Epidemic strength and speed: rethinking metrics for infectious disease spread and control.

SMB 2017

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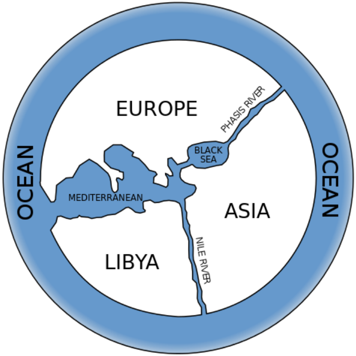
http://www.ici3d.org
https://github.com/dushoff/Generation_talks

Outline

Infectious diseases

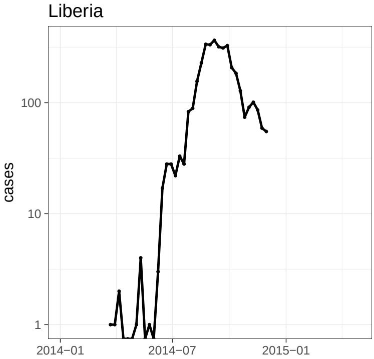
Models



- A model is a simplified view of the world
- Allows linking between assumptions and outcomes

Ebola

Dynamic modeling connects scales



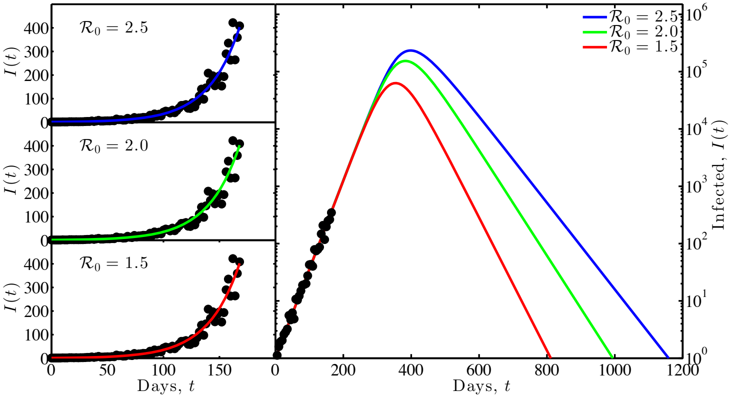
Statistics and theory

- Dynamical models are required to bridge scales
- Statistical frameworks are required to interpret noisy data
- We need tools that can incorporate dynamical mechanisms into frameworks that allow statistical inference
- Simple dynamical theories allow clearer interpretation and inspire better techniques

Speed

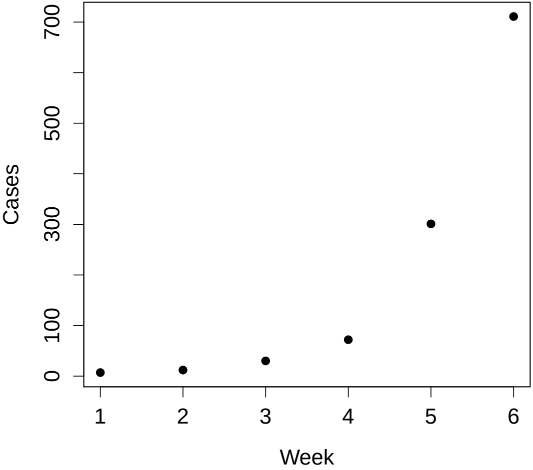
- We measure epidemic speed using little r:
  - The ratio of the *change* in disease impact to the *amount* of disease impact
  - *Units*: [1/time]
  - Disease increases like e^{rt}
- Time scale is $C = 1/r$

Ebola outbreak



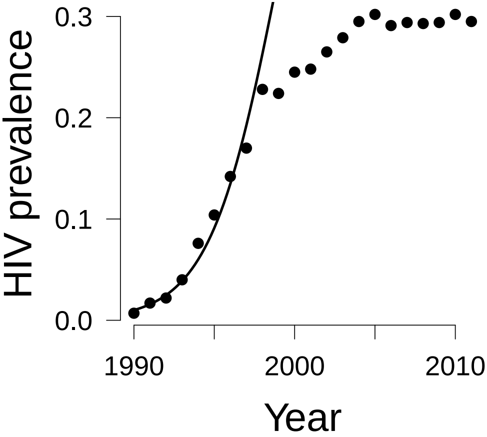
$C \approx 1\,\mathrm{month}$. Sort-of fast.

Mexican flu



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

HIV in sub-Saharan Africa



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

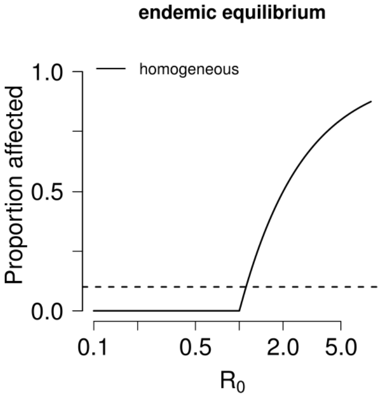
$\mathcal{R}$ and control

- 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 $V = 1 - 1/\mathcal{R}$

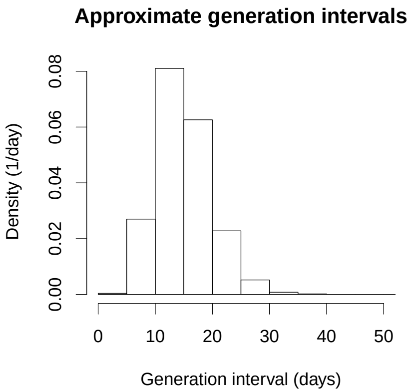
$\mathcal{R}$ and control



Outline

Outline

Generation intervals

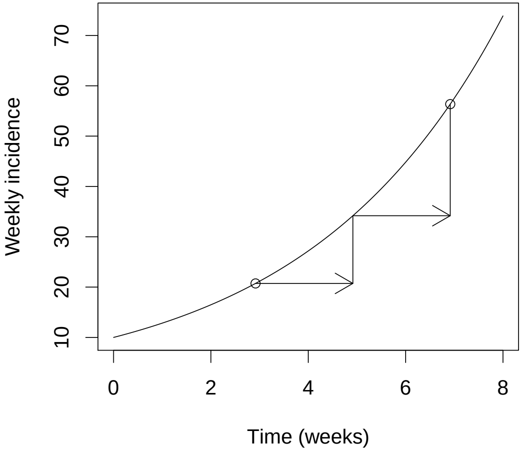


- The generation distribution measures generations of the disease
  - Interval between “index” infection and resulting infection
- Do fast disease generations mean more danger or less danger?

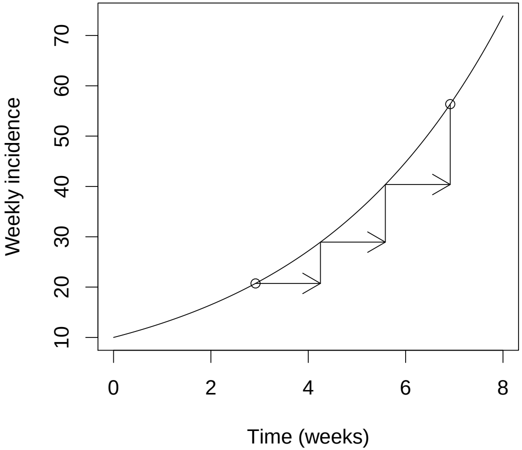
Conditional effect of generation time

- *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

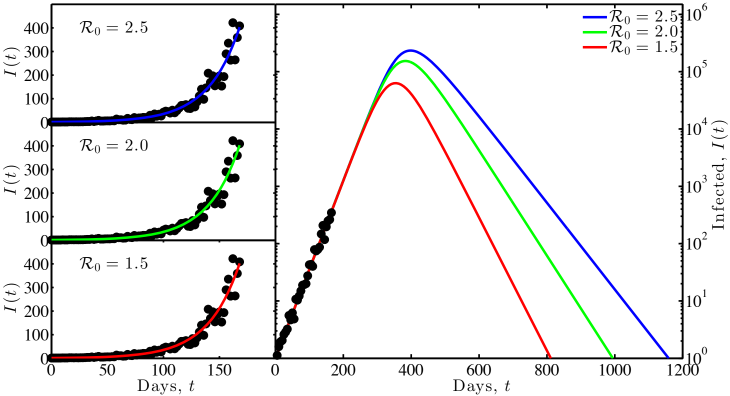
Generations and $\mathcal{R}$



Generations and $\mathcal{R}$

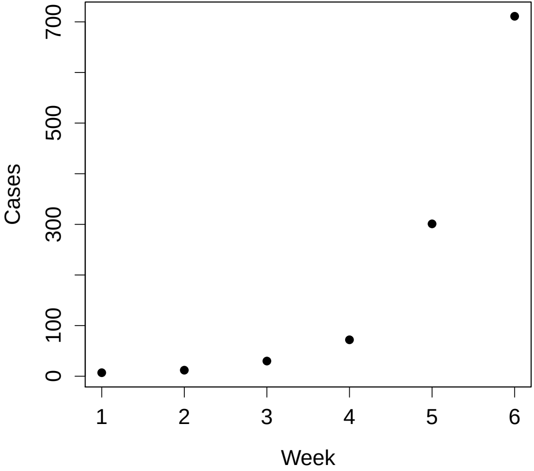


Ebola outbreak



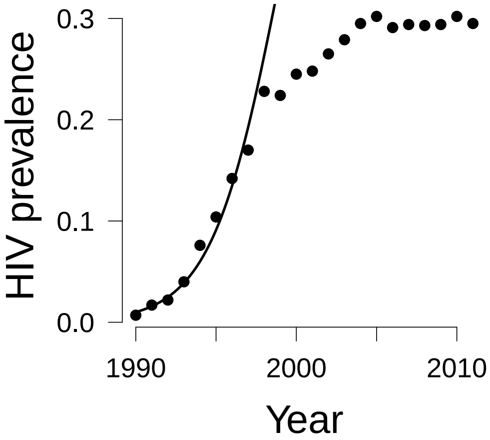
$C \approx 1\,\text{month}, \; G \approx 2\,\text{week}$

Mexican flu



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

HIV in sub-Saharan Africa



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

Linking framework

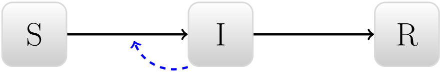
- Epidemic speed (r) is a *product*:
  - generation speed $\times$
  - epidemic strength
- WRONG

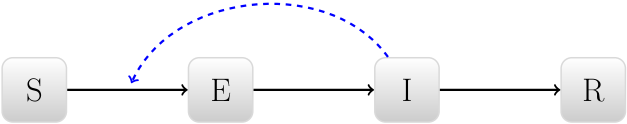
Linking framework

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

Outline

Box models



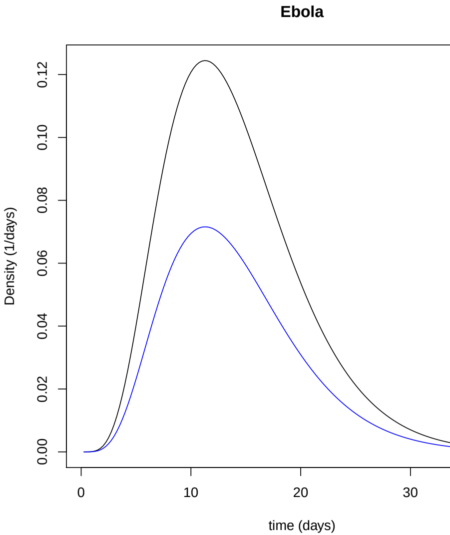


Renewal equation

- 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

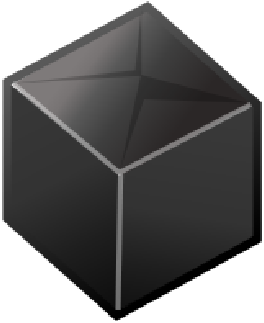


Euler-Lotka equation

- If we neglect S, we expect exponential growth
- $1 = \int k(\tau) \exp(-r\tau)\, d\tau$
  - i.e., the total of *discounted* contributions is 1
- $1/\mathcal{R} = \int g(\tau) \exp(-r\tau)\, d\tau$

Interpretation: generating functions

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



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

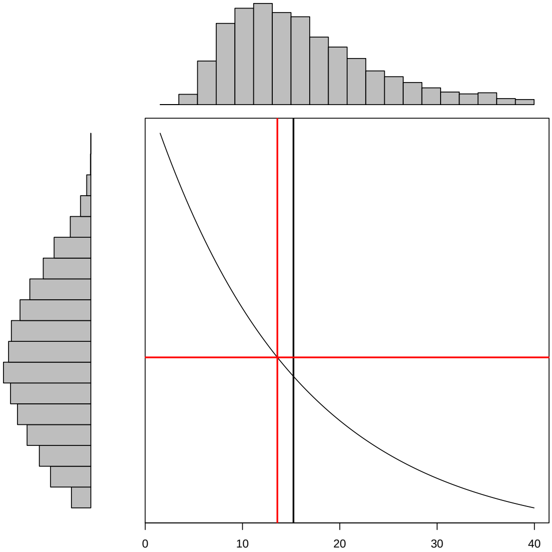
Filtered means

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

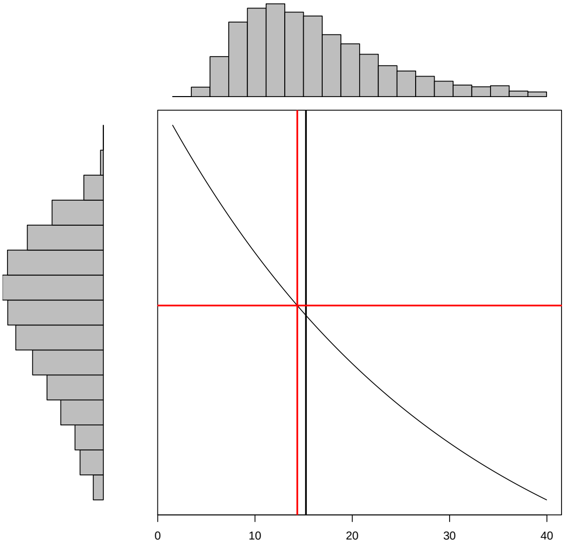
Linking framework

- 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

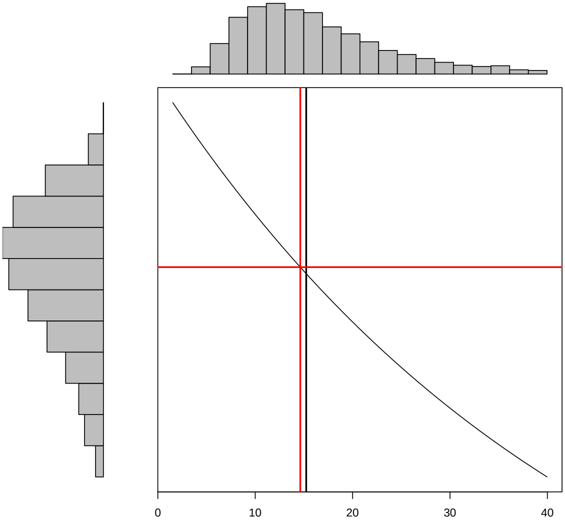
$C = 1/r = 15d$



$C = 1/r = 30d$



$C = 1/r = 45d$



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 $\bar{G}$

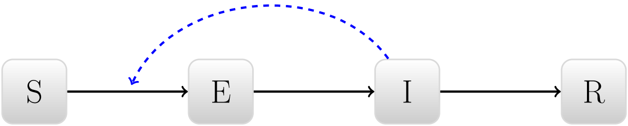
The filtering function

- $\exp(-r\hat{G}) = \langle \exp(-r\tau) \rangle_g$,
- $\hat{G}$ 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

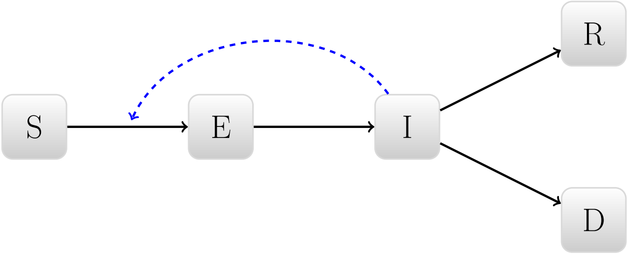
Example: Post-death transmission and safe burial

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

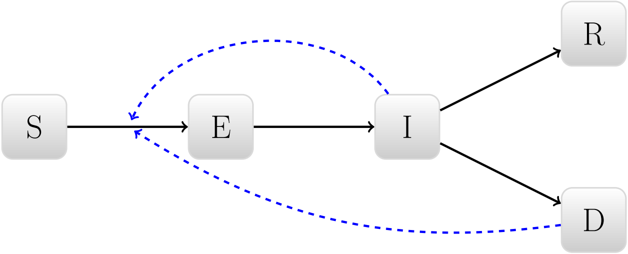
Standard disease model



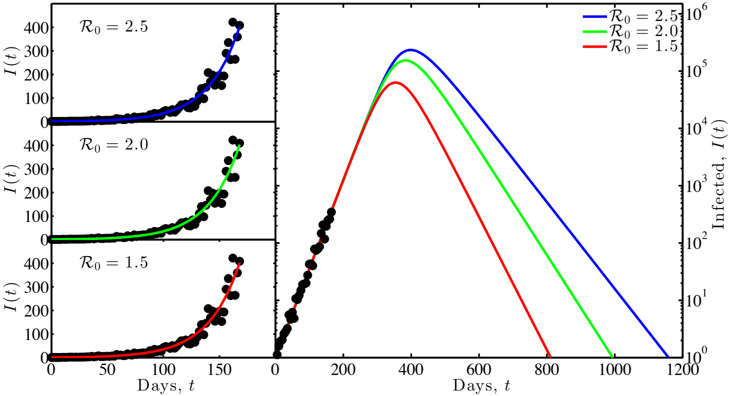
Disease model including post-death transmission



Disease model including post-death transmission



Scenarios



$\mathcal{R}_0 = 2.5$
$\mathcal{R}_0 = 2.0$
$\mathcal{R}_0 = 1.5$
$I(t)$
0
100
200
300
400
0
50
100
150
Days, t
0
200
400
600
800
1000
1200
Days, t
10^0
10^1
10^2
10^3
10^4
10^5
10^6
Infected, $I(t)$

Conclusions

- Different parameters can produce indistinguishable early dynamics
- More after-death transmission implies
  - Higher $\mathcal{R}_0$
  - Larger epidemics
  - Larger importance of safe burials

Outline

Tangled web

- The filtered mean is useful – but complicated
  - Filtering function is not scale free.
- Unless the generation interval is absolutely fixed, $\hat{G}$ will change even when g does not
- How is
  - $\mathcal{R} = \exp(r\hat{G})$
- Consistent with the result from ODEs
  - $\mathcal{R} = 1 + r\bar{G}$?

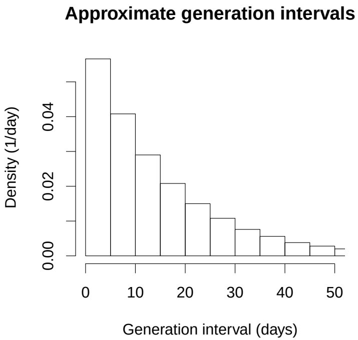
An approximation

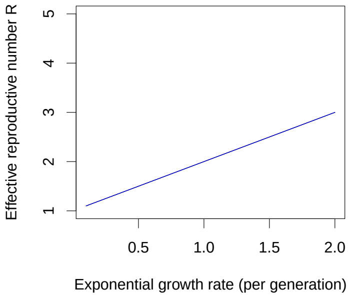
- We connect these quantities with a moment approximation
- Define $\kappa = \sigma_G^2/\mu_G^2$ – the squared coefficient of variation of the generation distribution
- $\mathcal{R} \approx (1 + r\kappa\bar{G})^{1/\kappa}$
  - Equal when $g(\tau)$ has a gamma distribution
  - Simple and straightforward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

Compound-interest interpretation

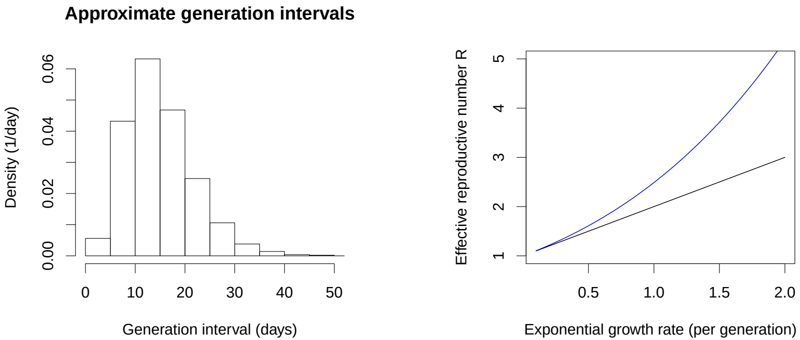
- Define $\mathcal{R} \approx (1 + r\kappa\bar{G})^{1/\kappa} \equiv X(r\bar{G}; 1/\kappa)$
- X is the compound-interest approximation to the exponential
  - Linear when $\kappa = 1$ (i.e., when g is exponential)
  - Approaches exponential as $\kappa \to 0$

Moment approximation

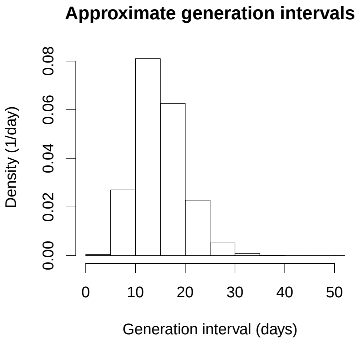


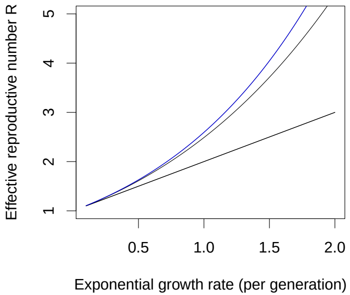


Moment approximation

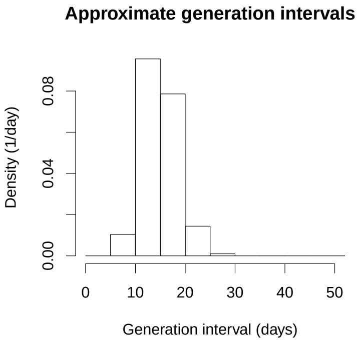


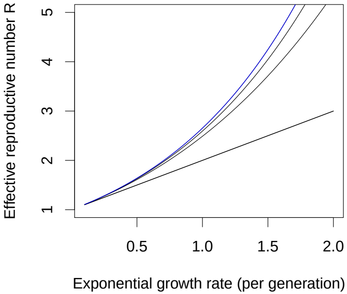
Moment approximation





Moment approximation





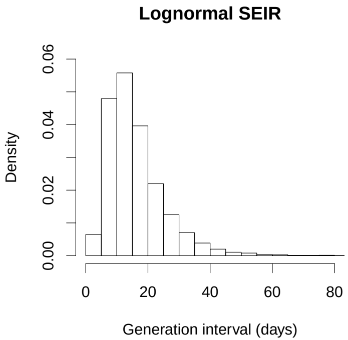
Qualitative response

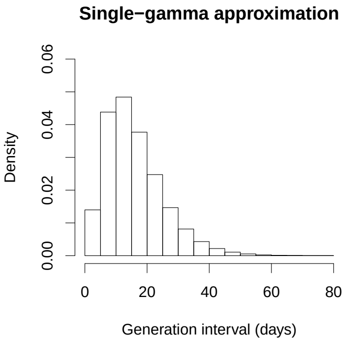
- For a given value of $\bar{G}$, smaller values of κ mean:
  - less variation in generation interval
  - less compounding of growth
  - greater $\mathcal{R}$ required for a given r

Fitting to Ebola

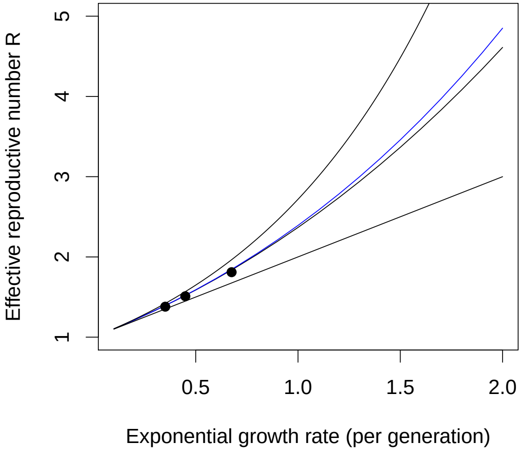
- Simulate generation intervals based on data and approach from WHO report
- Use both lognormals and gammas
  - WHO used gammas
  - Lognormals should be more challenging

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

Ebola burial example

- Burial transmission increases the mean generation interval
  - Increases estimate of $\mathcal{R}$
- ...increases variation
  - Decreases estimate of $\mathcal{R}$
- Based on filtered mean, we know that the net effect of shifting transmission later, must be to increase the estimate

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
- Filtered mean remains intuitively useful

Outline

Generation intervals through time

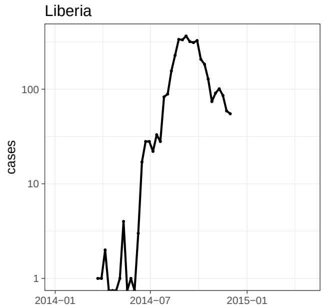
- Generation intervals can be estimated by:
  - Observing patients:
    - How long does it take to become infectious?
    - How long does it take to recover?
    - What is the time profile of infectiousness/activity?
  - Contact tracing
    - Who (probably) infected whom?
    - When did each become ill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

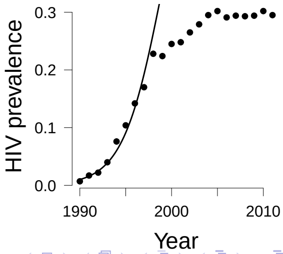
Types of interval

- 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

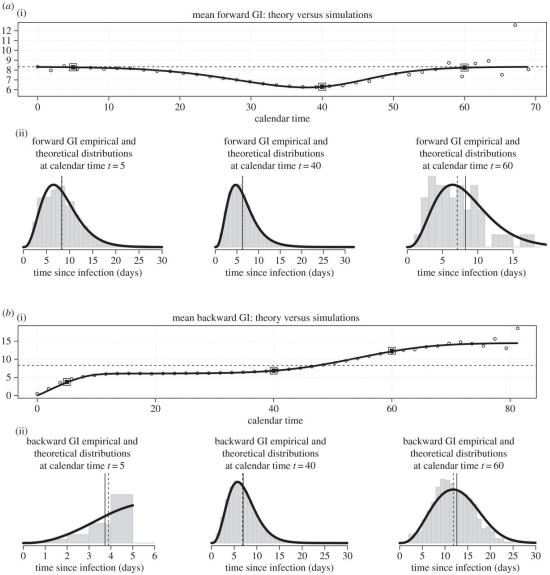




Correcting

- 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 $S(t)$

Theory and simulation



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

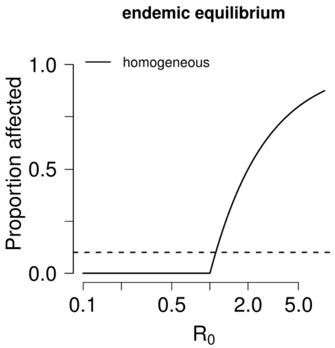
Conclusion

- 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
  - These biases can be corrected

Outline

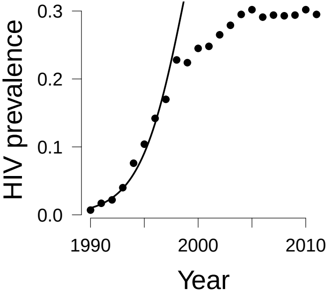
Strength: $\mathcal{R}$ – the reproductive number

- Expected number of new cases per cases



Speed: r – the growth rate

- Instantaneous rate of growth: $i(t) \approx i(0)\exp(rt)$



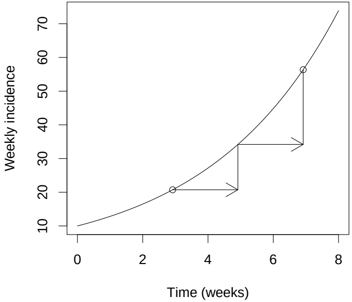
Is $\mathcal{R}$ better than r?

- $\mathcal{R}$ is better for long-term predictions
  - r is better for short-term predictions
- $\mathcal{R}$ gives a threshold for spread
  - So does r!
- $\mathcal{R}$ can be compared with intervention strength
  - ???

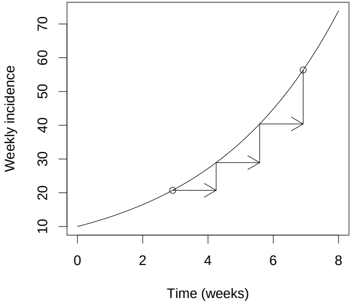
Can treatment stop the HIV epidemic?

- 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

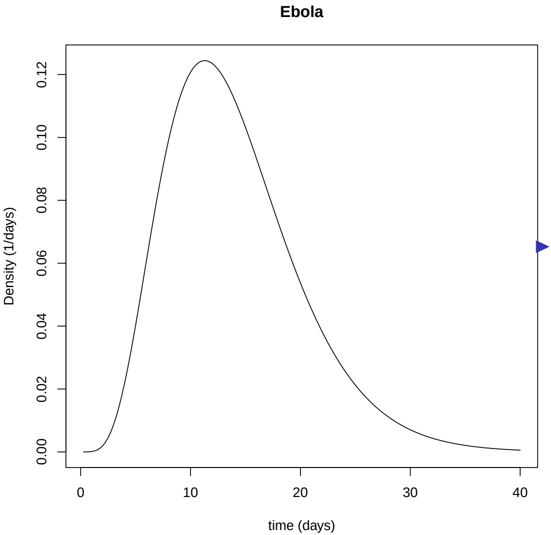
- Predicted effectiveness of test and treat intervention minimally sensitive to proportion of early transmission
- Fast transmission:
  - low proportion prevented, but low $\mathcal{R}$ estimate
- Slow transmission:
  - high proportion prevented, but high $\mathcal{R}$ estimate
- *Eaton JW, Hallett TB. Proc Natl Acad Sci U S A. 2014 Nov 11;111(45):16202-7.*

How fast do people need to be treated?

- Consider the idealized case where people are identified and removed at a constant rate
- Euler-Lotka
  - $1 = \int k(\tau) \exp(-r\tau) \, d\tau$
- Required treatment "hazard" (per-capita removal rate) is equal to r!

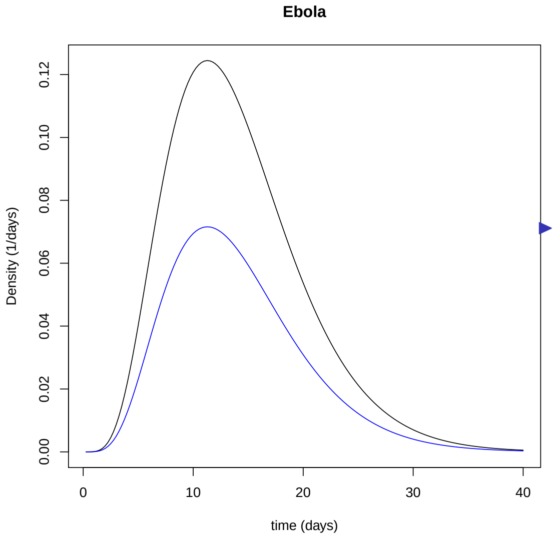
Outline

Epidemic strength



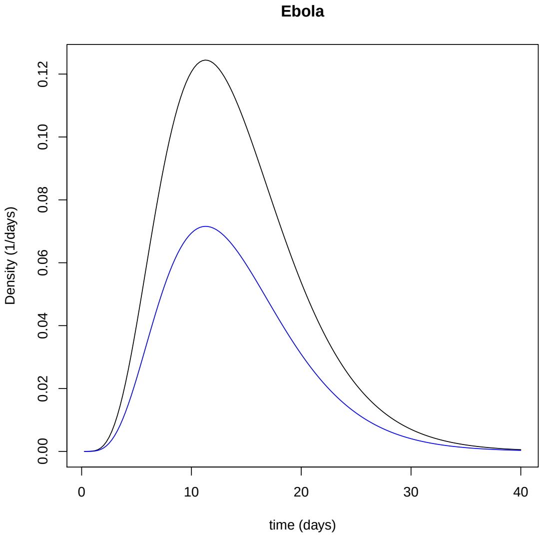
- $\mathcal{R}$, the epidemic strength, is the area under the curve.

Strength of intervention

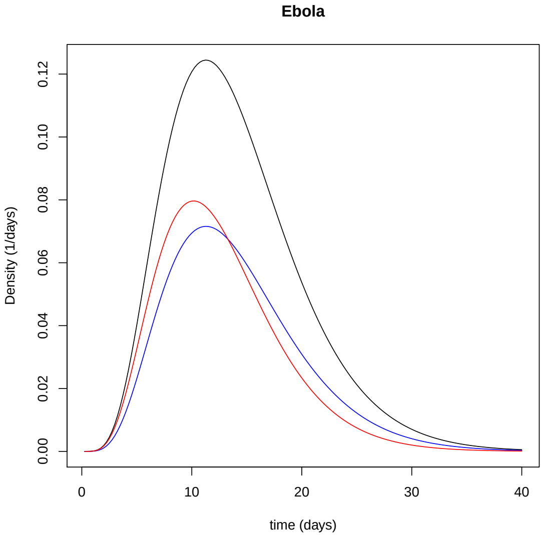


- . . . by what factor do I need to reduce this curve to eliminate the epidemic

Different interventions



Different interventions



Measuring the intervention

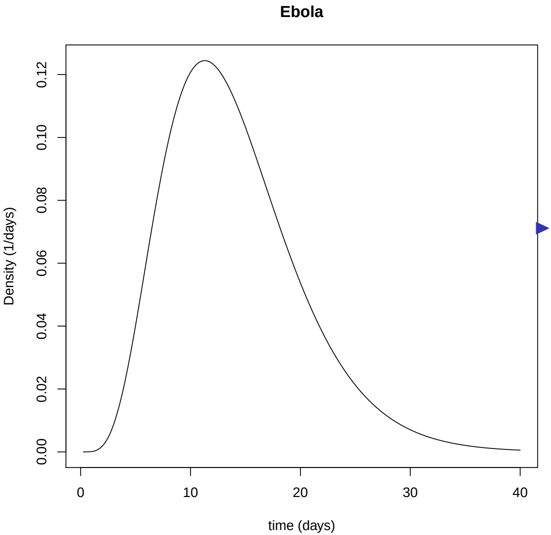
- We imagine an intervention with potentially variable effect over the course of infection, $L(\tau)$
- Assume the intervention takes
  - $k(\tau) \to \hat{k}(\tau) = k(\tau)/L(\tau)$

Measuring intervention strength

- Define intervention *strength* $\theta = \mathcal{R}/\hat{\mathcal{R}}$ – the proportional amount by which the intervention reduces transmission.
- $\theta = 1/\left\langle 1/L(\tau)\right\rangle_{g(\tau)}$
- θ is *the harmonic mean* of L, weighted by the generation distribution g.
- Outbreak can be controlled if $\theta > \mathcal{R}$

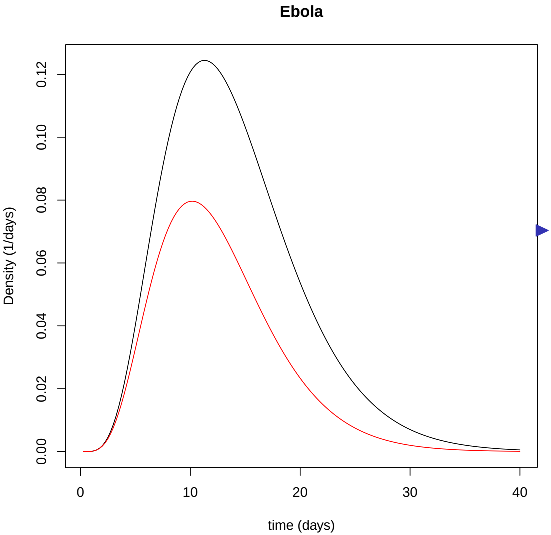
Outline

Epidemic speed



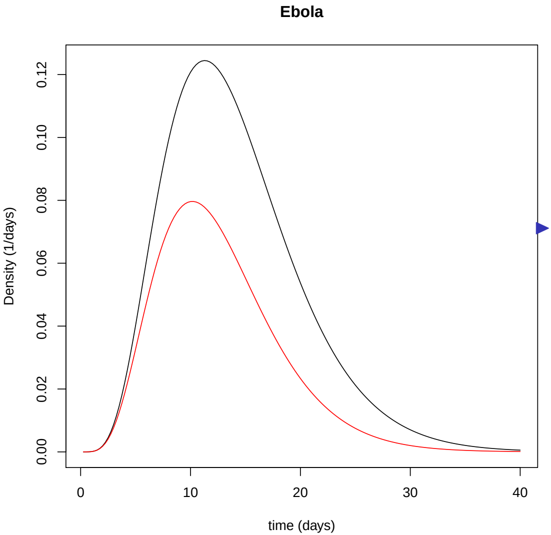
- r, the epidemic speed, is the "discount" rate required to balance the tendency to grow

Epidemic speed



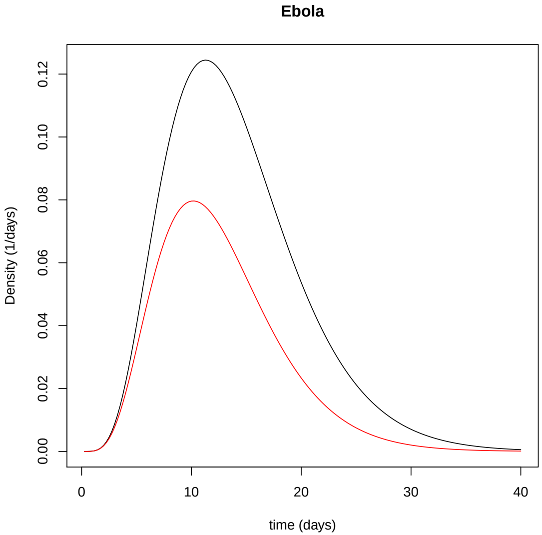
- $k(\tau) = \exp(r\tau)b(\tau)$, where $b(\tau)$ is the initial backward generation interval

Speed of intervention

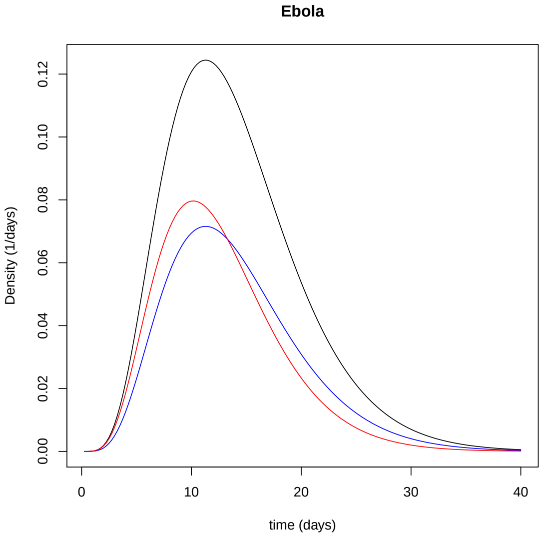


- . . . how *quickly* do I need to reduce this curve to eliminate the epidemic

Different interventions



Different interventions



Measuring intervention speed

- Define intervention *speed* $\phi = r - \hat{r}$ – the amount by which the intervention slows down spread.
- We then have:
  - $1 = \left\langle \frac{\exp(\phi\tau)}{L(\tau)} \right\rangle_{b(\tau)}$
- ϕ is *sort of a mean* of the *hazard* associated with L
  - Because $L(t) = \exp(ht)$ when hazard is constant
- Averaged over the initial *backwards* generation interval
- Outbreak can be controlled if $\phi > r$.

The strength paradigm

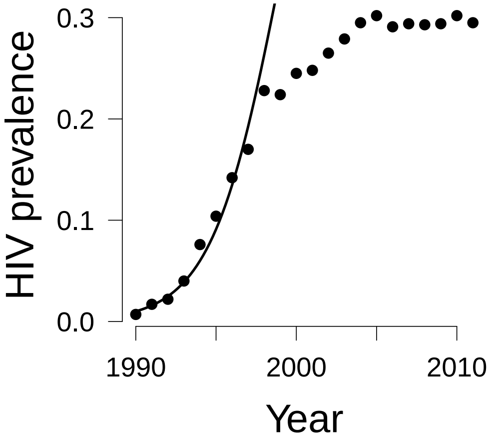
- $k(\tau) = \mathcal{R}g(\tau)$
  - g is the intrinsic generation interval
  - $\mathcal{R}$ is the strength of the epidemic
- If $L(\tau) \equiv L$, then $\theta = L$ is the strength of the intervention
- In general, θ is a (harmonic) mean of L
  - weighted by $g(\tau)$, but not affected by $\mathcal{R}$.
- Epidemic is controlled if $\theta > \mathcal{R}$

The speed paradigm

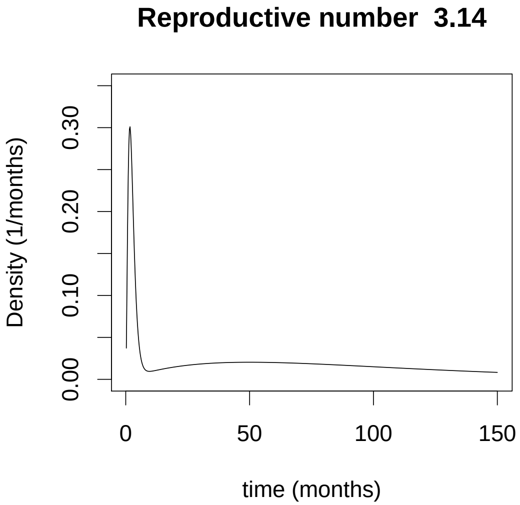
- $k(\tau) = \exp(r\tau)b(\tau)$,
  - r is the speed of the epidemic
  - b is the initial backward generation interval
- If $h(\tau) \equiv h$, then $\phi = h$ is the speed of the intervention
- In general, ϕ is a (weird) mean of h
  - weighted by $b(\tau)$, but not affected by r.
- Epidemic is controlled if $\phi > r$

Outline

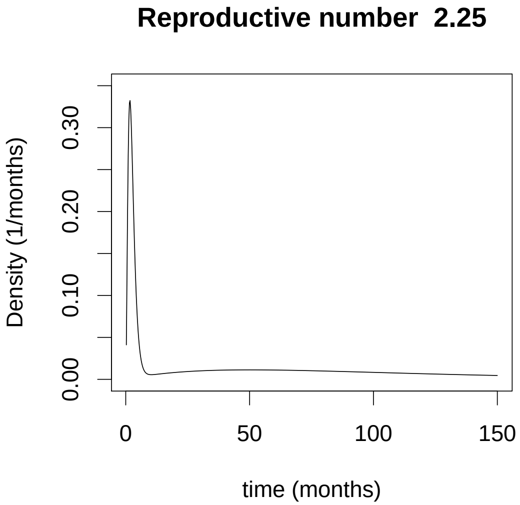
Epidemic speed



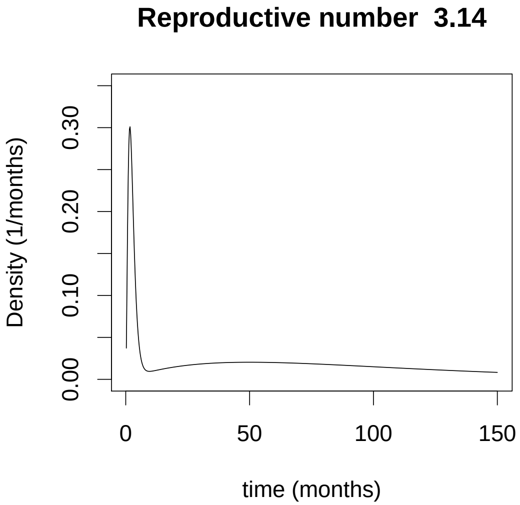
Baseline scenario



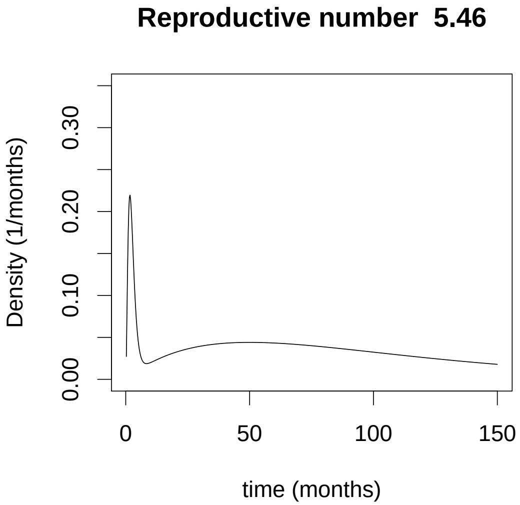
High early transmission



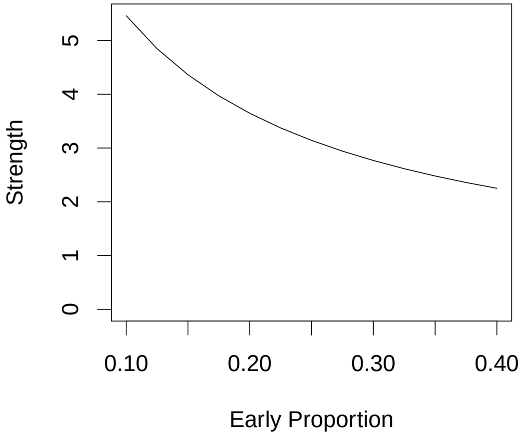
Baseline scenario



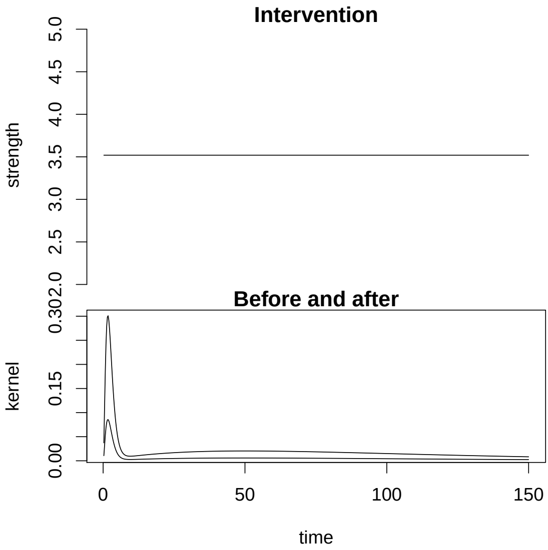
Low early transmission



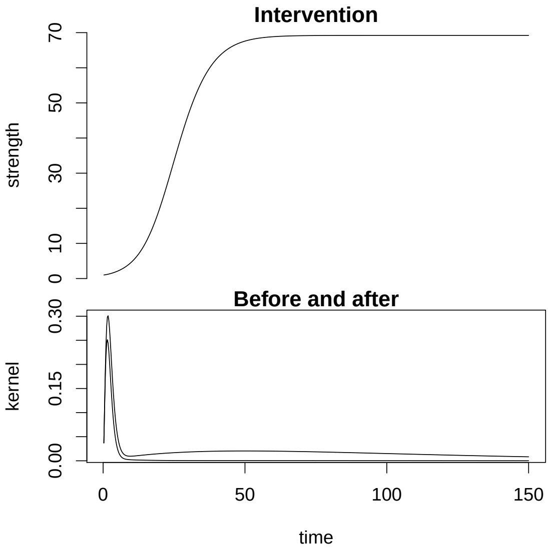
Range of estimates



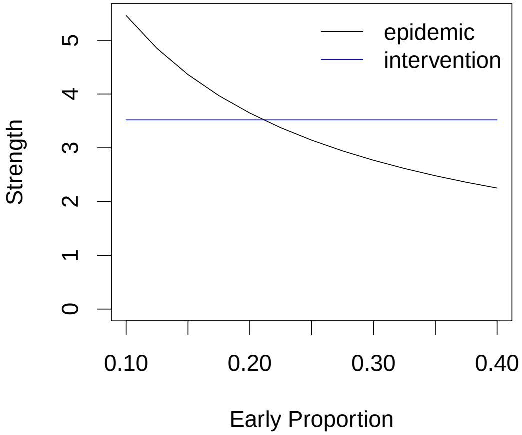
Condom intervention



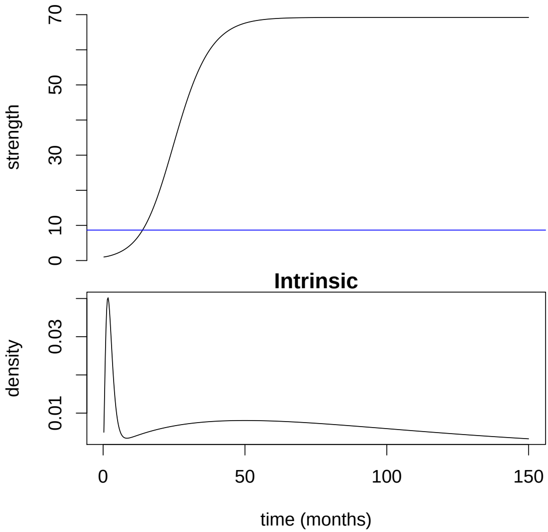
Test and treat



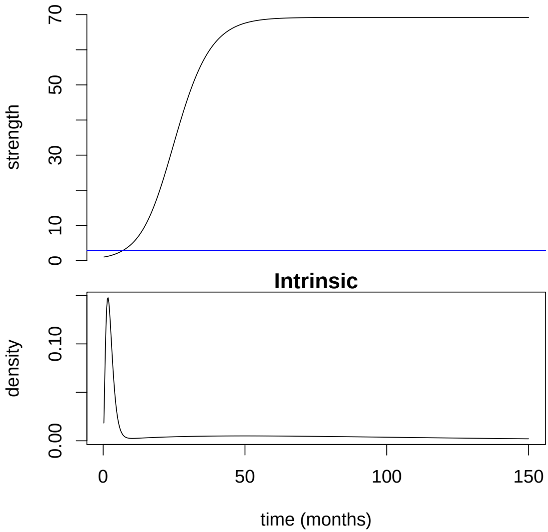
Condom intervention



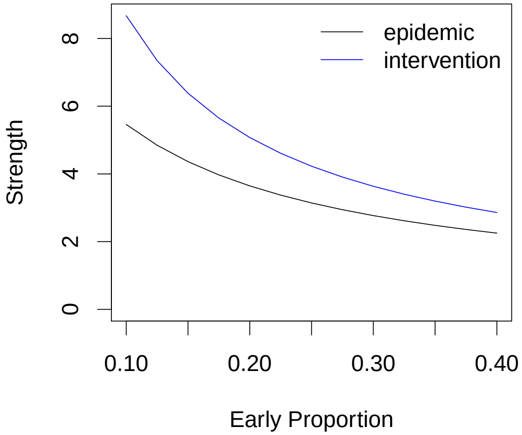
Test and treat (low early transmission)



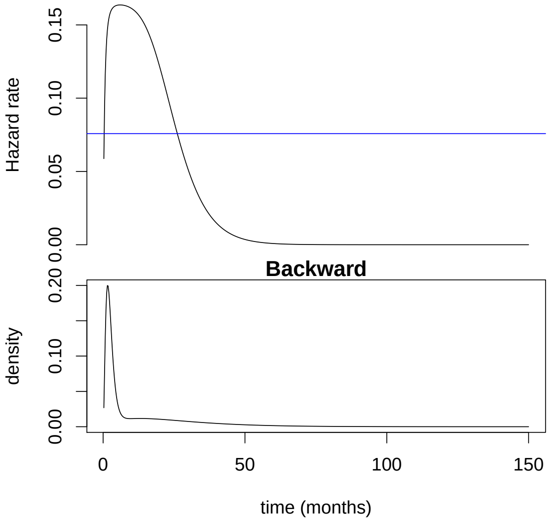
Test and treat (high early transmission)



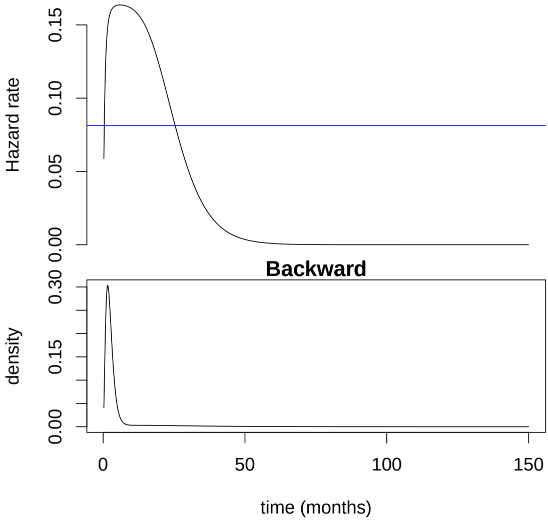
Range of estimates



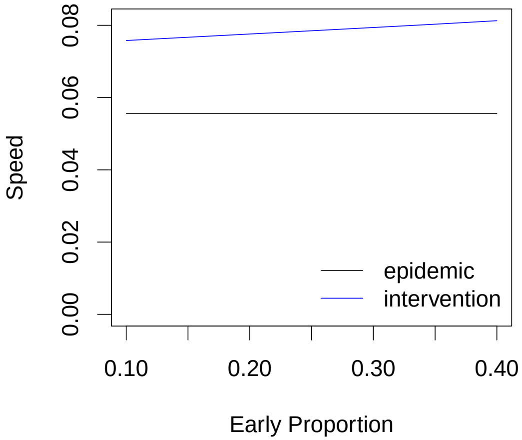
Low early transmission



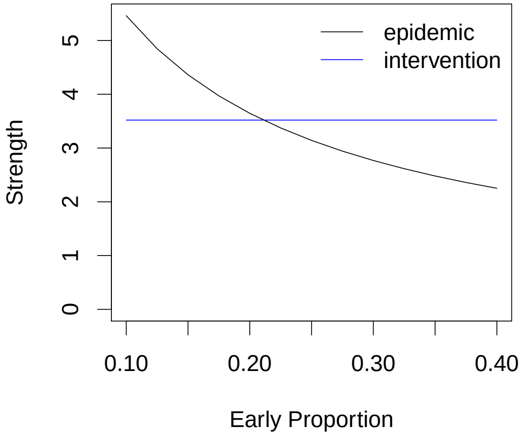
High early transmission



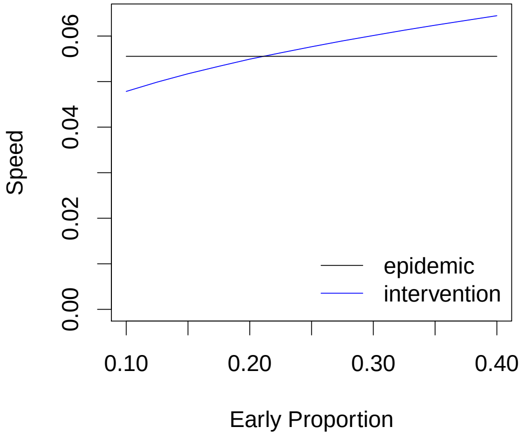
Range of estimates



Condom intervention



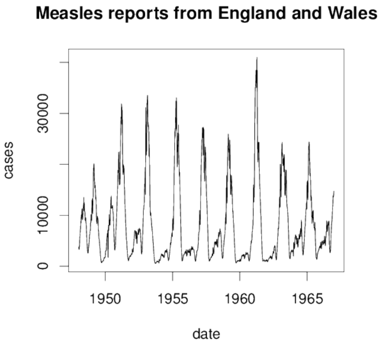
Condom intervention

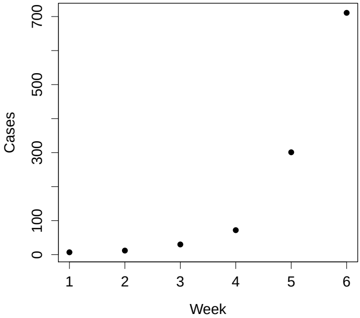


Outline

Ways of looking

Measuring the epidemic





Measuring the intervention

Examples

- Measles
  - Information (long-term) is strength-like
  - Intervention (vaccine) also strength-like
- HIV
  - Information and intervention are both "speed-like"
- Ebola vaccination
  - Information is speed-like
  - Interventions: vaccination (strength?); isolation and control (speed?)

Conclusion

- r and $\mathcal{R}$ have more in common than we think
- Sometimes "strength" and sometimes "speed" can help us see epidemic control questions more clearly
- This perspective helps us understand why test and treat predictions are robust to assumptions about transmission

Thanks

- Organizers
- Audience
- Collaborators
- Funders: NSERC, CIHR