Introduction to transmission dynamic models of infectious diseases

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Models – what are they?

A model is a simplified description of a complex entity or process

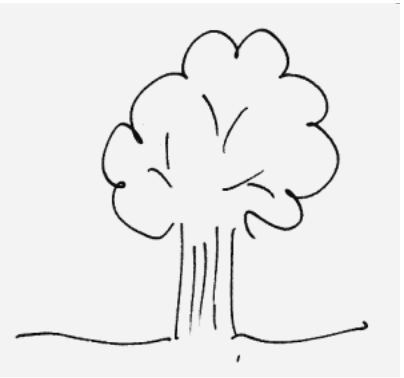
Why might we want a model?

- To improve our fundamental understanding of how a system works

- To predict or project how the system will change over time (and possibly in response to manipulation)

Desirable properties of models

Simplicity (understanding) ⟷ Realism (prediction)



Why do we use models for infectious diseases?

- The dynamics of infectious diseases are complex

- Non-linearities
  - Small changes in input can produce large changes in output

- Emergent properties
  - More is different

Overview

Simplicity (understanding) ⟷ Realism (prediction)

1. Compartmental Models

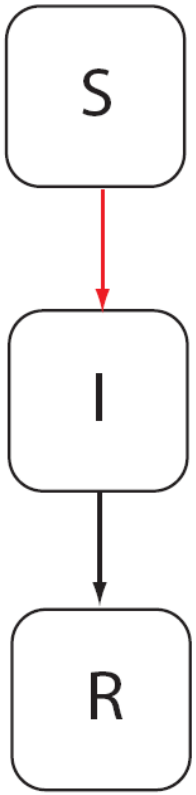
2. Other model types:

Metapopulation
Individual-based
Spatial
Network

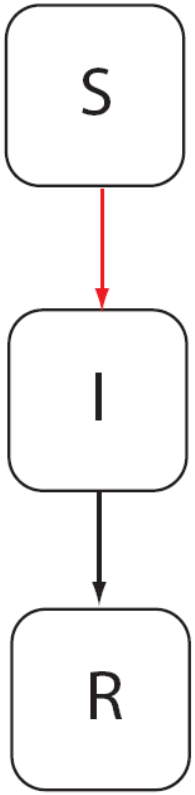
1. Compartmental models

- Population divided into categories defined by health/disease status

- SIR model as a prototype



SIR model (no demography)



$$\frac{dS}{dt} = -\beta IS$$

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

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

β = transmission parameter
(transmission probability/contact*contact rate)

γ = recovery rate (1/disease duration)

Closed system: no births/deaths
S, I, R are proportions: S+I+R=1
Disease is approximated by SIR: no latency, immunity is complete

R_0: Basic reproductive number

- Expected number of secondary cases of disease produced directly by an average infectious individual entering an entirely susceptible population

$R_0 > 1$ Epidemic occurs

$R_0 < 1$ No epidemic occurs

Threshold phenomenon

- Kermack & McKendrick 1927
- Minimum fraction of population that is susceptible necessary for an epidemic to occur.

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

$$I(\beta S - \gamma) > 0 \qquad \text{(if epidemic occurs, } \frac{dI}{dt} > 0\text{)}$$

$$\beta S - \gamma > 0$$

$$S > \frac{\gamma}{\beta} \qquad \left(\frac{\gamma}{\beta} \text{ is the relative removal rate}\right)$$

Threshold phenomenon & R_0

$$S > \frac{\gamma}{\beta}$$

$$1 > \frac{\gamma}{\beta}$$

(Basic reproductive number defined when S=1)

$$\frac{\beta}{\gamma} > 1$$

$$\frac{\beta}{\gamma} = R_0$$

Threshold phenomenon & critical proportion to vaccinate

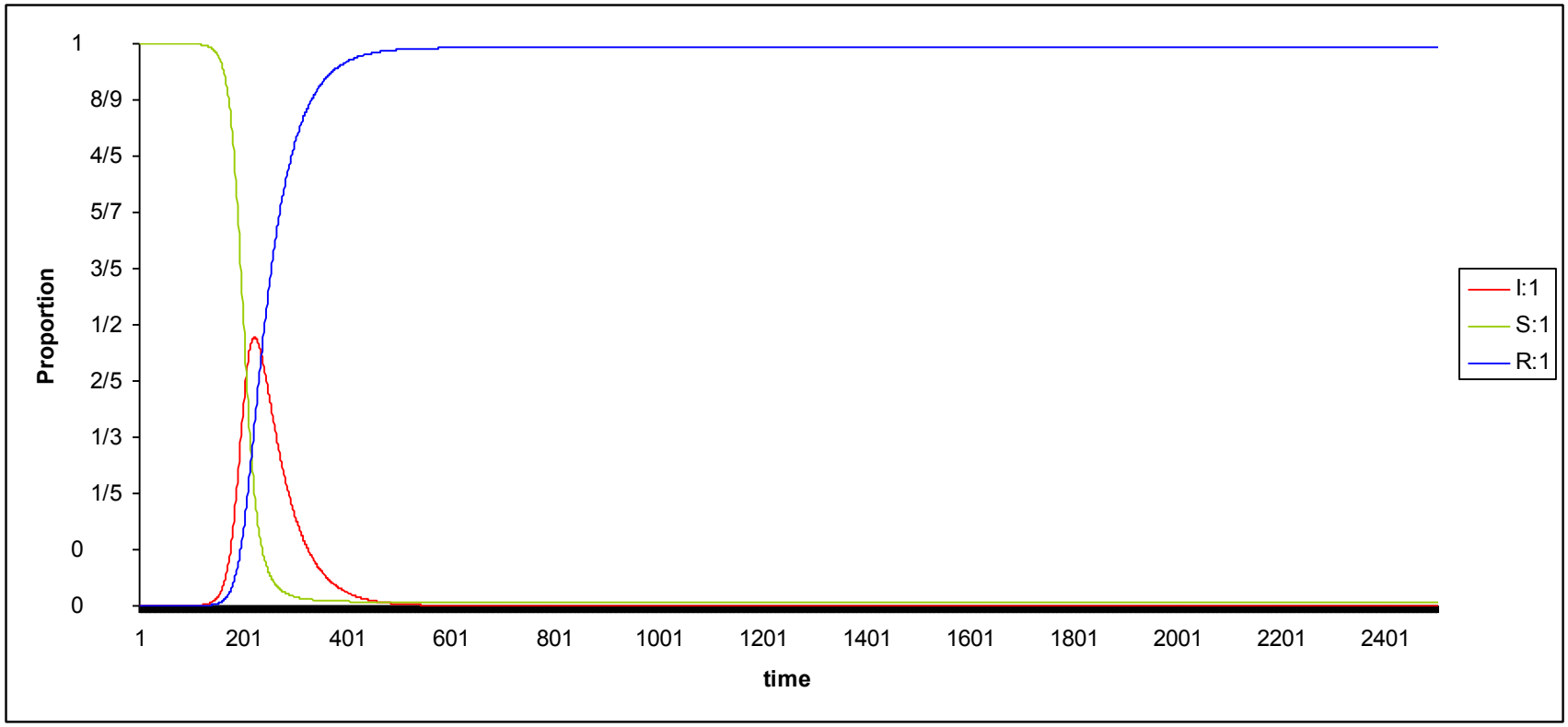
$$S > \frac{\gamma}{\beta}$$

(threshold proportion of susceptibles necessary for an epidemic)

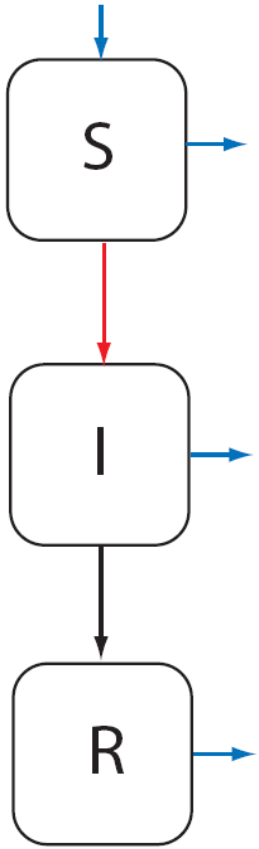
$$S > \frac{1}{R_0}$$

(therefore, we must vaccinate at least $1 - \frac{1}{R_0}$ of the population to prevent an epidemic)

Epidemic curve (SIR, no demography)



SIR model (with demography)



$$\frac{dS}{dt} = \mu(S + I + R) - \beta IS - \mu S$$

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

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

β = transmission parameter
(transmission probability/contact*contact rate)

γ = recovery rate (1/disease duration)

μ = mortality/fertility (1/life expectancy)

Fixed population size (deaths=births)
No disease induced mortality

R_0 in an SIR model with demography

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

(When is I increasing?: When the above equation is +.)

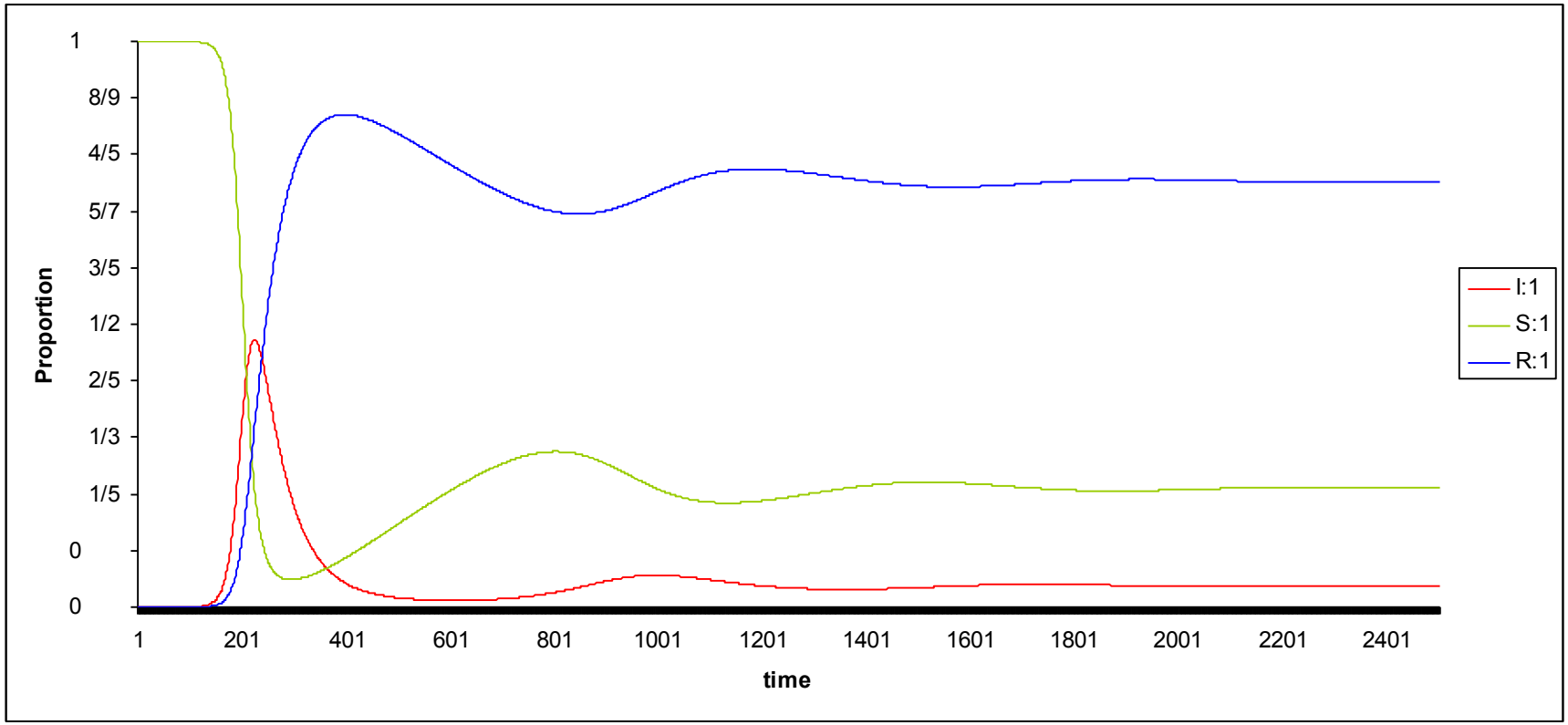
$$I(\beta S - \gamma - \mu) > 0$$

$$\beta > \gamma + \mu$$

$$\frac{\beta}{\gamma + \mu} > 1$$

$$\frac{\beta}{\gamma + \mu} = R_0$$

Epidemic curve (SIR, with demography)



Equilibrium condition: S

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

(At equilibrium the above equation = 0.)

$$I^*(\beta S^* - \gamma - \mu) = 0$$

(Let's examine the non-trivial case when $I^* \neq 0$)

$$\beta S^* = \gamma + \mu$$

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

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

Equilibrium condition: I

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

at equilibrium:

$$\mu - \beta I^* S^* - \mu S^* = 0$$

substituting for $S^* = \frac{1}{R_0}$

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

Average age of infection (at equilibrium)?

$$\frac{dS}{dt} = \mu(S + I + R) - \beta IS - \mu S$$

(Ignoring small rates of mortality/fertility)

$$\frac{dS}{dt} \approx -\beta IS$$

rate of leaving S = βI

mean duration of staying in S at equilibium = Average age of infection (A)

$$A \approx \frac{1}{\beta I^*}$$

substituting for I* = $\frac{\mu(R_0\text{-}1)}{\beta}$:

$$A \approx \frac{1}{\mu(R_0\text{-}1)} = \frac{L}{(R_0\text{-}1)}$$ (where L = average lifespan)

$$\frac{L}{A} = (R_0\text{-}1)$$

R_0 and the average age of infection

Type II mortality: constant hazard, exponentially distributed lifespans

$$\frac{L}{A} = (R_0 - 1)$$

Type I mortality: uniformly distributed lifespans

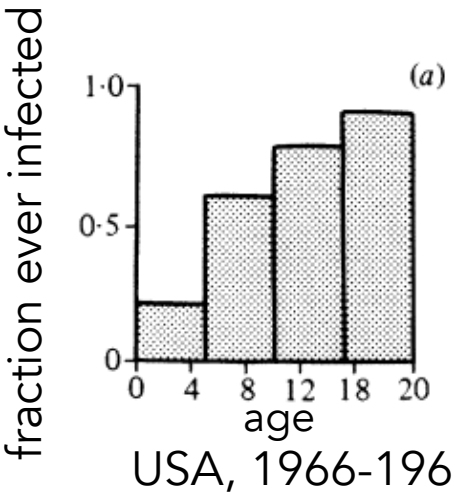
$$\frac{L}{A} = R_0$$

Infectious diseases with higher R_0 have lower average ages of infection

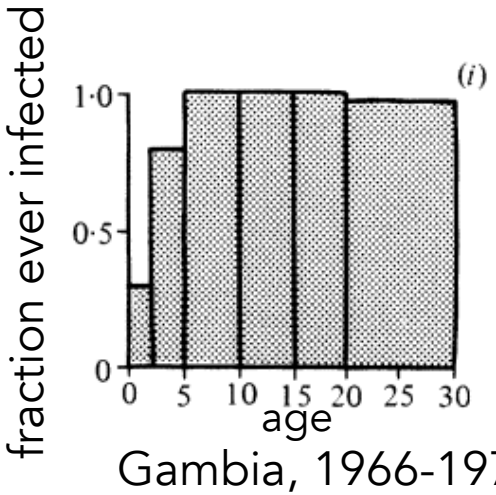
Rubella: a case study

- Pathogen: rubella virus (RNA virus); infection confers immunity
- Transmission:
  - respiratory (aerosol)
- Clincal symptoms:
  - generally mild (fever, rash, arthralgia/arthritis)
  - rarely more serious complications (encephalitis, hemorrhagic manifestations)

- Vertical transmission → Congenital Rubella Syndrome (CRS)
  - Infection of mother earlier in first trimester >85% babies will be affected
    - All organ systems involved (deafness, eye abnormalities, CV and neurological defects)
  - Indicates that fraction of women of child-bearing age who are susceptible is very important



USA, 1966-1968



Gambia, 1966-1976

Anderson and May, J Hyg 1983

Rubella intervention

- Vaccination
  - Goal is to reduce cases of CRS

- Expected to have both individual-level and population-level benefits
  - Individual-level: protect those who have been vaccinated
  - Population-level: indirectly protect those who have not been vaccinated

- Critical proportion of the population to vaccinate:
  - $1-(1/R_0)$

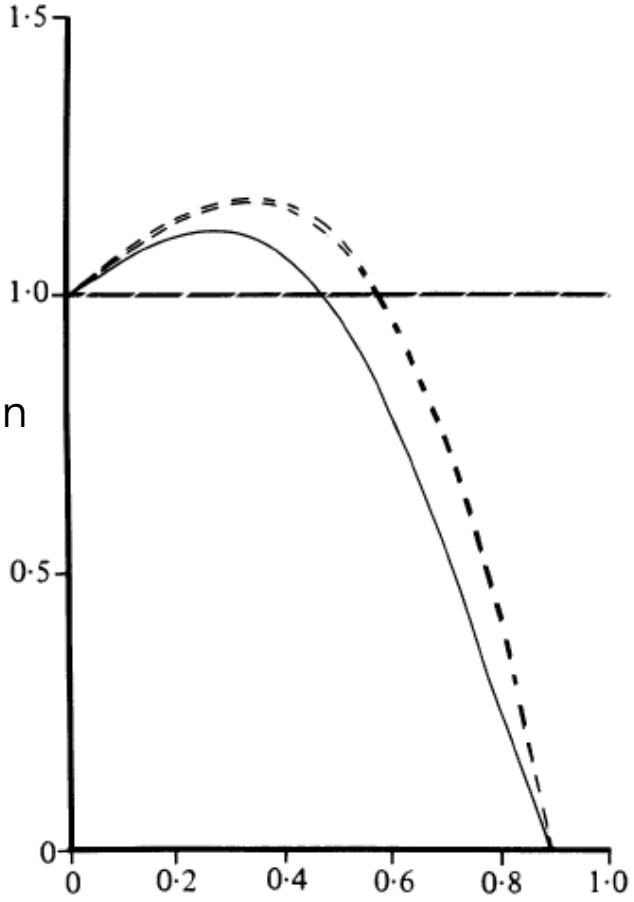
Possible perverse effects of a vaccination program?

- What if we do not achieve herd immunity?
  - Transmission persists (but lower force of infection)
  - Effect on the average age at infection?
    - Effect on expected number of CRS cases?

- Effects explored in compartmental models by Knox (1980), Anderson and May (1983)

Among women 16-40 years old

$$\frac{\text{Cases of rubella after vaccination}}{\text{Cases of rubella before vaccination}}$$



Fraction immunized at birth

Anderson and May, J Hyg 1983

Greece

- MMR vaccine introduced for 1 year old (girls and boys) ~1975

- No formal policies for achieving high coverage
  - Rubella vaccination classified as “optional” by MOH
  - Rubella vaccination given only on request to girls 10-14 yo in public sector
  - 1980s: vaccine coverage for rubella consistently below 50%

Panagiotopoulos BMJ 1999

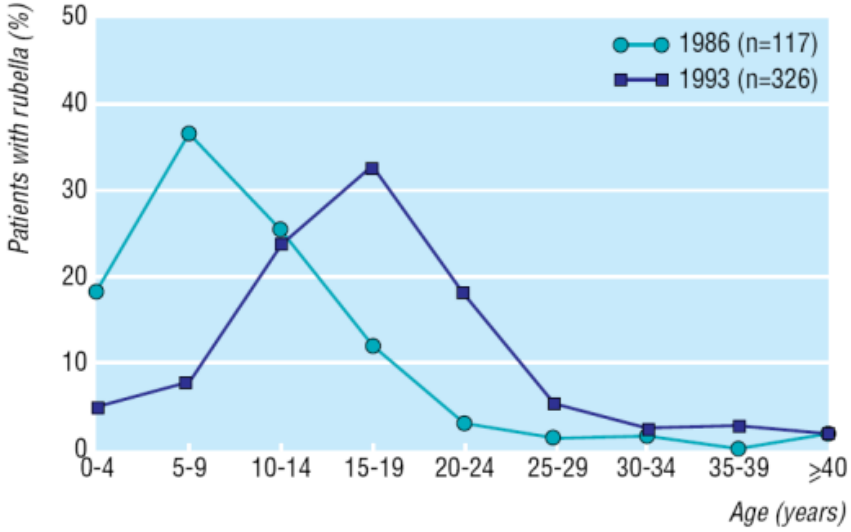


Fig 2 Age distribution of patients with rubella attending outpatient departments of general hospital in greater Athens, 1986 and 1993. Source: Panagiotopoulos et al 1996[20]

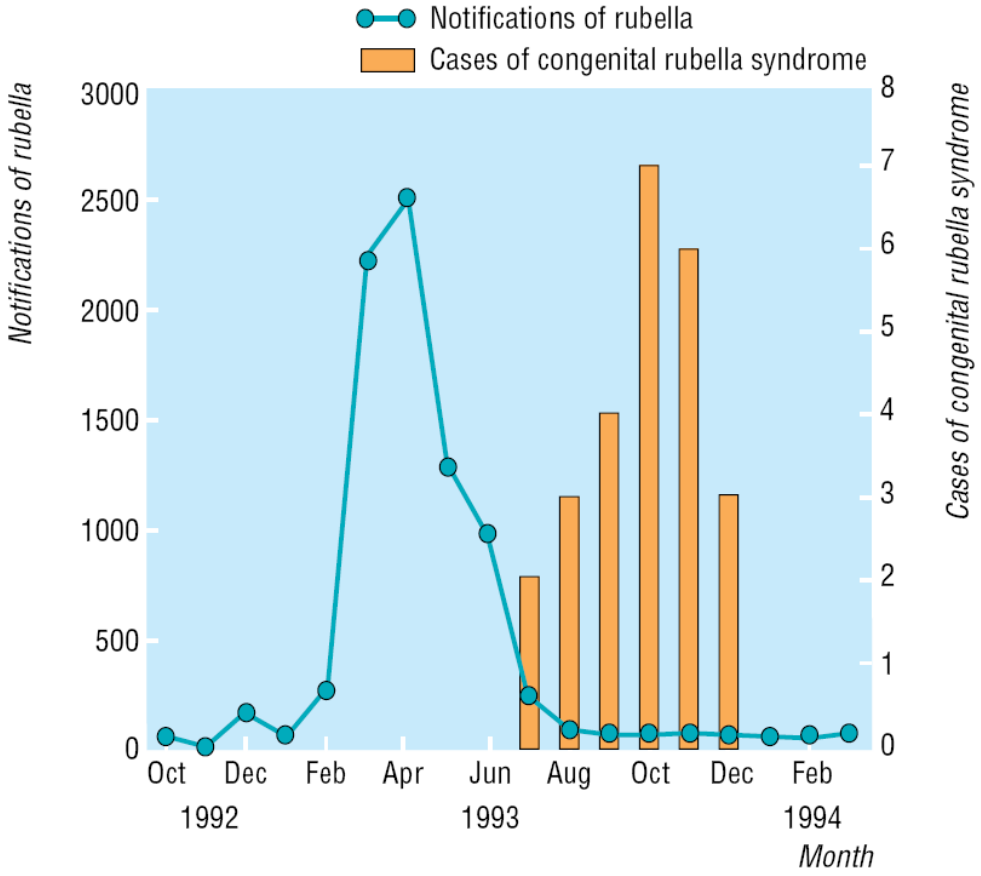


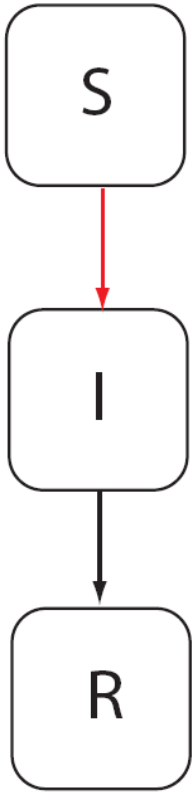
Fig 3 Notifications of rubella by month of diagnosis, and cases of congenital rubella by month of birth in epidemic in Greece, 1993. Source: National Statistical Service of Greece[18] (notifications of rubella) and Panagiotopoulos et al[22] (cases of congenital rubella syndrome)

Panagiotopoulos BMJ 1999

SIR models: What assumptions?

- SIR states effectively summarize categories of people
- Usually deterministic (but can include stochasticity)
- Homogenous mixing
- Exponentially distributed waiting times

- In summary, heterogeneity is largely ignored

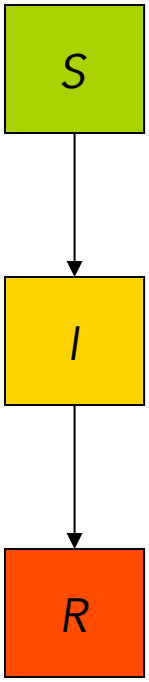


Can we include more "realism"?

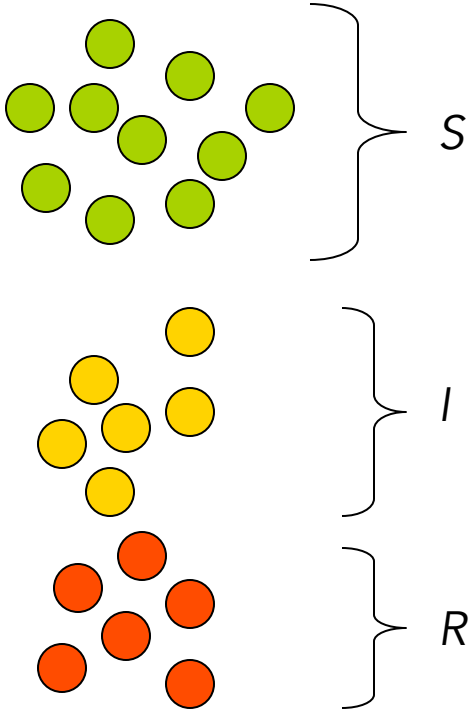
- Within compartmental model approach:
  - Represent different natural history (SIS, SI, SEIR)
  - Demographic characteristics (age, sex)
  - Behavioral categories (high/low activity groups)

- But, the number of compartments increases quickly
  - SEIR with 5 age groups, sex, and 2 activity groups
    - 4*5*2*2=80 compartments!

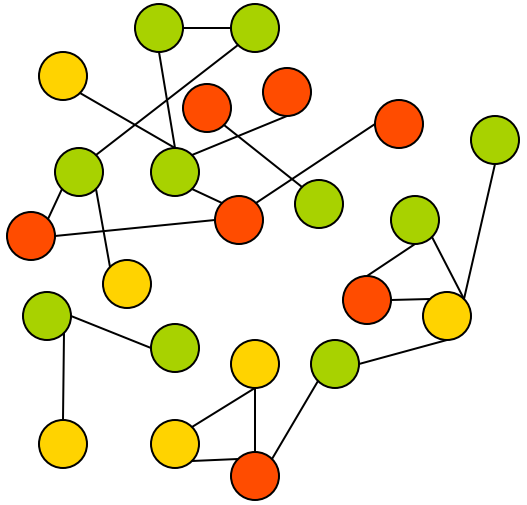
2. We can increase complexity with other modeling approaches



Compartmental



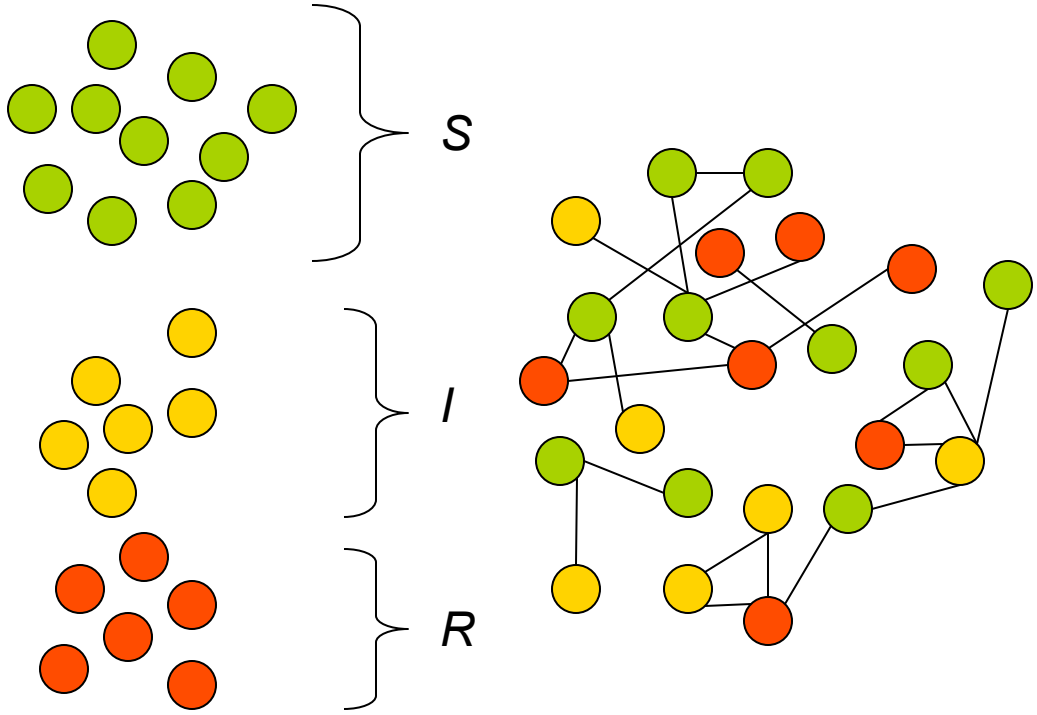
Individual-based



Network

- Stochasticity easily included and heterogeneity more naturally expressed in these types of models

- Focus is on experience of individuals, rather than on “classes” of individuals.

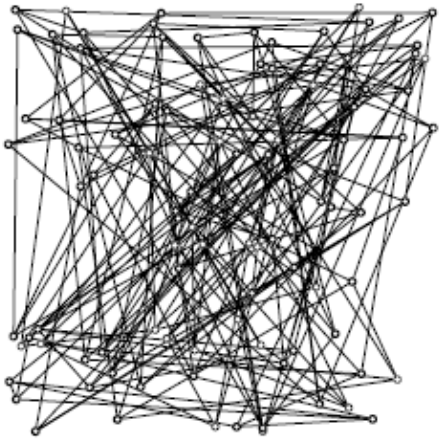


Questions/situations that often warrant other approaches*

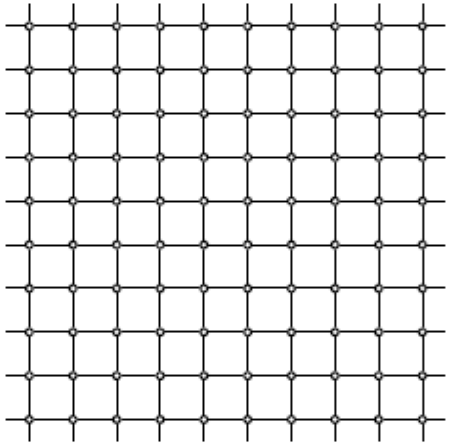
- Spatial spread of disease
- Explicit and detailed contact patterns between individuals
- Modeling complex interventions (e.g. targeting individuals via contact tracing)
- Elimination of pathogens
- Emergence of new pathogens in populations
- Nosocomial transmission
- Plus many others

*many of these issues can also be approximated using variations of compartmental models

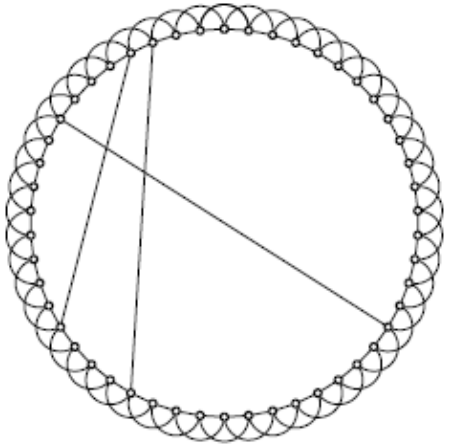
Random

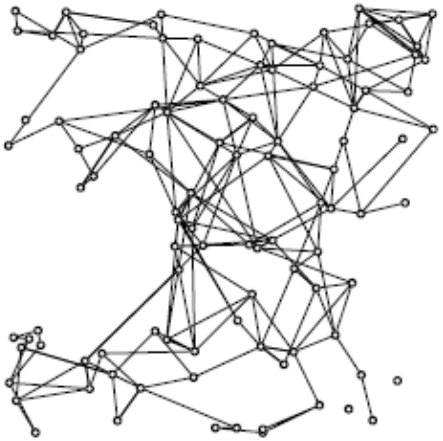


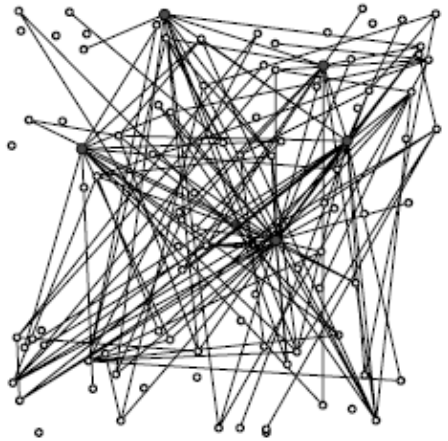
Lattice

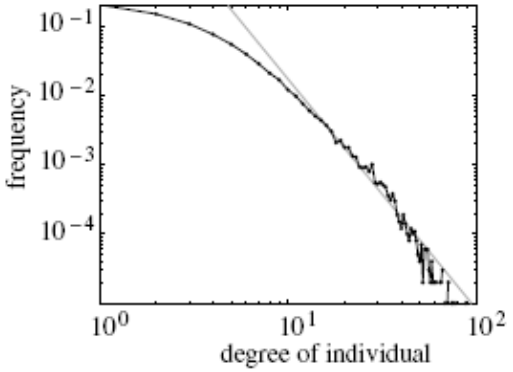


Small-world







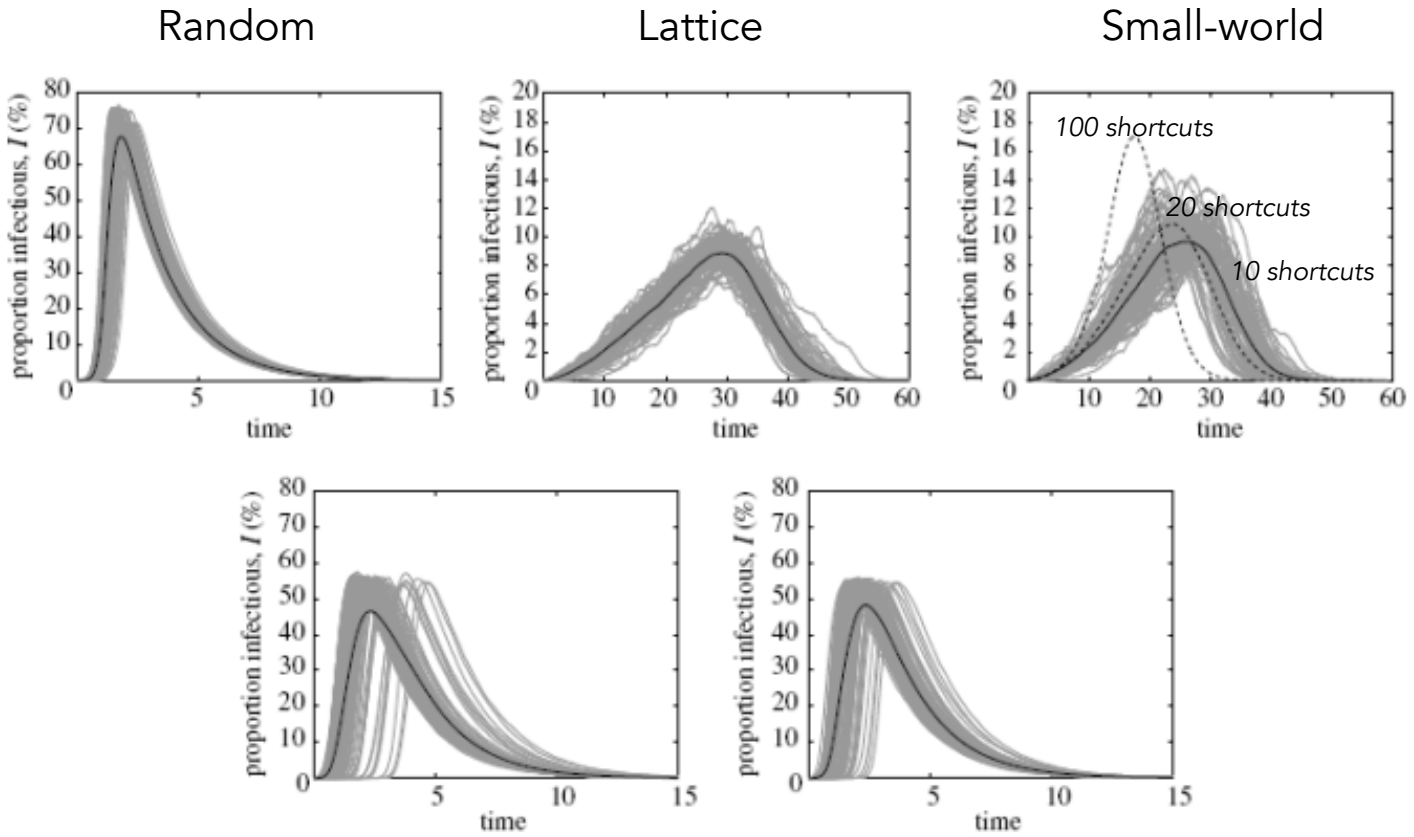


Spatial

Scale-free

N=100
Average degree = 4

Keeling J Roy Soc Interface 2005



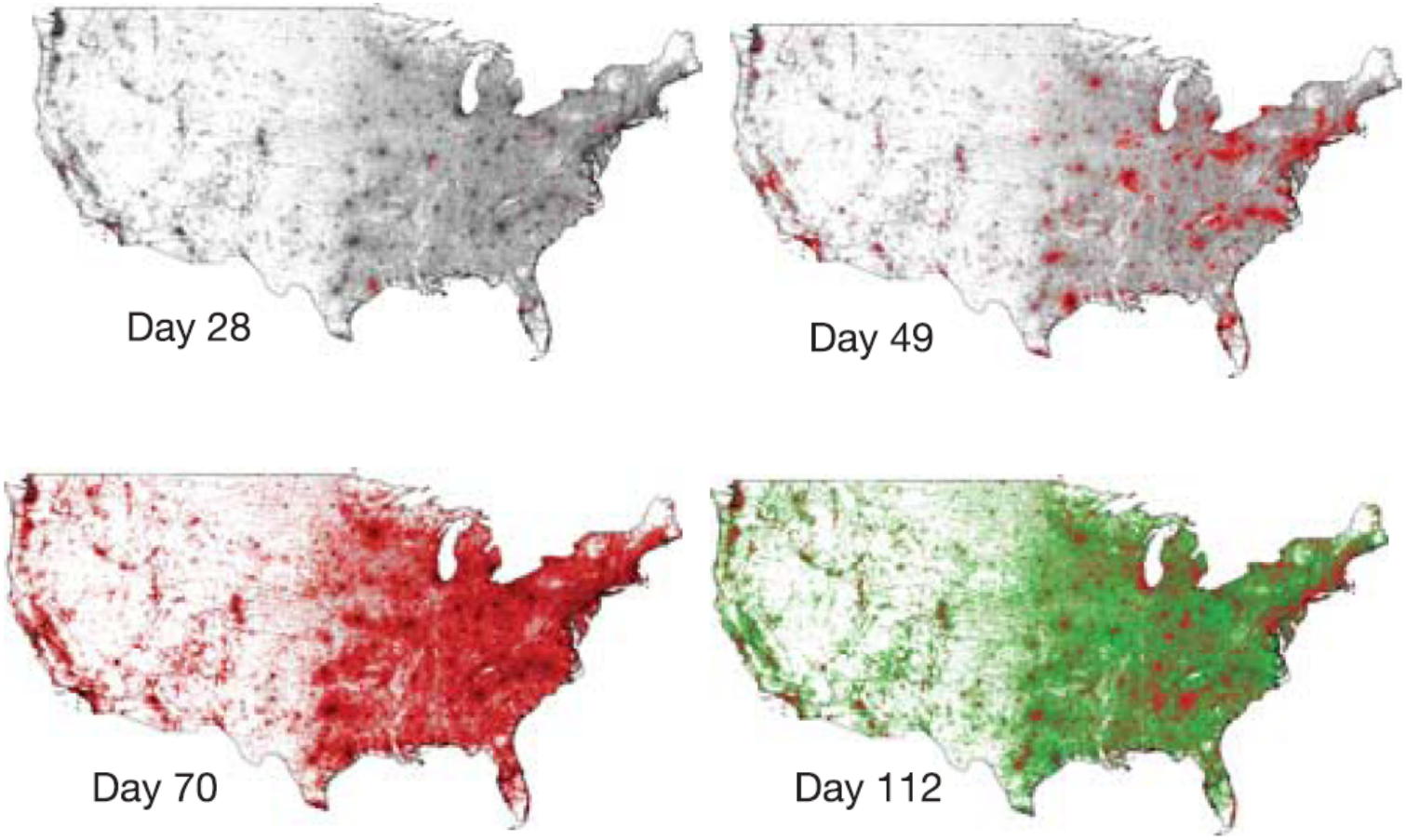
N=10,000
100 epidemics; black is mean

Keeling J Roy Soc Interface 2005

For policy-making, more complex models are sometimes required

- “Predictive” models
- Comparing the performance of alternative “realistic” interventions
- Coupling with economic considerations to generate cost-effectiveness comparisons of different control strategies

Projection for pandemic influenza



Individual-based model: UK and US populations; international travel (seeding); air travel within US; transmission within households, schools, workplaces, and in the community

Ferguson et al, Nature 2006

Summary

- Models of infectious diseases may be of various forms
- The structure and approach should be dictated by the research question and availability of data
- Both simple and more complex models have proven to be useful tools for understanding disease dynamics, projecting disease trends, and informing control policy