

# Transmission-interval distributions and coronavirus control

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PHAC Technical Tuesday  
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# Transmission intervals



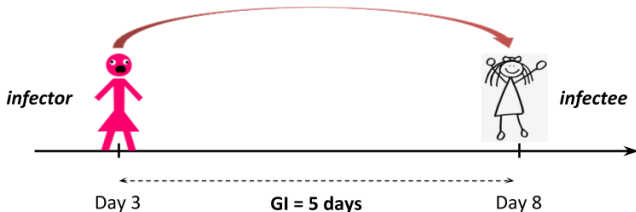
- ▶ Sort of the poor relations of disease-modeling world
- ▶ Ad hoc methods
- ▶ Error often not propagated

# How long is a disease generation? (present)

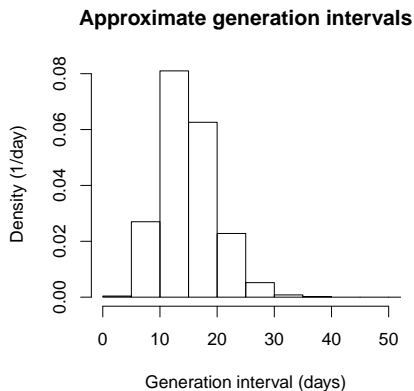
## Definition

### Generation Interval:

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



# Generation-interval distributions



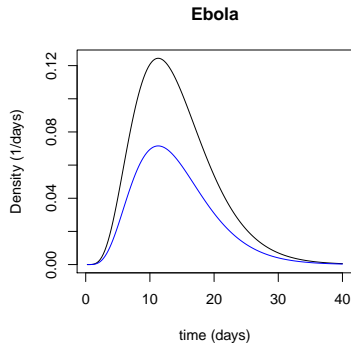
- ▶ The generation distribution measures generations of the disease
  - ▶ Interval between “index” infection and resulting infection
- ▶ Link  $r$  (exponential growth rate) and  $\mathcal{R}$  (effective reproductive number)

# Transmission intervals drive epidemics

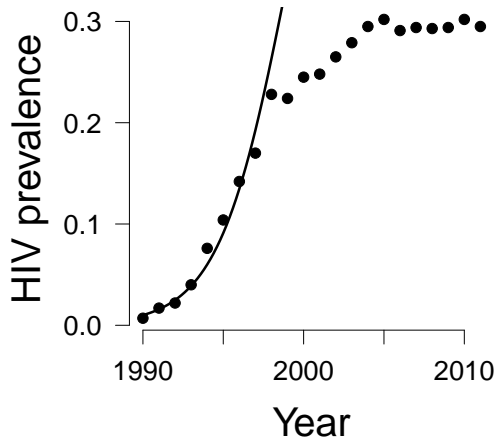
- ▶ Population-level speed of spread  $r$  is a product (sort of):
  - ▶ Strength  $\mathcal{R} \times \dots$
  - ▶ Individual-level speed of transmission  $g(\tau)$

# Mechanistic perspective

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

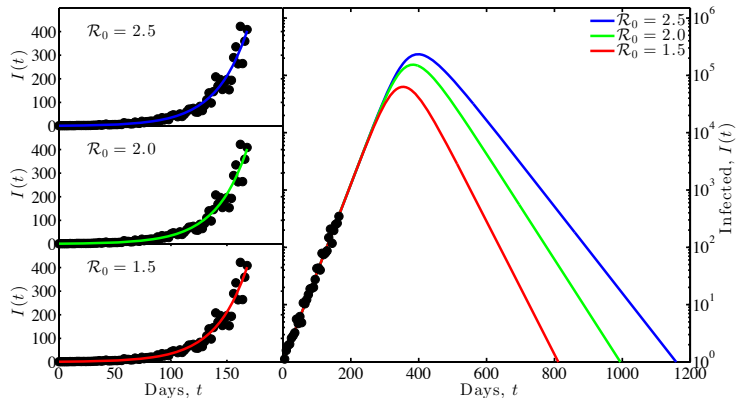


# HIV in sub-Saharan Africa



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

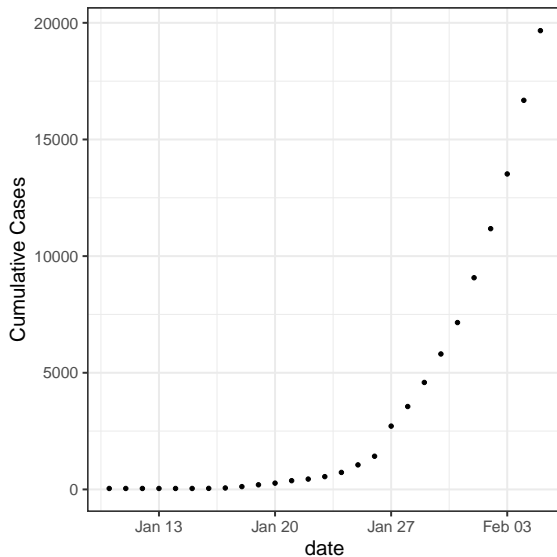
# Ebola outbreak



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



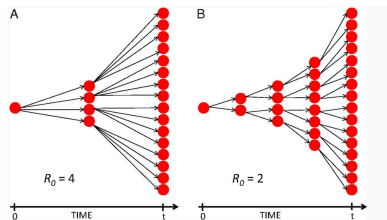
# Coronavirus speed



$C \approx 5$  day. Coronavirus!

# Phenomenological perspective

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

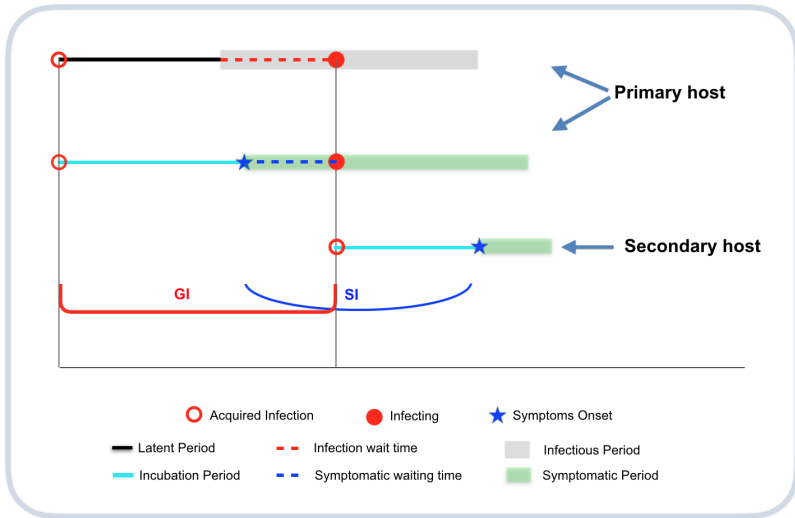


*Powers et al.,  
[https://www.pnas.org/  
content/111/45/15867](https://www.pnas.org/content/111/45/15867)*

# 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:
  - ▶ Incubation + symptomatic waiting
- ▶ Report
  - ▶ Are there good names for these intervals?
  - ▶ e.g., infection to recorded date

# Outline

Linking  $r\mathcal{R}$

Serial-interval distributions

Evaluating interventions

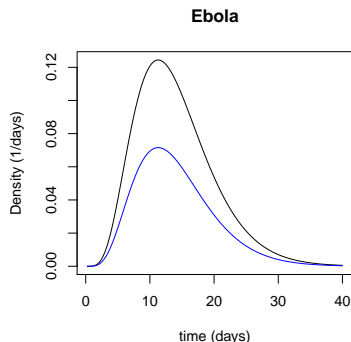
Variants

# 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)
  - ▶  $S(t)$  is the proportion of the population susceptible
  - ▶  $k(\tau)$  measures how infectious a person is (on average) at time  $\tau$  after becoming infected
- ▶  $k$  changes through time
  - ▶ proportion infected, control measures
- ▶ But we mainly focus on a particular profile  $k(\tau)$

# Infection kernel

- ▶  $k(\tau)$  is the expected rate at which you infect at time  $\tau$  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



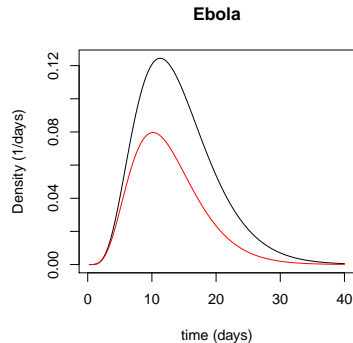


# Euler-Lotka equation

- ▶ 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
- ▶  $1/\mathcal{R} = \int g(\tau) \exp(-r\tau) d\tau$
- ▶ Note that  $b(\tau) = k(\tau) \exp(-r\tau)$  is also a distribution
  - ▶ The initial “backwards” generation interval

# Interpretation: generating functions

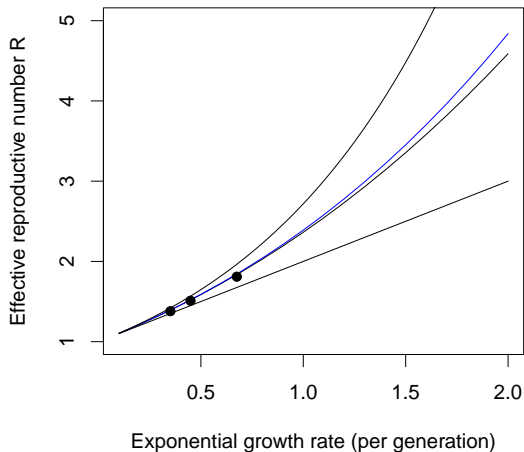
- ▶  $1/\mathcal{R} = \int g(\tau) \exp(-r\tau) d\tau$
- ▶  $\mathcal{R} = 1/M(-r)$
- ▶ *J Wallinga, M Lipsitch; DOI: 10.1098/rspb.2006.3754*



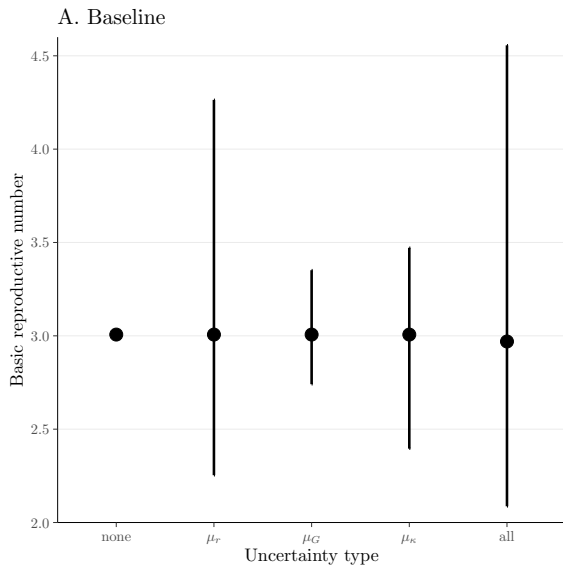
# Compound-interest interpretation

- ▶  $\mathcal{R} = (1 + r\kappa\bar{G})^{1/\kappa} \equiv X(r\bar{G}; 1/\kappa)$
- ▶  $\kappa$  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*

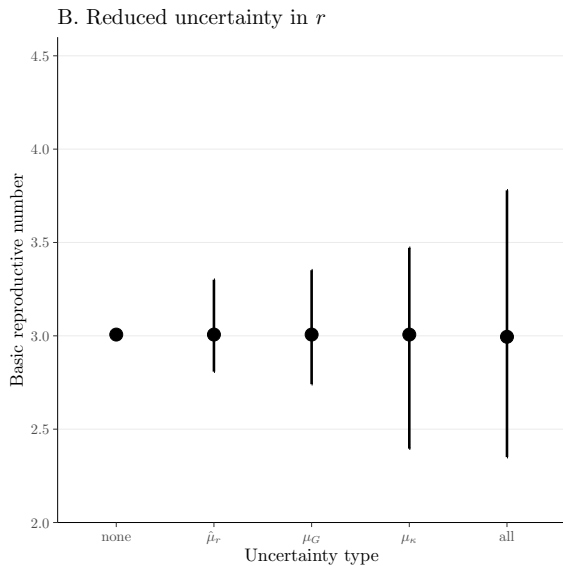
# Approximating the $r\mathcal{R}$ relationship



# Propagating error



# Propagating error

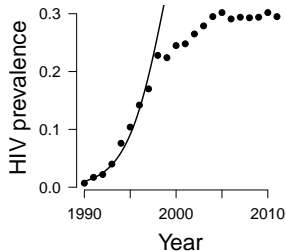
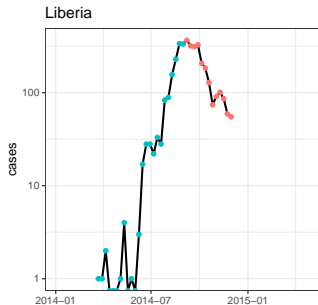


# Types of interval

- ▶ Define:
  - ▶ *Intrinsic interval*: How infectious is a patient at time  $\tau$  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

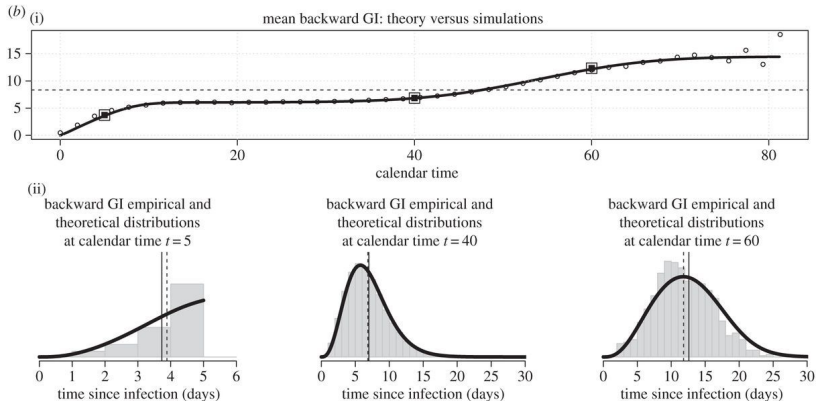
# Growing epidemics

- ▶ 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





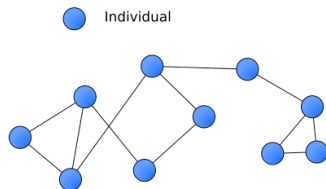
# Correcting backward intervals



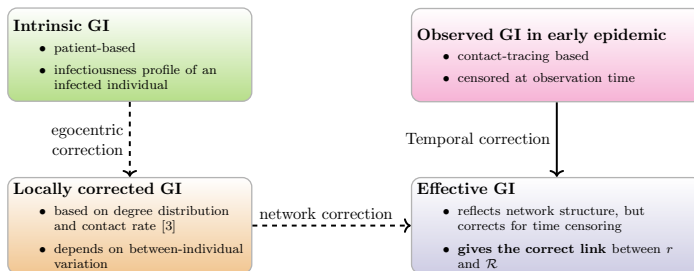
Champredon and Dushoff, 2015. DOI:10.1098/rspb.2015.2026

# Generations in space

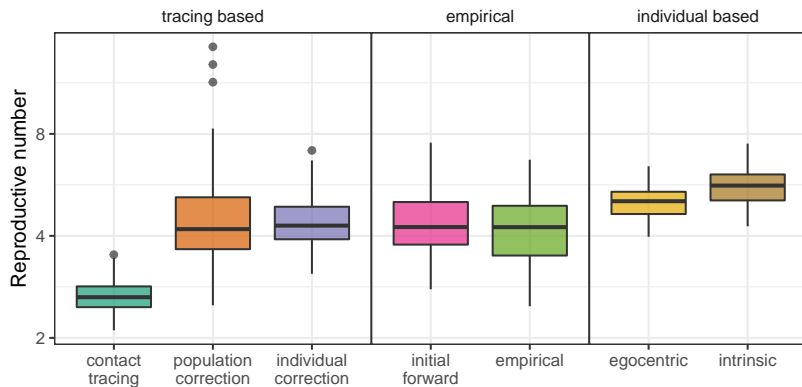
- ▶ Local interactions
- ▶  $\Rightarrow$  wasted contacts
- ▶  $\Rightarrow$  realized generation intervals smaller than intrinsic
- ▶  $\Rightarrow$  intrinsic GIs over-estimate  $\mathcal{R}$
- ▶ *Trapman et al., 2016. JRS Interface*  
*DOI:10.1098/rsif.2016.0288*



# Observed and estimated intervals



# Outbreak estimation



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

# Outline

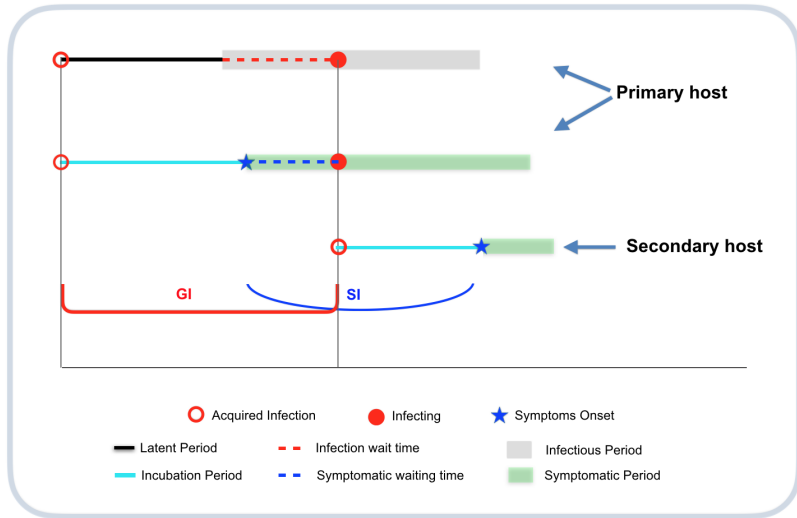
Linking  $r\mathcal{R}$

Serial-interval distributions

Evaluating interventions

Variants

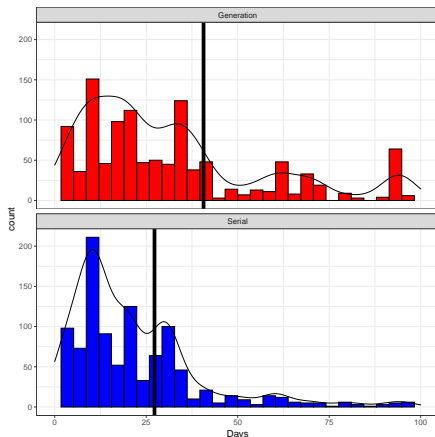
# Serial-interval distributions



# The serial-mean paradox

- ▶ Serial intervals measure generations of the same process as generation intervals
  - ▶ Should have the same mean
  - ▶ But often larger variance
- ▶ Empirically, even the means are not the same!

# Heterogeneity



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

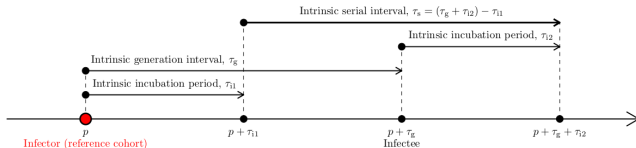


# The link paradox

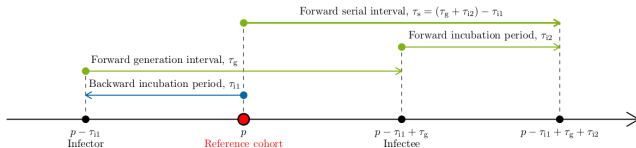
- ▶ Imagine a renewal process where symptoms in the infector cause symptoms in the infectee
  - ▶ Assume homogeneity
- ▶ This has to match the same  $r\mathcal{R}$  link as the true process
- ▶ But it also can't (because the serial interval is in general broader than the generation interval)
  - ▶ All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

# The forward serial interval

A. Intrinsic serial interval

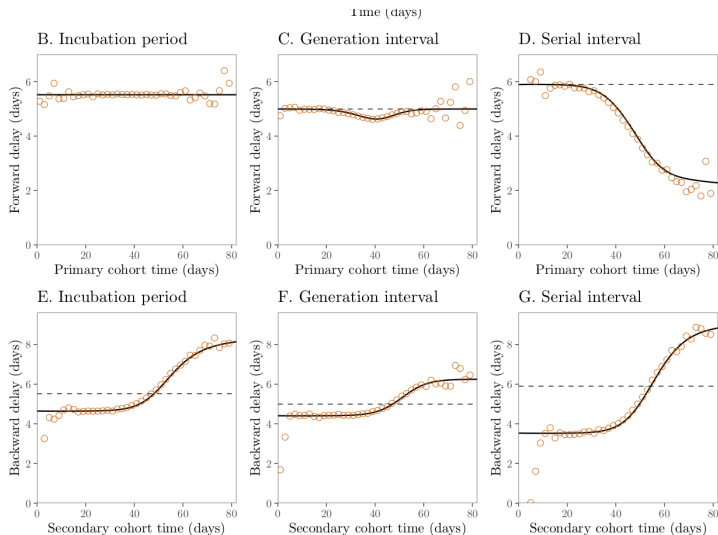


B. Forward serial interval



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

# Observed epidemiological intervals



# Outline

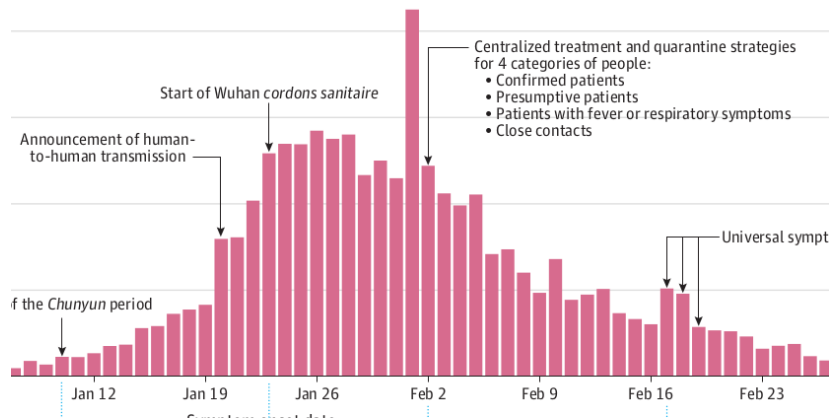
Linking  $r\mathcal{R}$

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# Wuhan control measures



<https://jamanetwork.com/journals/jama/fullarticle/2764658>

# Time-varying reproductive numbers

- ▶ Instantaneous  $\mathcal{R}_i$  (Cori):

- ▶  $i(t) = \int \mathcal{R}_i(t) g(\tau) i(t - \tau) d\tau$

- ▶ Counterfactual: how many cases per case if conditions were frozen at time  $t$

- ▶ Case  $\mathcal{R}_c$  (Wallinga):

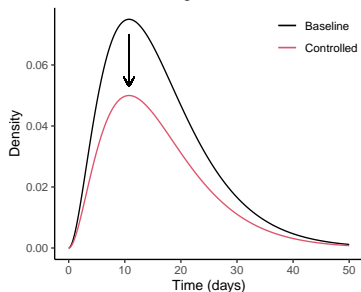
- ▶  $i(t) = \int \mathcal{R}_c(t = \tau) g(\tau) i(t - \tau) d\tau$

- ▶ Moving from reports to infections

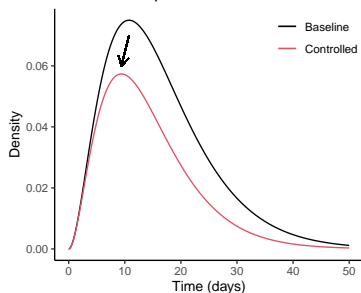
- ▶ Deconvolution

# Strength-like and speed-like interventions

A. Constant strength intervention



B. Constant speed intervention



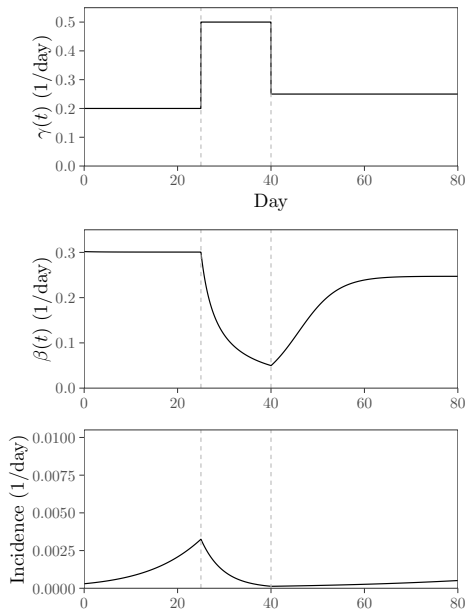
- Strength-like:  
lockdown, vaccination
- Speed-like: diagnosis,  
contact tracing
- *Dushoff and Park, DOI:  
10.1098/rspb.2020.1556*

# Estimating $r$ vs. $\mathcal{R}$

- ▶  $r$  is easier to estimate from time series
- ▶  $r$  is a better indicator if changes are speed-like
- ▶  $\mathcal{R}$  is a better indicator if changes are strength-like
  - ▶ and if it can be estimated well
- ▶ Both approaches require deconvolution



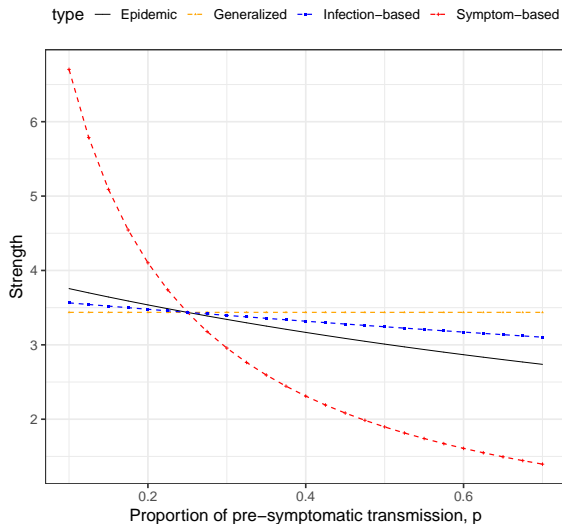
# Unidentifiability



- Strength-like and speed-like interventions can give exactly the same incidence curves

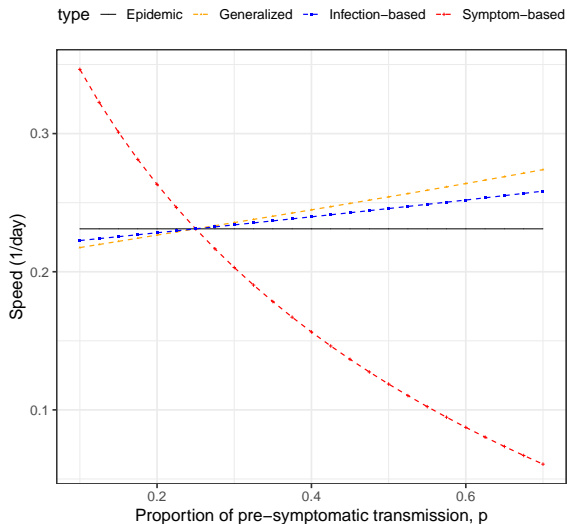
# Implications for intervention

B



# Implications for intervention

C



# Outline

Linking  $r\mathcal{R}$

Serial-interval distributions

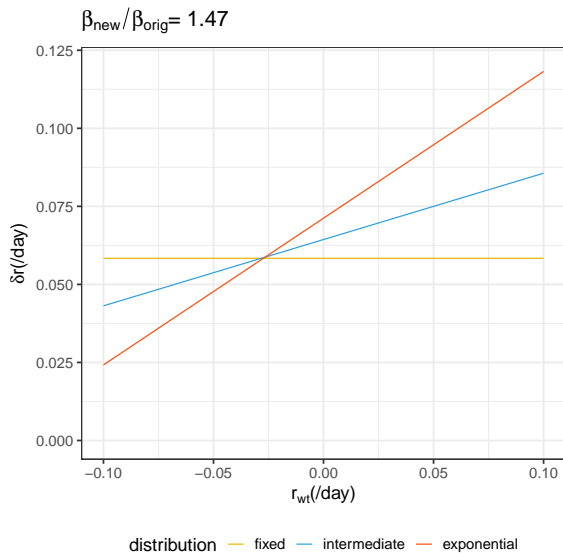
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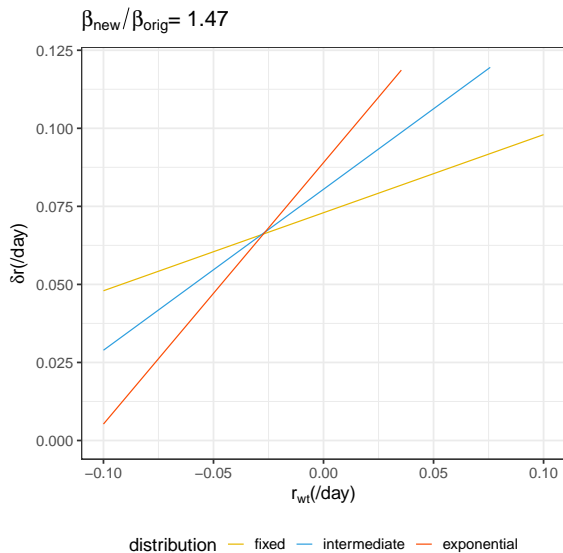
# Variants

- ▶ The clearest view is of the rate of logistic growth of variant proportion
  - ▶  $\delta = \mathcal{R}_{\text{var}} - \mathcal{R}_{\text{wt}}$
- ▶ Unaffected by sampling intensity
  - ▶ Also by “speed-like” changes in transmission intensity

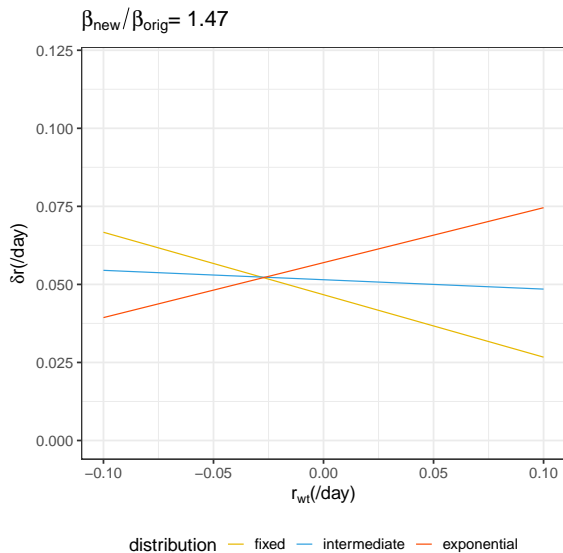
# Relationship between $\delta$ and $\mathcal{R}_{wt}$



# Variant has faster generations



## Variant has slower generations





# Thanks

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