

Estimating epidemic speed and strength

The role of generation intervals

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U. Glasgow, Oct 2019

Outline

Overview

Capacity building

Compartmental models

The $r\mathcal{R}$ relationship

Generation intervals

Generations through time

Other kinds of generation interval

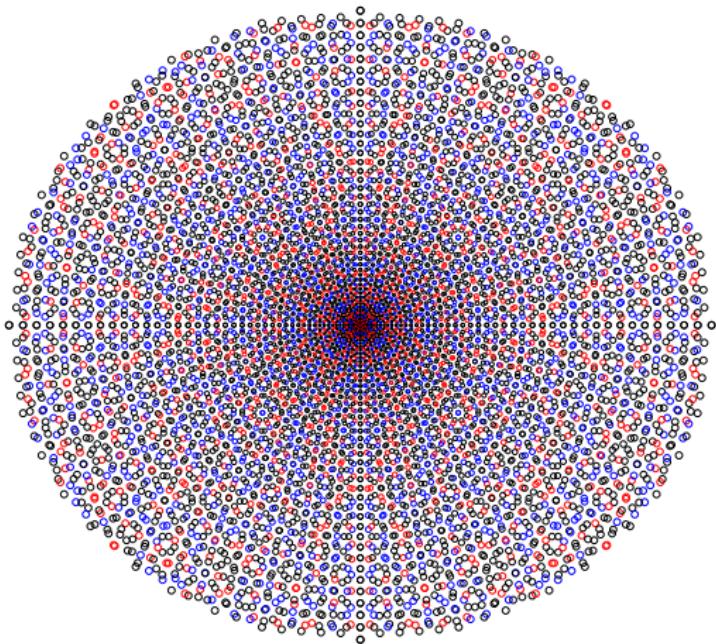
Speed and strength

Thanks

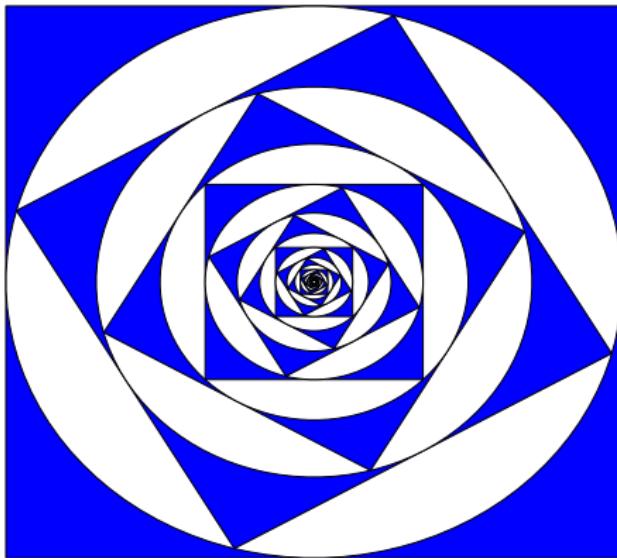
- ▶ Department
- ▶ Collaborators
- ▶ Funders: NSERC, CIHR

Problem (present)

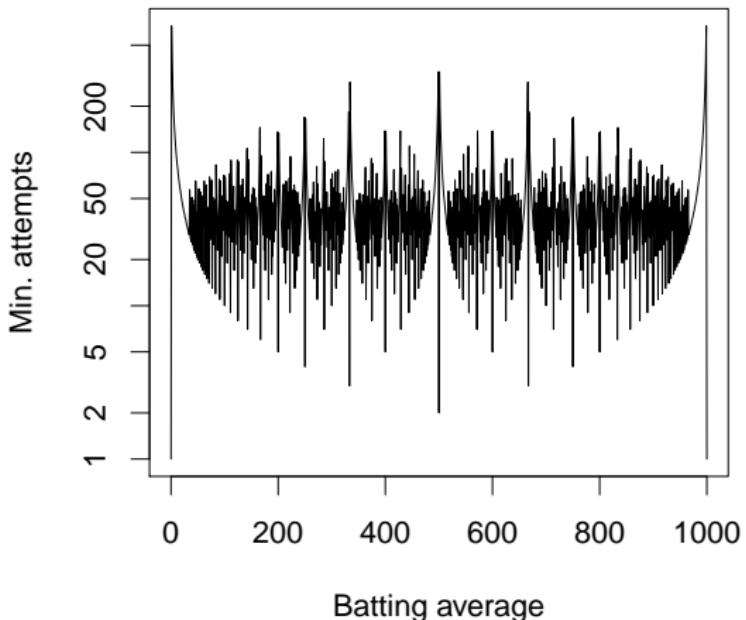
- ▶ I am fundamentally a math person ...



What is the pattern of Pythagorean triples of integers
 $a^2 + b^2 = c^2$?



Divide a square and a circle each into two complementary subsets
that are pairwise similar



How many at-bats does it take to get a given batting average?

Problem

- ▶ I am fundamentally a math person
 - ▶ but I want to do work that is relevant to people

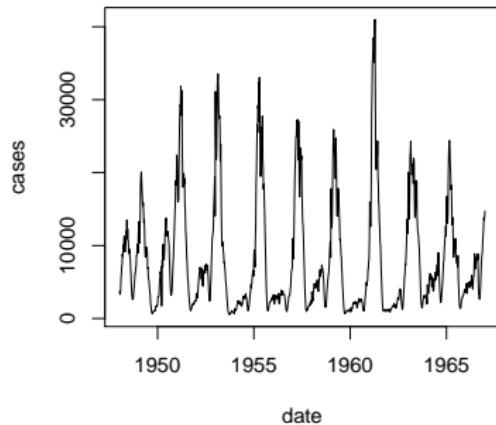
Solution

- ▶ Dynamical modeling is fun and useful
- ▶ ... and highly relevant to the spread of disease

Dynamical modeling connects scales

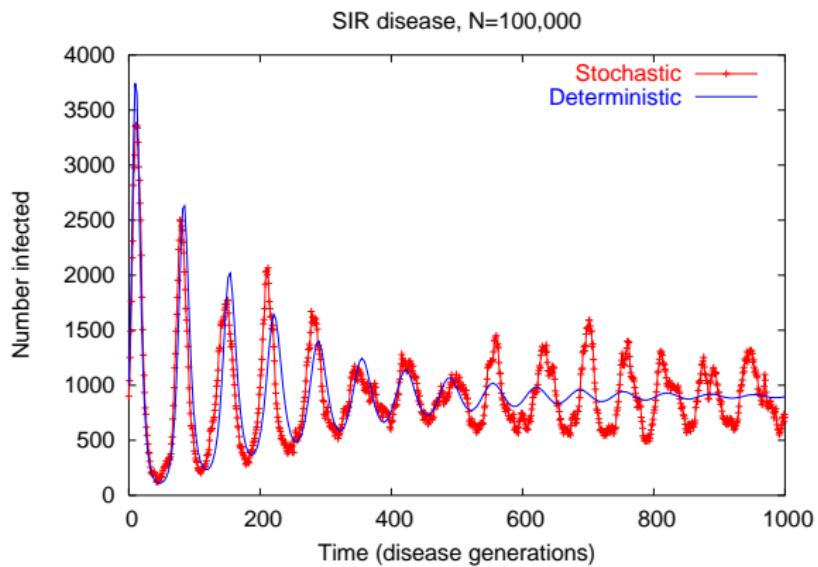


Measles reports from England and Wales



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

Fun and useful!

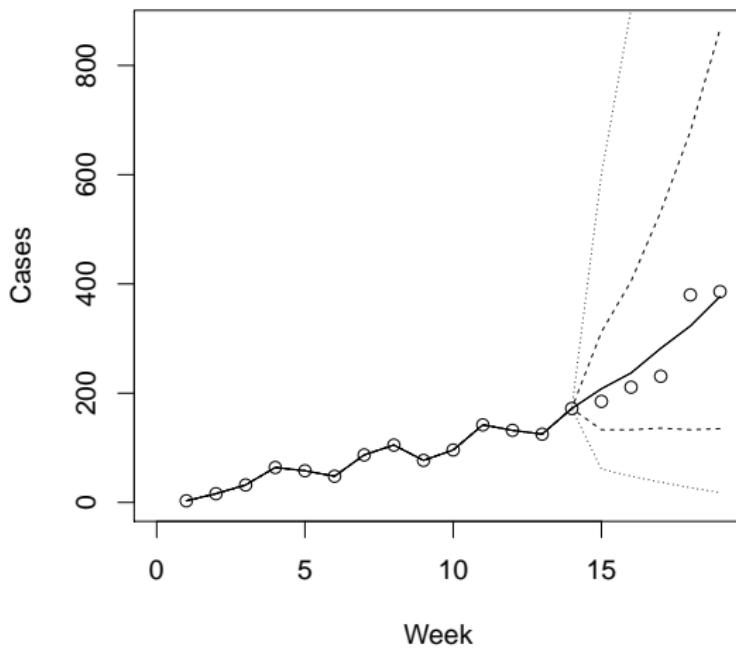


New problem

- ▶ There is a gulf between dynamical and statistical modeling
 - ▶ Dynamics are needed to incorporate mechanism
 - ▶ Statistics are needed to incorporate uncertainty
- ▶ Closing this gap is a very active area of research

Ebola forecasting

Sierra Leone



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- ▶ International Clinics on Infectious Disease Dynamics and Data
- ▶ ici3d.org
- ▶ At least two clinics a year, usually in South Africa
- ▶ MMED every year at the African Institute of Mathematical Sciences in Muizenberg
- ▶ Aimed at engaging dynamical models with infectious disease data

Prior distribution

- Priors are a unique feature of the Bayesian approach
 - May contain no information about parameters
 - Sometimes with information about parameters
- Beta-prior distribution of shape α and β
 - Has greater variance for lower values of α and β (shape) and smaller variance for higher values

Sarbo
 $\frac{1}{2}$

Jan = 3

Cold

2

Plots, fits







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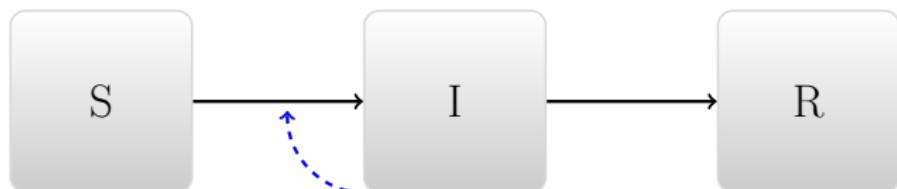
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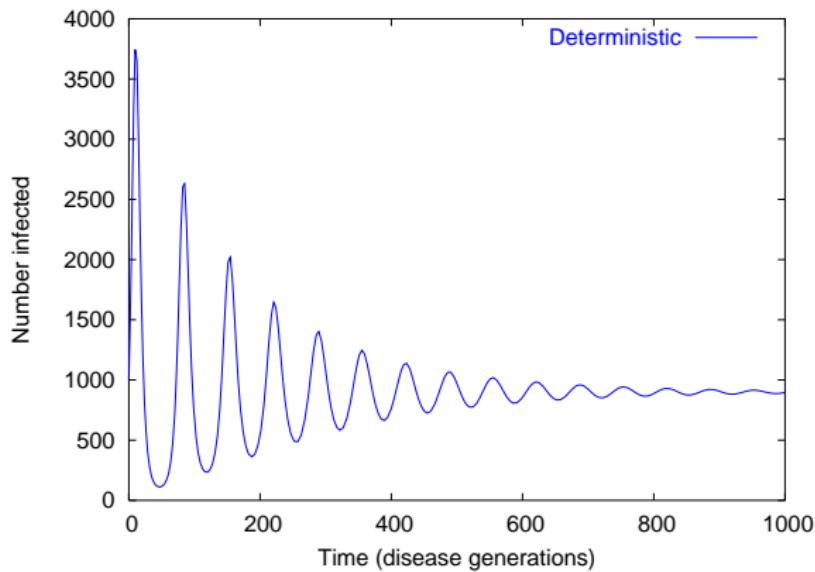
Compartmental models

Divide people into categories:

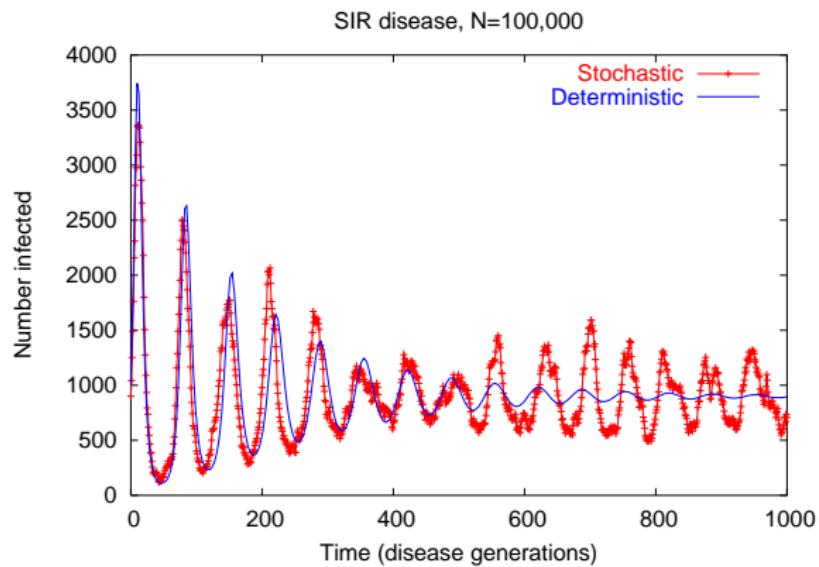


- ▶ Susceptible → Infectious → Recovered
- ▶ Individuals recover independently
- ▶ Individuals are infected by infectious people

Differential equation implementation



Individual-based implementation



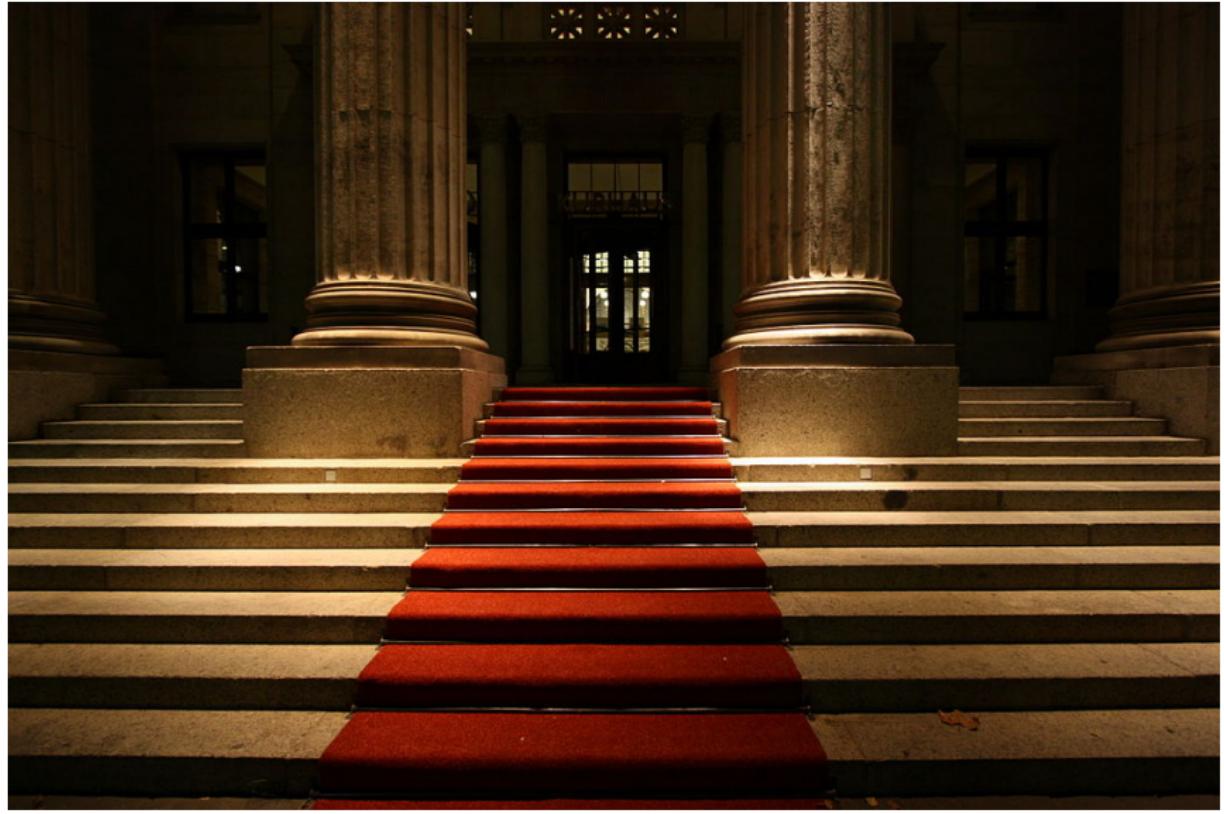
Lessons

- ▶ Exponential invasion potential
- ▶ Tendency to oscillate
- ▶ Thresholds

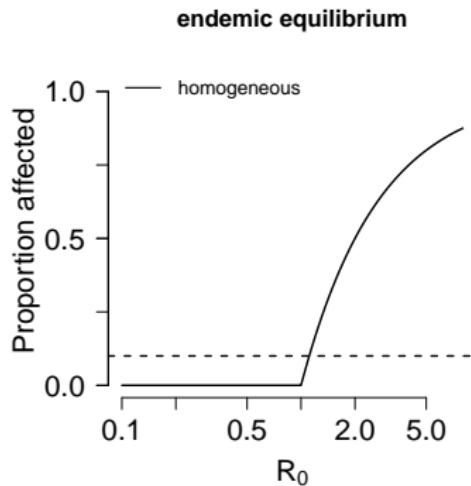
Big \mathcal{R}

- ▶ \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
- ▶ A disease can invade a population if and only if $\mathcal{R} > 1$.
- ▶ Often focus on initial period (may also say \mathcal{R}_0)

Big \mathcal{R}

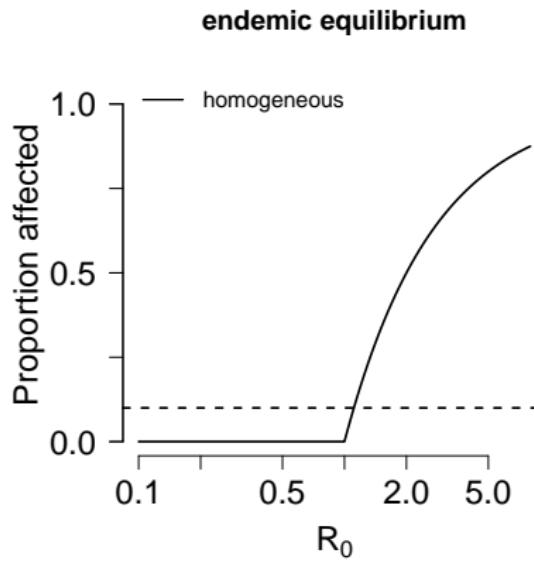


Homogeneous endemic curve



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

Yellow fever in Panama



Exponential growth

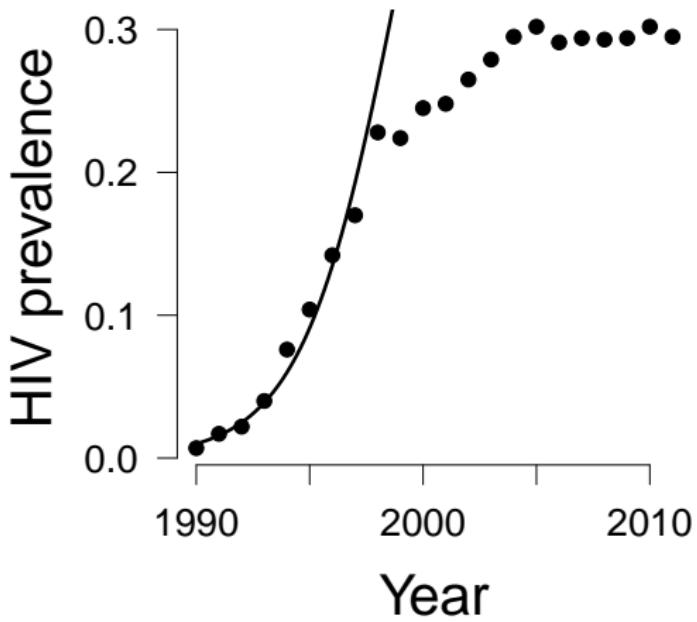
- ▶ Diseases have a tendency to grow exponentially at first
 - ▶ I infect three people, they each infect 3 people ...
 - ▶ How fast does disease grow?
 - ▶ How quickly do we need to respond?

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, $C \approx 18\text{month}$
- ▶ Often focus on initial period (may also say r_0)

little *r*

$$R_0 = 5.66$$



Limitations

- ▶ Many conclusions from this framework make strong assumptions:
 - ▶ **Spatial homogeneity:** everywhere is the same
 - ▶ **Individual homogeneity:** everyone is the same
 - ▶ and everyone is everywhere
 - ▶ **Temporal homogeneity:**
 - ▶ It doesn't matter how long I've been infected, I'm either infected or not

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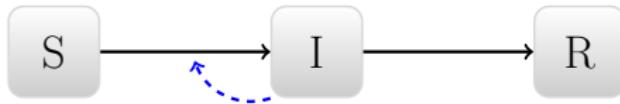
- ▶ We're very interested in the relationship between little r and \mathcal{R} .
- ▶ We might have good estimates of r only
 - ▶ e.g., West African Ebola outbreak, HIV in Africa
- ▶ Or we might have good estimates of \mathcal{R} only
 - ▶ Measles, influenza

Example: Post-death transmission and safe burial

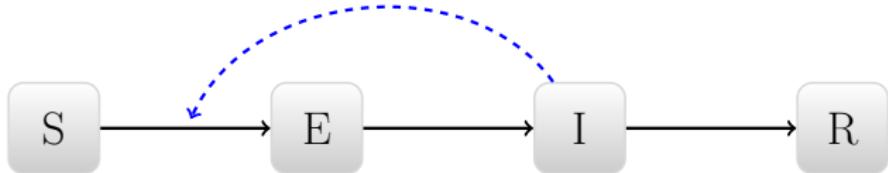
- ▶ How much Ebola spread occurs before vs. after death
- ▶ Highly context dependent
 - ▶ Funeral practices, disease knowledge
- ▶ *Weitz and Dushoff Scientific Reports 5:8751.*



Standard disease model

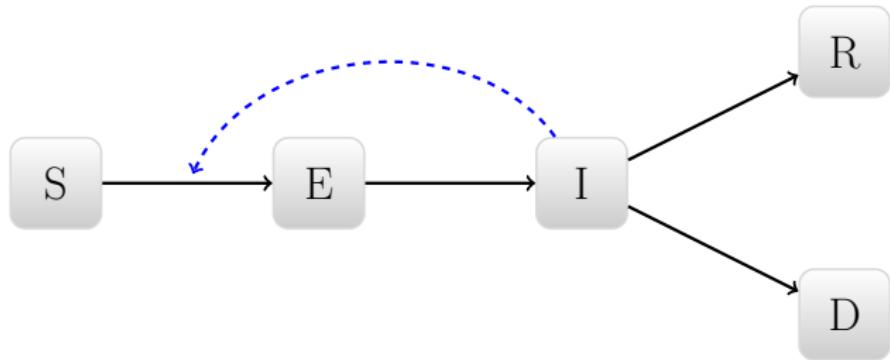


Add a latent period

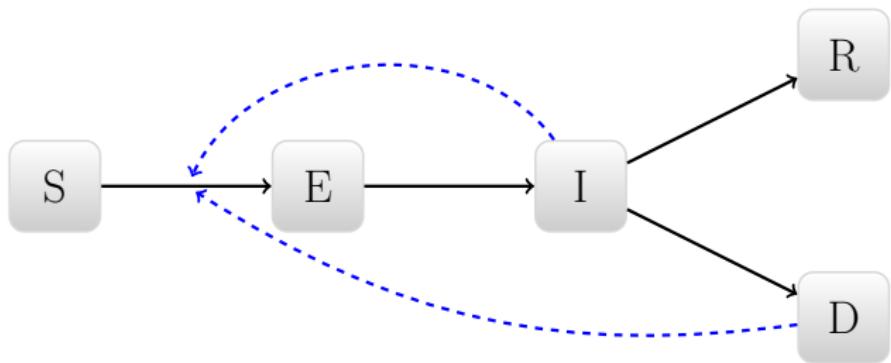


- ▶ (i.e., a lag between infection and infectiousness)

Add post-death transmission



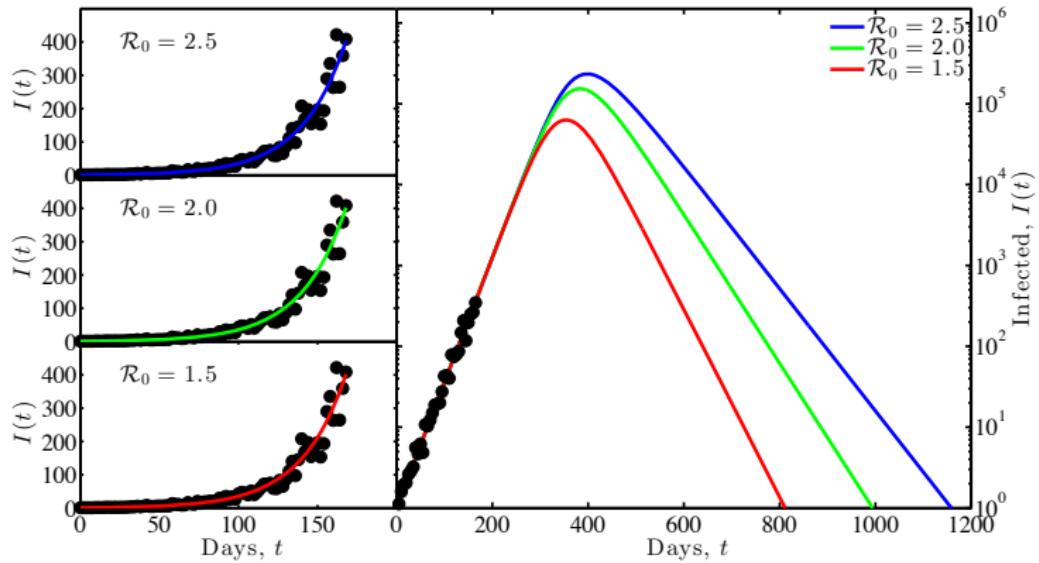
Add post-death transmission



What happens if we account for burial transmission?

- ▶ We've made the disease transmitting process slower, so obviously Ebola is *less* dangerous than we thought
- ▶ We've added another source of transmission, so obviously Ebola is *more* dangerous than we thought
- ▶ What we learn depends on what we know!

What do we know?



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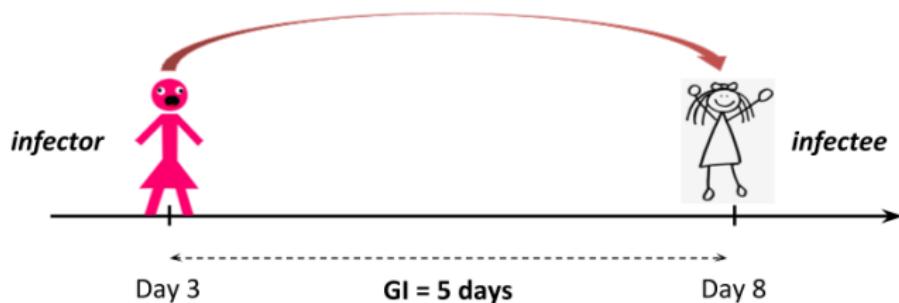
Speed and strength

How long is a disease generation? (present)

Definition

Generation Interval:

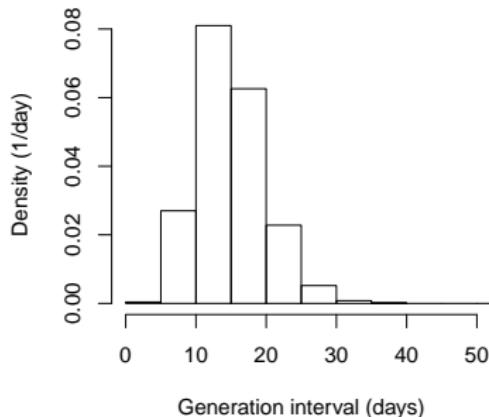
Interval between the time that an individual is infected by an infector and the time this infector was infected



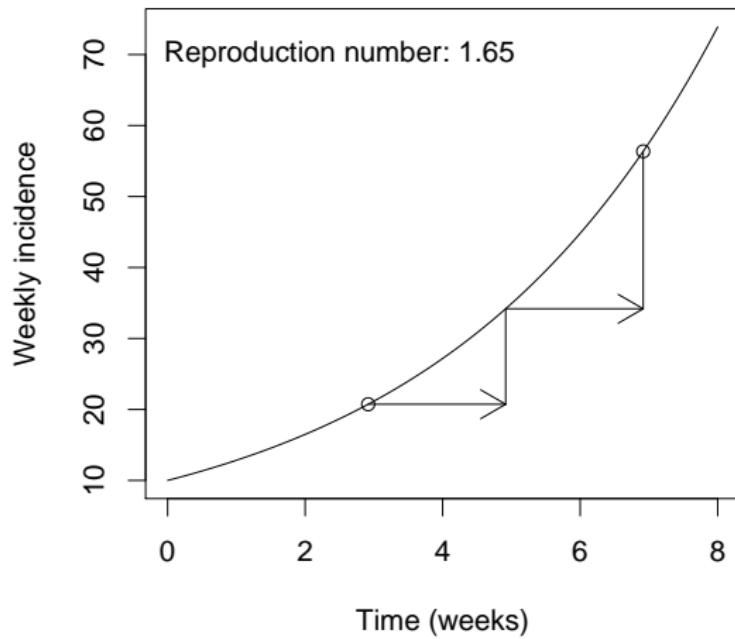
Generation intervals

- ▶ 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

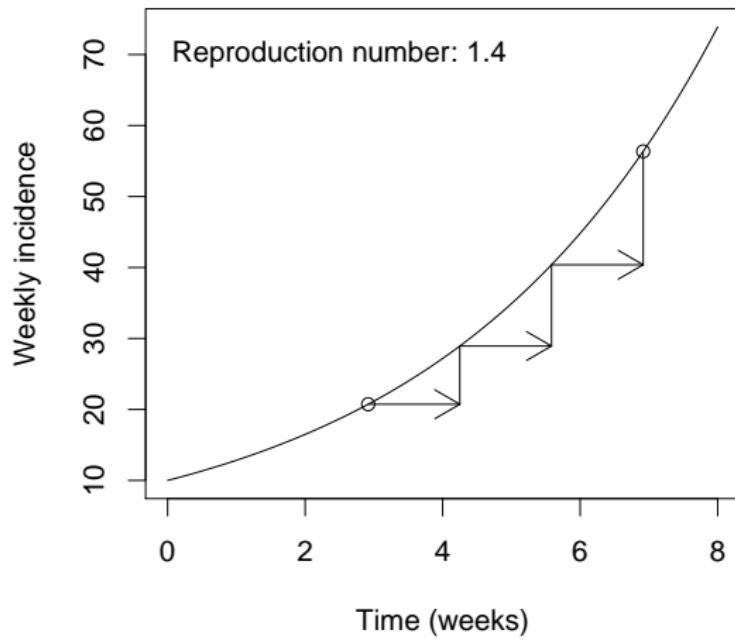
Approximate generation intervals



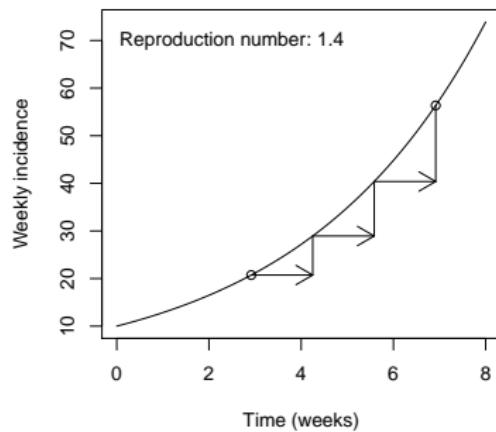
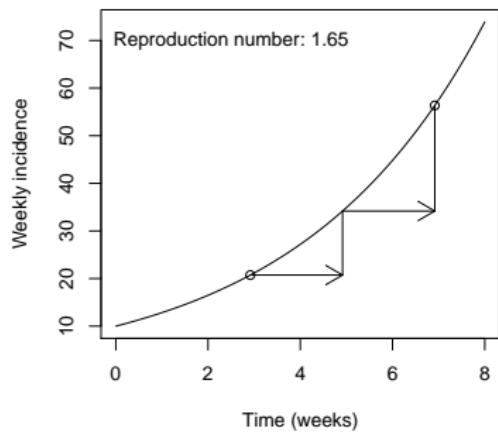
Generations and \mathcal{R}



Generations and \mathcal{R}



Generations and \mathcal{R}



Conditional effect of generation time

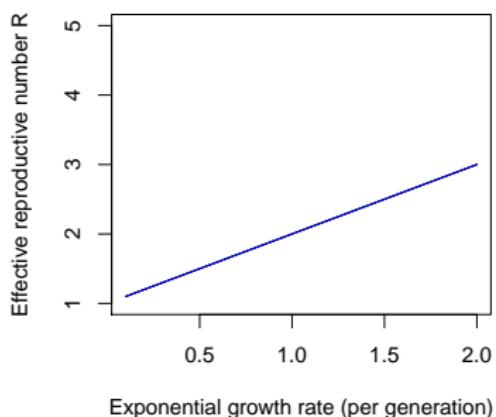
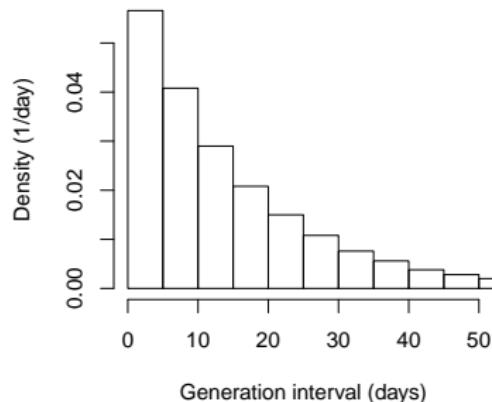
- ▶ Given the reproductive number \mathcal{R}
 - ▶ faster generation time G means higher r
 - ▶ More danger
- ▶ Given r
 - ▶ faster generation time G means smaller \mathcal{R}
 - ▶ Less danger

Linking framework

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

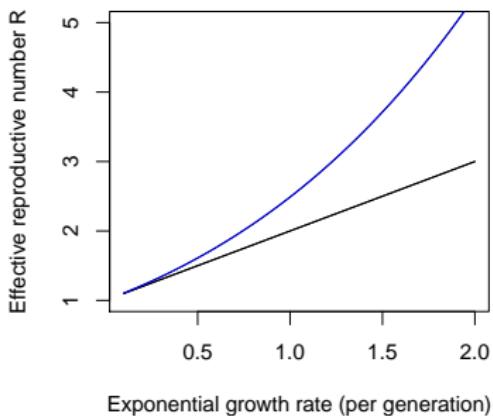
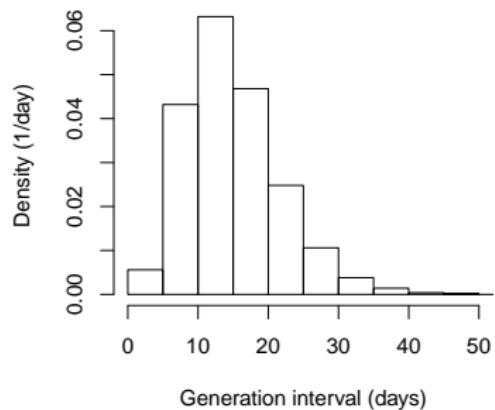
Approximations

Approximate generation intervals

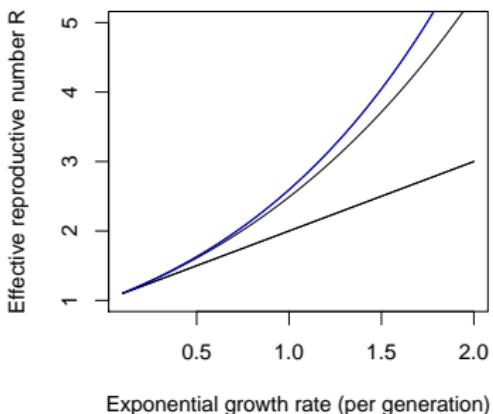
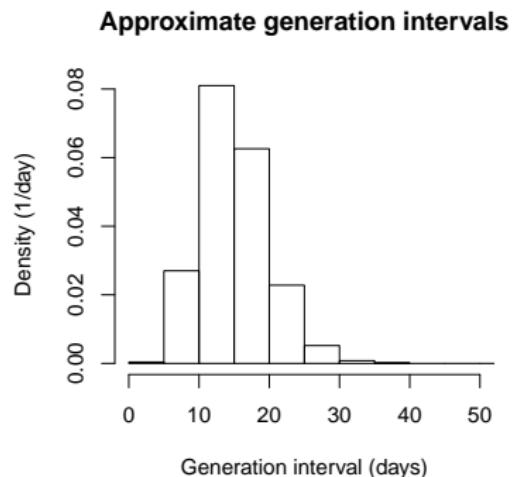


Moment approximation

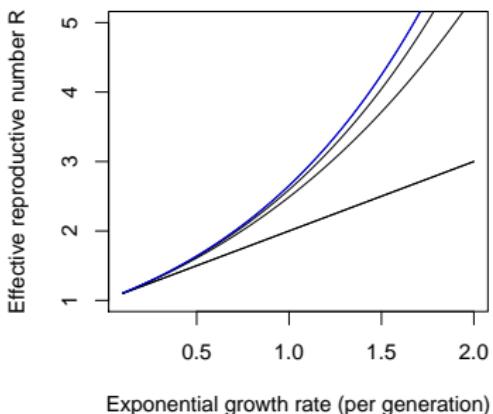
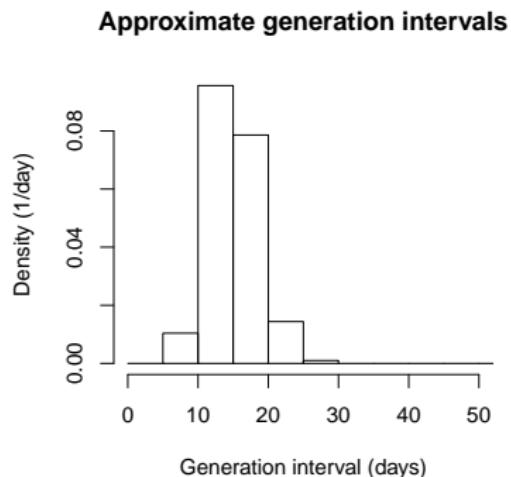
Approximate generation intervals



Moment approximation



Moment 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 $\kappa \rightarrow 0$
- ▶ Key quantity is $r\bar{G}$: the relative length of the generation interval compared to the characteristic time scale of spread

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

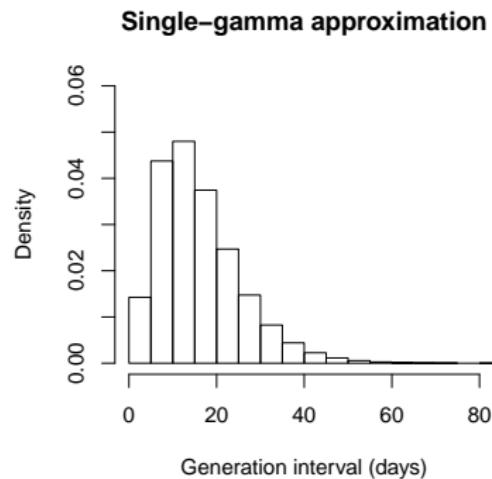
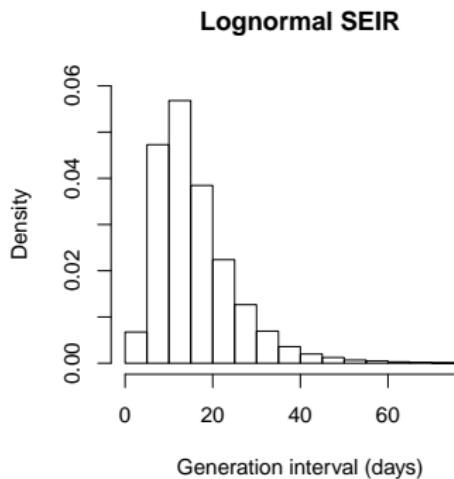
Intuition

- ▶ Longer generation times mean less speed
 - ▶ \implies more strength, when speed is fixed
- ▶ What about more variation?
 - ▶ 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
 - ▶ \implies less strength, when speed is fixed

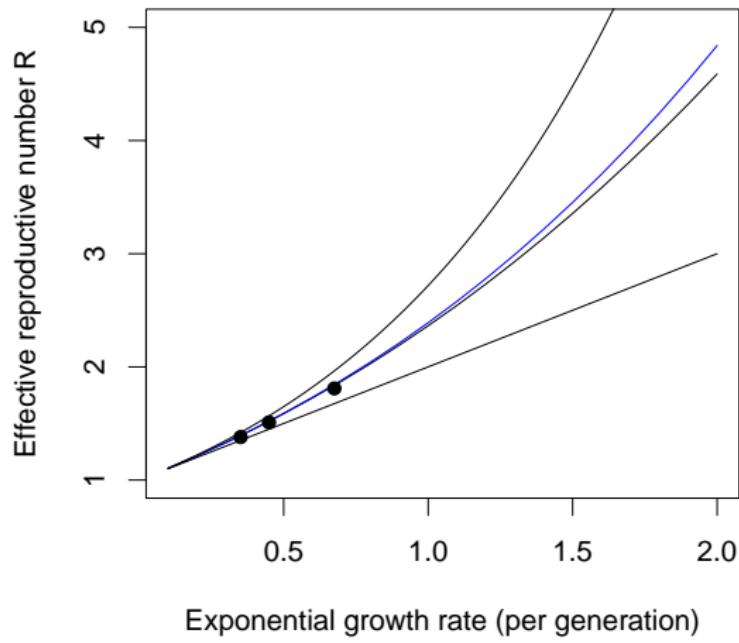
How well do approximations work

- ▶ 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

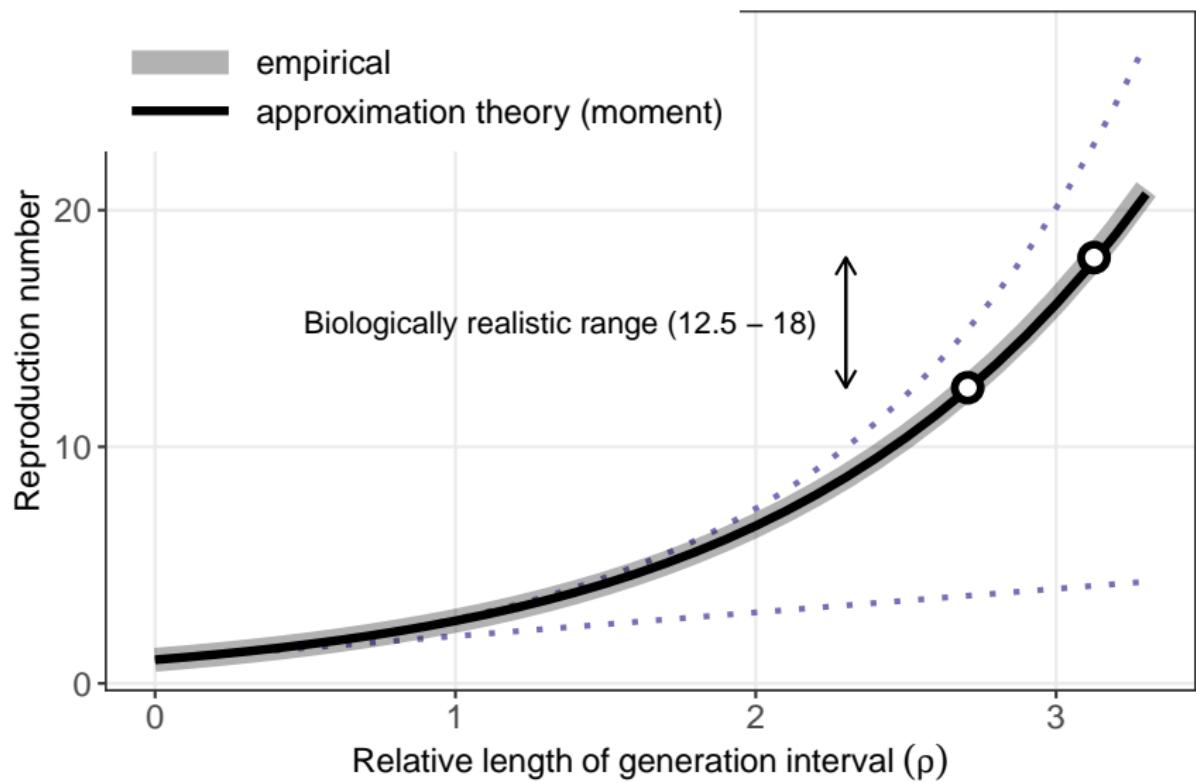
Ebola distribution



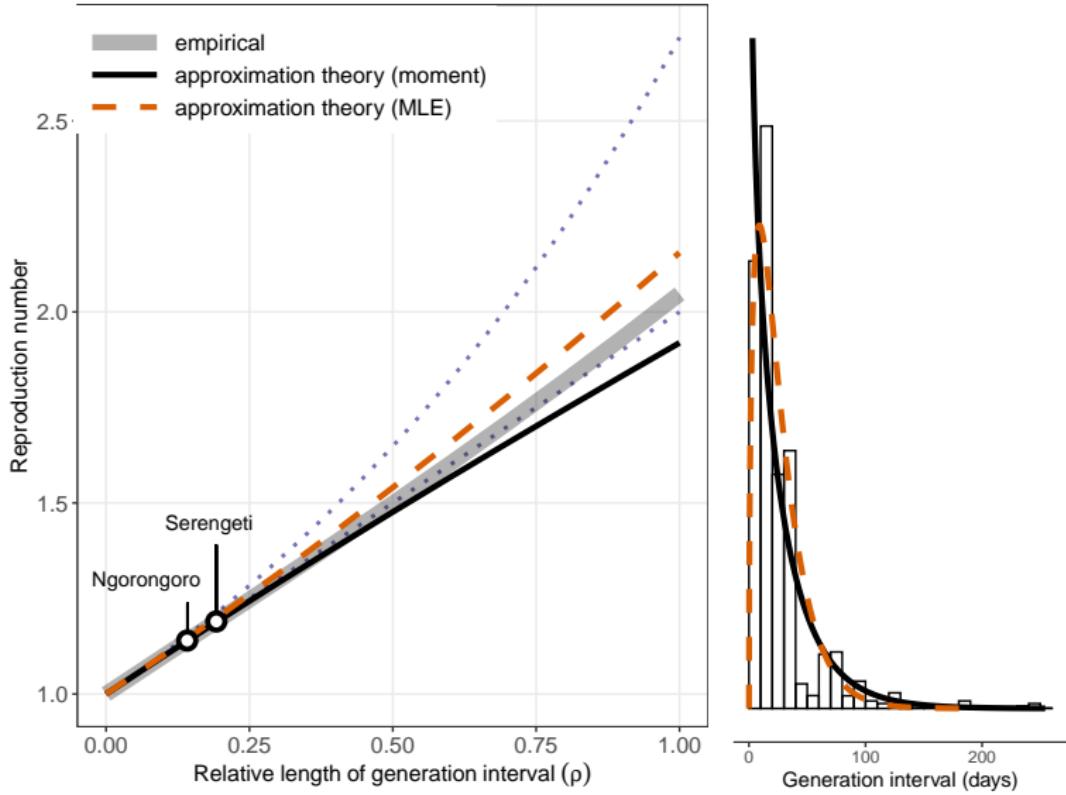
Ebola curve



Measles curve



Rabies curve



Generation intervals



"I cannot imagine how they will spend half of it."

- ▶ Sort of the poor relations of disease-modeling world
- ▶ Ad hoc methods
- ▶ Error often not propagated

Summary

- ▶ Generation intervals are the missing link between r and \mathcal{R}
- ▶ We need better methods for estimating them, and propagating uncertainty to other parts of the model
- ▶ For many practical applications:
 - ▶ Estimating the mean generation interval is not enough
 - ▶ But estimating the mean and CV may be enough
 - ▶ A good basis for understanding and propagating uncertainty

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- ▶ 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?

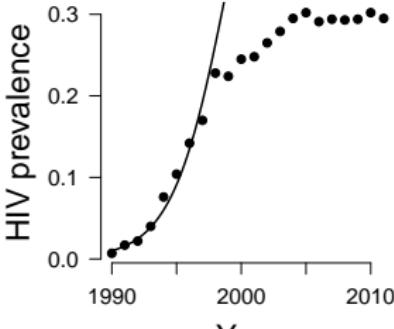
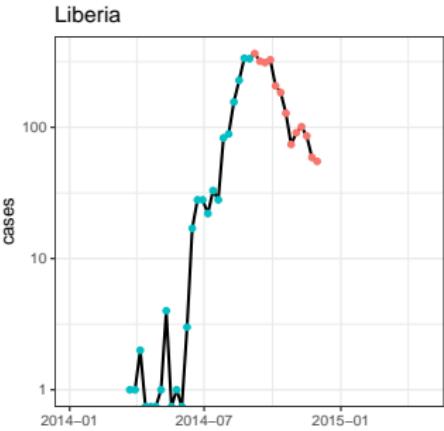
- ▶ Contact-tracing intervals look systematically different, depending on when you observe them.
- ▶ Observed in:
 - ▶ Real data, detailed simulations, simple model
- ▶ Also differ from intrinsic (infector centered) estimates

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

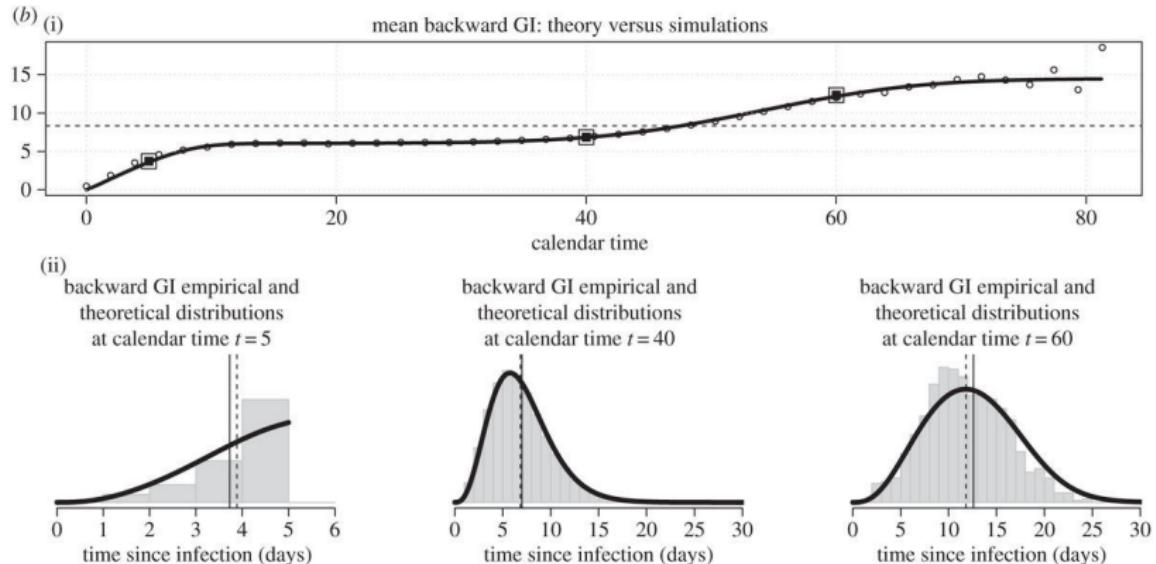
- ▶ Generation intervals look *shorter* at the beginning of an epidemic
 - ▶ A disproportionate number of people are infectious right now
 - ▶ They haven't finished all of their transmitting
 - ▶ We are biased towards observing faster events



What changes backward intervals?

- ▶ Who is likely to infect me depends on:
 - ▶ How infectious they are (intrinsic GI)
 - ▶ How many of them there are (changes in disease incidence)

Backward intervals

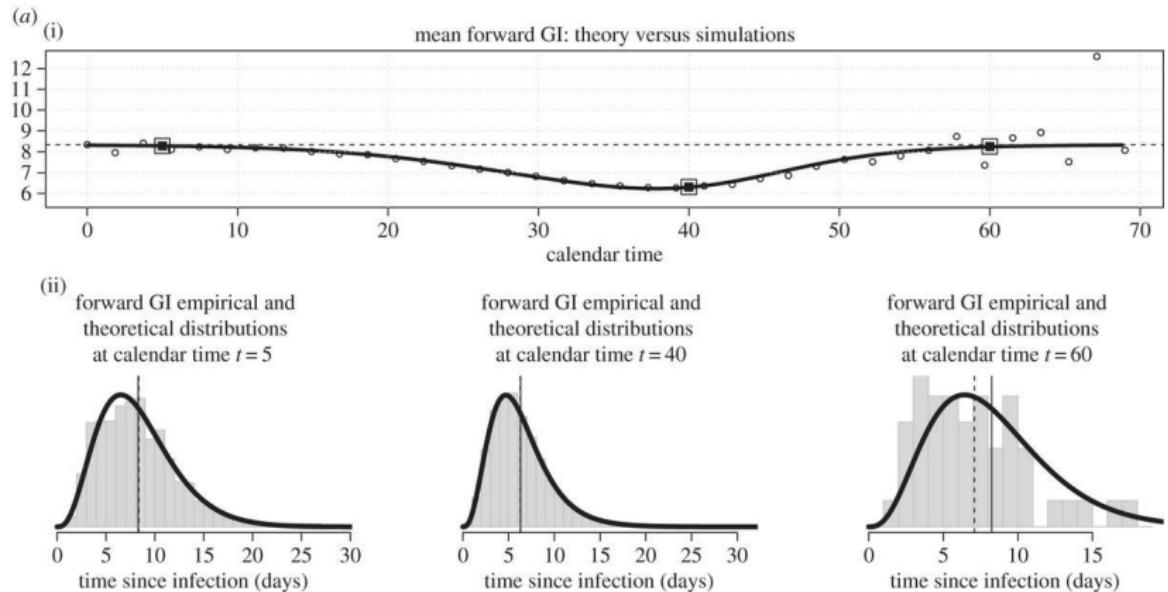


Champredon and Dushoff, 2015. DOI:10.1098/rspb.2015.2026

What changes forward intervals?

- ▶ Who I am likely to infect depends on:
 - ▶ How infectious I am (intrinsic GI)
 - ▶ How many of them there are (changes in numbers of susceptibles)

Forward intervals



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
 - ▶ Censored intervals look short \implies
 - ▶ underestimates of \mathcal{R}

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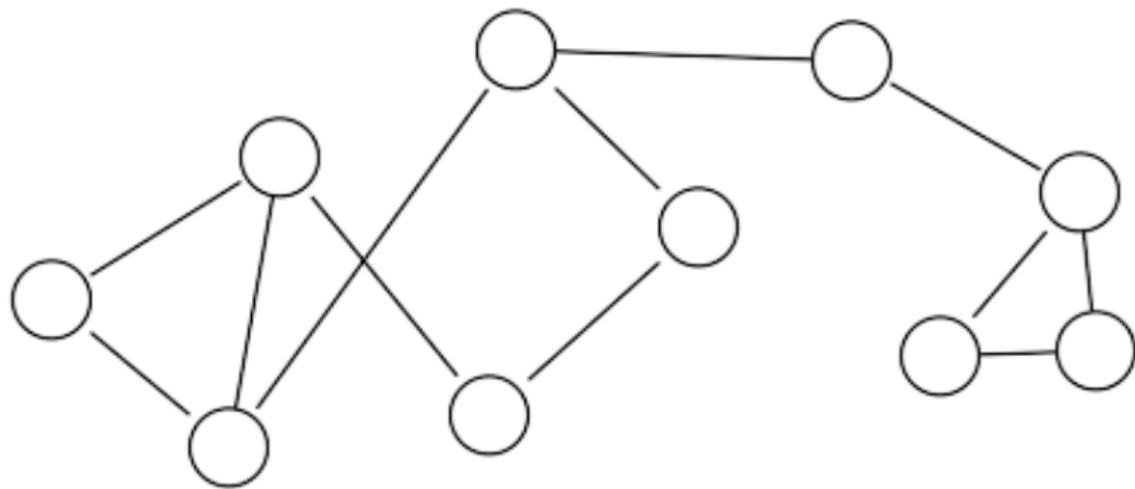
- ▶ Once you think carefully about generation intervals, they're everywhere
- ▶ Spatial heterogeneity
- ▶ Individual heterogeneity

Generations in space

- ▶ How do local interactions affect realized generation intervals?



Individual



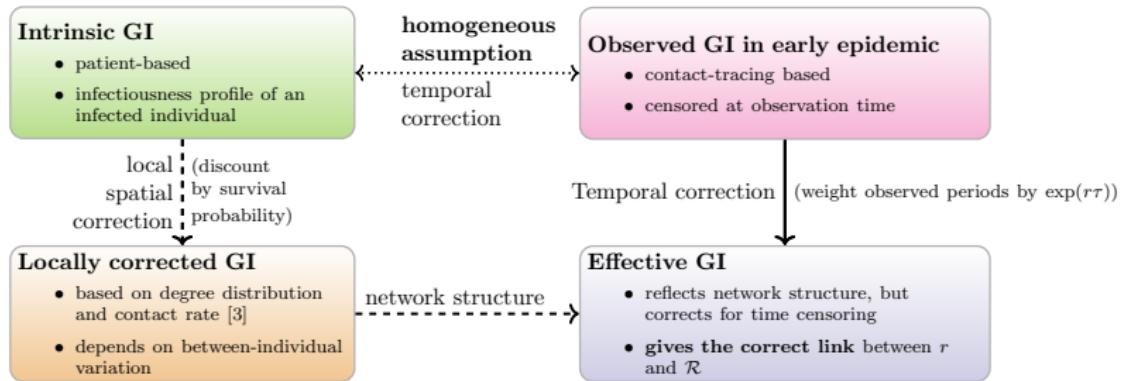
Surprising results

- ▶ We tend to think that heterogeneity leads to underestimates of \mathcal{R} , which 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

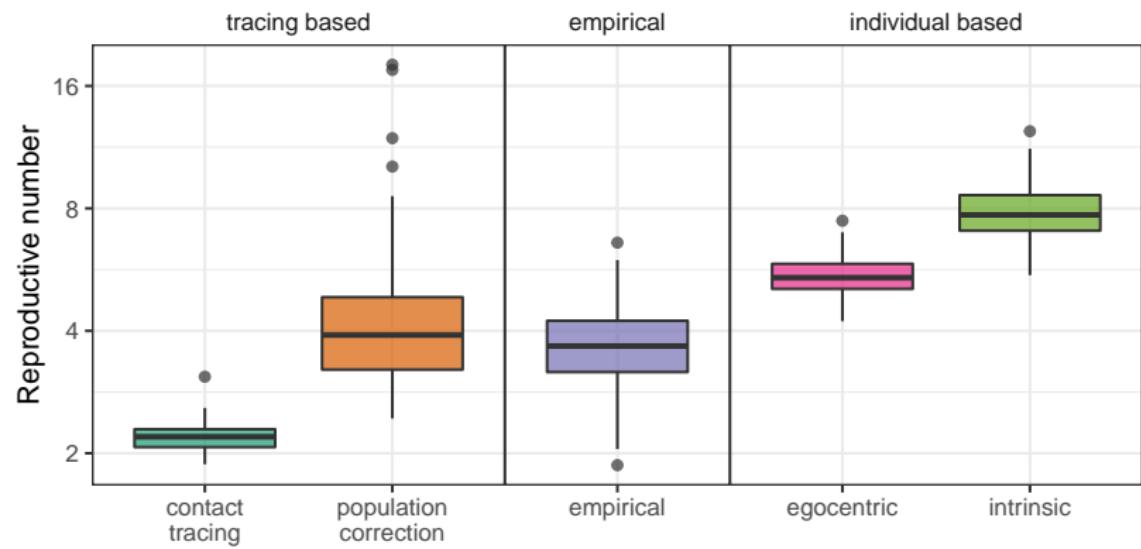
Generation-interval perspective

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

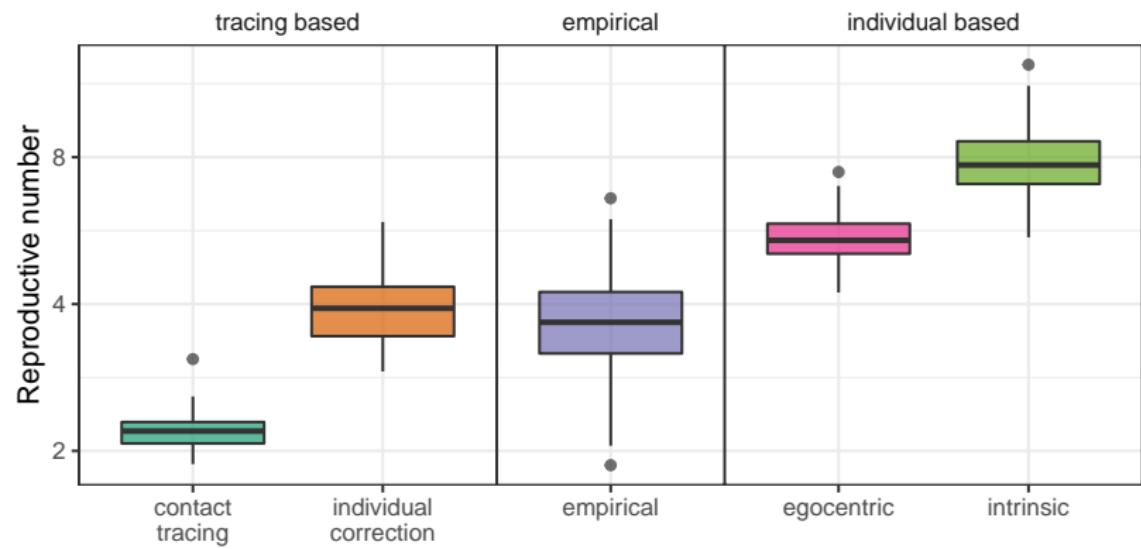
Observed and estimated intervals



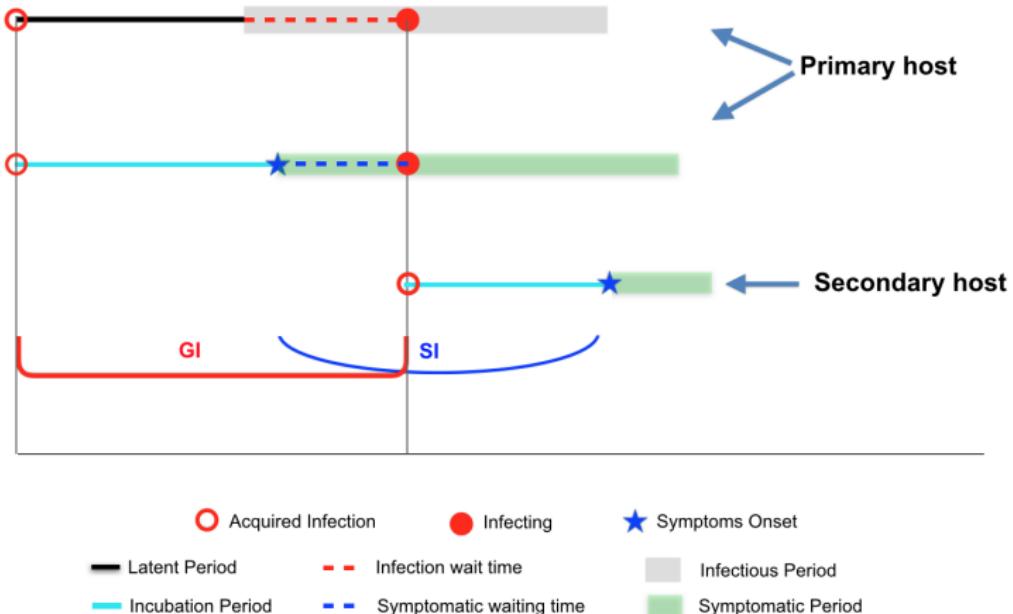
Outbreak estimation



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
- ▶ In fact, they don't
 - ▶ Serial intervals can even be negative!
 - ▶ You might report to the clinic with flu before me, even though I infected you
- ▶ For rabies, I have argued that serial intervals and generation intervals should be the same
 - ▶ Symptoms are closely correlated with infectiousness



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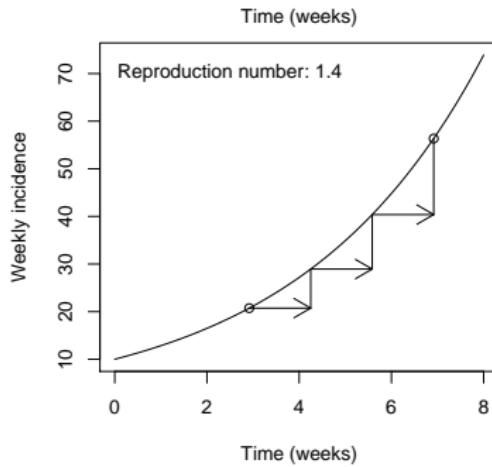
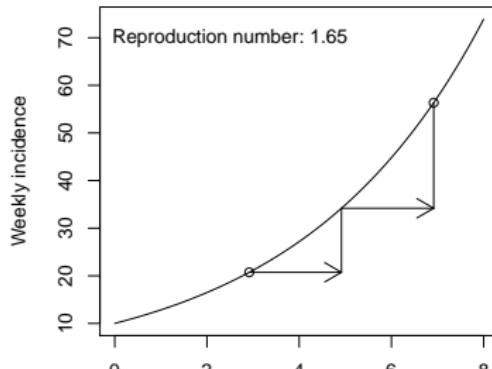
Can treatment stop the HIV epidemic?

- ▶ Modern treatments are well tolerated and highly effective
- ▶ Virus is undetectable, and transmission is negligible
- ▶ Can active testing and treatment stop the epidemic?



Are HIV generations fast or slow?

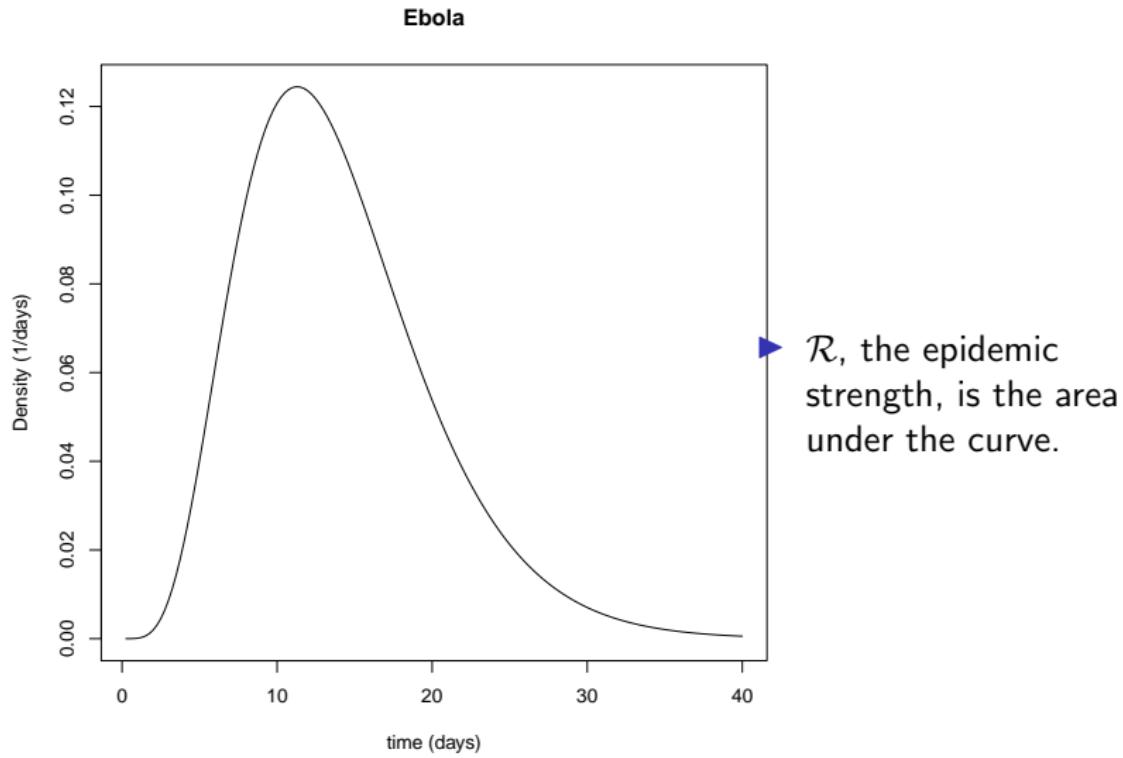
- ▶ Fast generations mean:
 - ▶ Testing and treating will help less
 - ▶ *but* lower epidemic strength



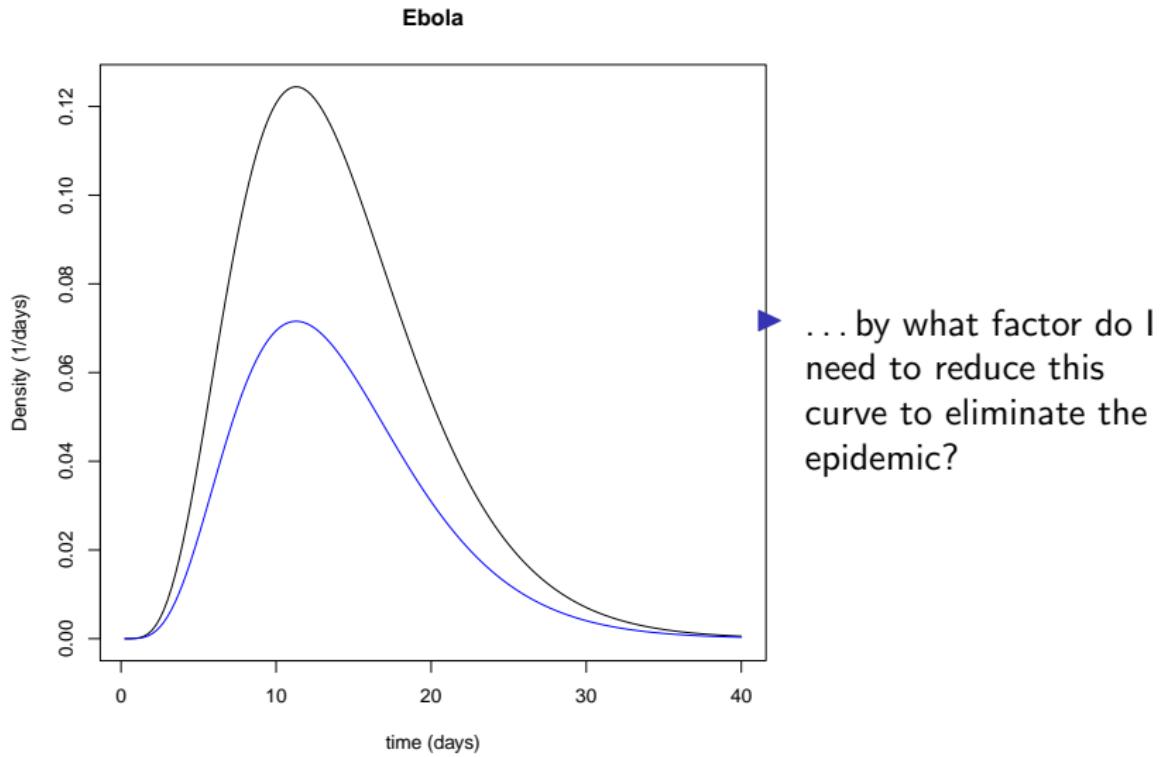
Eaton and Hallett

- ▶ Predicted effectiveness of test and treat intervention minimally sensitive to proportion of early transmission
- ▶ Fast transmission:
 - ▶ low proportion prevented, but low \mathcal{R} estimate
- ▶ Slow transmission:
 - ▶ high proportion prevented, but high \mathcal{R} estimate
- ▶ Conclusion: it doesn't matter as much as we thought!
- ▶ *Eaton JW, Hallett TB. Proc Natl Acad Sci U S A. 2014 Nov 11;111(45):16202-7.*

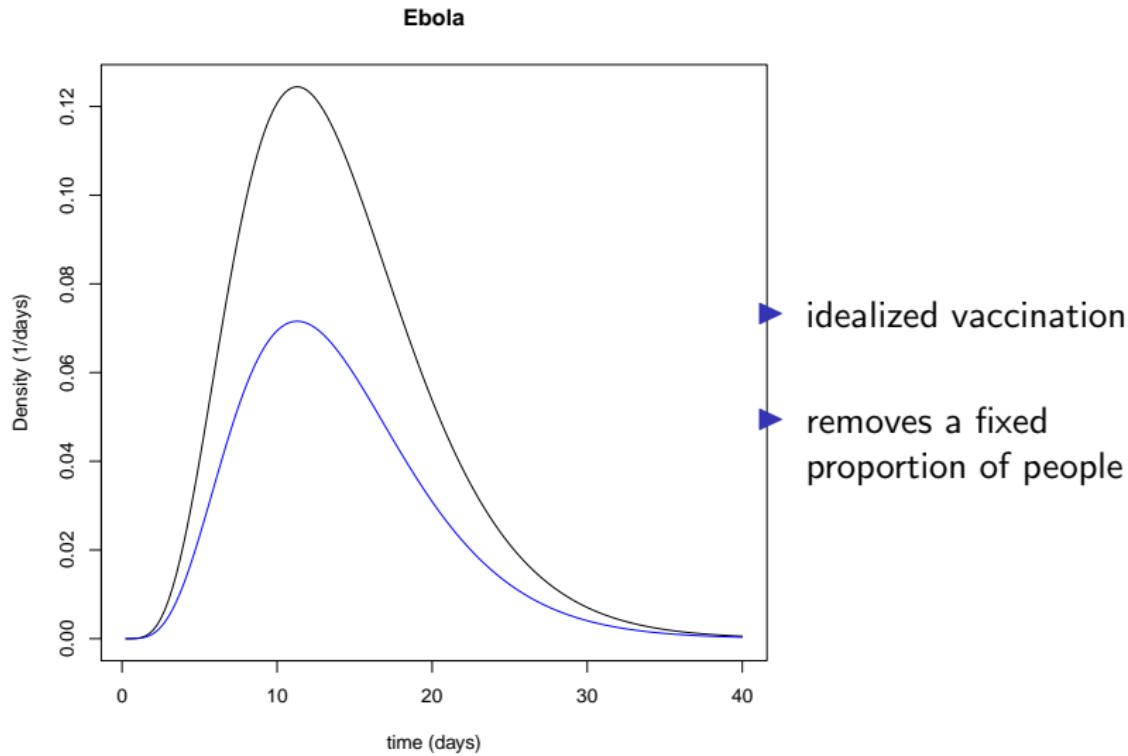
Epidemic strength (present)



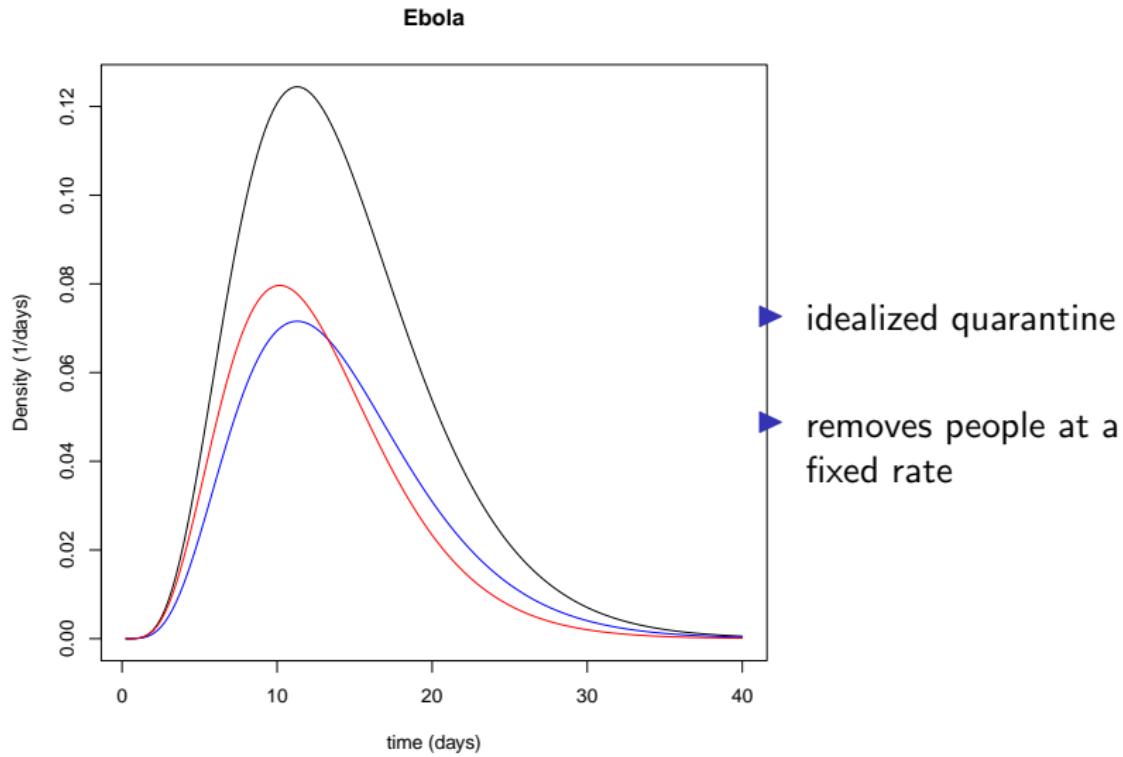
Strength of intervention



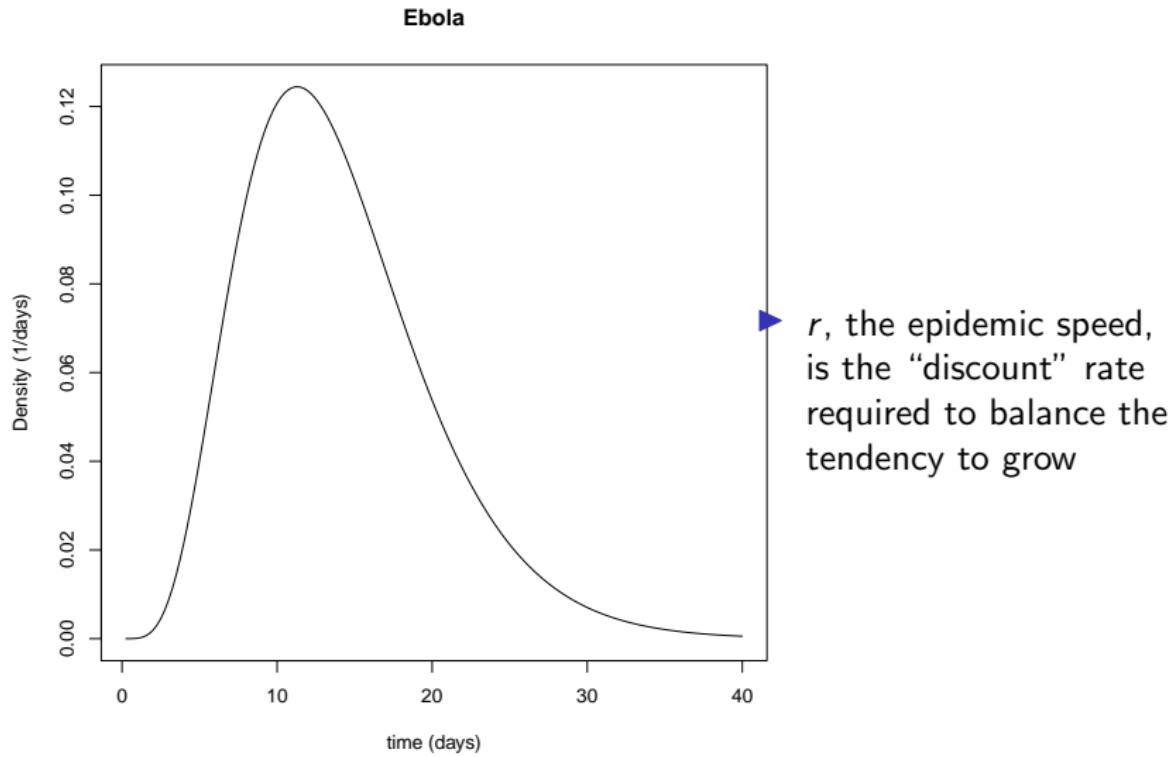
Different interventions (present)



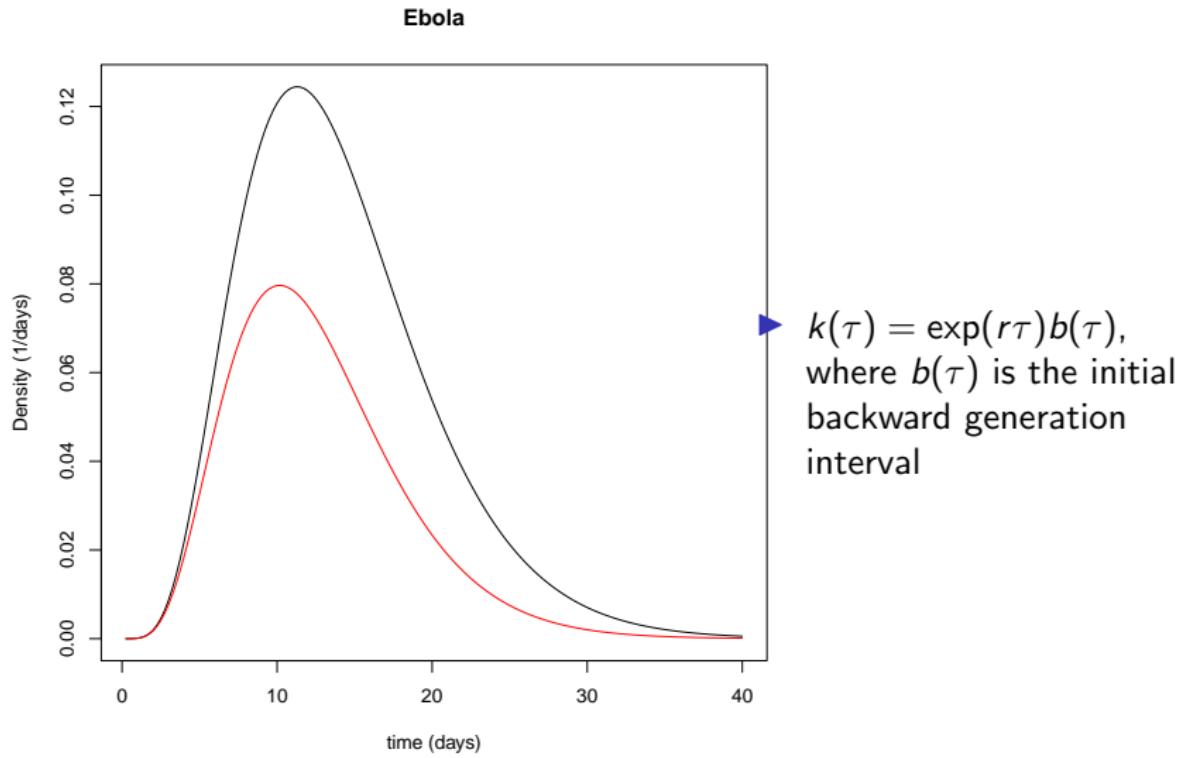
Different interventions (present)



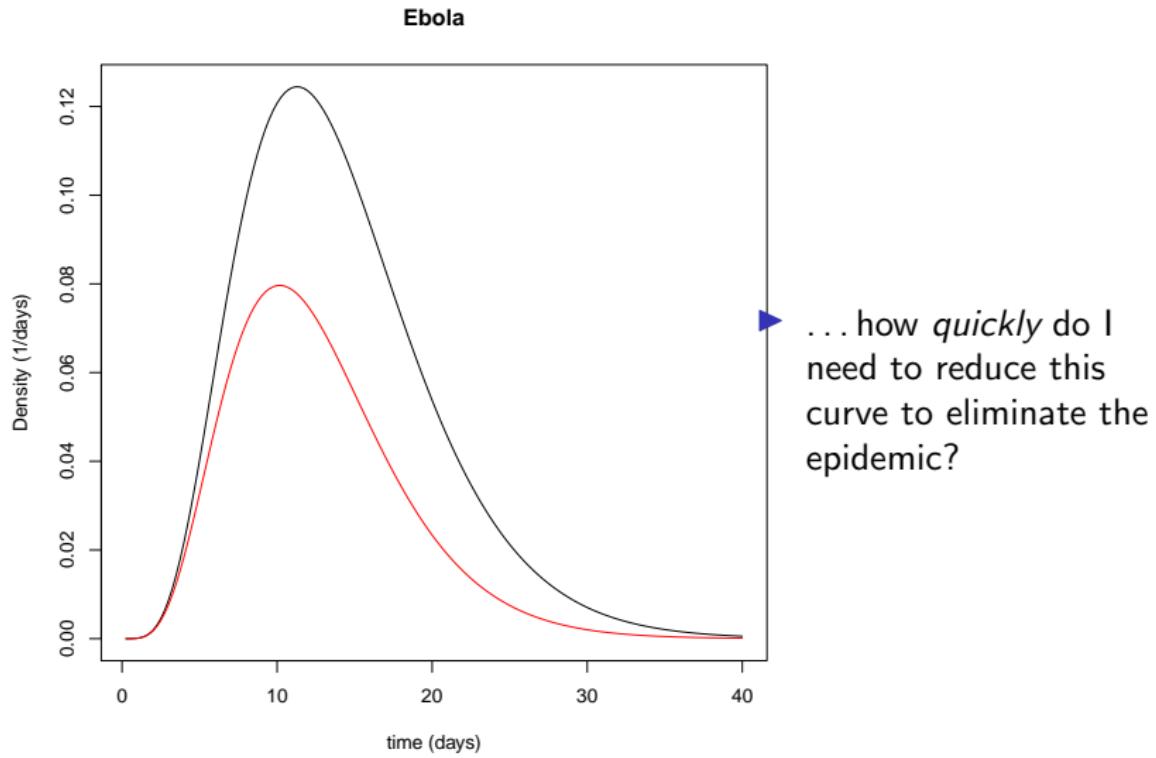
Epidemic speed



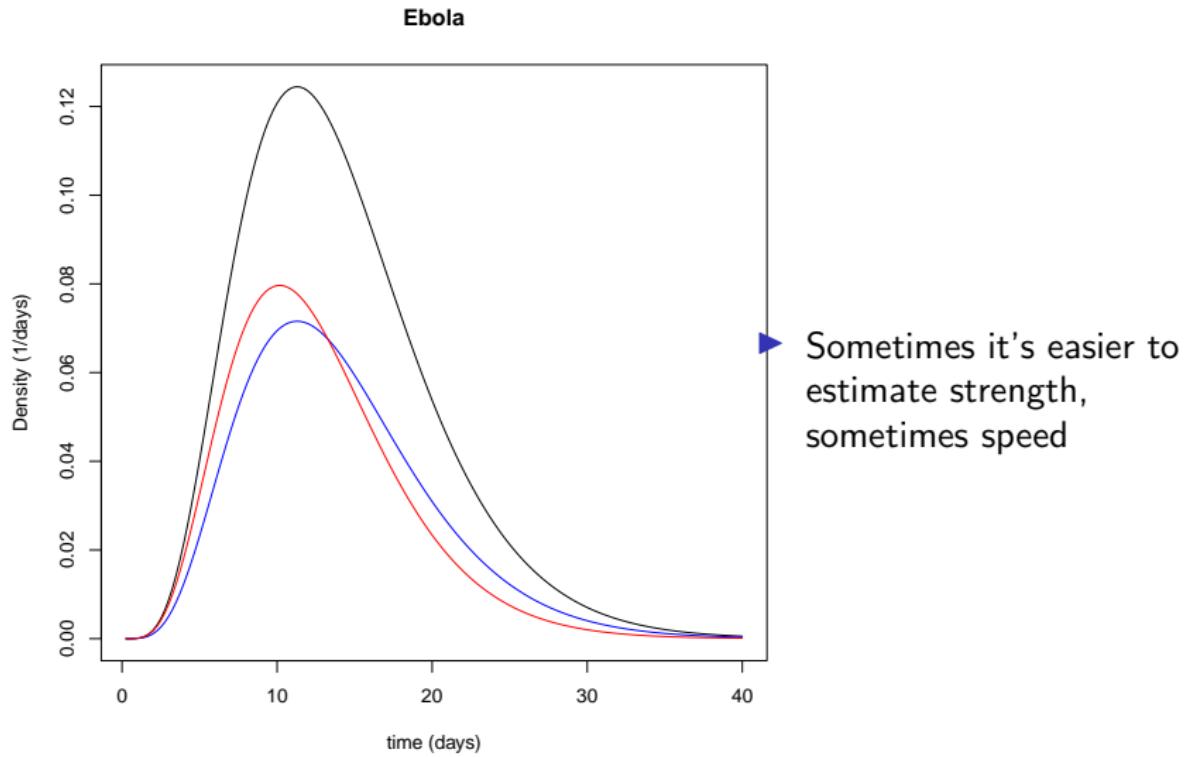
Epidemic speed



Speed of intervention



Different interventions (present)



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 $\theta > \mathcal{R}$

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 $\phi > r$

Measuring the intervention



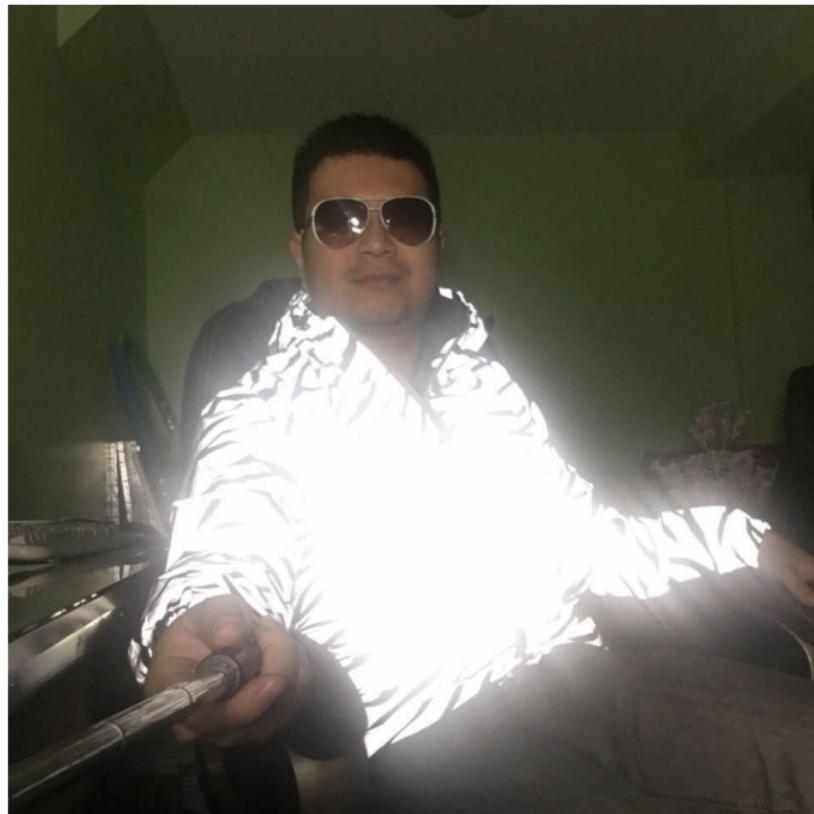
HIV

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

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





Linking framework

- ▶ Epidemic speed (r) is a *product*:
 - ▶ (something to do with) generation speed ×
 - ▶ (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