Modeling and estimating generation intervals

Tachikawa infectious boot camp, 2019

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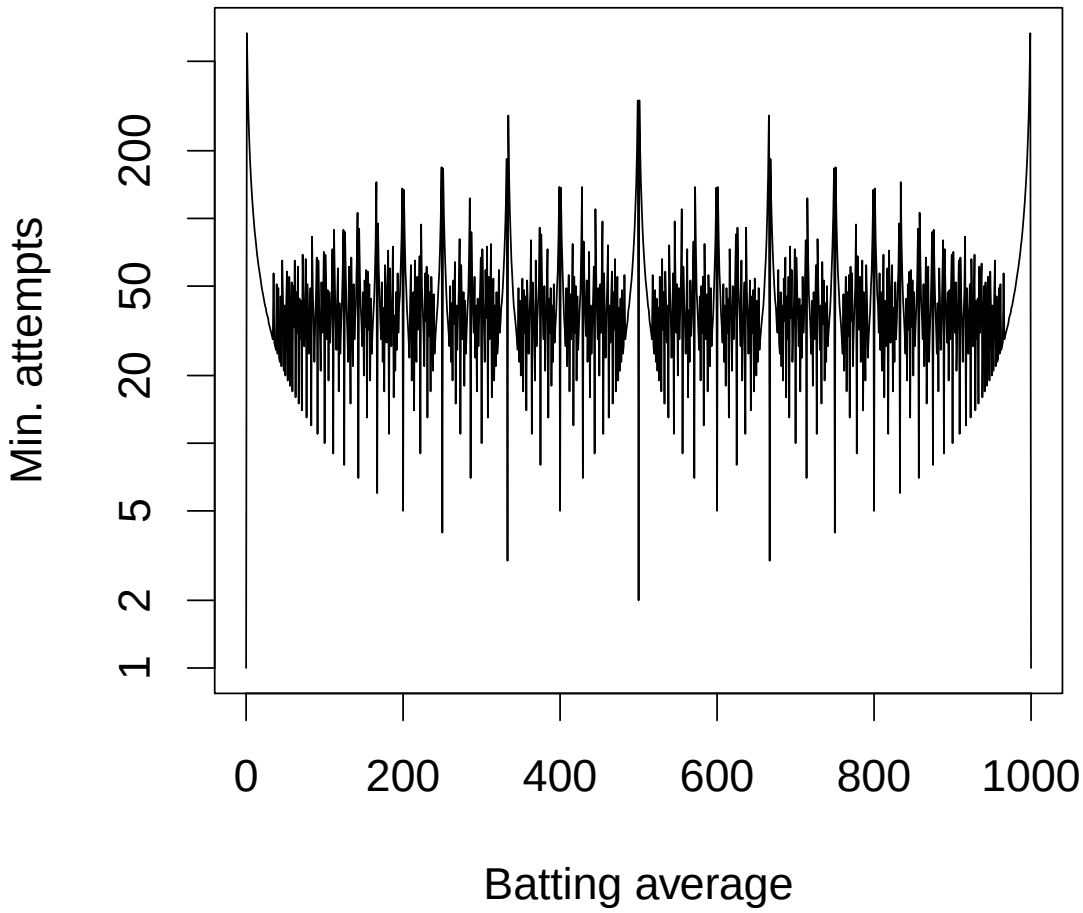
`https://github.com/dushoff/Generation_talks`

Outline

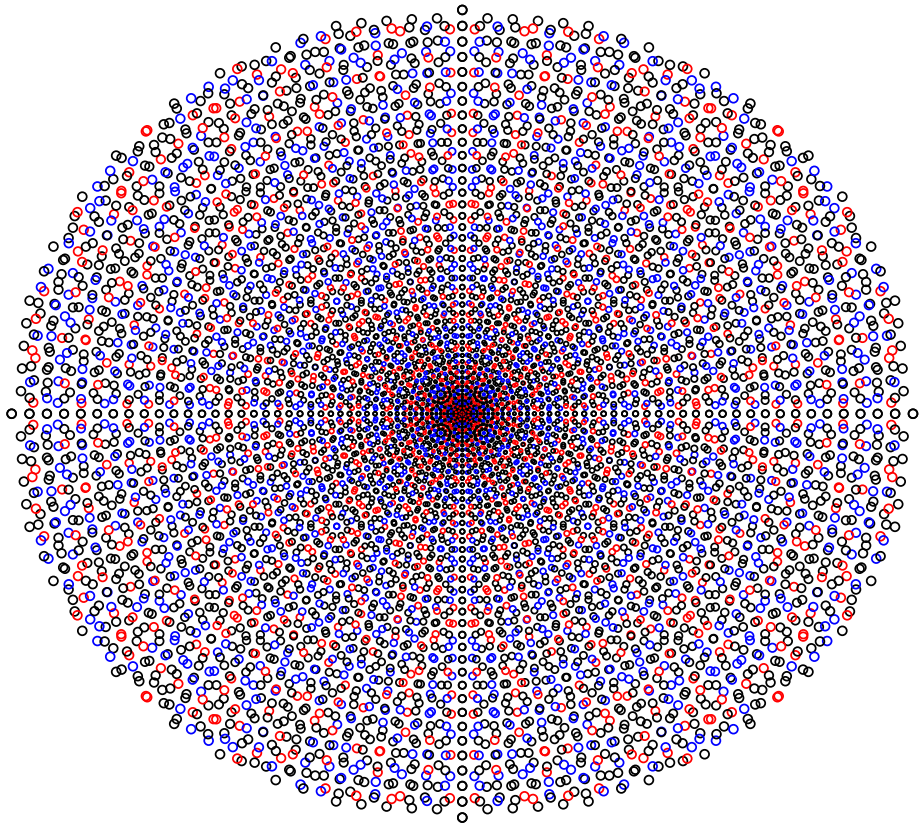
Introduction

- I talk too fast
- I have too much to tell you
- Interrupt me!

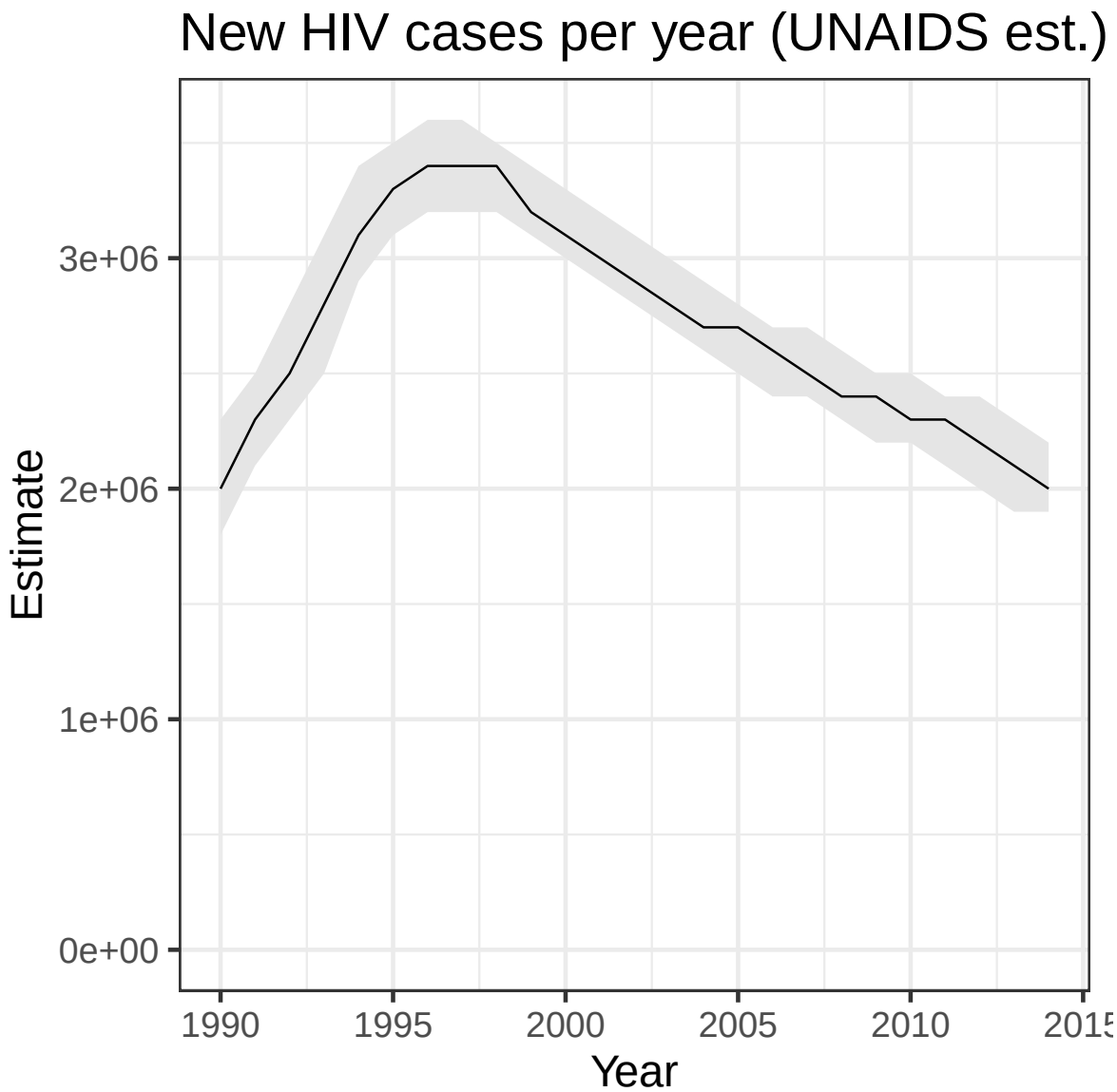
Who am I? Head (present)



Who am I? Heart (present)



Who am I? Stomach (present)

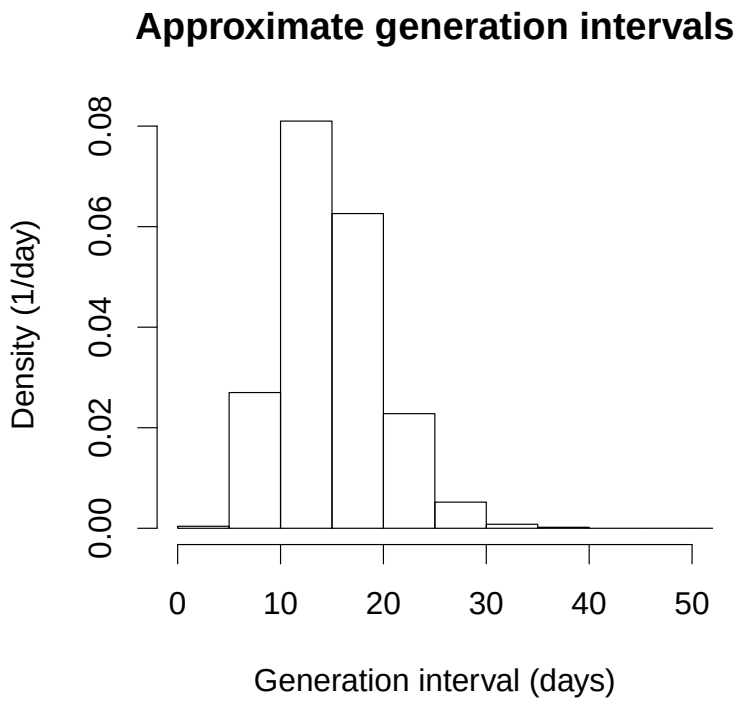


Who are you? (present)

- Math person
- Health person
- Biology person

How long is a disease generation?

- Introduced by Prof. Nakaoka
- If I am infected on day 0, when do I infect you?
- When do you infect Dr. Akhmetzhanov?

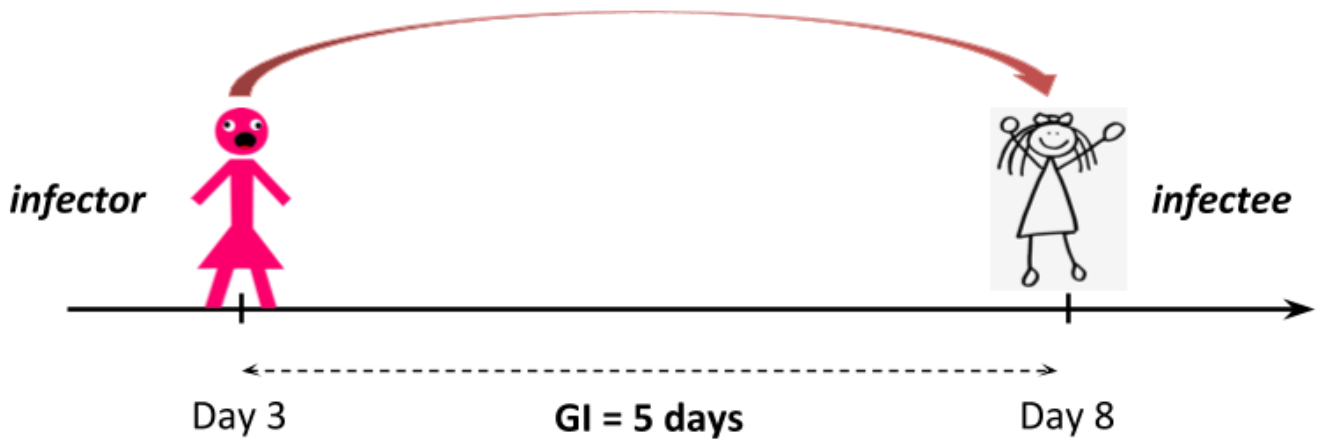


How long is a disease generation? (present)

Definition

Generation Interval:

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



Goals

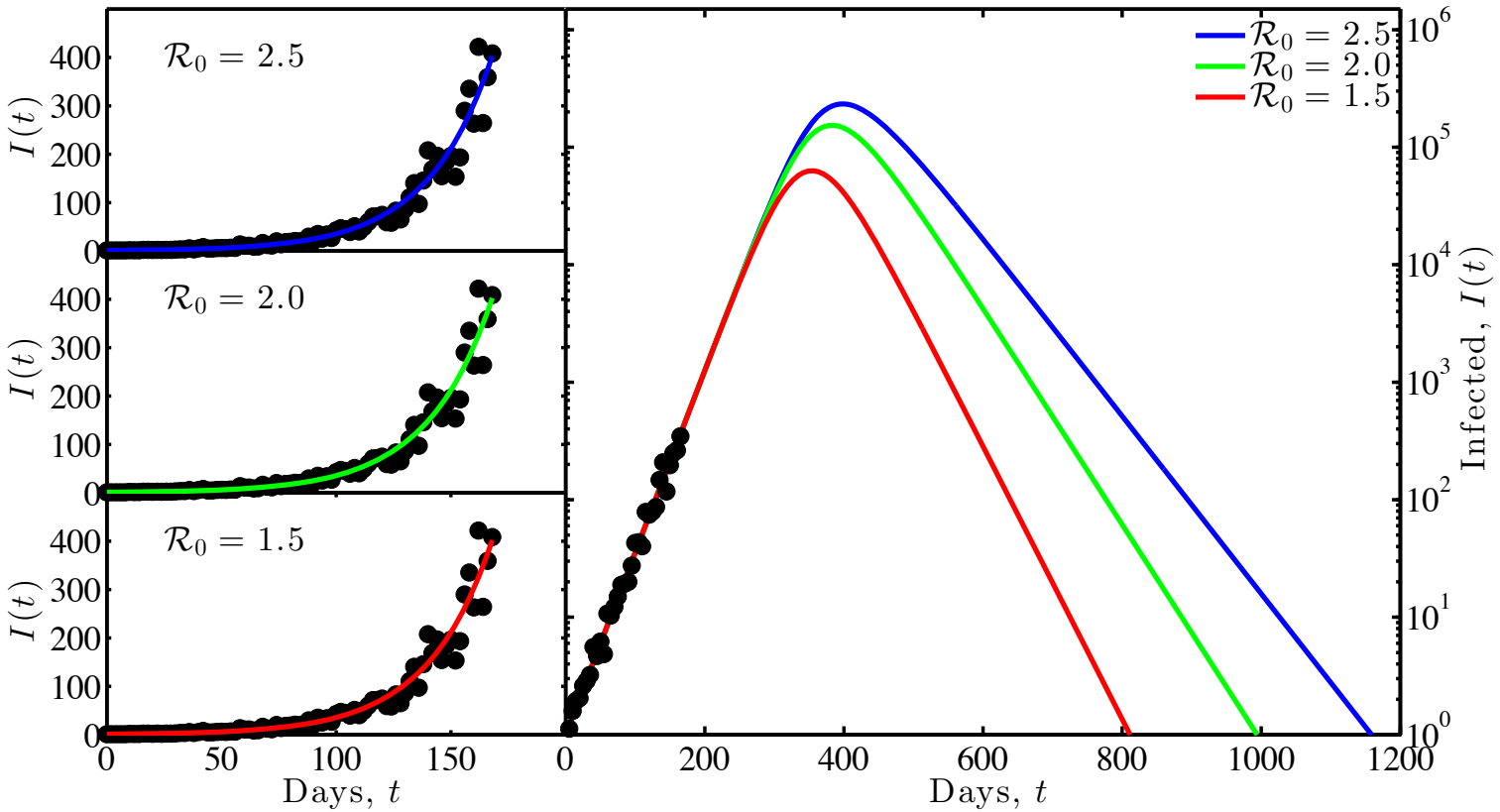
- Introduce a generation-based framework for modeling
- Discuss importance of generation intervals
- Discuss how generation intervals are defined and measured

Outline

Speed

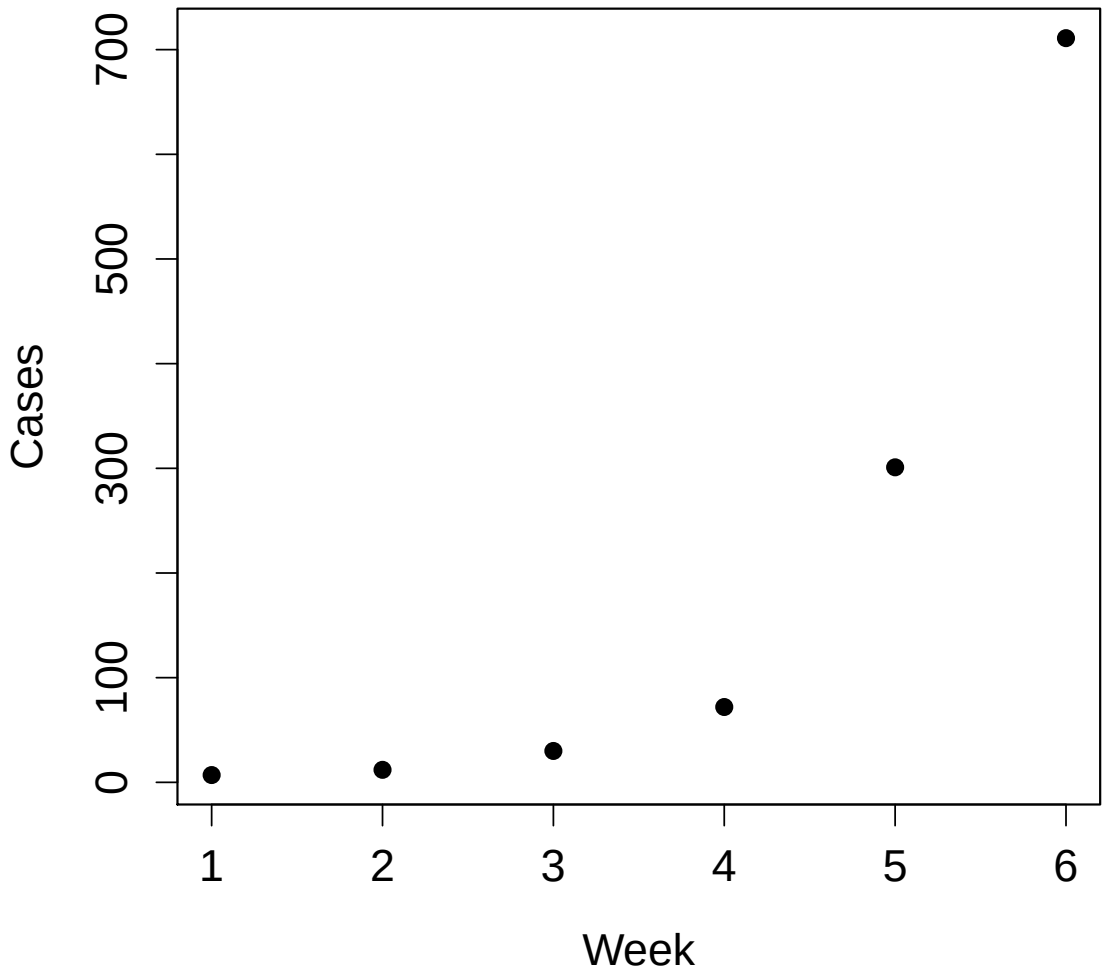
- We measure epidemic speed using little r:
  - The ratio of the *change* in disease impact to the *amount* of disease impact
  - *Units*: [1/time]
  - Disease increases like e^{rt}
- Time scale is $C = 1/r$

Ebola outbreak



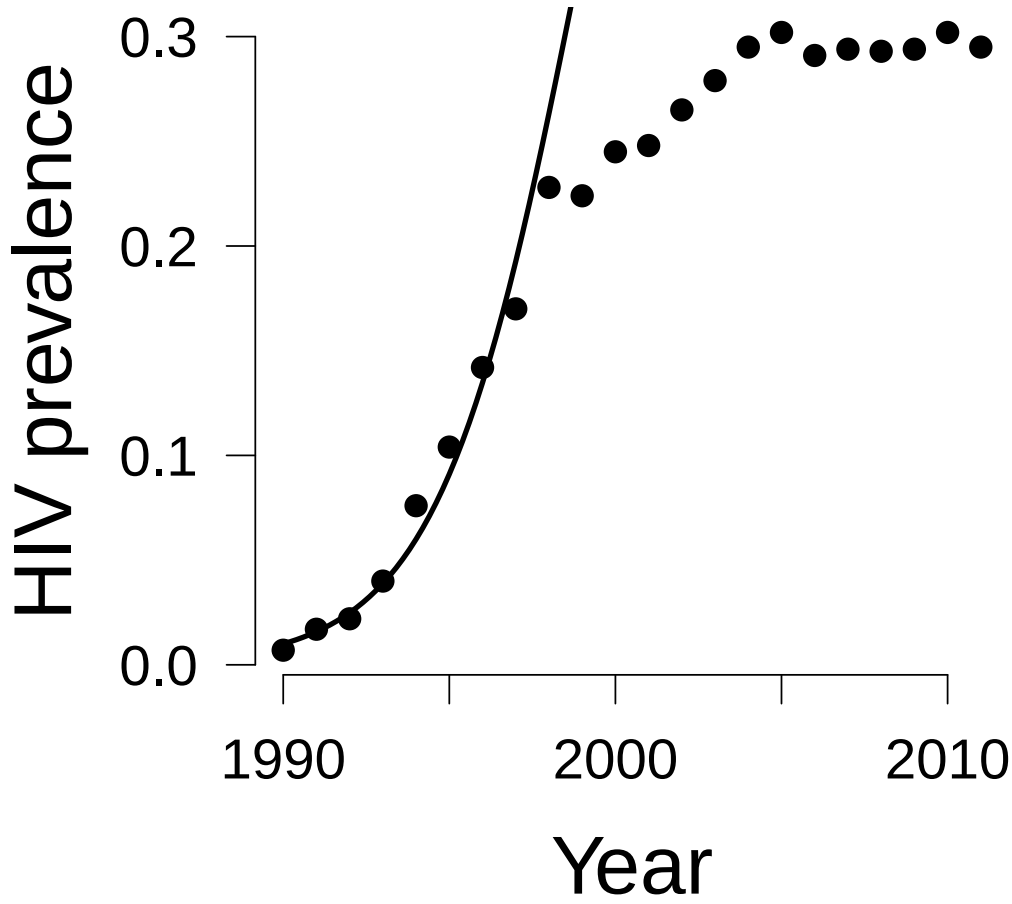
$C \approx 1\,\text{month}$. Sort-of fast.

Mexican flu



$C \approx 1\,\text{week}$. Sort-of fast.

HIV in sub-Saharan Africa



$C \approx 18\,\mathrm{month}$. Horrifyingly fast.

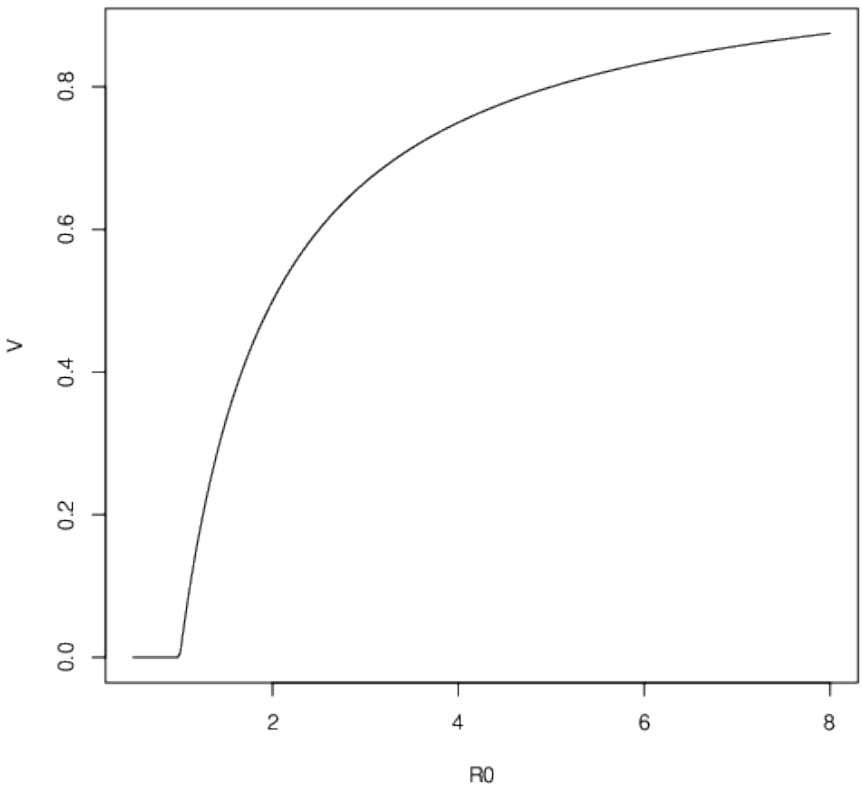
$\mathcal{R}$ and control

- We describe epidemic *strength* with big $\mathcal{R}$
- Number of potential new cases per case
  - Not accounting for proportion susceptible
- To eliminate disease, we must:
  - Reduce effective reproduction by a factor of $\mathcal{R}$

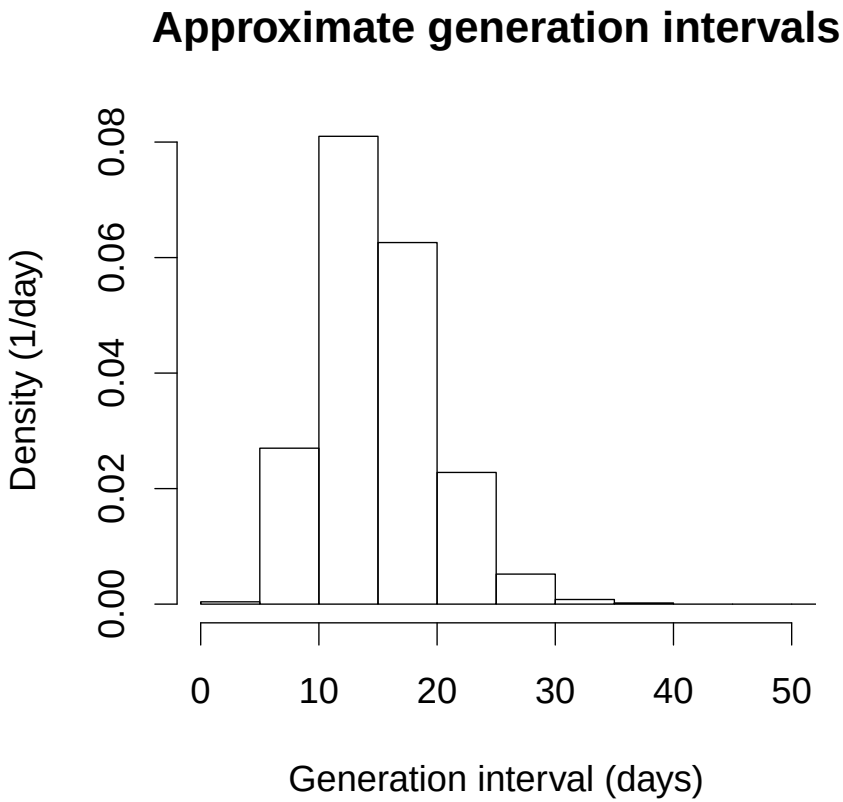
$\mathcal{R}$ and equilibrium

- If we have $\mathcal{R}$ new cases per case when everyone is susceptible
- And 1 case per case (on average) at equilibrium:
  - Proportion susceptible at equilibrium is $S = 1/\mathcal{R}$
  - Proportion affected at equilibrium is $V = 1 - 1/\mathcal{R}$

$\mathcal{R}$ and control (present)



Outline

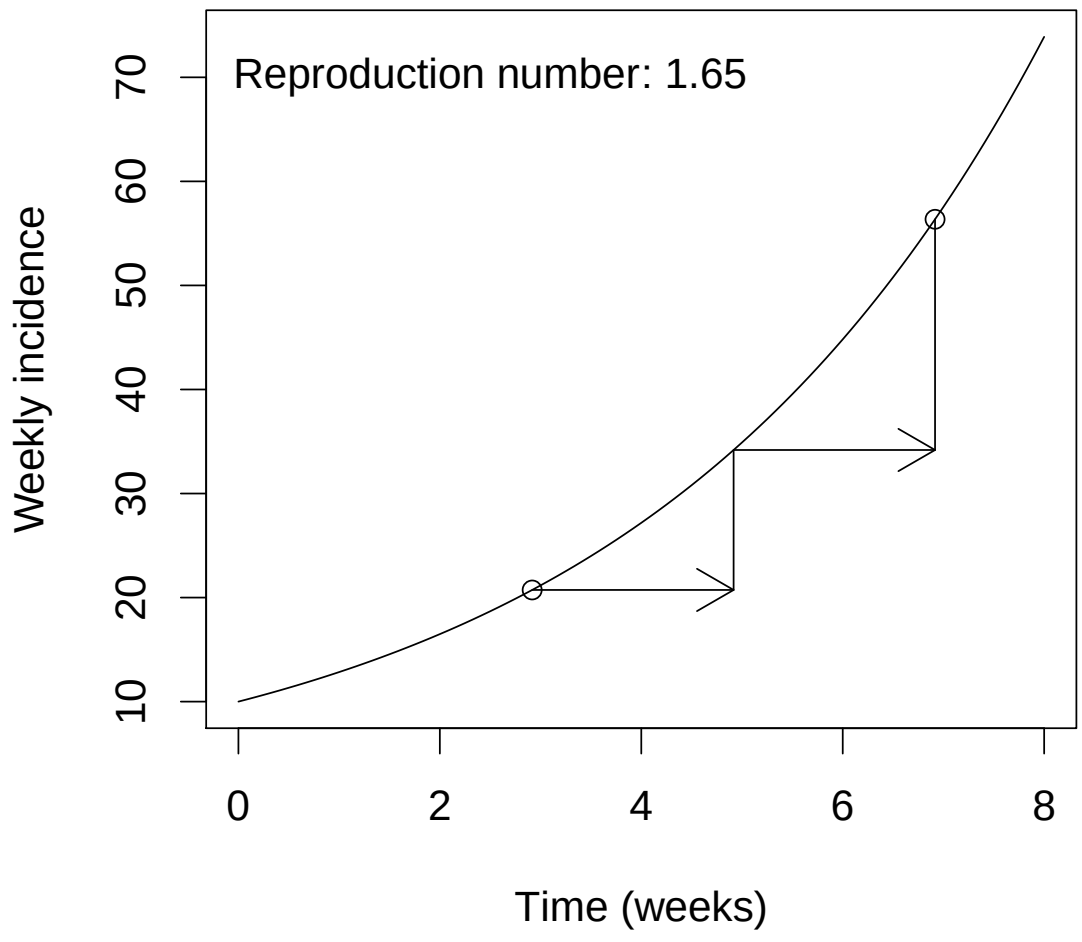


- The generation distribution measures generations of the disease
  - Interval between "index" infection and resulting infection
- Do fast disease generations mean more danger or less danger?

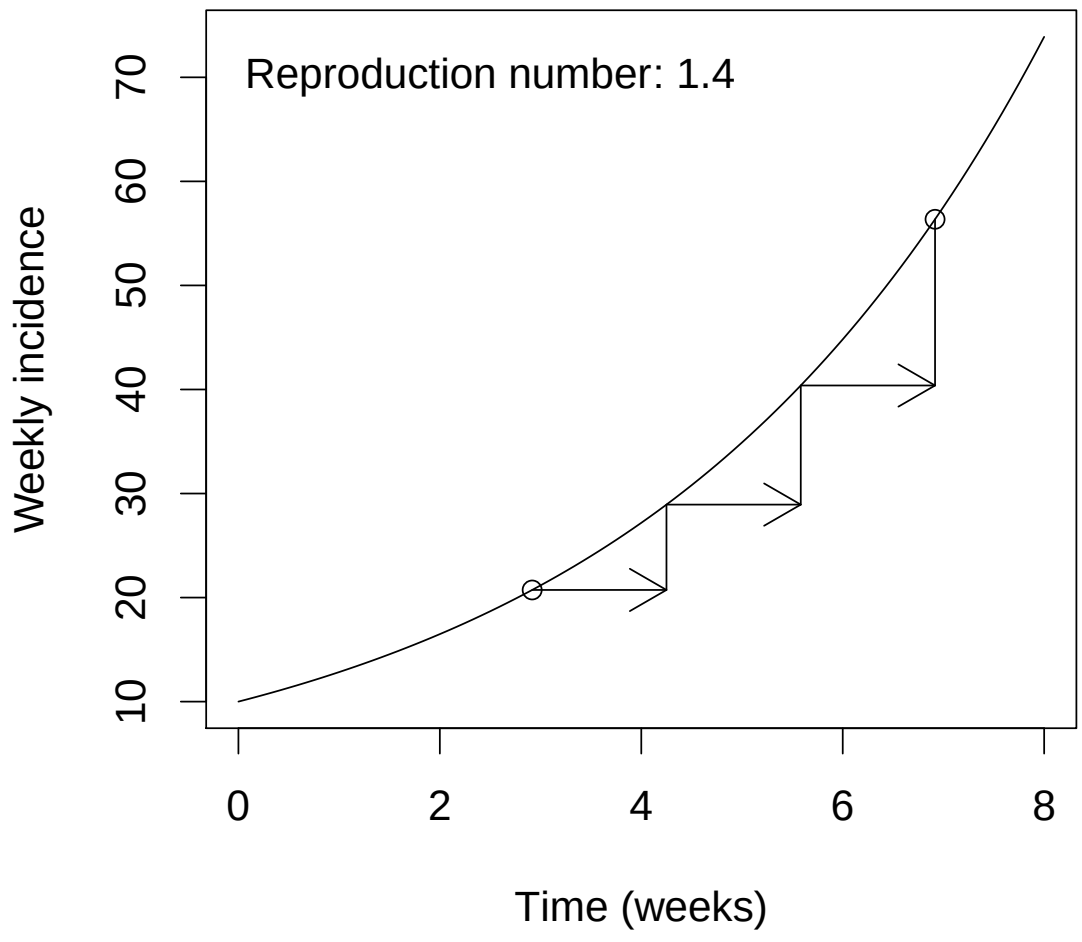
Conditional effect of generation time

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

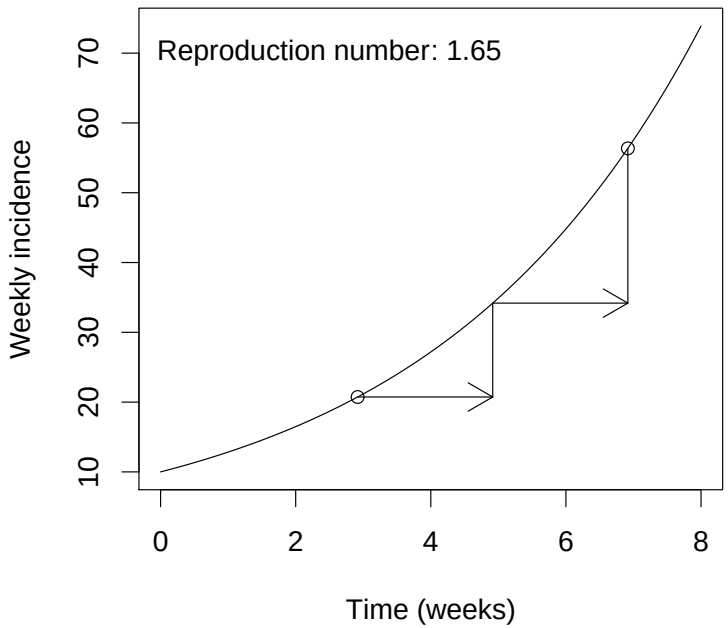
Generations and $\mathcal{R}$(present)

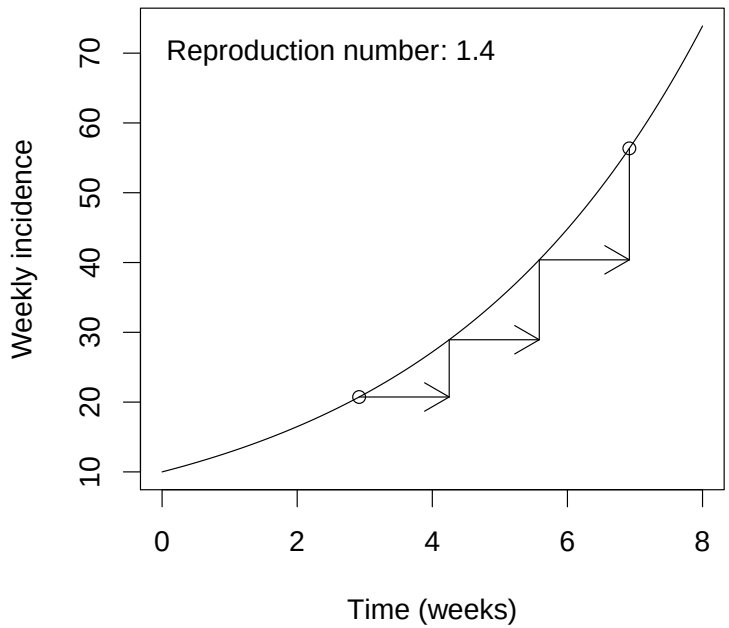


Generations and $\mathcal{R}$

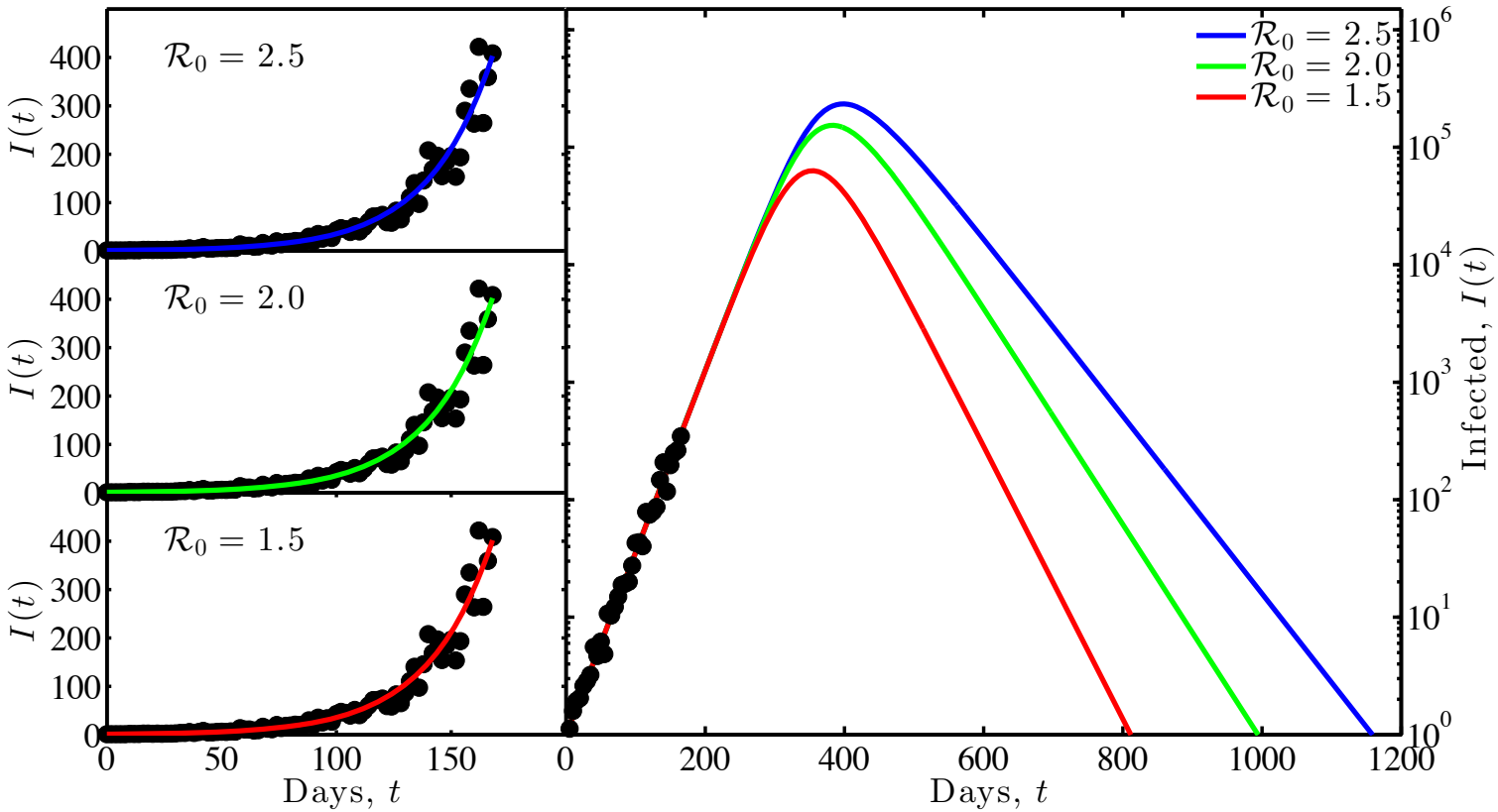


Generations and $\mathcal{R}$(present)



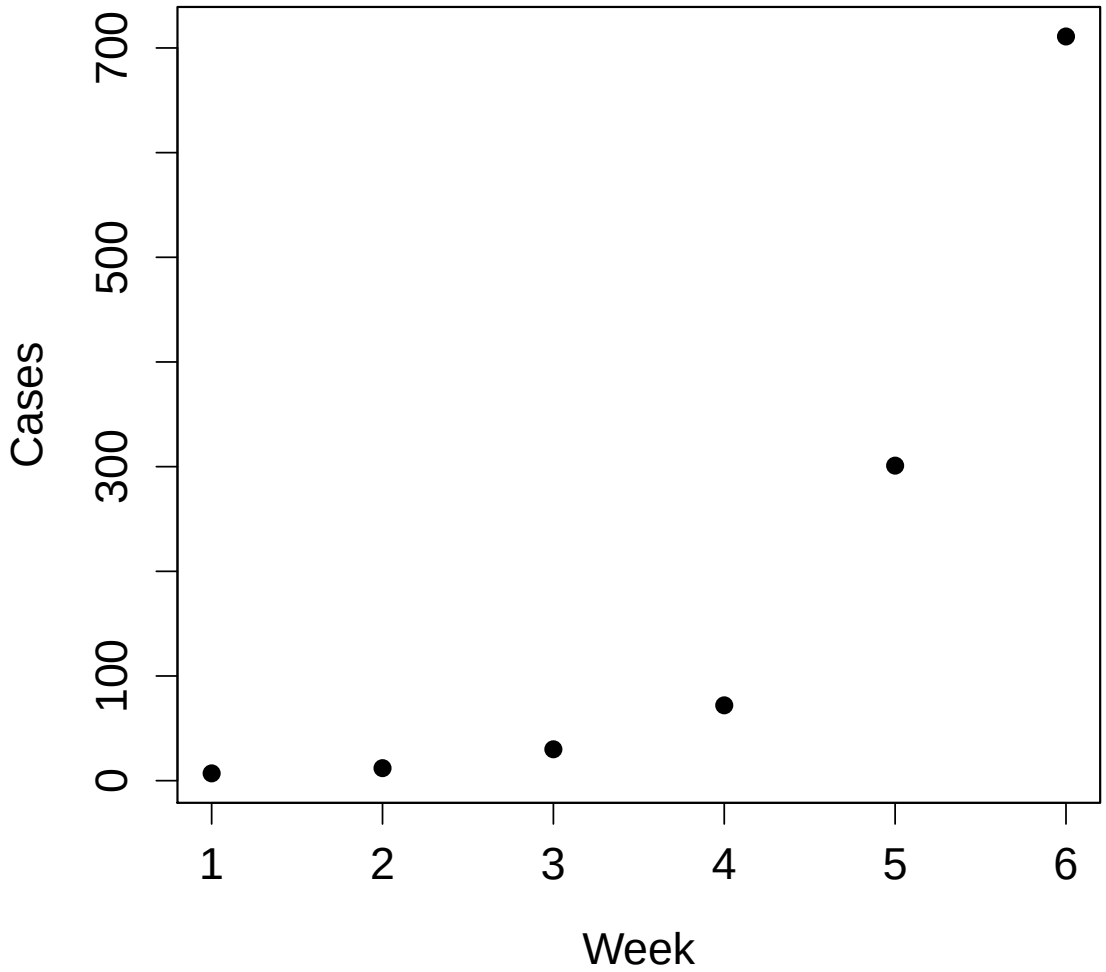


Ebola outbreak



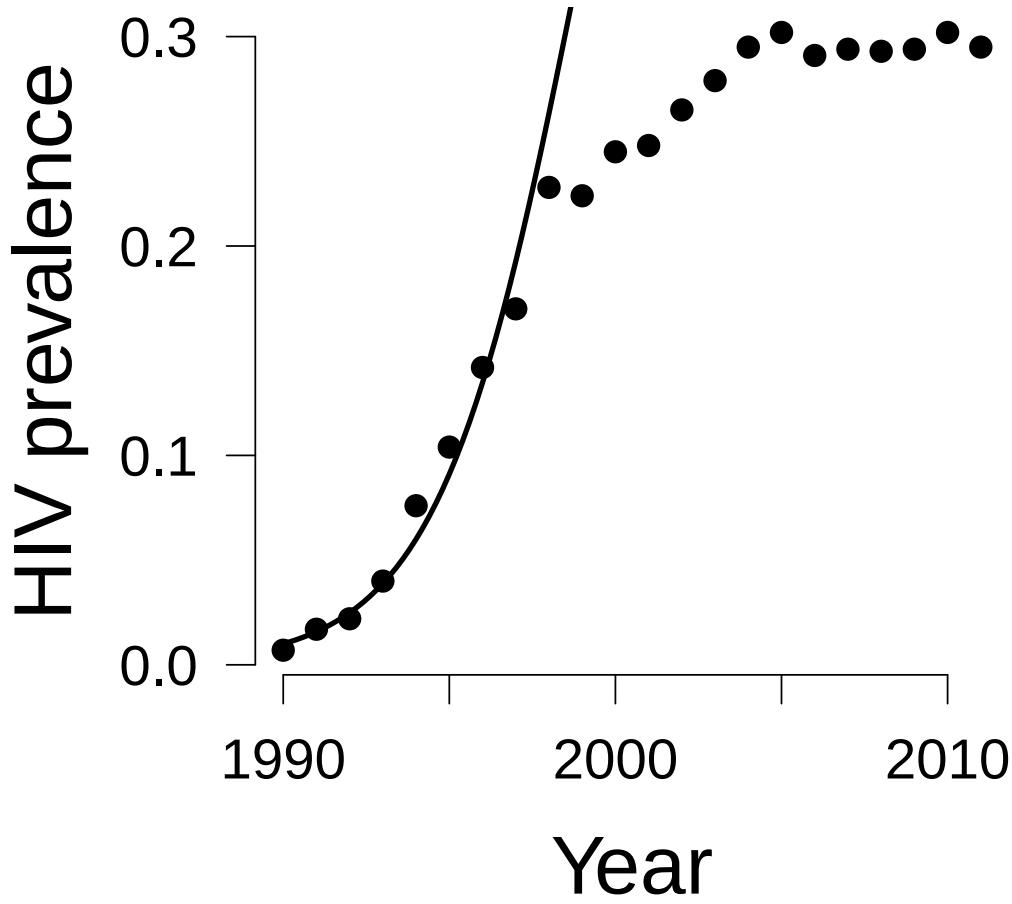
$C \approx 1\,\text{month},\ G \approx 2\,\text{week}$

Mexican flu



$C \approx 1\,\text{week},\ G \approx 3\,\text{day}$

HIV in sub-Saharan Africa



$C \approx 18\,\text{month},\ G \approx 4\,\text{years}$

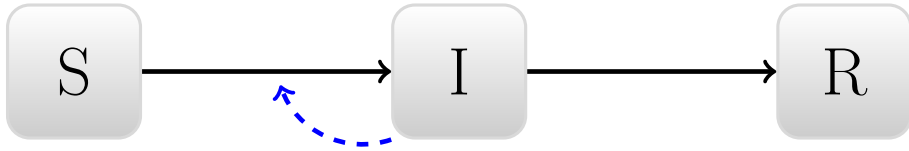
Linking framework

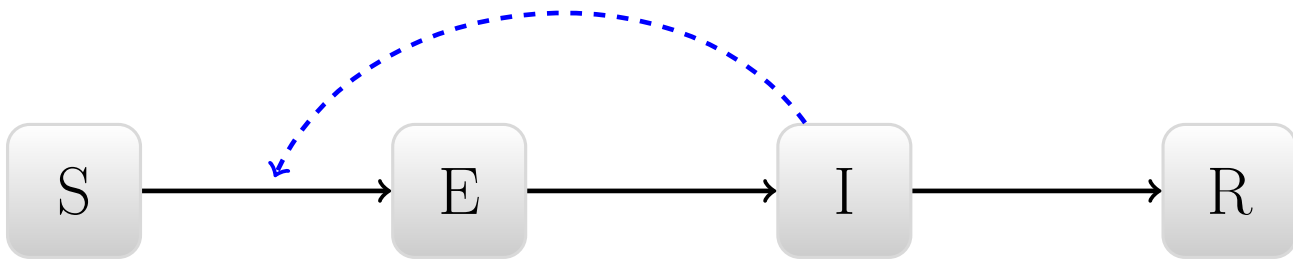
- Epidemic speed (r) is a *product*:
  - generation speed $\times$
  - epidemic strength
- WRONG

- Epidemic speed (r) is a *product*:
  - (something to do with) generation speed $\times$
  - (something to do with) epidemic strength

Outline

Box models



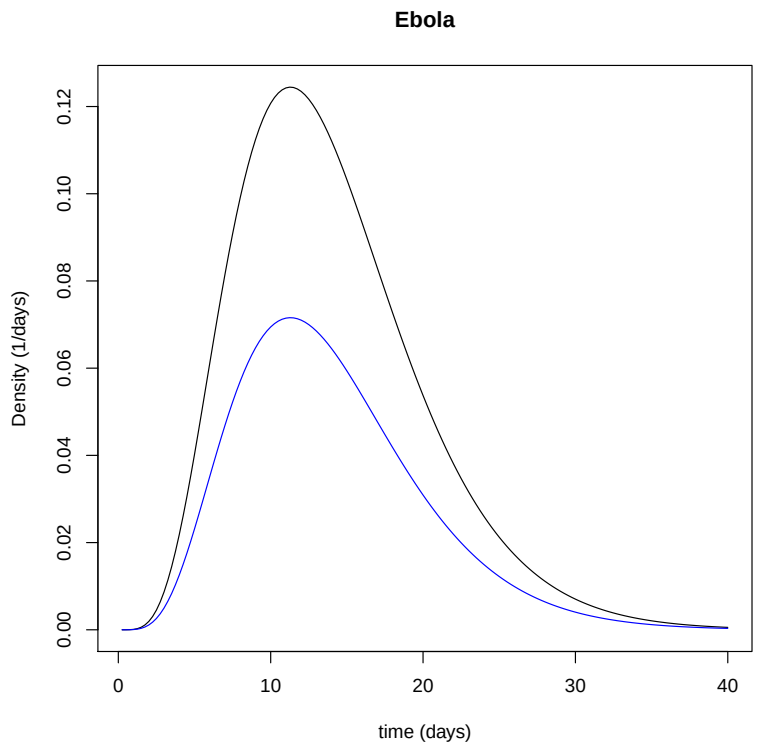


Renewal equation

- A broad framework that covers a wide range of underlying models
- $i(t) = S(t) \int k(\tau) i(t-\tau)\, d\tau$
  - $i(t)$ is the *rate* of new infections (per-capita incidence)
  - $S(t)$ is the *proportion* of the population susceptible
  - $k(\tau)$ measures how infectious a person is (on average) at time τ after becoming infected
- For invasion, treat S as constant

Infection kernel

- $k(\tau)$ is the expected rate at which you infect at time τ after being infected
- $\int_\tau k(\tau)d\tau$ is the expected number of people infected:
  - $\mathcal{R}$ the effective reproductive number
- $k(\tau)/\mathcal{R}$ is a distribution:
  - $g(\tau)$, the *intrinsic* generation distribution



Renewal equations

- More flexible than ODEs
  - Non-exponential distributions, variation in infectiousness through time
  - The ODEs we've seen can be rewritten as renewal equations!
- Can be parameterized by observing generation intervals
  - Contact tracing (realized intervals)
  - infectiousness of studied individuals (intrinsic distribution)

Outline

Euler-Lotka equation

- Model
  - $$i(t) = S \int k(\tau) i(t-\tau)\, d\tau$$
  - If we neglect changes in S, we expect exponential growth
- Exponential phase
  - Disease grows with characteristic time $C = 1/r$
  - $$i(t) = i(0) \exp(rt)$$

Euler-Lotka equation

- $$i(t) = S \int k(\tau) i(t-\tau)\, d\tau$$
- Substitute:
$$i(t) = i(0) \exp(rt)$$
- $1 = \int k(\tau) \exp(-r\tau)\, d\tau$
  - i.e., the total of *discounted* contributions is 1
- $1/\mathcal{R} = \int g(\tau) \exp(-r\tau)\, d\tau$

Interpretation: generating functions

- $1/\mathcal{R} = \int g(\tau) \exp(-r\tau)\, d\tau$
- *J Wallinga, M Lipsitch; DOI: 10.1098/rspb.2006.3754*

Outline

Interpretation: "effective" generation times

- Define the effective generation time so that
  - $$\mathcal{R} = \exp(r\hat{G})$$
- Then:
  - $$1/\mathcal{R} = \int g(\tau)\exp(-r\tau)\,d\tau$$
  - $$\exp(-r\hat{G}) = \langle \exp(-r\tau)\rangle_g.$$
  - A filtered mean:
    - The discounted value of $\hat{G}$ is the expectation of the discounted values across the distribution

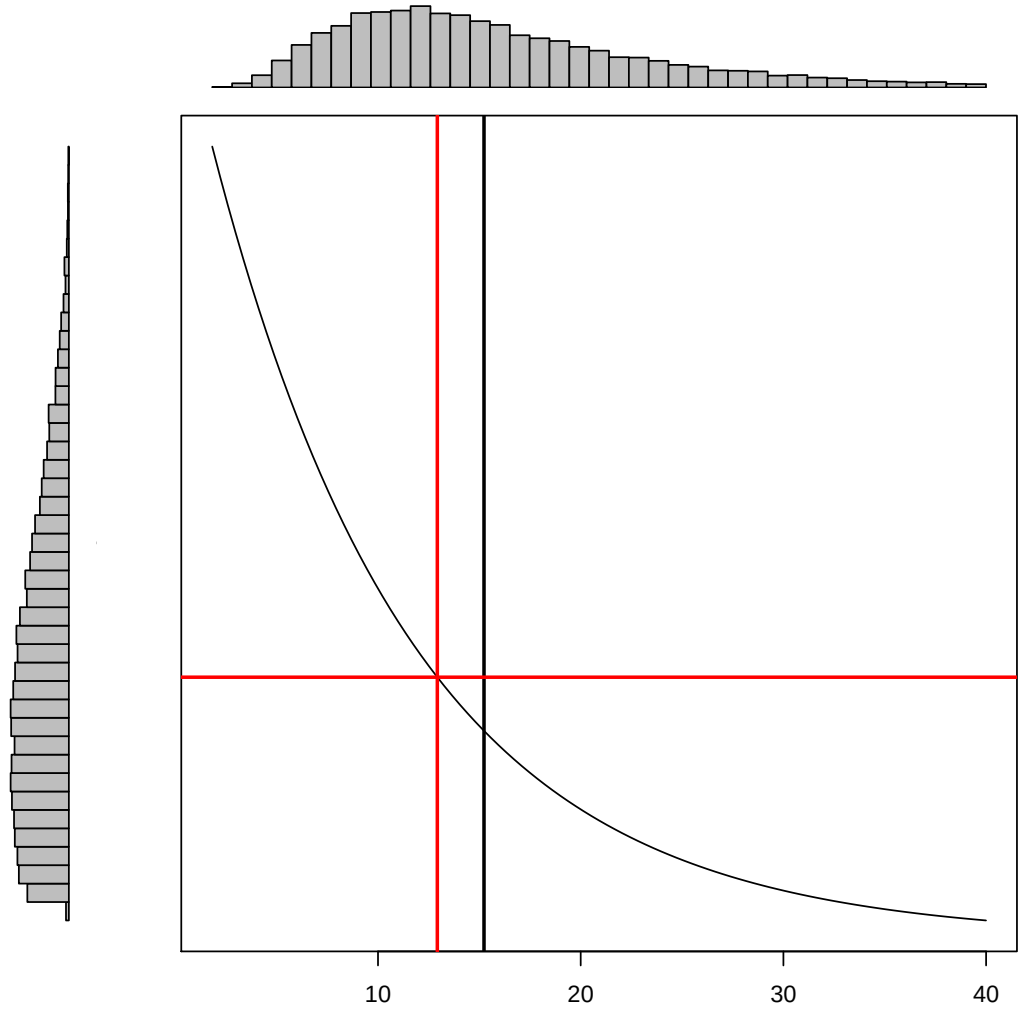
Filtered means

- Many things we know about are examples of filtered means
  - Geometric mean (log function)
  - Harmonic mean (reciprocal function)
  - Root mean square (square)

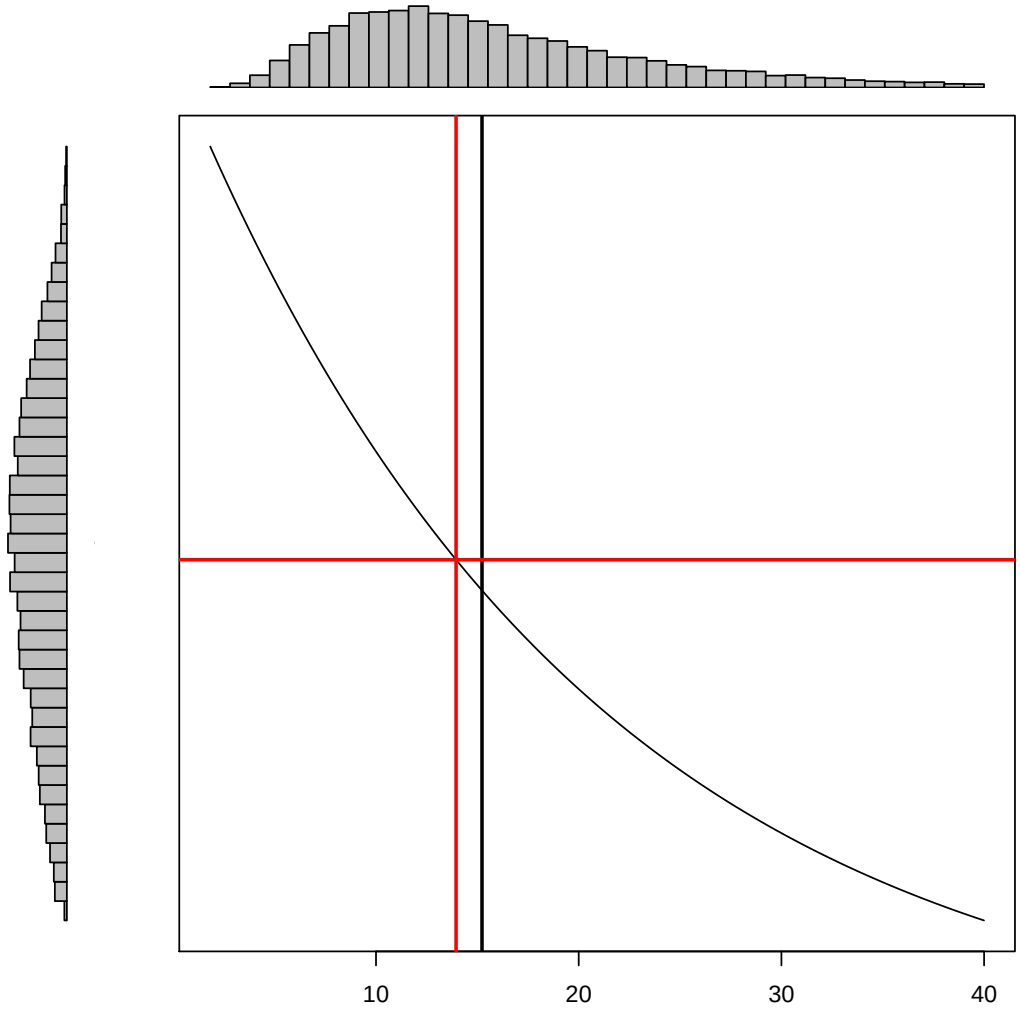
Linking framework

- Epidemic speed (r) is a *product*:
  - (something to do with) generation speed $\times$
  - (something to do with) epidemic strength
- In particular:
  - $r = (1/\hat{G}) \times \log(\mathcal{R})$
  - $\hat{G}$ is the effective mean generation time

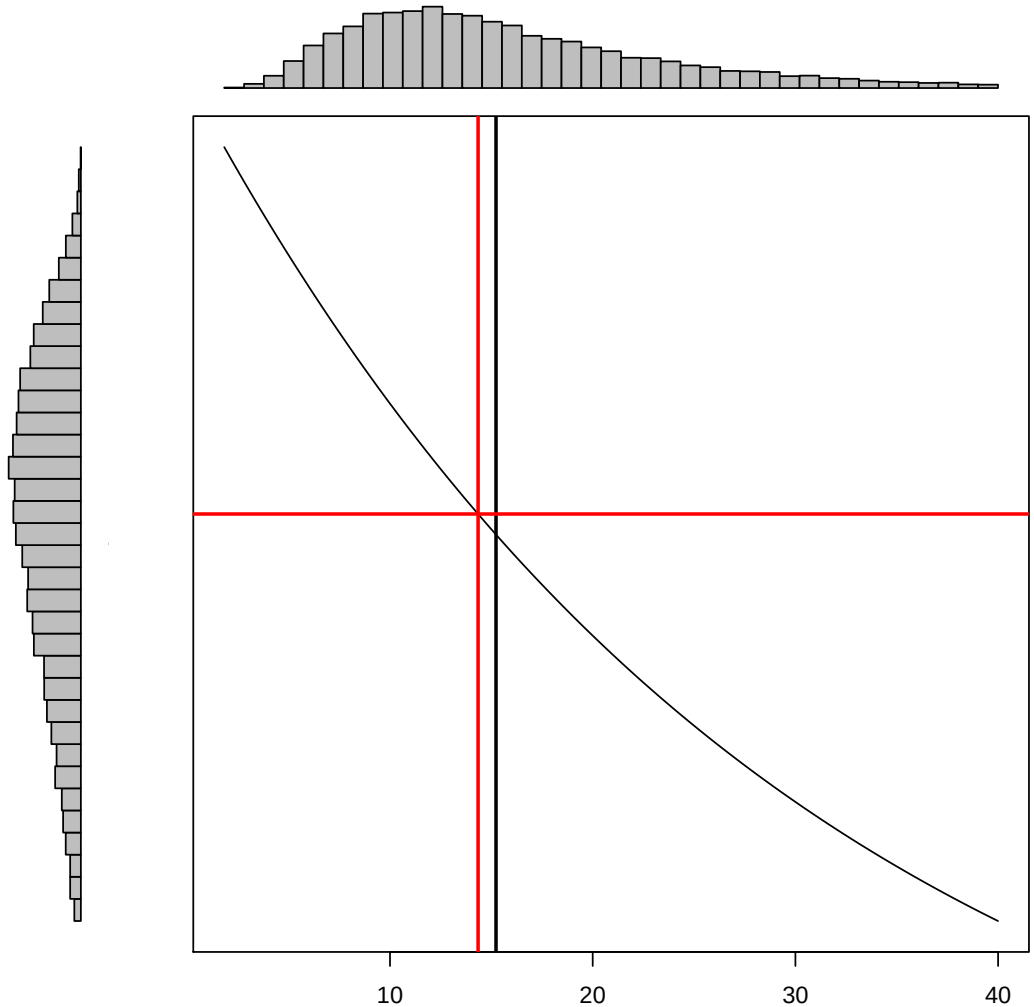
$$C = 1/r = 10d$$



$$C = 1/r = 20d$$



$C = 1/r = 30d$ *(present)*



Filtered means have intuitive properties

- Shifts in distribution shift the mean about how you would expect
  - More late transmission means longer $\hat{G}$
  - Longer $\hat{G}$ means higher $\mathcal{R}$ for a given r
- As distribution gets narrower, $\hat{G}$ increases toward the mean $\bar{G}$
- As distribution gets wider, $\hat{G}$ decreases
  - Scientific interpretation?

The filtering function

- $\exp(-r\hat{G}) = \langle \exp(-r\tau) \rangle_g$,
- $\hat{G}$ is the mean of the generation distribution $g(\tau)$ ...
- Filtered by the discount function associated with the rate of exponential growth of the epidemic
  - i.e., the relative importance of a contribution at that time

Outline

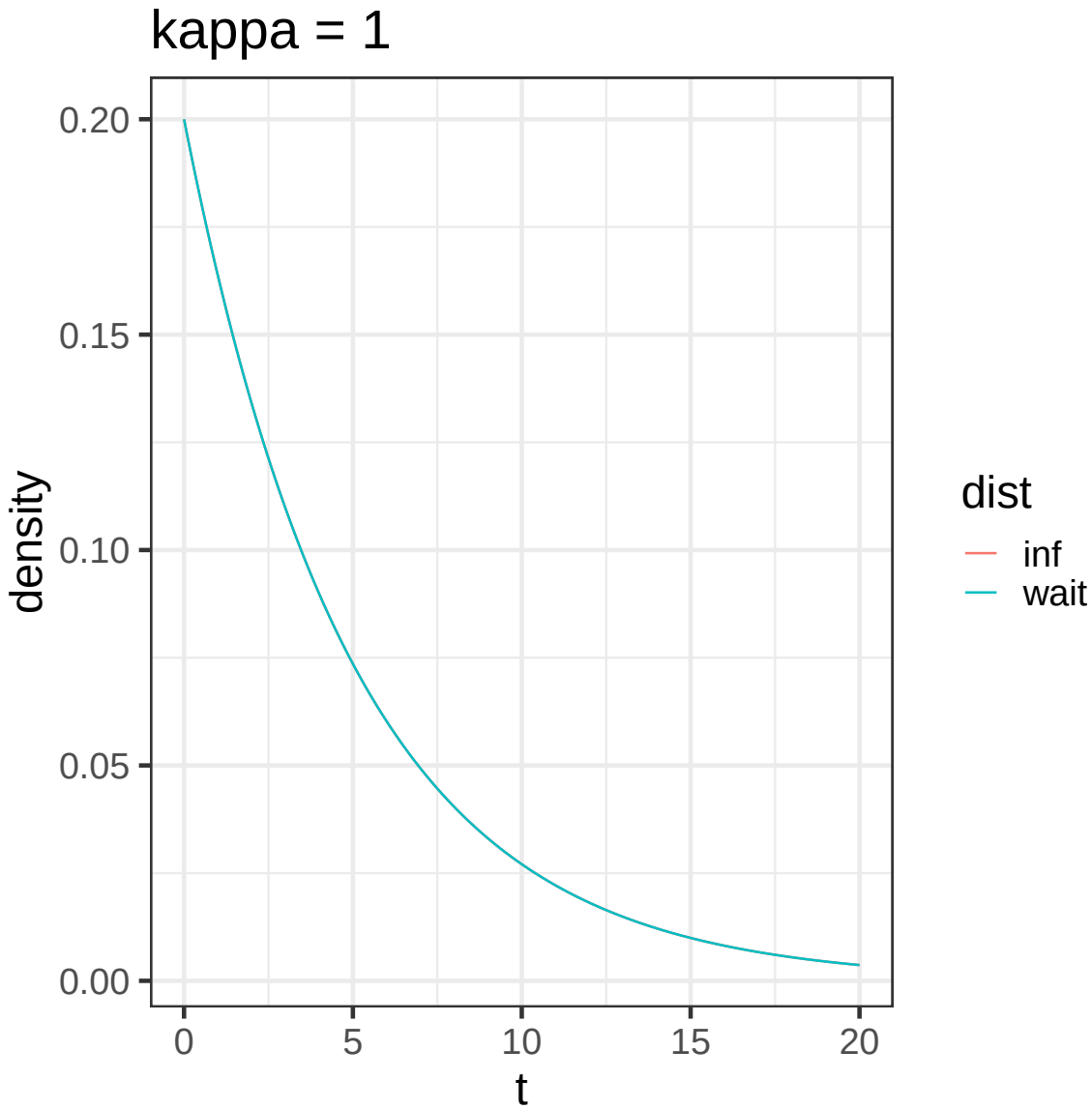
Problems

- The filtered mean has drawbacks
- $\hat{G}$ depends on r as well as G
- How is
  - $\mathcal{R} = \exp(r\hat{G})$
- Consistent with the result from ODEs
  - $\mathcal{R} = 1 + r\bar{G}$?

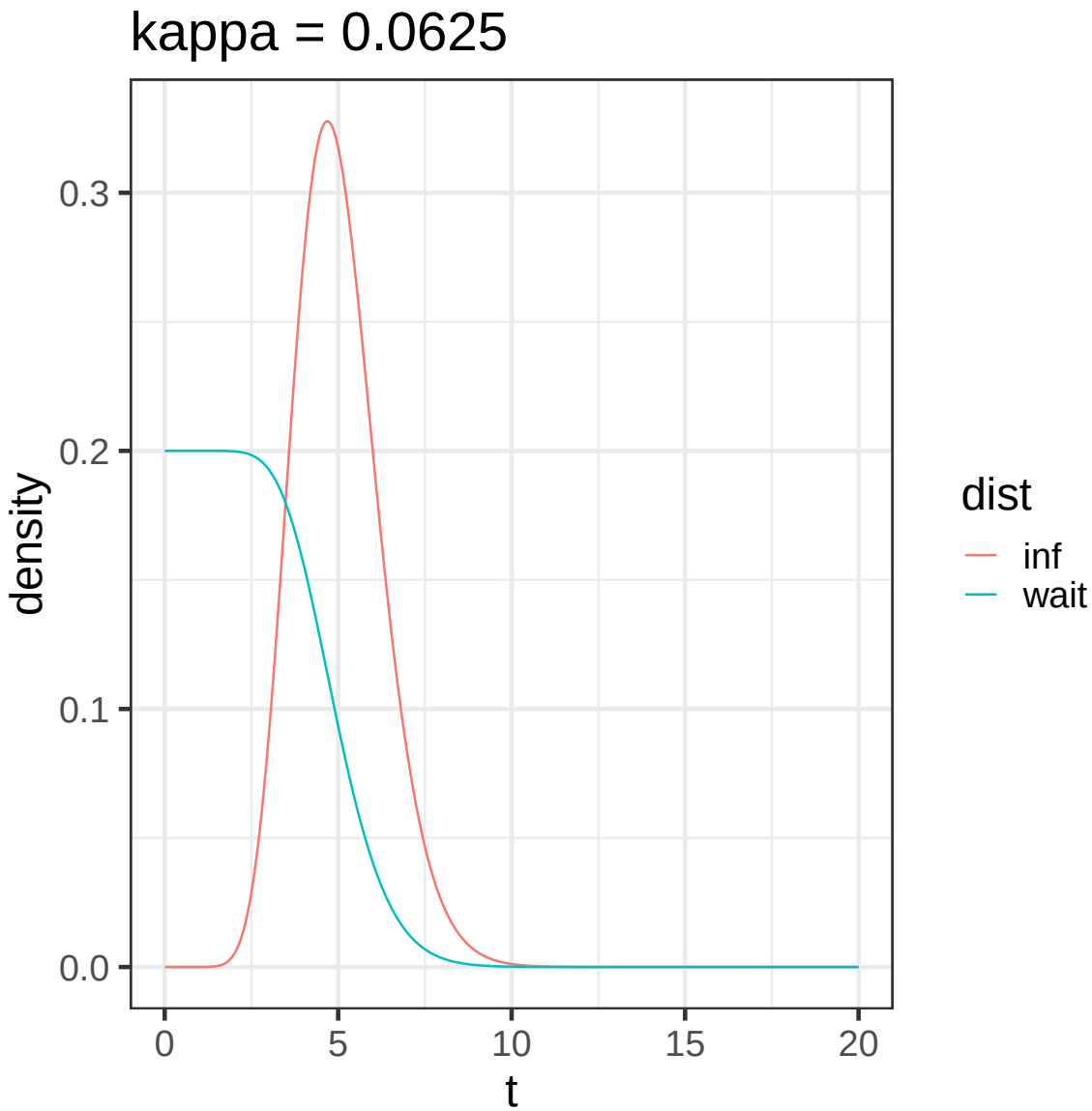
Infectious times and waiting times

- If the average infectious time is 5 days, what is the average generation time?
  - The average latent period plus the infectious-waiting period
- What is the average infectious-waiting period?
  - $5\mathrm{d}(1+\kappa)/2$
    - κ measures the relative variation of the infectious period
  - The waiting period is not the infectious period
    - The exponential distribution is trying to trick you!

Infectious and waiting periods (present)



Infectious and waiting periods



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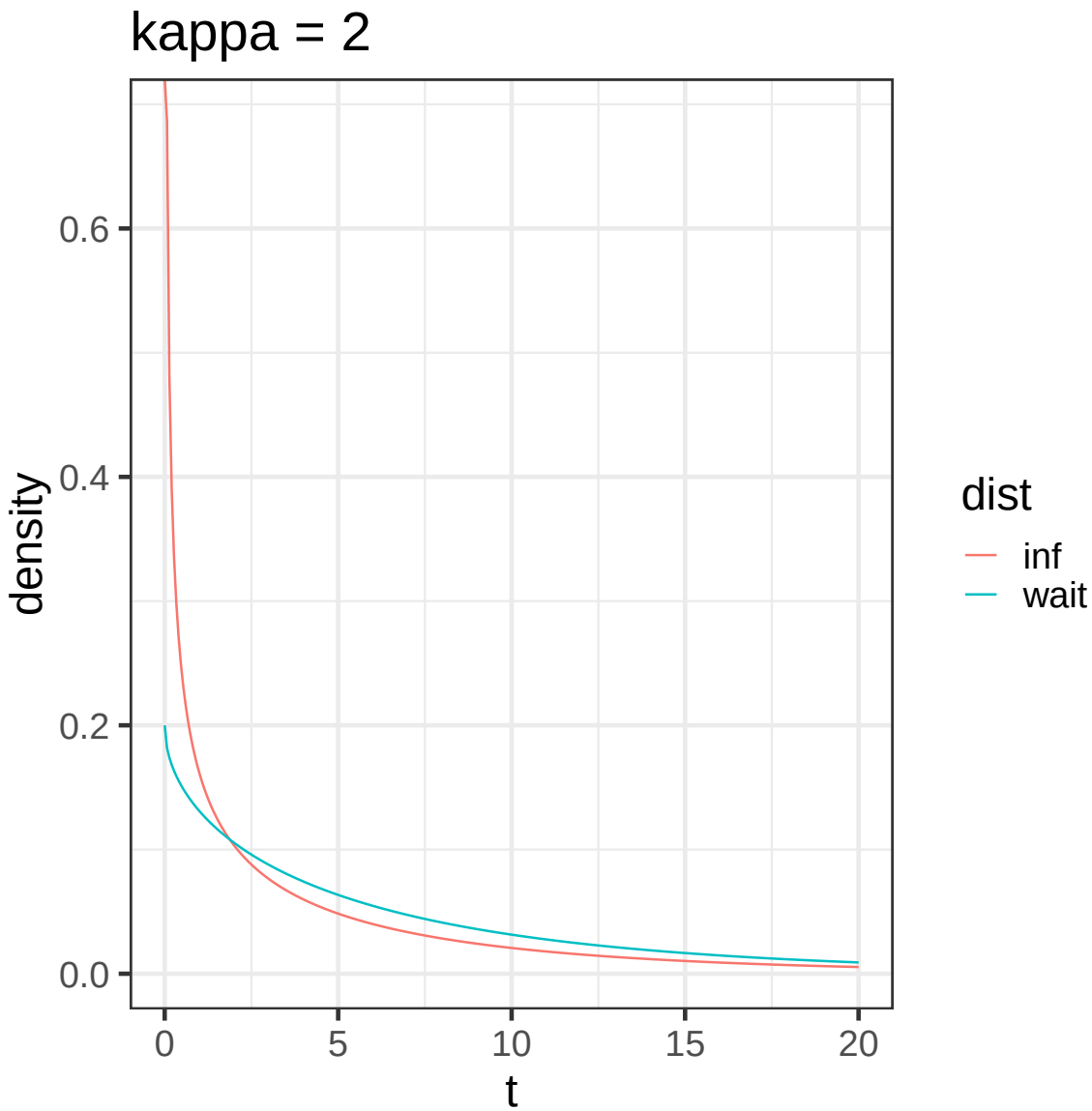


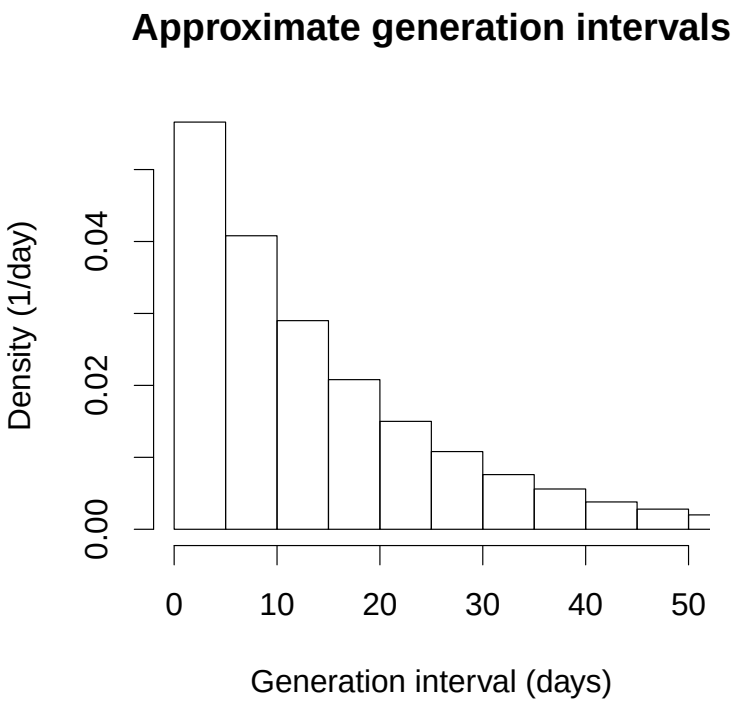
An approximation

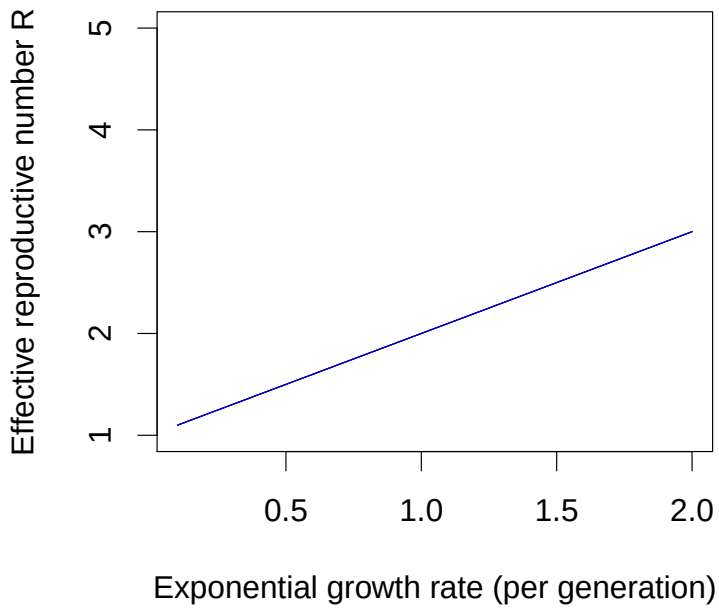
- We make the $r\mathcal{R}$ link with a moment approximation
- Define $\kappa = \sigma_G^2/\mu_G^2$ – the squared coefficient of variation of the generation distribution
- $\mathcal{R} \approx (1 + r\kappa\bar{G})^{1/\kappa}$
  - Equal when $g(\tau)$ has a gamma distribution
  - Simple and straightforward
  - When is it a useful approximation?

Compound-interest interpretation

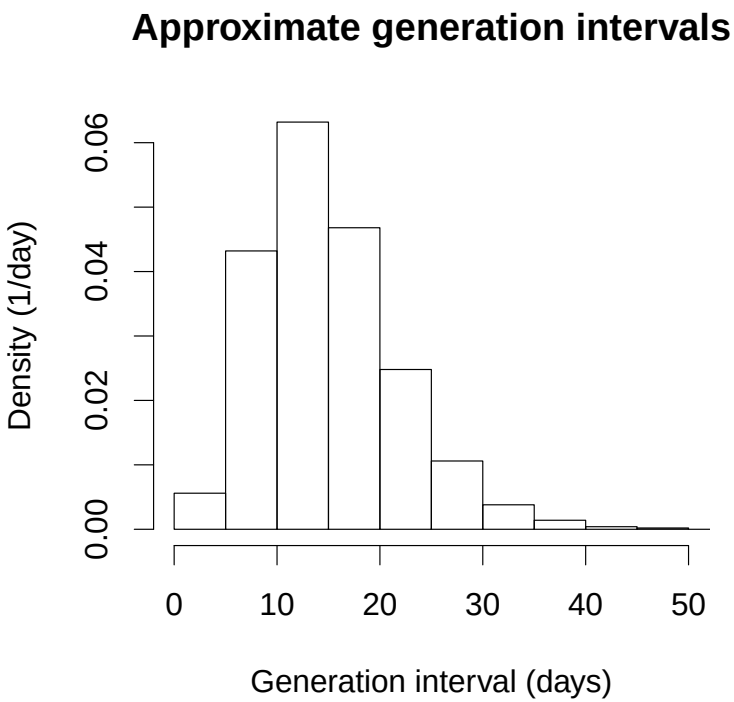
- Define $\mathcal{R} \approx (1 + r\kappa\bar{G})^{1/\kappa} \equiv X(r\bar{G}; 1/\kappa)$
- X is the compound-interest approximation to the exponential
  - Linear when $\kappa = 1$ (i.e., when g is exponential)
  - Approaches exponential as $\kappa \to 0$

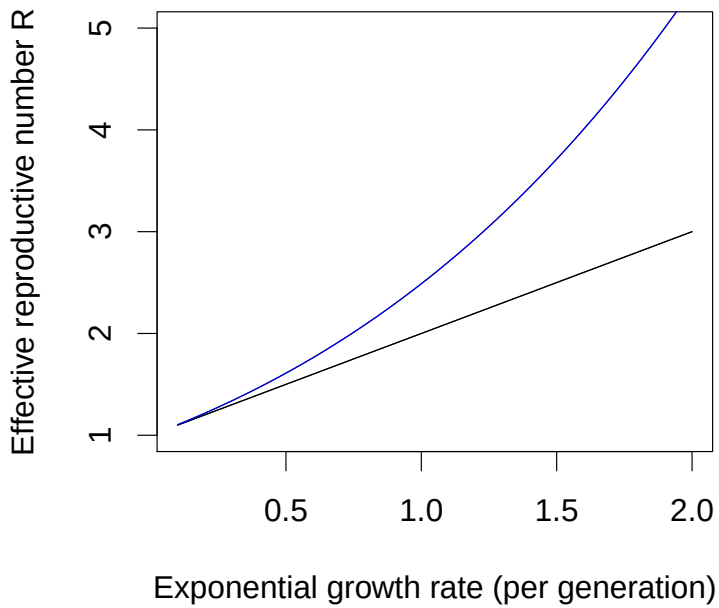
Moment approximation (present)



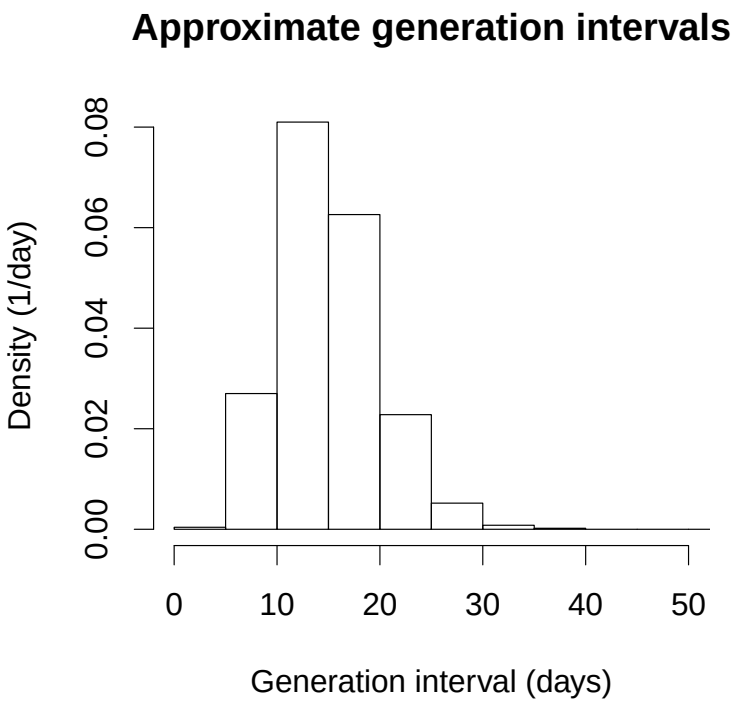


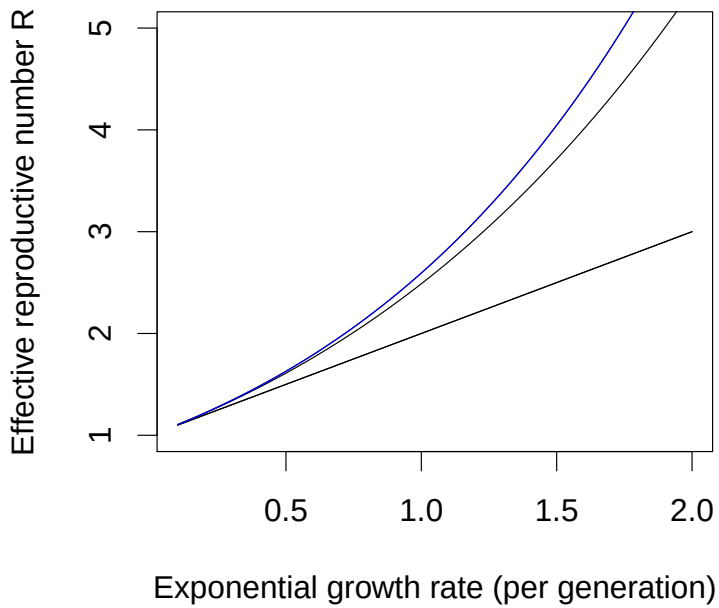
Moment approximation (present)



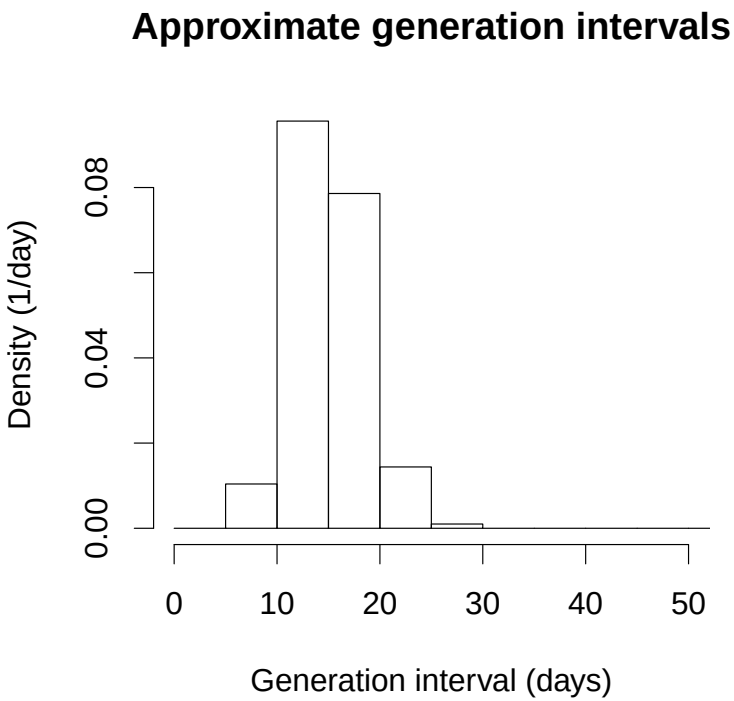


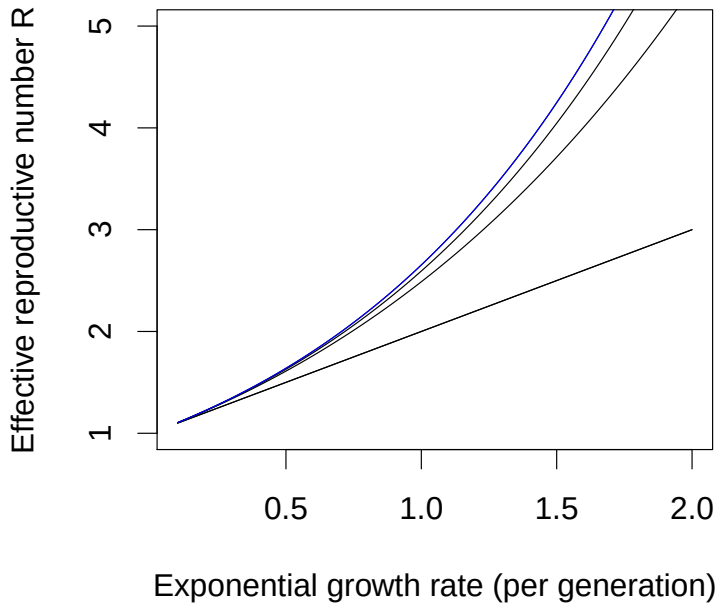
Moment approximation (present)





Moment approximation





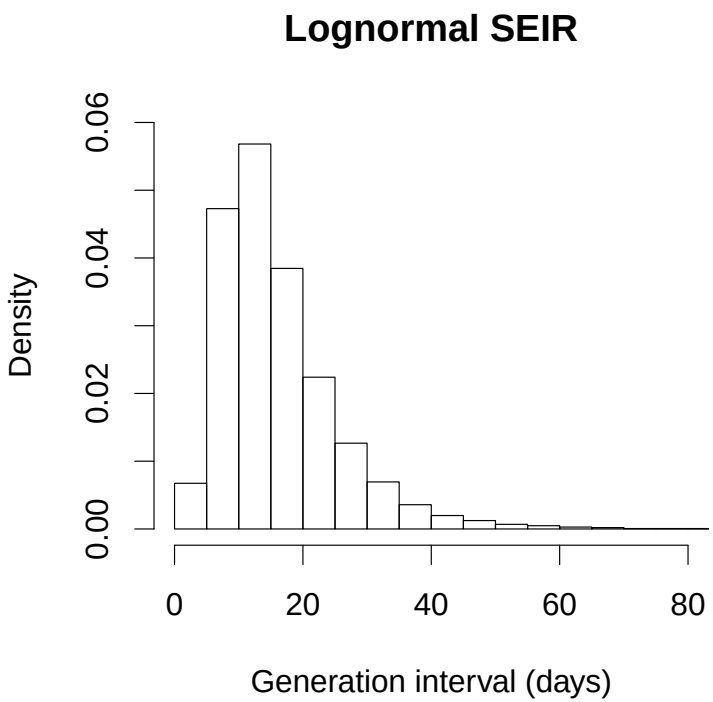
Qualitative response

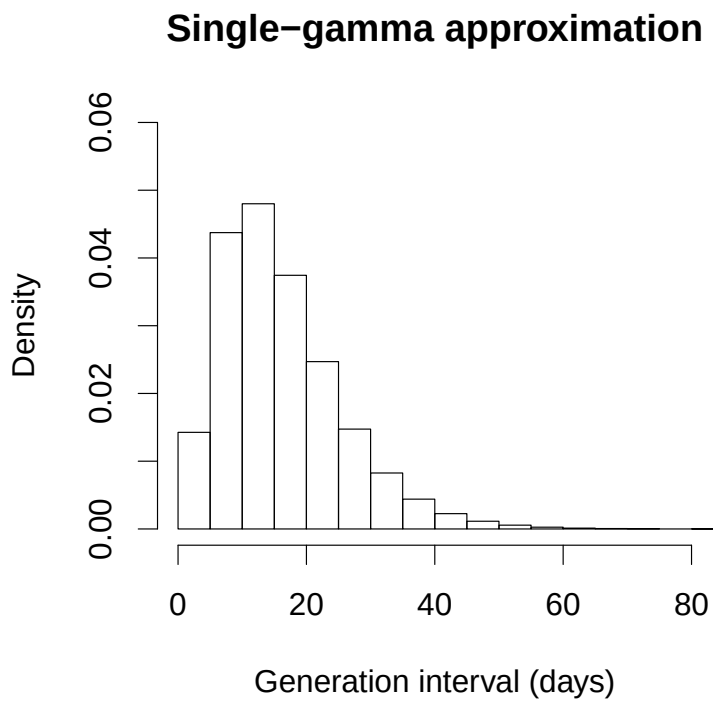
- For a given value of $\bar{G}$, smaller values of κ mean:
  - less variation in generation interval
  - less compounding of growth
  - greater $\mathcal{R}$ required for a given r

Fitting to Ebola

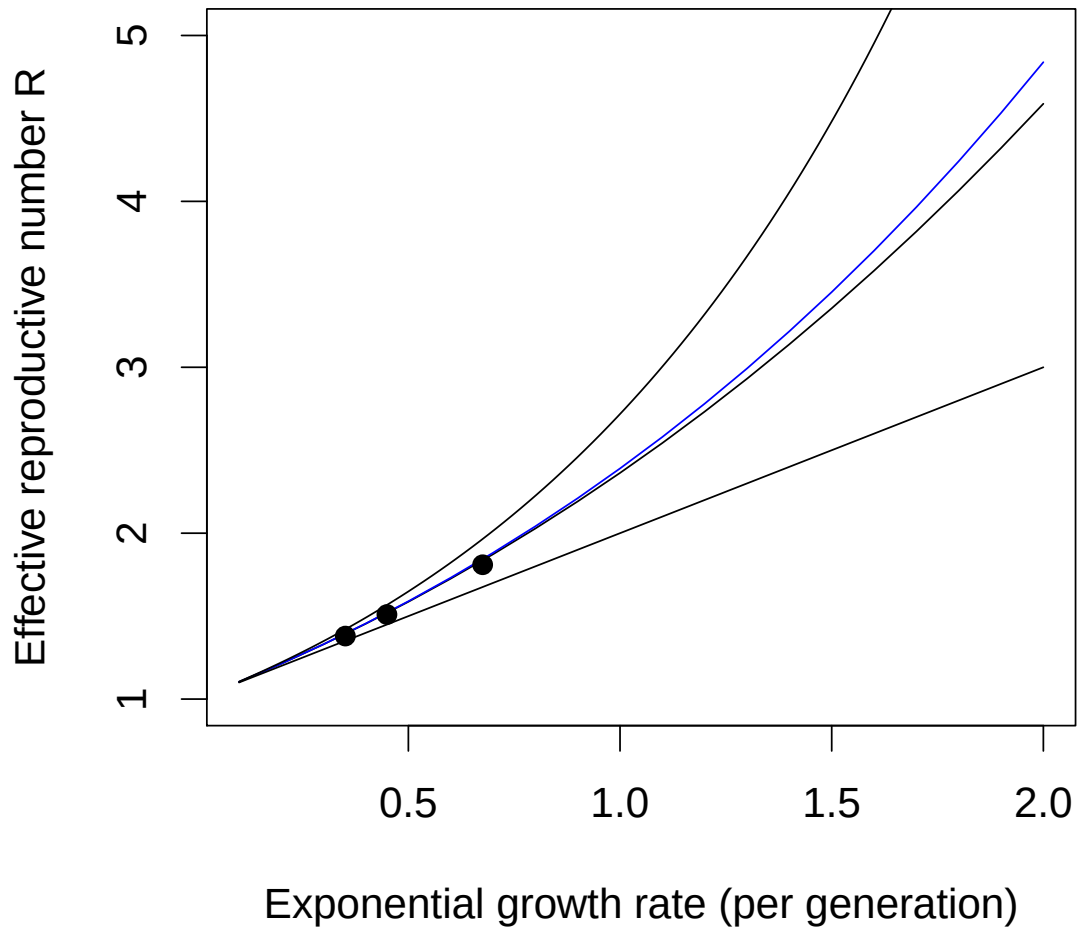
- Simulate generation intervals based on data and approach from WHO report
- Use both lognormals and gammas
  - WHO used gammas
  - Lognormals should be more challenging

Approximating the distribution





Approximating the curve



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

Other diseases

- This approximation works suspiciously well for measles parameters
- Noticeably less well for rabies parameters
  - Can be improved using gamma-based estimates of the moments

Summary

- For many practical applications:
  - Estimating the mean generation interval is not enough
  - But estimating the mean and CV may be enough
    - This can also allow us to address our uncertainty
- Filtered mean is useful for qualitative explanations
  - e.g., Ebola burial

Outline

Generation intervals through time

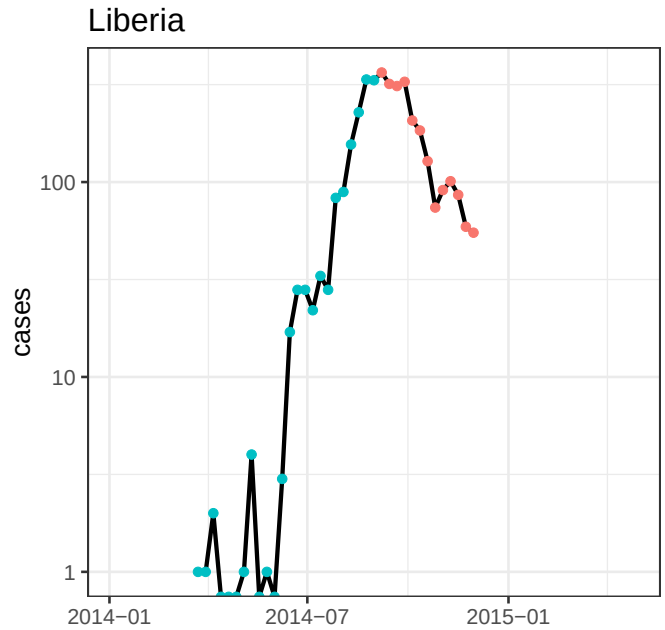
- Generation intervals can be estimated by:
  - Observing patients:
    - How long does it take to become infectious?
    - How long does it take to recover?
    - What is the time profile of infectiousness/activity?
  - Contact tracing
    - Who (probably) infected whom?
    - When did each become ill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

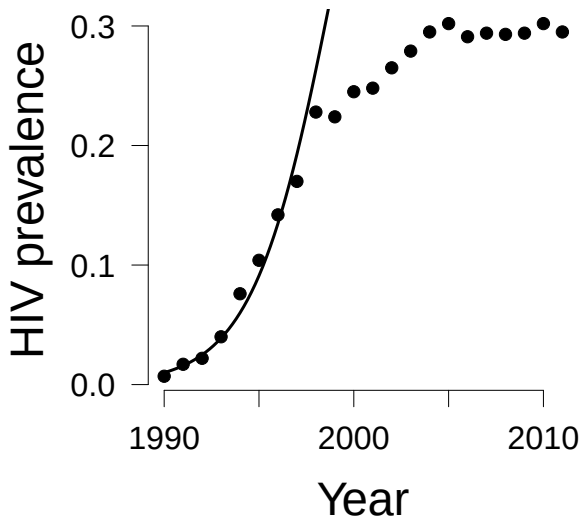
Types of interval

- Contact-tracing intervals look systematically different, depending on when you observe them.
- Define:
  - *Intrinsic interval*: How infectious is a patient at time τ after infection?
  - *Forward interval*: When do people infected at a particular time infect others?
  - *Backward interval*: When were the people who infect at a particular time infected?

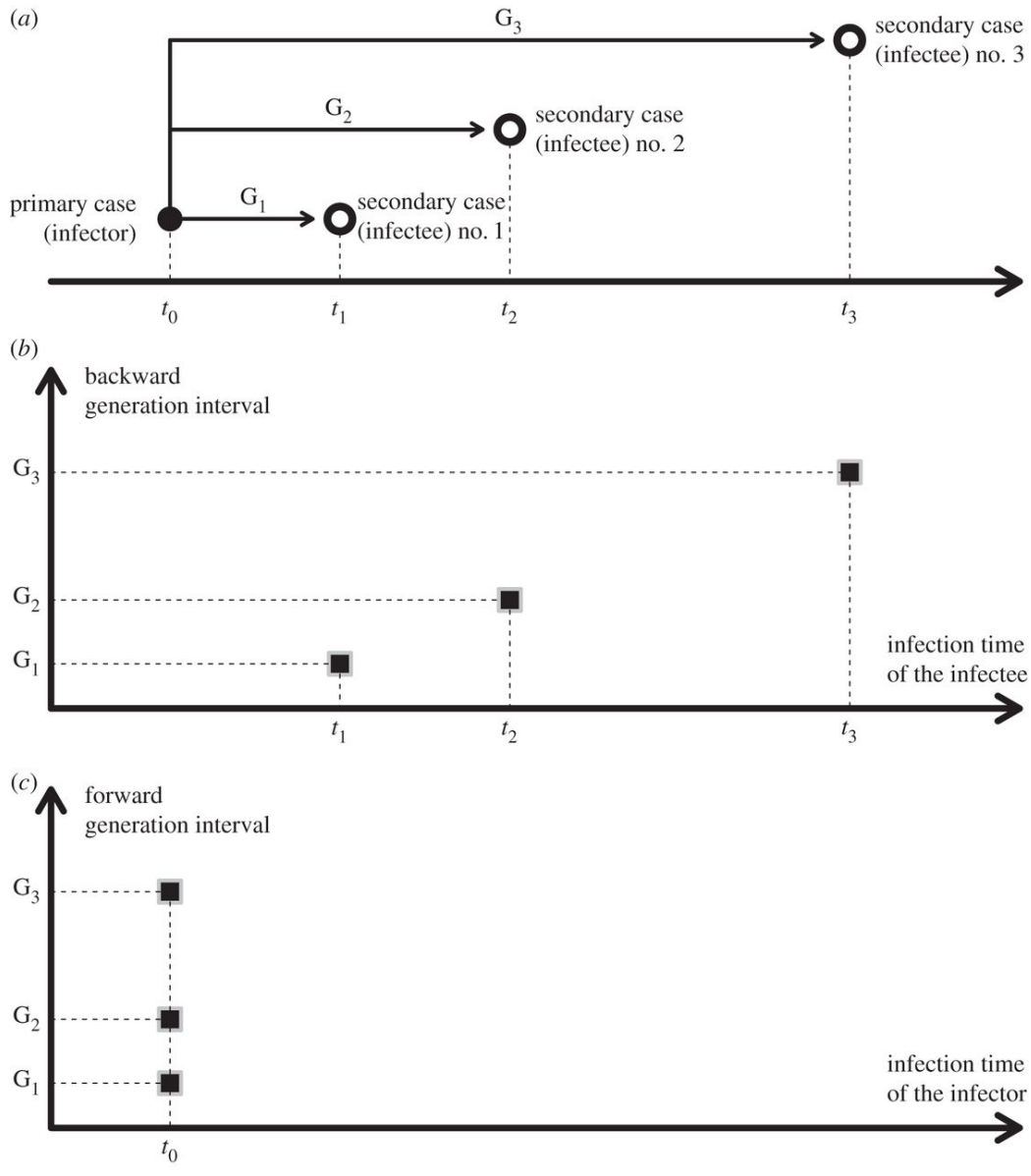
Growing epidemics

- 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





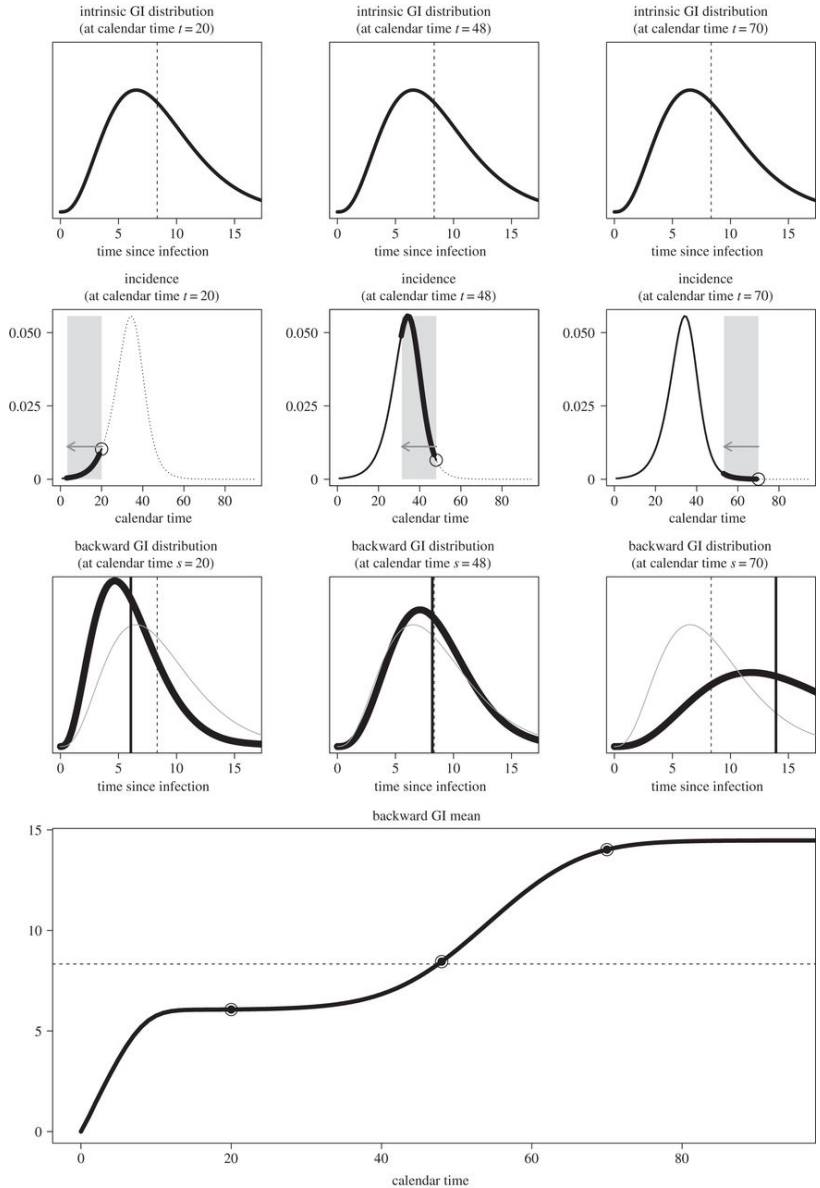
Forward and backward intervals



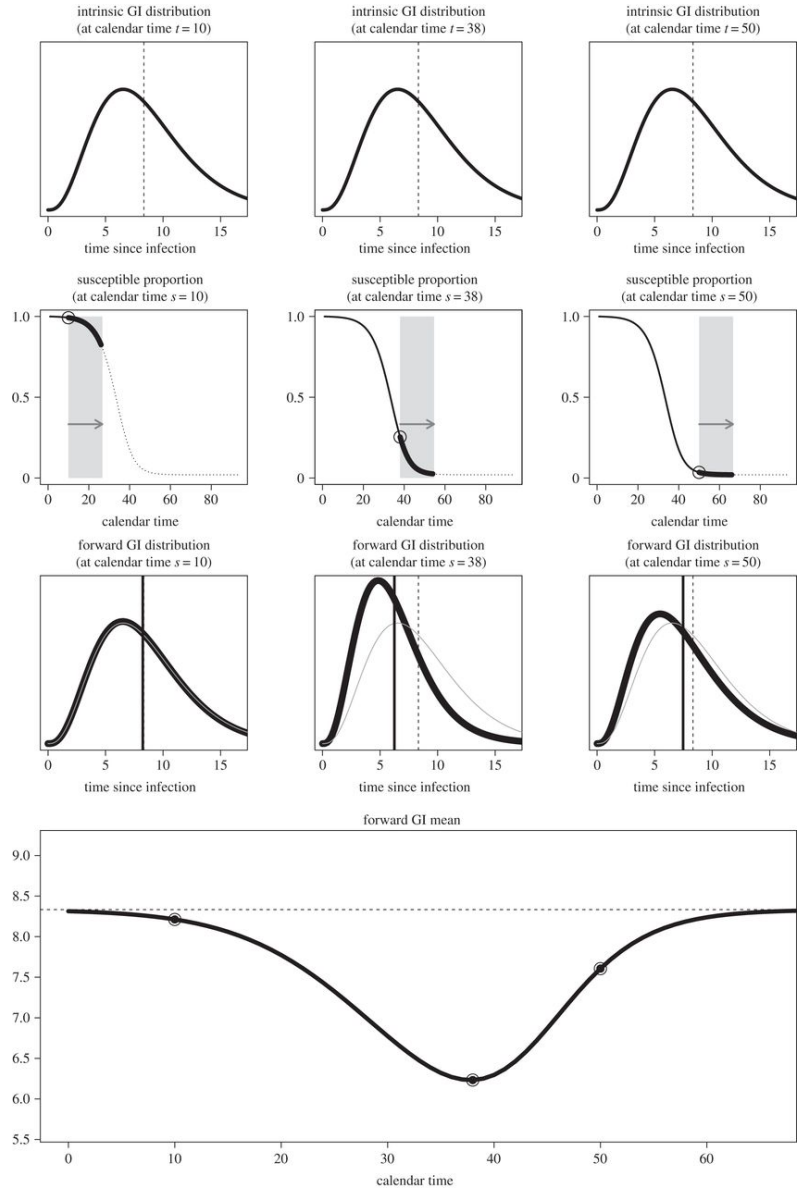
Correcting

- Infection events: someone infected at time s is infecting someone at time t
  - $i_s(t) = S(t)k(t-s)i(s)$
- Backward intervals
  - Who infected the people infected at time t?
    - $\propto k(t-s)i(s)$
  - Depends on k, but also on changes in $i(s)$
- Forward intervals
  - Who did the people infected at time s infect?
    - $\propto S(t)k(t-s)$
  - Depends on k, but also on changes in $S(t)$

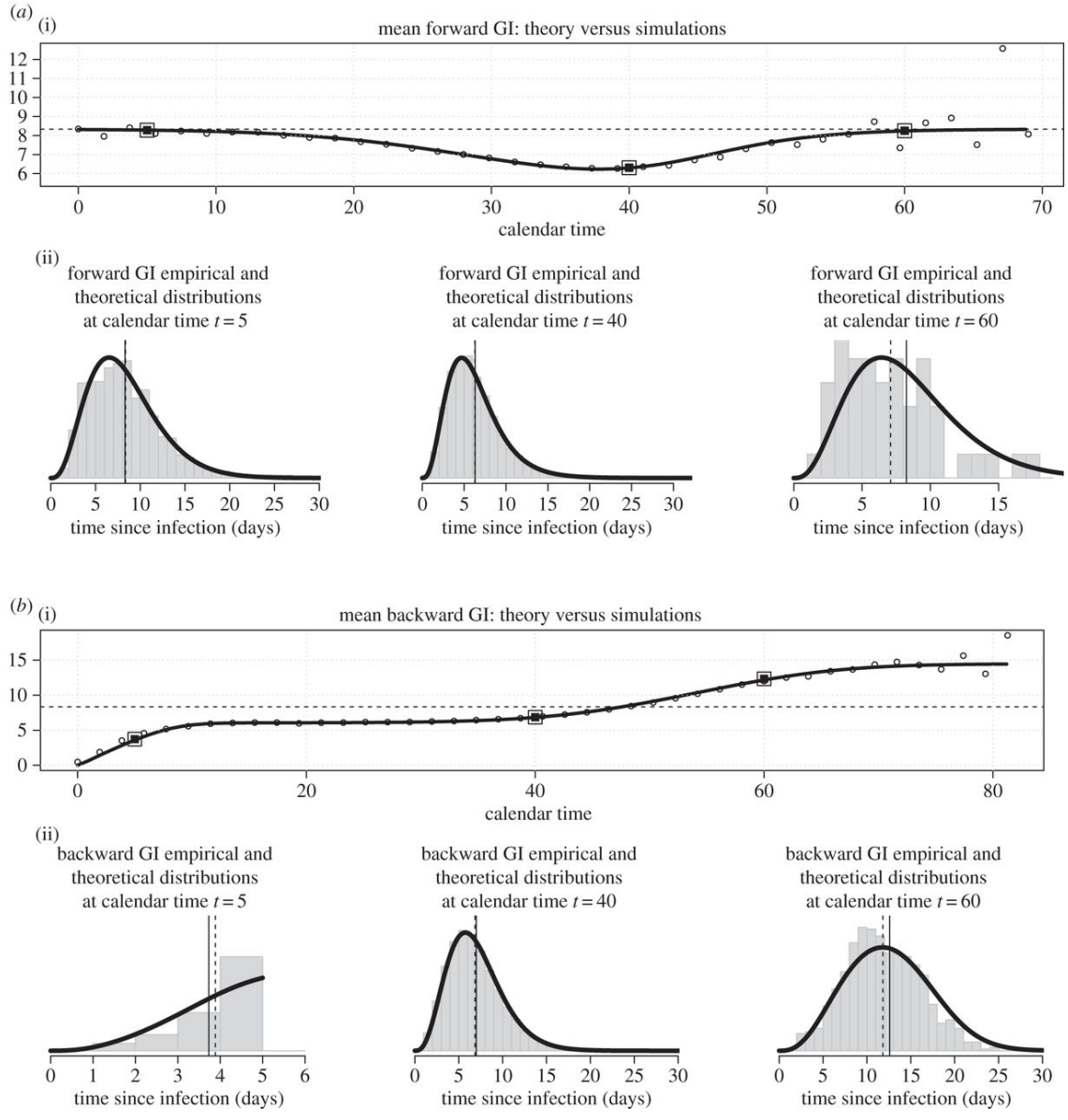
What changes backward intervals? (present)



What changes forward intervals? (present)



Theory and simulation



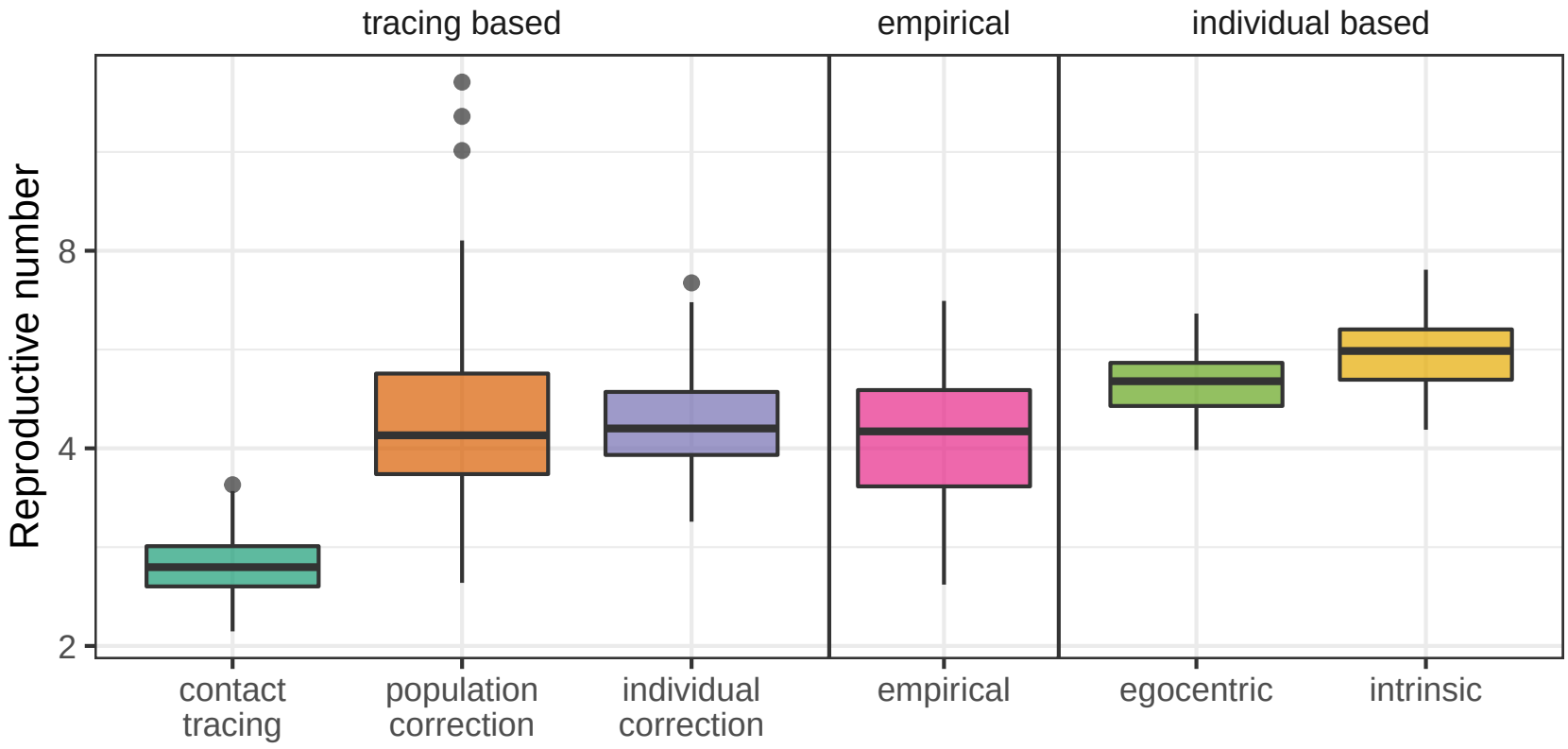
Champredon and Dushoff, 2015. DOI:10.1098/rspb.2015.2026

Conclusion

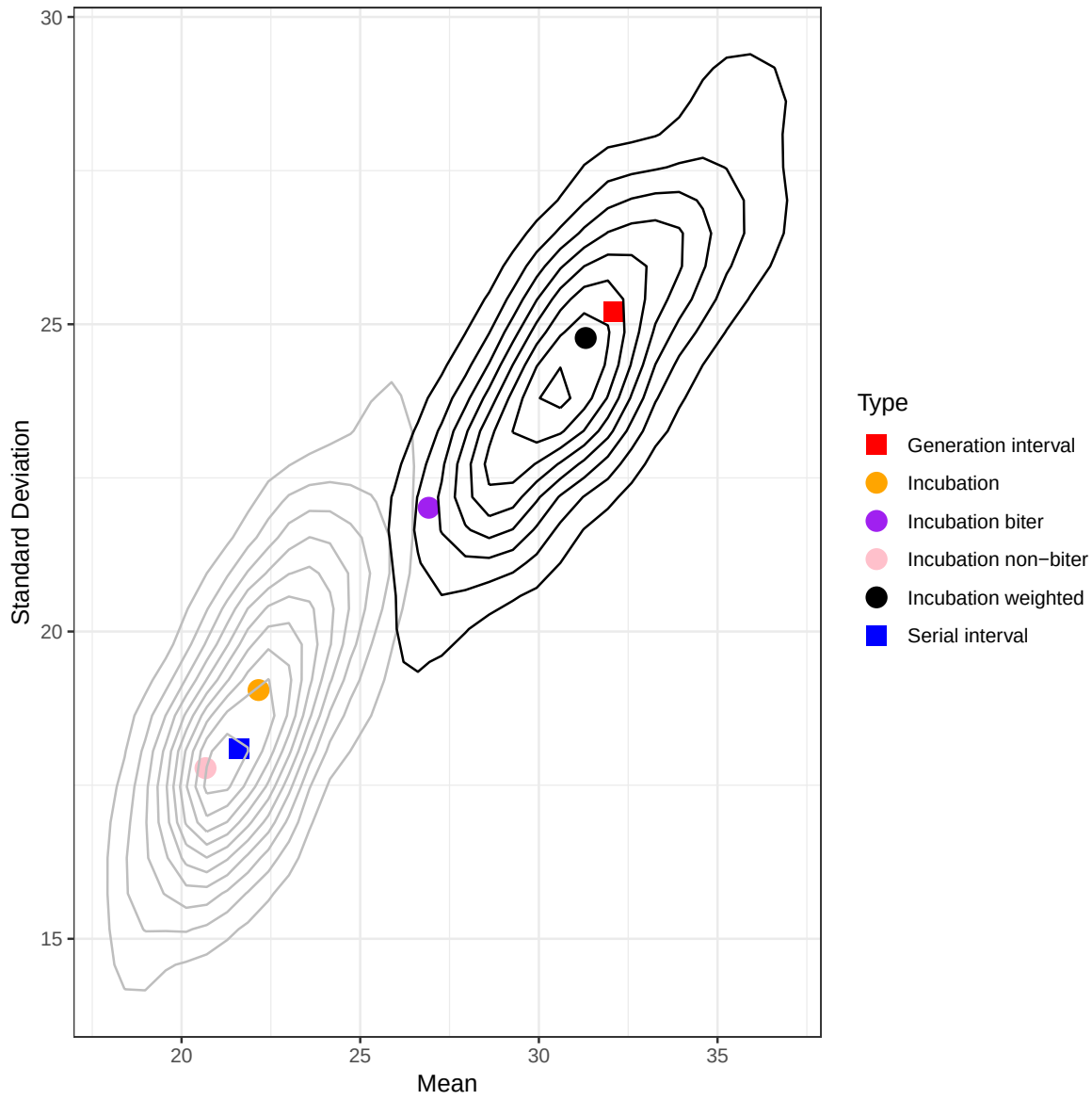
- Backward intervals change if the number of infectious individuals is changing as you look back
- Forward intervals change if the number of *susceptible* individuals is changing as you look forward
- Lack of care in defining generation intervals can lead to bias
  - In particular, generation intervals look short during an epidemic outbreak
    - Makes diseases look less dangerous!
  - These biases can be corrected

Outline

Spatial struture



Individual-level heterogeneity



Summary

- Generation intervals are often taken for granted
- We need better methods for defining different measures of disease generations
  - We need to consider our *uncertainty* about generations when making conclusions
- Generation intervals are fun conceptually, mathematically and practically

Outline

Compartments vs. cohorts

- We have a some simplified biological assumptions about how a disease spreads
- We can implement these assumptions into a model:
  - Track **compartments**: S, I, R, ...
  - *or* track **cohorts**: a group of people infected at the same time

Cohort approach

- Model
  - $$\frac{dS}{dt} = \mu S - \beta SI/N$$
  - $$\frac{dI}{dt} = \beta SI/N - \gamma I$$
- What happens to a cohort infected at time 0?
  - $$\frac{dI}{d\tau} = -\gamma I$$
  - $$I(\tau) = I(0)\exp(-\gamma\tau)$$
- We can write cohort equations for more complicated models as well

Another view of the model

- Model **incidence** i:
  - $$\frac{dS}{dt} = \mu S - i(t)$$
  - $$\frac{dI}{dt} = i(t) - \gamma I$$
  - $$i(t) = \beta SI/N$$

Cohort approach

- We can use standard methods for the differential equation:
  - $$\frac{dI}{dt} = i(t) - \gamma I$$
- or we can just write down the answer using a cohort approach:
  - $$I(t) = \int I(t-\tau, \tau))d\tau$$
  - $$= \int i(t-\tau)\exp(-\gamma\tau))d\tau$$
- This answer makes *biological* sense

Cohort-based equation

- We can eliminate I and write:
  - $$\frac{dS}{dt} = \mu S - i(t)$$
  - $$i(t) = \frac{S}{N} \int \beta i(t-\tau) \exp(-\gamma\tau)) d\tau$$
- This is the *same model*
  - Same assumptions, same dynamics
- We can generalize our compartmental assumptions:
  - $$i(t) = \frac{S}{N} \int i(t-\tau) k(\tau) d\tau$$

Renewal equation

- $$i(t) = \frac{S}{N} \int i(t-\tau) k(\tau) d\tau$$
- $k(\tau)$ is the infection "kernel" – it describes how an incident (new, occurring) case tends to cause other incident cases over time
  - As a function of time since infection
- What are the advantages or disadvantages of this cohort-based approach, compared to a general compartmental model?
- How would you estimate an infection kernel?