

## Introduction to infectious disease modelling

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with thanks to Ottar Bjornstad for sharing some slides...

## Why do we model infectious diseases?

Following Heesterbeek & Roberts (1995)

1. Gain insight into **mechanisms** influencing disease spread, and link individual scale 'clinical' knowledge with population-scale patterns.
2. **Focus thinking**: model formulation forces clear statement of assumptions, hypotheses.
3. Derive **new insights and hypotheses** from mathematical analysis or simulation.
4. Establish **relative importance** of different processes and parameters, to focus research or management effort.
5. **Thought experiments** and "what if" questions, since real experiments are often logistically or ethically impossible.
6. Explore **management options**.

Note the absence of **predicting future trends**. Models are highly simplified representations of very complex systems, and parameter values are difficult to estimate.

→ quantitative predictions are virtually impossible.

## Epidemic models: the role of data

### Why work with data?

Basic aim is to describe real patterns, solve real problems.

Test assumptions!

Get more attention for your work

→ jobs, fame, fortune, etc

→ influence public health policy

### Challenges of working with data

Hard to get good data sets.

The real world is messy! And sometimes hard to understand.

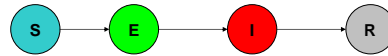
Statistical methods for non-linear models can be complicated.

### What about pure theory?

Valuable for clarifying concepts, developing methods, integrating ideas.

(My opinion) The world (and Africa) needs a few brilliant theorists, and *many* strong applied modellers.

## The SEIR framework for microparasite dynamics



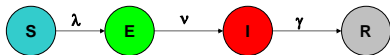
**Susceptible:** naïve individuals, susceptible to disease

**Exposed:** infected by parasite but not yet infectious

**Infectious:** able to transmit parasite to others

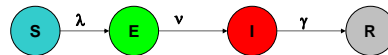
**Removed:** immune (or dead) individuals that don't contribute to further transmission

## The SEIR framework for microparasite dynamics



- λ "Force of infection"  
 =  $\beta I$  under density-dependent transmission  
 =  $\beta I/N$  under frequency-dependent transmission
- ν Rate of progression to infectious state  
 =  $1/\text{latent period}$
- γ Rate of recovery  
 =  $1/\text{infectious period}$

## The SEIR framework for microparasite dynamics



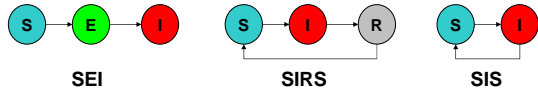
$$\frac{dS}{dt} = -\frac{\beta SI}{N}$$

$$\frac{dE}{dt} = \frac{\beta SI}{N} - \nu E$$

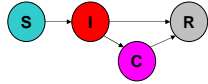
$$\frac{dI}{dt} = \nu E - \gamma I$$

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

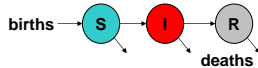
Ordinary differential equations are **just one approach** to modelling SEIR systems.



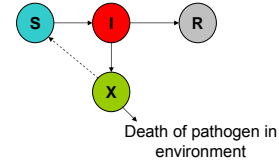
Adapt model framework to disease biology and to your problem!  
 No need to restrict to SEIR categories, if biology suggests otherwise.  
 e.g. leptospirosis has chronic shedding state → SICR



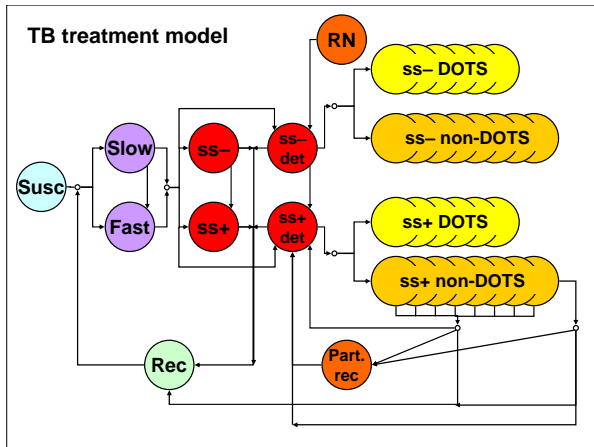
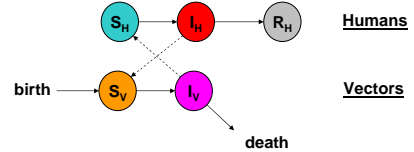
Depending on time-scale of disease process (and your questions),  
 add host demographic processes.



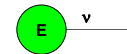
Disease with environmental reservoir (e.g. anthrax)



Vector-borne disease



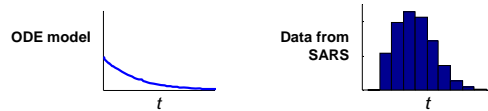
Residence times



How long does an individual spend in the E compartment?  
 Ignoring further input from new infections:

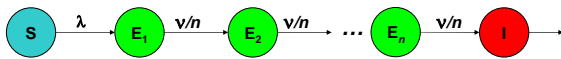
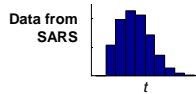
$$\frac{dE}{dt} = -vE \Rightarrow E(t) = E(0)e^{-vt}$$

For a constant per capita rate of leaving compartment, the residence time in the compartment is exponentially distributed.



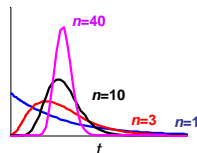
Residence times

How to make the model fit the data better?  
 • "Box-car model" is one modelling trick



Divide compartment into  $n$  sub-compartments, each with constant leaving rate of  $v/n$ .

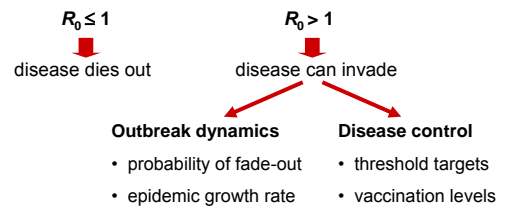
Residence time is now gamma-distributed, with same mean and flexible variance depending on the number of sub-compartments.



See Wearing et al (2005) PLoS Med 2: e174

Basic reproductive number,  $R_0$

Expected number of cases caused by a typical infectious individual in a susceptible population.



### Calculating $R_0$ – Intuitive approach

$R_0 =$  Per capita rate of infecting others  $\times$  Duration of infectiousness  
 ... in a completely susceptible population.

Under frequency-dependent transmission:

$$\begin{aligned} \text{Rate of infecting others} &= \beta S/N \\ &= \beta \text{ in wholly susceptible pop'n} \end{aligned}$$

$$\begin{aligned} \text{Duration of infectiousness} &= 1/\text{recovery rate} \\ &= 1/\gamma \end{aligned}$$

$$\rightarrow R_0 = \beta/\gamma$$

### $R_{\text{effective}}$ and herd immunity

$$R_{\text{effective}} = R_0 \times S/N$$

If a sufficiently high proportion of the population is immune, then  $R_{\text{effective}}$  will be below 1 and the disease cannot circulate.

The remaining susceptibles are protected by **herd immunity**.

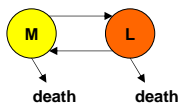
The critical proportion of the population that needs to be immune is determined by a simple calculation:

- For  $R_{\text{eff}} < 1$ , we need  $S/N < 1/R_0$
- Therefore we need a proportion  $1-1/R_0$  to be immune.

### The basic framework for macroparasite dynamics

For macroparasites the **intensity** of infection matters!

Basic model for a directly-transmitted macroparasite:



#### State variables

$N(t)$  = Size of host population

$M(t)$  = Mean number of sexually mature worms in host population

$L(t)$  = Number of infective larvae in the habitat

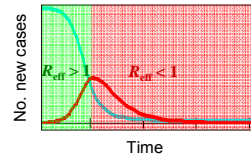
### Effective reproductive number

Expected number of cases caused by a typical infectious individual in a population that is not wholly susceptible.

$$R_{\text{effective}} = R_0 \times S/N$$

**Endemic disease:** At equilibrium  $R_{\text{eff}} = 1$ , so that  $S^*/N = 1/R_0$

**Epidemic disease:**  $R_{\text{eff}}$  changes as epidemic progresses, as susceptible pool is depleted.



**Note:** Sometimes "effective reproductive number" is used to describe transmission in the presence of disease control measures. This is also called  $R_{\text{control}}$ .

### What does $R_0$ tell you?

- Epidemic threshold  
 NOTE: not every epidemic threshold parameter is  $R_0$ !
- Probability of successful invasion
- Initial rate of epidemic growth
- Prevalence at peak of epidemic
- Final size of epidemic (or the proportion of susceptibles remaining after a simple epidemic)
- Mean age of infection for endemic infection
- Critical vaccination threshold for eradication
- Threshold values for other control measures

### The basic framework for macroparasite dynamics

$$\frac{dM}{dt} = d_1 \beta L(t - \tau_1) - (\mu + \mu_1)M$$

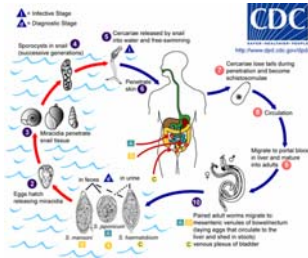
$$\frac{dL}{dt} = s d_2 \lambda N M(t - \tau_2) - \mu_2 L - \beta N L$$

- $\beta$  infection rate
- $\mu$  death rate of hosts
- $\mu_1$  death rate of adult worms within hosts
- $\mu_2$  death rate of larvae in environment
- $d_1$  proportion of ingested larvae that survive to adulthood
- $d_2$  proportion of eggs shed that survive to become infective larvae
- $\tau_1$  time delay for maturation to reproductive maturity
- $\tau_2$  time delay for maturation from egg to infective larva
- $s$  proportion of offspring that are female

**Further complexities:** parasite aggregation within hosts and density-dependent effects on parasite reproduction.

## $R_0$ for macroparasites

For macroparasites,  $R_0$  is the **average number of female offspring** (or just offspring in the case of hermaphroditic species) produced throughout the lifetime of a mature female parasite, which themselves **achieve reproductive maturity** in the absence of density-dependent constraints on the parasite establishment, survival or reproduction.



## Effective $R_0$ for macroparasites

For macroparasites,  $R_{\text{eff}}$  is the average number of female offspring produced in a host population within which **density dependent constraints** limit parasite population growth.

For microparasites,  $R_{\text{eff}}$  is the reproductive number in the presence of competition for hosts at the population scale.

For macroparasites,  $R_{\text{eff}}$  is the reproductive number in the presence of competition at the within-host scale.

For both, under conditions of stable endemic infection,  $R_{\text{eff}}=1$ .

## Major decisions in designing a model

Even after compartmental framework is chosen, still need to decide:

- Deterministic vs stochastic
- Discrete vs continuous time
- Discrete vs continuous state variables
- Random mixing vs structured population
- Homogeneous vs heterogeneous  
(and which heterogeneities to include?)

## Deterministic vs stochastic models

### Deterministic models

- Given model structure, parameter values, and initial conditions, there is no variation in output.

### Stochastic models incorporate chance.

- Stochastic effects are important when numbers are small, e.g. during invasion of a new disease
- Demographic stochasticity: variation arising because individual outcomes are not certain
- Environmental stochasticity: variation arising from fluctuations in the environment (i.e. factors not explicitly included in the model)

## Important classes of stochastic epidemic models

### *Monte Carlo simulation*

- Any model can be made stochastic by using a pseudo-random number generator to "roll the dice" on whether events occur.

### *Branching process*

- Model of invasion in a large susceptible population
- Allows flexibility in distribution of secondary infections, but does not account for depletion of susceptibles.

## Important classes of stochastic epidemic models

### *Chain binomial*

- Model of an epidemic in a finite population.
- For each generation of transmission, calculates new infected individuals as a binomial random draw from the remaining susceptibles.

### *Diffusion*

- Model of an endemic disease in a large population.
- Number of infectious individuals does a random walk around its equilibrium value → quasi-stationary distribution

### Continuous vs discrete time

Continuous-time models (ODEs, PDEs)

- Well suited for mathematical analysis
- Real events occur in continuous time
- Allow arbitrary flexibility in durations and residence times

$$\frac{dN}{dt} = \lambda N$$

Discrete-time models

$$N(t+1) = \lambda N(t)$$

- Data often recorded in discrete time intervals
- Can match natural timescale of system, e.g. generation time or length of a season
- Easy to code (simple loop) and intuitive
- Note: can yield unexpected behaviour which may or may not be biologically relevant (e.g. chaos).

### Continuous vs discrete state variables

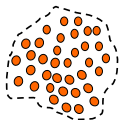
Continuous state variables arise naturally in differential equation models.

- Mathematically tractable, but biological interpretation is vague (sometimes called 'density' to avoid problem of fractional individuals).
- Ignoring discreteness of individuals can yield artefactual model results (e.g. the "atto-fox" problem).
- Quasi-extinction threshold: assume that population goes extinct if continuous variable drops below a small value

Discrete state variables arise naturally in many stochastic models, which treat individuals (and individual outcomes) explicitly.

### Models for population structure

Random mixing



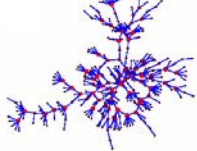
Multi-group



Spatial mixing



Network



Individual-based model



### Population heterogeneities

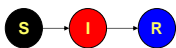
In real populations, almost everything is heterogeneous – no two individuals are completely alike.



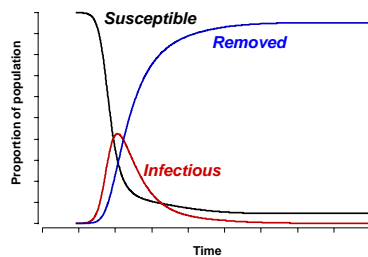
Which heterogeneities are important for the question at hand? Do they affect epidemiological rates or mixing? Can parameters be estimated to describe their effect?

- often modelled using multi-group models, but networks, IBMs, PDEs also useful.

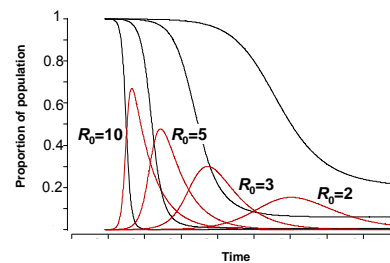
### SIR output: the epidemic curve



$$\begin{aligned} \frac{dS}{dt} &= -\frac{\beta SI}{N} \\ \frac{dI}{dt} &= \frac{\beta SI}{N} - \gamma I \\ \frac{dR}{dt} &= \gamma I \end{aligned}$$



### SIR output: the epidemic curve



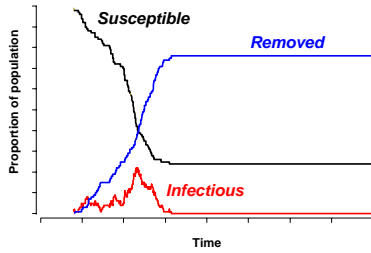
Basic model analyses (Anderson & May 1991):

Exponential growth rate,  $r = (R_0 - 1)/D$

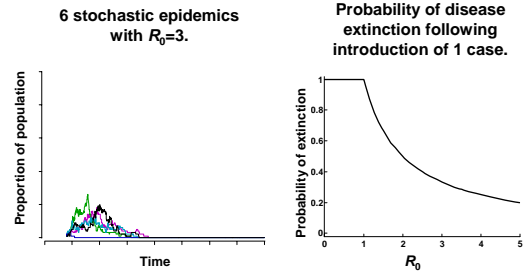
Peak prevalence,  $I_{max} = 1 - (1 + \ln R_0)/R_0$

Final proportion susceptible,  $f = \exp(-R_0[1-f]) \approx \exp(-R_0)$

### SIR output: stochastic effects

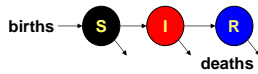


### SIR output: stochastic effects



Stochasticity → risk of disease extinction when number of cases is small, even if  $R_0 > 1$ .

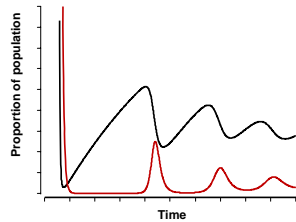
### SIR with host demographics: epidemic cycles



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

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

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

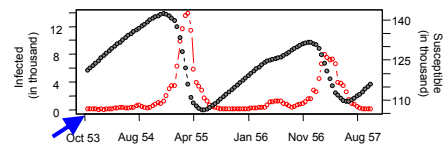


Cycle period  $T \approx 2\pi (AD)^{1/2}$

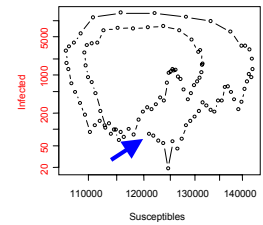
where  $A$  = mean age of infection

$D$  = disease generation interval

or can solve  $T$  in terms of SIR model parameters by linearization.

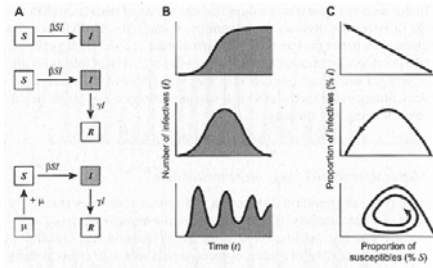


### The S-I phase plot



### Summary of simple epidemic patterns

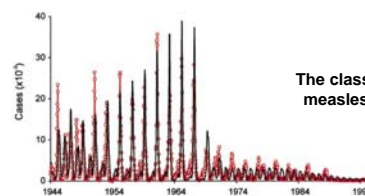
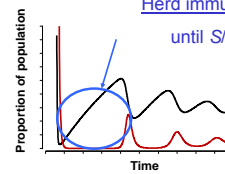
- Absence of recovery: logistic epidemic
- No susceptible recruitment (birth or loss of immunity): simple epidemics
- Susceptible recruitment through birth (or loss of immunity): recurrent epidemics



### Herd immunity and epidemic cycling

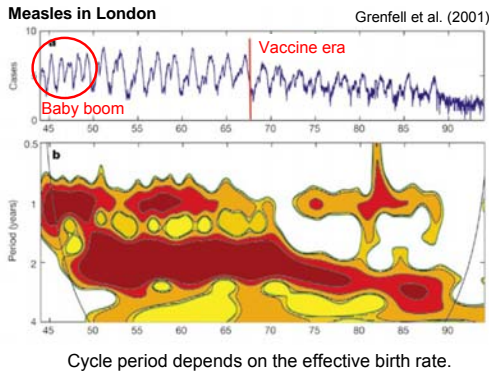
[Herd immunity](#) prevents further outbreaks

until  $S/N$  rises enough that  $R_{eff} > 1$ .



The classic example: measles in London

**Herd immunity and epidemic cycling**



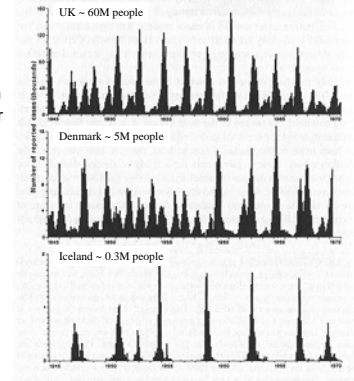
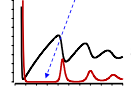
**Persistence and fadeouts**

**Measles again...**

Note that measles dies out between major outbreaks in Iceland, but not in the UK or Denmark.

What determines persistence of an acute infection?

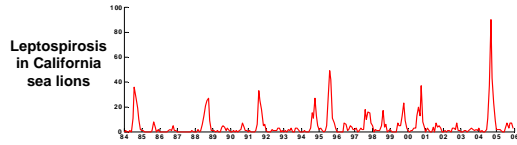
NB: Questions like this are where "atto-foxes" can cause problems.



**Intrinsic vs extrinsic forcing – what determines outbreak timing?**

Untangling the relative roles of **intrinsic forcing** (population dynamics and herd immunity) and **extrinsic forcing** (environmental factors and exogenous inputs) is a central problem in population ecology.

This is particularly true for 'outbreak' phenomena such as infectious diseases or insect pests, where dramatic population events often prompt a search for environmental causes.



**Intrinsic vs extrinsic forcing – what determines outbreak timing?**

*Example: leptospirosis in California sea lions*

**Intrinsic factors**

Host population size and structure, recruitment rates and herd immunity

**Extrinsic factors**

- Pathogen introduction: contact with reservoirs, invasive species, range shifts
- Climate: ENSO events, warming temperatures
- Malnutrition: from climate, fisheries or increasing *N*
- Pollution: immunosuppressive chemicals, toxic algae blooms
- Human interactions: Harvesting, protection, disturbance

**Data needs I. What's needed to build a model?**

**Individual "clinical" data**

- Latent period: time from infection to transmissibility
- Infectious period: duration (and intensity) of shedding infectious stages
- Immunity: how effective, and for how long?

**Population data**

- Population size and structure
- Birth and death rates, survival, immigration and emigration
- Rates of contact within and between population groups

**Epidemiological data**

- Transmissibility ( $R_0$ )
  - density dependence, seasonality

**Data needs II. What's needed to validate a model?**

**Time series**

- Incidence: number of new cases
- Prevalence: proportion of population with disease

Seroprevalence / sero-incidence: shows individuals' history of exposure.

Age/sex/spatial structure, if present.

e.g. mean age of infection → can estimate  $R_0$

**Cross-sectional data**

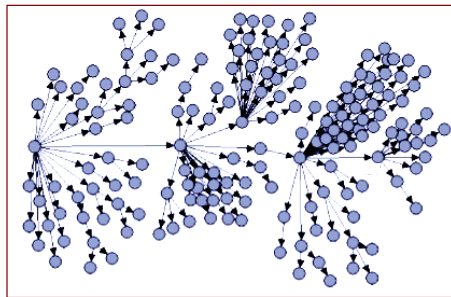
Seroprevalence survey (or prevalence of chronic disease)

**endemic disease** at steady state → insight into mixing

**epidemic disease** → outbreak size, attack rate, and risk groups

**Contact tracing**

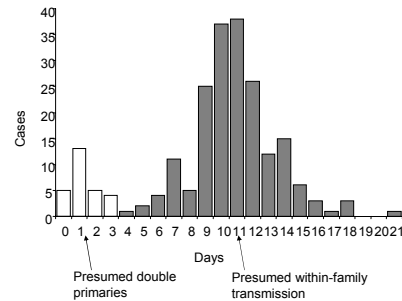
SARS transmission chain, Singapore 2003



Morbidity & Mortality Weekly Report (2003)

**Household studies**

Observed time intervals between two cases of measles in families of two children. Data from Cirencester, England, 1946-1952 (Hope-Simpson 1952)



**Measles:**

Latent period 6-9 d, Infectious period 6-7 d, Average serial interval: 10.9 d

**Long-term time series**



Historical mortality records provide data: London Bills of mortality for a week of 1665

<http://www.who.int/research/en/>



Today: several infections are 'notifiable'

Table 3.2 Notifiable infections in the United States (1984)

Acquired Immunodeficiency Syndrome (AIDS)	
Amoebiasis	
Anthrax	
Asplenic meningitis	
Botulism	
Brucellosis	
Chancroid	
Cholera	
Diphtheria	
Encephalitis, primary	
Encephalitis, post infectious	
Gonorrhoea	
Granuloma inguinale	
Hepatitis, serum	
Hepatitis, infectious	
Hepatitis, unspecified	
Leptospirosis	
Lymphogranuloma venereum	
Malaria	
Measles	
Meningococcal infections	
Mumps	
Pertussis	
Plague	
Poliovirus	
Poliovirus, acute	
Poliovirus, chronic	
Rabies, animal	
Rabies, human	
Rheumatic fever, acute	
Rubella	
Rubella Congenital Syndrome	
Salmonellosis	
Shigellosis	
Smallpox	

CDC Morbidity and Mortality Weekly Report

TABLE III. Provisional cases of selected notifiable diseases preventable by vaccination, United States, weeks ending August 18, 2001.

Notifiable Area	Weeks Ending August 18, 2001		Weeks Ending August 11, 2001		Weeks Ending August 4, 2001		Weeks Ending July 28, 2001	
	Weeks	Cases	Weeks	Cases	Weeks	Cases	Weeks	Cases
NEW ENGLAND	10	1,000	10	1,000	10	1,000	10	1,000
Maine	1	100	1	100	1	100	1	100
New Hampshire	1	100	1	100	1	100	1	100
Rhode Island	1	100	1	100	1	100	1	100
Vermont	1	100	1	100	1	100	1	100
MID. ATLANTIC	10	1,000	10	1,000	10	1,000	10	1,000
Delaware	1	100	1	100	1	100	1	100
District of Columbia	1	100	1	100	1	100	1	100
Maryland	1	100	1	100	1	100	1	100
North Carolina	1	100	1	100	1	100	1	100
Virginia	1	100	1	100	1	100	1	100
West Virginia	1	100	1	100	1	100	1	100
SOUTH ATLANTIC	10	1,000	10	1,000	10	1,000	10	1,000
Alabama	1	100	1	100	1	100	1	100
Florida	1	100	1	100	1	100	1	100
Georgia	1	100	1	100	1	100	1	100
Louisiana	1	100	1	100	1	100	1	100
Mississippi	1	100	1	100	1	100	1	100
South Carolina	1	100	1	100	1	100	1	100
Texas	1	100	1	100	1	100	1	100
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West Virginia	1	100	1	100	1	100	1	100
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South Carolina	1	100	1	100	1	100	1	100
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Mississippi	1	100	1	100	1	100	1	100
Alabama	1	100	1	100	1	100	1	100
Georgia	1	100	1	100	1	100	1	100
Florida	1	100						

<http://www.cdc.gov/mmwr/>  
<http://www.eurosurveillance.org>



Age-incidence

Grenfell & Anderson's (1989) study of whooping cough

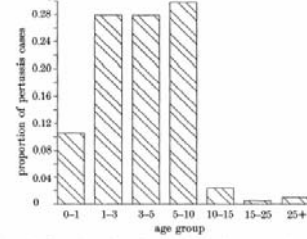
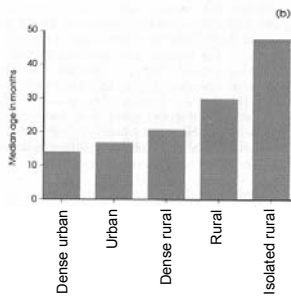


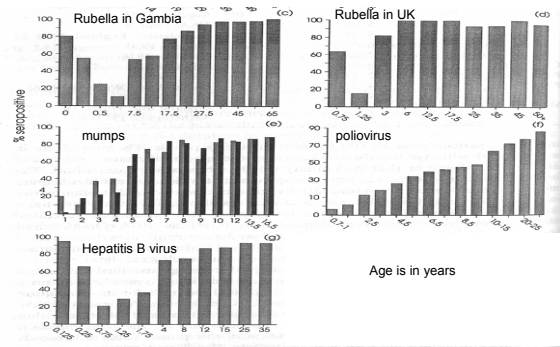
FIGURE 2. Proportional age distribution of whooping cough notifications in England and Wales for the period 1944 to 1946.

Age-incidence

e.g. Walsh (1983) of measles in urban vs rural settings in central Africa



Age-seroprevalence curves



**Seroprevalence:** Proportion of population carrying antibodies indicating past exposure to pathogen.

Increased transmission leaves signatures in seroprevalence profiles

e.g. measles in small (grey) and large (black) families

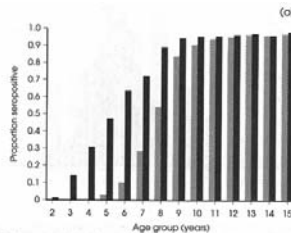
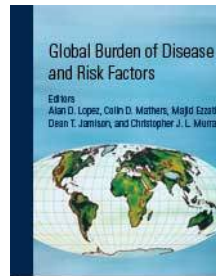
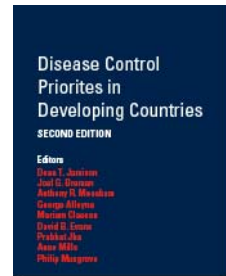


Fig. 3.10. (a) The proportion of an age group with antibodies specific to measles virus antigens in children from small and large families in the United States in 1957 prior to the introduction of mass vaccination (data from Black 1959). Family size clearly has an important influence on immunity to measles at different ages.

Two books full of data on important global health problems - PDF versions free to download.



<http://www.dcp2.org/pubs/GBD>

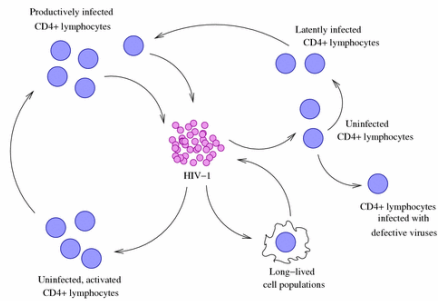


<http://www.dcp2.org/pubs/DCP>

**Other fields of disease modelling**

Within-host models

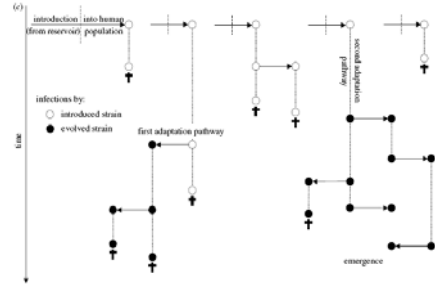
- pathogen population dynamics and immune response



**Other fields of disease modelling**

Pathogen evolution

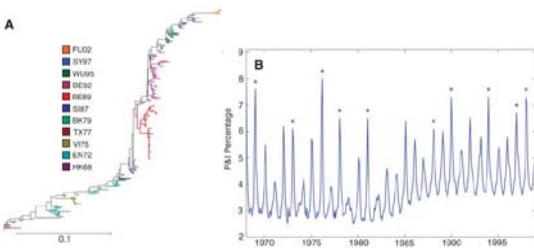
- adaptation to new host species, or evolution of drug resistance



**Other fields of disease modelling**

Phylodynamics

- how epidemic dynamics interact with pathogen molecular evolution



**Community dynamics of disease**

Co-infections

What happens when multiple parasites are present in the same host?  
 How do they interact? Resource competition? Immune-mediated indirect competition? Facilitation via immune suppression

Multiple host species

Many pathogens infect multiple species

- when can we focus on one species?
- how can we estimate importance of multi-species effects?

Zoonotic pathogens – many infections of humans have animal reservoirs, e.g. flu, bovine TB, yellow fever, Rift valley fever

Reservoir and spillover species

Host jumps and pathogen emergence