

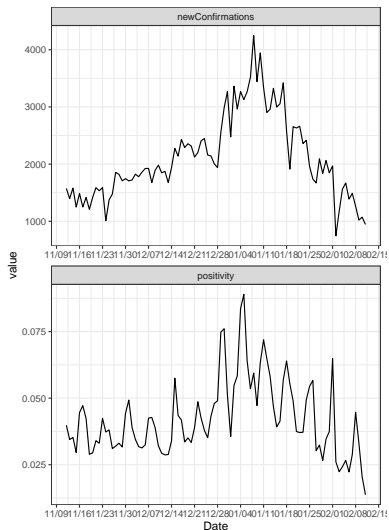
Transmission intervals and coronavirus control

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UT COVID-19 Consortium Colloquium (CCC), May 2021

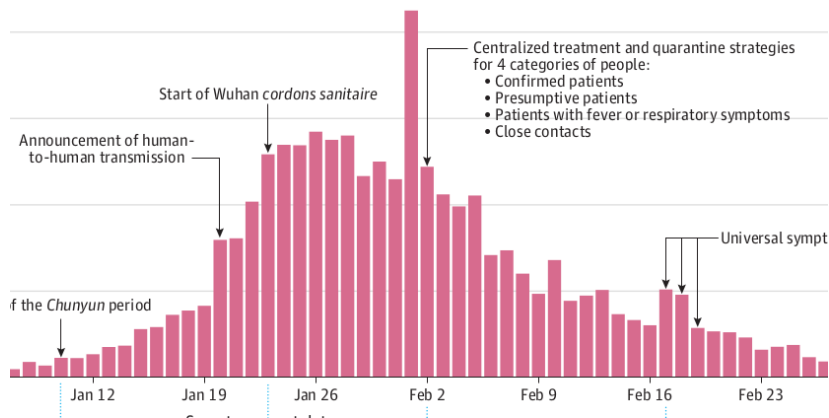
Covid modeling questions

- ▶ How far and fast would it spread if unchecked?
- ▶ How hard is it to eliminate?
- ▶ How are we doing on control in a particular place and time?



<https://wzmli.github.io/COVID19-Canada>

Wuhan control measures



https:

//jamanetwork.com/journals/jama/fullarticle/2764658

Time-varying reproductive numbers

- ▶ Case reproductive number \mathcal{R}_c (e.g., Wallinga and Teunis)
 - ▶ How many people will get infected by a case infected at time t ?
 - ▶
$$i(t) = \sum \mathcal{R}(t - \tau)g(\tau)i(t - \tau)$$
- ▶ Instantaneous reproductive number \mathcal{R}_c (e.g., Cori et al.)
 - ▶ What overall reproductive number predicts what I'm seeing now?
 - ▶
$$i(t) = \sum \mathcal{R}(t)g(\tau)i(t - \tau)$$
- ▶ Speed vs. strength
 - ▶ What if g is changing?
 - ▶ Are r -based tools available?

Transmission intervals



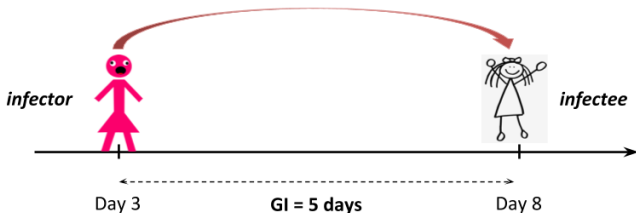
- ▶ Sort of the poor relations of disease-modeling world
- ▶ Ad hoc methods
- ▶ Error often not propagated

How long is a disease generation? (present)

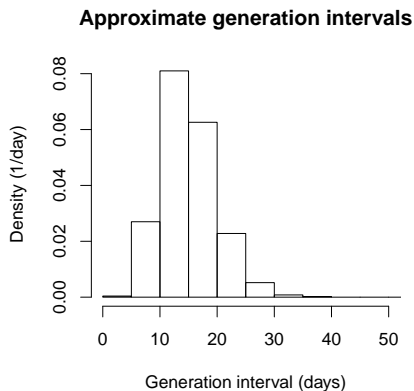
Definition

Generation Interval:

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



Generation-interval distributions



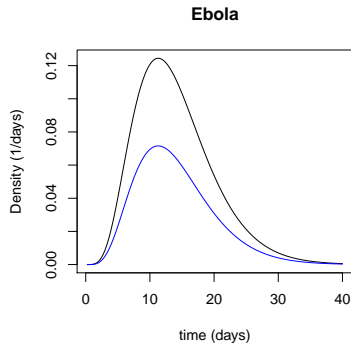
- ▶ The generation distribution measures generations of the disease
 - ▶ Interval between “index” infection and resulting infection
- ▶ Link r (exponential growth rate) and \mathcal{R} (effective reproductive number)

Transmission intervals drive epidemics

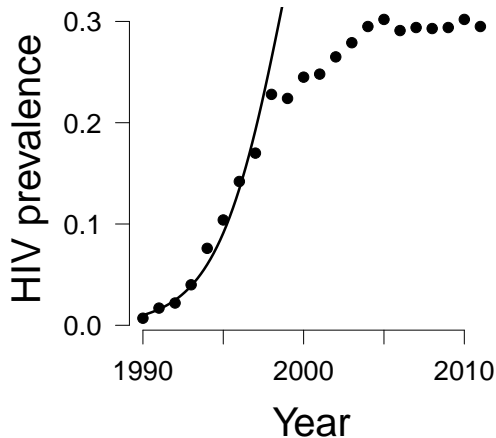
- ▶ Population-level *Speed* of spread r is a product:
 - ▶ Something about *Strength* \mathcal{R}
 - ▶ \times
 - ▶ Something about *Quickness*: Individual-level speed of transmission $g(\tau)$

Mechanistic perspective

- ▶ \mathcal{R} is known
- ▶ Quicker generations \Rightarrow faster population-level spread

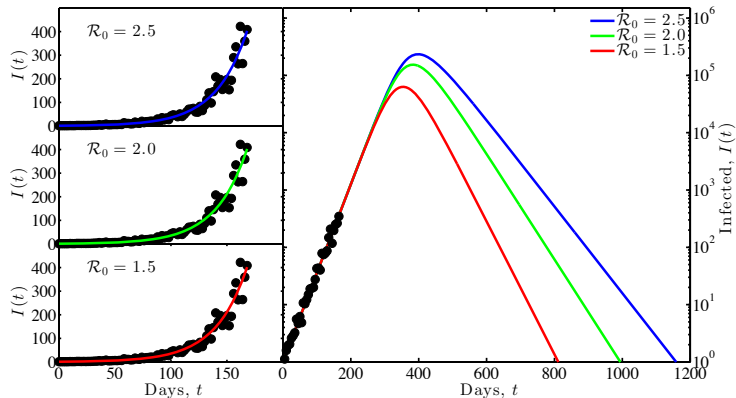


HIV in sub-Saharan Africa



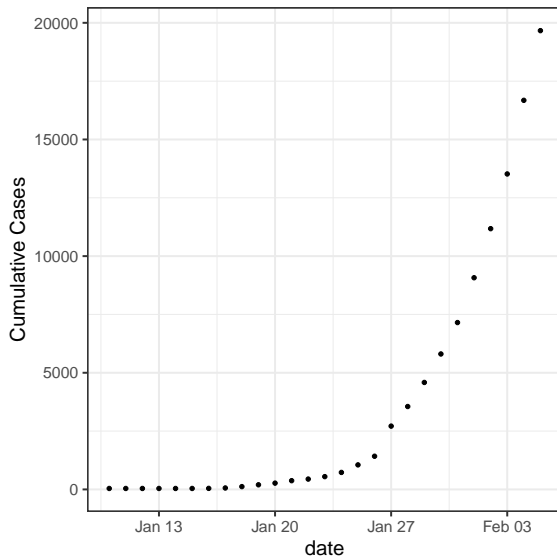
$C \approx 18$ month. Faster than expected.

Ebola outbreak



$C \approx 1$ month. Slower than expected.

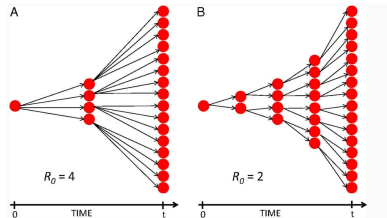
Coronavirus speed



$C \approx 5$ day. Coronavirus!

Phenomenological perspective

- ▶ Population-level speed r is observed
- ▶ Quicker generations (low \bar{G})
 \implies lower \mathcal{R}



*Powers et al.,
[https://www.pnas.org/
content/111/45/15867](https://www.pnas.org/content/111/45/15867)*

Generation interval

- ▶ One generation:
 - ▶ Latent period (time until infectiousness) +
 - ▶ Infectious waiting time (time until infection)
- ▶ Infectious waiting time
 - ▶ Drawn at random from infectious period
 - ▶ Equal to infectious period *only* when we assume a Markovian process

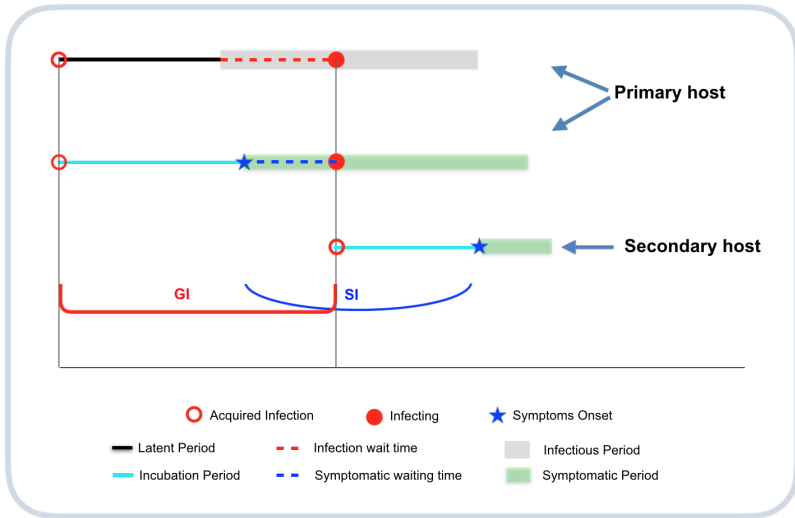
How long until the bus comes?



Transmission intervals

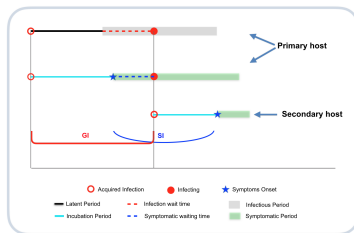
- ▶ Generation interval: infection \implies infection
 - ▶ Drives epidemic, often unobserved
- ▶ Serial interval: symptoms \implies symptoms
 - ▶ Observable. . . , may be hard to define
- ▶ Other:
 - ▶ diagnosis \implies diagnosis
 - ▶ notification \implies notification
- ▶ Some cases are never symptomatic, or never diagnosed

Serial intervals



Steps

- ▶ Generation interval:
 - ▶ Latent + infectious waiting
- ▶ Serial interval:
 - ▶ Symptomatic waiting + Incubation



Outline

Linking $r\mathcal{R}$

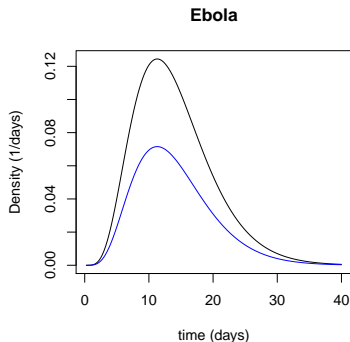
Serial-interval distributions

Renewal-equation

- ▶ A broad framework that covers a wide range of underlying models
- ▶ $i(t) = \int k(\tau, t)i(t - \tau) d\tau$
 - ▶ $i(t)$ is the *rate* of new infections (per-capita incidence)
 - ▶ $k(\tau)$ measures how infectious a person is (on average) at time τ after becoming infected
- ▶ k changes through time
 - ▶ proportion susceptible, control measures
 - ▶ we often think about fixed $k(\tau)$ though

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



Estimation framework

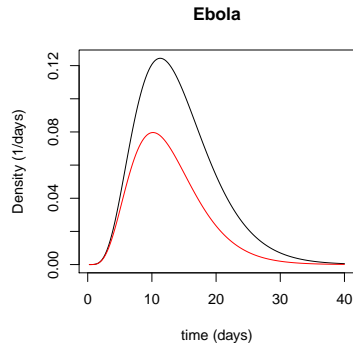
- ▶ $k(\tau, t)$ is basically everything we want to know
- ▶ Usually unobservable, though
- ▶ Typically try to observe r or \mathcal{R}
- ▶ and something about $g(\tau)$

Euler-Lotka equation

- ▶ If we assume k is not changing through time, we expect exponential growth
- ▶ $1 = \int k(\tau) \exp(-r\tau) d\tau$
 - ▶ i.e., the total of *discounted* contributions is 1
- ▶ $1/\mathcal{R} = \int g(\tau) \exp(-r\tau) d\tau$
- ▶ Note that $b(\tau) = k(\tau) \exp(-r\tau)$ is also a distribution
 - ▶ The initial “backwards” generation interval

Interpretation: generating functions

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



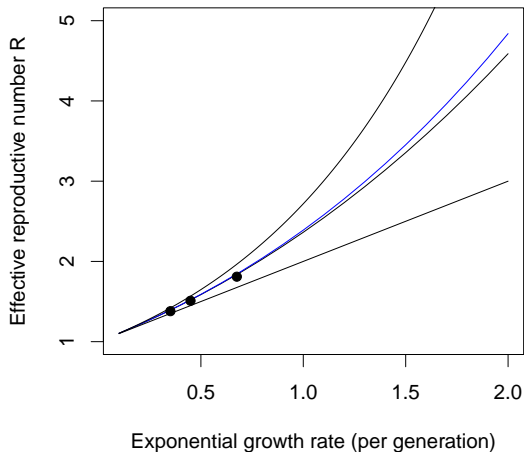
Compound-interest interpretation

- ▶ $\mathcal{R} = (1 + r\kappa\bar{G})^{1/\kappa} \equiv X(r\bar{G}; 1/\kappa)$
- ▶ κ is the 'effective dispersion'
 - ▶ Equal to the squared coefficient of variation when G is gamma-distributed
- ▶ X is the compound-interest approximation to the exponential
 - ▶ Linear when $\kappa = 1$ (i.e., when g is exponential)
 - ▶ Approaches exponential as $\kappa \rightarrow 0$
- ▶ $r = (1/\bar{G}) \times \ell(\mathcal{R}; \bar{\kappa})$
- ▶ *Park et al., Epidemics DOI:10.1101/312397*

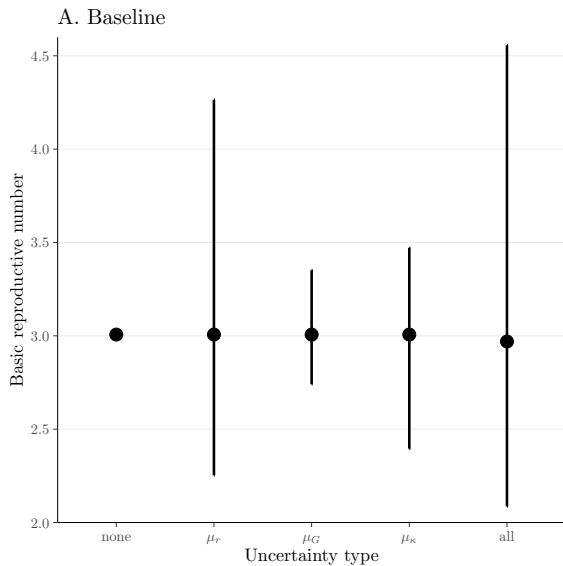
Product framework

- ▶ Quicker generations (small \bar{G}) mean faster r for fixed \mathcal{R}
 - ▶ \implies Weaker \mathcal{R} for fixed r
- ▶ More variation κ means more “compounding” of infections
 - ▶ \implies quicker spread, when epidemic is growing

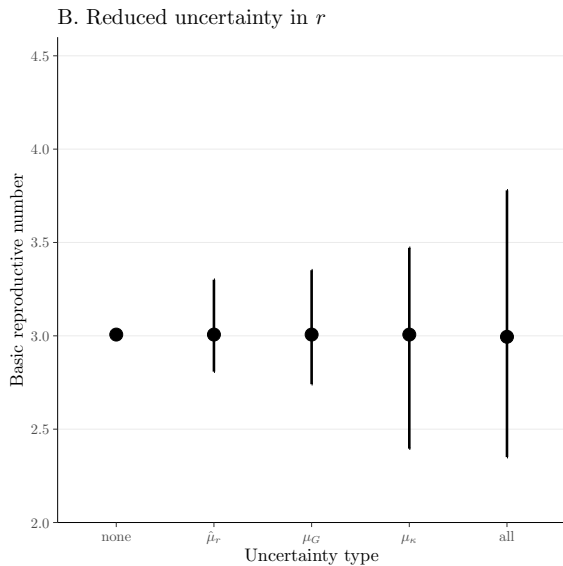
Approximating the $r\mathcal{R}$ relationship



Propagating error



Propagating error

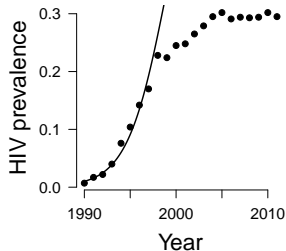
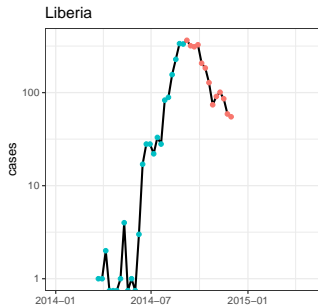


Types of interval

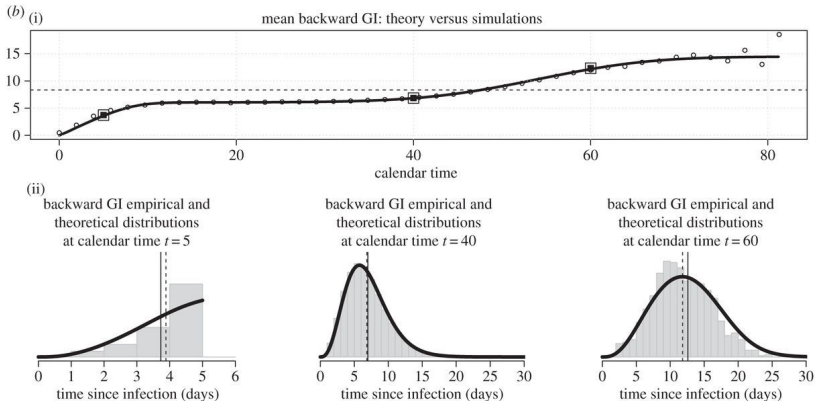
- ▶ Define:
 - ▶ *Intrinsic interval*: How infectious is a patient at time τ after infection?
 - ▶ *Forward interval*: When will the people infected today infect others?
 - ▶ *Backward interval*: When did the people who infected people today themselves become infected?
 - ▶ *Censored interval*: What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

Growing epidemics

- ▶ Measured 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



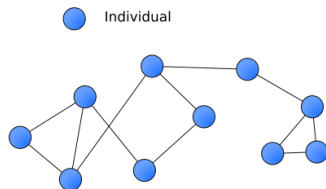
Correcting backward intervals



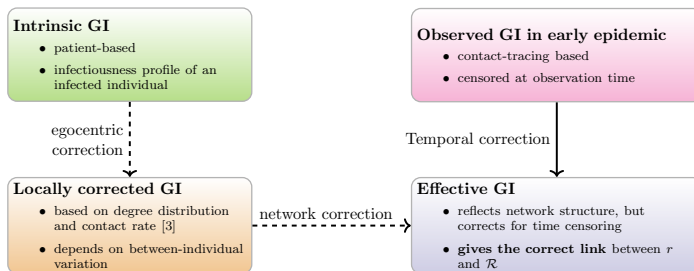
Champredon and Dushoff, 2015. DOI:10.1098/rspb.2015.2026

Generations in space

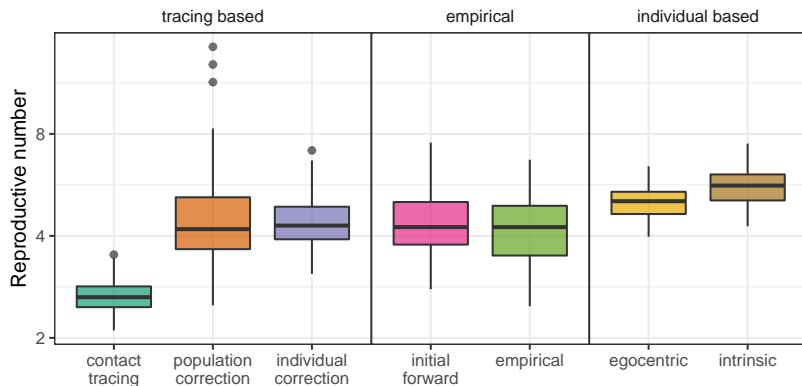
- ▶ Local interactions
- ▶ \Rightarrow wasted contacts
- ▶ \Rightarrow realized generation intervals smaller than intrinsic
- ▶ \Rightarrow intrinsic GIs over-estimate \mathcal{R}
- ▶ *Trapman et al., 2016. JRS Interface*
DOI:10.1098/rsif.2016.0288



Observed and estimated intervals



Outbreak estimation



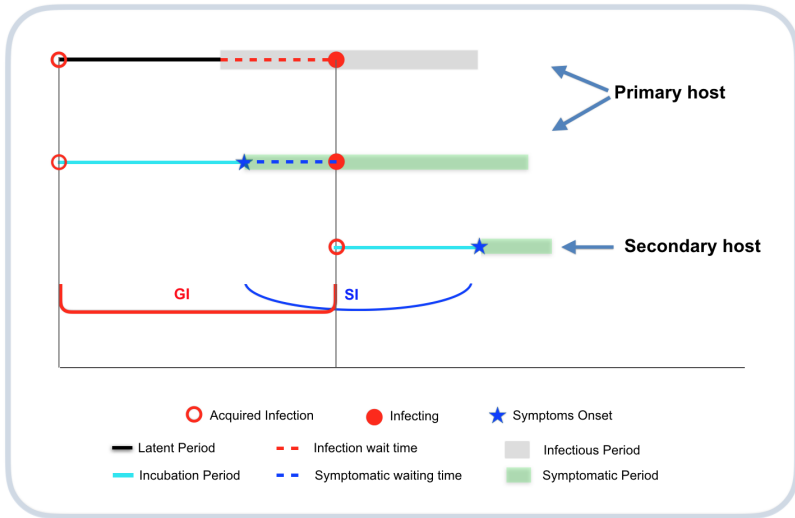
Park et al. JRSI, DOI: 10.1098/rsif.2019.0719

Outline

Linking $r\mathcal{R}$

Serial-interval distributions

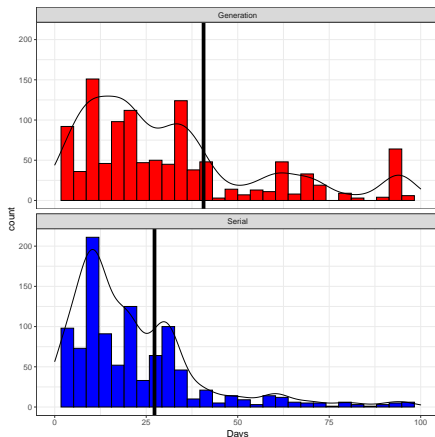
Serial-interval distributions



The serial-mean paradox

- ▶ Serial intervals measure generations of the same process as generation intervals
 - ▶ Should have the same mean
 - ▶ But often larger variance (flu example)
- ▶ Empirically, even the means are not the same!
- ▶ Generation interval:
 - ▶ Latent + infectious waiting ... of infector
- ▶ Serial interval:
 - ▶ Symptomatic waiting (infector) + Incubation (infectee)

Heterogeneity



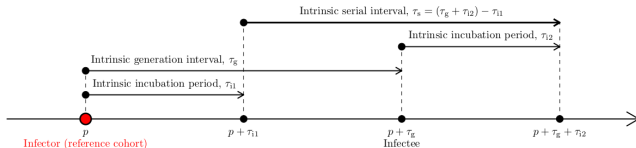
- ▶ Generation intervals include latent period of infectors only (often strongly weighted)
- ▶ Serial intervals average over infectees (everyone is infected once)
- ▶ Coronavirus: people diagnosed early are less likely to transmit

The link paradox

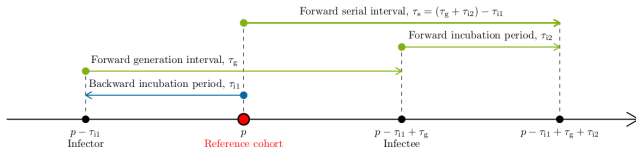
- ▶ Imagine a renewal process where symptoms in the infector cause symptoms in the infectee
 - ▶ Assume homogeneity
- ▶ This has to match the same $r\mathcal{R}$ link as the true process
- ▶ But it also can't (because the serial interval is in general broader than the generation interval)
 - ▶ All else equal, a broader interval means lower \mathcal{R} .

The forward serial interval

A. Intrinsic serial interval

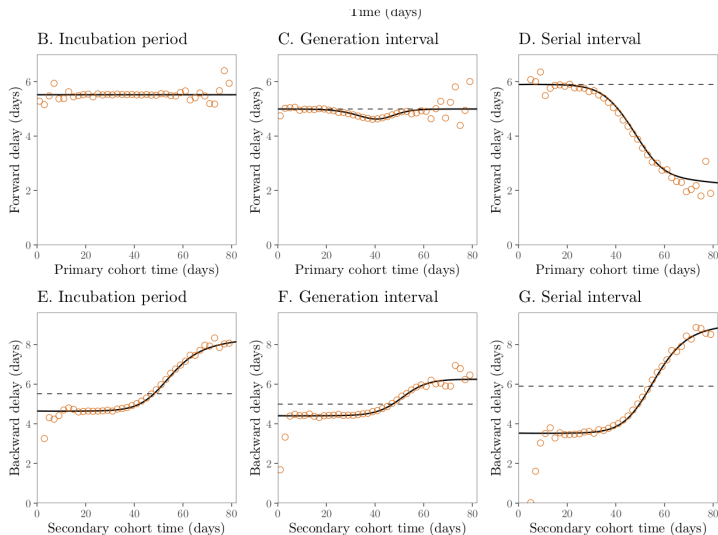


B. Forward serial interval



- Dynamical effects mean that the forward serial interval is shortened!

Observed epidemiological intervals



Summary

- ▶ Strength \mathcal{R} and speed r are complementary ways to understand epidemic growth and control
- ▶ Transmission intervals are key to linking these measurements
 - ▶ Clear definitions
 - ▶ Combining different sources of information
 - ▶ Propagating error

Thanks

- ▶ Organizers and audience
- ▶ Collaborators:
 - ▶ Li, Park, Weitz, Bolker, Earn, Champredon, Gharouni, Papst, Hampson, So ...
- ▶ Funders: NSERC, CIHR, PHAC, WHO, McMaster