Introduction to mathematical modelling of infectious diseases

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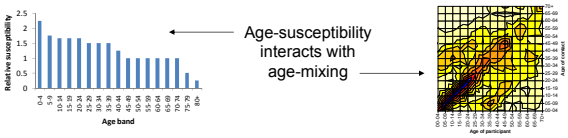
Applications of modelling

- Multiple interacting factors affect transmission patterns – so complex
- Modelling should be multidisciplinary: needs clinical, behavioural, biological, statistical, mathematical knowledge

- Planning & response (real-time analysis)
- What do we know, based on current data? (↑ during epidemic)
  - *Modelling synthesises data from multiple sources*
- What might happen, based on what we know – and don't know?
  - *Quantification of uncertainty is a key strength of modelling*
- What would be the effects of different interventions?
  - e.g. school closures, travel restrictions
  - Vaccination: which should be the priority groups?



Interaction between modellers and public health

• **UK** – embedded in planning & response: meetings with government at least weekly, including dedicated subcommittee. Health Protection Agency, Imperial College, LSHTM, Warwick University

• **US** – CDC linked with academic modellers within first week, personnel embedded. Interactions at all tiers of government.

• **WHO**
  - Embedded personnel from Imperial.
  - Informal Modelling Network – 40 participants from >20 countries.

• **ECDC** planning guidance incorporated modelling analyses

• Many other countries using modelling, to varying extents: Australia, Canada, China, France, Netherlands, New Zealand, Singapore...

Models: what are they?

• Simplification of a system, suitable for analysis.
• They are tools for thinking.

• *"All models are wrong, but some are useful."* G.E.P. Box

• *"Describing complex, poorly-understood reality with a complex, poorly-understood model is not progress."*
J. Maynard Smith

• Needs to capture essential behaviour of interest and incorporate essential processes.

• **Everyone uses models** in their head: making them explicit mathematically clarifies thinking & allows others to examine them.
• Mathematical models allow precise, rigorous analysis and quantitative prediction.

Infectious disease transmission is dynamic

An uninfected individual's risk of becoming infected during a time-interval ("force of infection") depends upon the prevalence of infectious individuals

Therefore, incidence depends upon prevalence…
... and of course prevalence depends upon incidence

So transmission of infection in a population is a dynamic process, with the individual risk of infection changing over time.

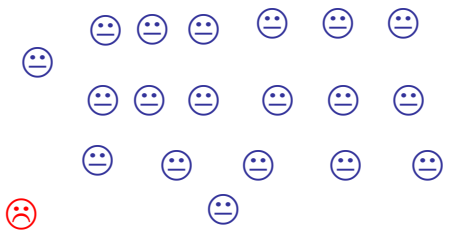
Initially in an epidemic, spreading accelerates as transmission increases the number of infectious individuals, which increases further the rate of spread.

Then spreading slows as the number of susceptibles declines.

Evaluation of policy options needs to account for infections averted as well as treated.

Transmission (1)

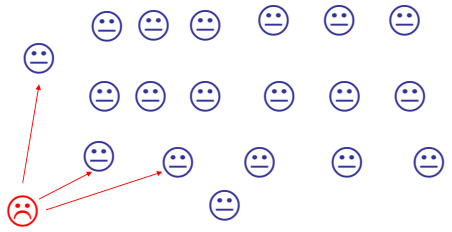
😐 Naive; ☹ Infected; ☺ Immune



One has acquired infection

Transmission (2)

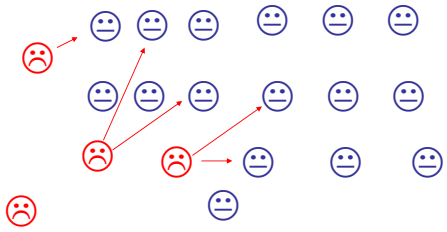
😐 Naive; ☹ Infected; ☺ Immune



Transmission

Transmission (3)

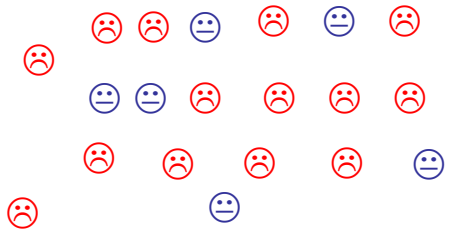
😐 Naive; ☹ Infected; ☺ Immune



More transmission: prevalence ↑ → per-susceptible risk ↑

Transmission (4)

😐 Naive; ☹ Infected; ☺ Immune



Transmission (5)

😐 Naive; ☹ Infected; ☺ Immune

Recovery to immunity

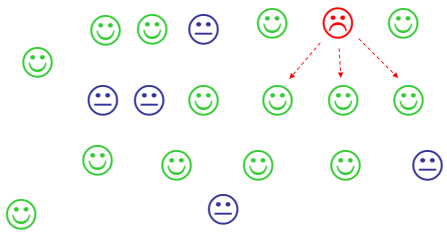
Transmission (6)

😐 Naive; ☹ Infected; ☺ Immune

Another acquires infection from elsewhere

Transmission (7)

😐 Naive; ☹ Infected; ☺ Immune



No transmission due to herd immunity – naives not infected

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Modelling considerations

- Population structure & demography
  - e.g. stratify by age, sex?
- Natural history of infection
  - e.g. latency, infectious period, immunity
- Transmission of infection
  - e.g. direct or indirect? What affects contact rate?
- Interventions
  - What parts of the disease-transmission process are targeted?

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Modelling natural history

- Divide population into compartments (categories), according to biological properties of different states (e.g. stages of infection).
  - In the model, all those in a category have the same properties
  - These are the average properties of those in the 'real world'

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Latent period

- In simple models, we assume individuals become infectious as soon as they are infected.
- However, there may be a significant *latent period* between being infected and becoming infectious.
- *In modelling literature, latently-infected are often called "Exposed".*

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Incubation period

- This is the time between becoming infected and becoming symptomatic.
- Often infections are only treated when a person becomes symptomatic and so becomes aware that they have an infection.
- For some diseases, symptoms occur before the person is infectious (e.g. SARS) whilst for others symptoms begin after the person is infectious (e.g. HIV, maybe influenza).
- For some diseases, symptoms and infectiousness occur together (e.g. pulmonary TB).

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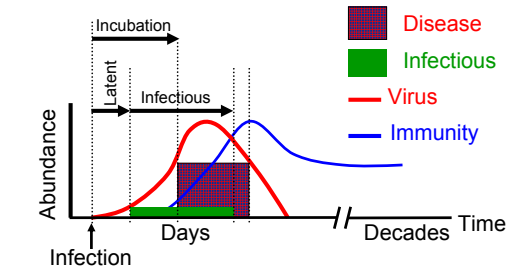
Natural history of an example viral infection

Latent: infected but not yet infectious.

Incubation: infected but not yet diseased.



Susceptible → Latent → Infectious → Recovered

(Often called "Exposed" in the literature)

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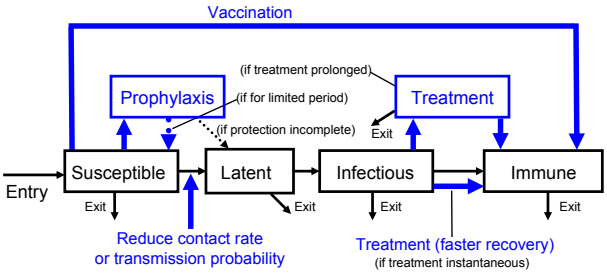
Some infection control measures

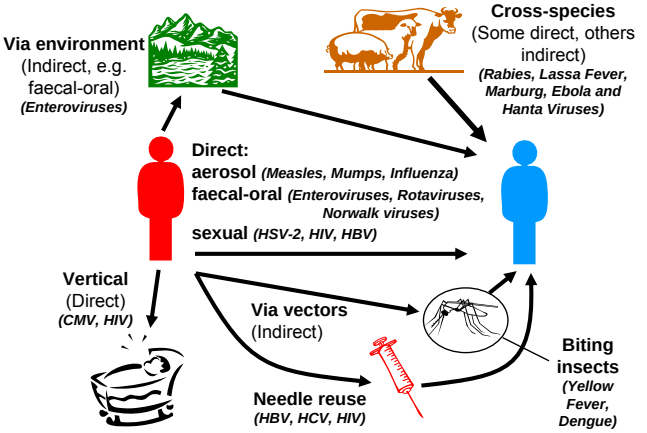


Transmission and 'contact'

- Transmission requires:
  (i) a source of infection;
  (ii) a susceptible individual;
  (iii) contact between them. (But transmission does not occur every time.)

- What 'counts' as a contact depends upon the infection.
  - e.g. briefly sitting next to a person may be a 'contact' for influenza but not for TB.
  - Different types of contact will have different dynamics – e.g. sexual, 'social', 'casual' – some are affected by population density, whilst others are not.
  - For malaria, a contact would be a mosquito biting a person.

Transmission routes of some viral infections



Some transmission routes

Direct
- Physical contact – e.g. sexually-transmitted infections (STI)
- Respiratory:
  - Close proximity – e.g. TB
  - Longer-range, can be very rapidly-spread – e.g. influenza, measles
- Zoonoses – e.g. rabies, hantavirus.
- Vertical – e.g. HIV (mother-to-child).

Indirect
- Vector-borne – e.g. malaria, dengue, schistosomiasis
- Faecal-oral: water-borne & food-borne – e.g. Hepatitis A virus; typhoid
- Needles – e.g. HIV, Hepatitis B virus

Long-distance transmission between populations
- Birds – e.g. West Nile Virus
- Insects – e.g. Rabbit Haemorrhagic Disease Virus?
- Vehicles, people – e.g. Foot & Mouth Disease Virus (FMDV)
- Airborne over long distances – e.g. FMDV?

Transmission rate formula

(for direct transmission)

Consider one susceptible individual…

Rate of contacting other individuals: c ← Contact rate

Transmission requires contact with infectious individuals…

Rate of contacting infectious individuals: cI/N ← Proportion of population infectious (I = no. infectious; N = no. in total population)

Rate of transmission from infectious individuals: pcI/N ← Probability of transmission when an infectious individual contacts a susceptible

pcI/N = Force of infection, λ

Now consider all susceptible individuals…

Total transmission rate in population: $pcSI/N$ ← No. susceptible individuals

(NB. S, I, N are state variables, which can change intrinsically, whilst p, c are parameters and cannot.)

Often β is written in place of pc.

Behaviour of simple models

- The point is to understand fundamental processes rather than to make models 'realistic' initially.

- Realistic models are complicated and hard to understand unless fundamental processes that occur are understood first.

- *Analysis involves varying parameter values singly and in combination to see how model outputs change (but no time to do it here).*

Example epidemic

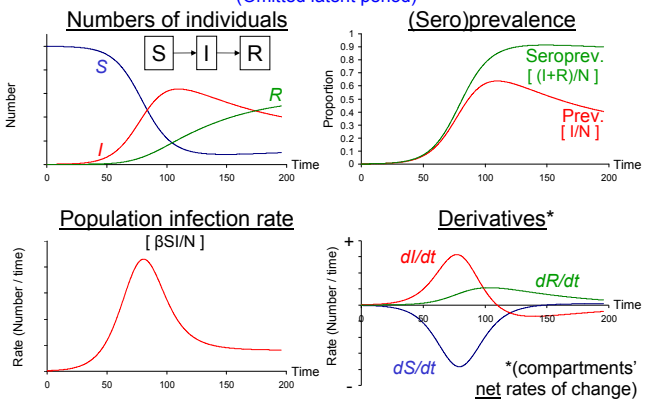
- Initially in an epidemic in a naïve population, the rate of spread accelerates as transmission ↑ Infecteds, which ↑ force of infection which ↑ further the rate of spread.

- Then spreading slows as Susceptibles ↓ significantly, (even though force of infection continues to ↑).

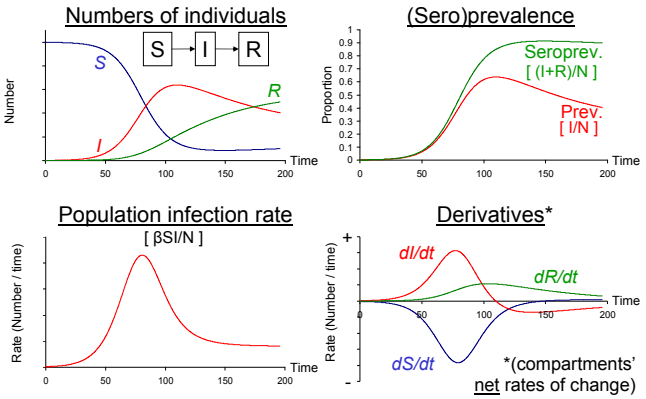
- If Infecteds recover to become immune then the epidemic can fade out, unless
  - new naive individuals enter the population, or
  - immunity wanes, returning individuals to susceptibility.

SIR model: dynamics

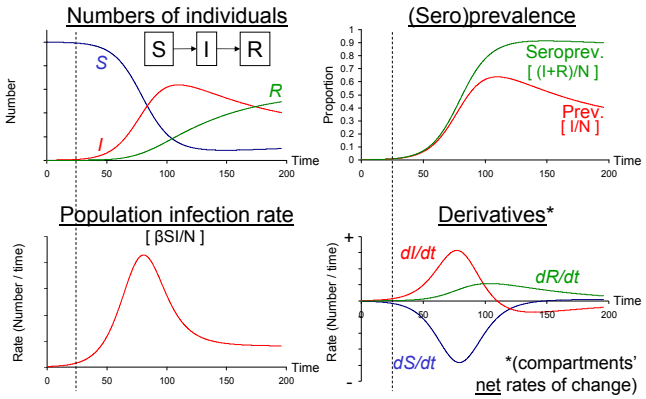
(Omitted latent period)



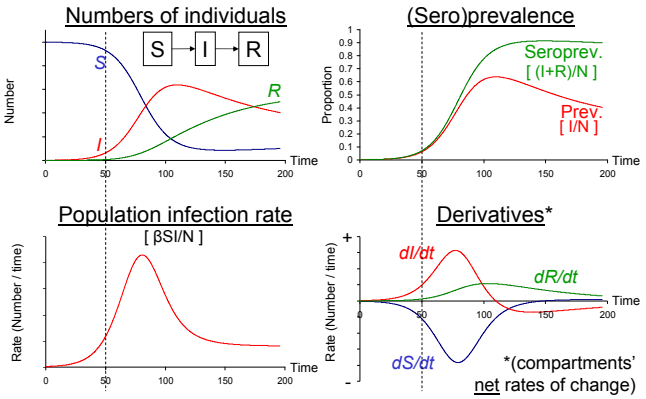
Time 0: low transmission rate, as *I*=1 so *I*/*N* tiny



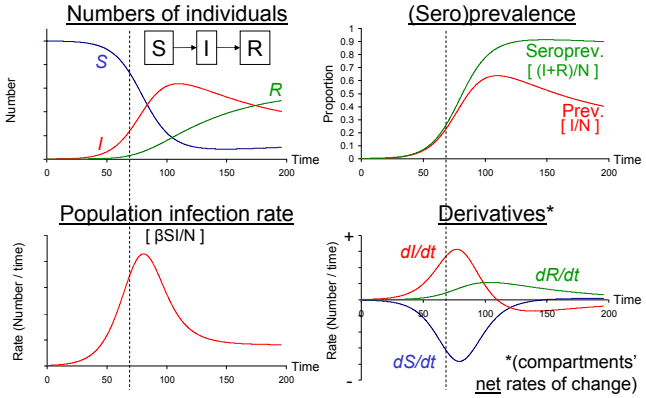
Exponential growth: transmission rate >> than at time 0 but still low, as *I*/*N* still small



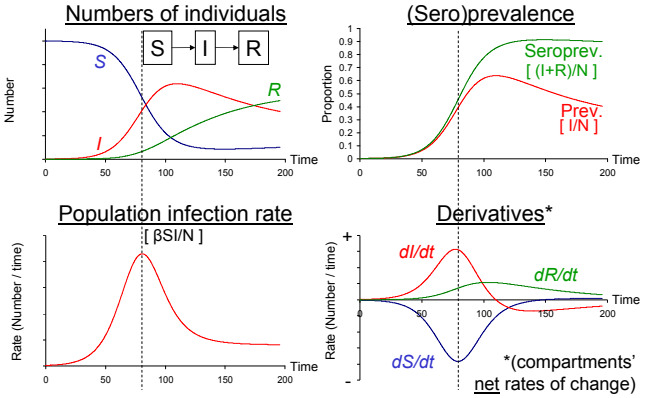
Exponential growth: transmission rate ↑, as *I*/*N* ↑



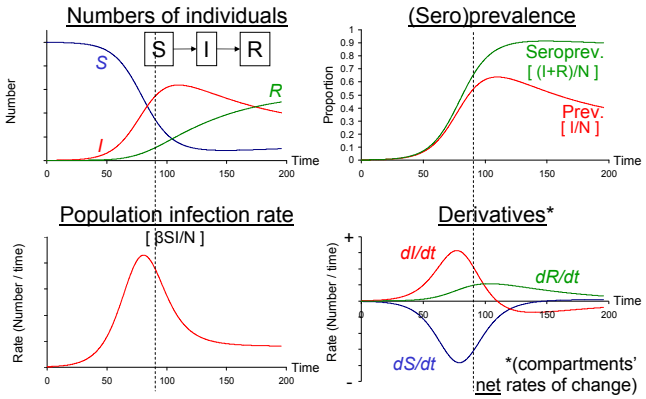
Transmission rate still growing as *I*/*N* ↑ but growth slower than exponential, as *S* ↓



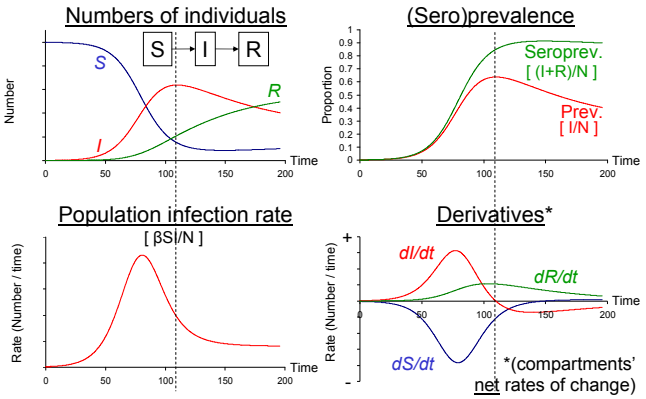
Peak transmission rate, due to S ↓: *I*/*N* still ↑



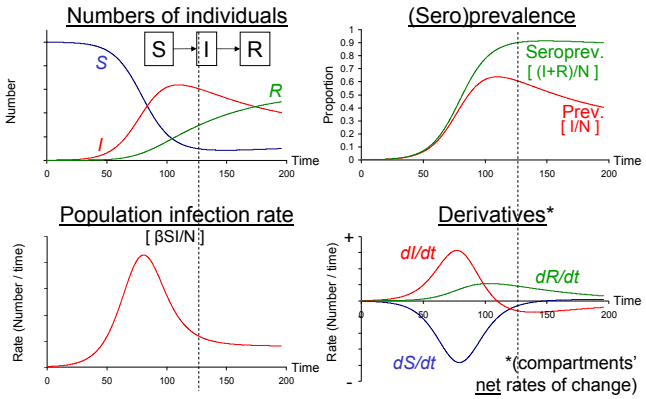
Transmission rate ↓, due to S ↓: *I*/*N* still ↑



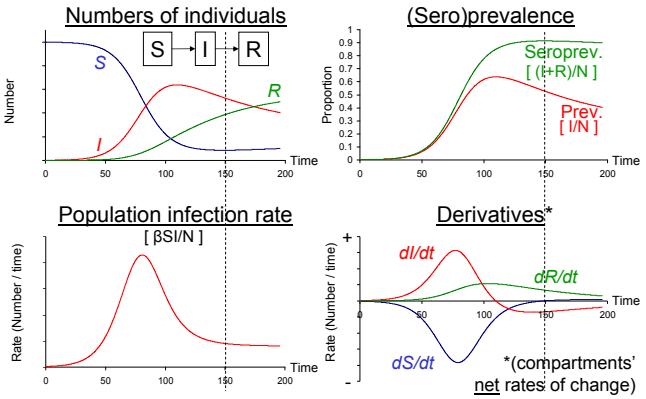
Transmission rate ↓↓, due to *S* ↓: *I*/*N* at its peak (i.e. force of infection is at its peak)



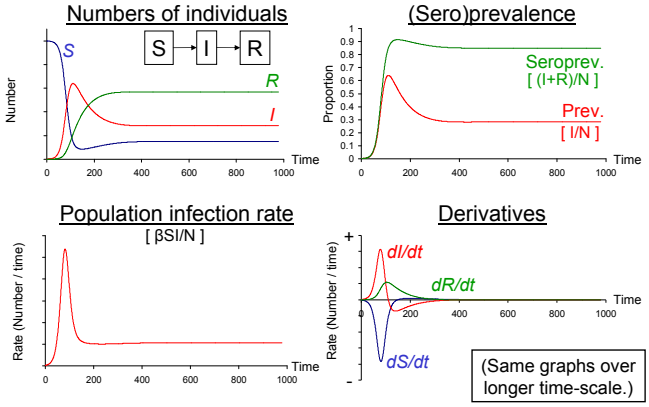
Transmission rate ↓ continues, due to *S* ↓ and now *I*/*N* ↓



Transmission rate ↓ continues, approaching steady state



SIR model: steady state



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Basic reproductive number, R_0

Also called
Basic reproductive rate
Basic reproductive ratio
Basic reproduction number
…

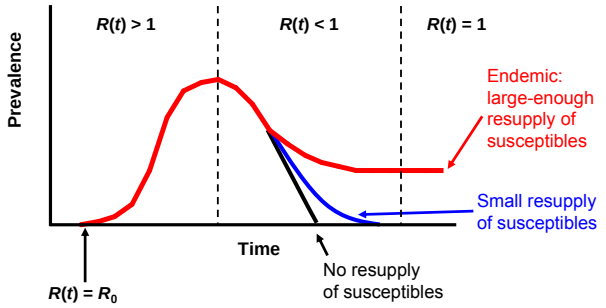
Basic reproductive number, R_0

- Measures how effectively infection spreads – higher R_0 means harder to control.
- It is the average number of secondary infections occurring from a single infected individual in a totally susceptible population.
- For an epidemic to occur requires that transmission from an infected individual causes on average more than one new infection (i.e. $R_0 > 1$) so amplification occurs.
- Fundamentally, R_0 depends upon
  (i) how long individuals are infectious for (on average), and
  (ii) how rapidly they transmit infection (on average).
  These vary amongst populations and can be changed.
- Interventions aim to reduce $R_0<1$, to eliminate infection that is present and/or prevent an epidemic occurring if it should be (re)introduced.

Effective reproductive number, $R(t)$

- R_0 is "the average number of secondary infections caused by a single infected individual in a totally susceptible population"
  - i.e. it is the infection's maximum 'transmission potential'.
- $R(t)$ is "the average number of secondary infections caused by a single infected individual at any point in time"
  - "(t)" indicates that it varies intrinsically over time, as infection spreads and the proportion of the population that is susceptible changes.
- $R(t) = R_0(S/N)$ where S/N = proportion of population susceptible
- If all of population is susceptible [i.e. $S/N=1$] then $R(t) = R_0$
- NB. $R(t) \leq R_0$
- Elimination of established infection requires making $R(t)<1$.

Epidemic time-course



Summary

Summary of infectious-disease modelling

- Models are tools for understanding systems.
- Infectious disease dynamics are important.
- Mathematics allows precise, rigorous analysis.
- Expressing ideas mathematically clarifies thinking.
- Quantitative predictions can be made.
- Can evaluate policy options.
- Accurate quantitative predictions require good data.
- However, models can investigate scenarios where data are lacking.
  - e.g. to identify what processes could be occurring, or what parameters it is most important to measure.