac{\beta S_0/N}{\mu+\nu+\gamma}$$

- How to control a disease:
  - Reduce transmission (β)
  - Reduce the duration of the infections (γ, ν)
  - Reduce the fraction of susceptibles (S_0/N)

Reduce Transmission

- Reduce vector population (malaria, dengue)
- Stop movement (Ebola)
- Use of mosquito nets (malaria)
- Use of condoms (STDs)
- Isolate infected hosts (tuberculosis, plague, SARS, Ebola)

Reduce duration of infection

- Treatment with antibiotics (bacterial infections) or antivirals
- Treatment of malaria

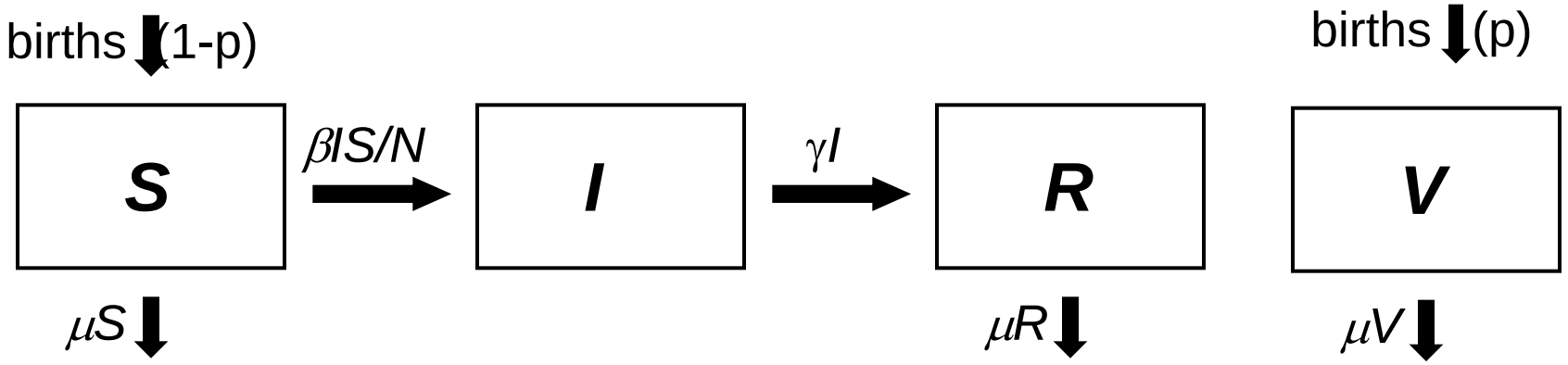
But some treatments can prolong infectious period, e.g. suppression of fever

Increase disease induced mortality

- Not a realistic option for human population
- Can be applied to animal diseases:
- Culling (FMD, swine fever)

Decrease number of susceptibles

- Vaccination



Vaccination

If a fraction p is vaccinated, a fraction 1-p is susceptible

The basic reproductive number in a vaccinated population is:

$$R_{0p} = \frac{\beta(1-p)S_0/N}{\mu+v+\gamma} = (1-p)R_0$$

The fraction that needs to be vaccinated to eradicate the disease is:

$$p_c = 1-1/R_0$$

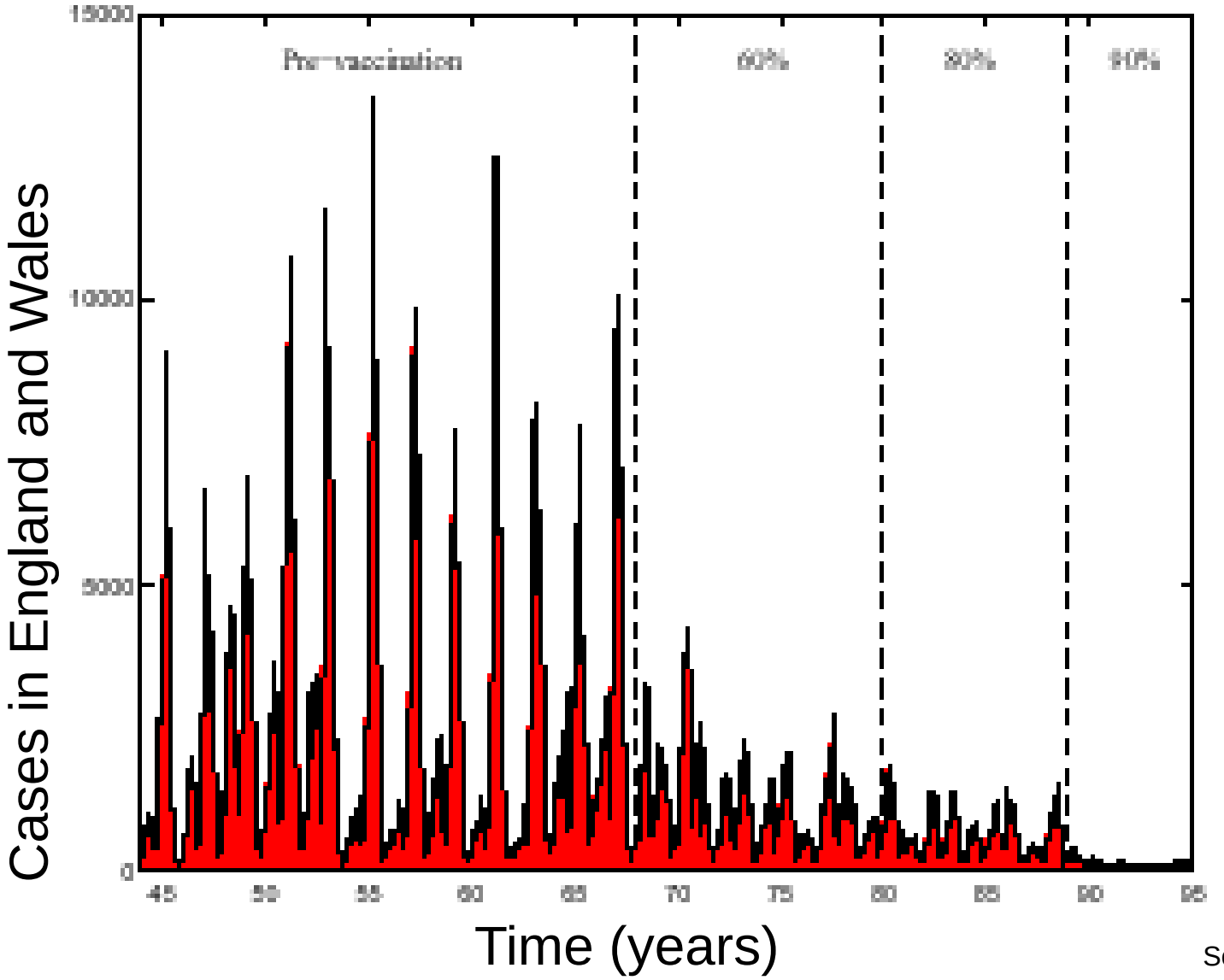
exercise

The calculation of the basic reproductive number

Measles

- Symptoms include coughing, runn
  malaise, red eyes, tearing and feve
- Two to four days after these initial
  white spots with a red backgroun
  located on the inside of the cheek
  molars start to appear.
- They are accompanied, either at t
  slightly later, by the appearance o

Measles in England and Wales (1945-1995)



Source: M. Keeling

A model for measles

- We can use the SIR model to describe measles
- We will assume a constant population size: on the time scale of interest population growth is limited
- We will assume a fixed nr of contacts hence the transmission is $\beta IS/N$
- We will assume that there is no disease caused mortality, i.e. $\nu=0$

A model for measles

- the SIR model:

$$\frac{dS}{dt} = \mu N - \mu S - \beta SI / N$$

$$\frac{dI}{dt} = \beta SI / N - \gamma I - \mu I$$

$$\frac{dR}{dt} = \gamma I - \mu R$$

$$S+I+R=N$$

A model for measles

- The parameters:
- Let's say the average life time is 75 years, hence the mortality rate $\mu=1/75\ [yr]^{-1}$
- The duration of the infectious period is about one week, hence $\gamma=50\ [yr]^{-1}$
- There are about 3 infectious contacts per day, hence $\beta=1000\ [yr]^{-1}\ [individual]^{-1}$
- The R_0 in this model is $\beta/(\mu+\gamma)$
- R_0 is then about 20.
- R_0 has been estimated to be between 15 and 25

A model for measles

- the equilibria of the model

$$\frac{S^*}{N} = \frac{\gamma + \mu}{\beta} = \frac{1}{R_0}$$

$$\frac{I^*}{N} = \frac{\mu}{\gamma + \mu}\frac{\beta - \gamma - \mu}{\beta} = \frac{\mu}{\gamma + \mu}(1 - \frac{1}{R_0})$$

$$\frac{R^*}{N} = \frac{\gamma}{\gamma + \mu}\frac{\beta - \gamma - \mu}{\beta} = \frac{\gamma}{\gamma + \mu}(1 - \frac{1}{R_0})$$

A model for measles

- the equilibria of the model

$$\frac{S^*}{N} = \frac{1}{R_0} = 0.05$$

$$\frac{I^*}{N} = \frac{\mu}{\gamma + \mu}(1 - \frac{1}{R_0}) \approx \frac{\mu}{\gamma}(1 - \frac{1}{R_0}) = 1/4000$$

$$\frac{R^*}{N} = \frac{\gamma}{\gamma + \mu}(1 - \frac{1}{R_0}) \approx (1 - \frac{1}{R_0}) = 0.95$$

A model for measles

- On the basis of these parameters you can work out what the average age of contraction measles is, if the disease is endemic
- The force of infection at equilibrium is $\beta I^*/N$
- The average time until infection is

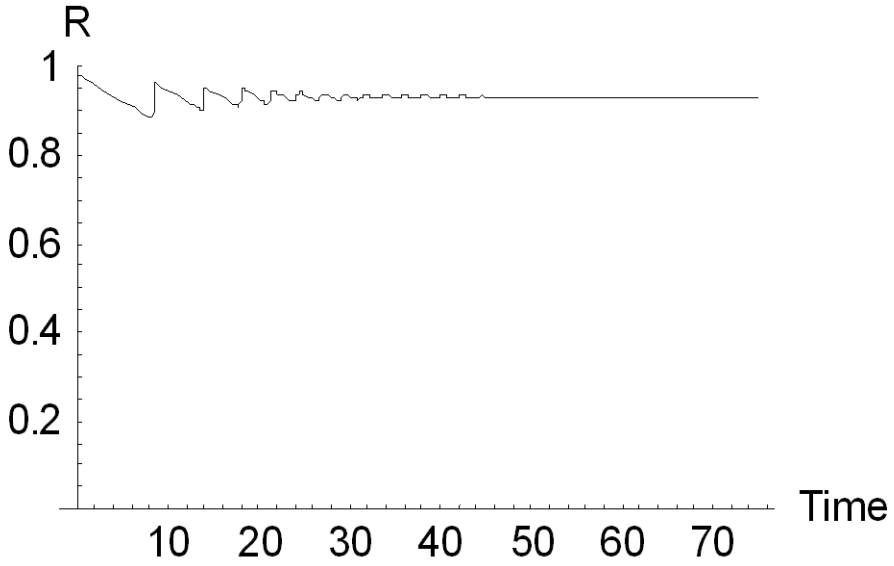
$$\left(\beta \frac{I^*}{N}\right)^{-1} = \frac{\gamma+\mu}{\mu}\frac{1}{\beta-\mu-\gamma} = \frac{1}{\mu}\frac{1}{R_0-1}$$

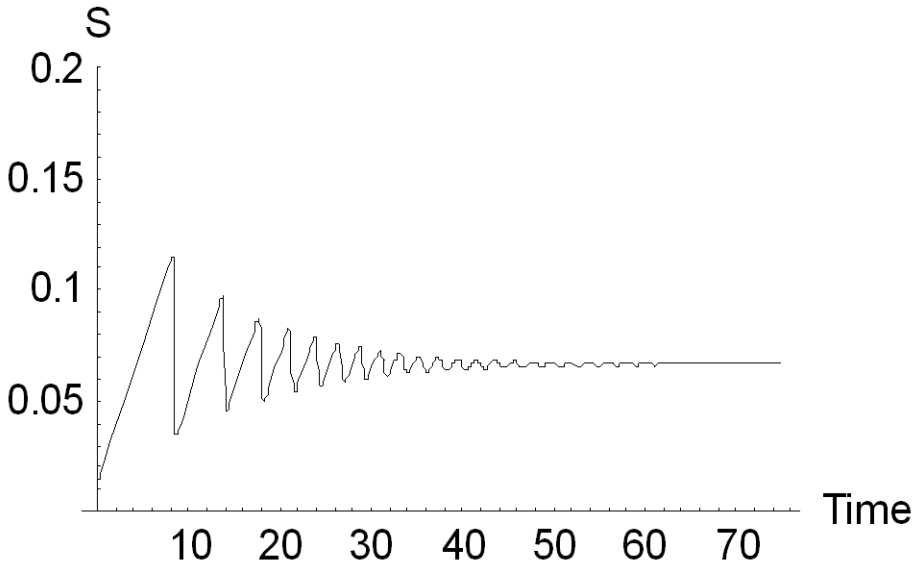
- This is the average lifetime divided by R_0-1
- This is about 4-5 years of age
- **Measles is a childhood disease because the R_0 is high, not because it cannot infect adults**

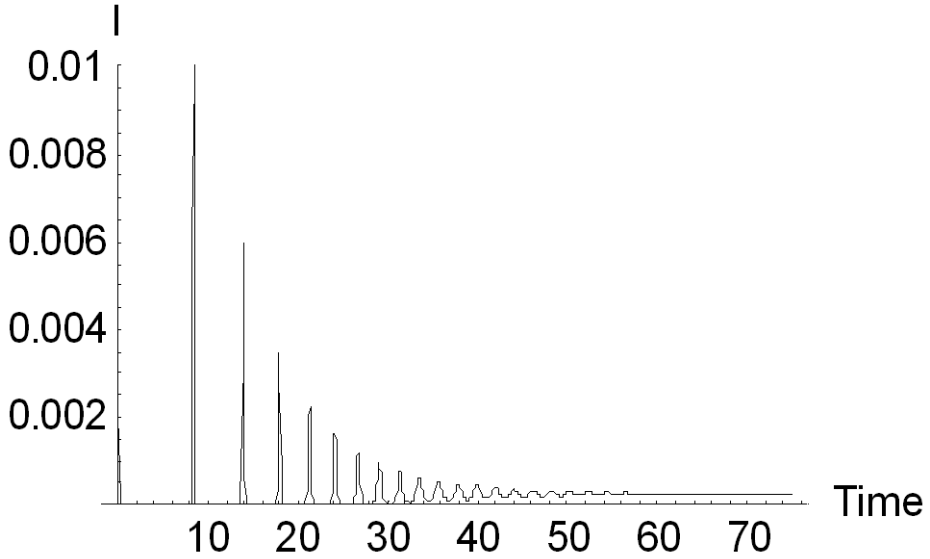
exercise

- **Investigate the dynamics of the SIR model**

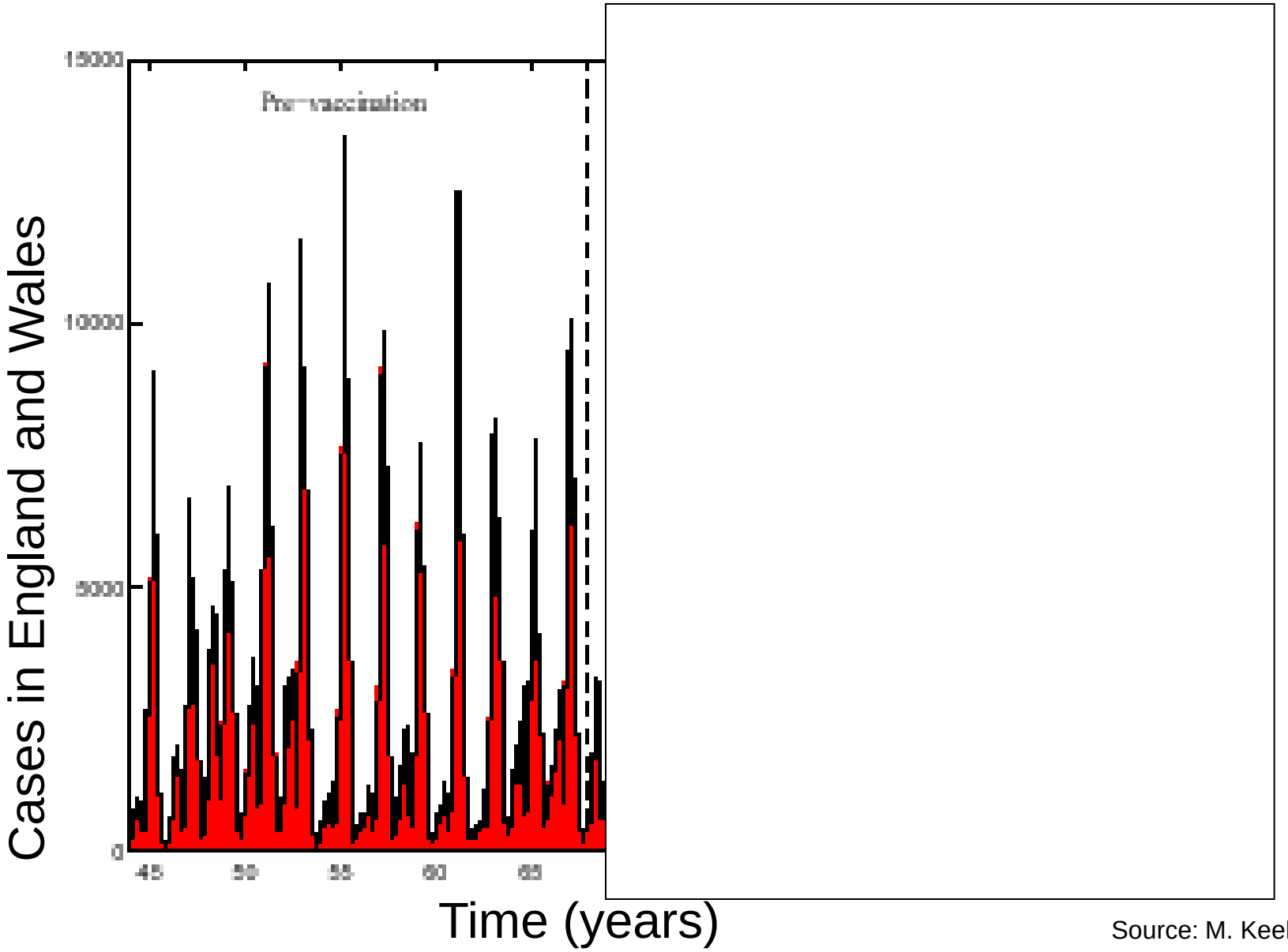
Solutions:


R
1
0.8
0.6
0.4
0.2
10 20 30 40 50 60 70
Time


S
0.2
0.15
0.1
0.05
10 20 30 40 50 60 70
Time


I
0.01
0.008
0.006
0.004
0.002
10 20 30 40 50 60 70
Time

Measles in England and Wales (1945-1995)



Source: M. Keeling

Variation in transmission

- Measles incidence peaks every second year
- It has been suggested that this is because the transmission is not constant but varies over the season (school terms)
- We can include this in the model by changing β with time, so that it changes periodically

A model for measles

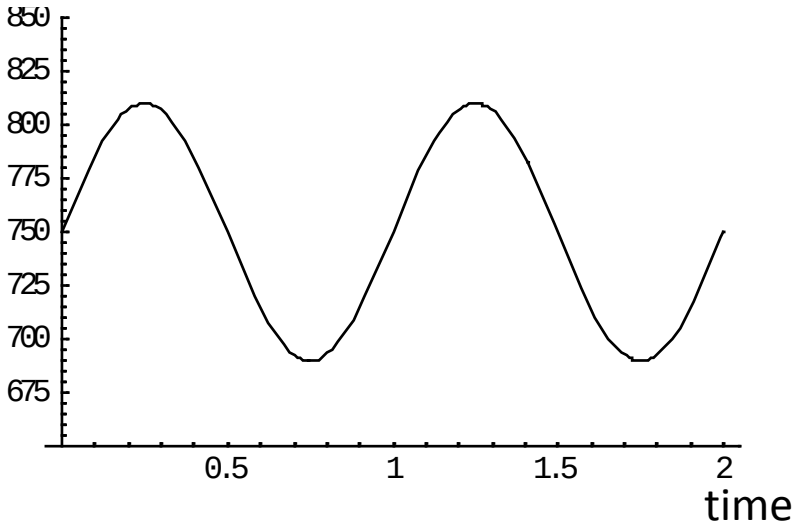
- the SIR model:

$$\frac{dS}{dt} = \mu N - \mu S - \beta(t) SI / N$$

$$\frac{dI}{dt} = \beta(t) SI / N - \gamma I - \mu I$$

$$\frac{dR}{dt} = \gamma I - \mu R$$

But now $\beta(t) = \overline{\beta}(1 + \alpha \sin(\omega t))$

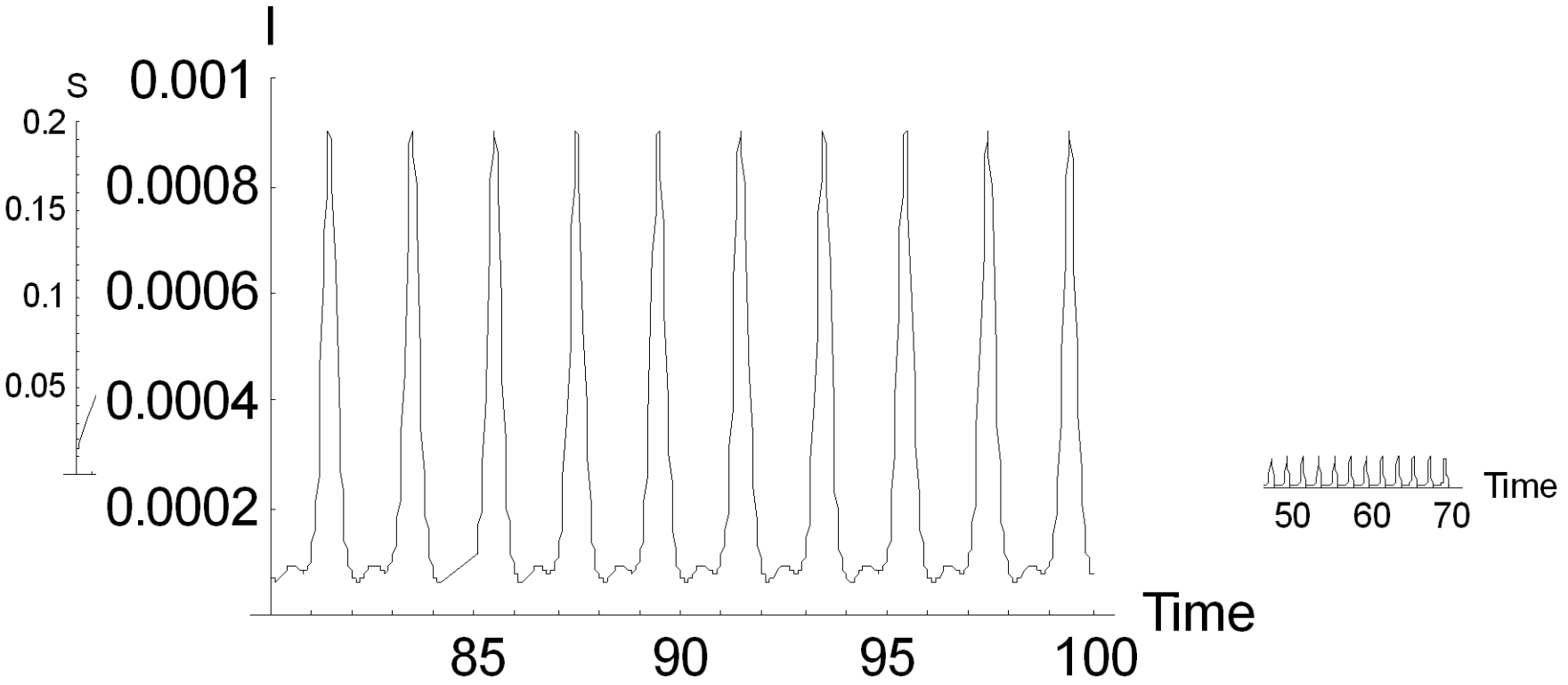


exercise

- **Investigate the periodically forced SIR model**

If variation in transmission included in the model:

- Result:

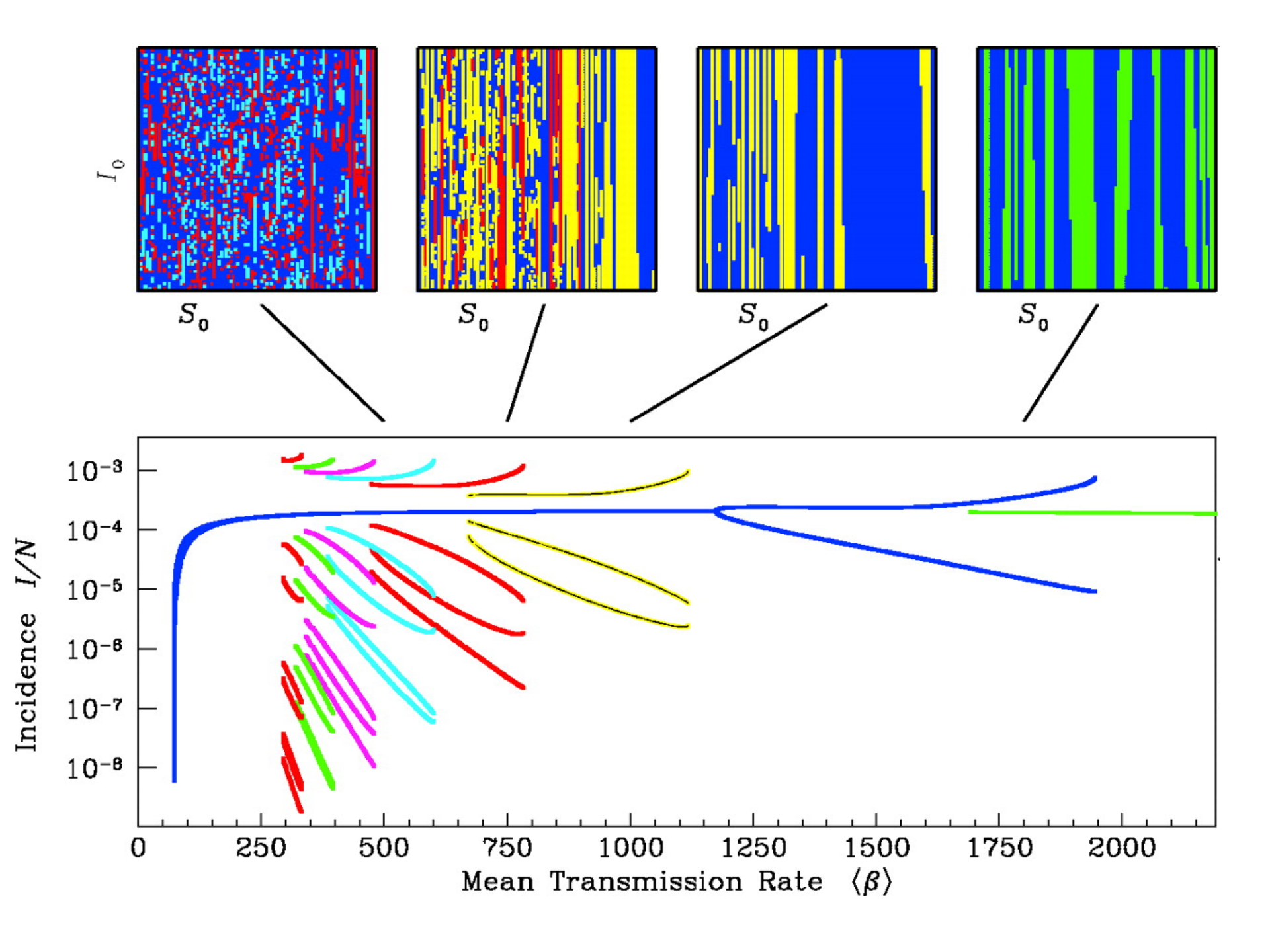


Variation in transmission

- This lends support to the suggestion that the periodicity is caused because of the seasonal forcing of the transmission rate

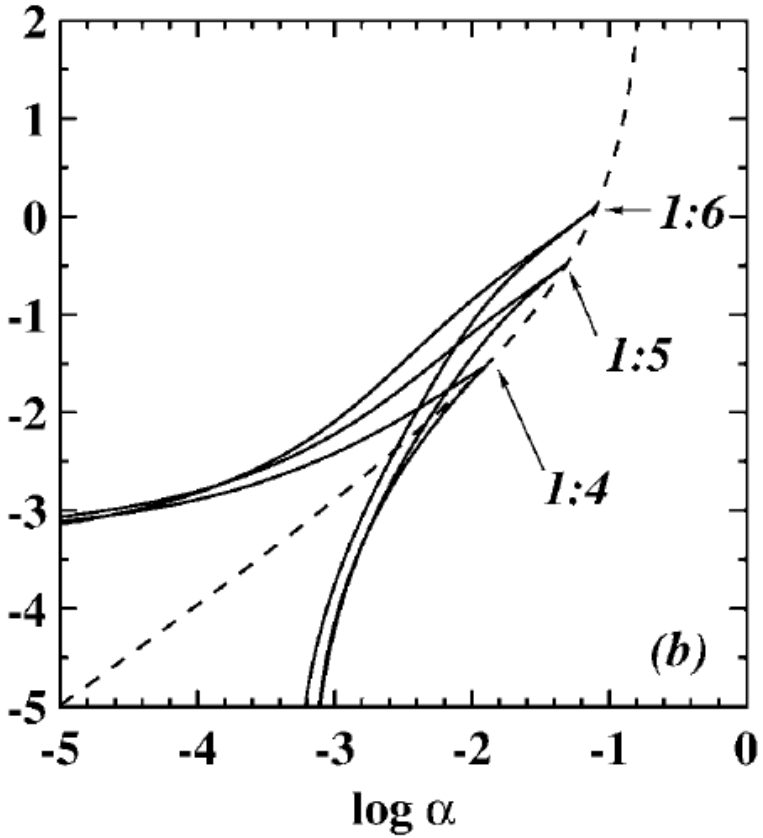
Seasonal variation in transmission

- Earn et al. (2000) studied a SEIR (susceptible-exposed-infected-recovered) model with seasonal forcing
- They produced the following figure


I_0
S_0
S_0
S_0
S_0
Incidence I/N
10^{-3}
10^{-4}
10^{-5}
10^{-6}
10^{-7}
10^{-8}
0
250
500
750
1000
1250
1500
1750
2000
Mean Transmission Rate $\langle\beta\rangle$

Seasonal variation in transmission

- This is caused by resonance
- The is a general phenomenon in forced systems where the original system has its own amplitude
- “Arnold tongues”



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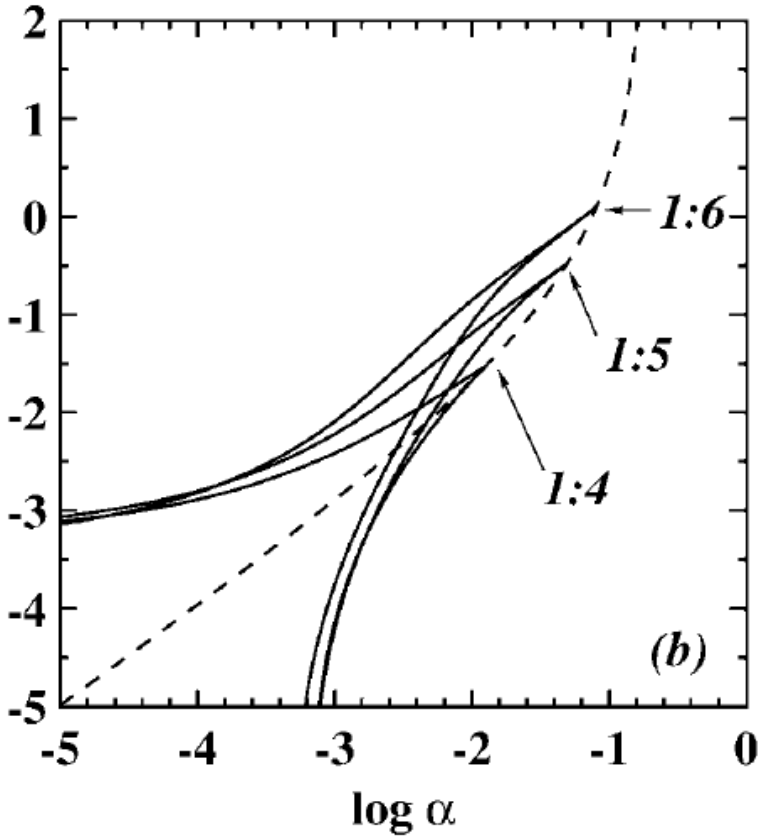
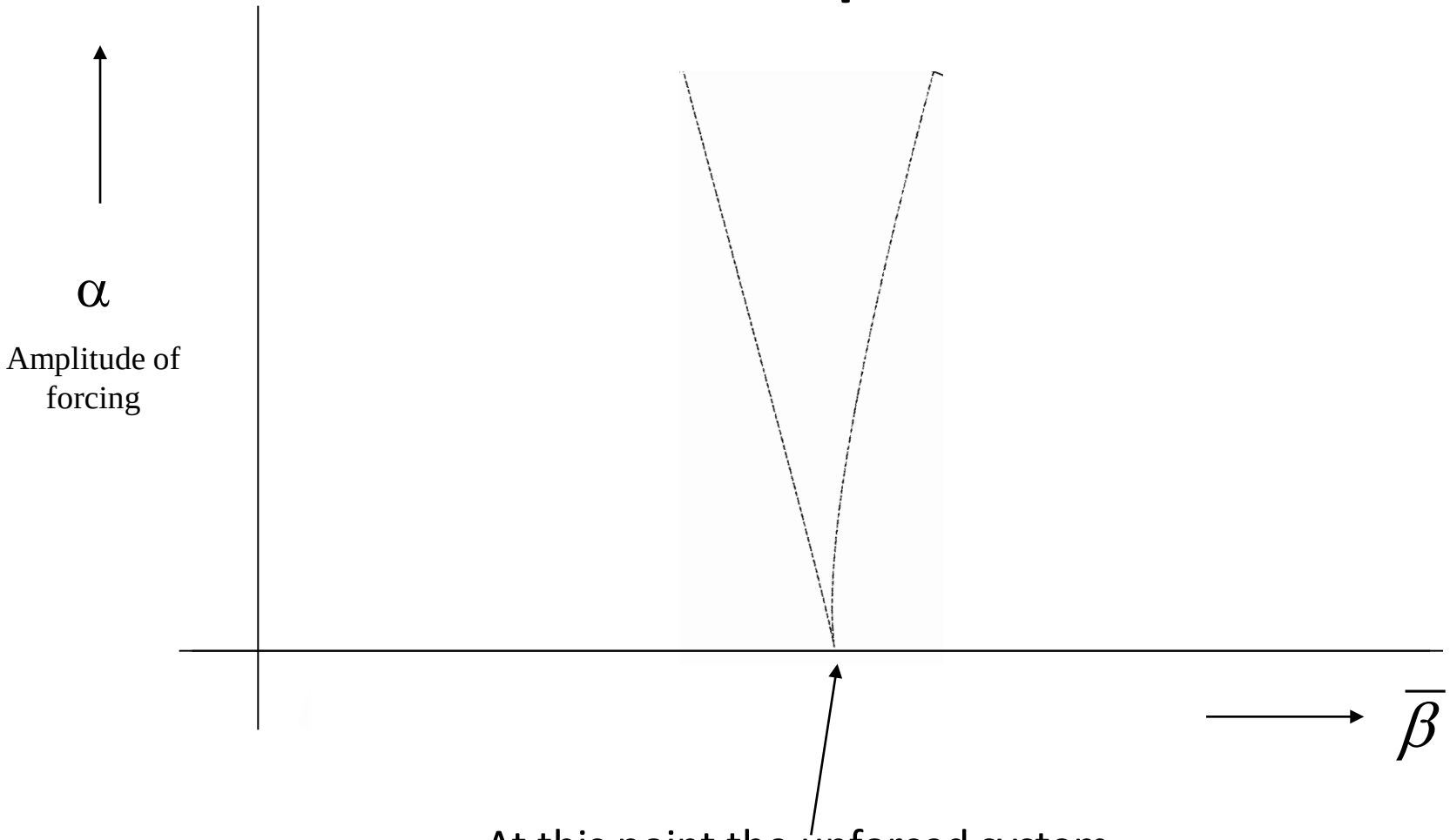
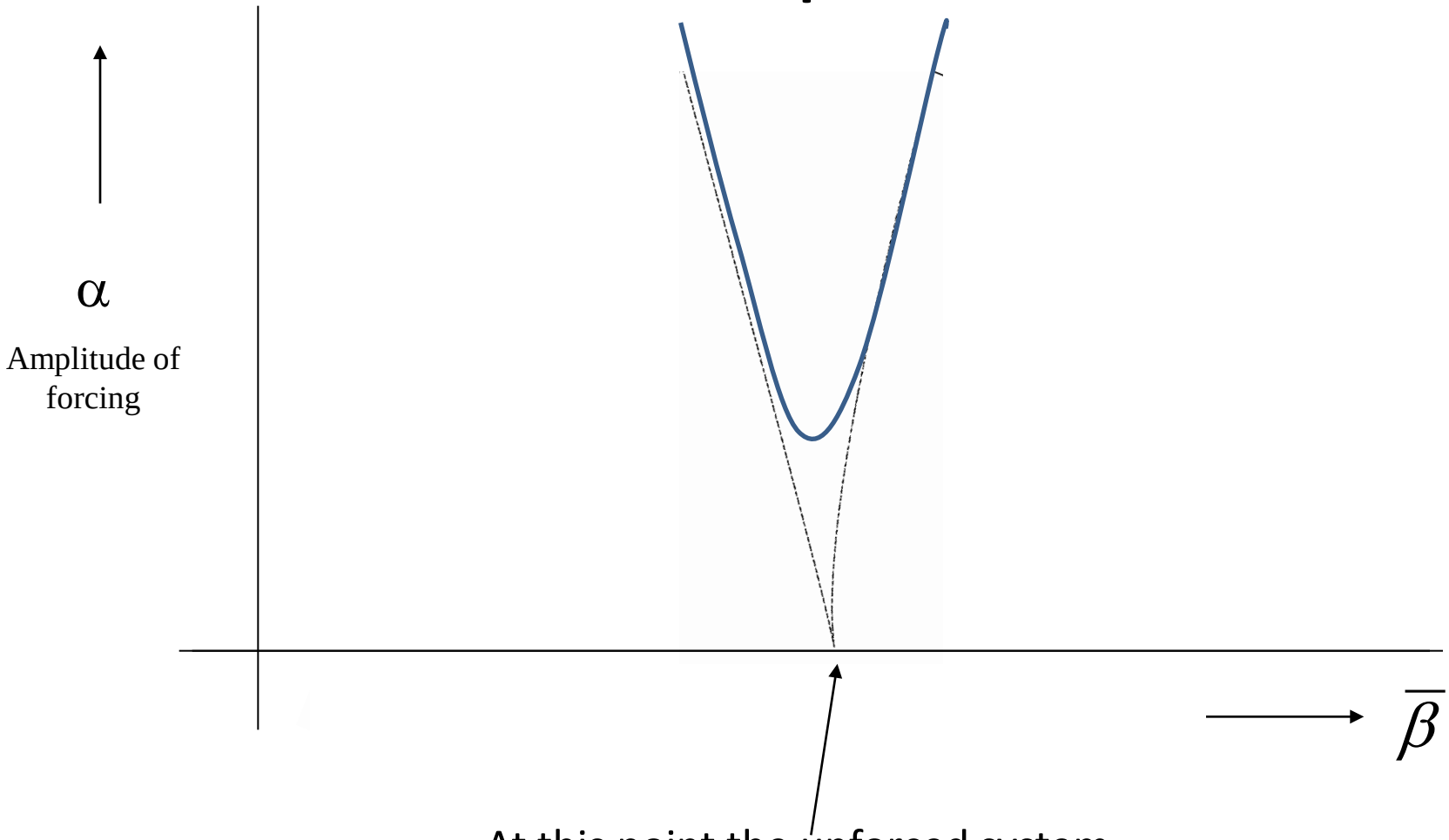


Seasonal variation in transmission: resonance of an undamped oscillator



Seasonal variation in transmission: resonance of a damped oscillator



Variation in transmission rates

- The period of the unforced system follows from the eigenvalue.
- If the system has a complex eigenvalue of $\lambda=v+iw$, the linearised dynamics are of the form:

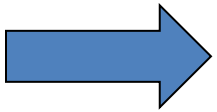
$$e^{\lambda t} = e^{(v+iw)t} = e^{vt}(i\sin wt + \cos wt)$$

- The frequency of the dynamics is therefore w and the period $2\pi/w$

Variation in tranmission rates

- To find the period of the unforced system we need the imaginary part of the eigenvalues at equilibrium

$$\frac{dS}{dt} = \mu N - \mu S - \beta SI / N$$
$$\frac{dI}{dt} = \beta SI / N - \gamma I - \mu I$$
$$\frac{dR}{dt} = \gamma I - \mu R$$

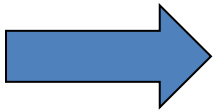


$$J = \begin{pmatrix} -\beta \frac{I^*}{N} - \mu & -\beta \frac{S^*}{N} & 0 \\ \beta \frac{I^*}{N} & 0 & 0 \\ 0 & \gamma & -\mu \end{pmatrix}$$

Variation in tranmission rates

- To find the period of the unforced system we need the imaginary part of the eigenvalues at equilibrium

$$J = \begin{pmatrix} -\beta\frac{I^*}{N} - \mu & -\beta\frac{S^*}{N} & 0 \\ \beta\frac{I^*}{N} & 0 & 0 \\ 0 & \gamma & -\mu \end{pmatrix}$$



One eigenvalue is -μ

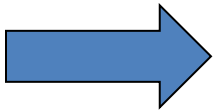
The other two come from the matrix

$$\begin{pmatrix} -\frac{\beta\mu}{\gamma+\mu} & -\mu-\gamma \\ \frac{\beta\mu}{\gamma+\mu} - \mu & 0 \end{pmatrix}$$

Variation in transmission rates

- To find the period of the unforced system we need the imaginary part of the eigenvalues at equilibrium

$$\begin{pmatrix} -\dfrac{\beta\mu}{\gamma+\mu} & -\mu-\gamma \\ \dfrac{\beta\mu}{\gamma+\mu}-\mu & 0 \end{pmatrix}$$



Has eigenvalues with approximate imaginary part

$$\sqrt{\mu(\beta-\gamma)}$$

$$Det\begin{pmatrix} -\dfrac{\beta\mu}{\gamma+\mu}-\lambda & -\mu-\gamma \\ \dfrac{\beta\mu}{\gamma+\mu}-\mu & -\lambda \end{pmatrix} = \lambda^2 + \lambda\frac{\beta\mu}{\gamma+\mu} + (\mu+\gamma)\left(\frac{\beta\mu}{\gamma+\mu}-\mu\right)$$

$$\lambda = -\frac{1}{2}\frac{\beta\mu}{\gamma+\mu} \pm \frac{1}{2}\sqrt{\left(\frac{\beta\mu}{\gamma+\mu}\right)^2 - 4(\mu+\gamma)\left(\frac{\beta\mu}{\gamma+\mu}-\mu\right)}$$

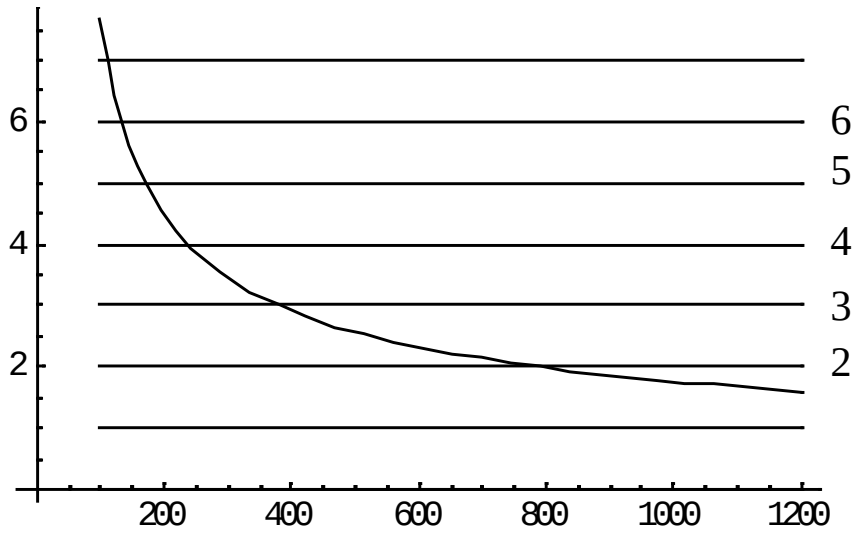
$$\approx -\frac{1}{2}\frac{\beta\mu}{\gamma+\mu} \pm i\sqrt{(\mu+\gamma)\left(\frac{\beta\mu}{\gamma+\mu}-\mu\right)}$$

$$\approx -\frac{\beta\mu}{2\gamma} \pm i\sqrt{\mu(\beta-\gamma)}$$

Variation in transmission rates

- We can now find the period ($\frac{2\pi}{\sqrt{\mu(\beta-\gamma)}}$) and predict the position of the Arnold tongues from

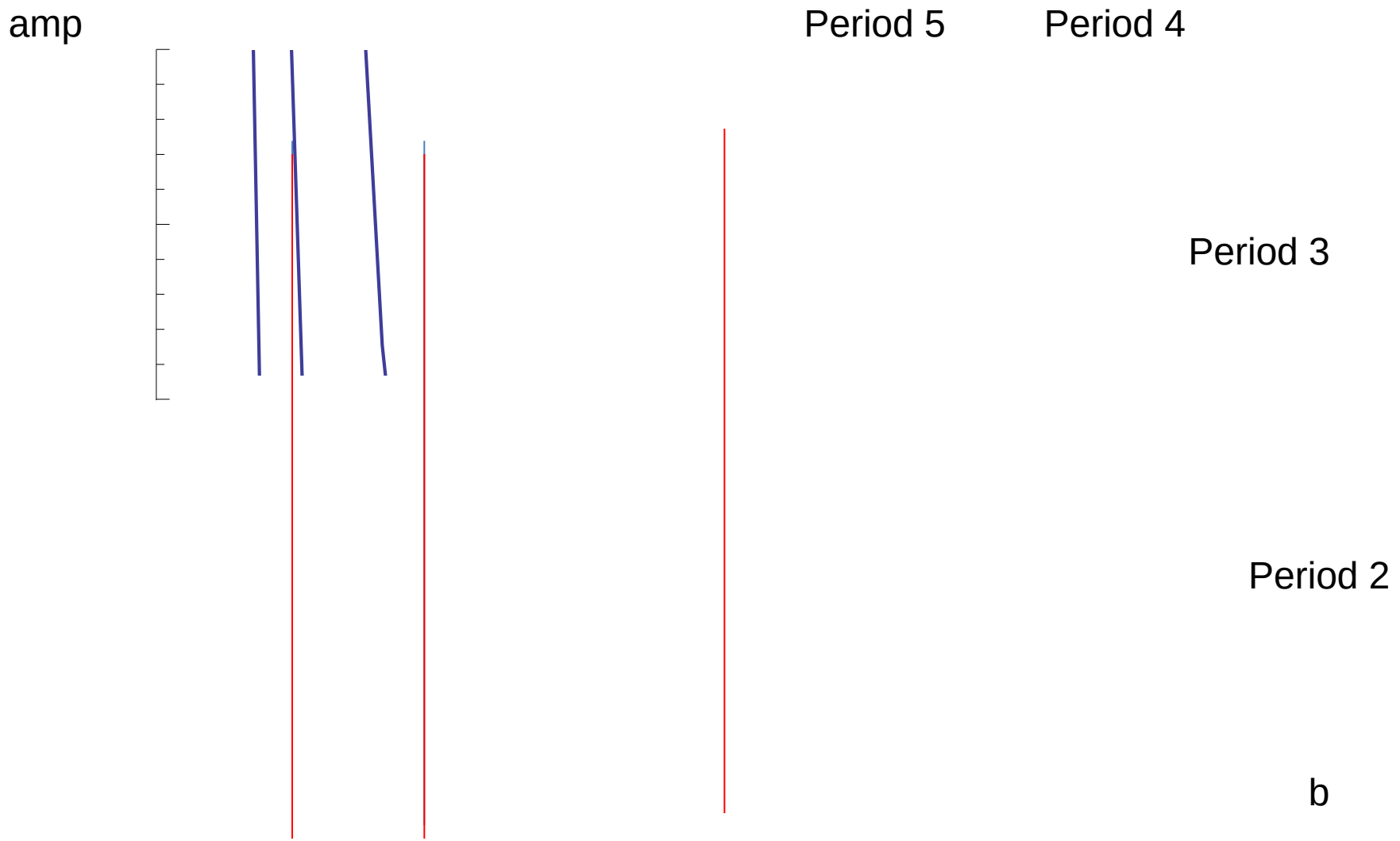
$$\frac{2\pi}{\sqrt{\mu(\beta-\gamma)}}$$



791
379
235

β

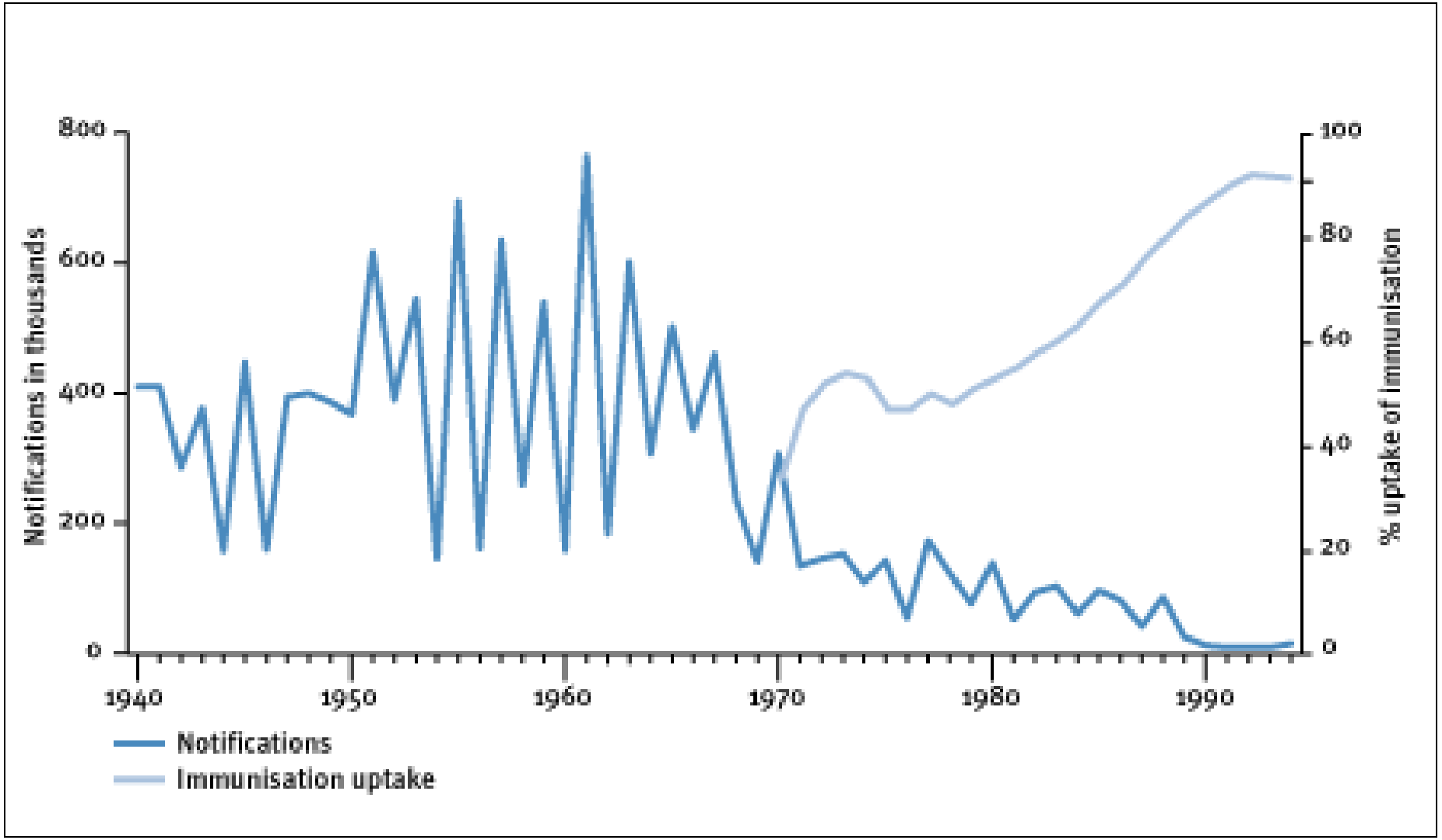
some Arnold tongues



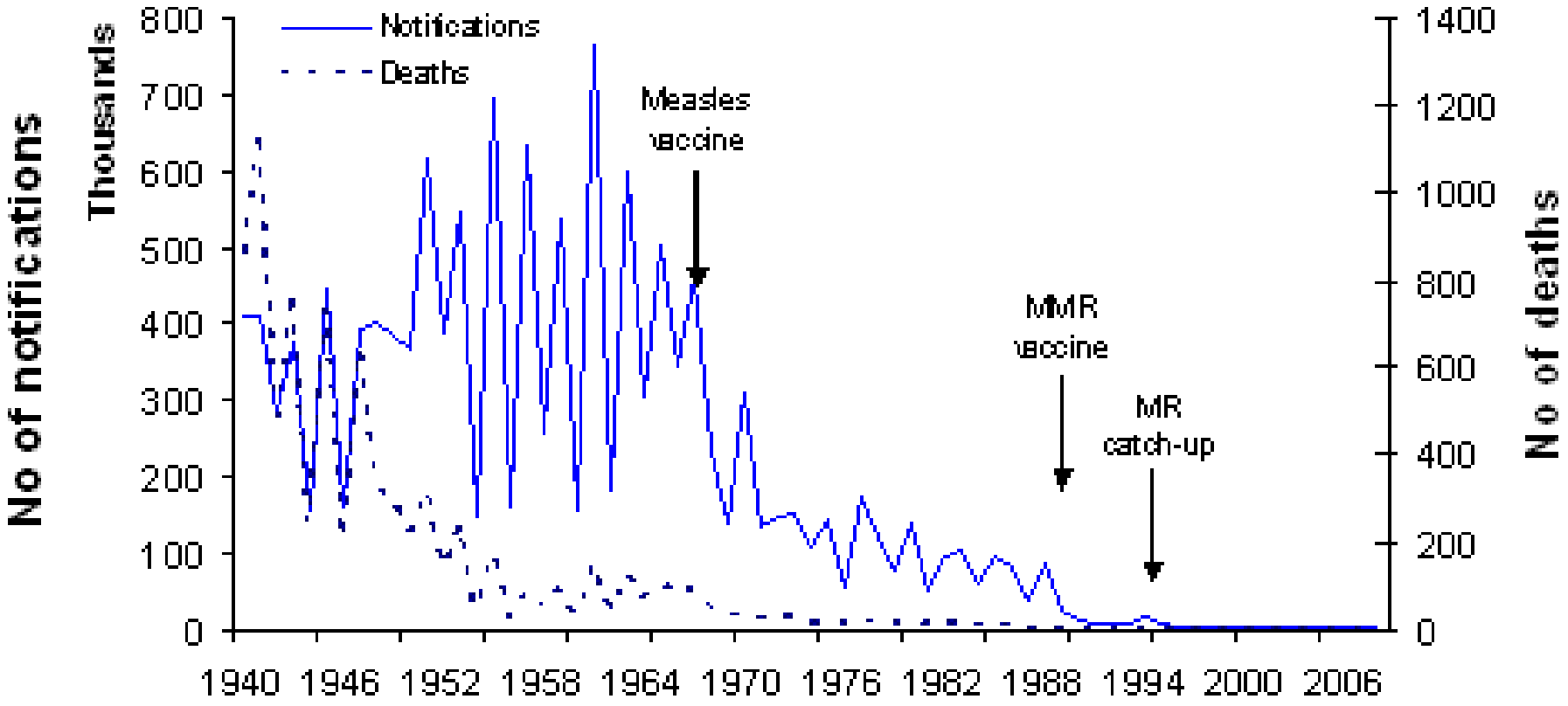
Effects of seasonal variation

- The dynamics of a seasonally forced epidemic strongly depend on the R0 (approx β/γ)
- High R0: annual or biannual cycles.
- Low R0: outbreaks followed by years of absence, e.g influenza
- For low R0 the densities can reach very low numbers, and lead to “fade out”
- Therefore the disease can disappear, even if the R0>1

Vaccination



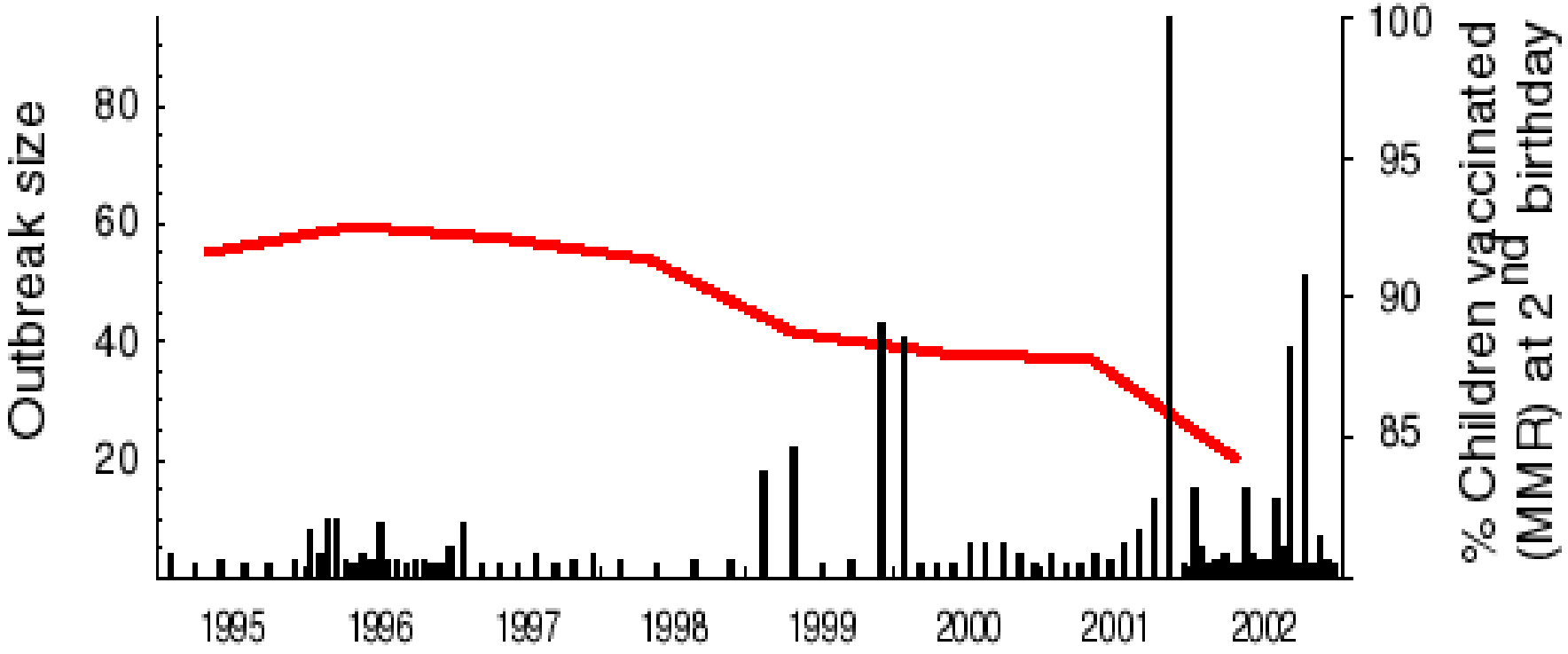
Vaccination



Vaccination

- But measles still occasionally appears if it is imported in the population from abroad

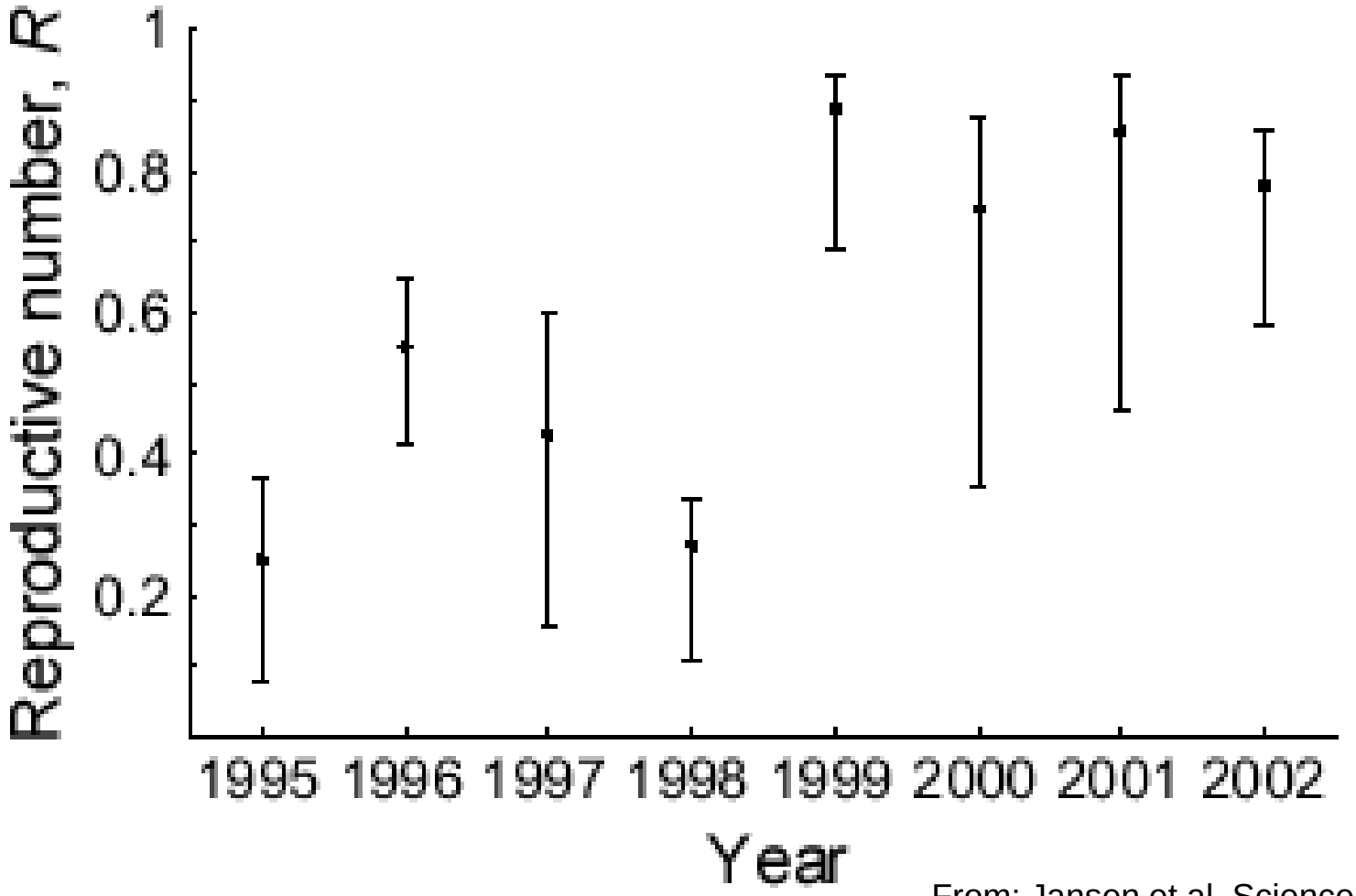
Measles outbreaks in England and Wales in 1995-2002



Vaccination

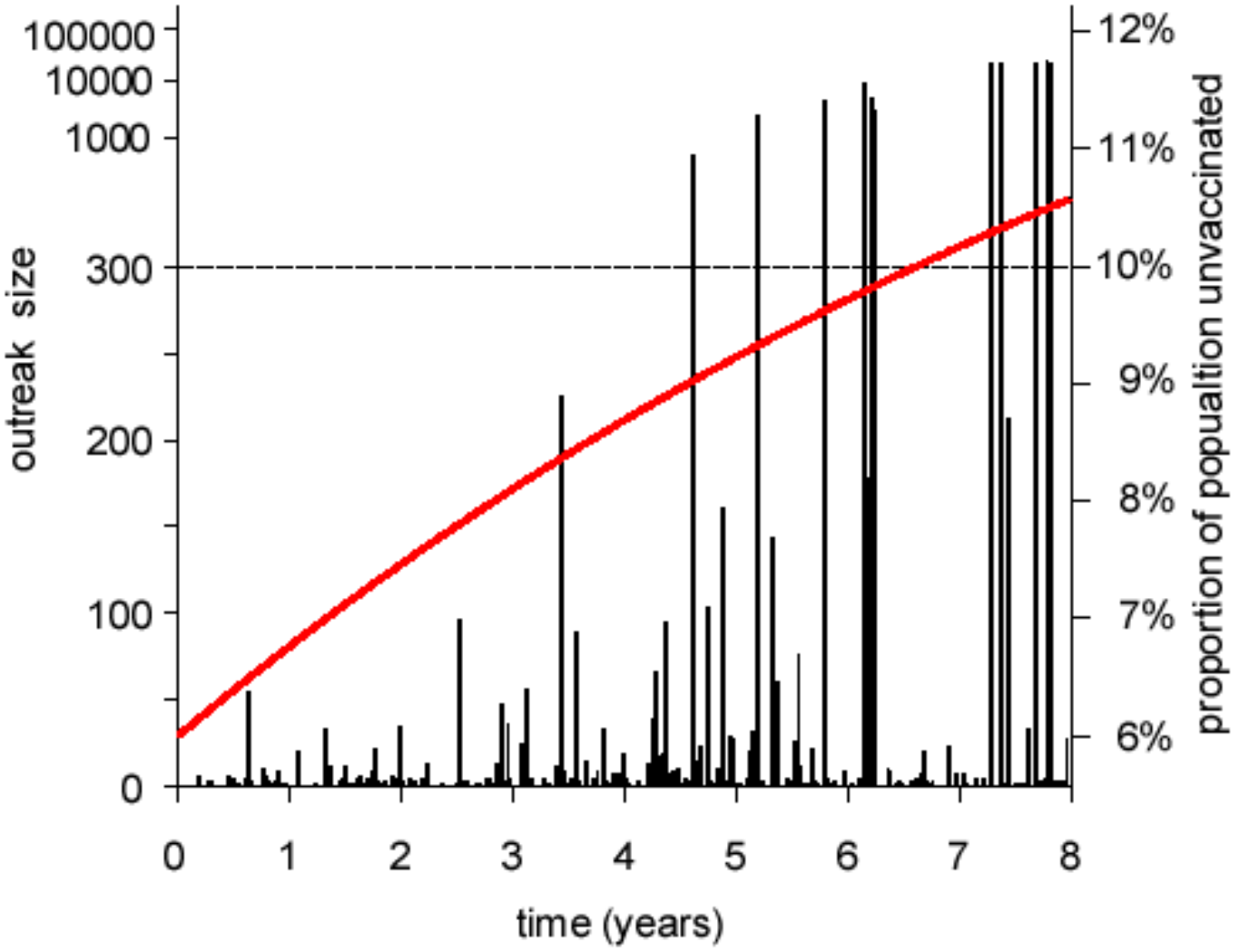
- After 1999 vaccination levels decreased due to (unfounded) claims that MMR could lead to autism.
- This has led to large outbreaks and an increase in the reproductive number

Reproductive number after vaccination $R_0(1-p)$

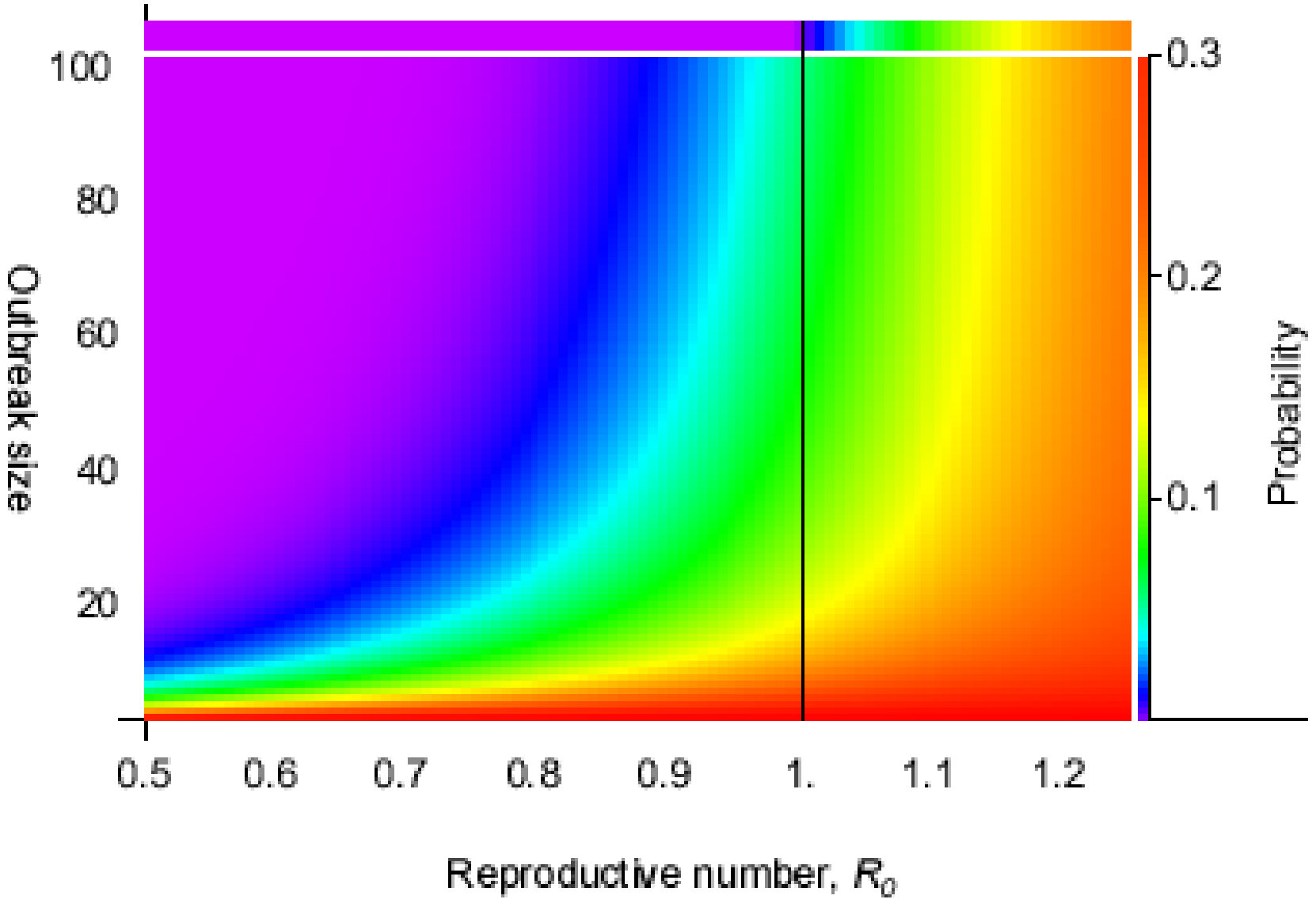


From: Jansen et al. Science, 301, 804 (2003)

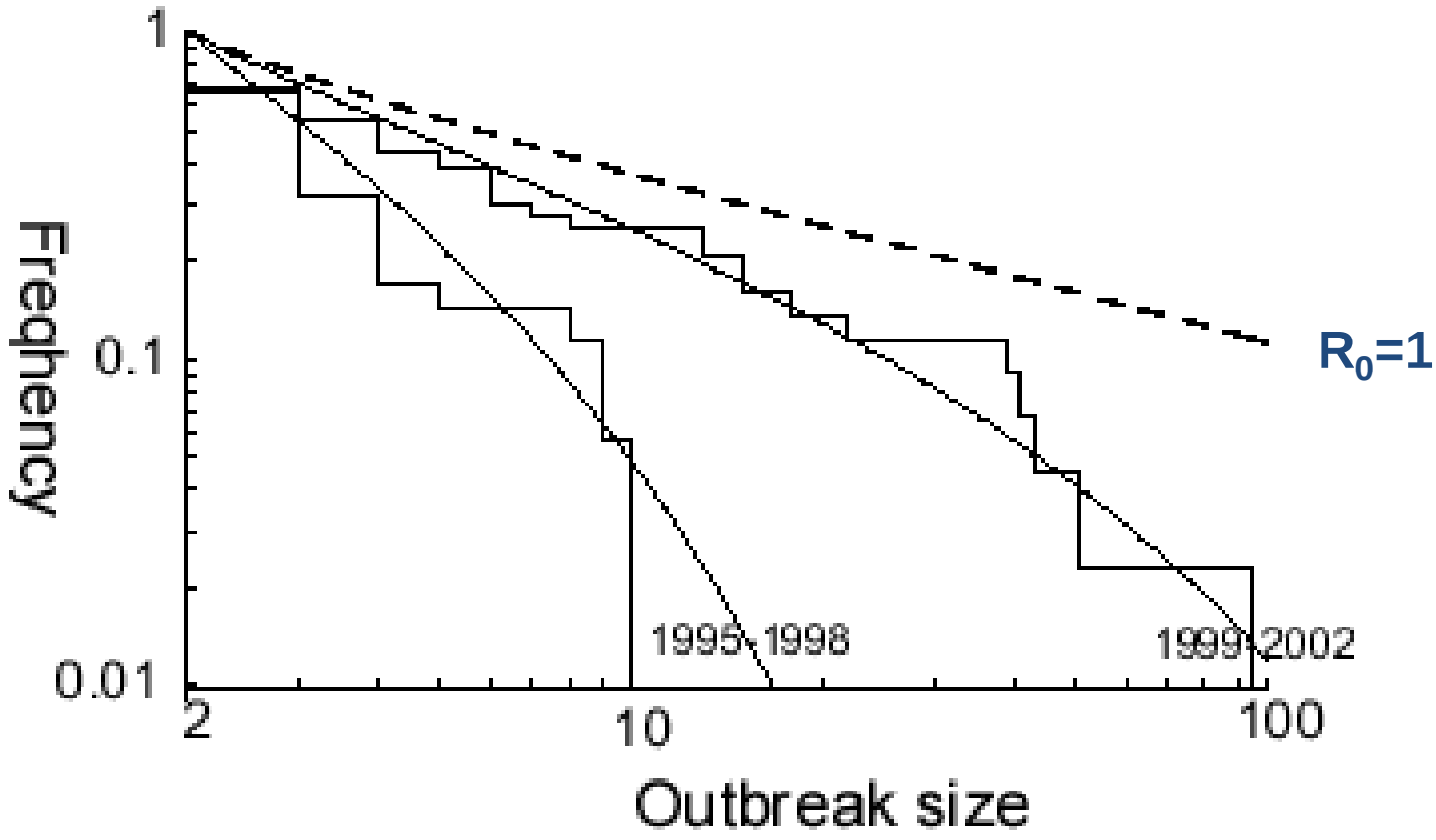
Outbreak size depends on R_0



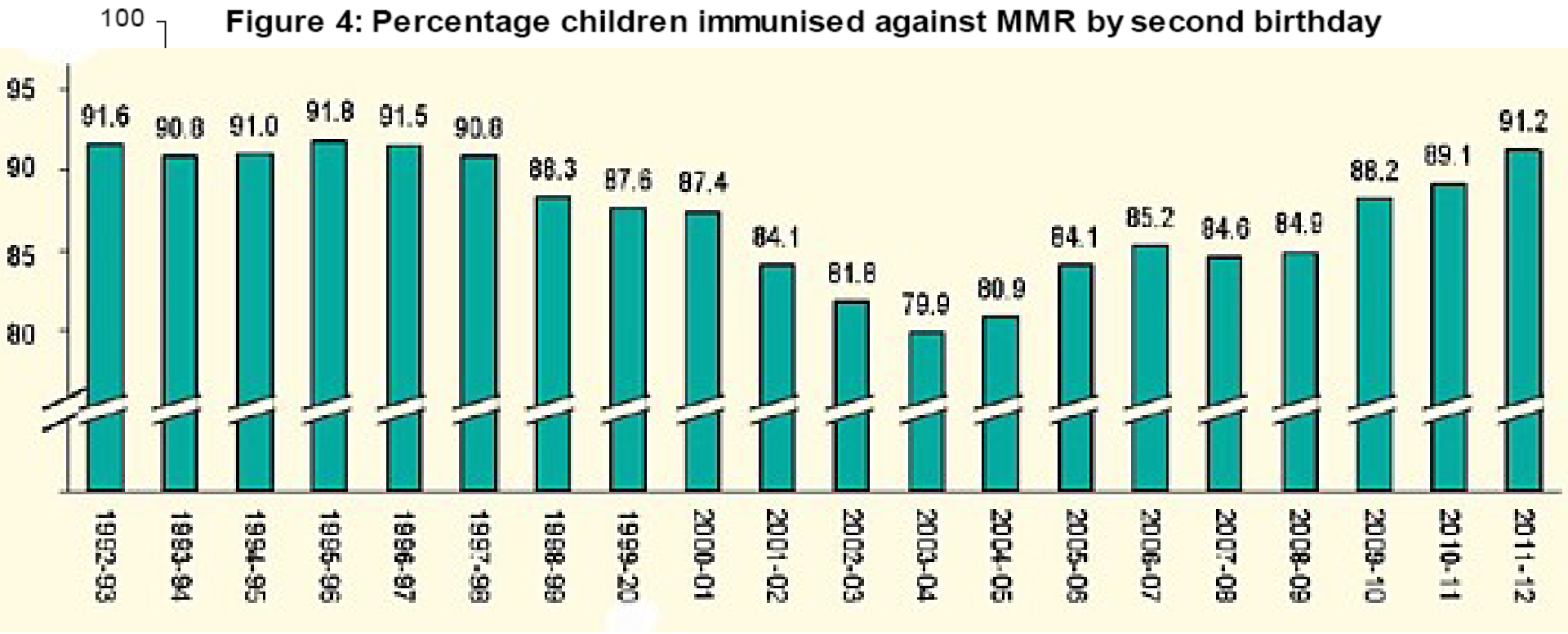
Probability of getting a outbreak of certain size or larger



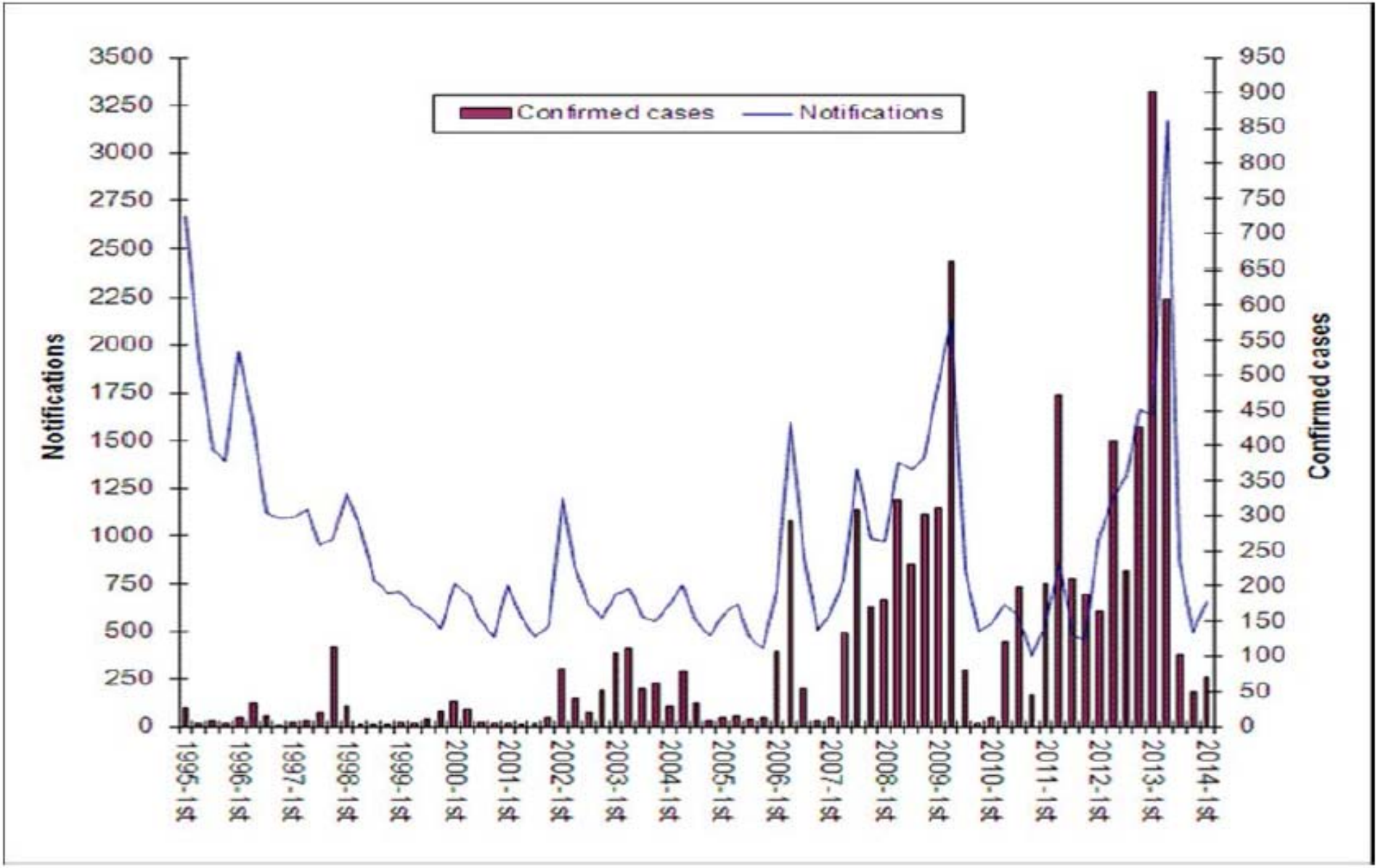
Outbreak distribution shows progression toward R_0=1



Vaccine uptake at 2nd birthday



Measles cases since 1995



Nr of cases of 1996-2014

	Measles	Mumps	Rubella
1996	112	94	2770
1997	177	180	99
1998	56	119	119
1999	92	372	162
2000	100	703	60
2001	70	777	43
2002	308	502	65
2003	438	1556	17
2004	191	8130	14
2005	77	43322	28
2006	740	4426	32
2007	990	1476	35
2008	1370	2405	27
2009	1144	7662	9
2010	380	3965	12
2011	1086	2465	6
2012	2030	2564	65
2013	1843	4035	12
2014	130	2604	1

Catch-up campaign

- In the first 3 months of 2013 there was an increase in number of cases of measles, which was most marked among 10 to 16 year-olds. A national catch-up campaign was launched to ensure that 95% of children aged 10 to 16 years received at least one dose of MMR vaccine by 30 September 2013.

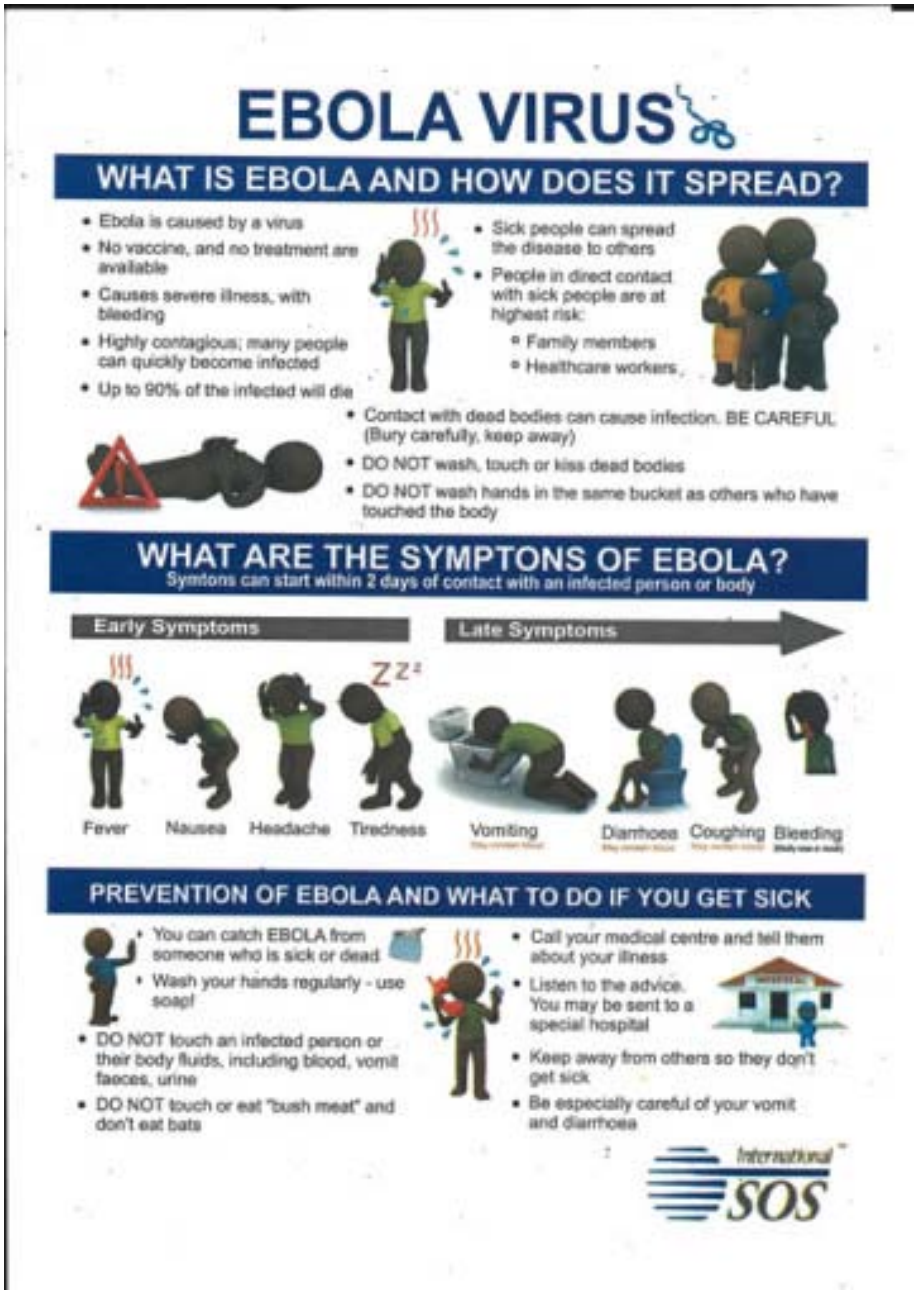
Still ongoing

- The presence of an unvaccinated cohort in the population is still very visible in the measles incidence and for years we saw substantial measles outbreaks
- Following the 2013 catch-up campaign the vaccine coverage appears to be back to a safer level.
- All these efforts are possible because we can calculate the critical level of vaccination and estimate the reproductive number.

Ebola

- Ebola virus disease (EVD), is a severe, viral illness in humans.
- Fatality rate between is around 50% (25%-90%)
- There is no treatment, there are no vaccines but candidate vaccines are undergoing evaluation.

- Early symptoms: fever fatigue, muscle pain, headache and sore throat.
- Later:vomiting, diarrhoea, rash in some cases, both internal and external bleeding (e.g. oozing from the gums, blood in the stools)



Ebola

- We know very little about the disease.
- There is an incubation period (interval from infection with the virus to onset of symptoms) from 2 to 21 days, with mean approx. 10 days
- Humans are not infectious until they develop symptoms.
- They remain infectious as long as their blood and body fluids contain the virus. Men who have recovered can still transmit through their semen for up to 7 weeks after recovery.

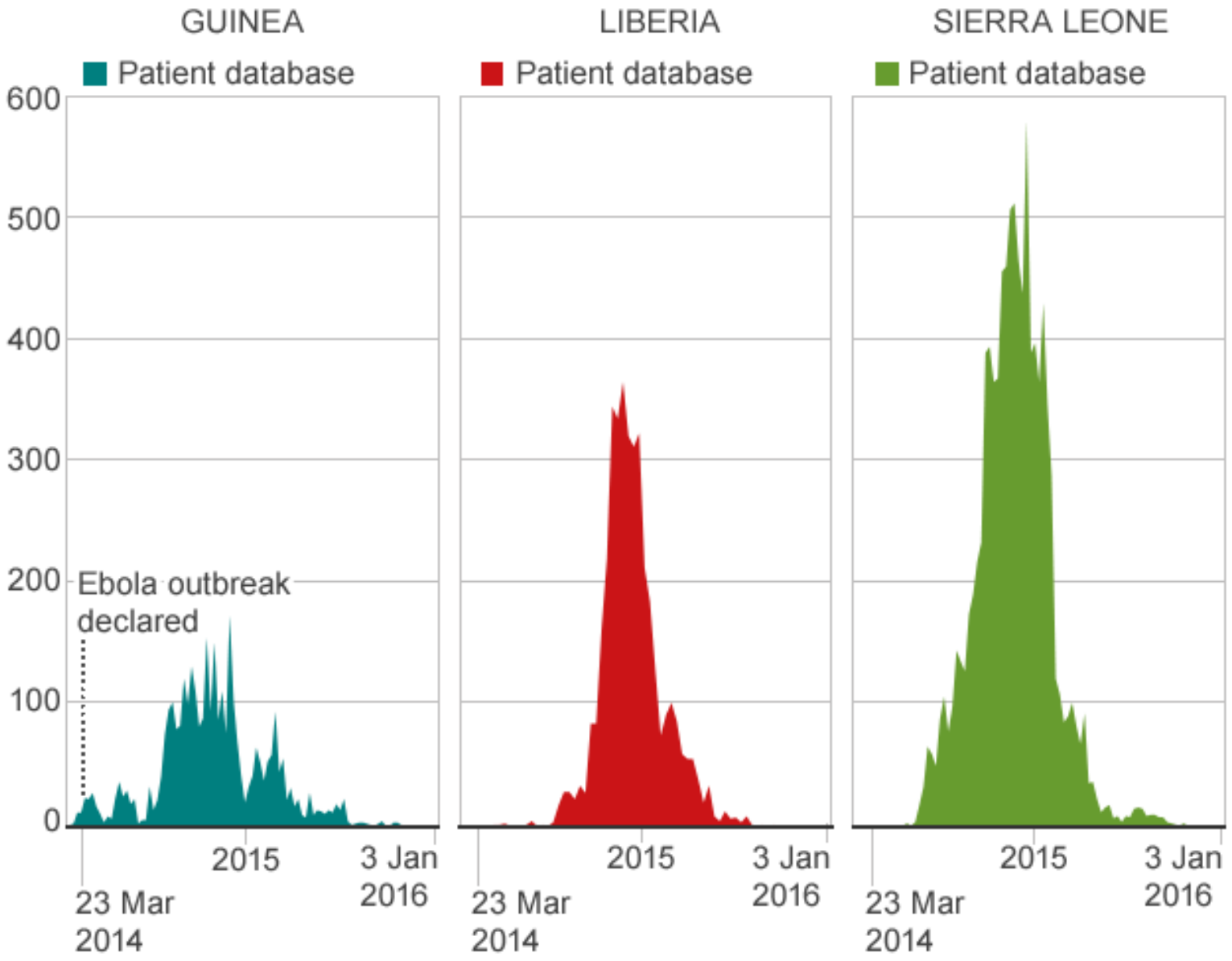
Ebola

- The R0 has been estimated between 1.83 (Congo 1995) and 1.34 (Uganda 2000) and 1.63 (West Africa 2014)
- burial practices can contributed to transmission: cleaning of the dead body by family members, kissing and touching the body can cause infection as do large gatherings

Current outbreak

- Currently there is an outbreak in West Africa with over 28000 cases, and over 11000 deaths
- The current outbreak hasn't followed the same know pattern in a number of West African countries
- The proportion of transmission occurring in the community appears much higher
- Outbreak appears to have end, although there are still some cases reported in the last month

Weekly reported Ebola cases



Source: WHO

BBC

Ebola response

An Ebola treatment centre in Kailahun, Sierra Leone

Current outbreak

- Interventions:
- case isolation,
- contact tracing with quarantine
- promoting sanitary funeral practices
- Screening at airports (outgoing travellers)
- Outreach and information to communities

- The effect the interventions have had is not known

Current outbreak

- The measures to control Ebola consisted mainly at trying to isolate and treat people, and thus stop transmission
- Also education and stopping of unsafe practices (burials) is important to stop transmission
- Has it worked? It seems to have worked in that a large nr of deaths have been avoided (see Kucharski et al. 2015)

Current outbreak

- For Ebola, a factor that appears particularly important is that the amount of transmission might depend on awareness about the disease.
- This can create an interplay between awareness and disease transmission, that can lead to a disease finding new communities in which to transmit

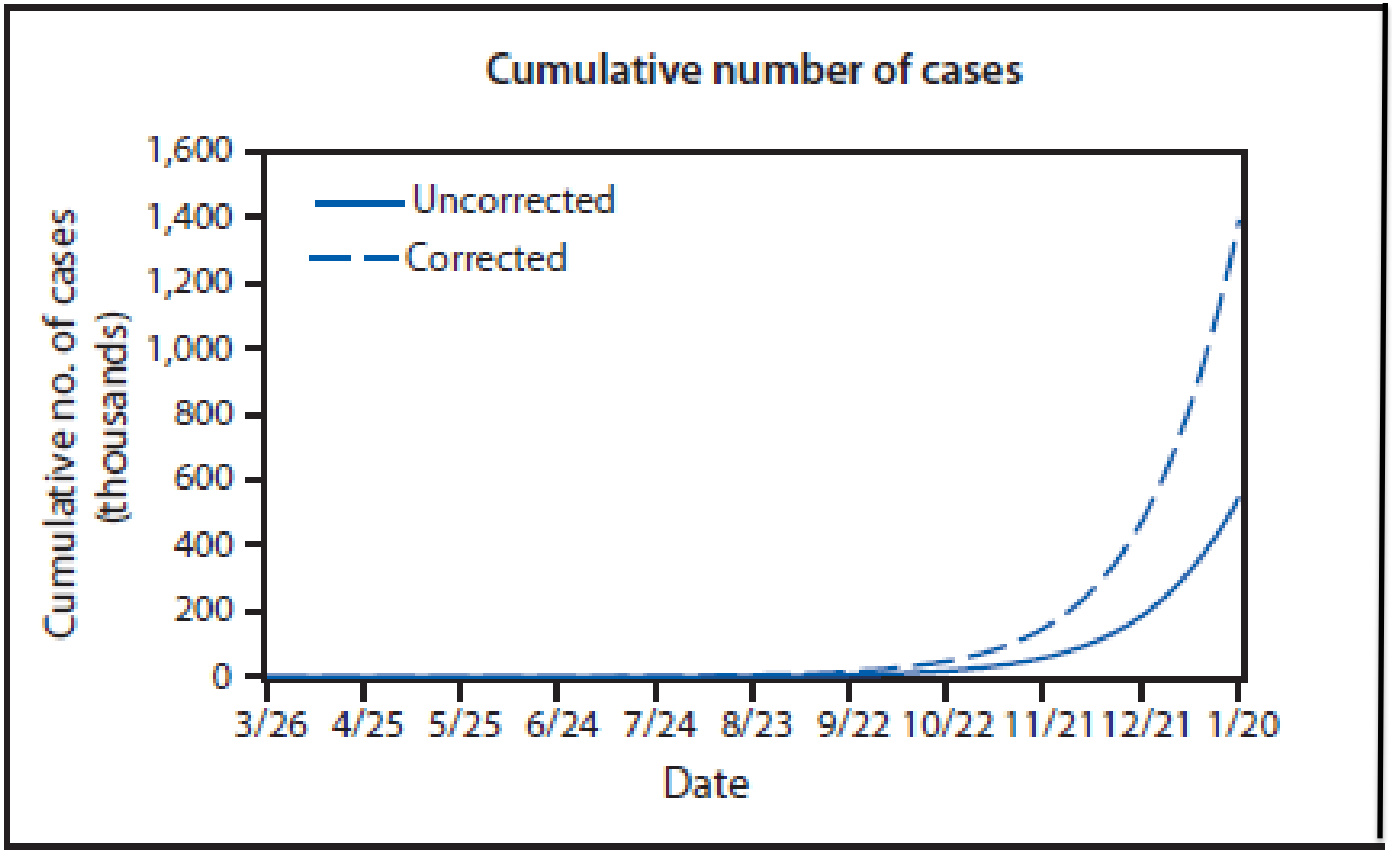
Ebola

- Practices often changed once it was realised this was a dangerous disease (Camacho et al. 2014).
- Northern Uganda, residents began to use a different word for the disease, indicating the disease was contagious and dangerous after a while (Hewlett and Amola, 2003)
- This is a possible reason why the disease disappeared in the past because the change in behaviour could have reduced the R0 below 1.

Ebola

- Various models were produced
- Form of the model: SEIR (susceptible, exposed, infected, removed)
- Models tend not to take the behavioural change into account
- This could be a reason why the models tend to overestimate

CDC prediction of Ebola numbers without intervention in Liberia and Sierra Leone



http://www.cdc.gov/mmwr/preview/mmwrhtml/su6303a1.htm

Current outbreak

- The behavioural response can change the course of an epidemic
- Most models do not account for this.

A model where transmission is affected by spreading awareness

From Funk et al. PNAS. 2009

Learning outcomes

- Understand what the imaginary part of an eigenvalue means for the population dynamics
- Understand how models and knowledge of the reproductive number can be used to understand the dynamics of a disease
- Understand how this can be used as a basis for public health policies and disease management

Learning outcomes (overall)

I hope that:

- you have gained an appreciation of what sort of dynamics models can show
- you have learned how to interrogate the output of models, and how to interpret dynamics
- You appreciate that being able to characterise the qualitative behaviour of model is useful