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Infectious Disease Dynamics

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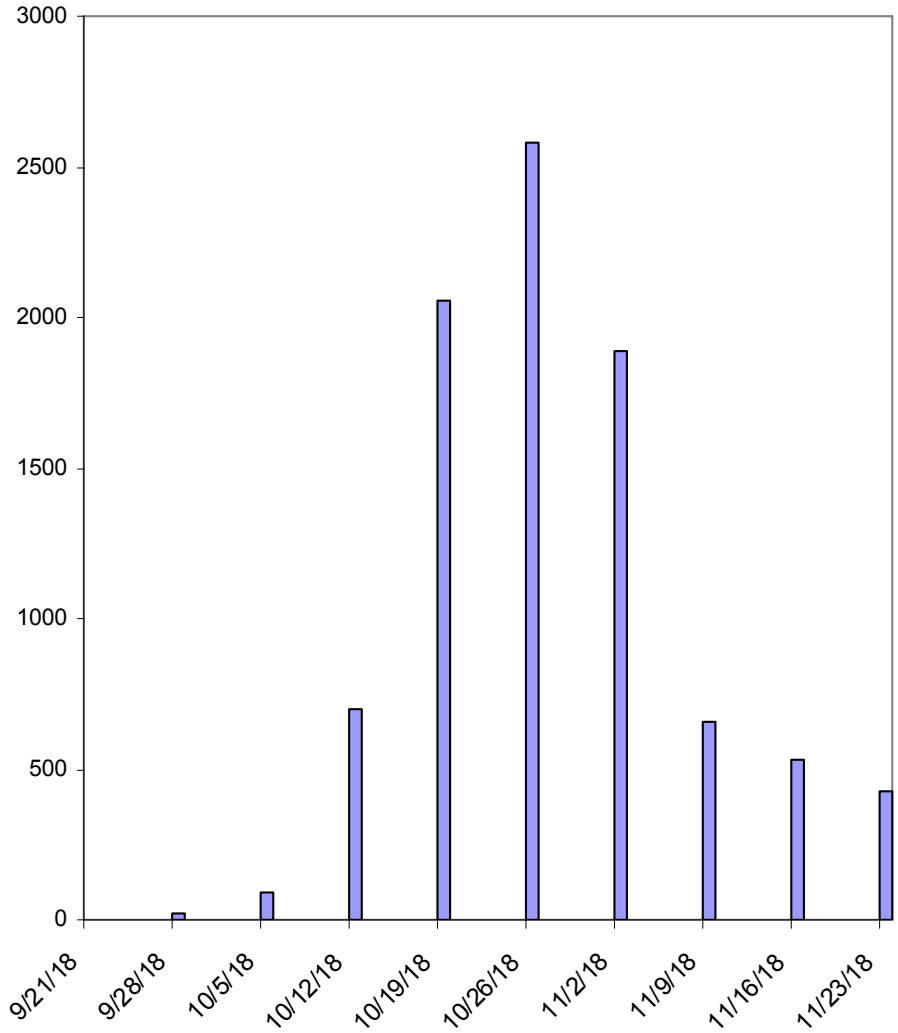
Protecting Health, Saving Lives—*Millions at a Time*

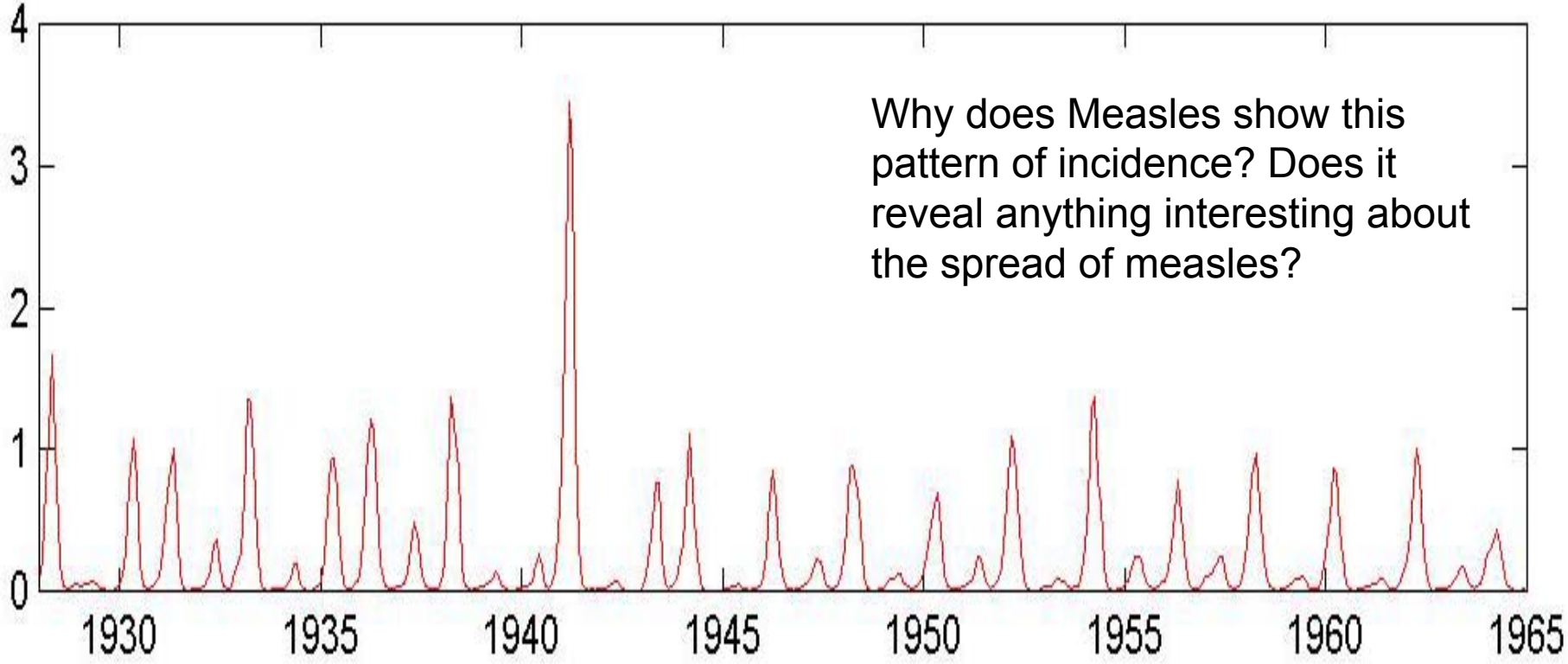
What is Infectious Disease Dynamics?

- The study of contagion
- Who gets infected, by whom, at what rates? What are the impacts of control measures?
- Interested in temporal progression (dynamics)

Deaths from Influenza in Atlanta in 1918

Why do cases increase at this rate? Why do they stop? What if we intervened on week 3?





Monthly measles incidence (per 1000) in New York City, US, 1928-1965

Learning Objectives

- Gain familiarity with basic concepts and terminology in infectious disease theory
- Understand the types of data needed to understand the temporal dynamics of contagion
- Be able to critically assess simulation studies

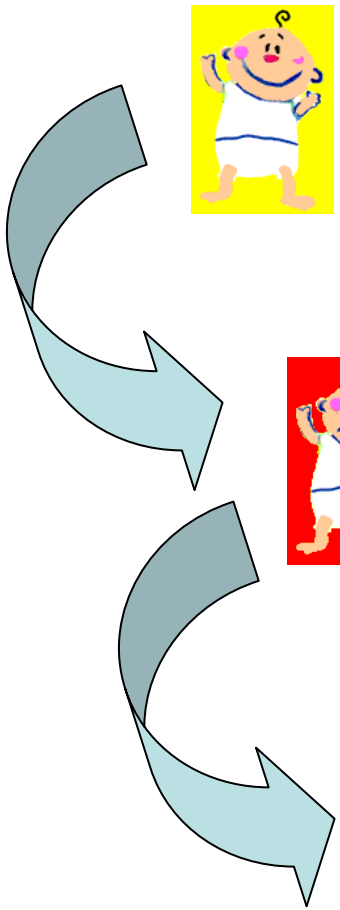
Outline

- Today
  - Present key concepts of transmission
    - Doubling time
    - R_0
    - Serial interval
  - Discuss features that make a pathogen more or less controllable
- Tomorrow
  - Present models and examples of simulation studies

Please Ask Questions!!

If you have a question, please don't hesitate to stop me and ask

Measles in a cohort of unimmunized infants



Healthy Baby

Measles Infected Baby

Immune Baby

Modified from Ralph Frerichs, UCLA (http://www.ph.ucla.edu/epi/200/epi200_01.html)

If these babies contact each other, how many will become sick?

How long will it take?

As transmission occurs, what aspects of the process are most important in determining the course of spread?

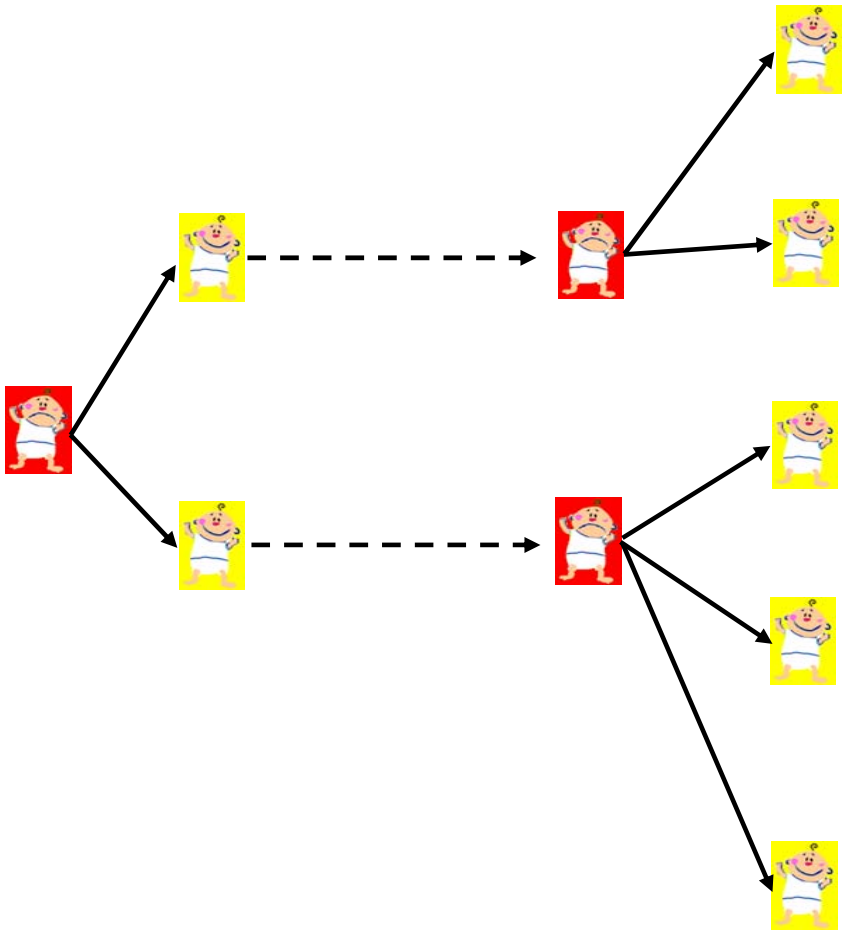
1 2 3 4 5 6 7 Weeks

Modified from Ralph Frerichs, UCLA (http://www.ph.ucla.edu/epi/200/epi200_01.html)

Why would it be useful to forecast the epidemic?

- Know the scale of the epidemic
  - Number of people involved
  - Spatial scale (how big of an area might be affected?)
  - Temporal scale (how long will it last?)
- Be able to evaluate the impact of interventions
  - Is the epidemic speeding up or slowing down?
  - Where should we devote more resources to control?

What dictates the rate of increase of an epidemic of an infectious disease?



At least two things affect the speed of the outbreak or epidemic

The number of individuals infected by each infectious case.

The time it takes between when a case Is infected and when they infect other people.

We'll focus on the details of these two factors including how to measure each

- The number of individuals infected by each infectious case.

- The time it takes between when a case is infected and when that case infects other people.

R_0, the basic reproductive number

R_0 : the average number of individuals directly infected by a single infectious case when s/he enters a totally susceptible population in the absence of interventions

R_0 in this case is 4

R_0, the basic reproductive number

R_0 : represents both the contact process (i.e. how many people does an infectious case come into contact with) and the transmission process (i.e. of those contacts, what proportion become infected)

R_0 sometimes expressed as

$$R_0 = \beta \times c \times D$$

β is the proportion of contacts that become infected
c is the number of contacts per day
D is the duration of infectiousness

Determinants of transmission of a Sexually Transmitted Infection

$$R_0 = \beta c D$$

β	Risk of transmission given contact
c	Rate of sexual partner change
D	Duration of infectivity

Control measures target different parts of R_0
STI Control Strategies

$$R_0 = \beta c D$$

β	condoms, acyclovir, zidovudine
c	health education, negotiating skills
D	case ascertainment (screening, partner notification), treatment, compliance, health seeking behaviour, accessibility of services

What is c for a respiratory pathogen?

$$R_0 = \beta c D$$

$$R_0 = \lambda D$$

Estimates of R_0 of several pathogens

Measles – 12

Pertussis – 15

Chicken Pox – 9

Diptheria – 4

Scarlet Fever – 6

Mumps – 10

Rubella – 8

Polio – 6

Smallpox – 6

Influenza – 2

HIV – 5

Dengue – 4

Schistosoma japonicum – 3

Anderson and May, 1991

R_0 is disease and setting specific (depends on population density, social factors, more)

- Estimates for Measles
  - England and Wales, 1950-1968 16-18
  - Ontario, Canada, 1912-1913 11-12
  - Kansas, USA, 1918-1921 5-6
  - Ghana, 1960-1968 14-15
  - Niger, 2003 5-6

For any setting, R_0 describes transmission only at the very beginning of the epidemic

- When there is no immunity
- It is the extrinsic transmissibility of a pathogen in a particular setting

- The presence of immunity reduces transmission
- R(t) describes the average number of people each case transmits to at a particular time t
- Late in an epidemic, most people have been infection so we expect R(t) > R(t+n)

The average number of people this baby transmits to is R_0

The average number of people this baby transmits to is R(t)

R_0 establishes a threshold for an epidemic to occur

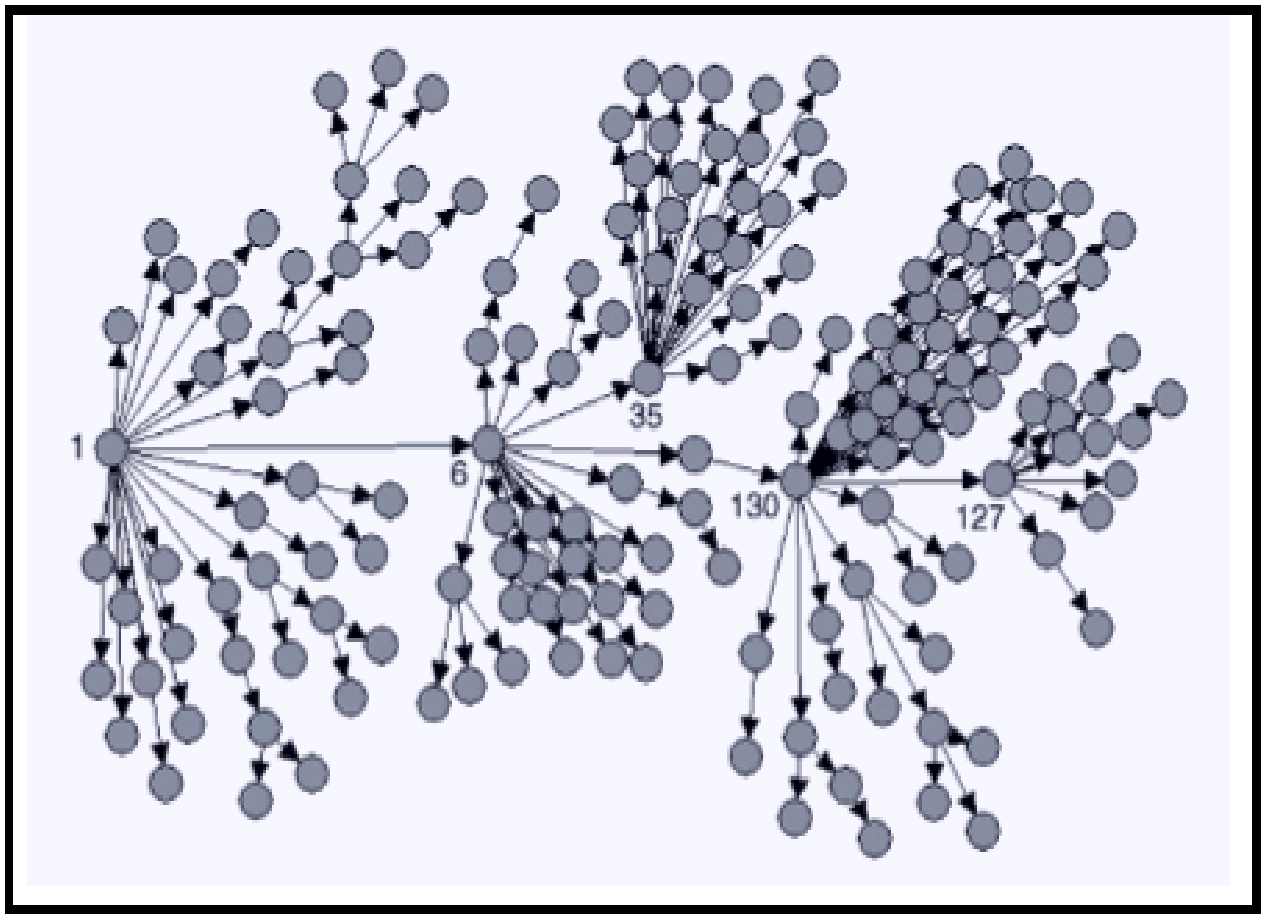
If $R_0>1$, disease can spread and an epidemic can occur

If $R_0<1$, each infection does not (on average) replace itself, so the disease can't spread

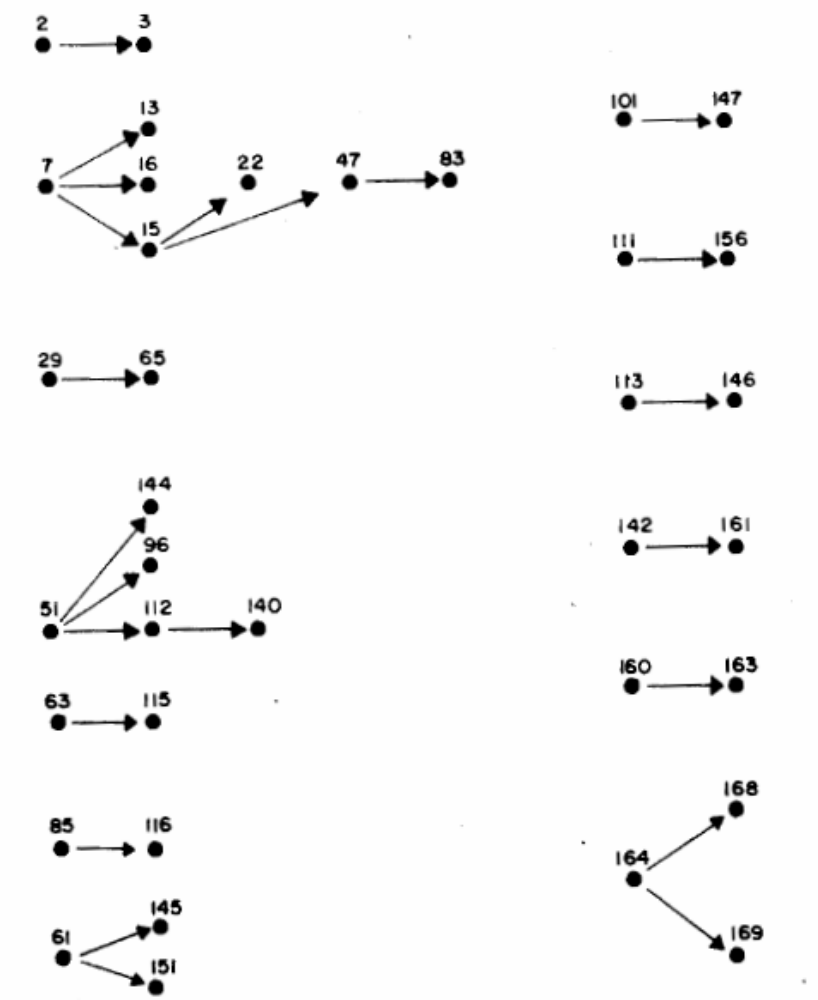
How do we estimate R_0?

Could directly observe epidemiologically linked cases

Epidemiologically linked cases of SARS in Singapore



Smallpox cases



Cases of Variola minor linked by evidence of transmission

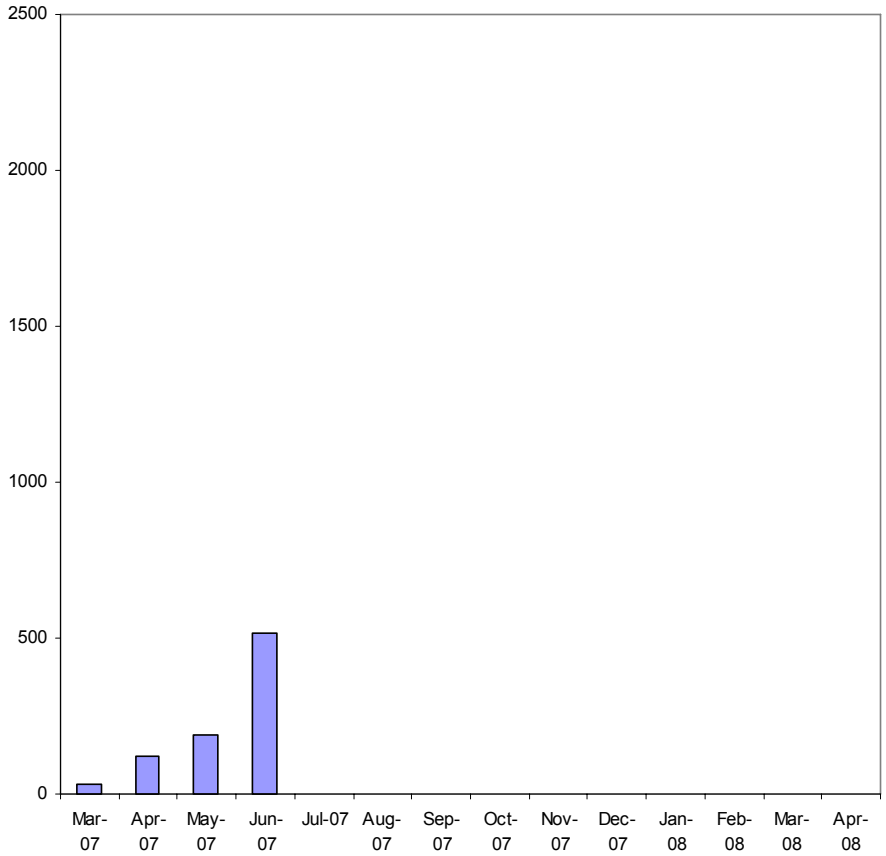
- Even if you can't trace infections by epidemiological evidence, R_0 and R(t) can be estimated from onset times of observed cases
- We'll look at methods to do this tomorrow

So,

pathogens that have a greater R_0 should have faster epidemics

What do I mean when I talk about the speed of an epidemic?

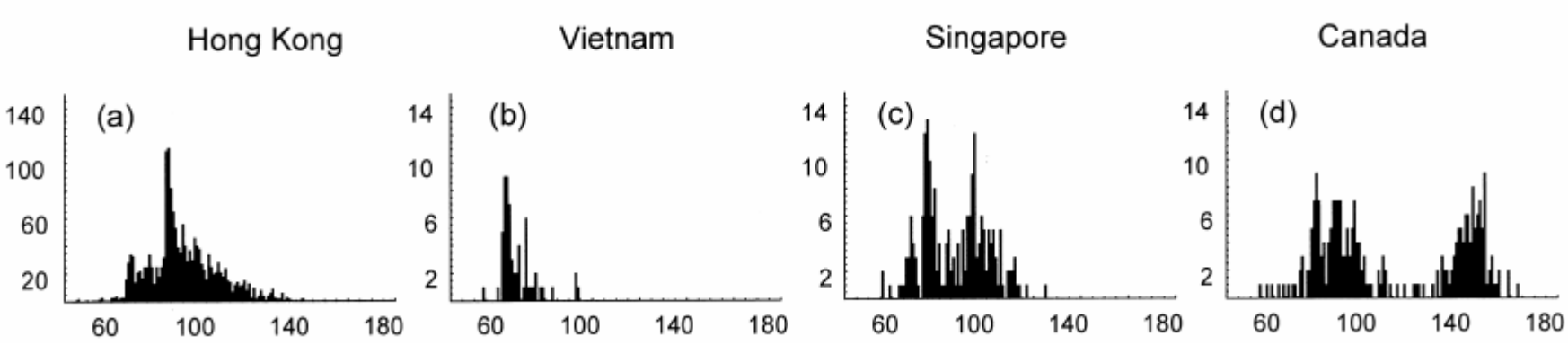
What metric is appropriate to measure the rate of increase of cases in an epidemic?



Measles Cases in an outbreak in Iceland in 1907

Cliff, Measles: An Historical Geography, 1991

If we had a good metric, we could use it to compare the rate of increase
In cases across settings



For example, in which setting were SARS cases growing the fastest?

Wallinga, 2004

Doubling Time

- The doubling time of an epidemic is the period of time required for the number of cases in the epidemic to double.

Doubling Times

Where N_τ is the number of cases at time τ

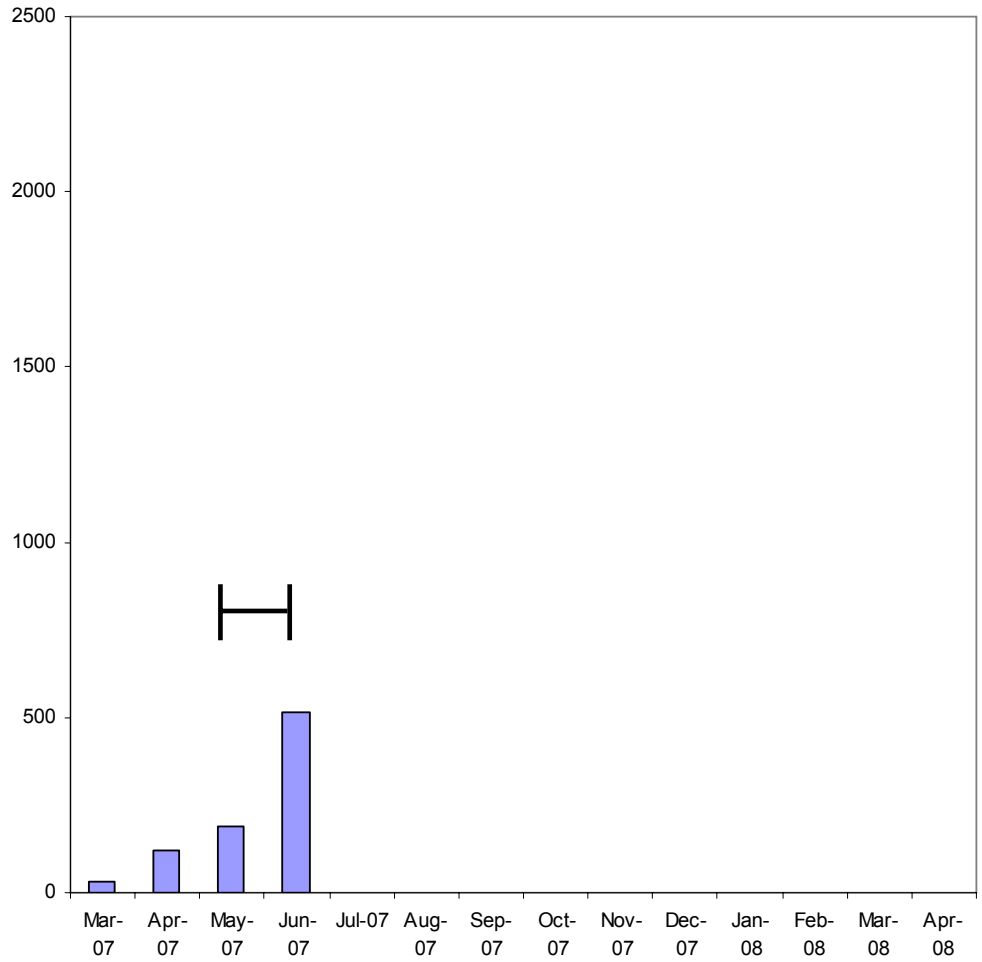
$$\frac{t_\tau - t_{\tau-1}}{\log_2\left(\frac{N_\tau}{N_{\tau-1}}\right)}$$

Doubling Times

So if cases double in one week let's say increasing from 10 to 20 in one week we have:

$$\frac{1week}{\log_2\left(\frac{20}{10}\right)} = \frac{1}{\log_2(2)} = \frac{1}{1} = 1week$$

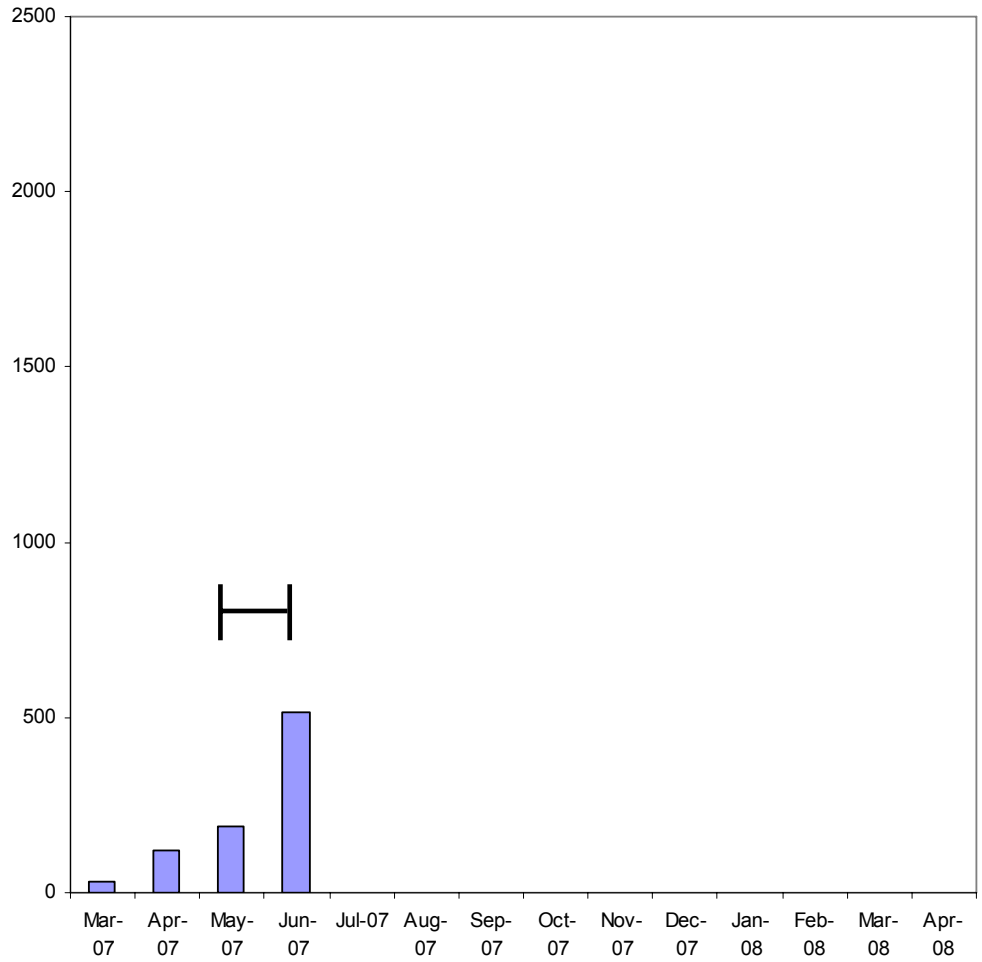
Doubling Time for Measles Outbreak in Iceland



Cases in May: 191
Cases in June: 514

What is the doubling time?

Doubling Time for Measles Outbreak in Iceland



$$= \frac{June - May}{\log_2\left(\frac{514}{191}\right)}$$

$$= \frac{1mo.}{\log_2\left(\frac{514}{191}\right)}$$

$$= 0.7 \text{ months}$$

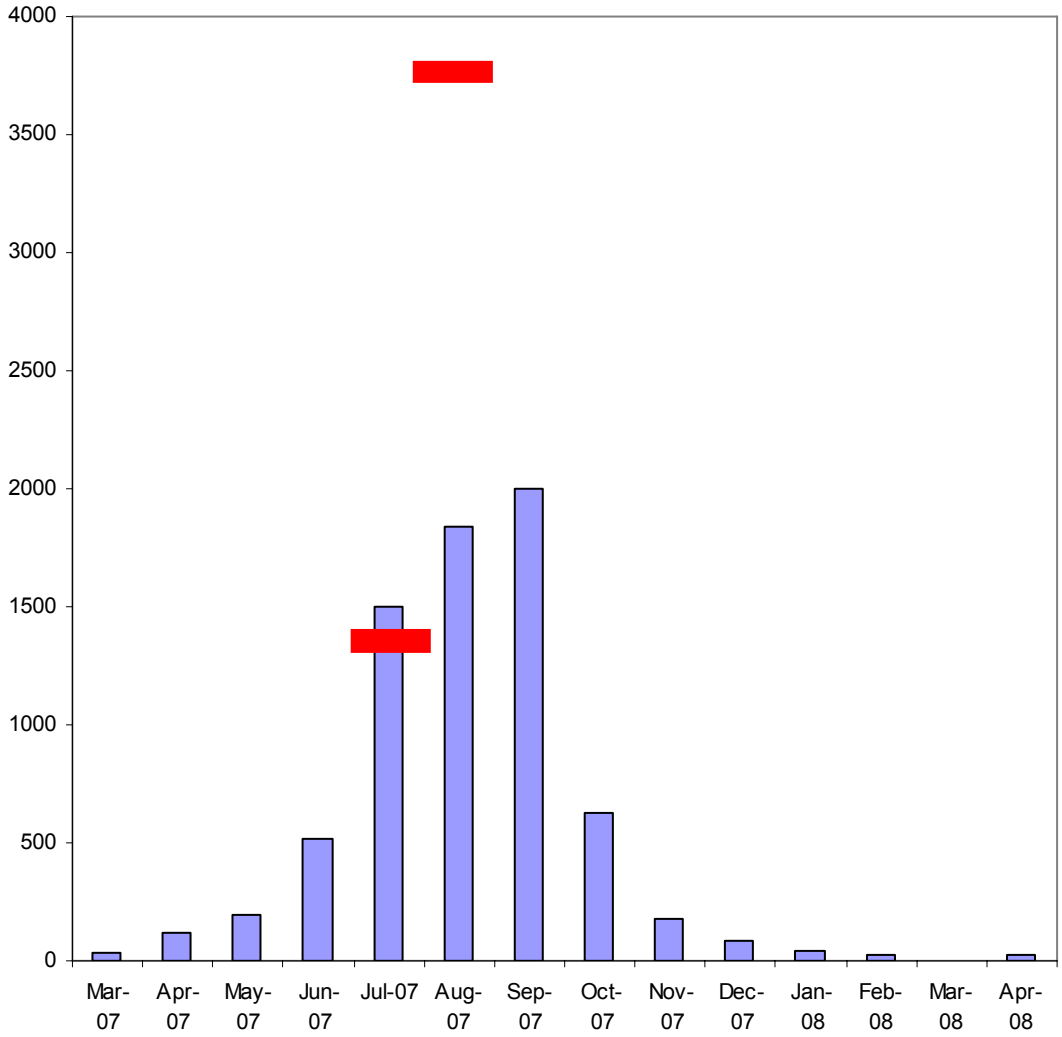
Estimates for intervals where cases are rising range from 0.5 to 1.5 months

We could use this simple formula to forecast future case numbers (we'll see later why we shouldn't)

$$0.7 = \frac{1\ month}{\log_2\left(\frac{X}{514}\right)}$$

$$Cases\ in\ July = X = 1384$$

Measles Cases in an outbreak in Iceland in 1907



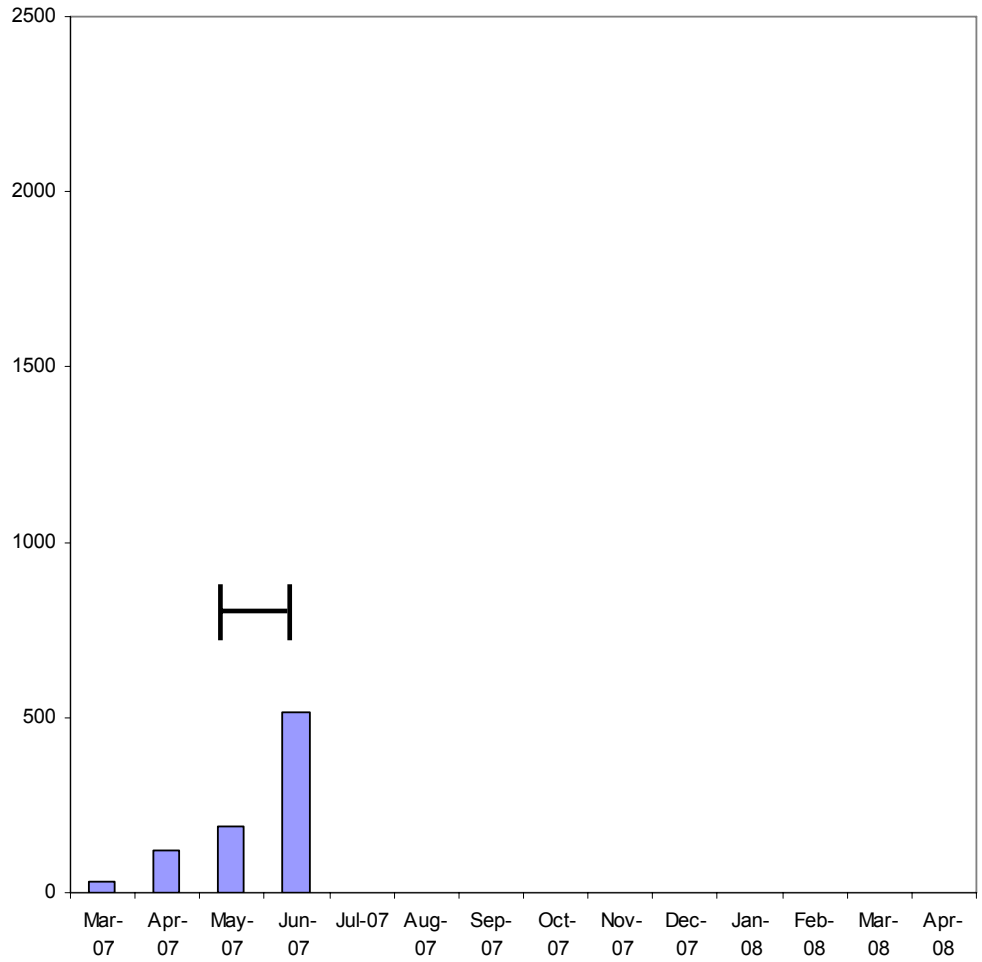
Cliff, Measles: An Historical Geography, 1991

Now we have our metric of epidemic speed let's compare the rate of increase of an epidemic of two diseases with different values of R_0

R_0 for influenza is ~2

R_0 for measles is ~6-15

Doubling Time for Measles Outbreak in Iceland



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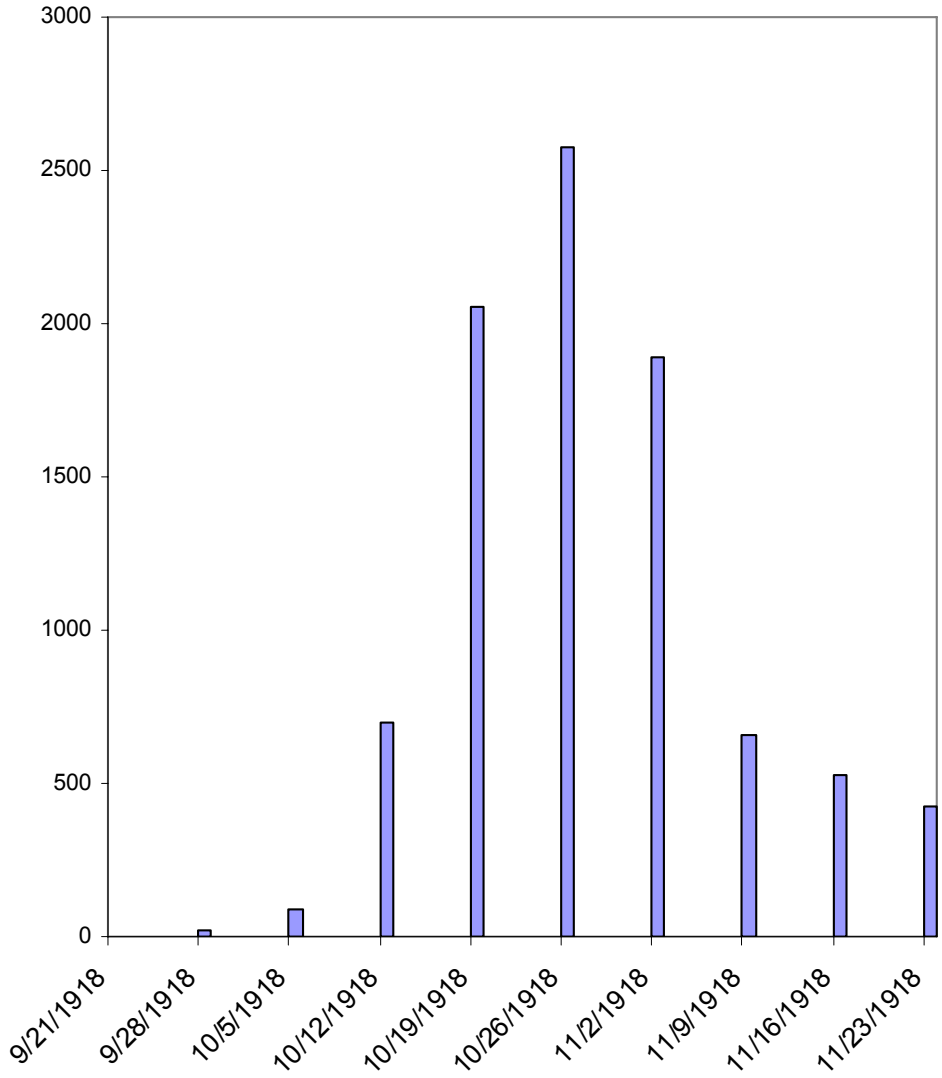
Estimates for intervals where cases are rising range from 0.5 to 1.5 months

Compare to Influenza in Atlanta in 1918



Estimates of the doubling time for influenza for the early part of the curve range from 0.3 to 0.6 weeks

What accounts for this?

- Even though each infectious case with measles is infecting more people than each infectious case of influenza, cases of influenza are growing faster (doubling time is shorter)

Remember there were two factors

- The number of individuals infected by each infectious case. (R_0)

- The time it takes between when a case is infected and when that case infects other people.

Difference in the Serial Interval

The average length of time between when a case is infected and when s/he infects others, the *serial interval* is different for these two pathogens

- Influenza ~2.5 days
- Measles ~ 18 days

Important Time Intervals in the Natural History of an Infectious Disease

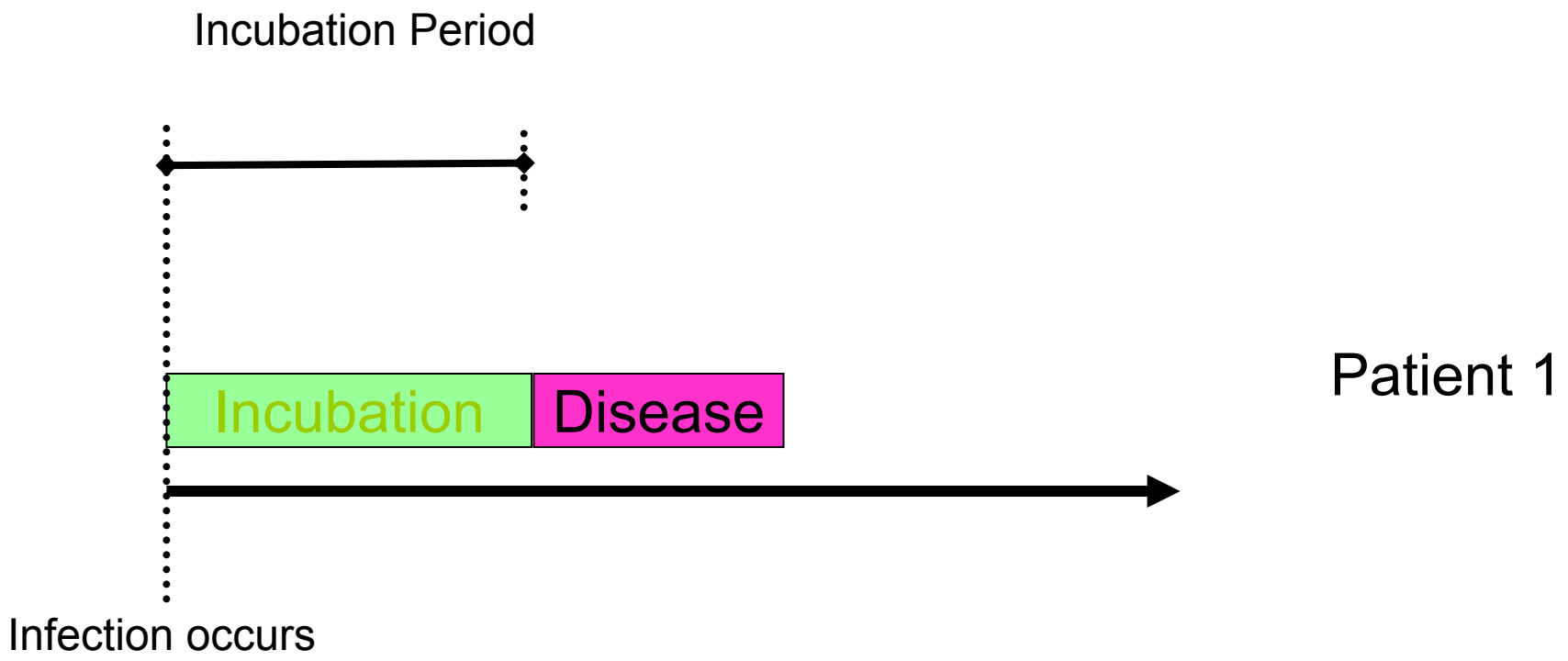
Incubation period, Latent Period and the Serial Interval

Incubation Period – average length of time between infection and the onset symptoms in each case

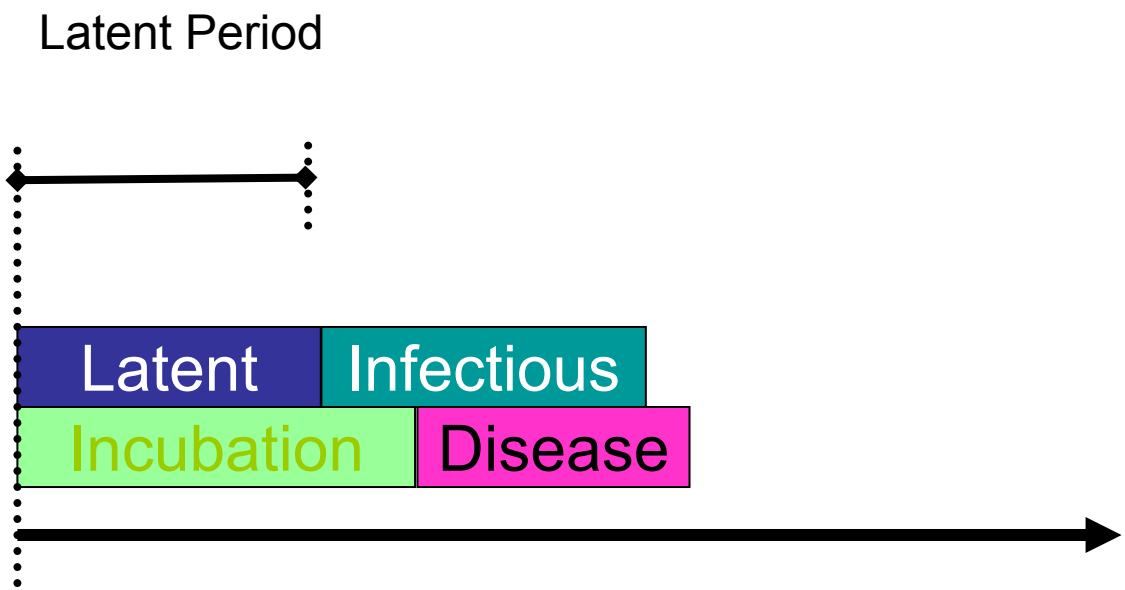
Latent Period – average length of time between infection and the onset of transmissibility

Serial Interval – average length of time between a case being infected and that case infecting subsequent cases (also called the Generation Time) denoted T_g

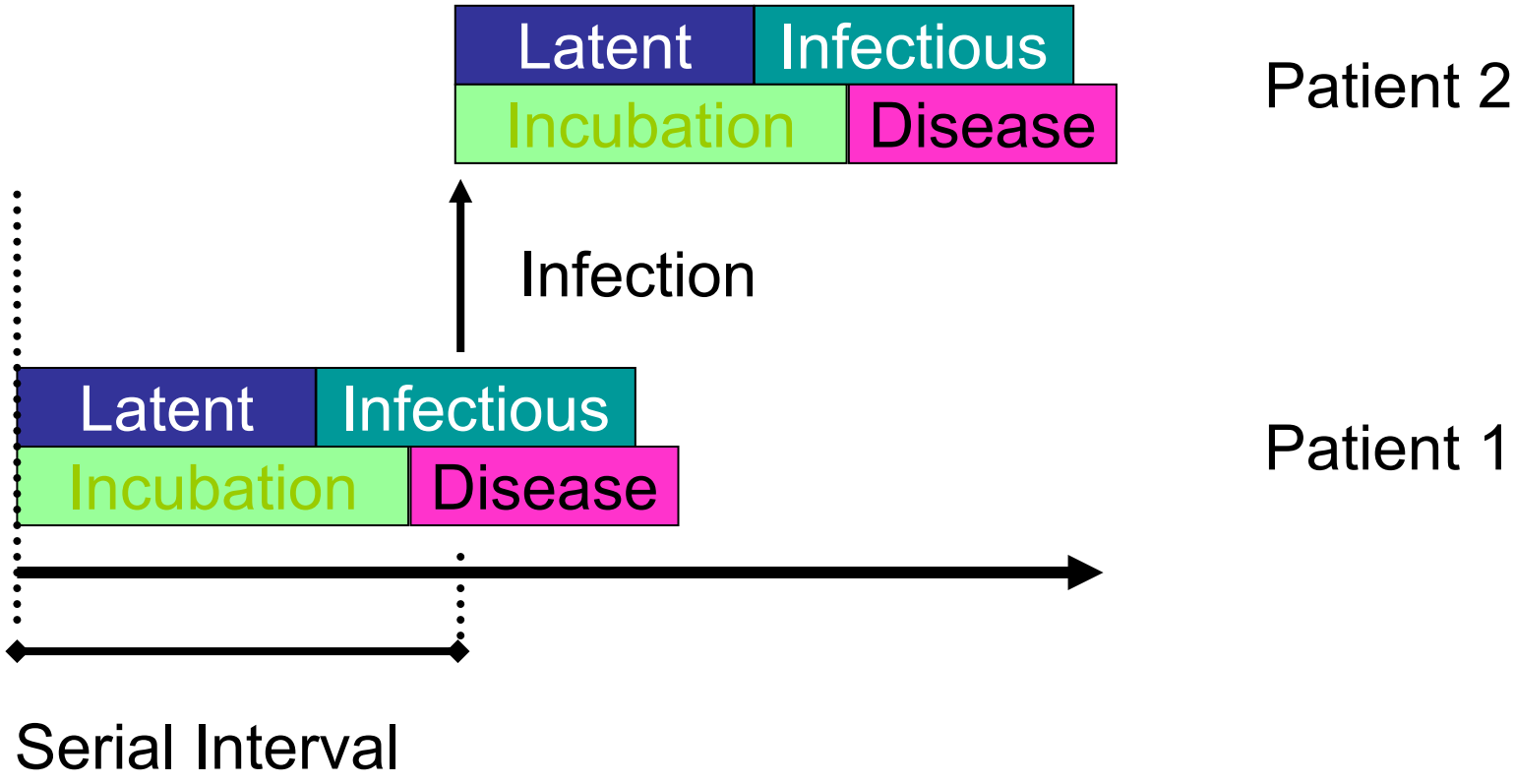
Incubation Period

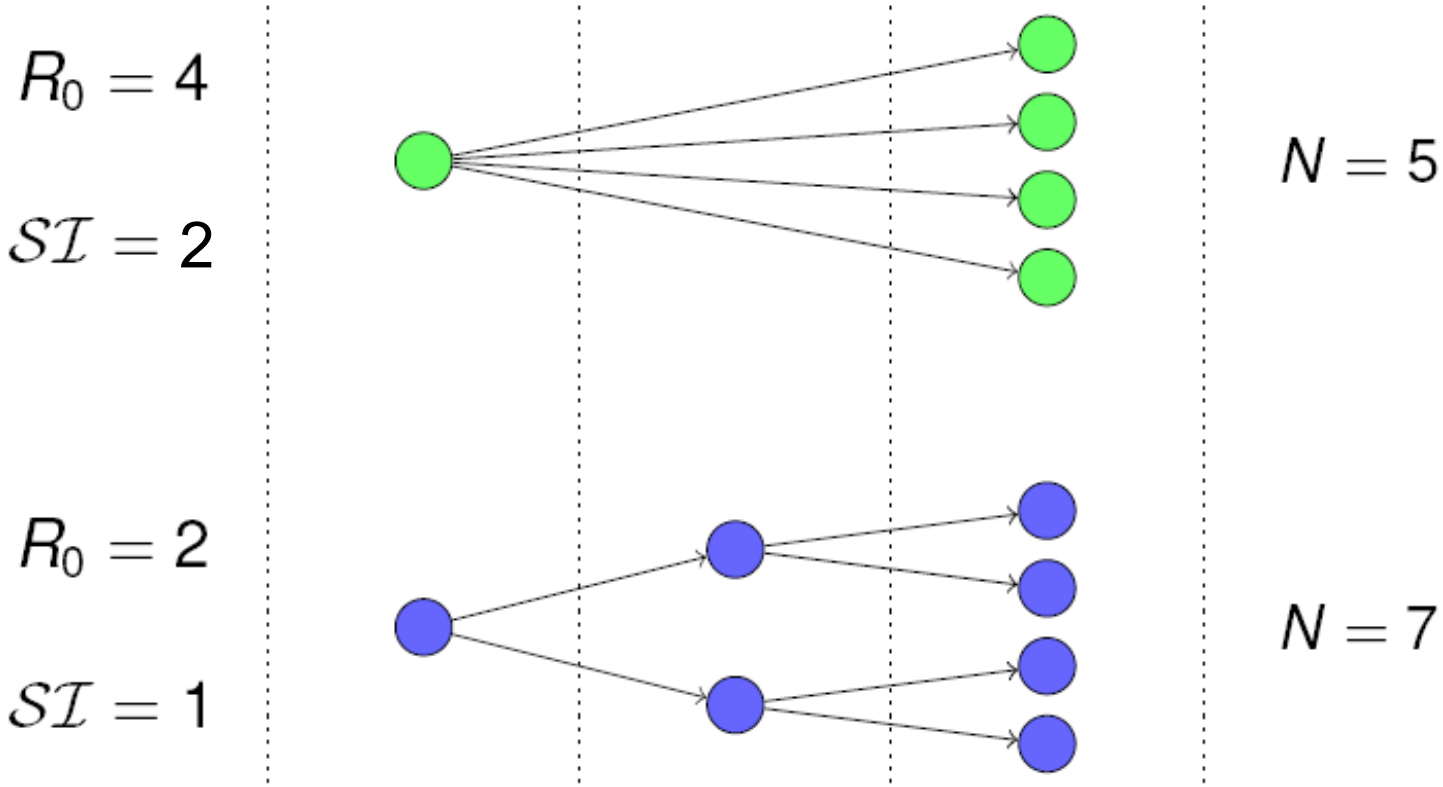


Latent Period



Serial Interval





Two Offers

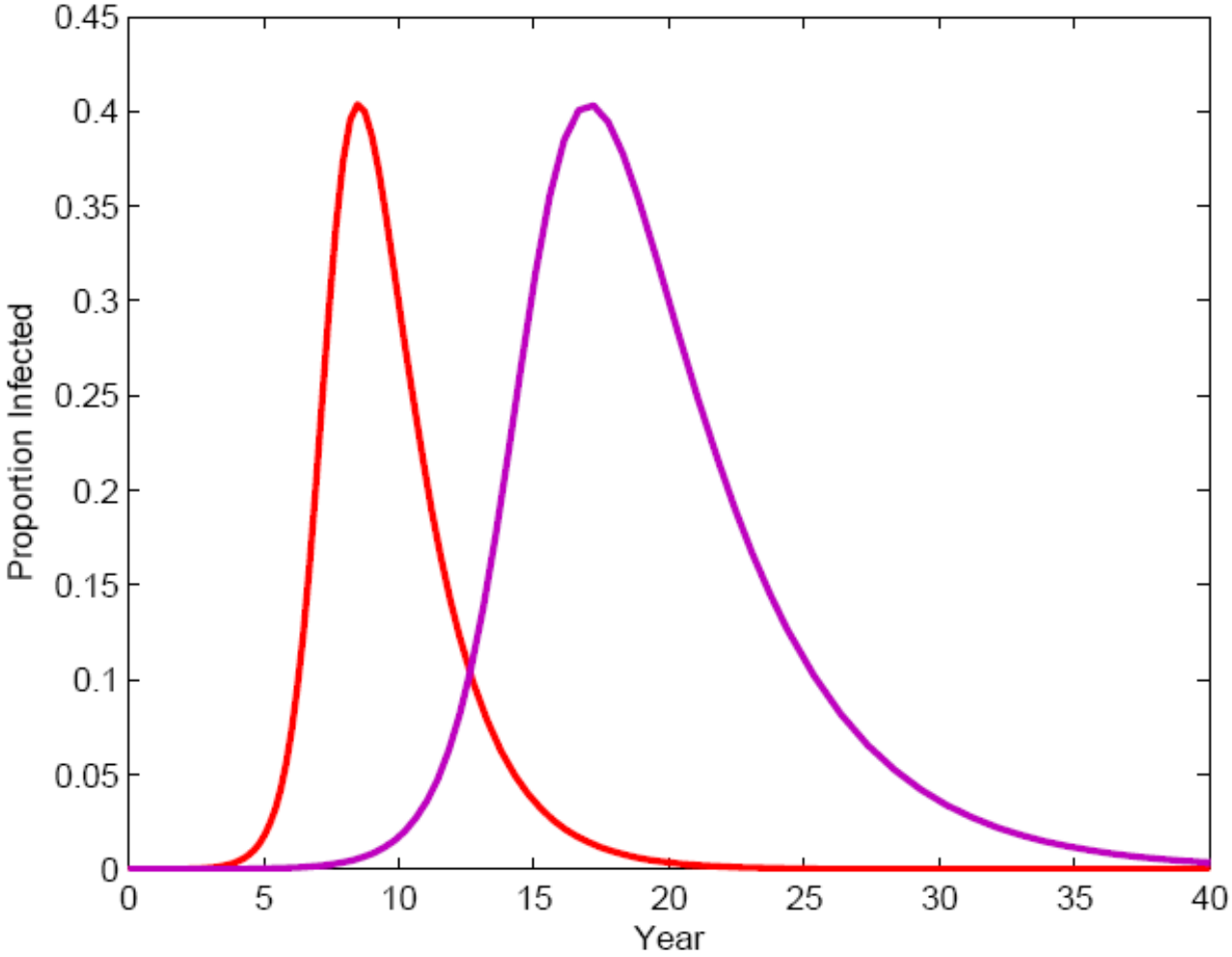
- A bank offers you 50% return on your investment annually
- A second bank offers you 10% return on your investment monthly

Which do you choose?

Two Offers

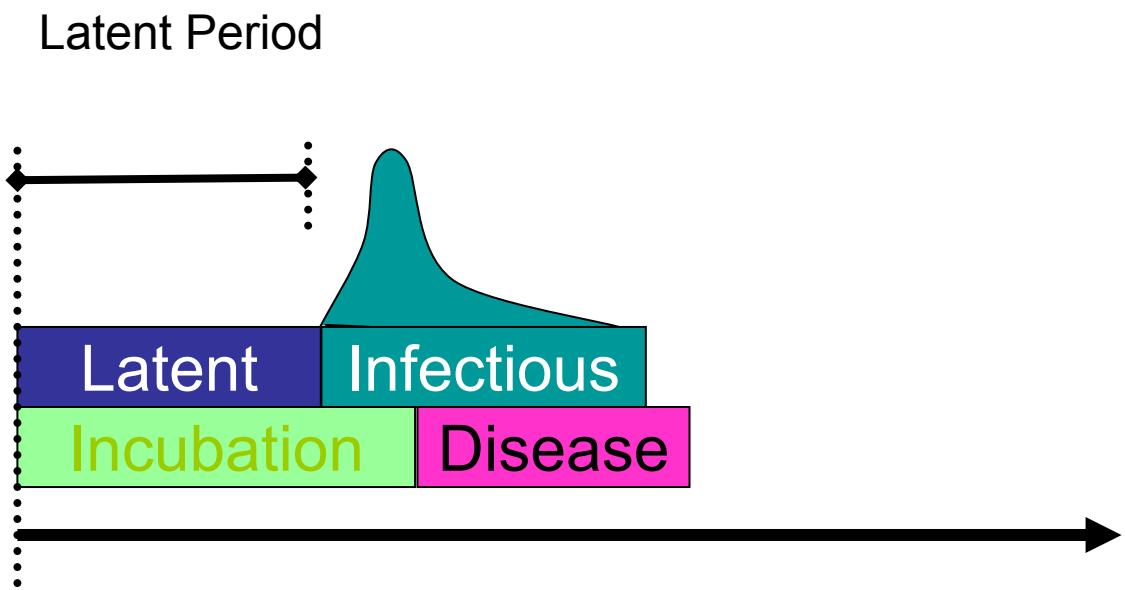
- A bank offers you 50% return on your investment annually (~measles)
- A second bank offers you 10% return on your investment monthly (~influenza)

Which do you choose?

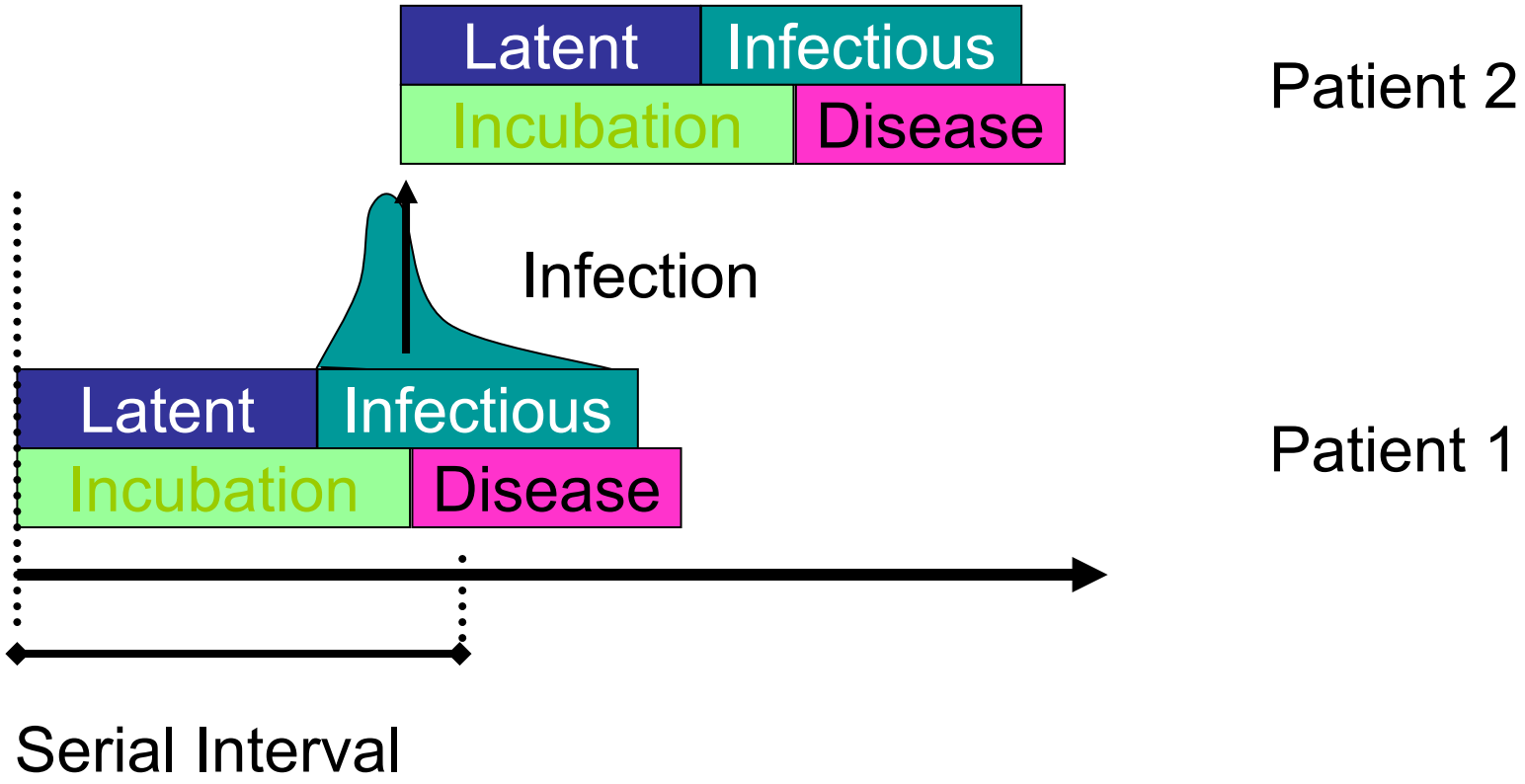


Two simulations: total incidence the same, serial interval different
It's day 6 of the outbreak, which outbreak would your rather control?

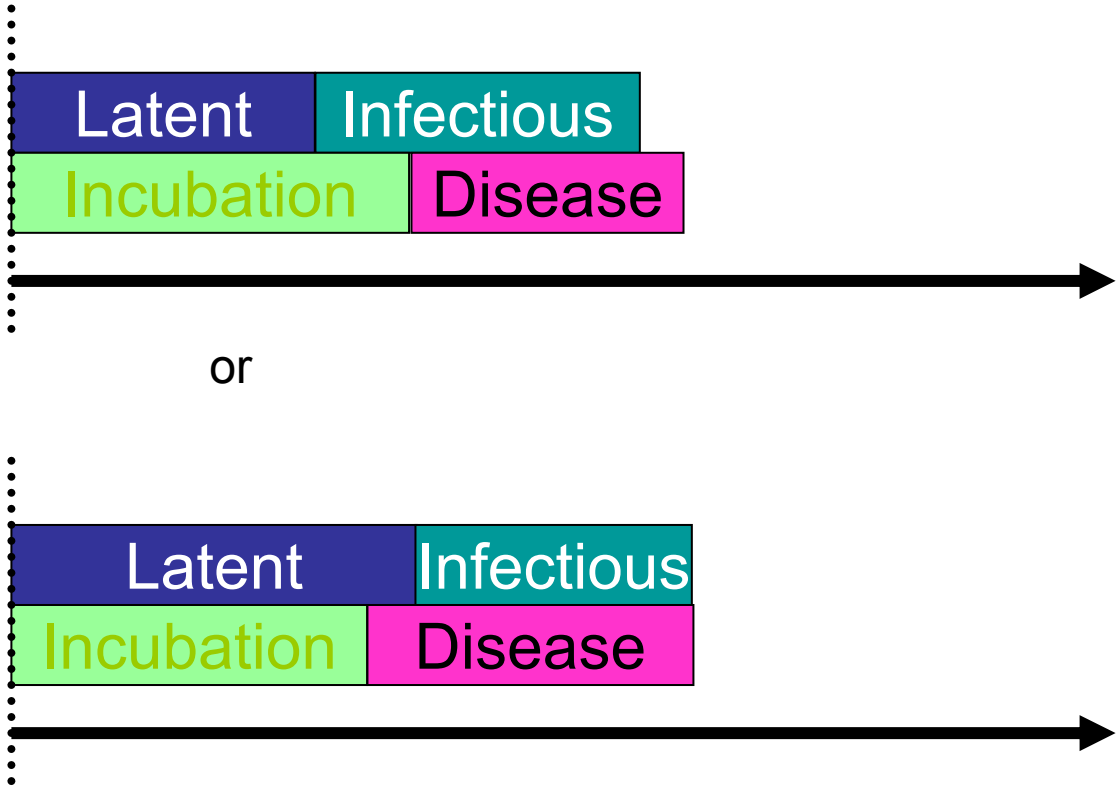
Infectiousness may not be uniform throughout infectious period



Serial Interval, T_g



Question: Which comes first infectiousness or symptomatic illness?



Depends upon the disease

- Influenza?
- Varicella?
- Smallpox?
- SARS?
- HIV?
- Tuberculosis?

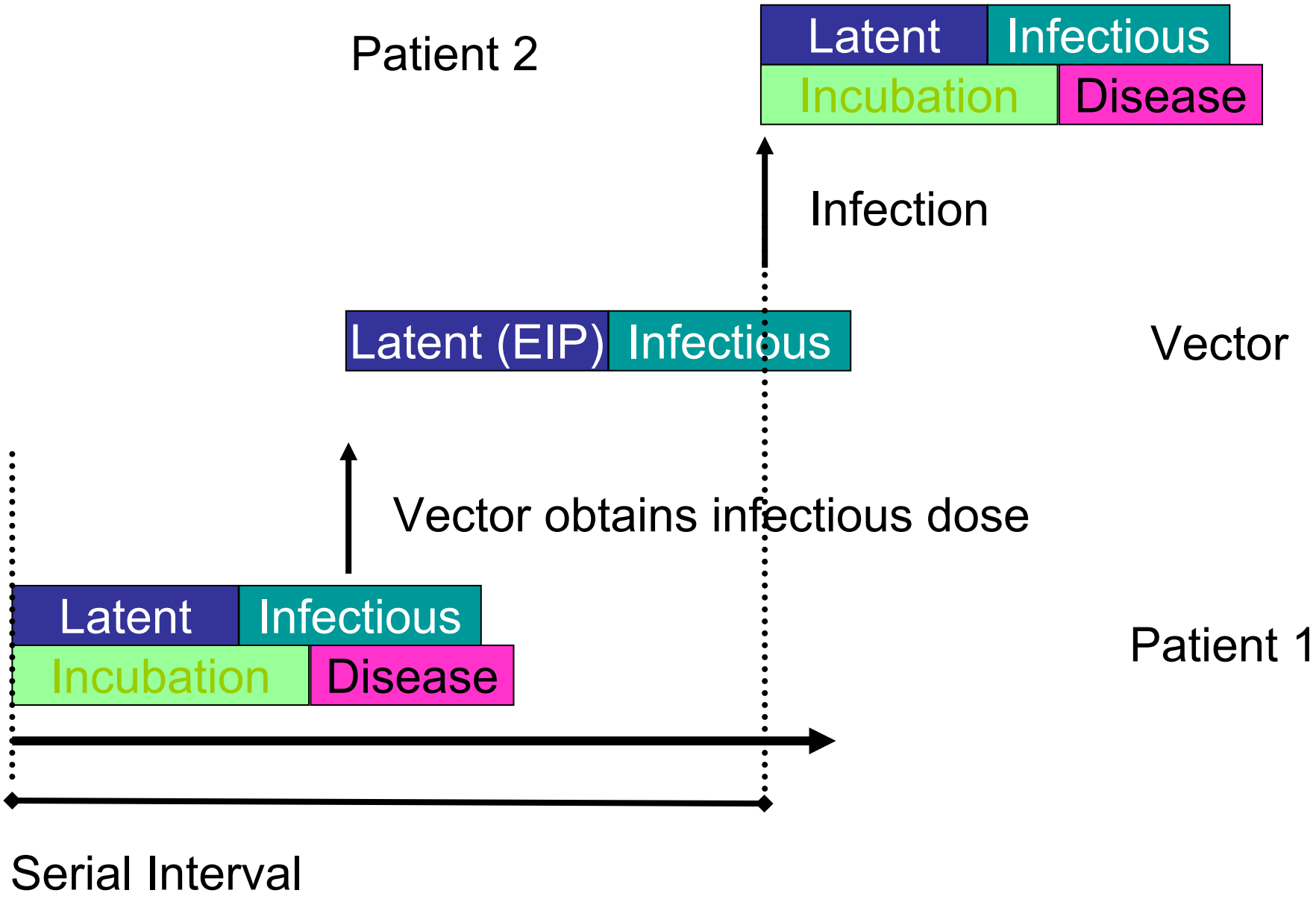
Depends upon the disease

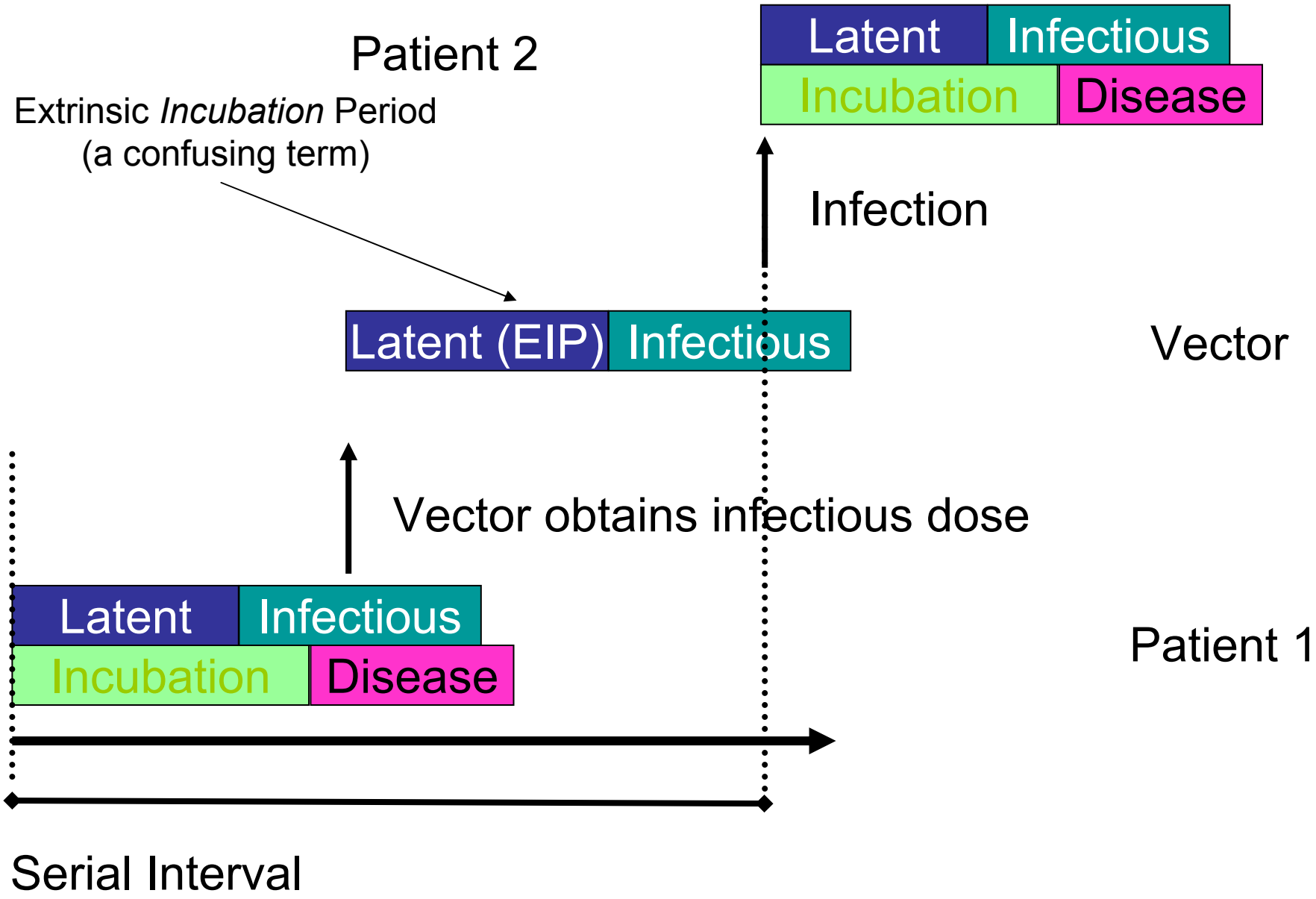
- Influenza latent period < incubation period
- Varicella latent period < incubation period
- Smallpox latent period > incubation period
- SARS latent period > incubation period
- HIV latent period << incubation period
- Tuberculosis latent period = incubation period

Question: Is it possible for an individual to express symptomatic disease before the person that infected him?

For which diseases might this be possible?

Question: What is the serial interval for a vector-borne disease?





How do you measure the serial interval?

How do you measure the serial interval?

- Actually measure the interval between transmissions in a highly surveilled population (household transmission studies)
- Assume transmissibility is proportional to pathogen load (in throat swabs, blood levels, etc.)
- Obtain molecular epidemiologic evidence of specific transmission events and the interval separating them

Usually have data on separation of clinical onsets

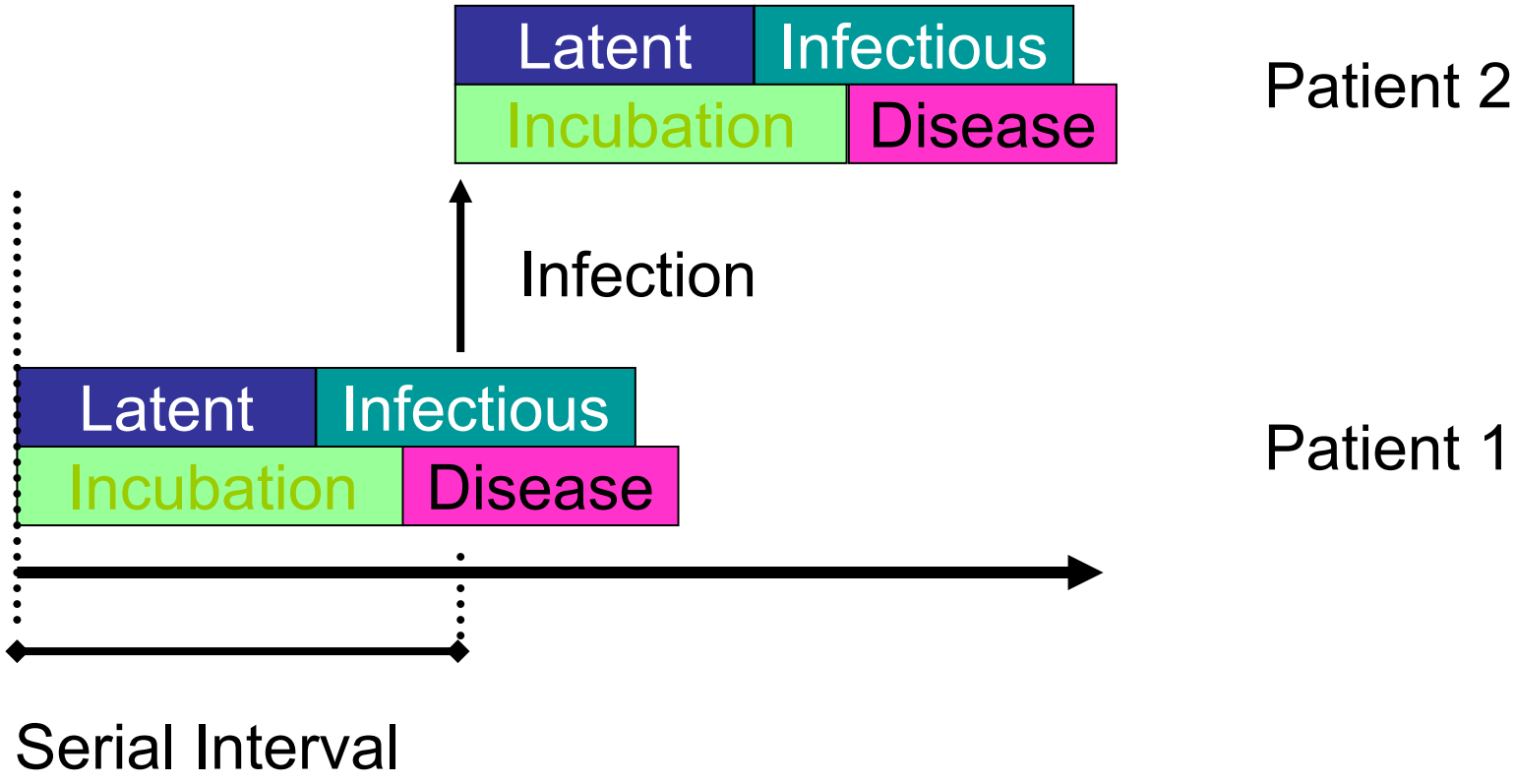
- Interval between onset of symptoms to onset of symptoms of secondary cases
- Actual transmission events hard to observe
- Assume that the time between appearance of symptoms is the same as the time between infections

Onset to Onset is the addition of two intervals

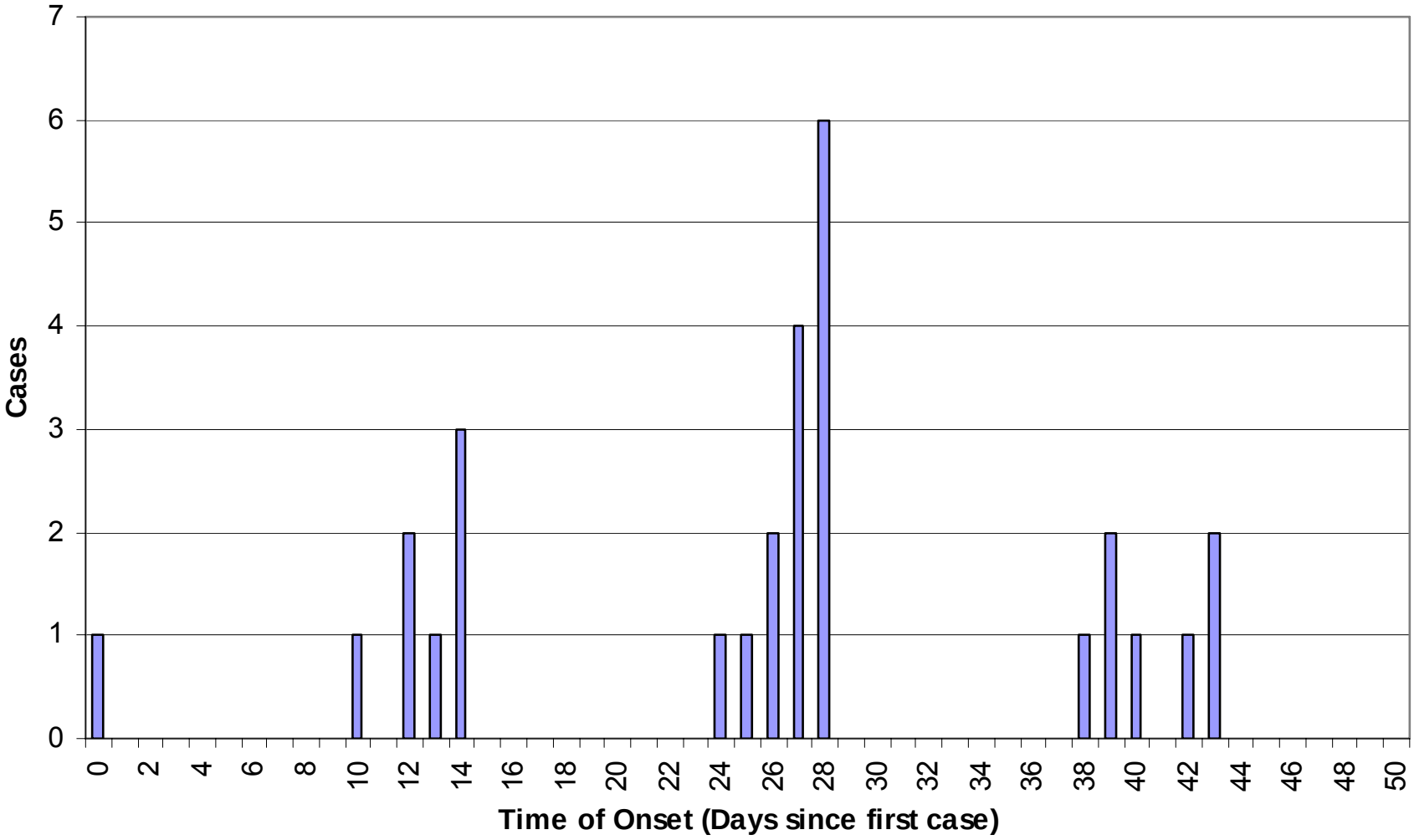
(1) The interval between onset of symptomatic illness of first case and infection of secondary case (*as we saw above, this may be negative*)

(2) The interval between infection in secondary case and onset of symptomatic illness

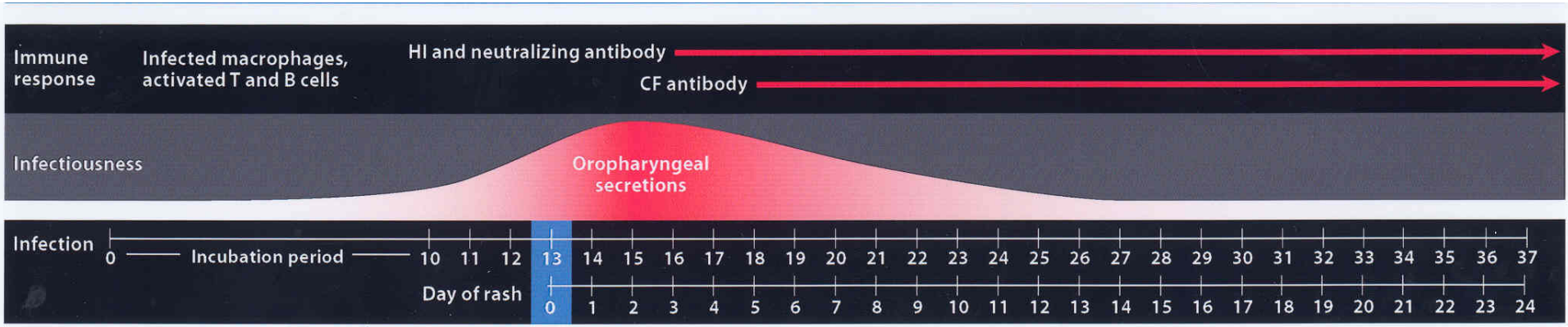
Using Time of Onset data assumes that the serial interval is equivalent to….

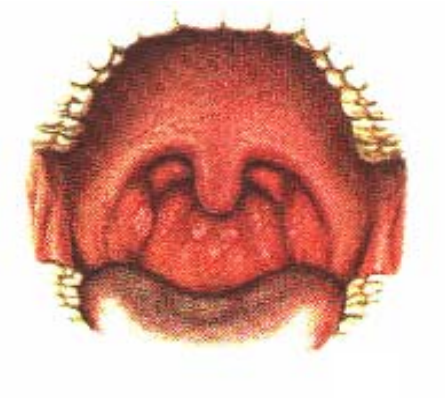


Times of Onset from a measles outbreak starting with one case in a boarding school

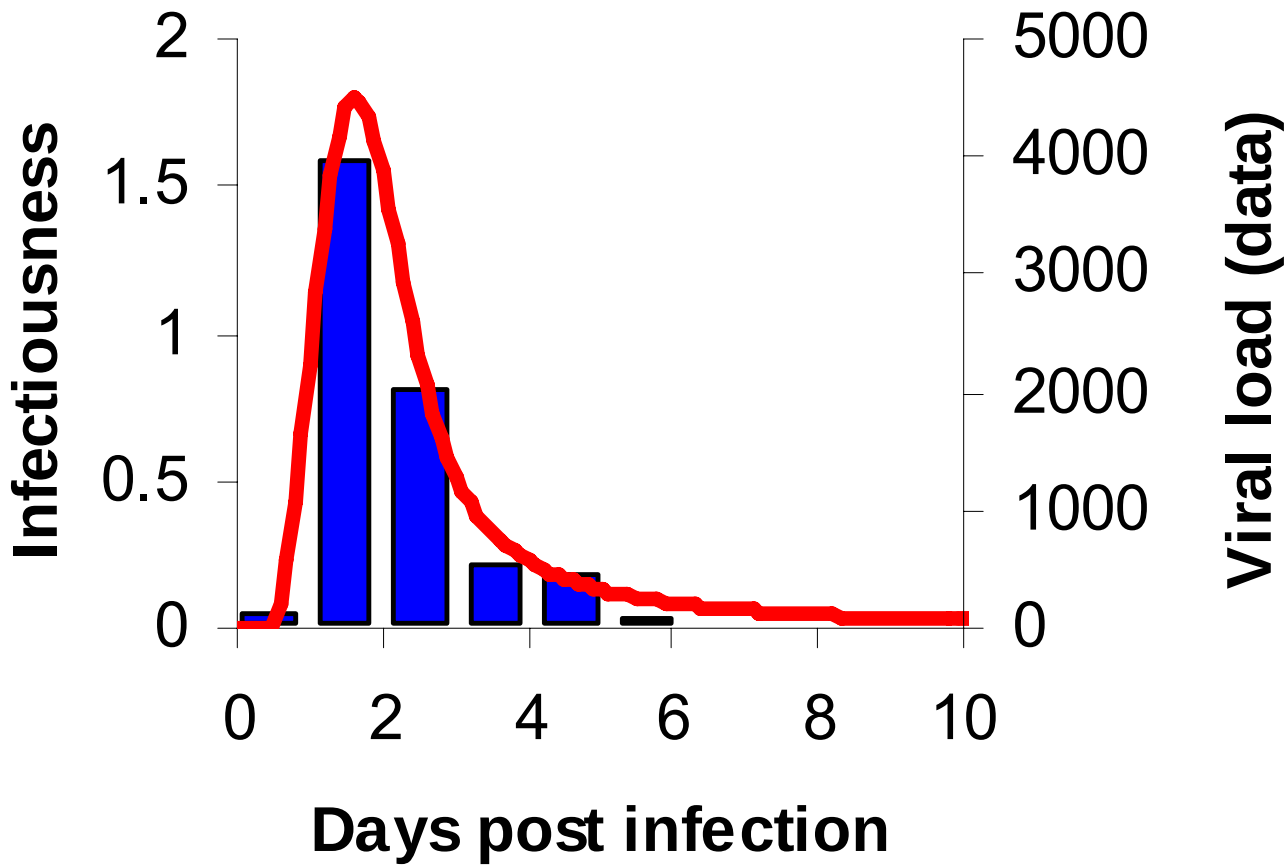


Could also use a proxy for infectiousness, viral load in oropharyngeal secretions for example

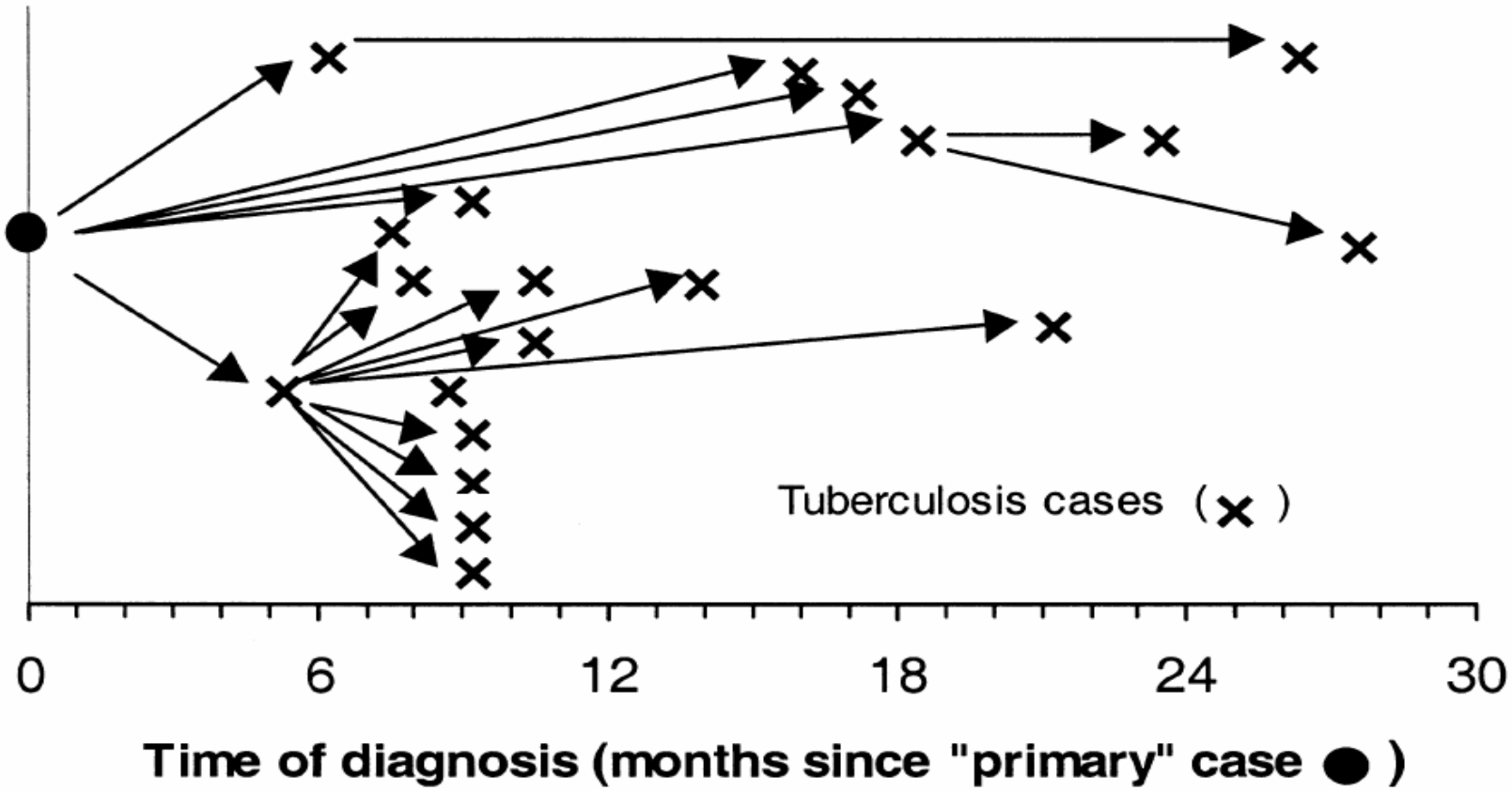




Transmissibility and viral load data for influenza show good correspondence



Molecular Epidemiology data (cases linked by molecular fingerprinting)



Fine, 2003

Doubling time is a function of both R_0 and the Serial Interval, T_g

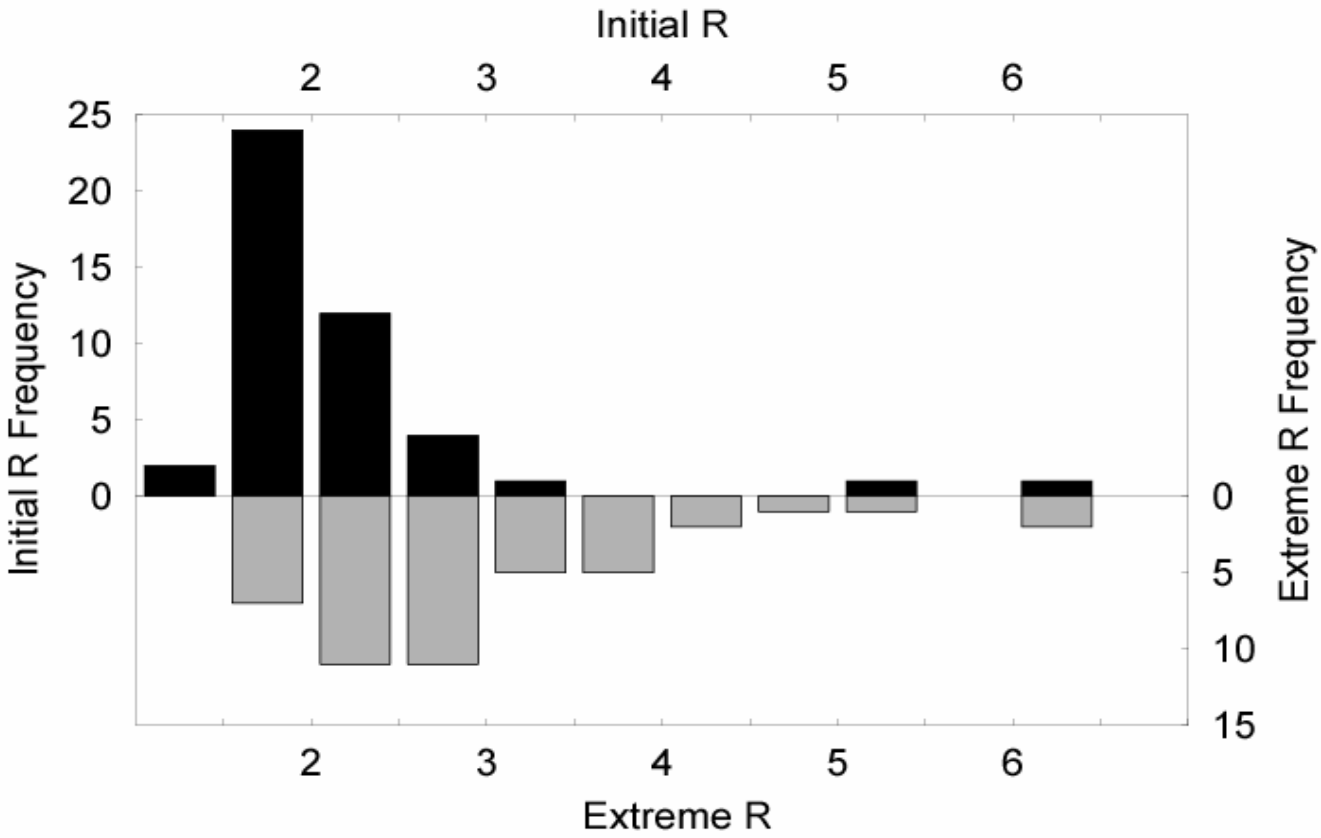
$$\text{Doubling Time} \approx \frac{\ln(2) * T_g}{(R_0 - 1)}$$

As Tg increases, doubling time increases
As R_0 increases, doubling time decreases

Influenza

- Influenza has a short serial interval and a relatively small R_0
- This is a new finding, widely recognized only in recent years
- Used to be assumed to be 10 to 15
- Assumptions made sense to people because of the explosiveness of influenza epidemics
  - 60% of the world's population was infected in ~6 months in 1918

Estimates of R_0 for Influenza



Mills, Robins & Lipsitch, *Nature* 2004

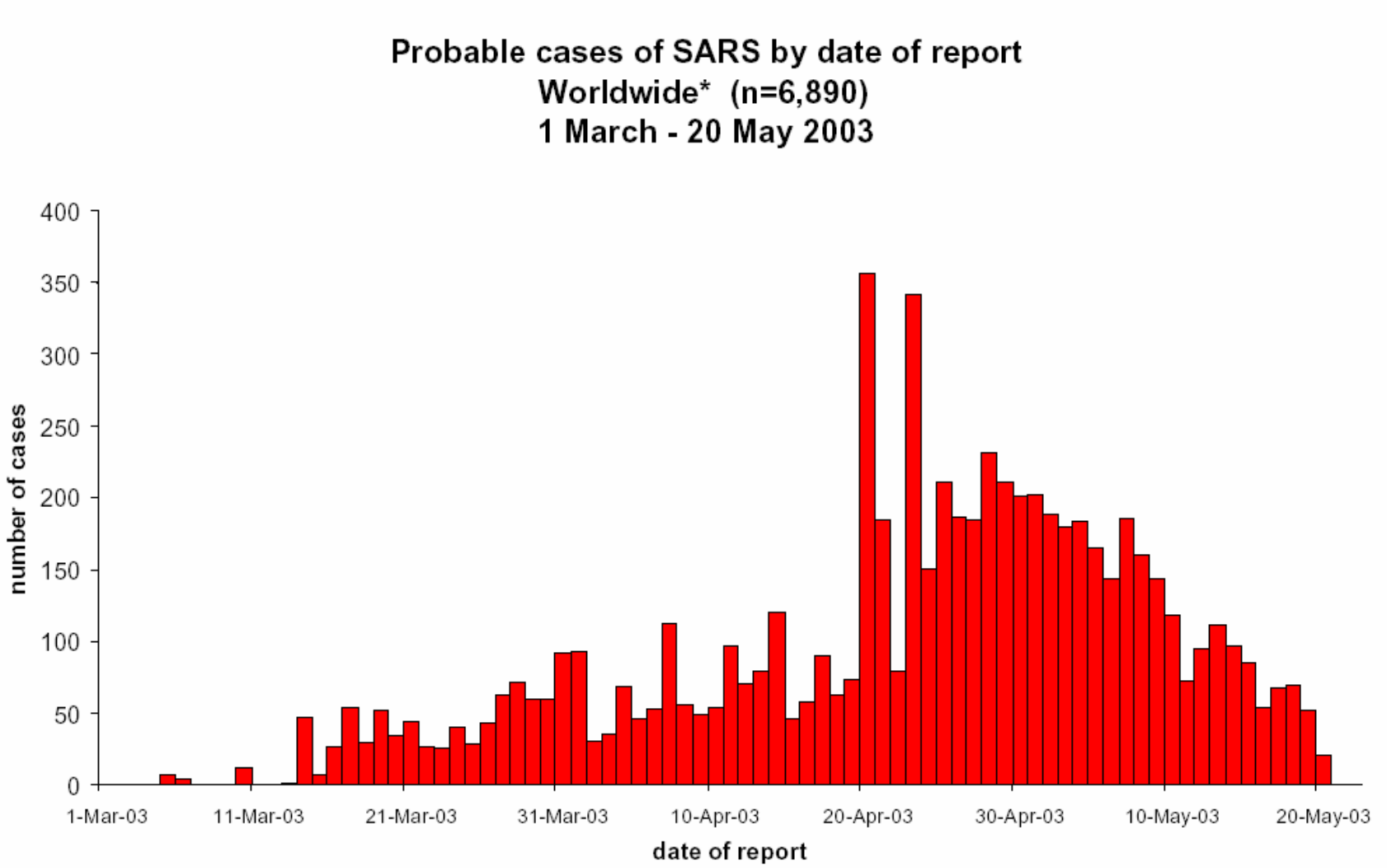
What does this mean for control?

- Need to bring R_0 (really R(t)) under 1
- If R_0 is 2, need to prevent only 50% of infections to reduce R_0 to 1 instead of 90% of transmission if R_0 is 10
- The serial interval describes how much time there is to respond

Serial interval and the Basic Reproductive Number impact the speed of epidemics—What else?

- From the serial interval and R_0, you can get a rough idea of the temporal progression of the disease

- What else would we like to know in order to estimate the speed of an epidemic and more specifically *the impacts of controls*?



SARS

- Estimates of serial interval ~8.5 days
- Estimates of R0 ~2 to 3

- Are all pathogens that have these characteristics equally difficult (or easy to control)?

What about SARS made it controllable?

We had fewer tools to combat SARS than we do for influenza (no antivirals, no vaccine) but no one thinks that a pandemic of influenza will be as easy to contain as SARS

Targeted interventions to stop transmission depend upon being able to identify cases

- Isolation, quarantine, screening of travelers, prophylactic use of drugs all depend on identifying people before they transmit

- Delays dramatically reduce effectiveness
  - if your interventions don't identify people until after they've done the bulk of their transmission, they don't work

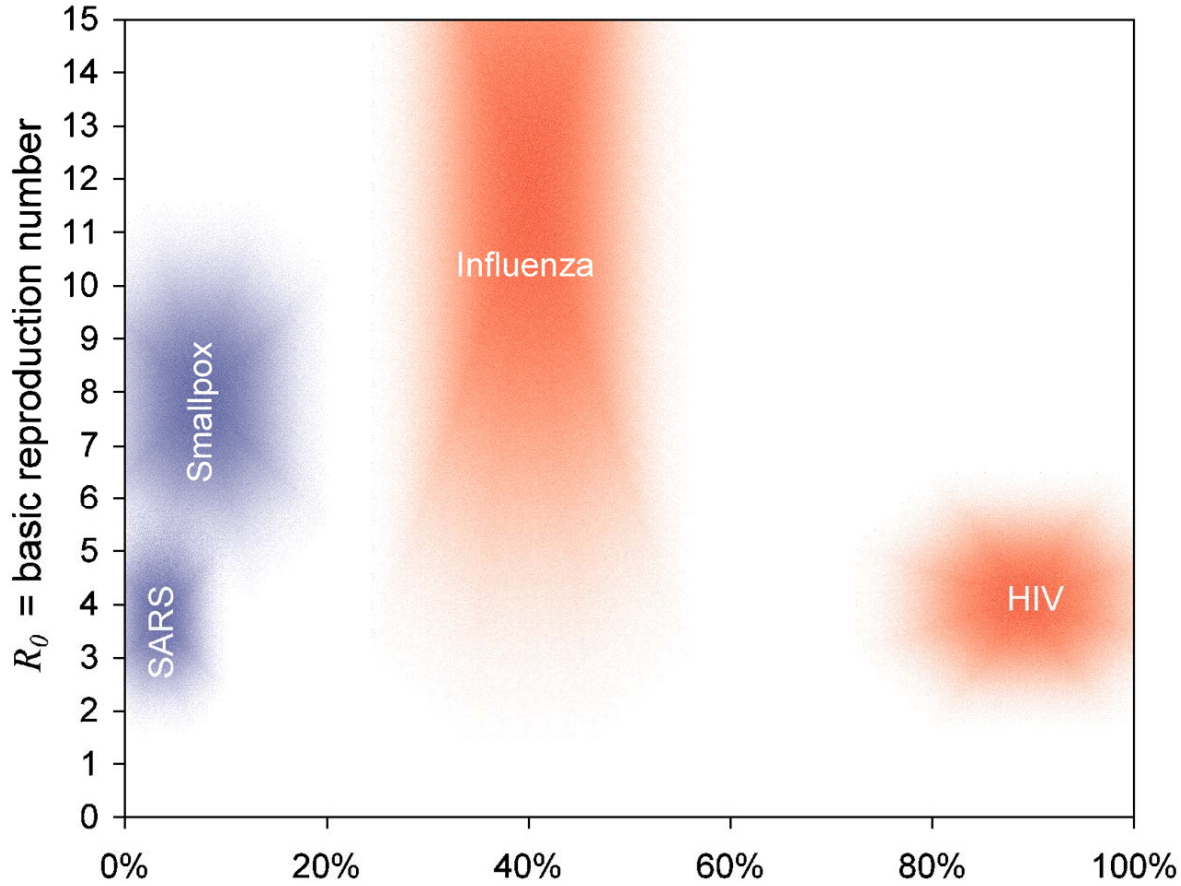
- The serial interval identifies the time-scale of response

- How quickly can we identify cases?

θ

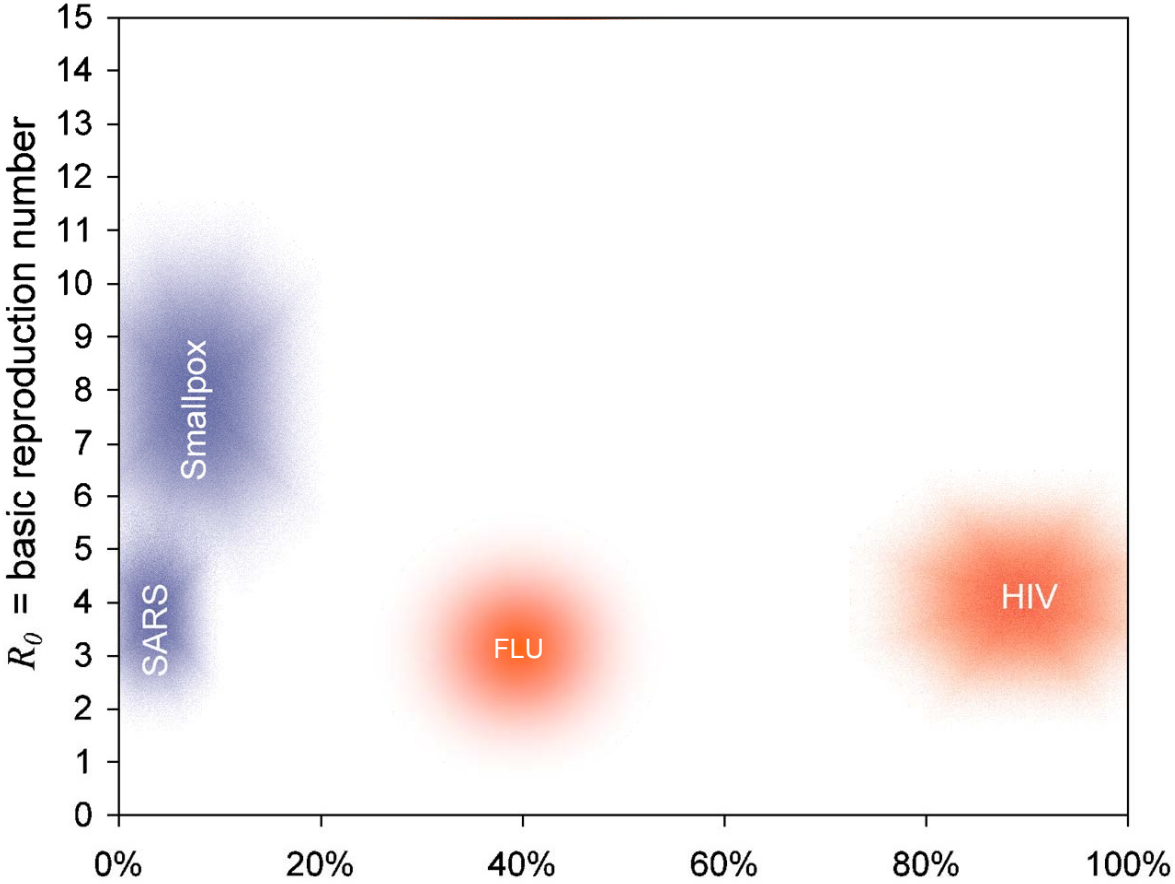
- Defined as the proportion of transmission occurring prior to symptoms
- Measure of how much shorter latent period is than incubation period
- Proposed by Fraser and colleagues

Control by case-finding: factors influencing success



Fraser et al. (2004) Proc. Natl. Acad. Sci. USA 101, 6146-6151

Control by case-finding: factors influencing success

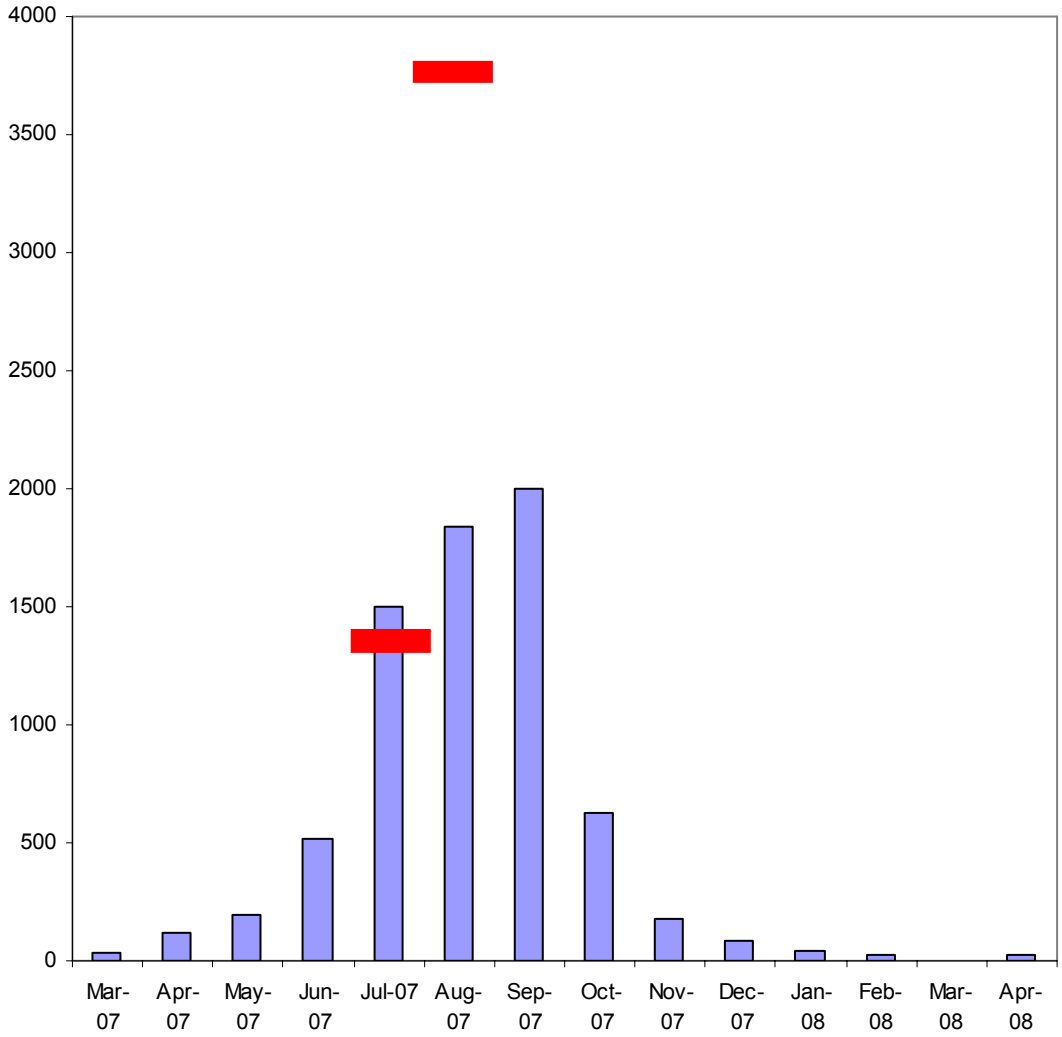


Fraser et al. (2004) Proc. Natl. Acad. Sci. USA 101, 6146-6151

What's next?

- If we have information on R_0, the serial interval, theta, etc. can we forecast the spread of infectious disease for the purposes of
  - Evaluating response
  - Comparing intervention strategies

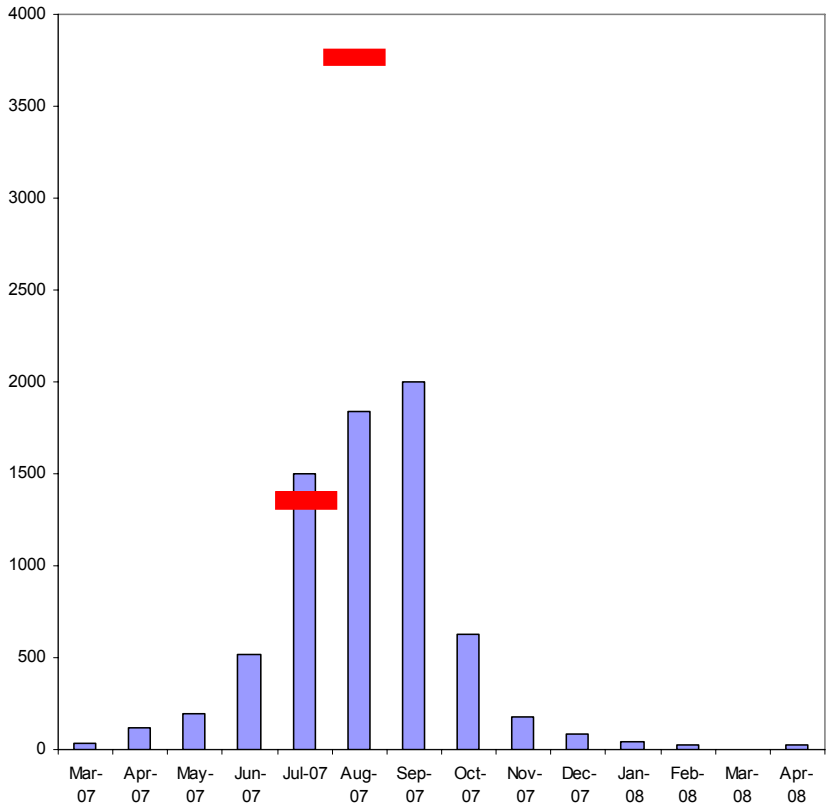
Remember this projection? Why is it wrong?



Cliff, Measles: An Historical Geography, 1991

A major point of debate in the late 1800's early 1900's was why epidemics stop when large number of people still appear to be susceptible

John Brownlee led a school that said this can't be the way epidemics proceed and offered the explanation that transmissibility changes over time due to intrinsic biological changes in the pathogen over the course of an outbreak



Cliff, Measles: An Historical Geography, 1991

One of Brownlee's major questions: Why do some individuals escape Infection in large outbreaks?

"The assumption that the infectivity of an organism is constant, leads to epidemic forms which have no accordance with the actual facts. If there be given a number of susceptible persons in a community, and if one, say, infect three, the whole body of the susceptible persons will become involved, and the last remaining few finally swept off. Even when allowance is made, on various hypotheses, for the chance of infection being small, because of dilution of the susceptibility by the insusceptibility, the epidemic is

Others won the argument

- Fundamental assumption of infectious disease spread
  - The number of new cases is a function of both the number of individuals who are infectious and the number of individuals who are susceptible

Tomorrow

- We'll look at infectious disease models that use this assumption and apply them to specific examples
  - Influenza spread
  - Measles spread

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- Theta
  - Fraser, Riley, Anderson et al. Factors that make an infectious disease outbreak controllable. 2004. PNAS. 101:6146-6151.