The dynamics of infectious disease outbreaks

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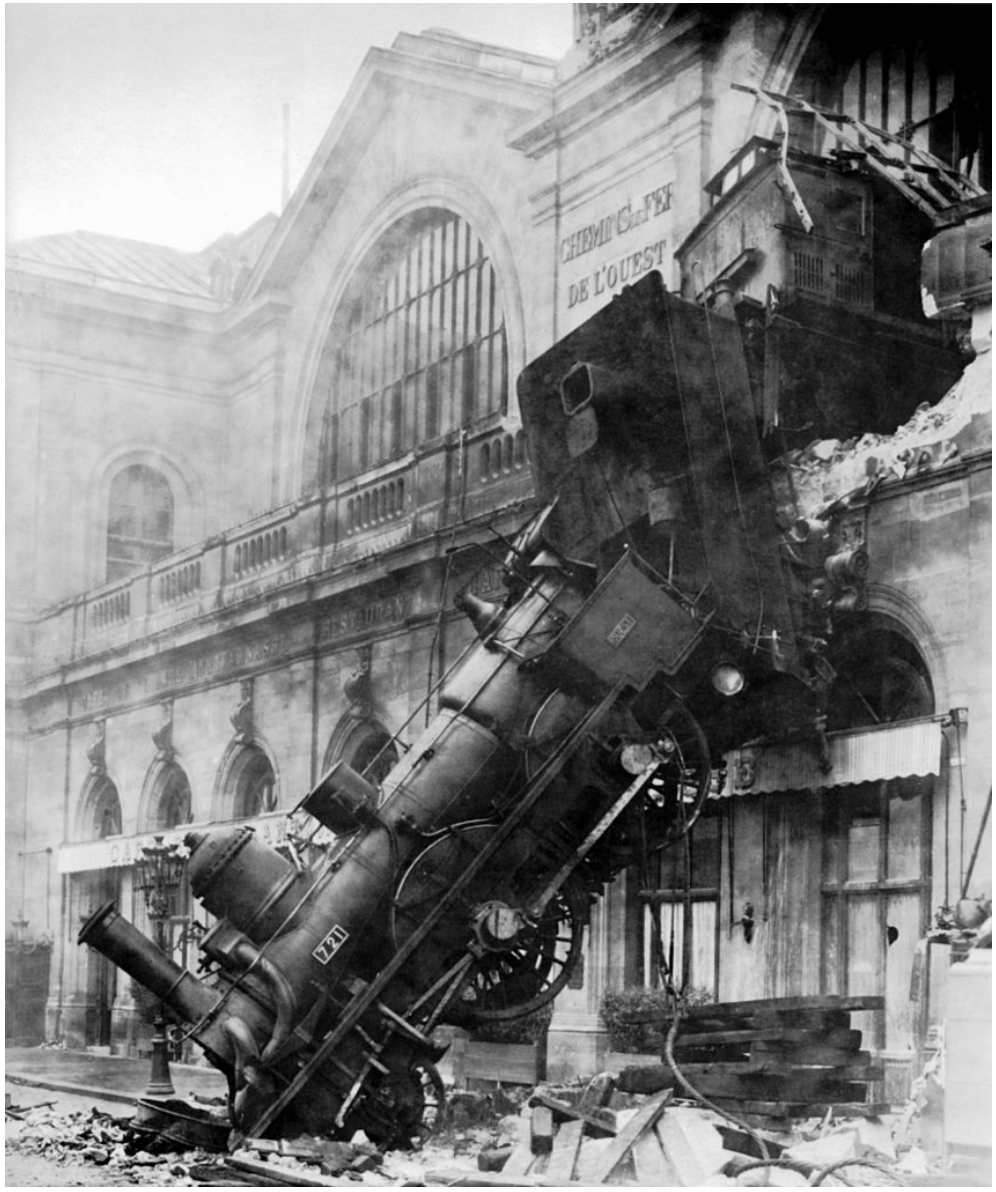
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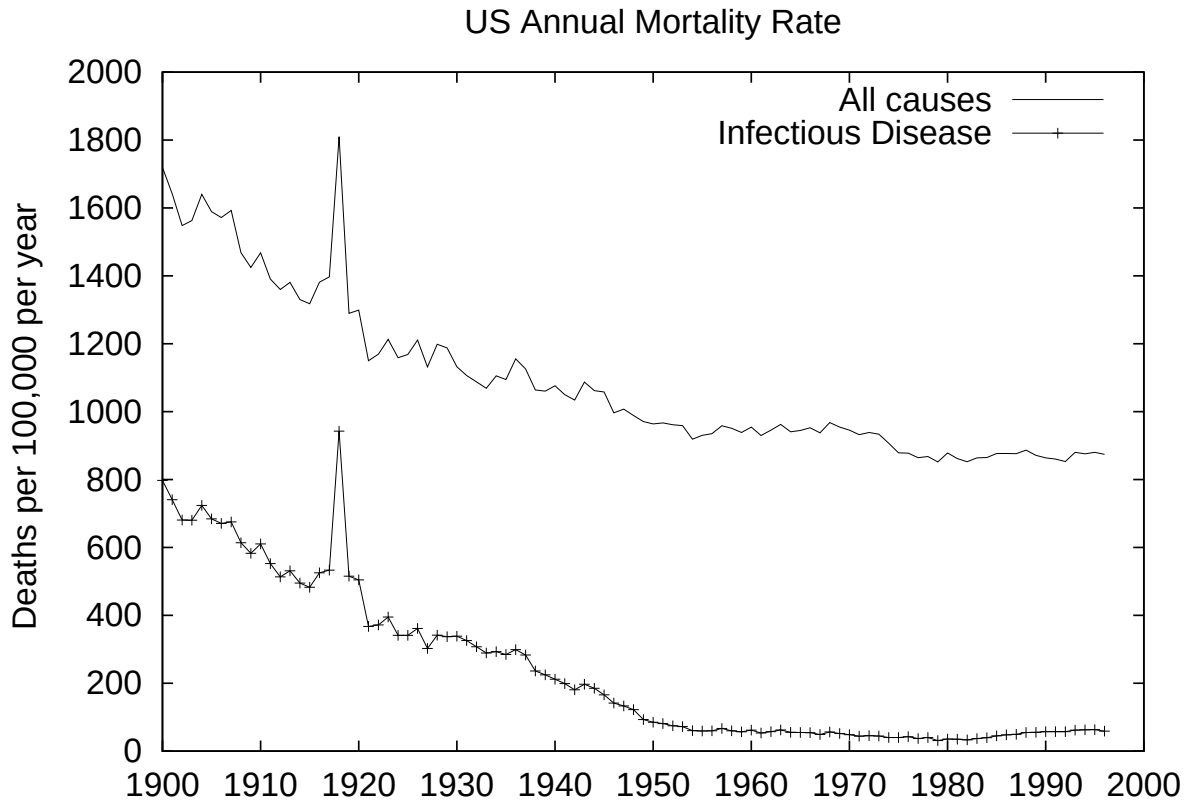
Novel Coronavirus: What do we need to know?

- How deadly is the disease?
- Can spread be stopped?
  - What resources will be needed?
- How much time do we have to prepare?
- Can virus evolution be affected?

How can modelers help?

- Analysis of quantitative information
- Propagating uncertainty
- Linking local and global phenomena

Outline



Dushoff, from Armstrong et al.

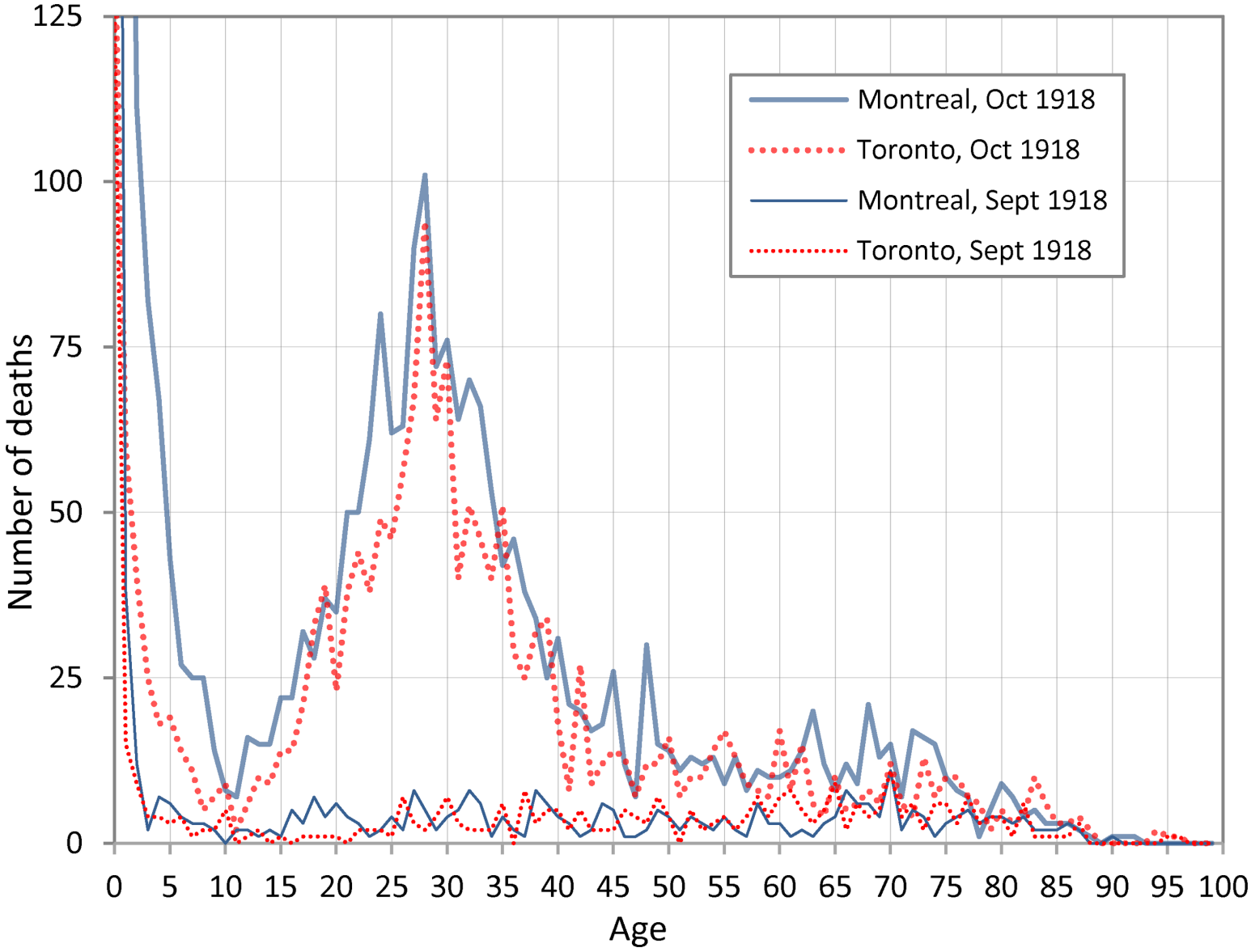
Case fatality proportion

- Worst-case scenario; most of us get the infection
- Fatalities per case
  - We know what a fatality is, but what is a case?
- Denominators!
  - People with (detected) severe disease
  - people with (detected) recognizable disease
  - people who develop antibodies

Case-fatality proportion

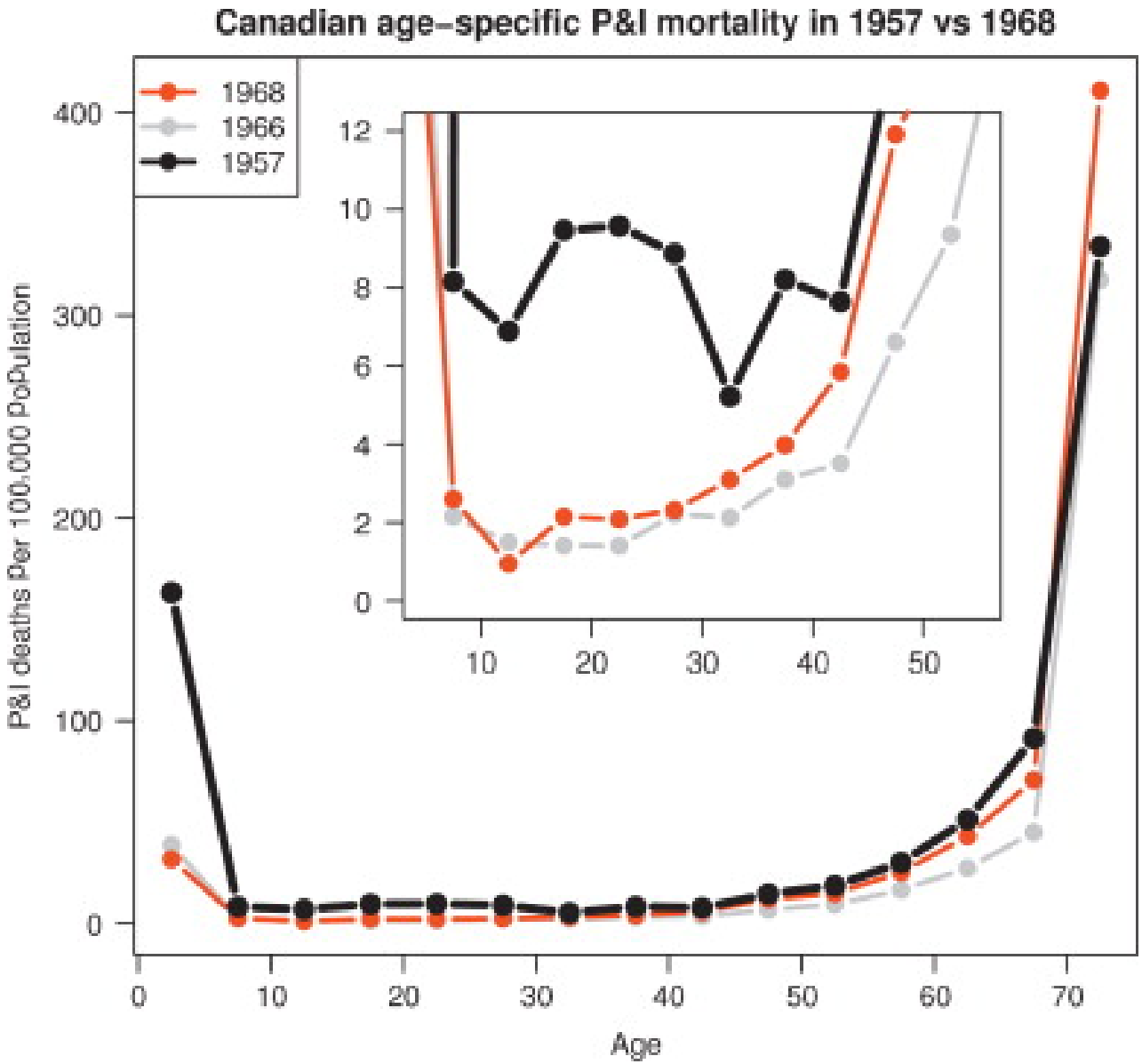
- Currently estimated at 2–4%
- Denominators not reported clearly
- As time goes on (and we focus on general public) this number should go down

1918 Age distribution



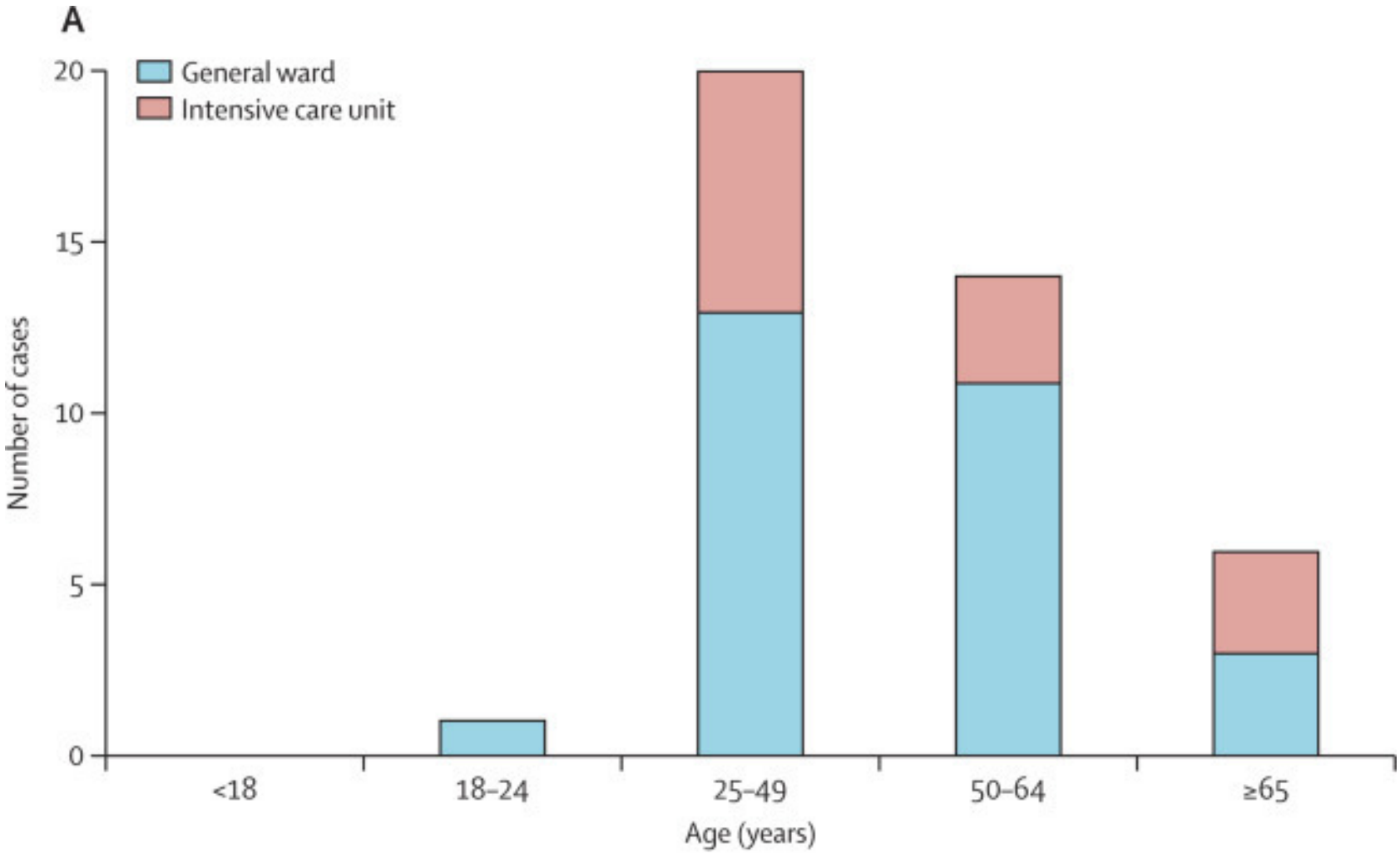
Gagnon et al. 10.1371/journal.pone.0069586

Influenza Age distribution



Ma et al. 10.1016/j.jtbi.2011.08.003

What do we know?



Huang et al. 10.1016/S0140-6736(20)30183-5

What do we know?

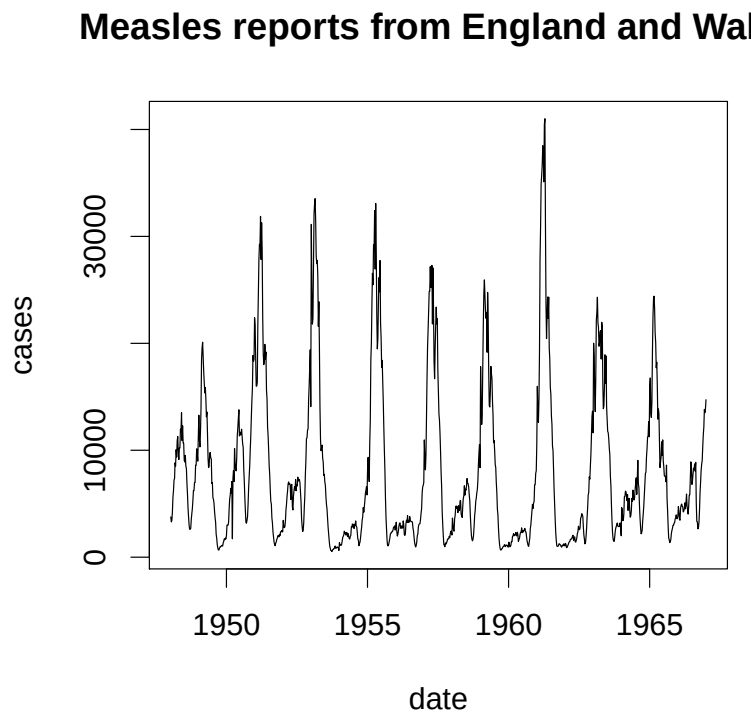
- 80% of reported deaths age > 60
- Life expectancy, harvesting and attributable risk
  - The older the profile, the smaller the overall impact

Will everyone get nCoV?

- Why did everyone get the flu?
  - Fast generations
  - Pre-symptomatic and sub-clinical transmission
  - Effective antigenic evolution
- Can we control nCoV?
- How will nCoV *evolve*

Outline

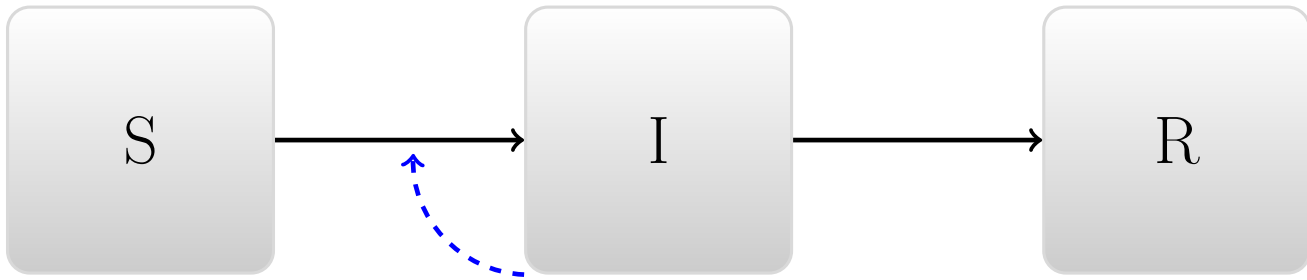
Dynamical modeling connects scales



- Start with rules about how things change in short time steps
  - Usually based on *individuals*
- Calculate results over longer time periods
  - Usually about *populations*

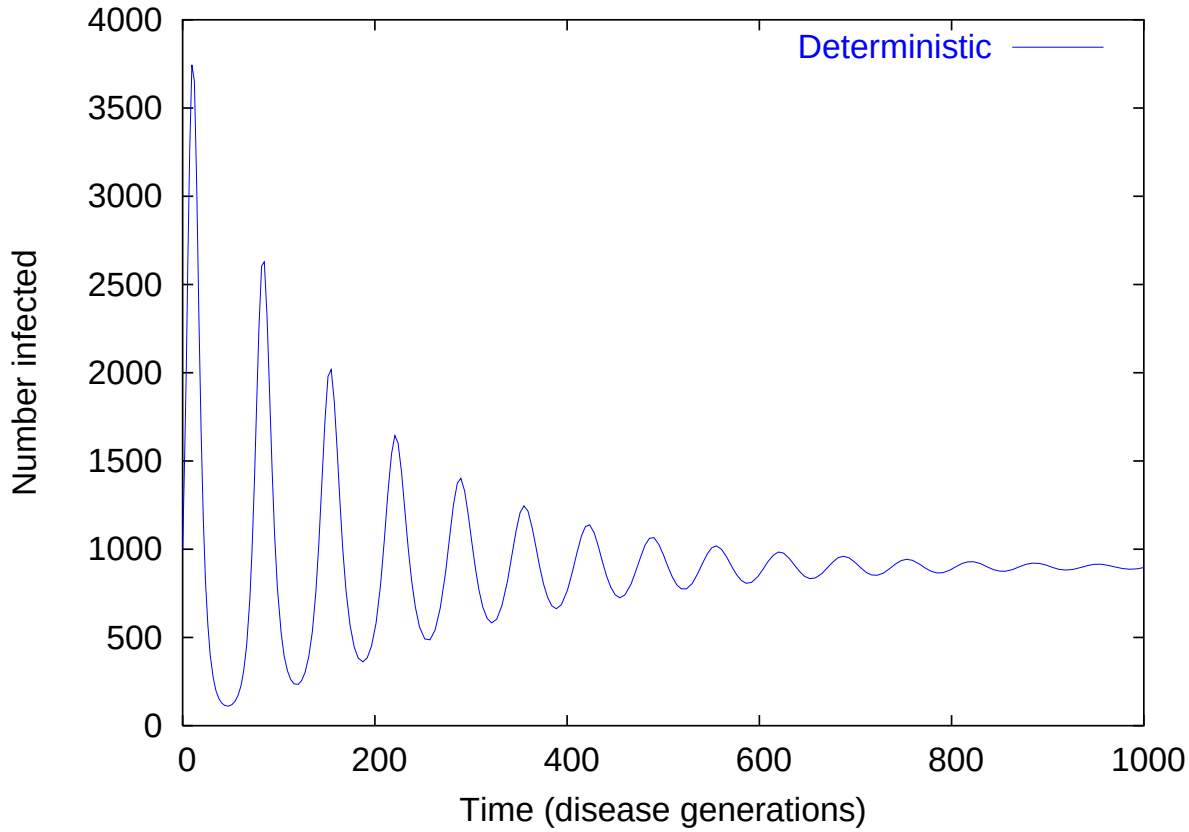
Compartmental models

Divide people into categories:

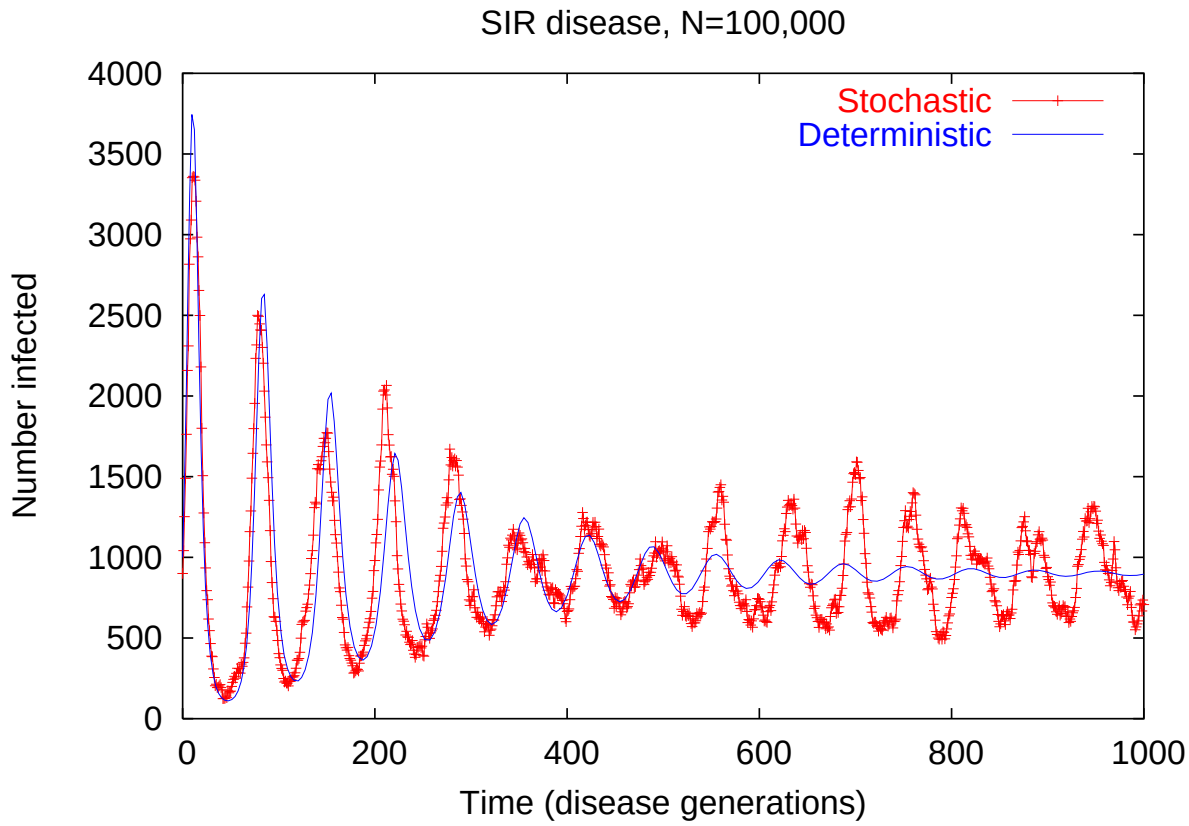


- Susceptible $\rightarrow$ Infectious $\rightarrow$ Recovered
- Individuals recover independently
- Individuals are infected by infectious people

Differential equation implementation



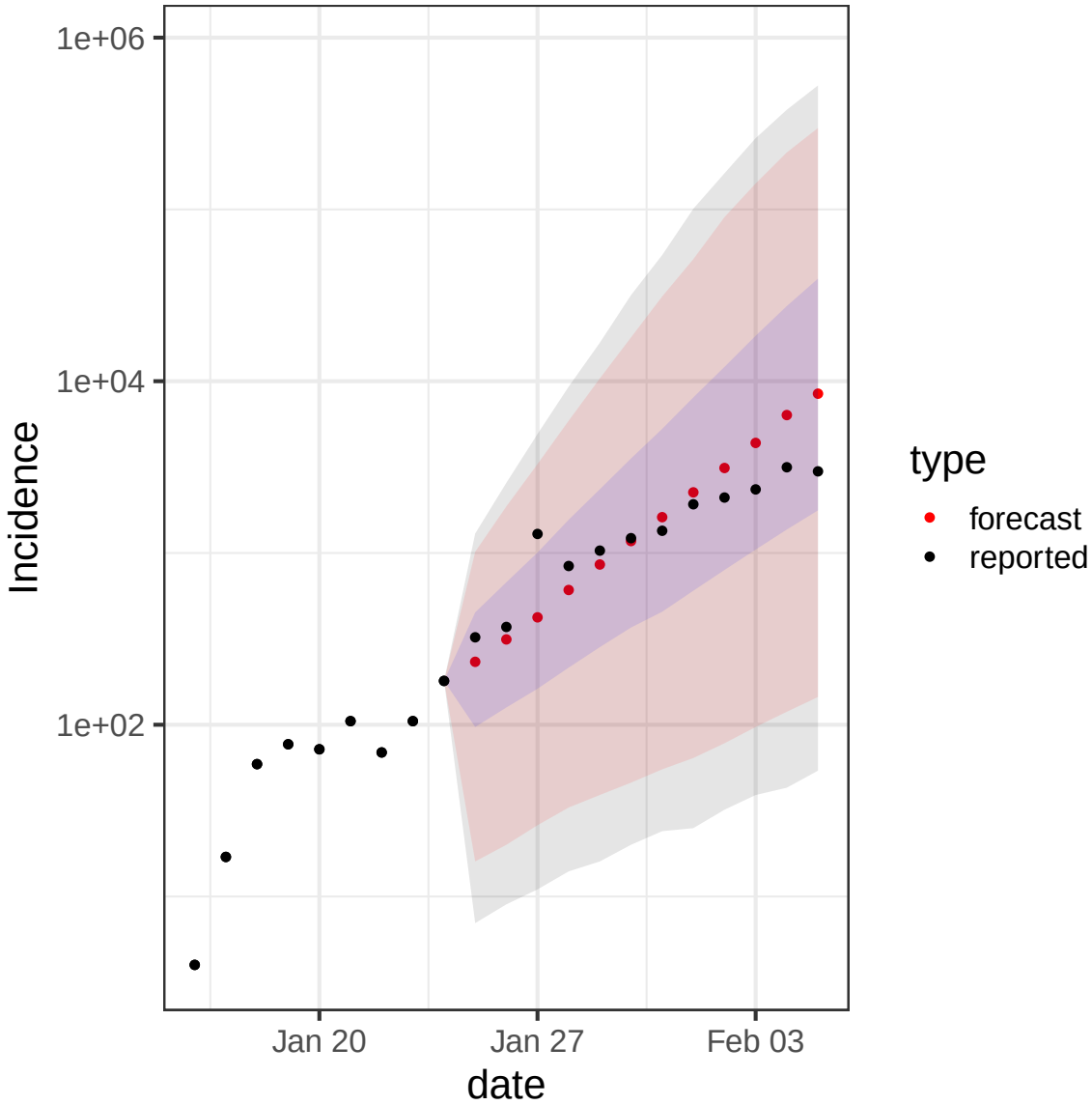
Individual-based implementation



Lessons

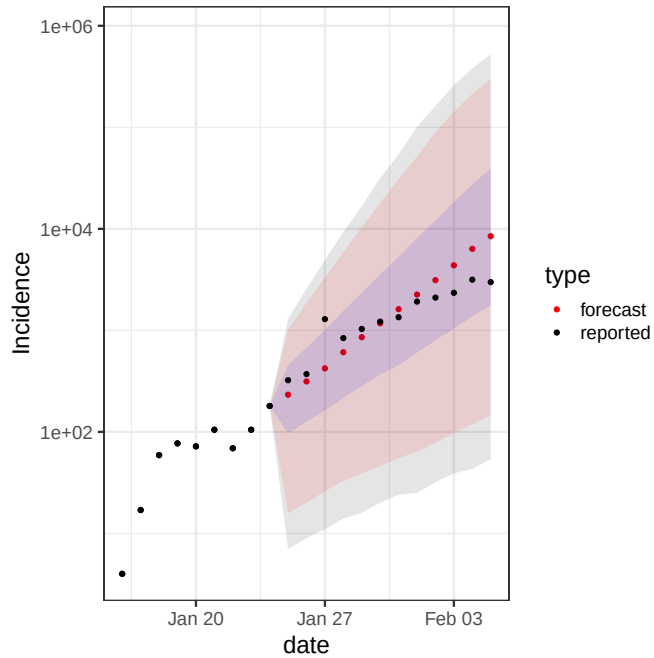
- Exponential invasion potential
- Tendency to oscillate
- Thresholds

Coronavirus forecasting



Coronavirus forecasting

- Counterfactual forecasting
- Relationship between forecasts and cases



Outline

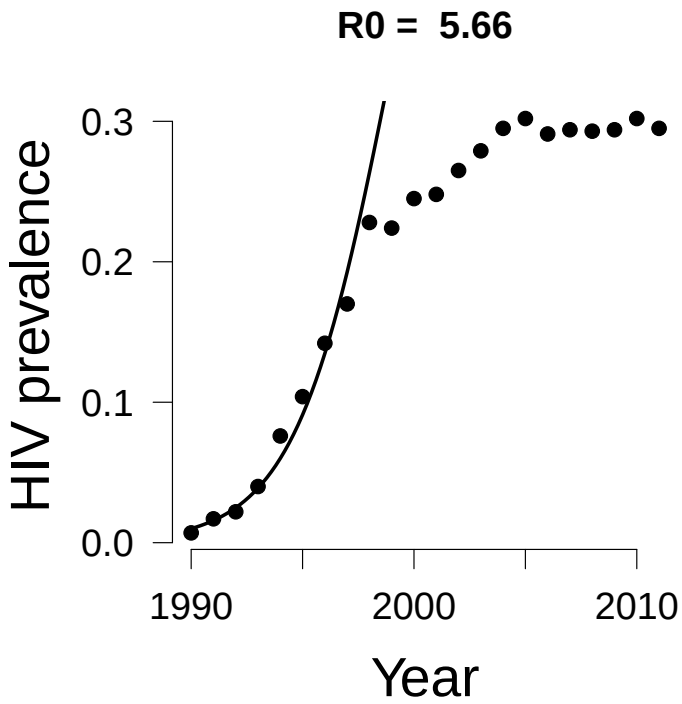
Speed and strength

- Current coronavirus modeling is largely focused on inferring $\mathcal{R}_0$.
  - The "basic reproductive number"
- Modelers are essentially trying to infer the *strength* of the epidemic
- By observing the *speed* of the epidemic
  - And making explicit or implicit assumptions about generation intervals

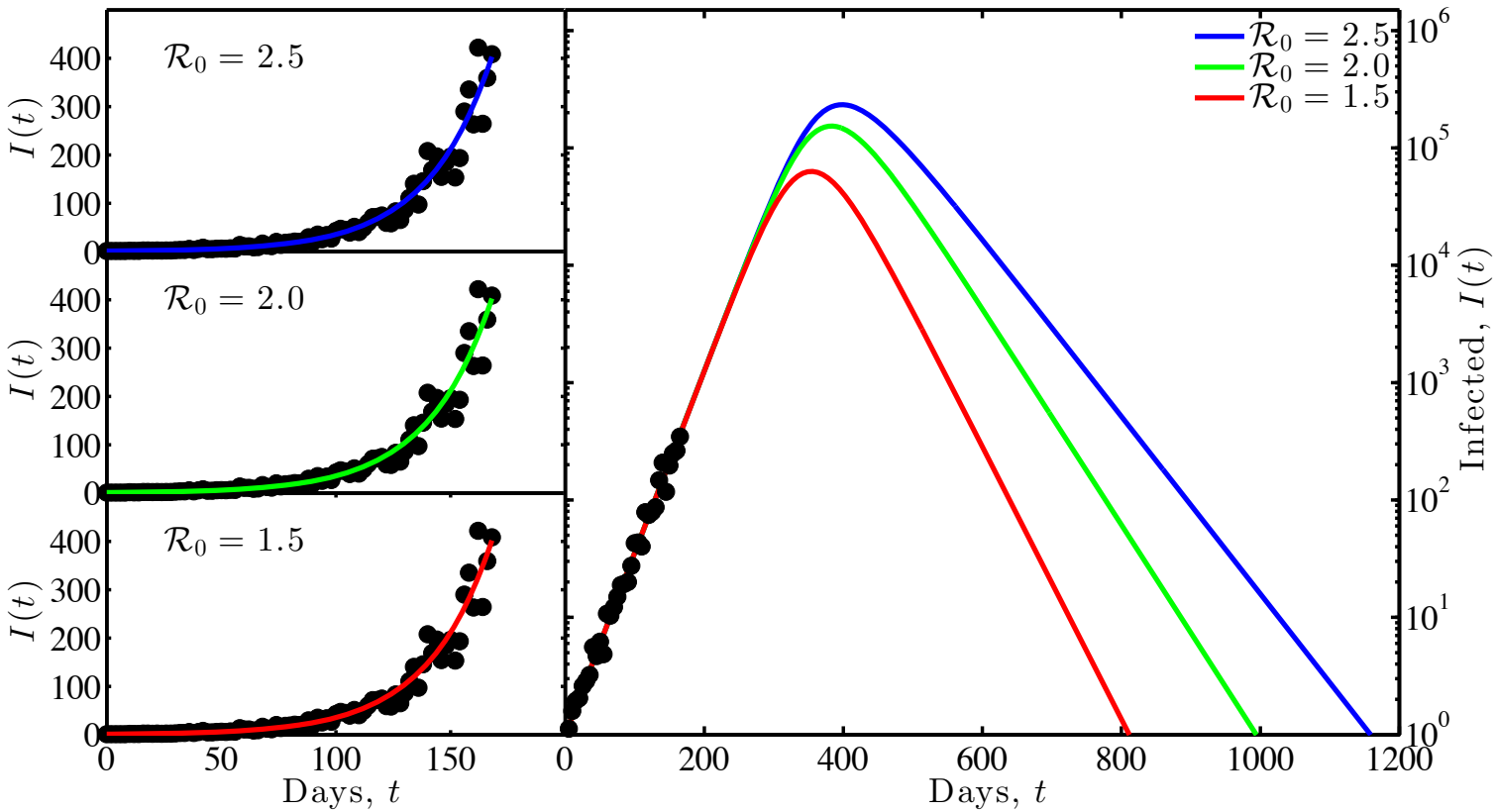
Outline

Epidemic

- Diseases have a tendency to grow exponentially at first
  - I infect three people, they each infect 3 people . . .
  - How fast does disease grow?
  - How quickly do we need to respond?



West African Ebola

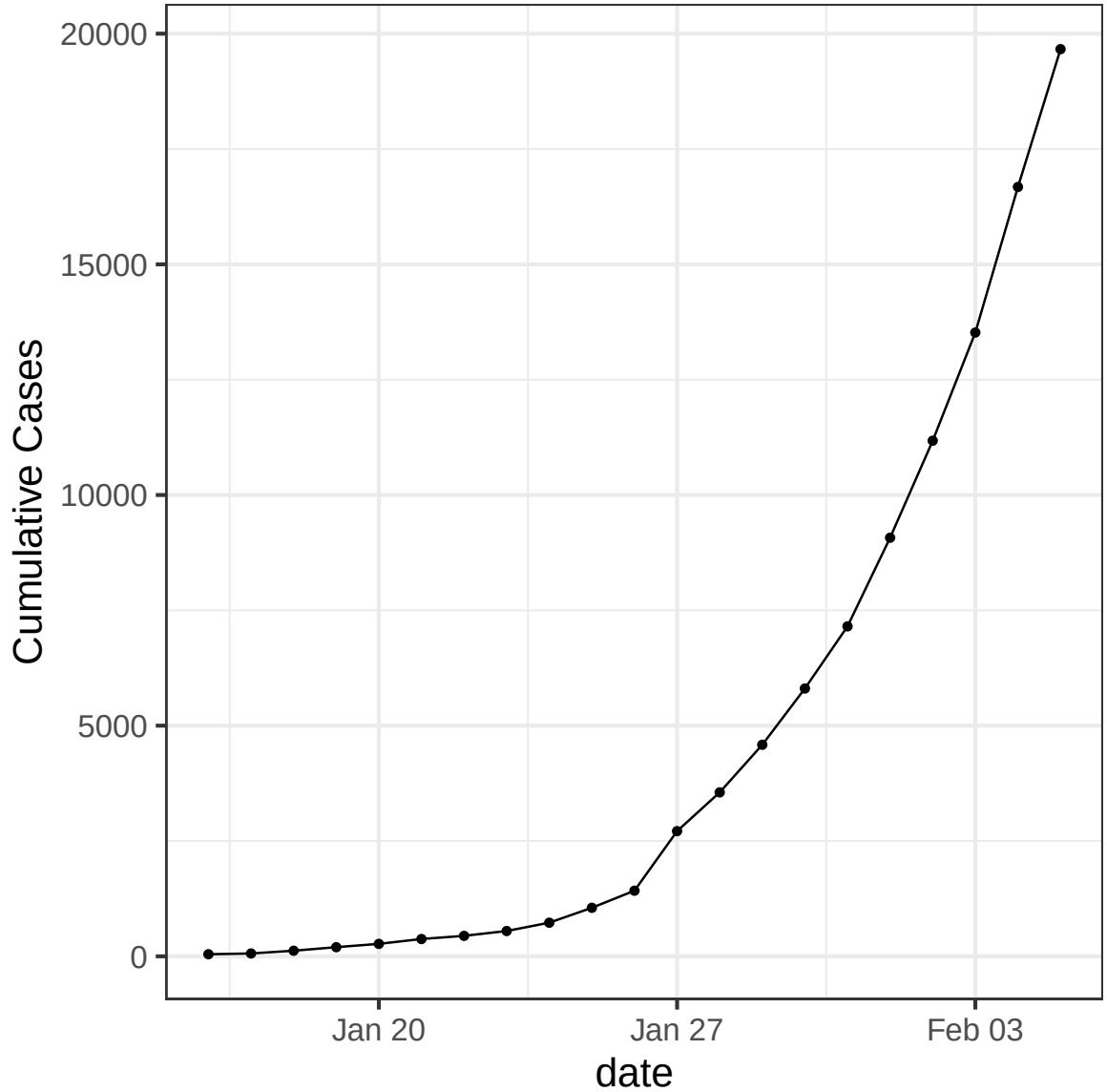


little r

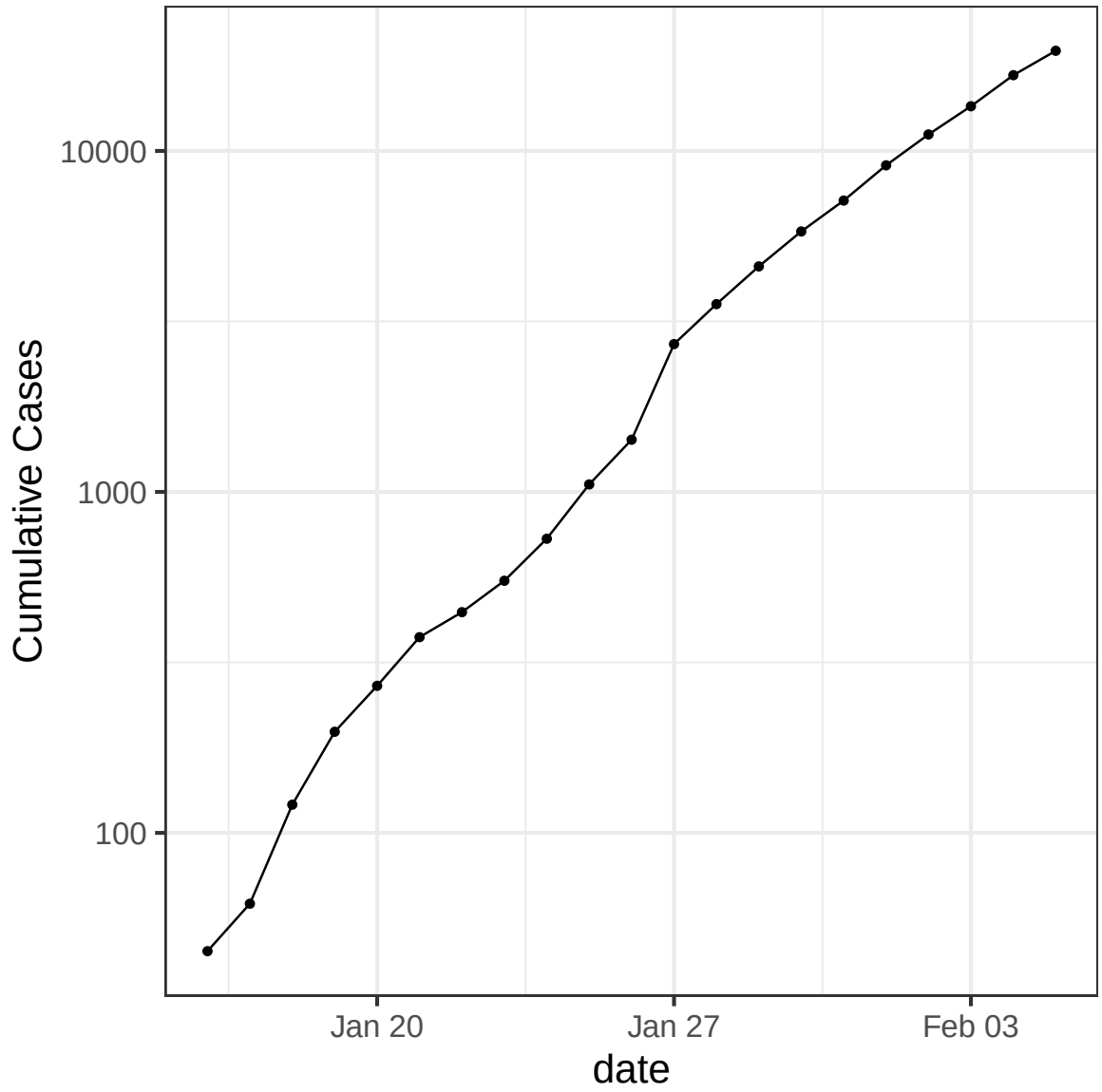
- We measure epidemic *speed* using little r:
  - *Units*: [1/time]
  - Disease increases like e^{rt}
- Time scale is $C = 1/r$
  - Ebola, $C \approx 1\text{month}$
  - HIV in SSA, $C \approx 18\text{month}$


CORNELL

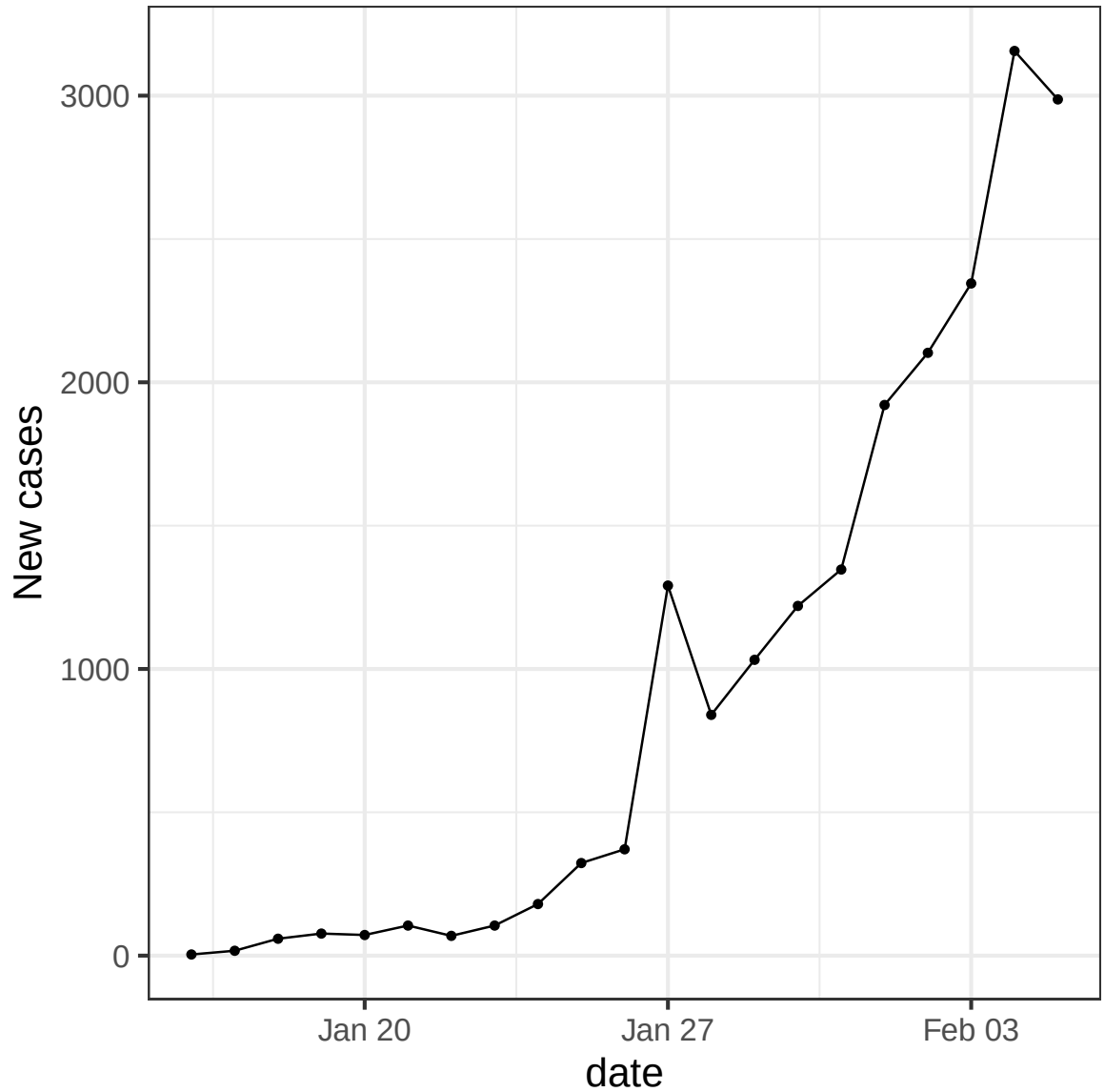
Coronavirus speed



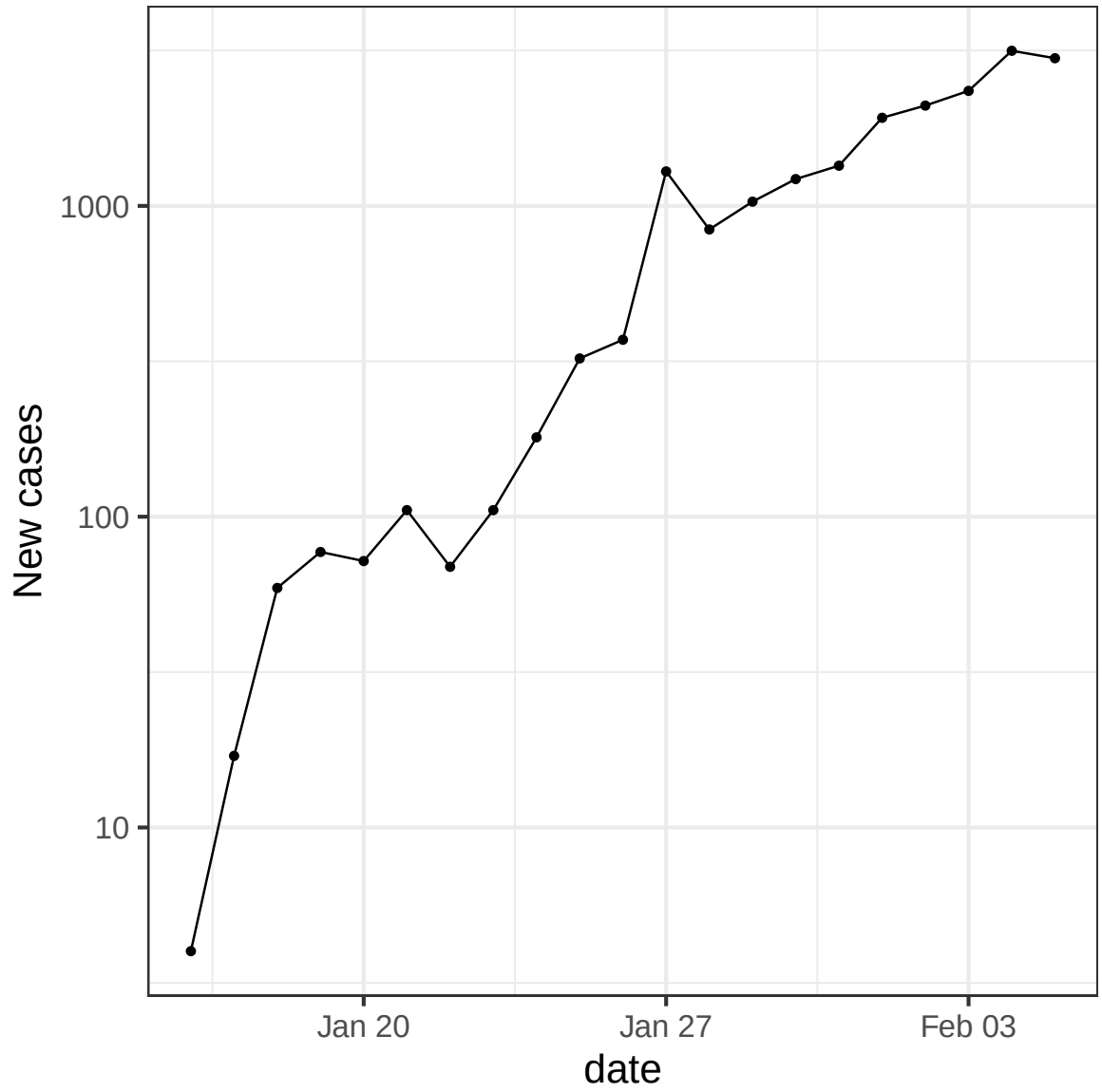
Coronavirus speed



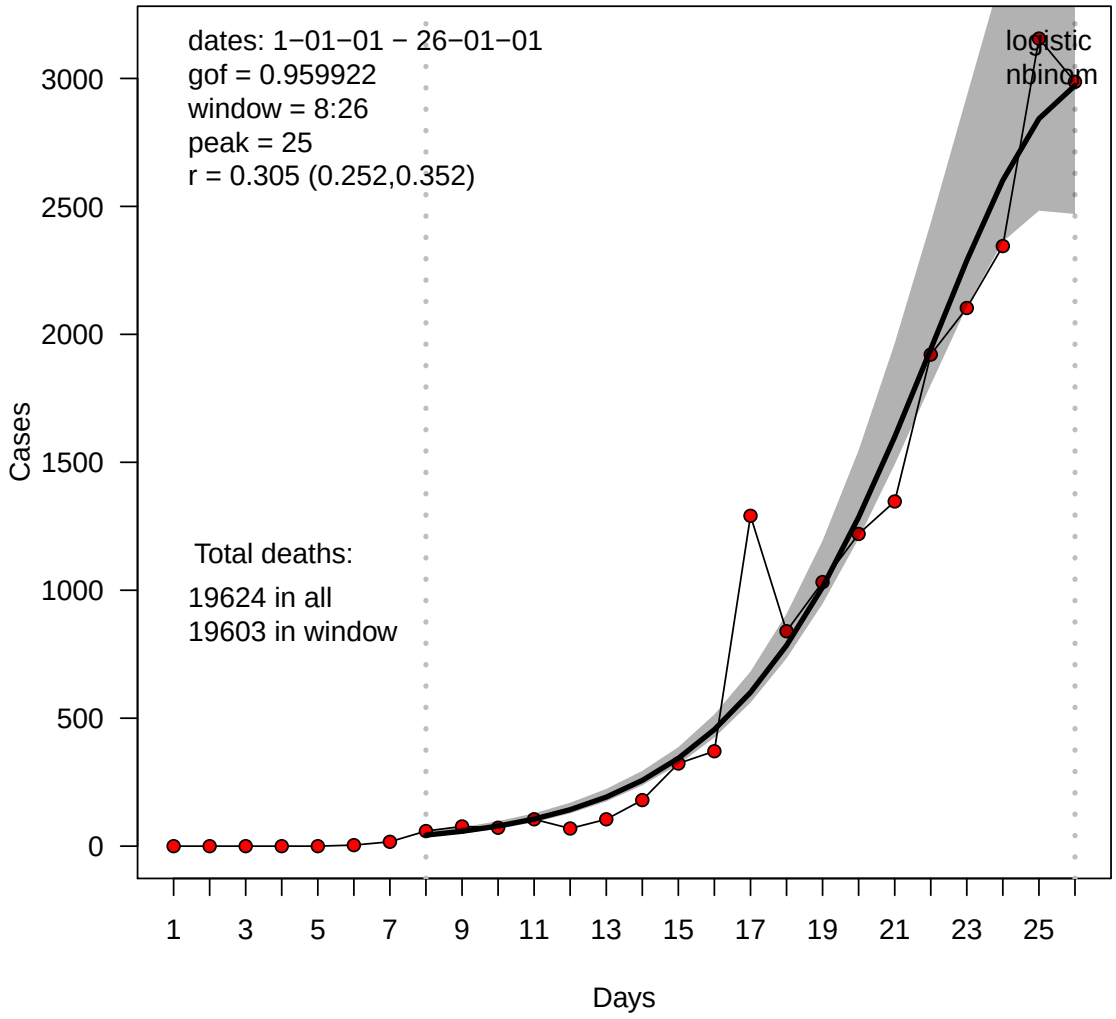
Coronavirus speed



Coronavirus speed



Coronavirus speed



Ma et al., 10.1007/s11538-013-9918-2

Outline

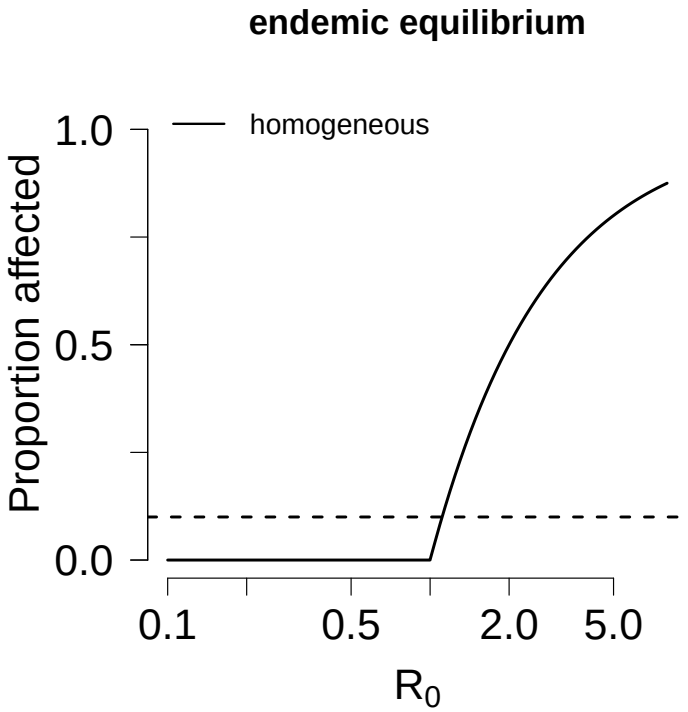
Epidemic strength

- We estimate epidemic strength using $\mathcal{R}$.
- $\mathcal{R}$ is the number of people who would be infected by an infectious individual *in a fully susceptible population.*
- $\mathcal{R} = \beta/\gamma = \beta D = (cp)D$
  - c: Contact Rate
  - p: Probability of transmission (infectivity)
  - D: Average duration of infection

Big Rx

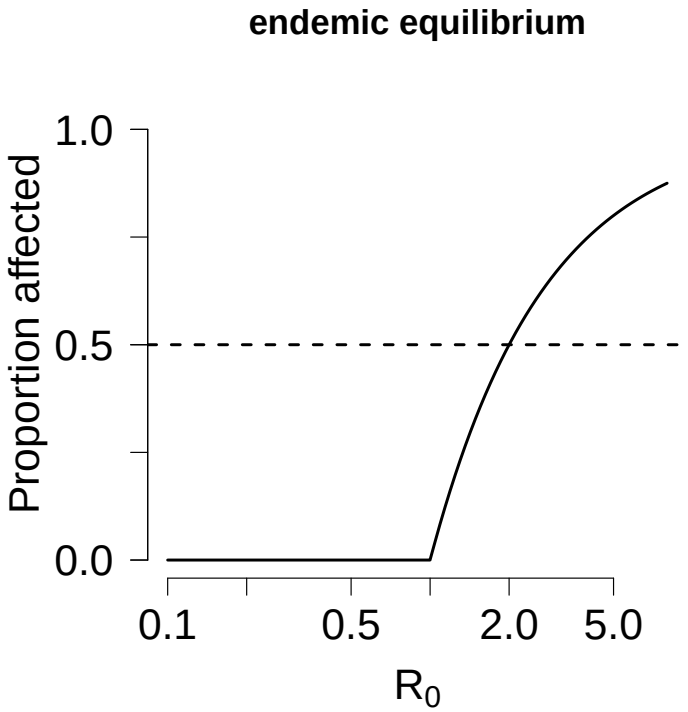
- A disease can invade a population if and only if $\mathcal{R} > 1$.
- In a purely "naive" population $\mathcal{R}$ is called $\mathcal{R}_0$

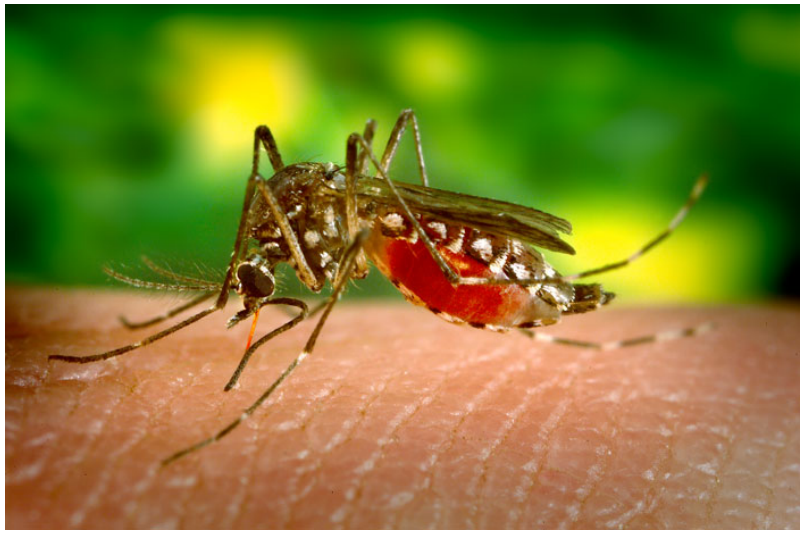
Homogeneous endemic curve



- Threshold value
- Sharp response to changes in factors underlying transmission
- Works – sometimes
  - Sometimes predicts unrealistic sensitivity

Yellow fever in Panama





Outline

Linking

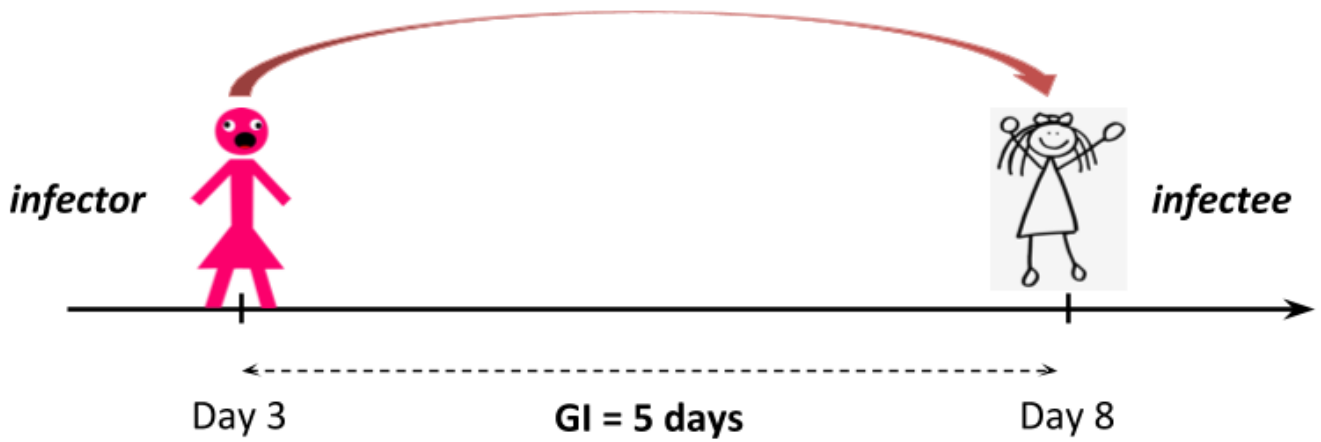
- We're very interested in the relationship between little r and $\mathcal{R}$.
- We might have good estimates of r and want to know more about equilibrium burden or expected outbreak size
  - e.g., West African Ebola outbreak, HIV in Africa
- Or we might have good estimates of $\mathcal{R}$ and want to know how fast disease would spread if introduced to a new population
  - Measles, influenza
- Much coronavirus modeling has explicitly or implicitly estimated $\mathcal{R}$ from r.

How long is a disease generation? (present)

Definition

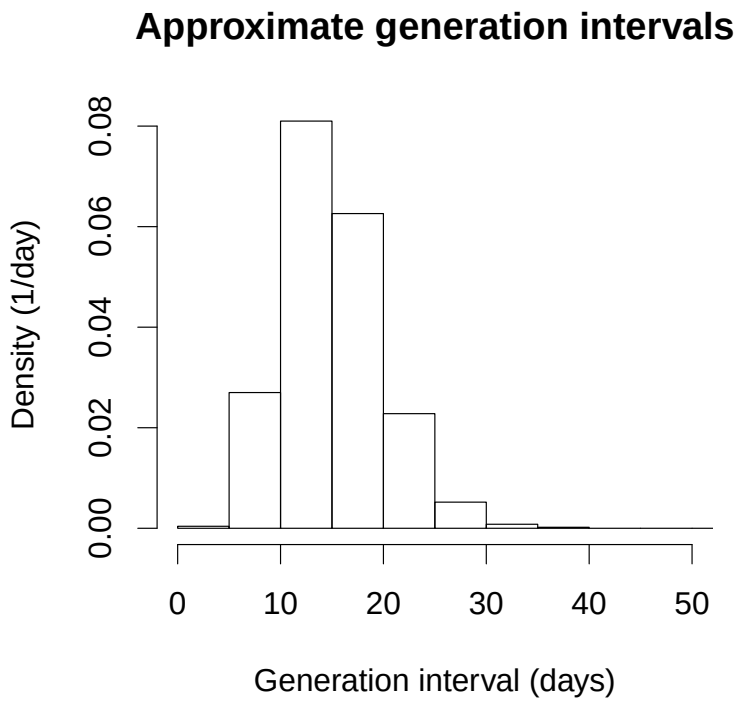
Generation Interval:

Interval between the time that an individual is infected by an infector and the time this infector was infected

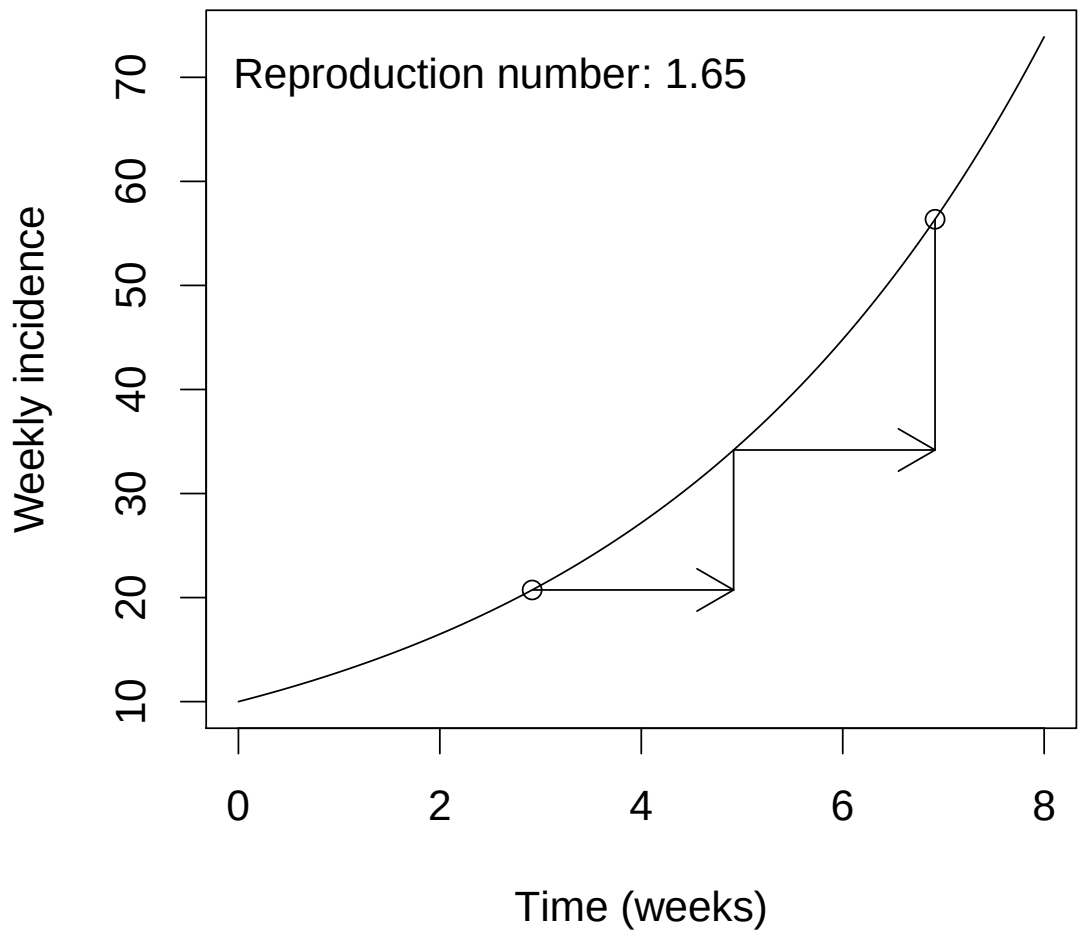


Generation intervals

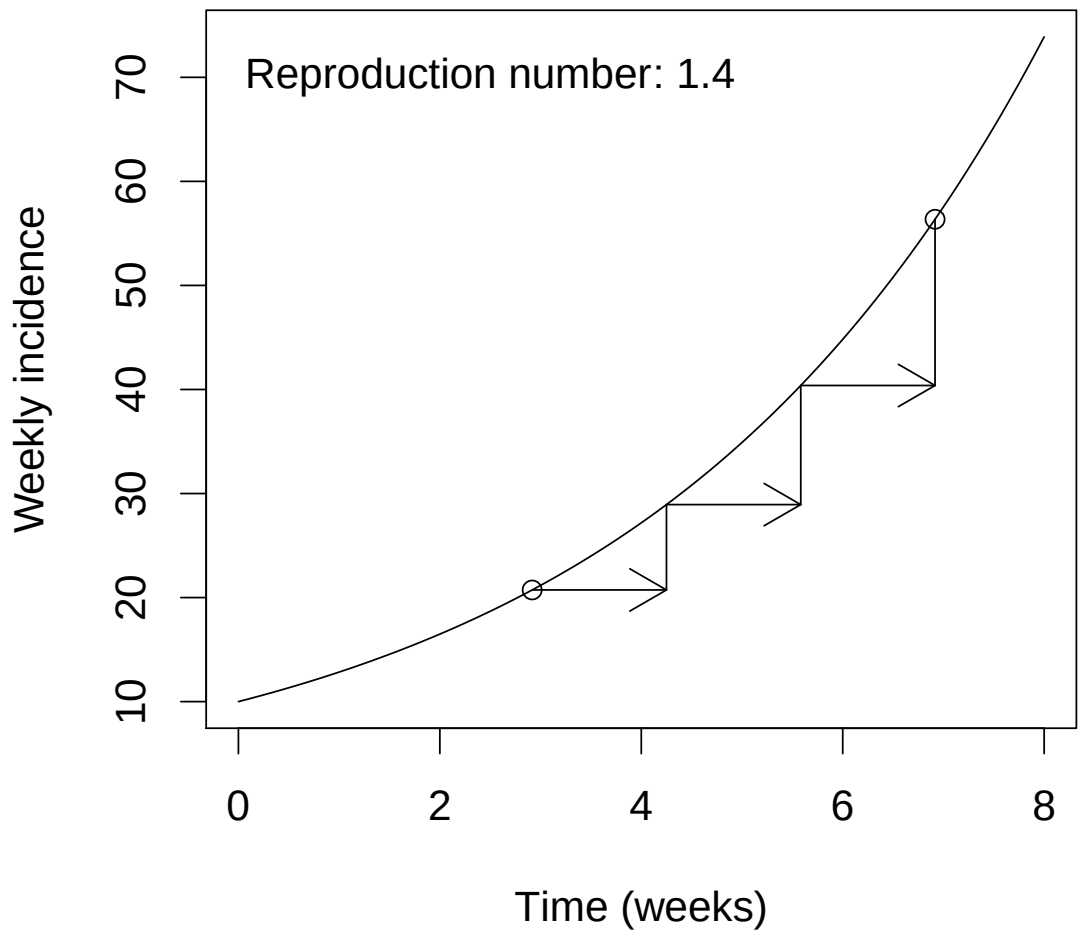
- The generation distribution measures the time between generations of the disease
  - Interval between "index" infection and resulting infection
- Generation intervals provide the link between $\mathcal{R}$ and r



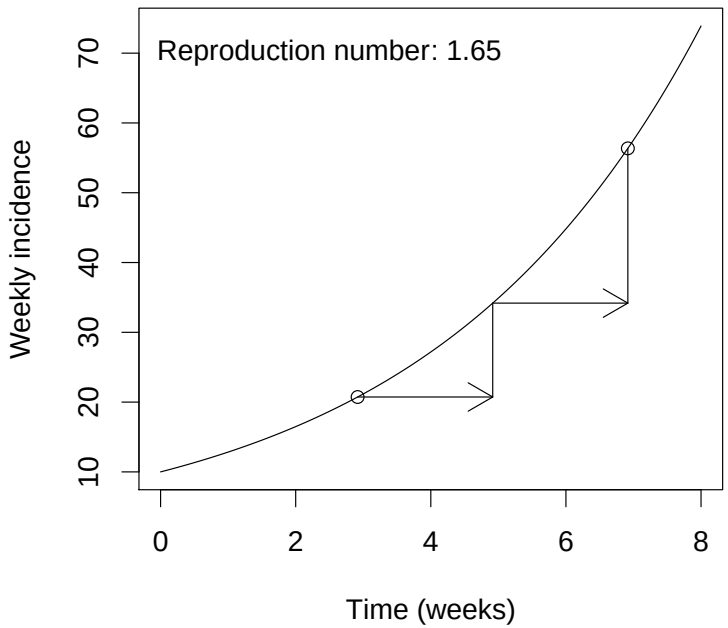
Generations and $\mathcal{R}$

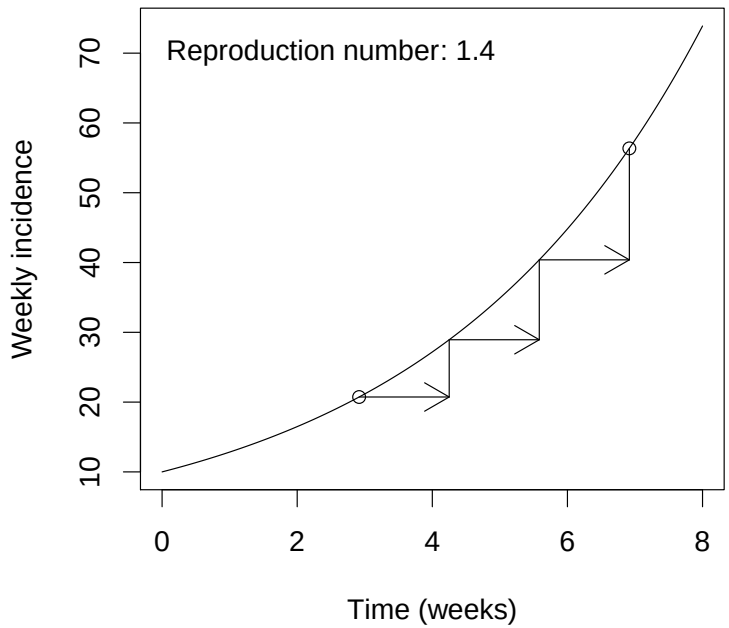


Generations and $\mathcal{R}$



Generations and $\mathcal{R}$





Example: Post-death transmission and safe burial

- How much Ebola spread occurs before vs. after death
- Highly context dependent
  - Funeral practices, disease knowledge
- *Weitz and Dushoff Scientific Reports 5:8751.*

Conditional effect of generation time

- *Given* the reproductive number $\mathcal{R}$
  - faster generation time G means higher r
  - More danger
- *Given* r
  - faster generation time G means *smaller* $\mathcal{R}$
  - Less danger

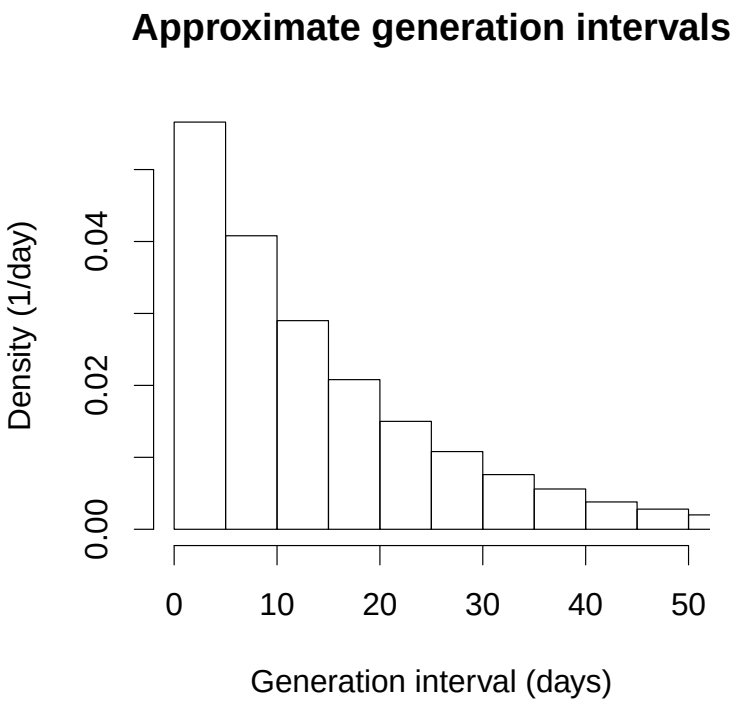
Linking framework

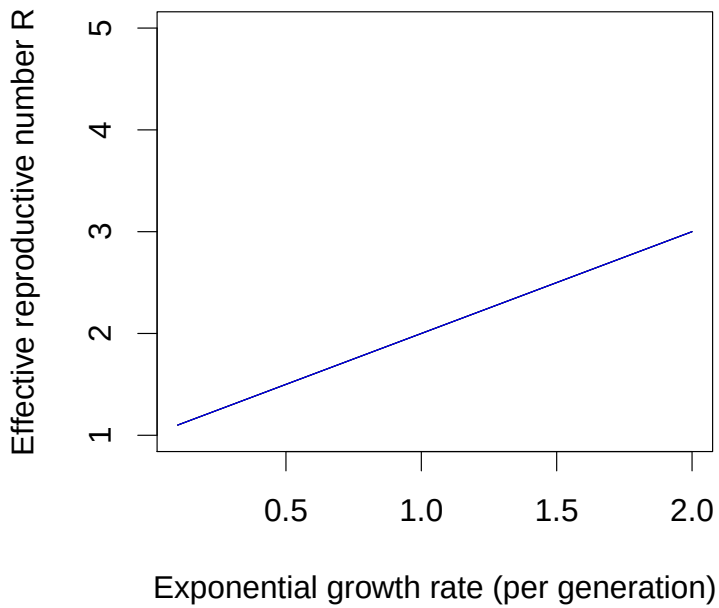
- Epidemic speed r is a *product*:
  - (something to do with) generation speed
  - $\times$ (something to do with) epidemic strength
- Epidemic strength $\mathcal{R}$ is therefore (approximately) a *quotient*
  - Epidemic speed
  - $\div$ (something to do with) generation speed

Effect of variation in generation time

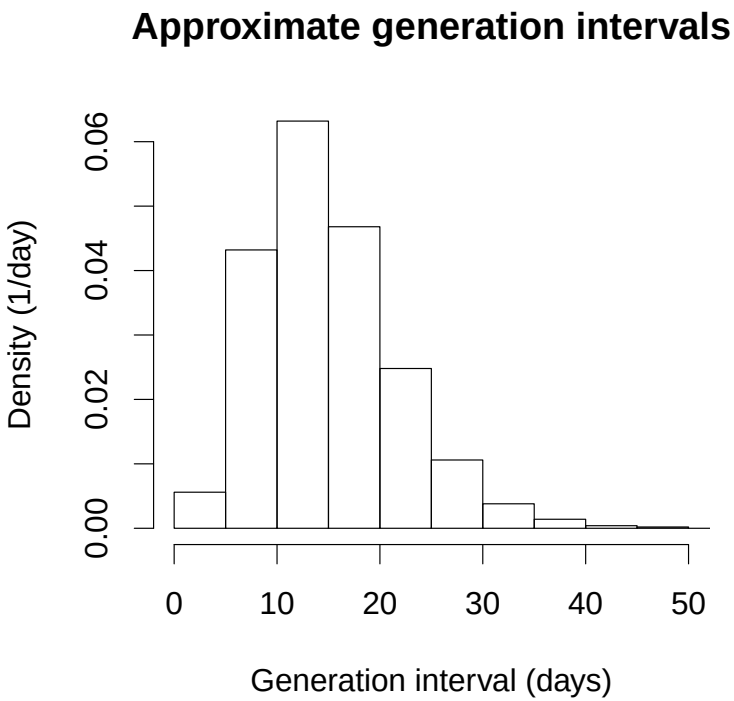
- For a given value of mean generation time, what happens if we have more *variation* in generation time?
  - Events that happen earlier than expected compound through time
  - If $\mathcal{R}$ is fixed then r will be higher $\Longrightarrow$
  - If r is fixed then $\mathcal{R}$ will be lower

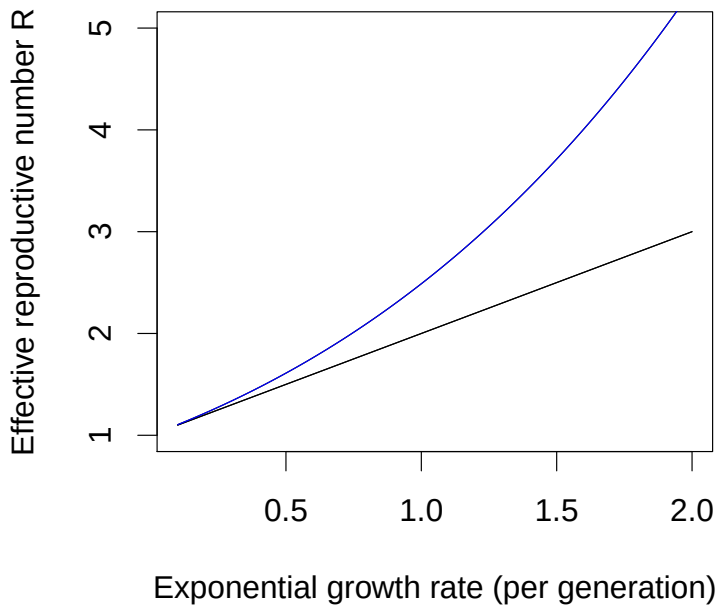
Approximations



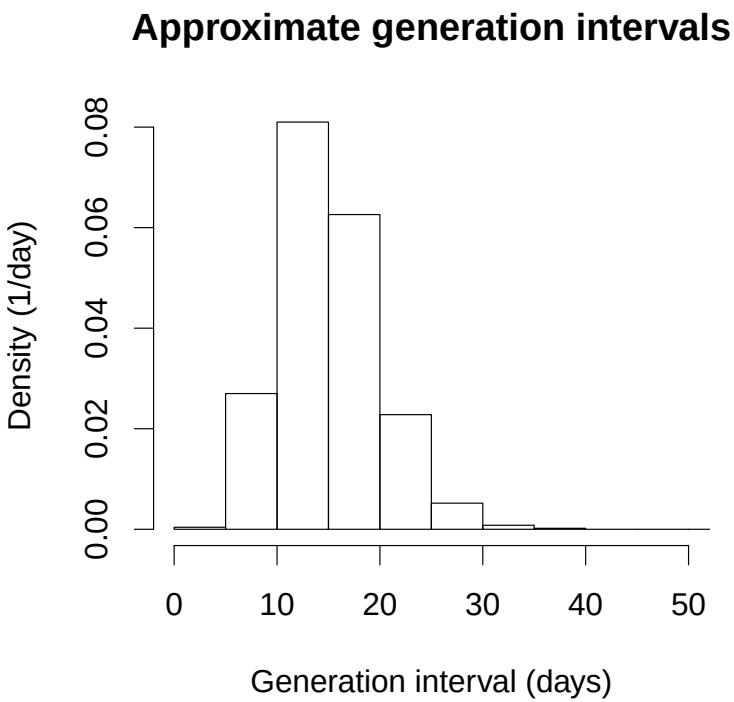


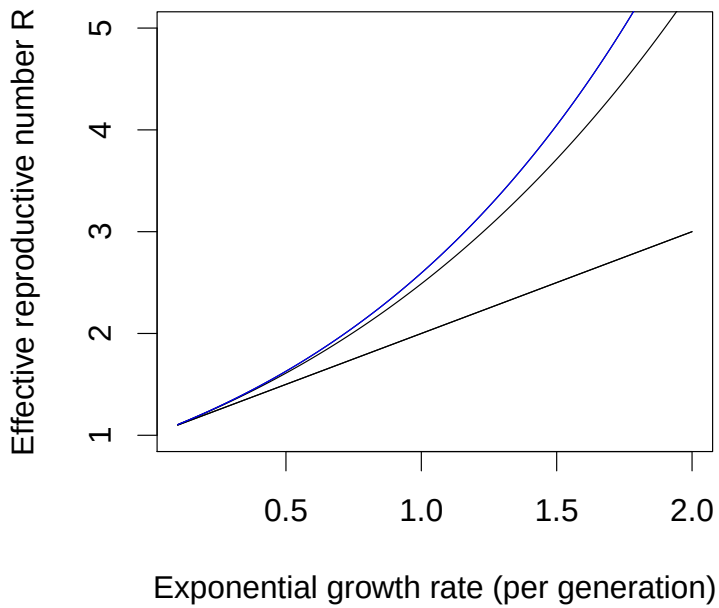
Moment approximation





Moment approximation





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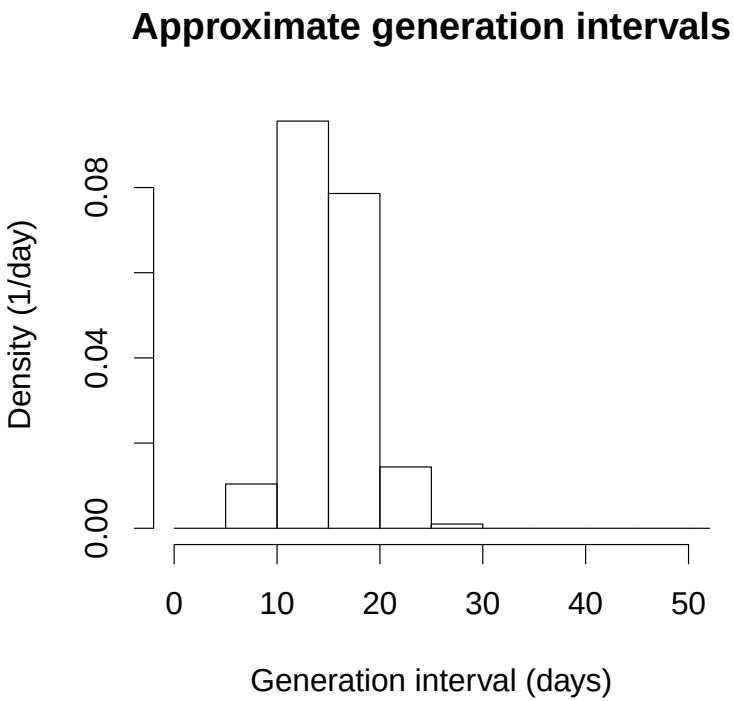
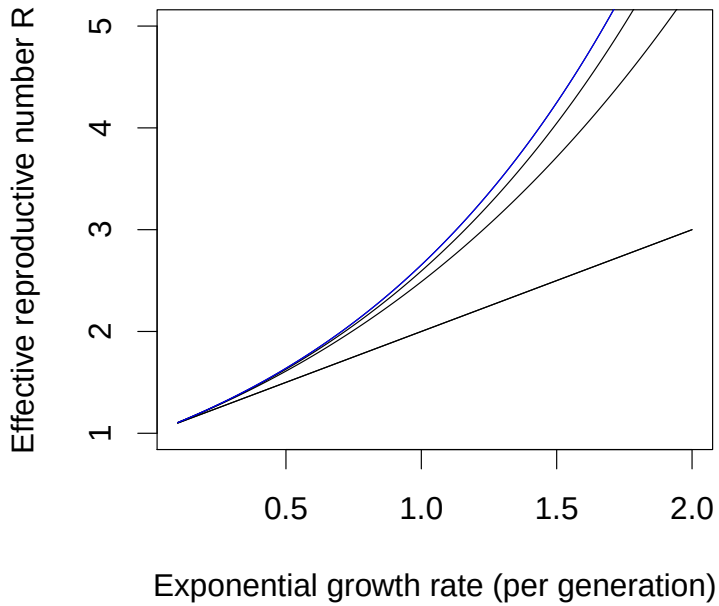




Approximation framework

- $\mathcal{R} \approx X(r\bar{G}; 1/\kappa)$
  - κ is the dispersion parameter of the generation-interval distribution (measures the effective amount of variation
- X is the compound-interest function
  - $\mathcal{R} \approx 1 + r\bar{G}$ when variation is large
  - $\mathcal{R} \approx \exp(r\bar{G})$ when variation is small
- Key quantity is $r\bar{G}$: the relative length of the generation interval compared to the characteristic time scale of spread

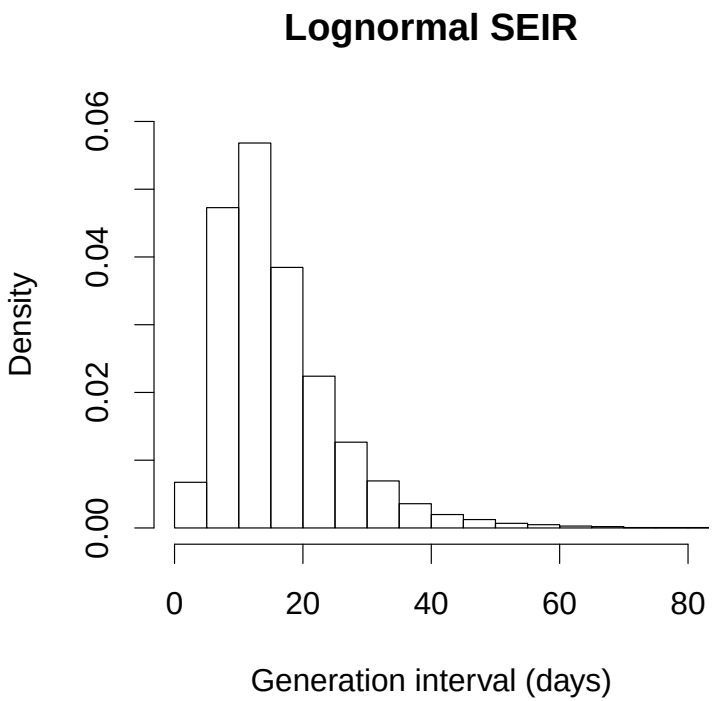
Intuition

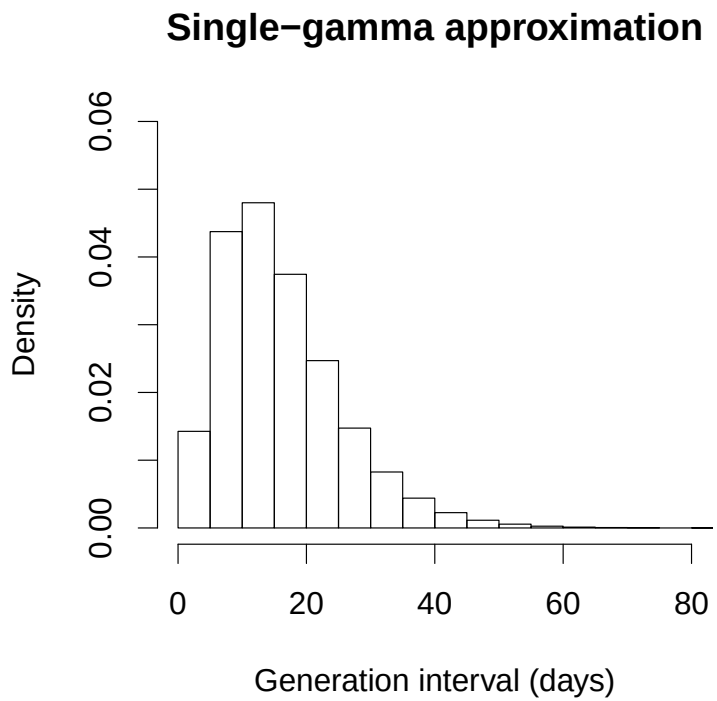
- Longer generation times mean less speed
  - $\Longrightarrow$ more strength, when speed is fixed
- What about more variation in generation times?
  - More action (both before and after the mean time)
  - But what happens early is more important in a growing system
- More variation means more speed
  - $\Longrightarrow$ less strength, when speed is fixed

Test the approximations

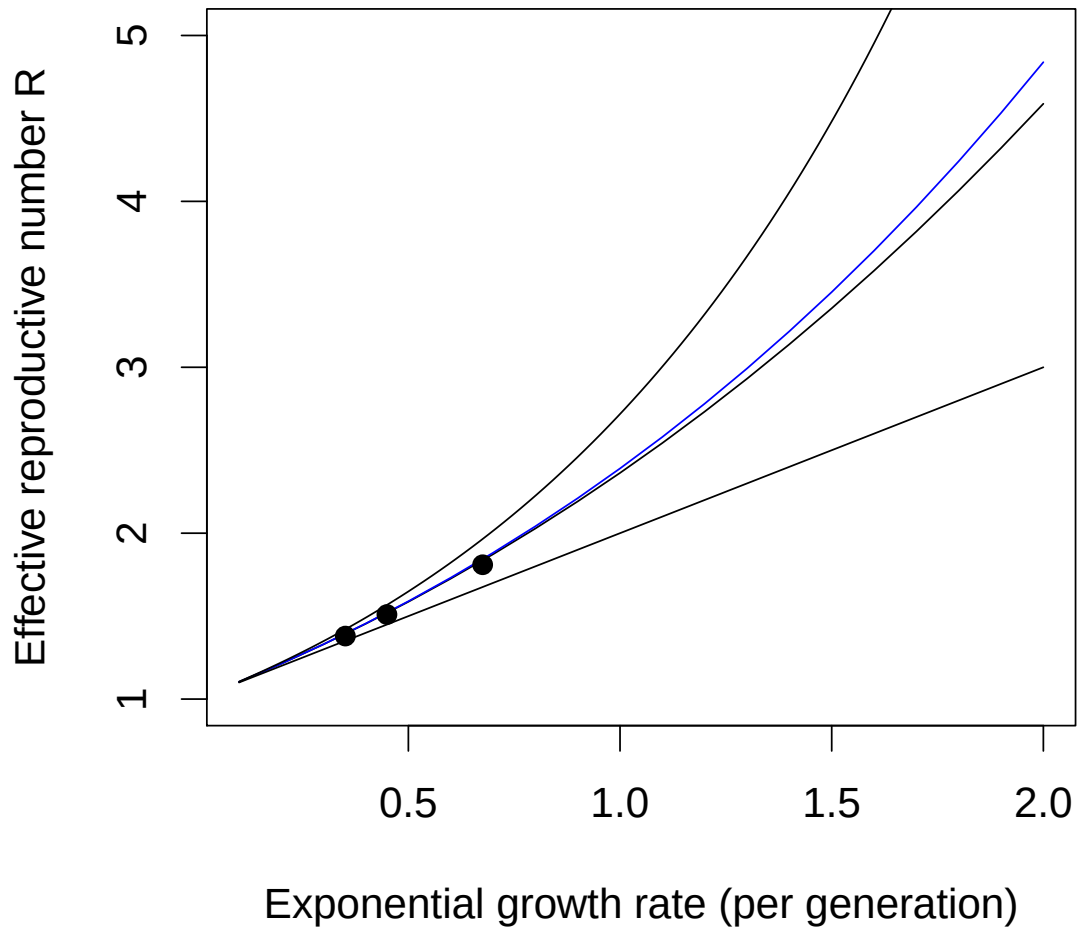
- Simulate realistic generation intervals for various diseases
- Compare approximate $r\mathcal{R}$ relationship with known exact relationship
  - Known because we are testing ourselves with simulated data

Ebola distribution

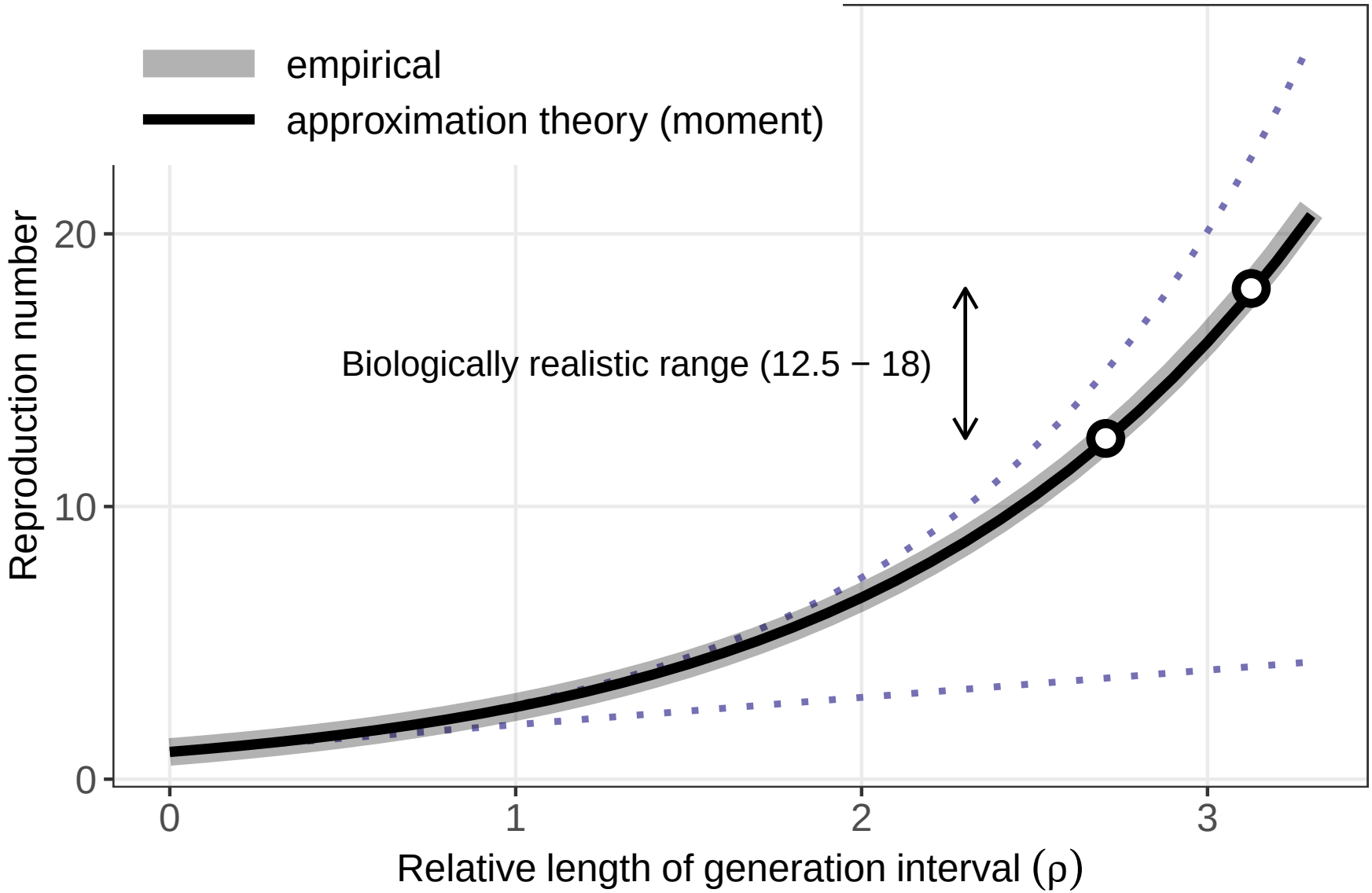




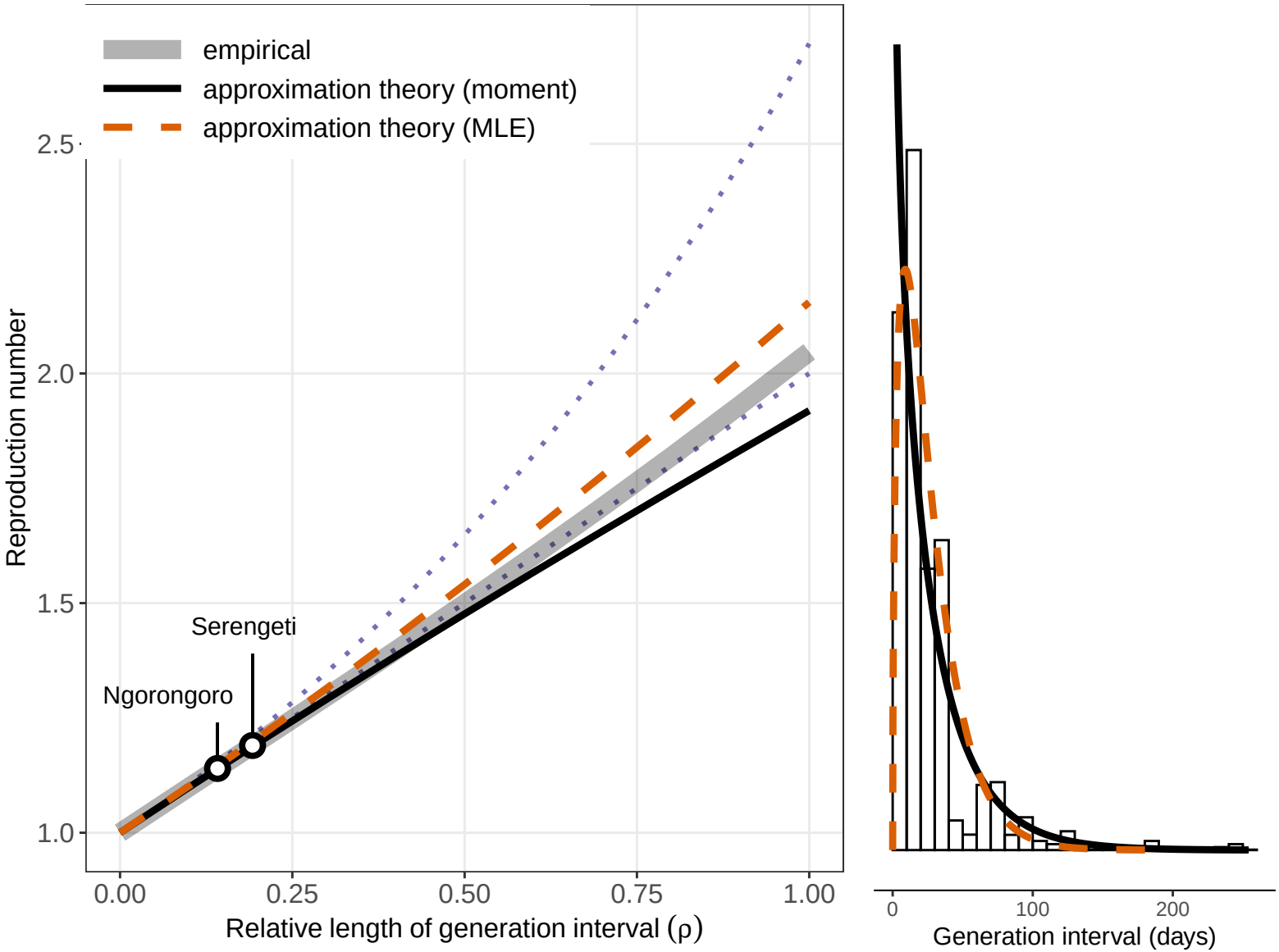
Ebola curve


Effective reproductive number R
1
2
3
4
5
0.5
1.0
1.5
2.0
Exponential growth rate (per generation)

Measles curve

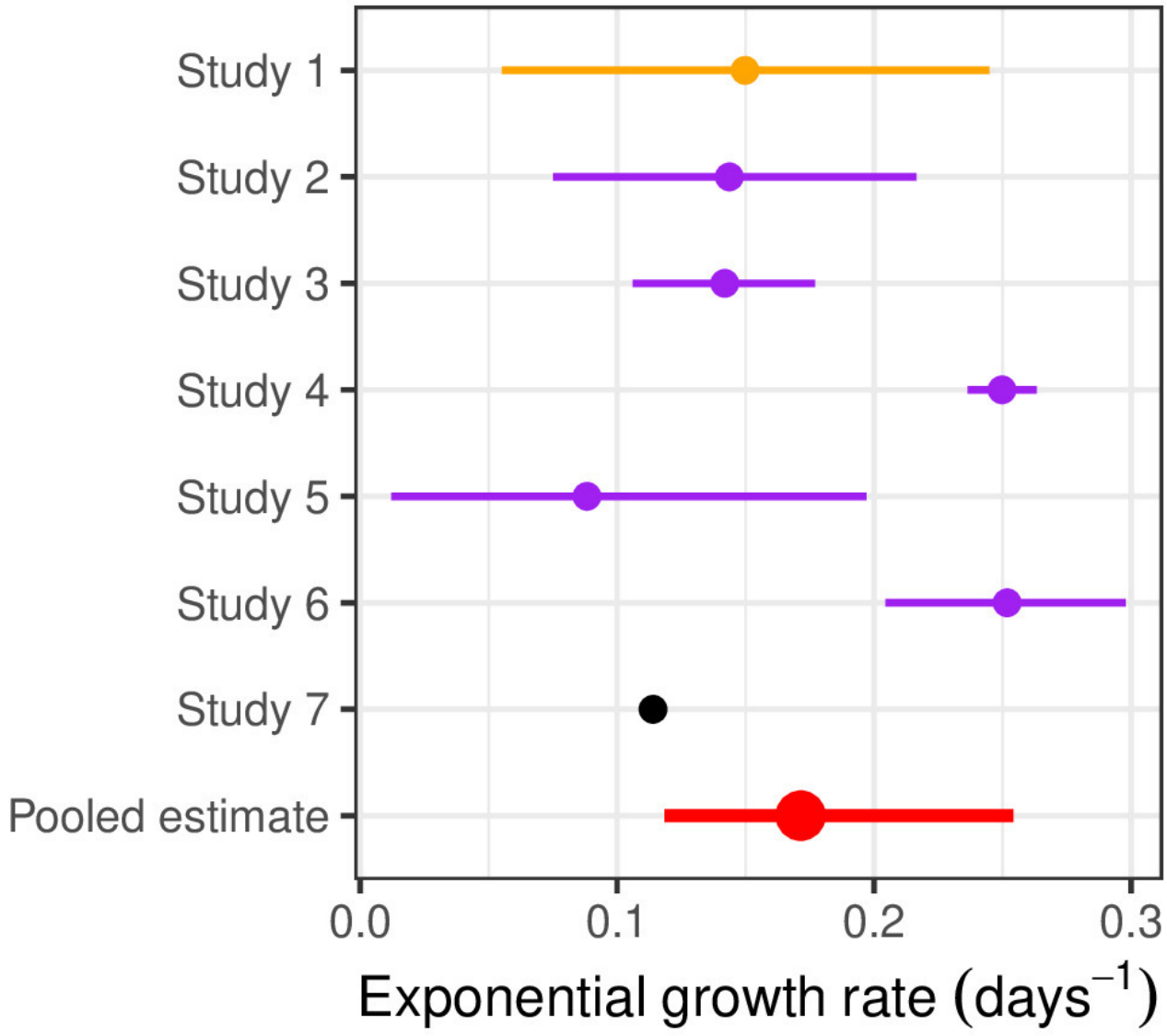


Rabies curve



Outline

Assumptions



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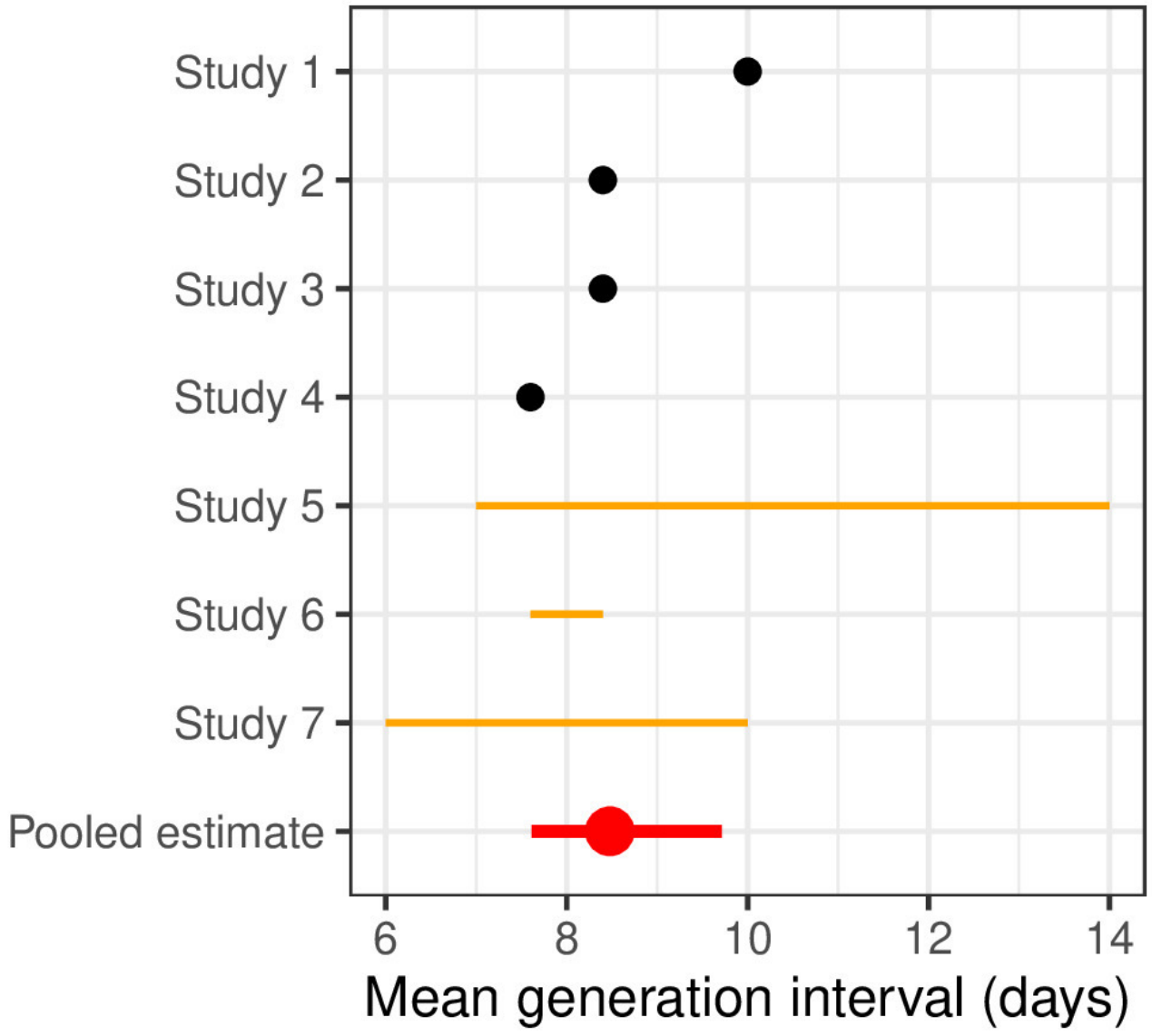
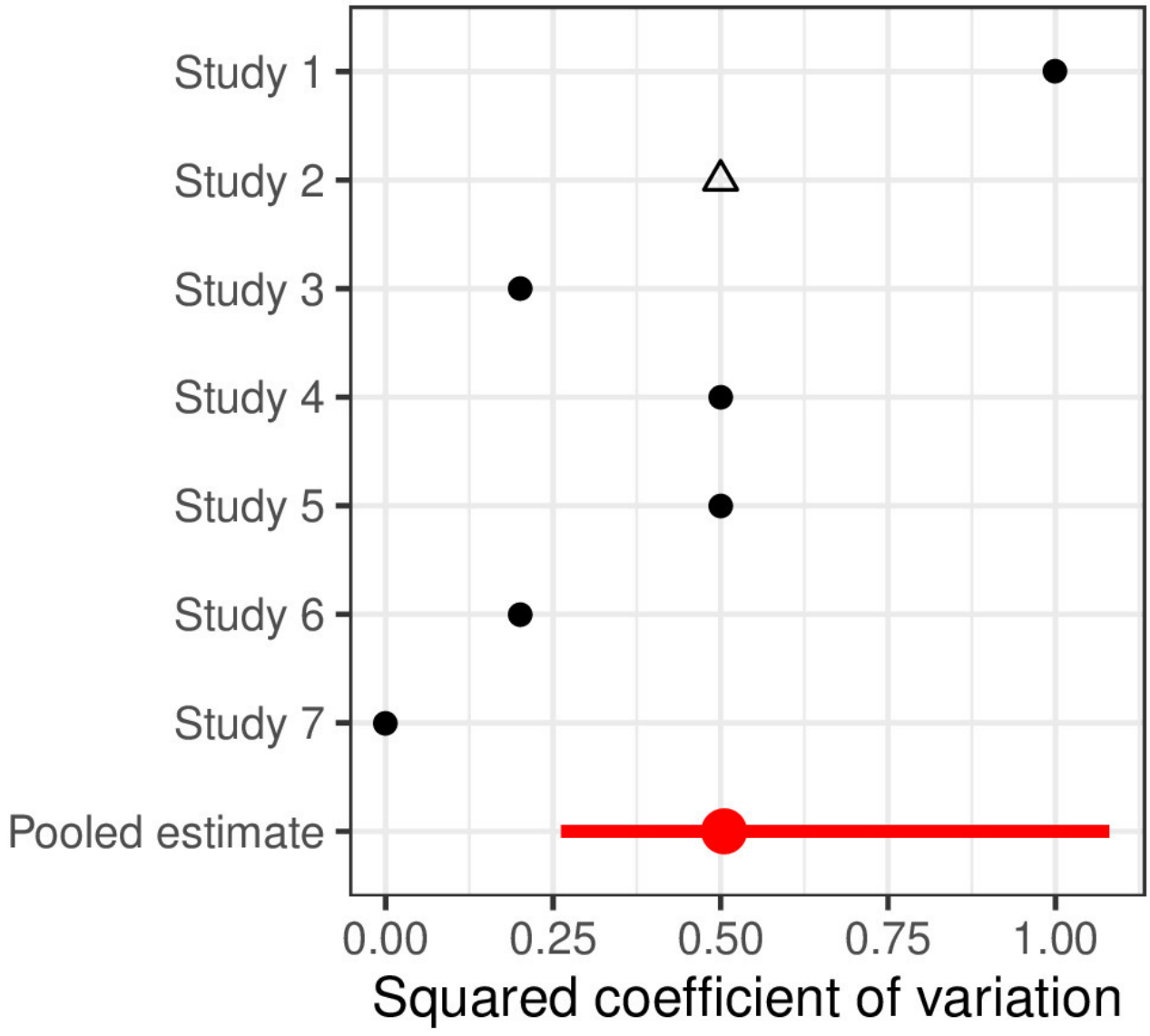
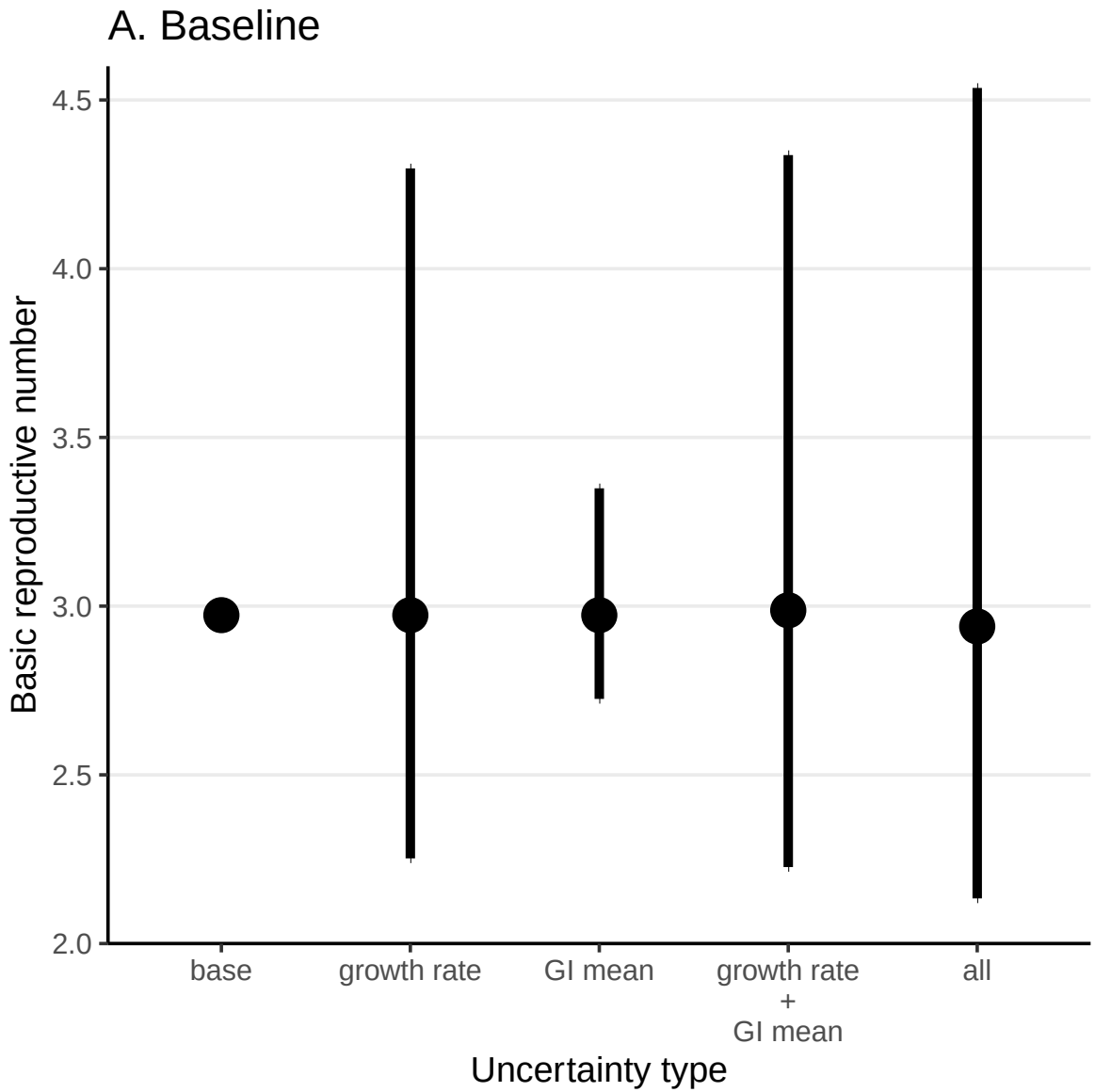


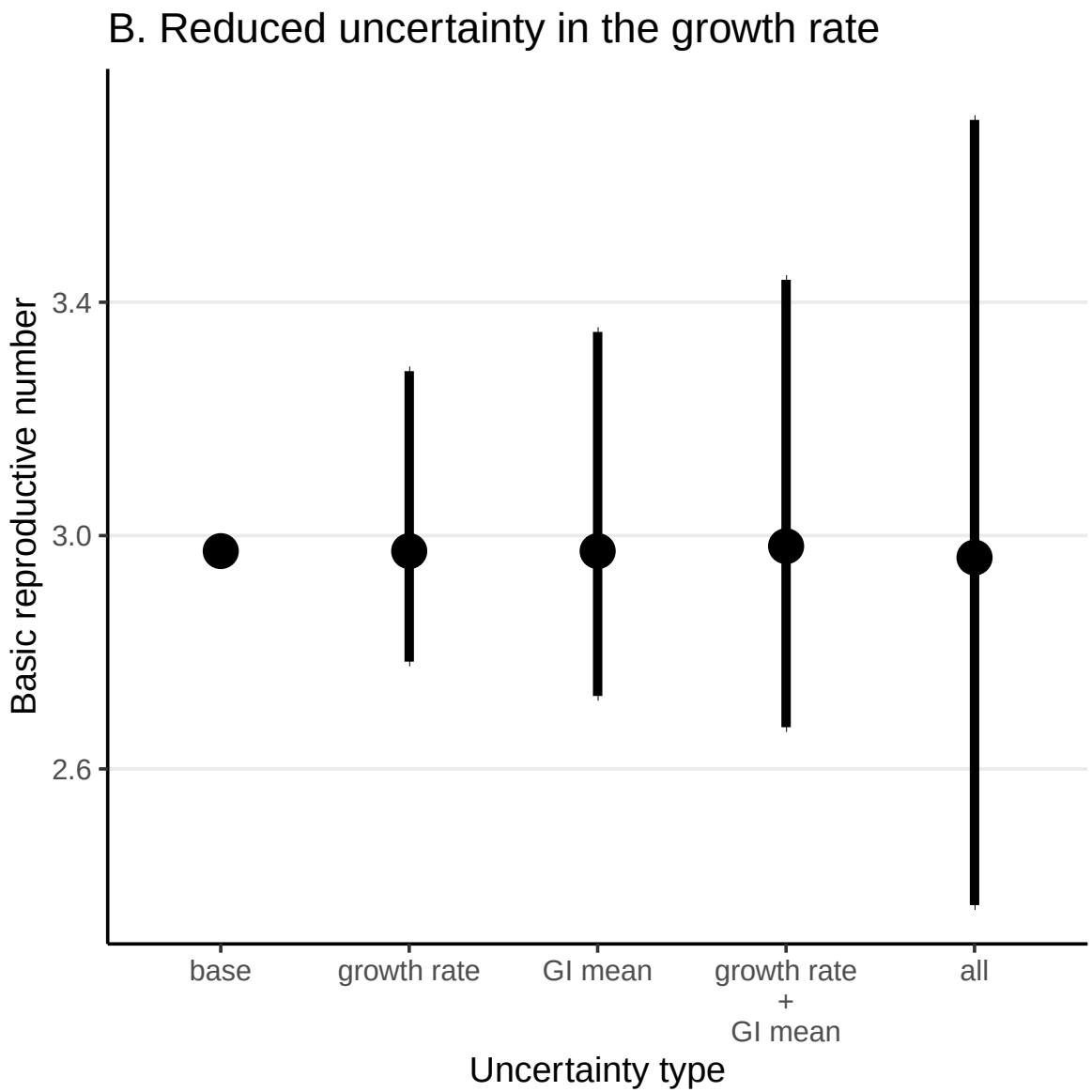
Assumptions



Propagating error



Propagating error



Outline

A false dichotomy

- Why are people scrambling to estimate $\mathcal{R}$ and mostly ignoring r?
  - History
  - Modelers gotta model

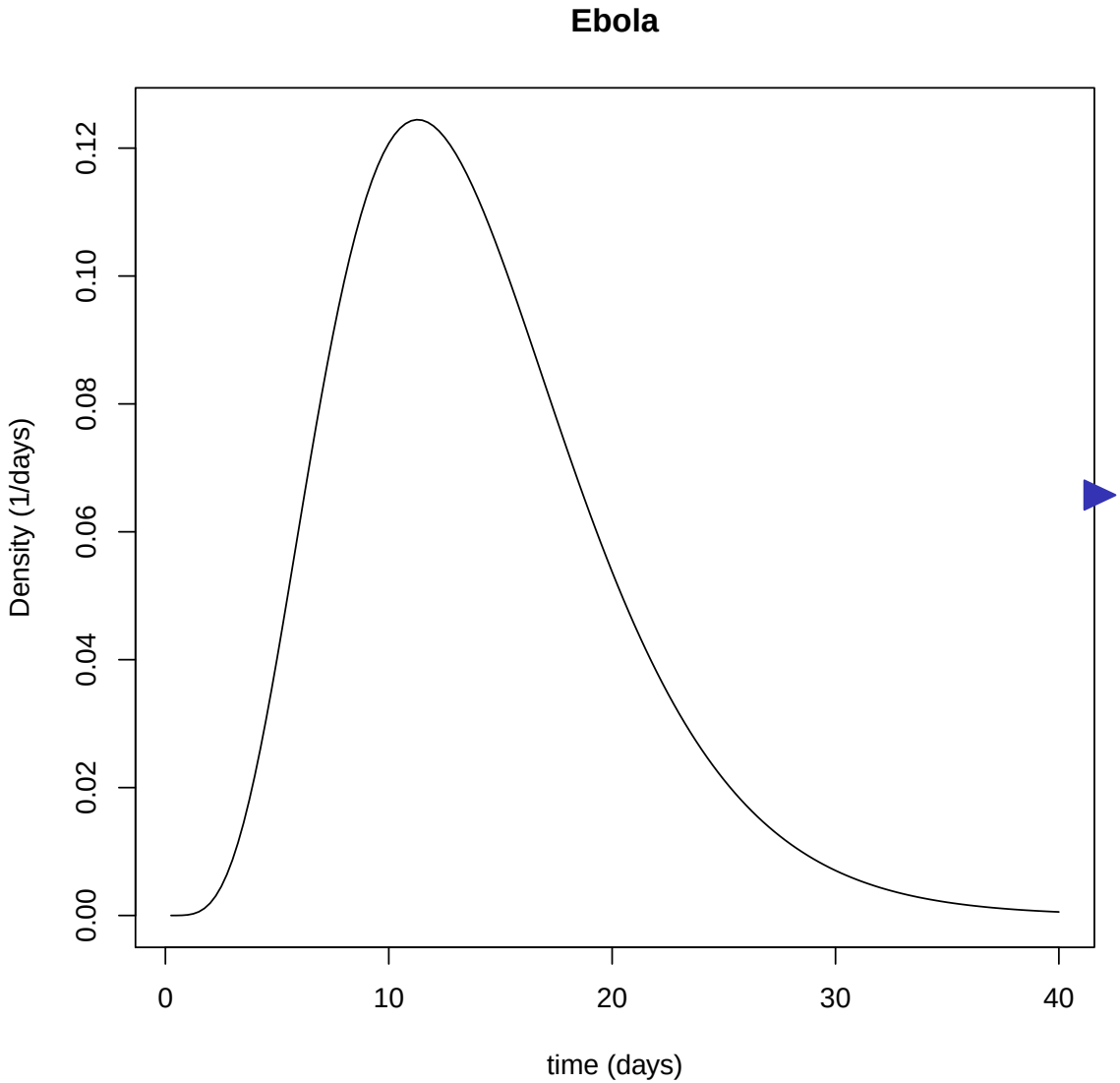
The strength paradigm

- $\mathcal{R} > 1$ is a threshold
- If we can reduce transmission by a constant *factor* of $\theta > \mathcal{R}$, disease can be controlled
- In general, we can define θ as a (harmonic) mean of the reduction factor over the course of an infection
  - weighted by the *intrinsic* generation interval
- Epidemic is controlled if $\theta > \mathcal{R}$
- More useful in long term (tells us about final size, equilibrium)

The speed paradigm

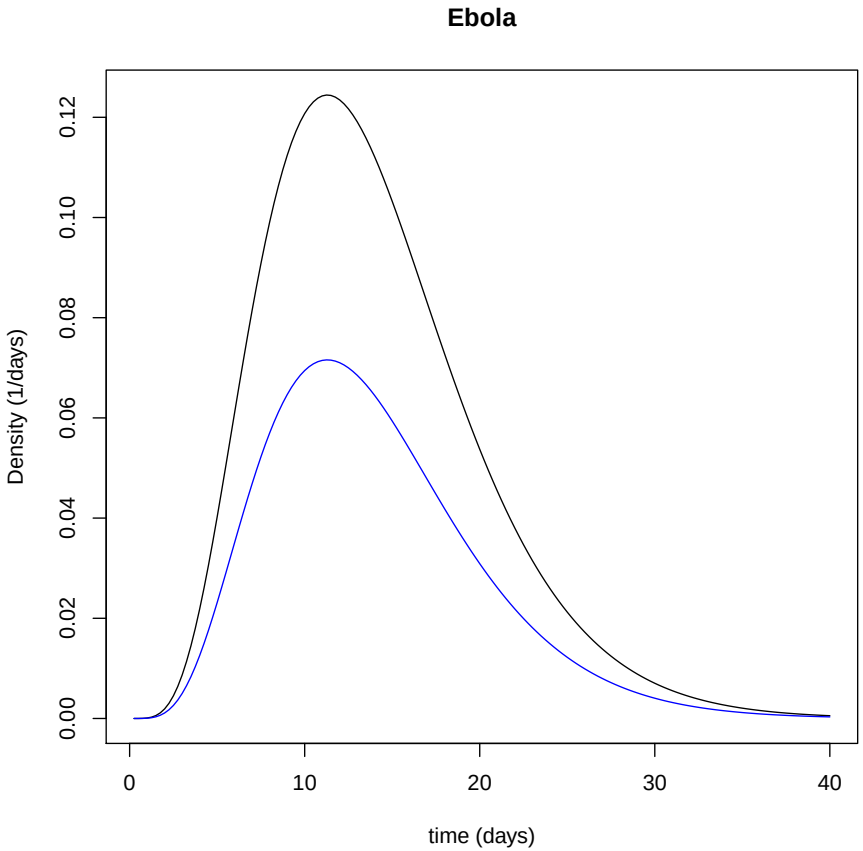
- $r > 0$ is a threshold
- If we can reduce transmission at a constant *hazard rate* of $\phi > r$, disease can be controlled
- In general, we can define ϕ as a (very weird) mean of the reduction factor over the course of an infection
  - weighted by the *backward* generation interval
- Epidemic is controlled if $\phi > r$
- More useful in short term (tells us about, um, speed)

Epidemic strength (present)



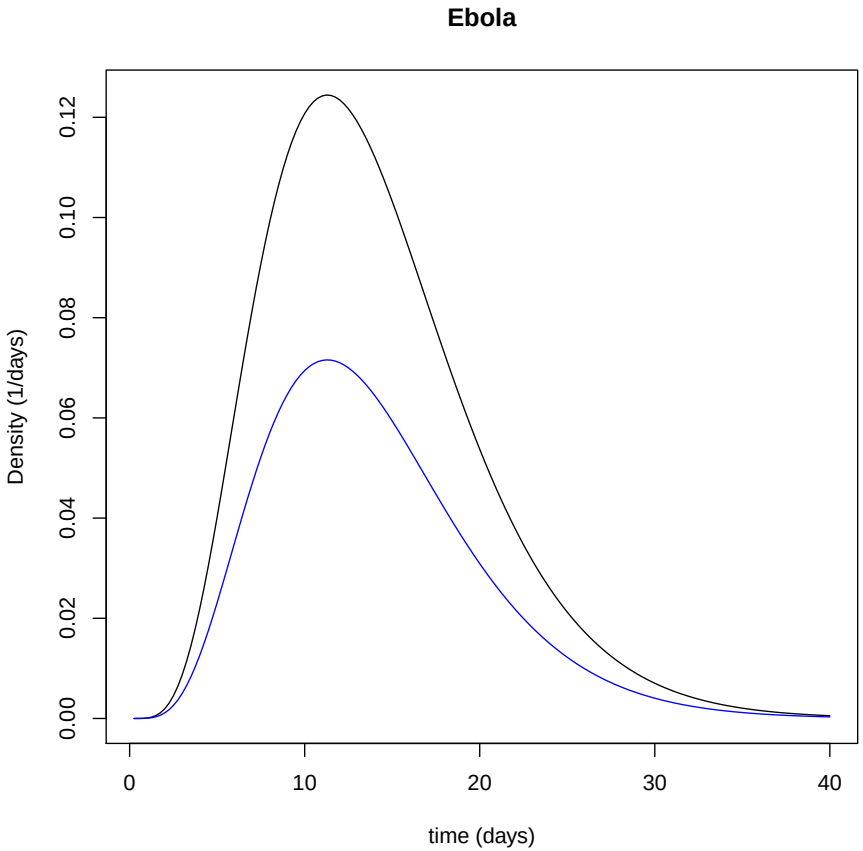
- $\mathcal{R}$, the epidemic strength, is the area under the curve.

Strength of intervention



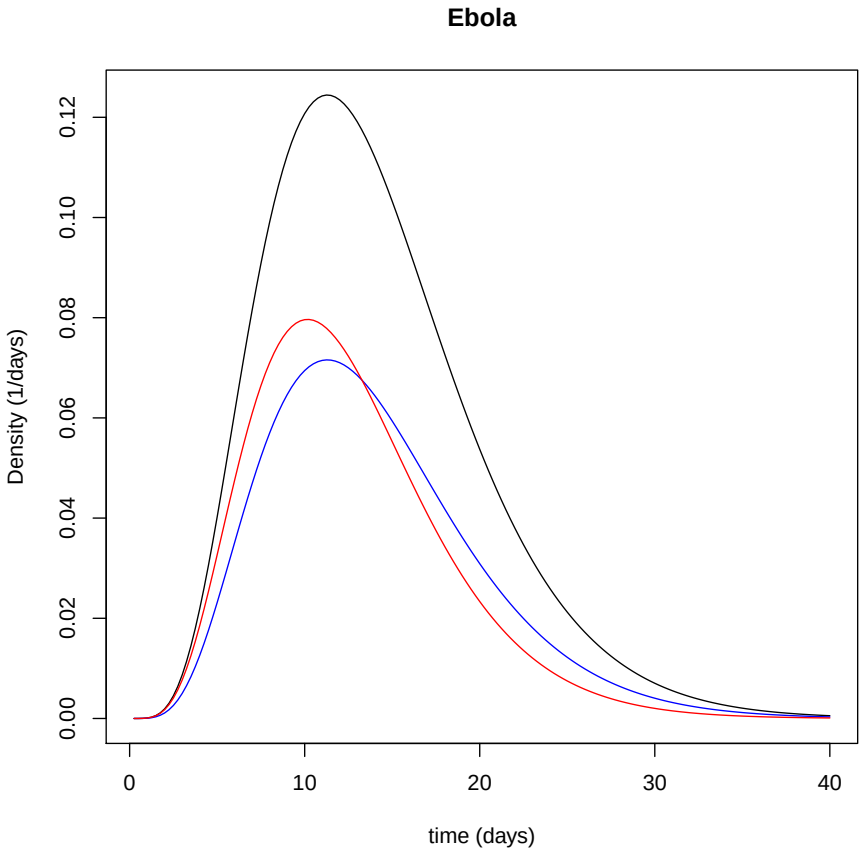
- . . . by what factor do I need to reduce this curve to eliminate the epidemic?

Different interventions (present)



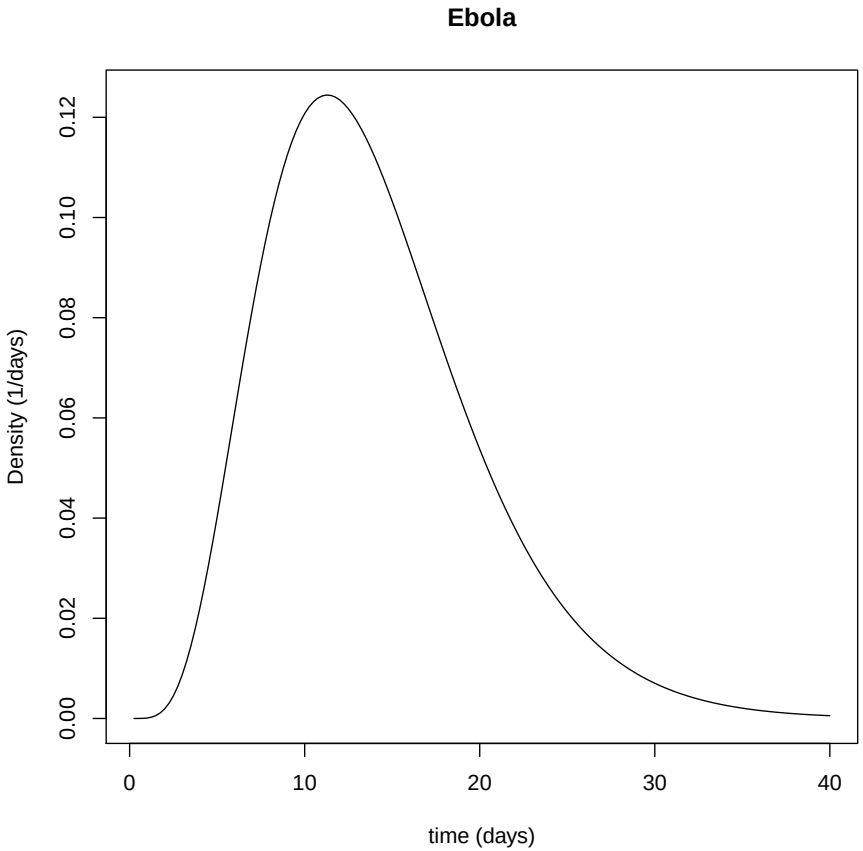
- idealized vaccination
- removes a fixed proportion of people

Different interventions (present)



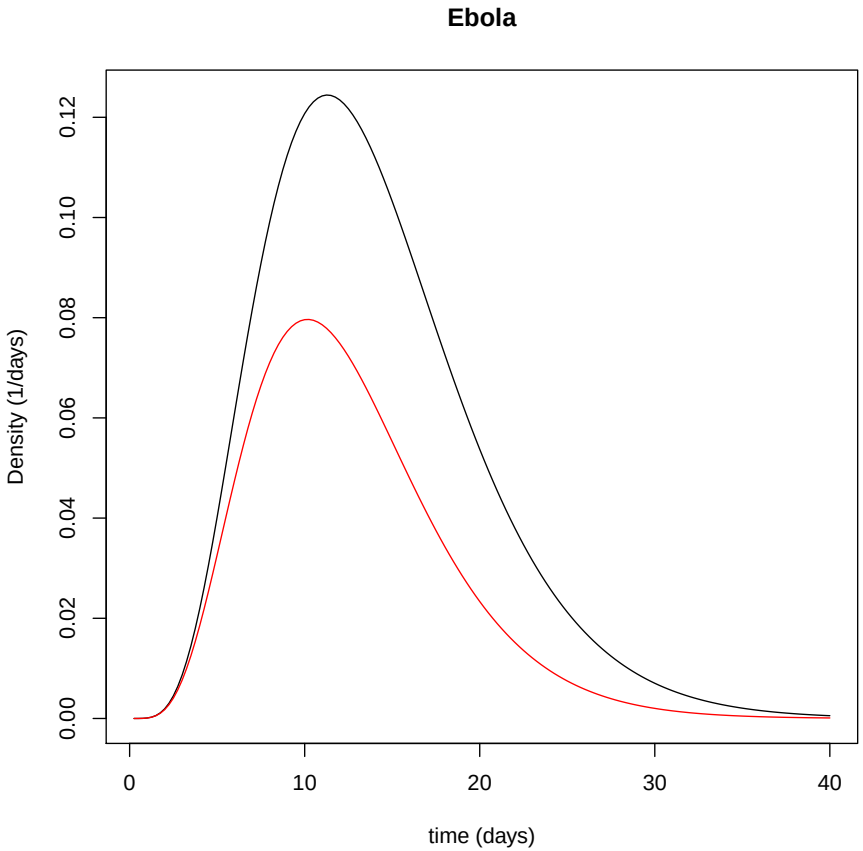
- idealized quarantine
- removes people at a fixed rate

Epidemic speed



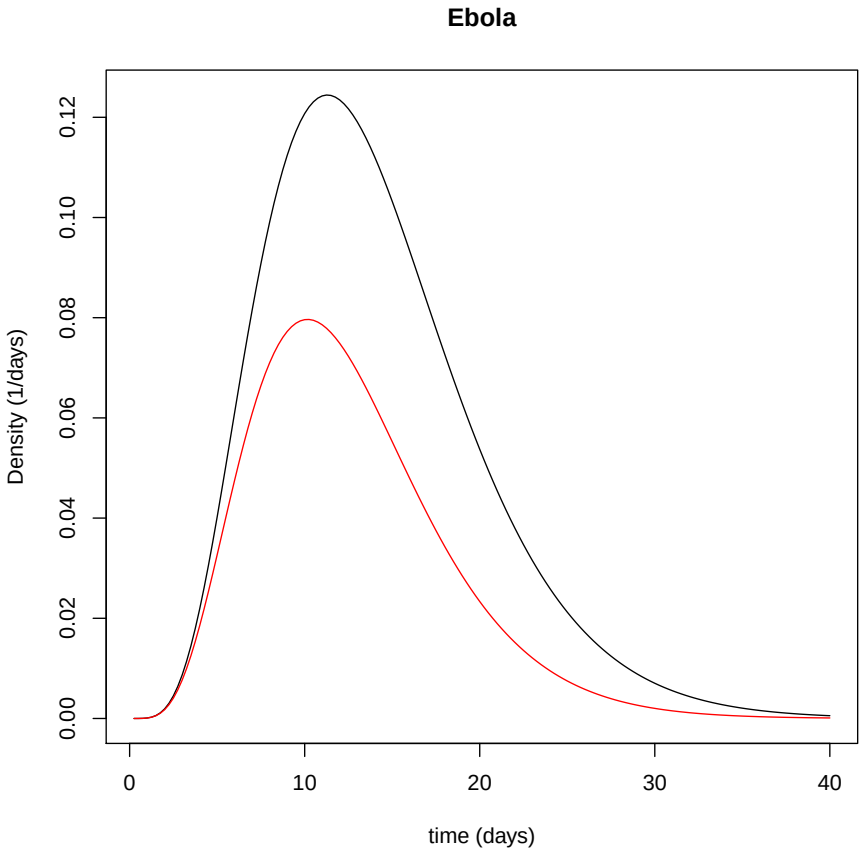
- r, the epidemic speed, is the "discount" rate required to balance the tendency to grow

Epidemic speed



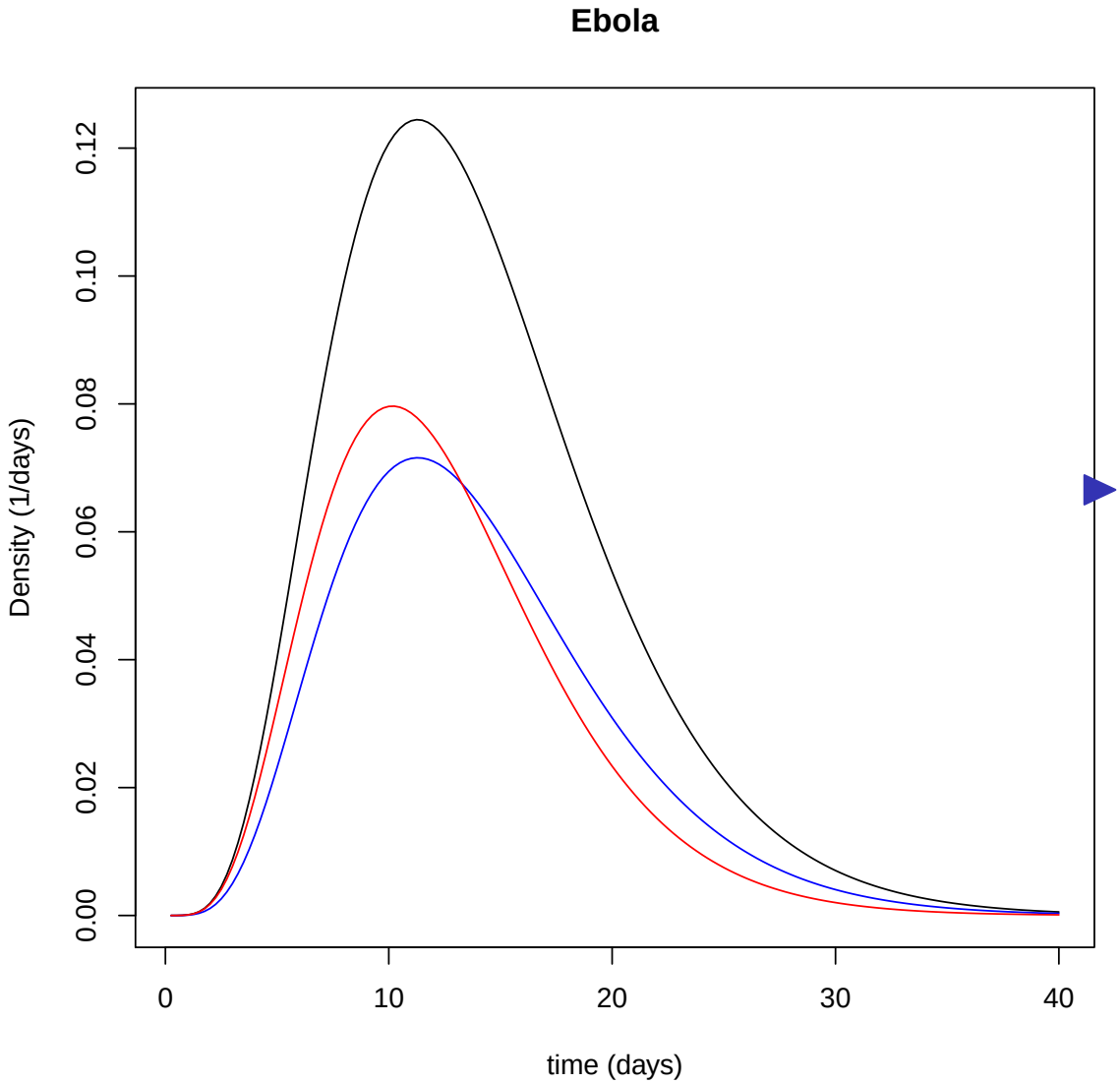
- $k(\tau) = \exp(r\tau)b(\tau)$, where $b(\tau)$ is the initial backward generation interval

Speed of intervention



- . . . how *quickly* do I need to reduce this curve to eliminate the epidemic?

Different interventions (present)



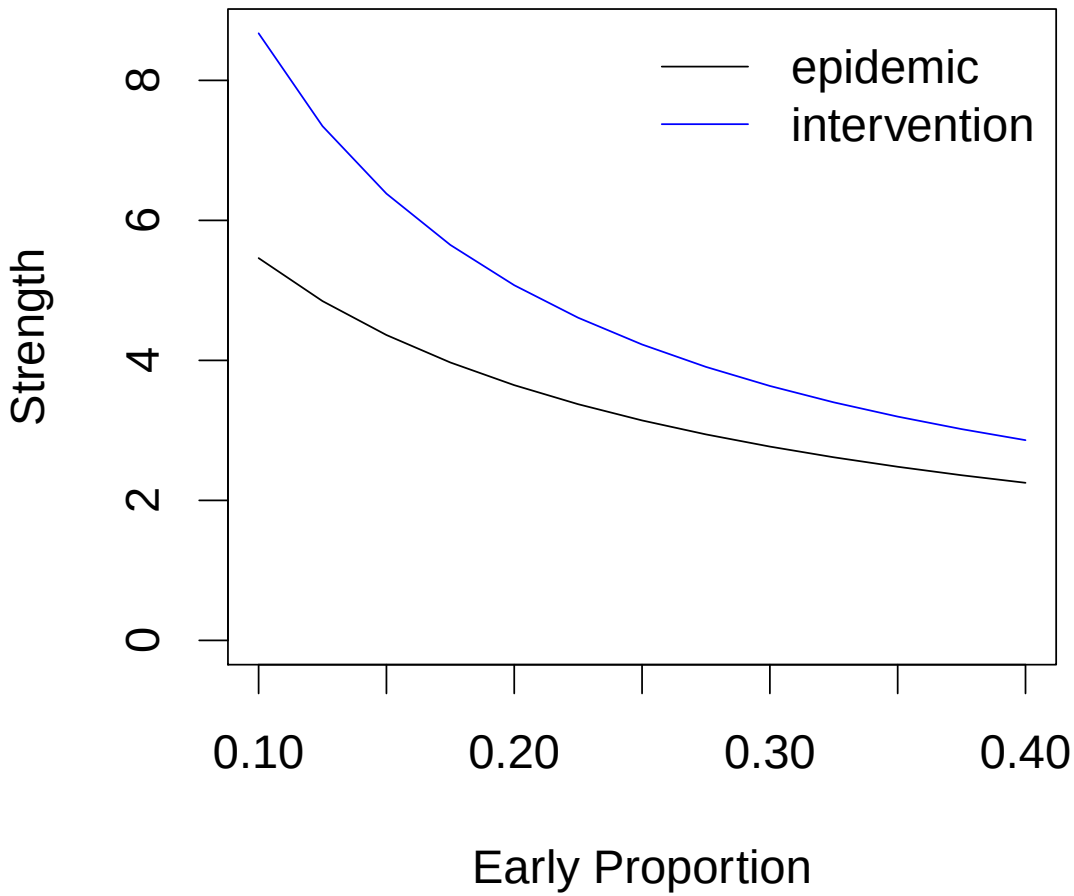
- Sometimes it's easier to estimate strength, sometimes speed

Measuring the intervention

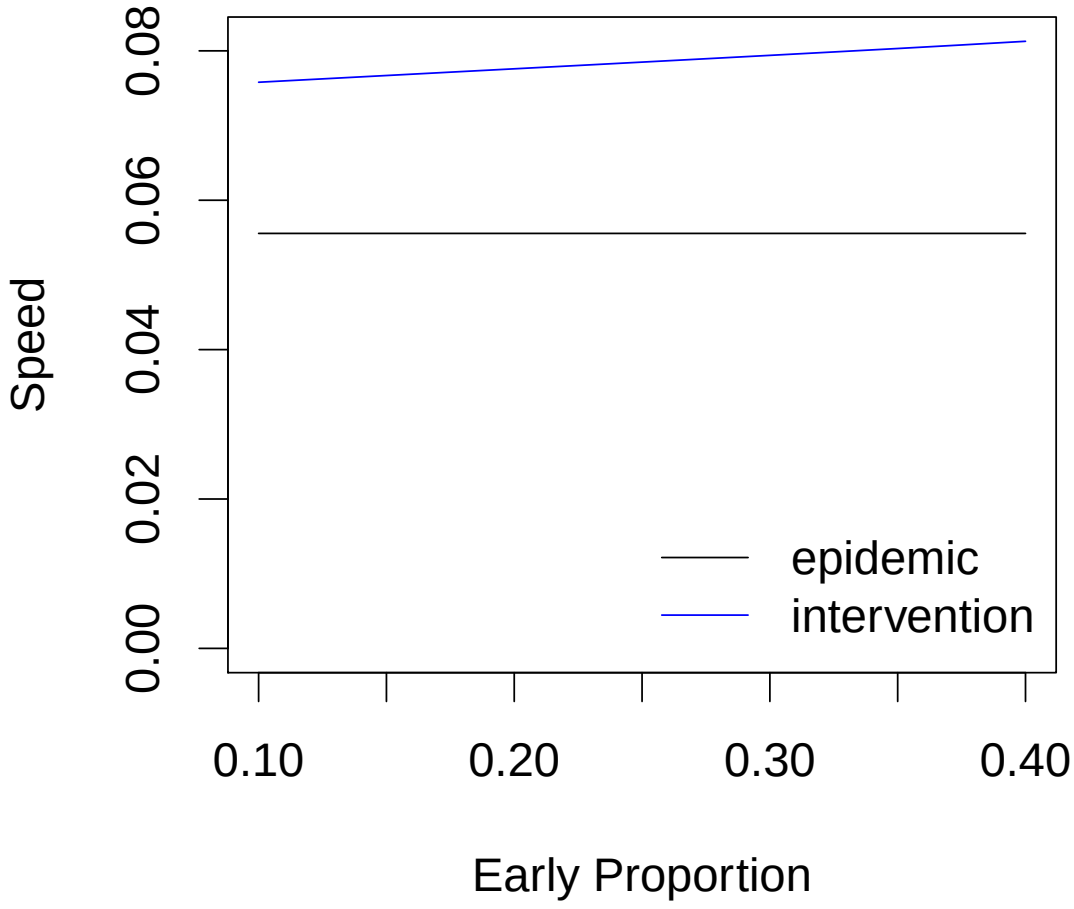
HIV

- The importance of transmission speed to HIV control is easier to understand using the speed paradigm
  - We know the speed of invasion
    - $\approx 0.7/\mathrm{yr}$
    - Characteristic scale $\approx 1.4\mathrm{yr}$
  - And can hypothesize the speed of intervention
    - Or aim to go fast enough

HIV test and treat



HIV test and treat



Paradigms are complementary

- HIV
  - Information and current intervention are both "speed-like"
- Measles
  - Information (long-term) is strength-like
  - Intervention (vaccine) also strength-like
- Ebola outbreak
  - Information is speed-like
  - Pre-emptive vaccination is strength-like
  - Quarantine or reactive vaccination may be more speed-like

Outline

Measuring generation intervals

- Ad hoc methods
- Error often not propagated
- Importance of heterogeneity

Generations through time

- Generation intervals can be estimated by:
  - Observing patients:
    - How long does it take to become infectious?
    - How long does it take to recover?
    - What is the time profile of infectiousness/activity?
  - Contact tracing
    - Who (probably) infected whom?
    - When did each become infected?
    - — or ill (serial interval)?

Which is the real interval?

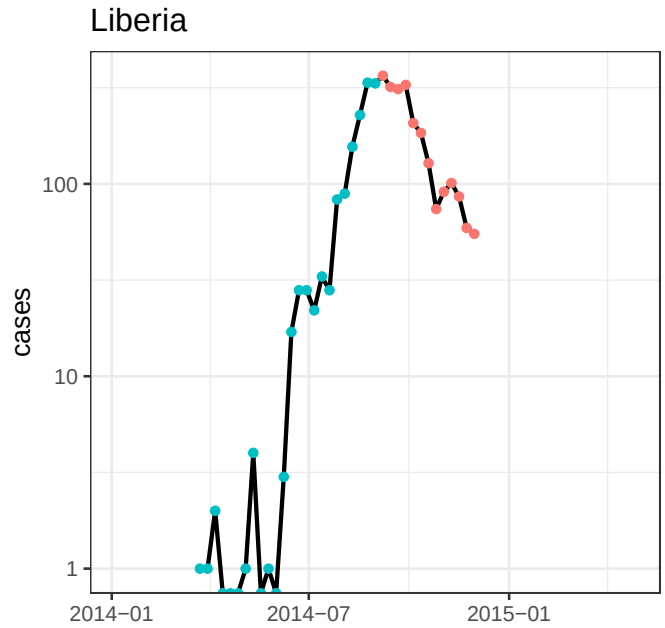
- Contact-tracing intervals look systematically different, depending on when you observe them.
- Observed in:
  - Real data, detailed simulations, simple model
- Also differ from intrinsic (infector centered) estimates

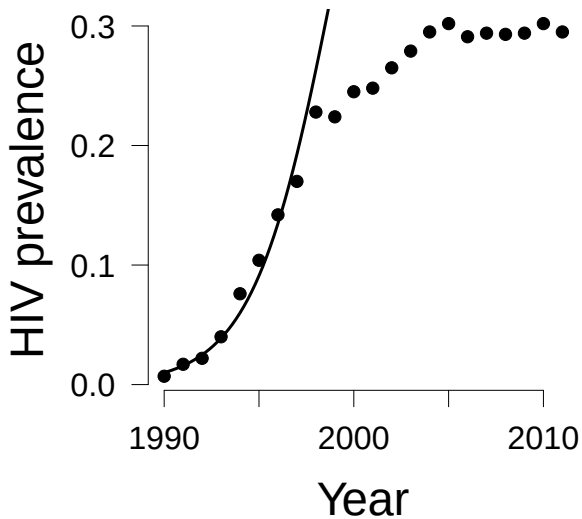
Types of interval

- Define:
  - *Intrinsic interval*: How infectious is a patient at time τ after infection?
  - *Forward interval*: When will the people infected today infect others?
  - *Backward interval*: When did the people who infected people today themselves become infected?
  - *Censored interval*: What do all the intervals observed up until a particular time look like?
    - Like backward intervals, if it's early in the epidemic

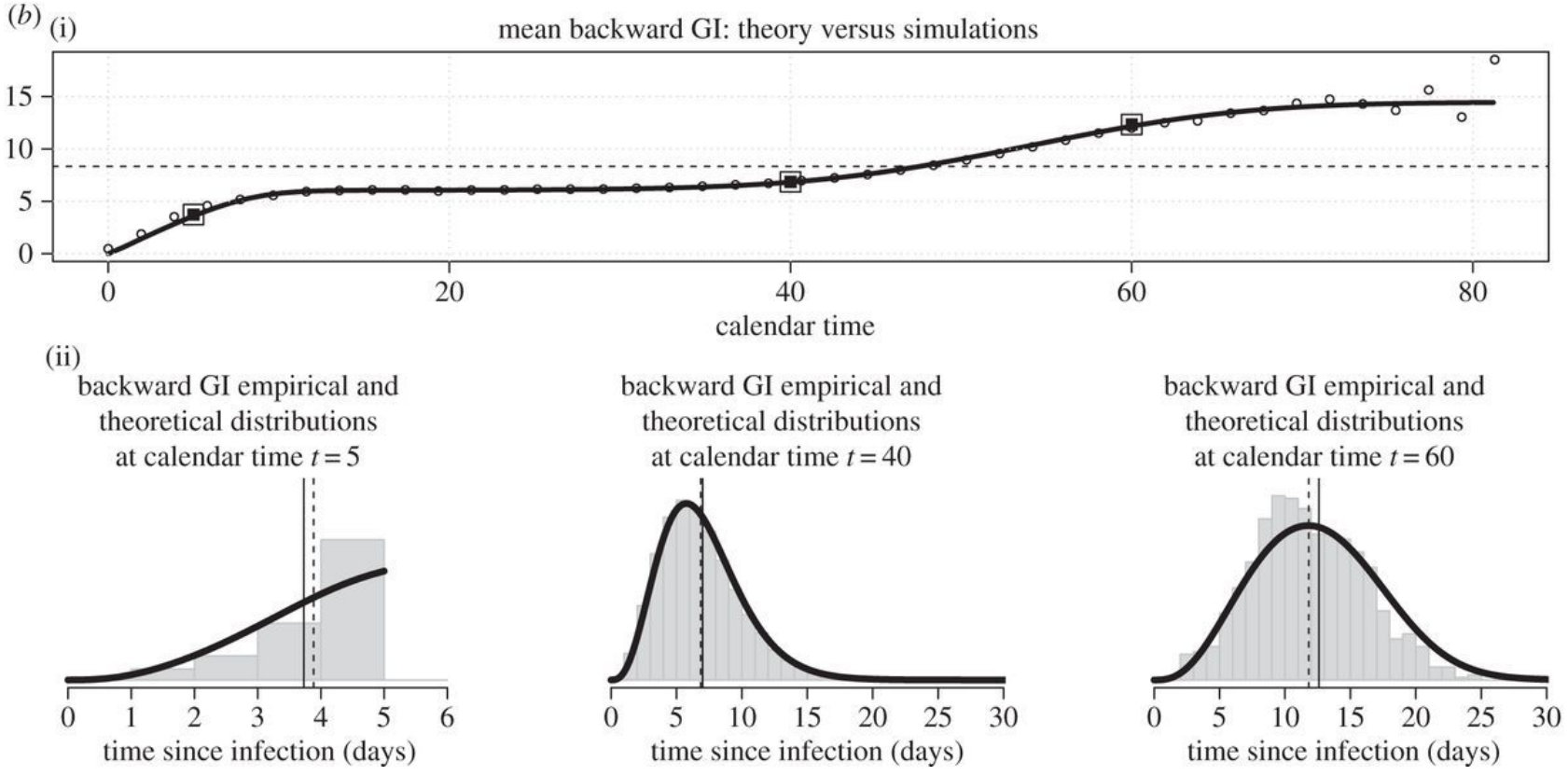
Growing epidemics

- Generation intervals look *shorter* at the beginning of an epidemic
  - A disproportionate number of people are infectious right now
  - They haven't finished all of their transmitting
  - We are biased towards observing faster events





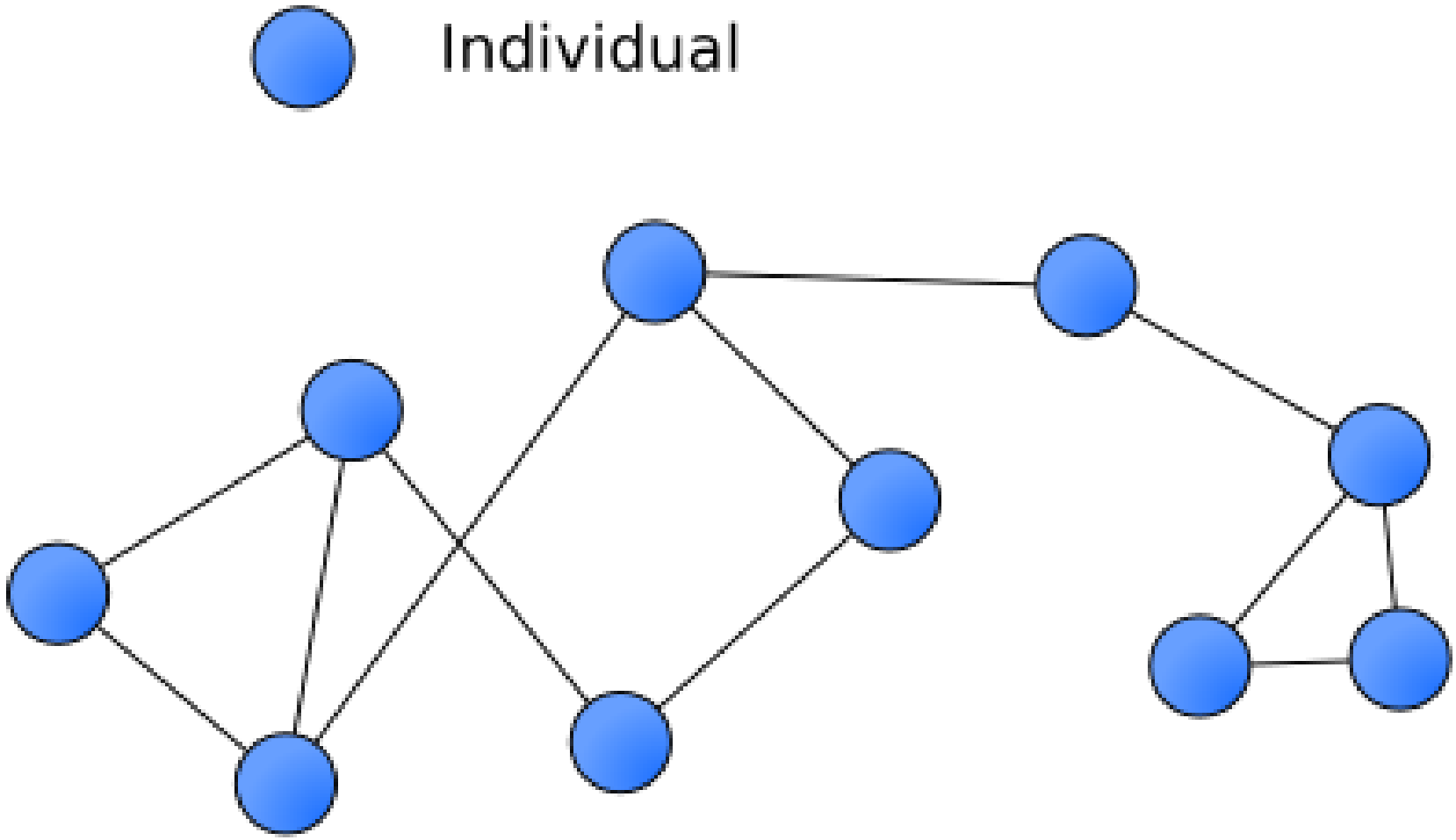
Backward intervals



Champredon and Dushoff, 2015. DOI:10.1098/rspb.2015.2026

Generations in space

- How do local interactions affect realized generation intervals?



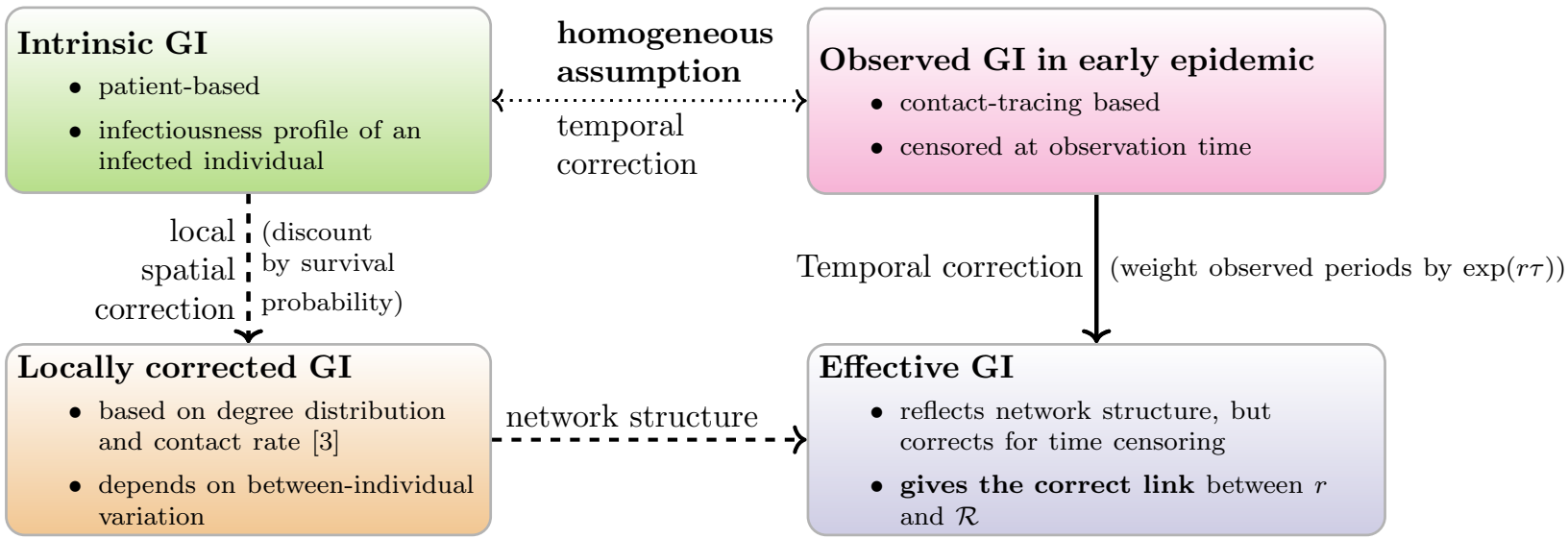
Surprising results

- We tend to think that heterogeneity leads to underestimates of $\mathcal{R}$, whican can be dangerous.
- $\mathcal{R}$ on networks generally *smaller* than values estimated using r.
  - *Trapman et al., 2016. JRS Interface DOI:10.1098/rsif.2016.0288*

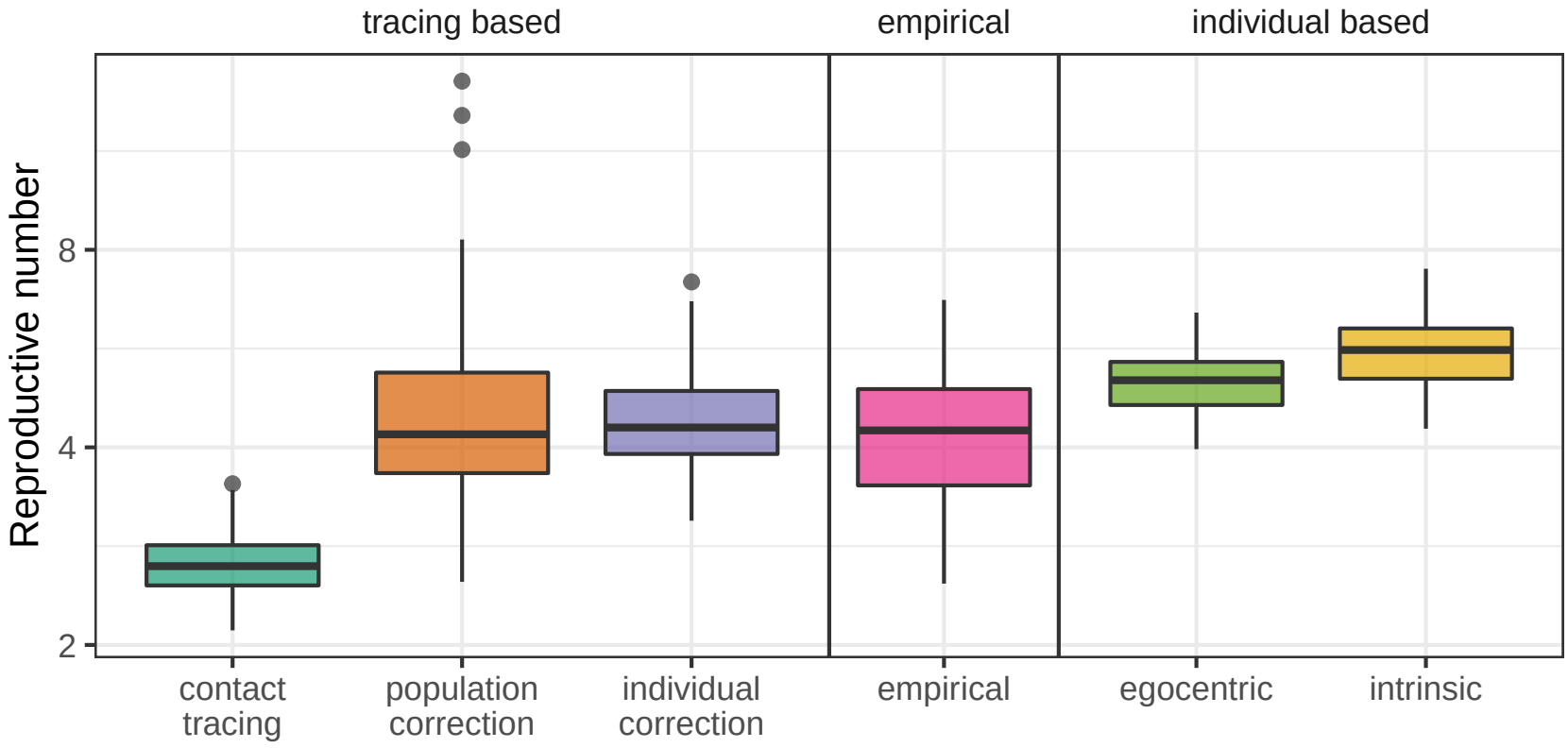
Generation-interval perspective

- Modelers don't usually question the intrinsic generation interval
- But spatial network structure does change generation intervals:
  - Local interactions
  - $\Longrightarrow$ wasted contacts
  - $\Longrightarrow$ shorter generation intervals
  - $\Longrightarrow$ smaller estimates of $\mathcal{R}$.

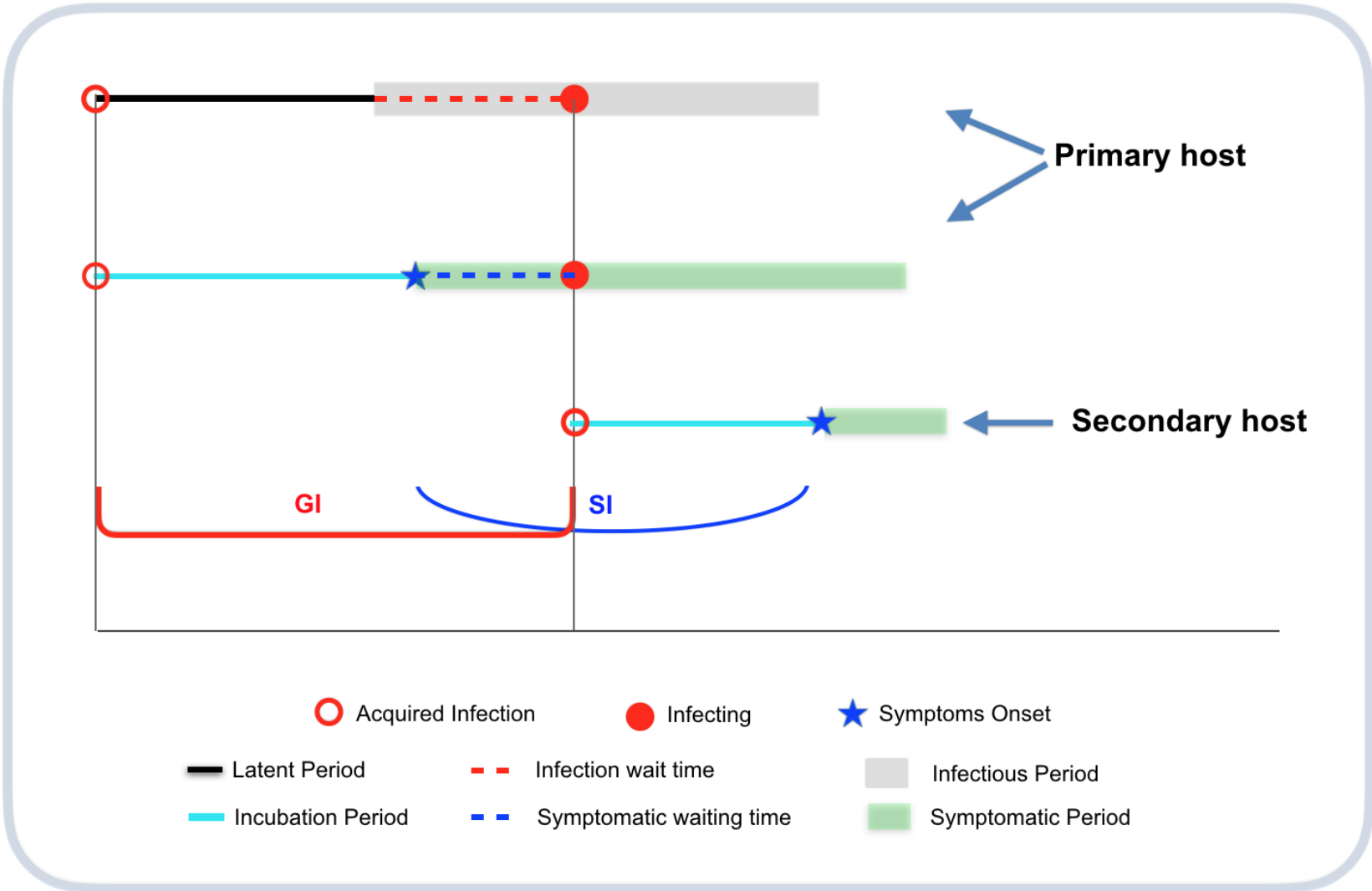
Observed and estimated intervals



Outbreak estimation

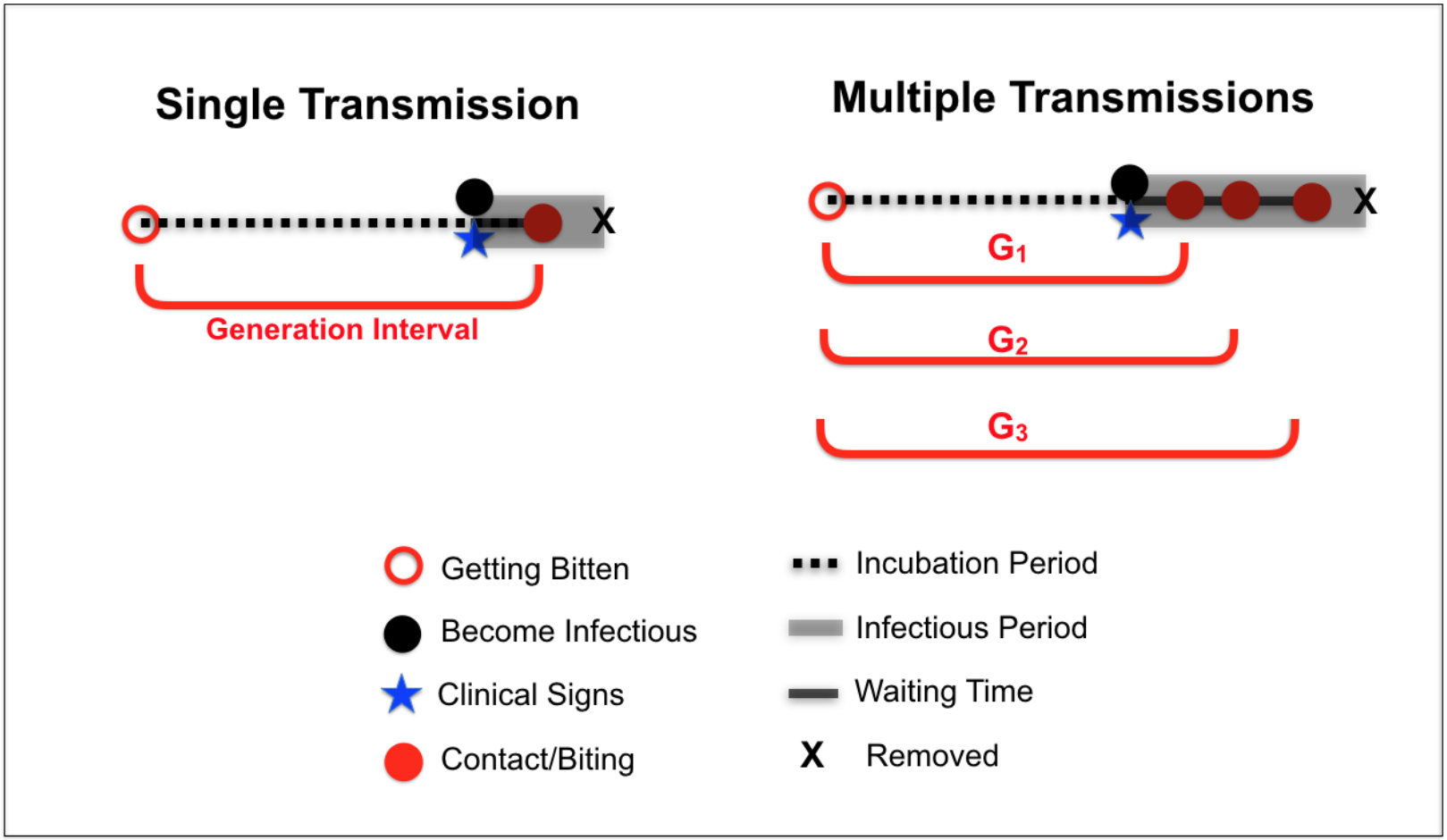


Serial intervals



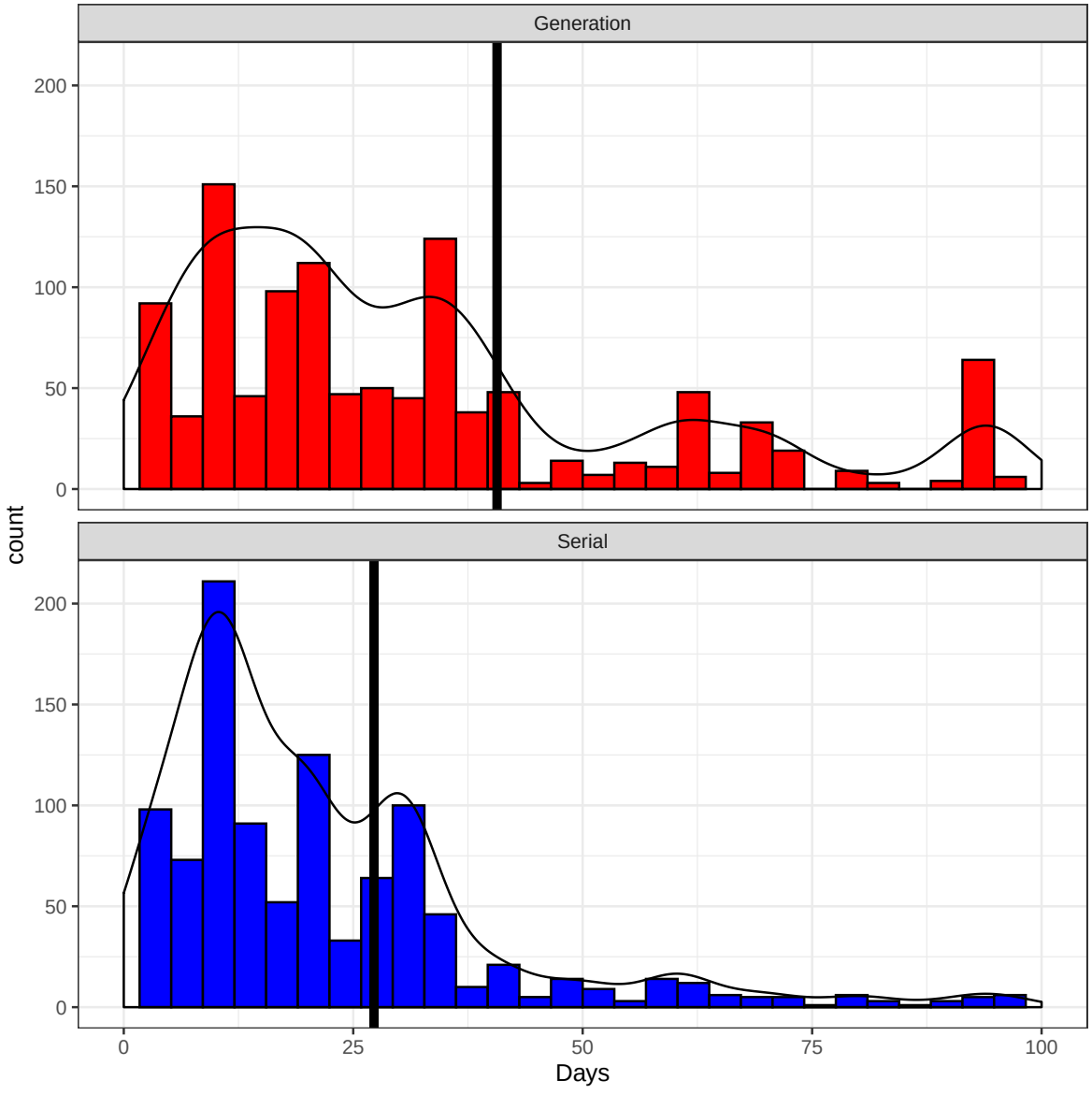
Serial intervals

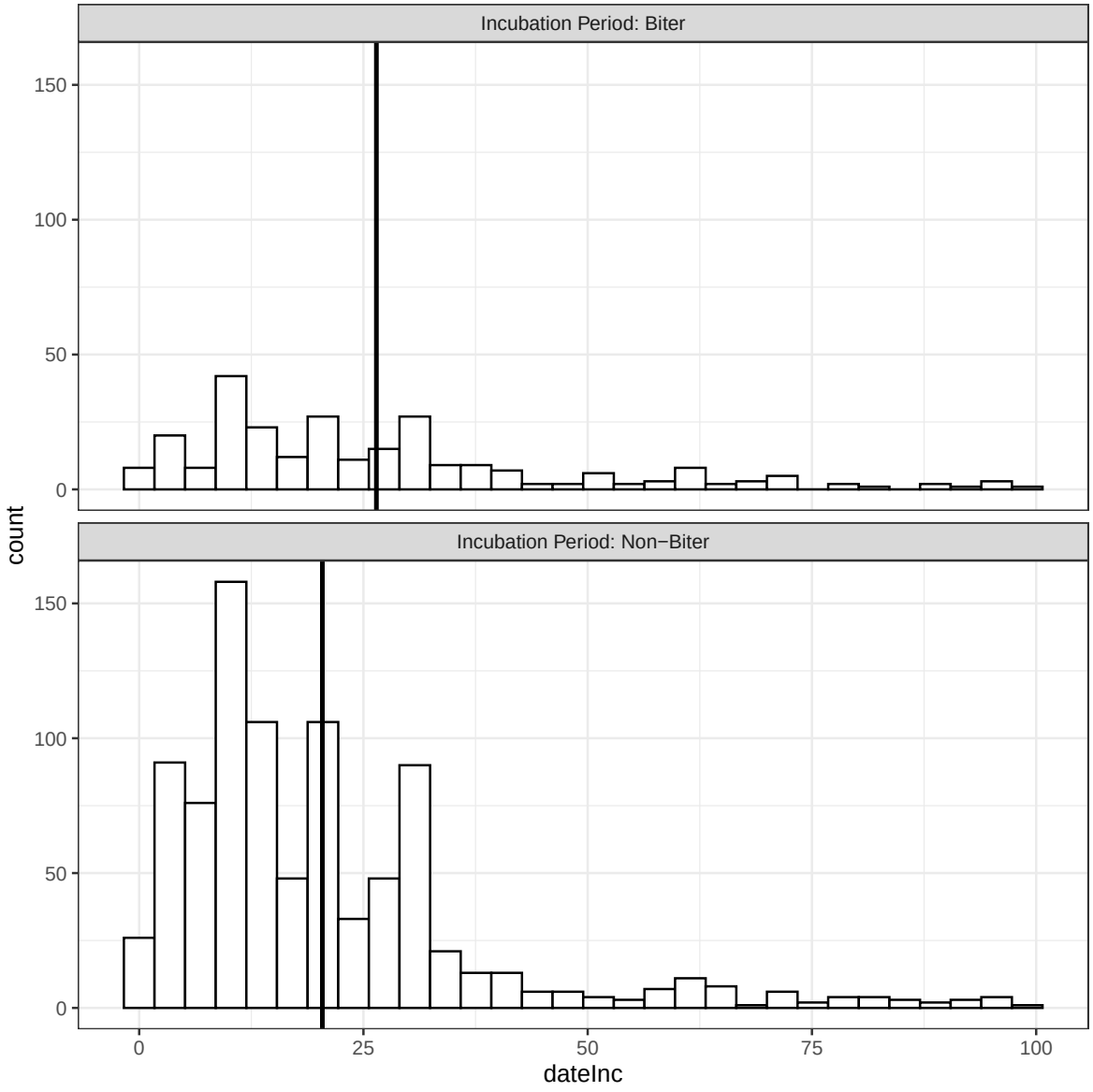
- Do serial intervals and generation intervals have the same distribution?
- It seems that they should: they describe generations of the same process
  - But serial intervals can even be very different
  - Even negative! You might report to the clinic with flu before me, even though I infected you
- For rabies, we *thought* that serial intervals and generation intervals should be the same
  - Symptoms are closely correlated with infectiousness


Single Transmission
X
Generation Interval
Multiple Transmissions
X
G1
G2
G3
Getting Bitten
Become Infectious
Clinical Signs
Contact/Biting
Incubation Period
Infectious Period
Waiting Time
X
Removed

Rabies

- If symptoms always start *before* infectiousness happens, then serial interval should equal generation interval:
  - incubation time + extra latent time + waiting time
  - extra latent time + waiting time + incubation time


Generation
Serial
count
Days
0
50
100
150
200
0
25
50
75
100


Incubation Period: Biter
Incubation Period: Non−Biter
count
dateInc
0
50
100
150
0
25
50
75
100

Thanks

- Department
- Collaborators
- Funders: NSERC, CIHR

Linking framework

- Epidemic speed (r) is a *product*:
  - (something to do with) generation speed $\times$
  - (something to do with) epidemic strength
- In particular:
  - $r \approx (1/\bar{G}) \times \ell(\mathcal{R}; \kappa_g)$
  - ℓ is the inverse of X