Clinical Trial Phases

Phase I	Phase II	Phase III	Phase IV
20-80 participants	**100-300 participants**	**1,000-3,000 participants**	**Thousands of participants**
Up to several months	Up to (2) years	One (1) - Four (4) years	One (1) year +
Studies the safety of medication/treatment	Studies the efficacy	Studies the safety, efficacy and dosing	Studies the long-term effectiveness; cost effectiveness
70% success rate	33% success rate	25-30% success rate	70-90% success rate

Infectious disease dynamics:

The study of how the distribution and transmission of infectious diseases vary across space and time

Infectious disease dynamics answer the following types of questions

- Given the introduction of a pathogen to a population, will cases increase?
- If so, how quickly and how far?
- Will the pathogen persist in the population?
- What are the drivers of spatial and temporal variation in the disease incidence?
- What is the best way to intervene to minimize the burden and spread of disease?
- Can transmission be eliminated?

Some key measures of disease occurrence

Prevalence: Proportion of persons with a specific disease at a specific time point in the population

Incidence: Proportion of persons acquiring a specific disease during a time period in the population

Attack rate: Proportion of new cases developing disease among all persons who were exposed to the disease during a time period

Secondary attack rate: Proportion of new cases who develop disease among all contacts of known cases during a time period

Case fatality rate or ratio: Proportion of persons dying from a specific disease among all persons with the disease

Mortality: Number or proportion of persons dying during a time period; a product of incidence and the case fatality rate

Some key terms to describe individuals

- **Susceptible:** uninfected, but able to become infected if exposed
- **Infectious:** infected and able to transmit the infection to other susceptible individuals
- **Immune:** possessing cell-mediated or humoral antibody protection against an infection
- **Diseased/clinical infection:** implies the presence of clinical signs of pathology (not synonymous with infected)
- **Latent infection / subclinical infection:** implies presence of infectious agent but absence of clinical disease
- **Carrier:** implies a protracted infected state with shedding of the infectious agent. Carriers may be diseased, recovering, or healthy.

Some key terms to describe the case

- **Primary case:** Person who brings the disease/infection into a population
- **Secondary cases:** Persons who are infected by primary case
- **Generation of infections (waves):** Secondary cases are infected at about the same time and consequently tertiary cases
- **Index case**: First case discovered during an outbreak

Infectious Disease dynamics depend on…..

- **Basic Reproductive number (R0):** the average number of secondary cases generated by an index case when an epidemic begins in a completely susceptible population

- **Mean Generation time (serial interval) (T):** the average time it takes an index case to infect other individuals after he becomes infected

- **Epidemic growth rate (r):** the rate of change in the number of infections, e.g. during the early phase, the epidemic doubling time is ln2/r

Basic Infectious Disease Model

- The simplest transmission model includes:
  - Susceptible/Infected/Recovered with/without immunity
  - Duration of infection
  - Stage of infection (may influence infectivity or activity)
- We can complicate the model by including:
  - Pathogen reproduction and vital dynamics
  - Pathogen evolution states (different infectivity levels)
  - Population dynamics (births/death rates; migration)

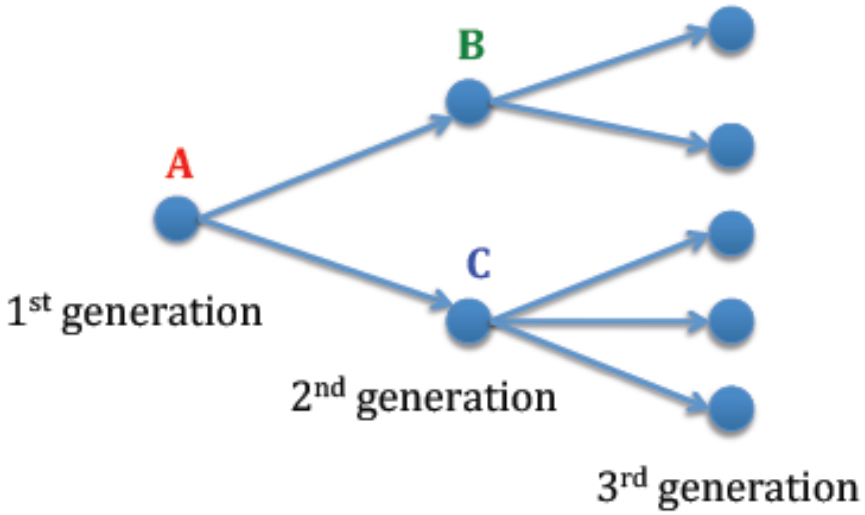
Example: The simple measles model has two transitions:

Reproductive 'rate', R

- Also called "reproductive number" = potential for an infectious disease to spread
- Average number of new infections caused by 1 infected individual
- In an entirely susceptible population
  - **Basic reproductive rate, R_0**
- In a population where <100% are susceptible
  - **Effective reproductive rate, R** = proportion susceptible x R_0

Basic Reproductive number, R

- The average number of secondary cases generated by an index case in a fully susceptible population:
  - Reproductive number, R: Same as R_0 except that the population needs not be completely susceptible. Examples:
    - Some time after the epidemic has started, in which case we denote the reproductive number by R_t.
    - If the population is partially vaccinated before the outbreak.



$$R_0 = \frac{2+2+3}{3} = 1.67$$

Basic reproductive number, R_0

$R_0 > 1$ Infection spreads (epidemic)

$R_0 = 1$ Infection remains constant (endemic)

$R_0 < 1$ Infection dies out (herd immunity)

Why is R_0 important?

Indicates controllability of an outbreak, e.g. how many people do we need to vaccinate to prevent an epidemic?

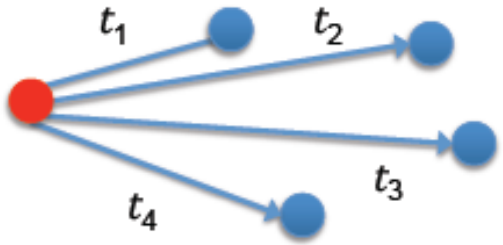
How to measure it?

contact tracing and cohort follow-up

fitting mathematical models to epidemic curves

Generation Time

- The average time it takes an index case to infect other individuals after he becomes infected.



T_g = the average of t_1, t_2, t_3, t_4

- Why is it important?
  - Indicates how long it takes for an infected individual to spread his infection.
  - R_0 indicates how many people an index case infects but not how fast these infections happen.
  - R_0, T_g and epidemic growth rate are interrelated:
    - For a given R_0, a shorter T_g ➔ higher growth rate.

Some R_0 and generation times for typical pathogens

Pathogen	R_0	Generation Time
Cholera	5.0*,[121] 2.6,[122] 4–15[123]	7.1–9.3 days,[124] 7–10 days[123]
Dengue	1.3–6.3[125]	19–22 days,[126] 24 days[127]
Influenza	1.5–2[57]	3.6 days (s.d. 1.6 days); [128] 2.3 days (H1N1, range 1.5–2.7 days),[30] 3.1 days (H3N2, range 2.2–4.0 days),[30] 2.7 days (H1N1 pdm)[73]
Malaria	1–10 low transmission areas/100–1000 high transmission areas, [123] 1–3000[129]	~60–120 days,[123] > 200 days[129]
Measles	7.7,[130] 7.1–29.3,[131] 11–18[16]	9–17 days,[132] 12 days[19]
Rubella	2.9–7.8,[131] 3.4–5.6[133]	22 days,[133] 15–23 days[134]
SARS	2.7,[135] 1.2,[136] 2.2–3.6[137]	8.4 days[137]
Smallpox	3.2,[138] 3.5–6,[139] 6.87 (95% CI 4.52–10.1)[140]	14–16 days,[138] 16 days (s.d. 4 days),[141] 14–20 days[132]

*reproductive number estimate, not R_0 estimate.

Kenrad N. *Infectious Disease Epidemiology* . 2014

Mathematical Models of Infectious Disease Transmission Dynamics

- Frequently used in infectious disease epidemiology
- Major goal is to "further understanding of the interplay between the variables that determine the course of infection within an individual, and the variables that control the pattern of infection within communities of people"

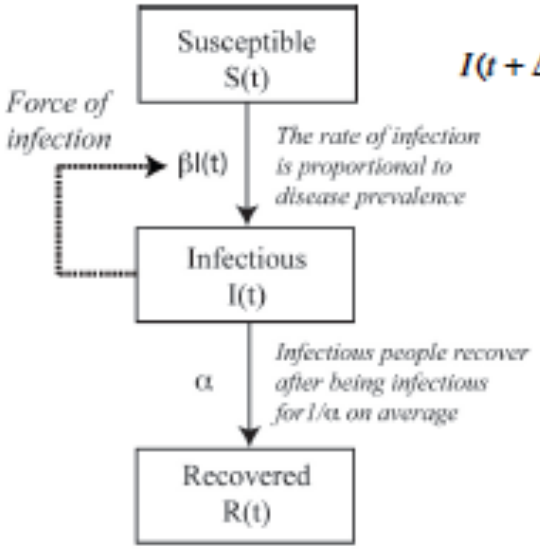
Anderson RM & May RM. *Infectious Diseases of Humans. Dynamics and Control.* 1991.

Why develop a model?

- To understand the system of transmission of infections in a population
- To help interpret observed epidemiological trends
- To identify key determinants of epidemics
- To guide the collection of data
- To forecast the future direction of an epidemic
- To evaluate the potential impact of an intervention

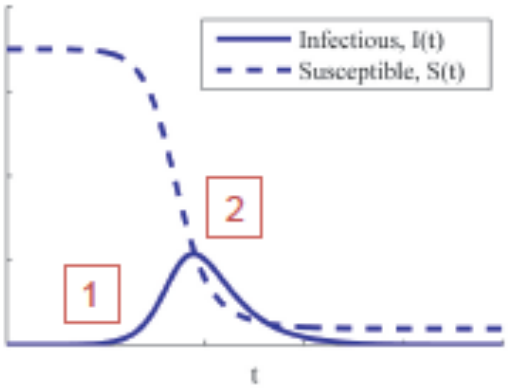
The simplest epidemic model

- A closed large population of size ***N*** is partitioned into three classes of individuals: "Susceptible", "Infectious", and "Recovered" (SIR model).
- All individuals are assumed to be identical in terms of their (i) susceptibility to infection, (ii) infectiousness if infected, and (iii) mixing behavior associated with disease transmission (the so-called homogenous mixing assumption).



$$S(t+\Delta t) = S(t) - \underbrace{\beta S(t) I(t) \Delta t}_{\text{number of infections between time } t \text{ and } t+\Delta t}$$

$$I(t+\Delta t) = I(t) + \underbrace{\beta S(t) I(t) \Delta t}_{\text{number of infections between time } t \text{ and } t+\Delta t} - \underbrace{\alpha I(t) \Delta t}_{\text{number of recovery between time } t \text{ and } t+\Delta t}$$



Hallmarks of an epidemic:

1. The number of infections increases exponentially during the early phase of a growing epidemic
2. The epidemic curve is unimodal and peaks when the susceptible pool has been sufficiently depleted (such that $R_t < 1$)

Epidemiologic parameters:

$R_0 = \beta/\alpha$, $T_g = 1/\alpha$

$r = (R_0 - 1)/T_g = \beta - \alpha$

Determinants of R_0

For a pathogen with direct person-to-person transmission

$$R_0 = \beta c_r D$$

where β is the probability of transmission per contact between infected and susceptible persons

c_r is the contact rate

D is the duration of infectivity

Example SIR Model

- Consider the following values
  - N = 1000 people
  - Transmission probability, $\beta = 0.15$
  - Contact rate, $c_r = 12$ contacts per week
  - Infection duration, D = 1 week

- Basic reproductive rate: $R_0 = 0.15 * 12 * 1 = 1.8$

- Effective reproductive rate at time t: $R_t = S_t * R_0$

Sources of data for model parameters:
The example of sexually transmitted infections (STI)

- Recall the three main parameters are:
  - Transmissibility (β)
  - Duration of infectivity (D)
  - Contact rate (c_r)

- Where do estimates of these parameters come from?

Table 3-1. Transmission Probabilities and Durations of Infectiousness.

Infectious agent	Disease	Transmission probability β (per partnership)	Mean duration of infectiousness D (untreated) in years
Neisseria gonorrhoeae	Gonorrhoea	0.5	0.5
Chlamydia trachomatis	Urethritis/ Salpingitis	0.2	1.0
Treponema pallidum	Syphilis	0.6	0.5
Haemophilus ducreyi	Genital ulcer	0.8	0.08
HIV-1	AIDS	0.05–0.15	8–12

Anderson RM. Transmission dynamics of sexually transmitted infections. In: *Sexually Transmitted Diseases*. Holmes KK et al., eds. 1999. pp. 25-37

Transmissibility (β): Measurement

- Measured as the probability of transmission from an infected to a susceptible partner (attack rate)
- Sources of data
  - Contact tracing
  - Discordant couples
  - Studies of sexually active individuals who report partners with known STI status, or if the prevalence of the STI in the pool of partners is well known
- Challenges
  - Enrollment of sexual partners may be difficult
  - Identification of contacts between infected and susceptibles, and direction of transmission
  - What is a “contact”?

Duration of infectivity (D): Measurement

- Sources of data
  - Duration of clinical disease
  - Duration of infection

- Challenges in measurement
  - Duration of disease = duration of infectivity?
  - Asymptomatic versus symptomatic
  - Ethical obligation to treat identified infections
  - May need to rely on historical data of questionable quality

Contact rate (c_r)

- Typically measured as the rate of new partner acquisition (e.g.., per year)
- Model so far assumes homogeneity in contact rate
- Data source is sexual behavior surveys
  - General population
  - Selected populations (e.g.., adolescents, adults aged 18-45, students, gay and bisexual men, drug users)

Mathematical Model of Transmission Dynamics: Susceptible-Infectious-Recovered (SIR) model

- Assumptions
  - Population is fixed (no entries/births or departures/deaths)
  - Latent period is zero
  - Infectious period = disease duration
  - After recovery, individuals are immune
- People can be in one of three states
  - Susceptible to the infection (S)
  - Infected and infectious (I)
  - Recovered/immune (R*)

** Not to be confused with R denoting reproductive number… unfortunate nomenclature!*

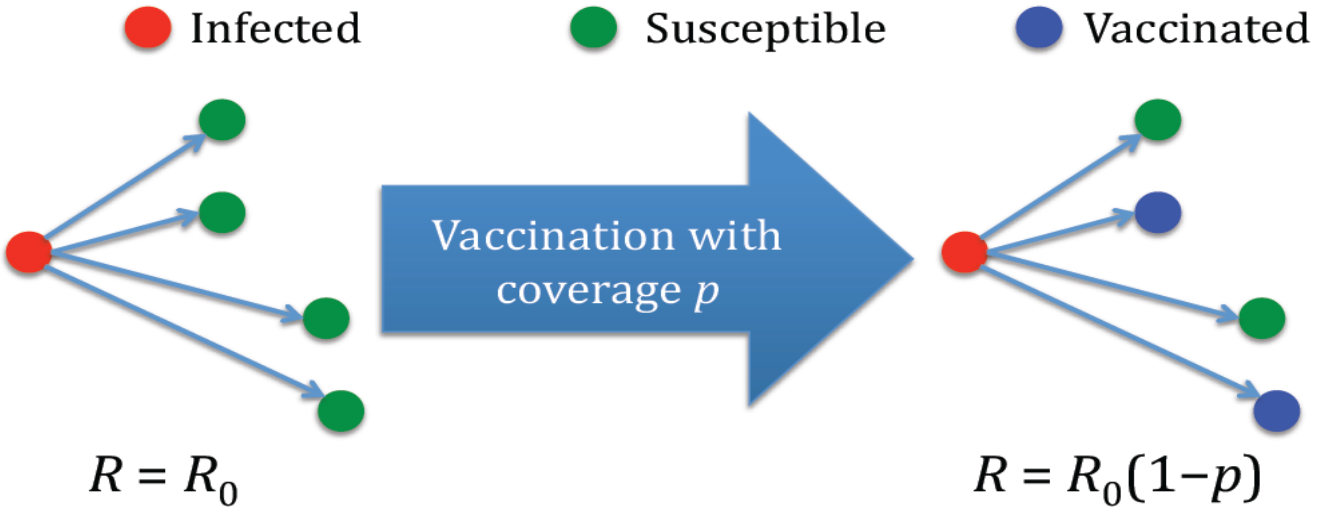
Giesecke J. *Modern Infectious Disease Epidemiology*. 2002. pp. 126-130

β, c_r, and D estimates: Bottom line

- Uncertainty and limitations in parameter estimates
- Well-written papers will
  - Identify the source or reasoning behind parameter estimates
  - Conduct sensitivity analysis to determine how much the model results depend on parameter values
- Sometimes the transmission model will identify a lack of knowledge in these parameters, and can direct empirical research to obtain more data

Vaccination

- Suppose the vaccine is 100% efficacious
- It is not necessary to vaccinate the whole population to halt a growing epidemic. Why?
  - Vaccinating an individual indirectly reduces the risk of infection of this individual's contacts (herd immunity)



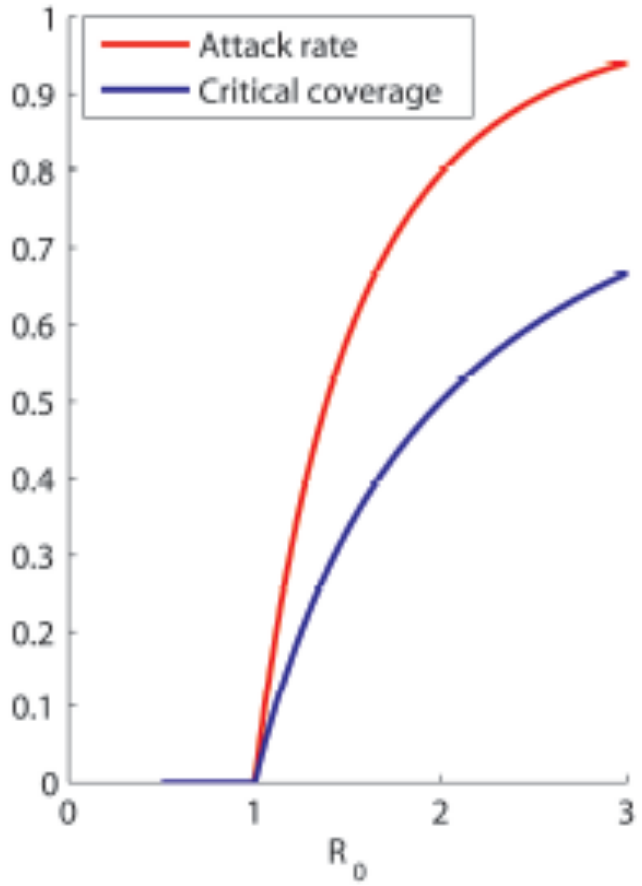
Vaccination

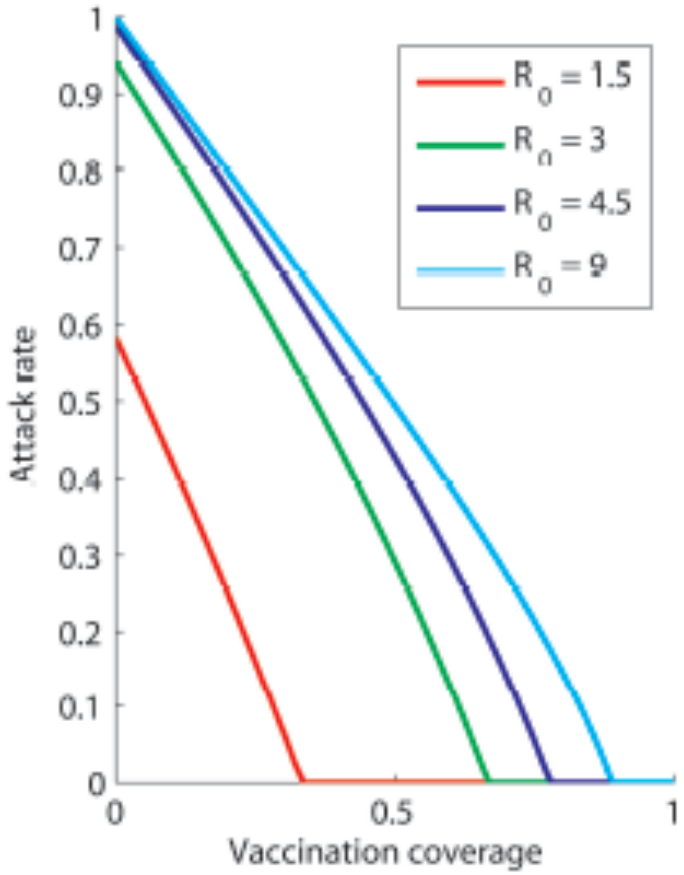
- Suppose the vaccine is 100% efficacious.
- Critical vaccination coverage, V_c*
  - The minimal proportion needed to vaccinate in order to prevent an epidemic
- In the SIR model, $V_c = 1-1/R_0$, i.e. vaccinating a proportion $p > 1-1/R_0$ of the population is sufficient to prevent an epidemic. Why?
  - After vaccination, the reproductive number is

$$R = (1-p)\,R_0 < 1 \iff p > 1-1/R_0$$

** Not to be confused with c_r denoting contact rate… unfortunate nomenclature!*

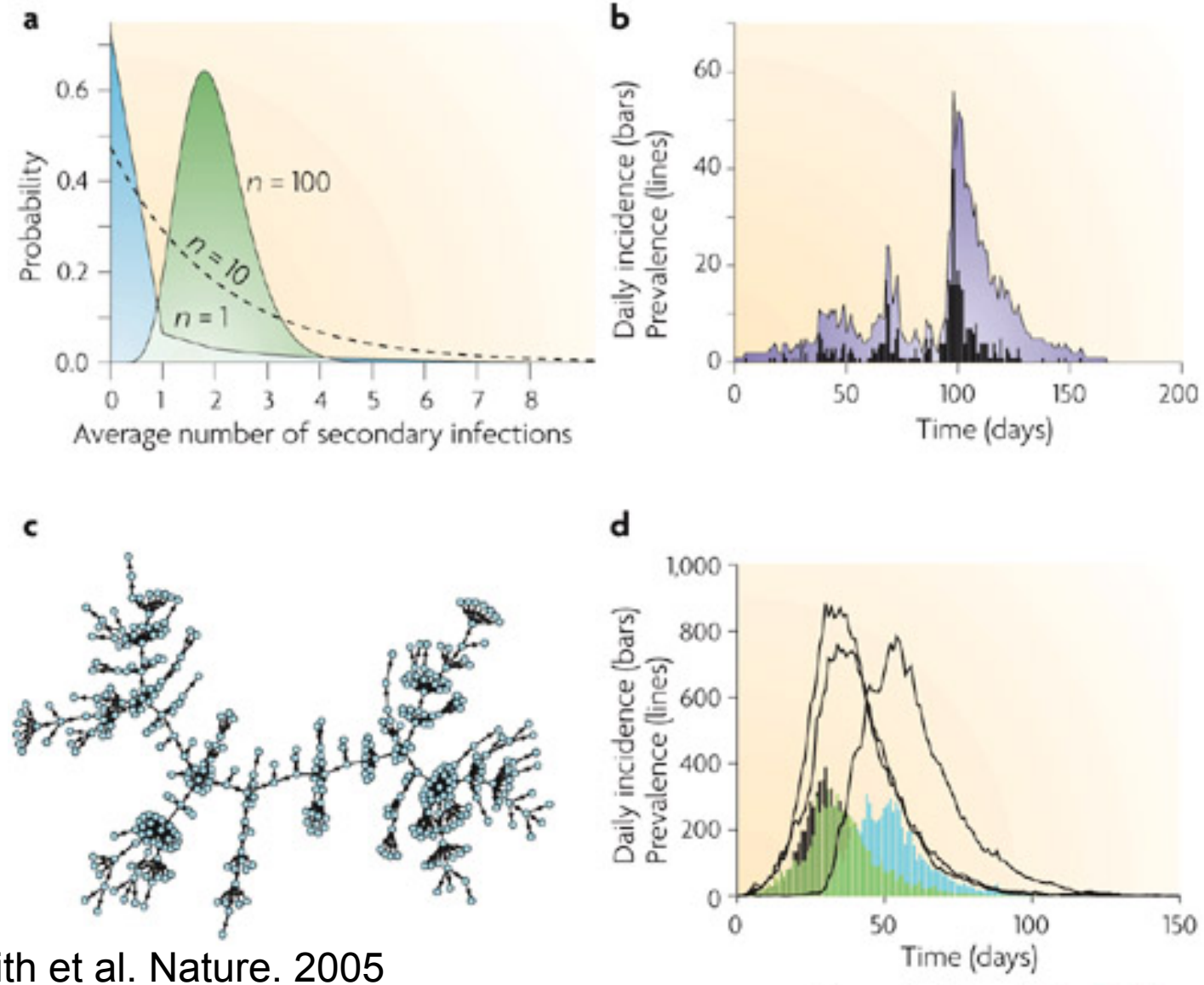
Attack rate & R_o





Examples of how models can be useful and informative

SIR model: SARS vs. Measles



Lloyd-Smith et al. Nature. 2005

Articles:

1. Griffin et al. *U.S. hospitalizations for pneumonia after a decade of pneumococcal vaccination*. N Engl J Med 2013.
2. Gaglani M, et al. *Influenza Vaccine Effectiveness Against 2009 Pandemic Influenza A(H1N1) Virus Differed by Vaccine Type During 2013-2014 in the United States*. J Infect Dis. 2016