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Mathematical models for epidemics including Covid-19

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Short introduction followed by 3 selected topics:
Optimal prevention
Herd immunity
Generation times

Consider a fixed population of size n (assumed large)

The Markovian SIR epidemic model:

- Individuals are classified as *Susceptible*, *Infectious* and *Recovered*
- $S(t), I(t), R(t)$ denote correspondning *numbers* at time t
- $(S(0), I(0), R(0)) = (n-1, 1, 0)$. $S(t) + I(t) + R(t) \equiv n$ for all t
- An infectious individuals has "infectious contacts" at rate β, each time with a uniformly at random selected individual
- Infectious contacts with susceptibles imply infection – other contacts have no effect
- Infectious individuals recover (and become immune) at rate γ
- Model parameters: β and γ ($n =$ population size)

Model properties (proven 20-50 years ago):

a) As $n \to \infty$: $R(\infty)/n$ (= final fraction getting infected) converges to a 2-point distribution: 0 or, if $R_0 = \beta/\gamma > 1$,

τ = the positive solution to the equation $1 - x = e^{-R_0 x}$

b) If instead $I(0)/n = \epsilon > 0$ fixed, then $(S(\cdot)/n,\ I(\cdot)/n,\ R(\cdot)/n)$ converges in probability to the deterministic ODE-system ("the deterministic SIR epidemic")

$$
\begin{aligned}
s'(t) &= -\beta s(t) i(t) \\
i'(t) &= \beta s(t) i(t) - \gamma i(t) \\
r'(t) &= \gamma i(t)
\end{aligned}
$$

Illustration of a): $R_0 = 0.8$

Histogram of final sizes from 10 000 simulations in a population with $n = 1000$ individuals

When $R_0 < 1$ no positive solution

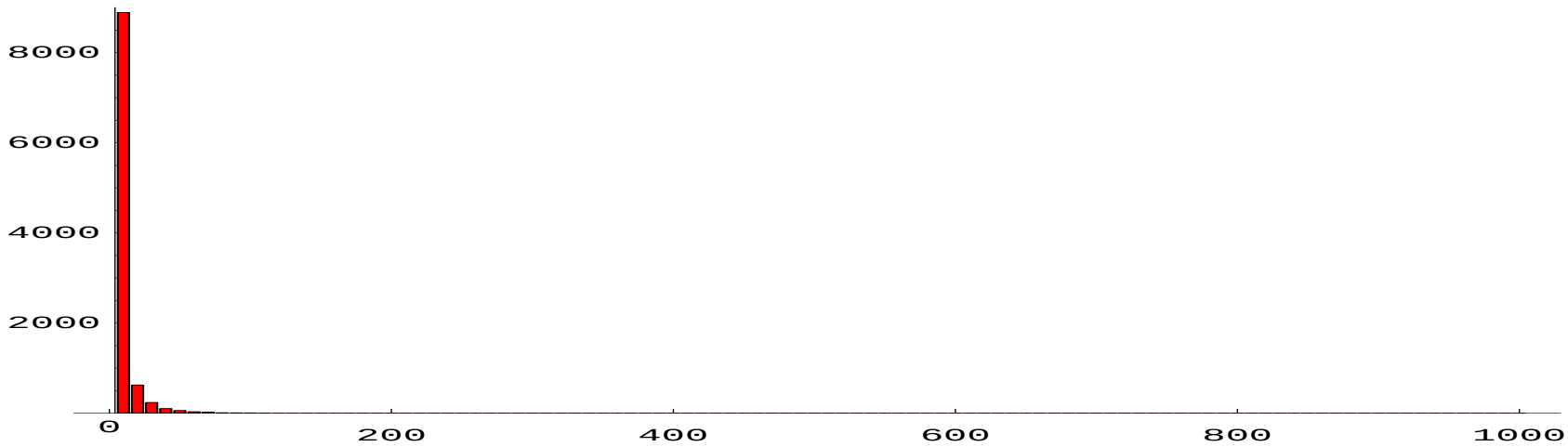

Illustration of a): $R_0 = 1.5$

Histogram of final sizes from 10 000 simulations in a population with $n = 1000$ individuals

When $R_0 = 1.5$ positive solution of $1 - x = e^{-R_0 x}$ equals 0.583

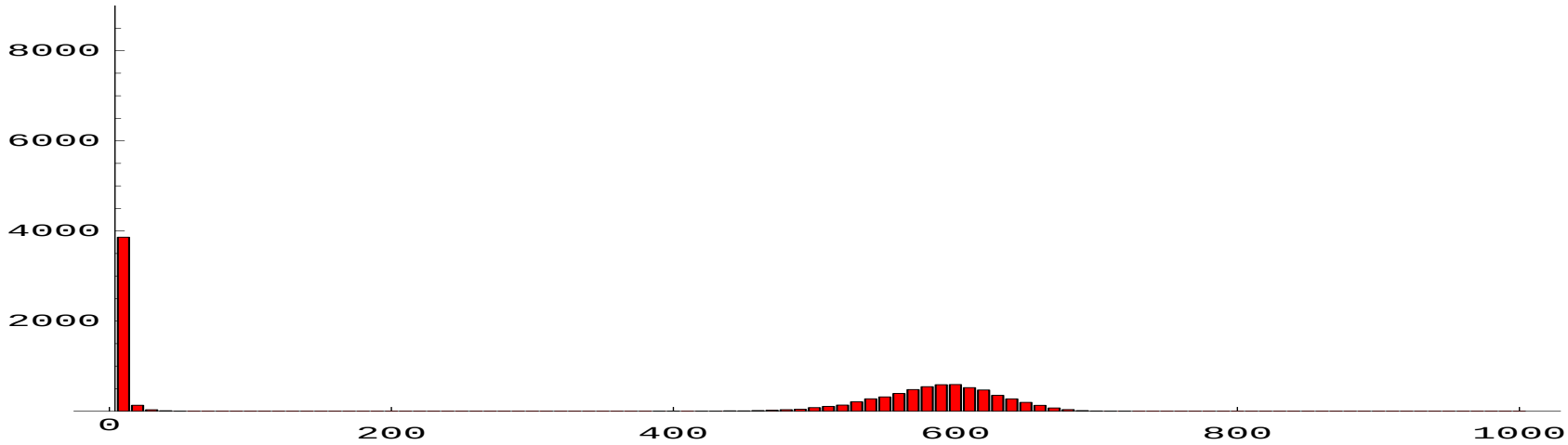

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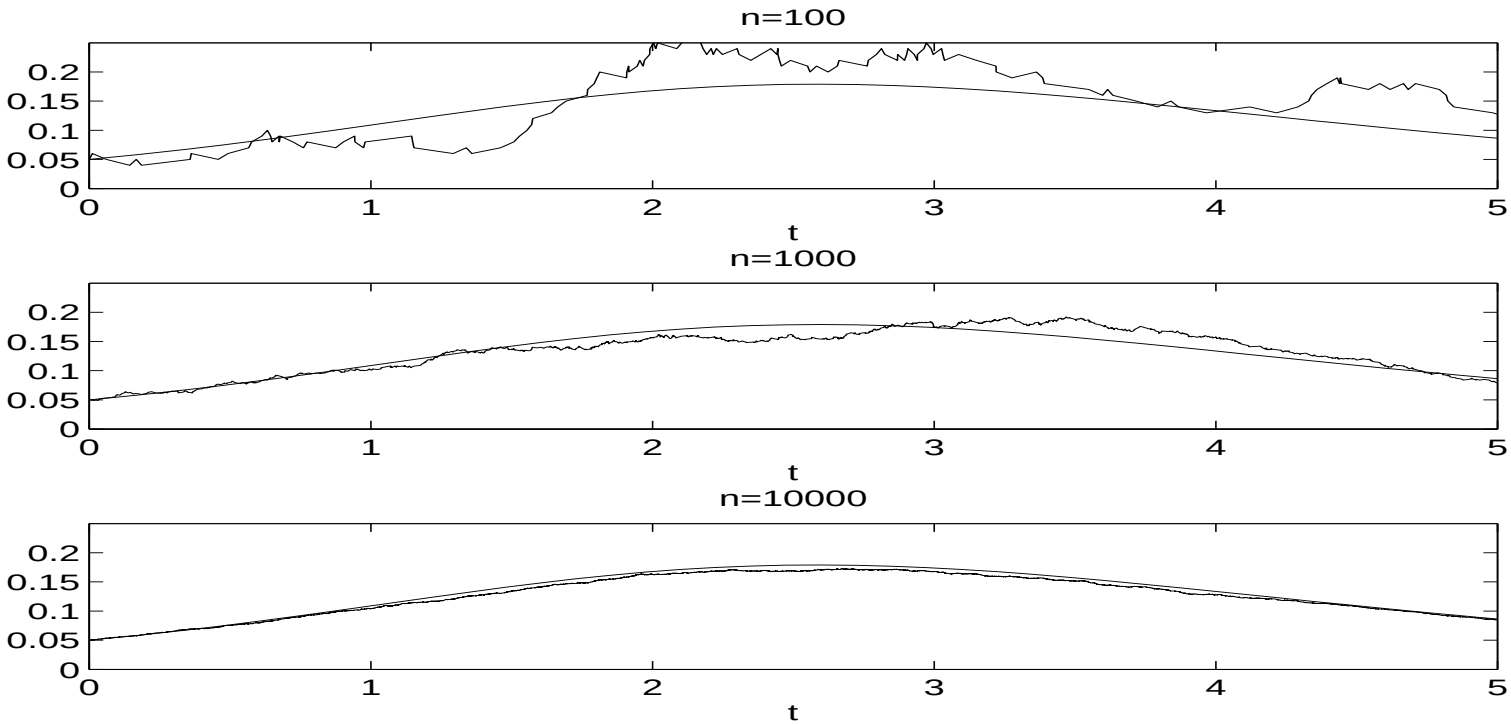
Illustration of b) Plots of deterministic and simulated stochastic curve



Extensions

Many solved *as well as* open problems for various extentions

- Considering different types of individual (Multitype epidemic)
- Including vaccination and other preventive measures
- Including social structures: network epidemics, household epidemics, ...
- SEIR, SIRS, ,,,
- Dynamic population and dynamic behaviour
- Spatial aspects and mobility
- Effects of individual preventive measures
- Estimation!!!
- ...

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A natural optimizing problem (joint with Lasse Leskelä)

The determinstic SIR epidemic with intervention

Assume no vaccine is available (or expected to arrive) + no seasonality

Introduce a (non-pharmaceutical) prevention strategy
$P = \{p(t); 0 \leq t < \infty\}$: contacts reduced by fraction $p(t)$ at t:

$$
\begin{aligned}
s_P'(t) &= -\beta(1-p(t))s_P(t)i_P(t) \\
i_P'(t) &= \beta(1-p(t))s_P(t)i_P(t) - \gamma i_P(t) \\
r_P'(t) &= \gamma i_P(t)
\end{aligned}
$$

Final size: $z_P = r_P(\infty) = 1 - s_P(\infty)$

Total cost of prevention strategy: $\int_0^\infty p(t)dt$

Optimization problem: Which preventive strategy P, with cost satisfying $\int_0^\infty p(t)dt \leq c$, *minimizes* final size z_P?

Comments on model

Of course **many simplifications**. Most crucial for conclusions:

– No vaccine available (or expected to arrive in near future)

– No seasonality

– Linear cost function $\int_0^\infty p(t)dt$

Here Aim is to minimize *total* number of infeced.

Alternative: minimize *peak* prevalence (see later)

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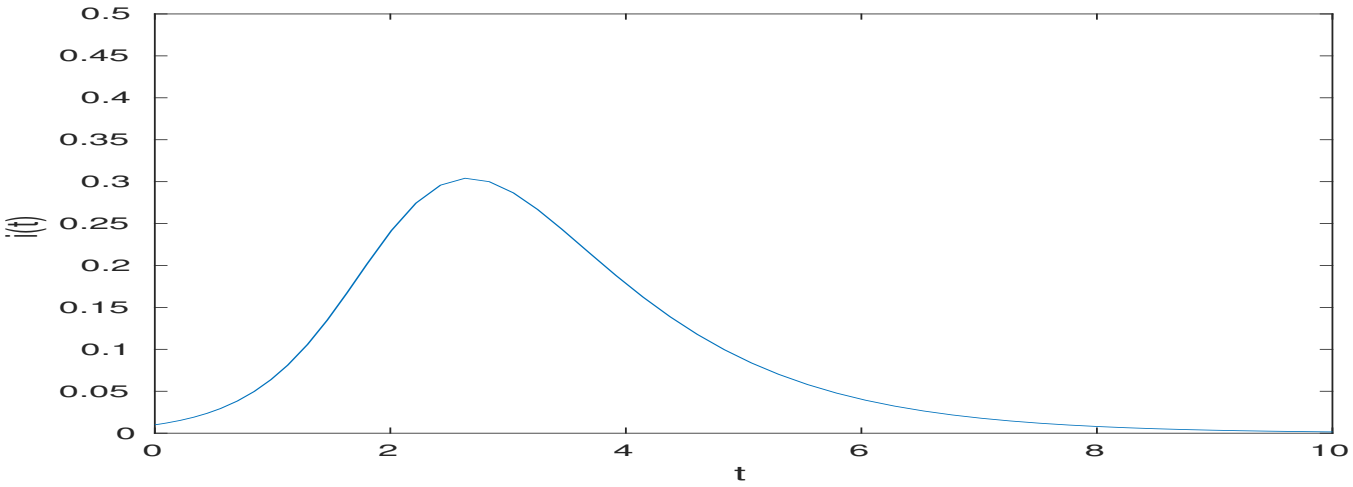
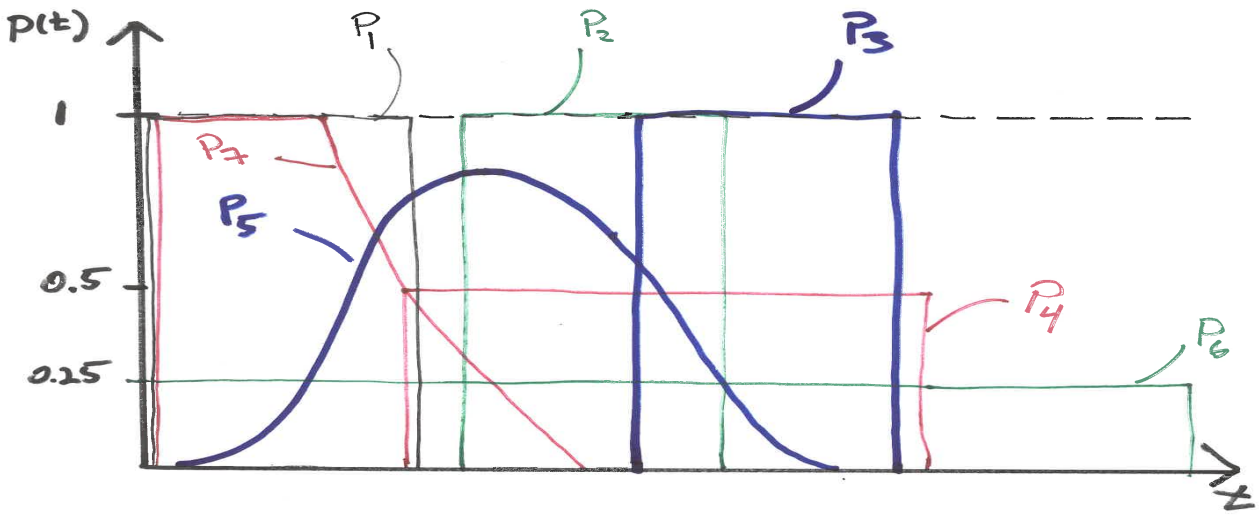
Uncontrolled incidence (top), some preventions (bottom)





Optimizing prevention in time and size

Solution is presented at end of talk - come up with suggestions during the talk!!

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Herd immunity in a heterogeneous community

(Britton, Ball, Trapman, 2020)

Consider an epidemic where individuals have different social activity, susceptibility and infectivity: **multitype epidemic**

R_0 = average # infections caused by a "typical" infected in beginning of outbreak (= largest eigenvalue to "next generation matrix")

If a uniformly selected fraction v of individuals are vaccinated with a perfect vaccine: new reproduction number $R_v = R_0(1-v)$

$R_v \leq 1 \Longleftrightarrow v \geq 1 - 1/R_0$

Critical vaccination coverage: $v_c = 1 - 1/R_0$ (Classical result)

If more than v_c vaccinated: **Herd immunity**

First wave in Sweden: $R_0 \approx 2.5$ "Herd immunity when 60% infected"

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Herd immunity cont'd

What if we instead vaccinate socially active and highly susceptible? (n.b. not elderly – varying severity is a different problem not considered here)

$\Longrightarrow$ We should be able to reach herd immunity when vaccinating less than $1 - 1/R_0$!! (also known result)

So: Uniform vaccination has $v_c = 1 - 1/R_0$, but if vaccinating socially active and highly susceptible then $v_c < 1 - 1/R_0$

Without vaccination: When an epidemic without vaccination and preventive measures is over, then herd immunity is reached (also known)

But what if the epidemic is stopped earlier thanks to preventive measures? What fraction infected is required for Herd immunity? **A question never addressed before!**

How is immunity distributed when immunity comes from infection in an epidemic outbreak?

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Herd immunity cont'd

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But what if the epidemic is stopped earlier thanks to preventive measures? What fraction infected is required for Herd immunity? **A question never addressed before!**

How is immunity distributed when immunity comes from infection in an epidemic outbreak?

Answer: Susceptible and socially active are over-represented! So immunity level to reach herd immunity is smaller than $1 - 1/R_0$!!

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Herd immunity from disease-induced immunity

In Britton, Ball, Trapman (2020) we analysed an epidemic model fitted to Covid-19 and allowing for heterogeneity due to

1) age (using empirical contact matrix from social studies),

2) varying social activity by assuming 50% "normal" and 25% twice/half as social

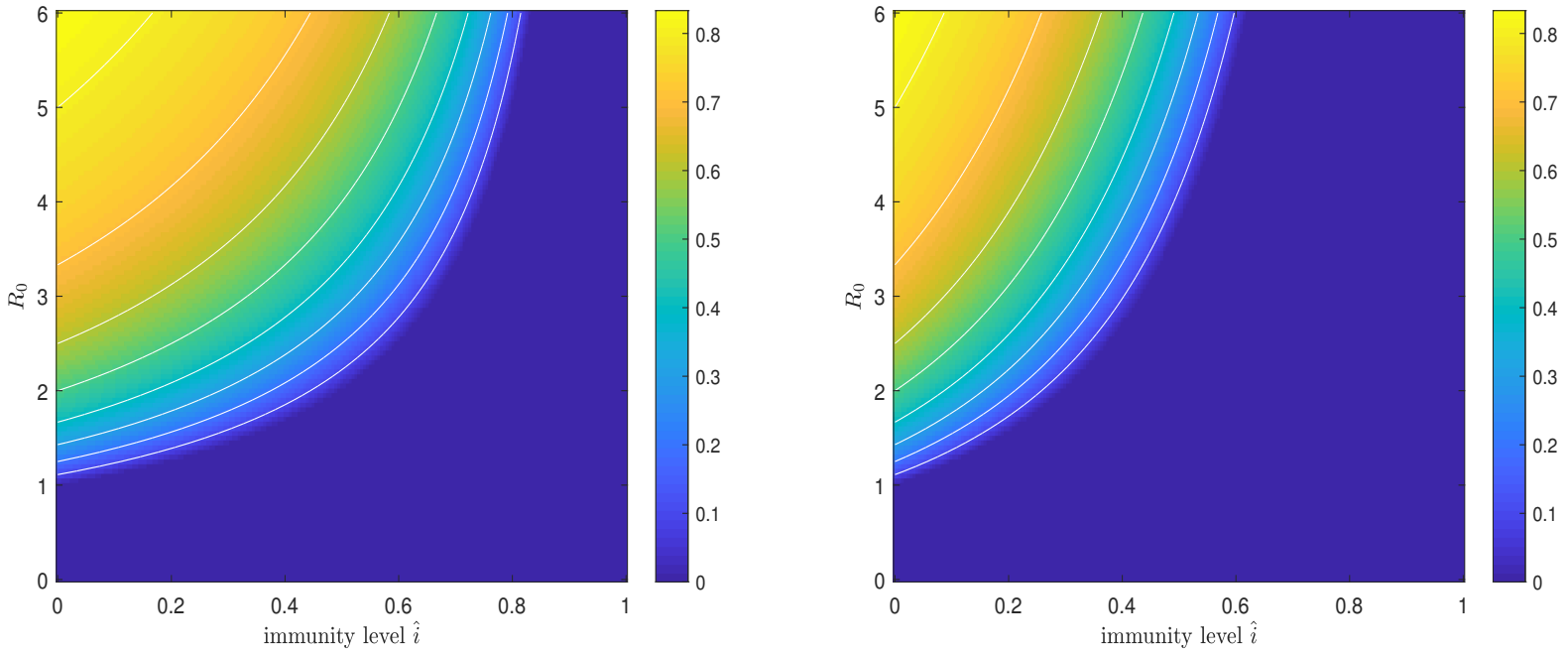
3) varying susceptibility by assuming 50% "normal" and 25% twice/half as susceptible

Suppose preventive measures (reducing all contacts equally) are put in place during the outbreak, when will herd immunity be reached if $R_0 = 2.5$?

Answer (for our **model**!): between 40-45% rather than 60%

Disease induced immunity is more effectively distributed

Left: Vaccine-induced immunity (assuming uniform vaccination)
Right: Disease-induced immunity in a heterogeneous community



Example: $R_0 = 2.5$, $\hat{i} = 25\%$: $p_{Min}^{(Vac)} = 47\%$ and $p_{Min}^{(Dis)} = 29\%$

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Definition of generation time

The **generation time** G describes the time between getting infected and infecting others

G is a random variable, affected by: latent period, incubation period, length of infectious period, infectivity over time, ...

Given an epidemic model, then the **generation time distribution** (GTD) $p_G(t) = P(G = t)$ can often be computed

Knowledge of GTD is important because it is used when estimating the **daily reproduction number** R_t from (reported) incidence $I(t); t = 1, \ldots, t_{obs}$:

Based on (reported) incidence $I(1), I(2), ...I(t_{obs})$ and knowledge about GTD $p_G(\cdot)$, R_t can be **estimated** from the (Euler-Lotka) equation:

$$I(t) = R_t \sum_k I(t-k) p_G(k), \;\; t = 1, \ldots, t_{obs}$$

Estimating the generation time distribution (GTD)

Britton and Scalia Tomba (2019)

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But how to estimate GTD?

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But how to estimate GTD?

Contact tracing (during early stage of outbreak)

Potential problems:

1. In a growing epidemic, short generation times will be over-represented when sampling backwards in time

2. Times of infections not observed, but onset of symptoms. Both end points of generation time shifted by random times, so observed gen-times will have correct mean but larger variance

3. Often there are multiple possible infectors. If these are discarded remaining gen-times will be systematically shorter

Toy example

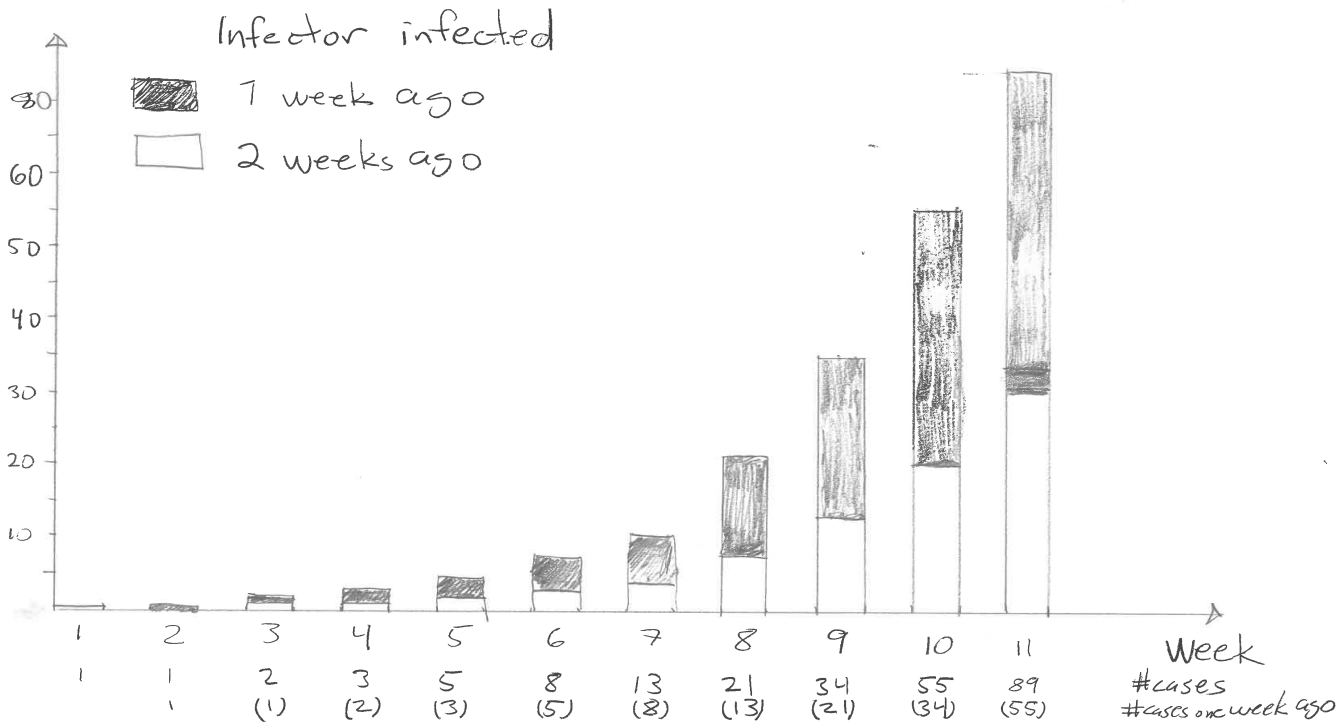
Suppose that $R_0 = 2$, and each infected infects one individual after 1 week and one individual after 2 weeks ($g(1) = g(2) = 0.5$)

What is $E(G)$?

Toy example

Suppose that $R_0 = 2$, and each infected infects one individual after 1 week and one individual after 2 weeks ($g(1) = g(2) = 0.5$)

What is $E(G)$? 1.5 weeks, and $st.d.(G)$? 0.5 weeks (below plot of # infections each week)



Looking backwards: contact tracing

Fibonacci numbers and the Golden ratio ...

$\Longrightarrow$ The mean generation time when contact tracing will be < 1.5

So if you estimate $E(G)$ (or all of G) from contact tracing you will *under-estimate* $E(G)$

Generation times vs Serial intervals

Serial intervals instead of generation times

(We now "forget" problem of looking backwards)

Infection times are hardly ever observed, but onset of symptoms are

G = time between infection times (unobserved)

S = time between onset of symptoms (observed)

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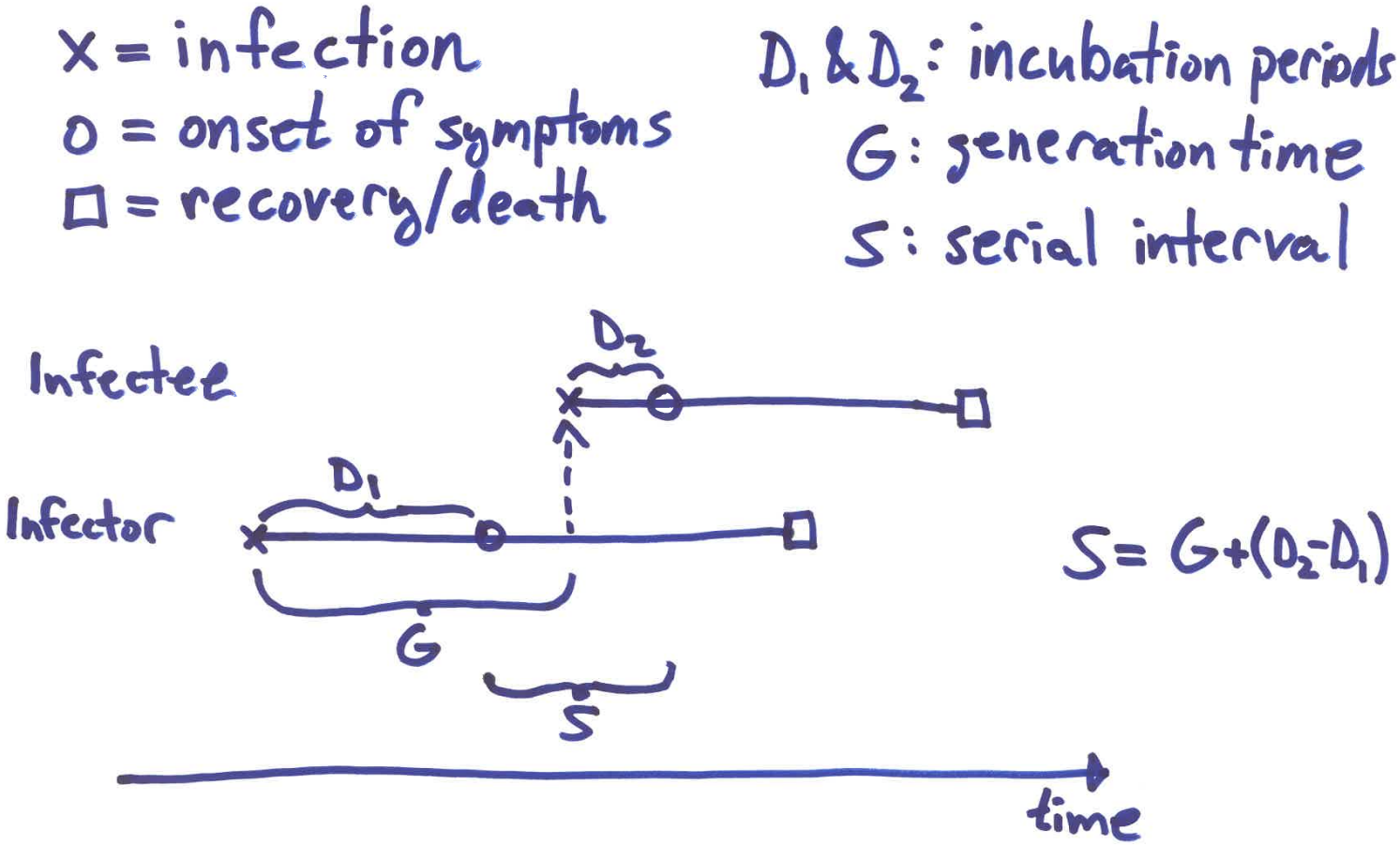
Generation times vs Serial intervals, cont'd

Generaton times vs Serial intervals



Generation times vs Serial intervals, cont'd

$\Longrightarrow S = G + (D_2 - D_1)$ (D_1 and D_2 = incubation periods of infector and infectee)

So, if incubation times are independent and independent of G, then

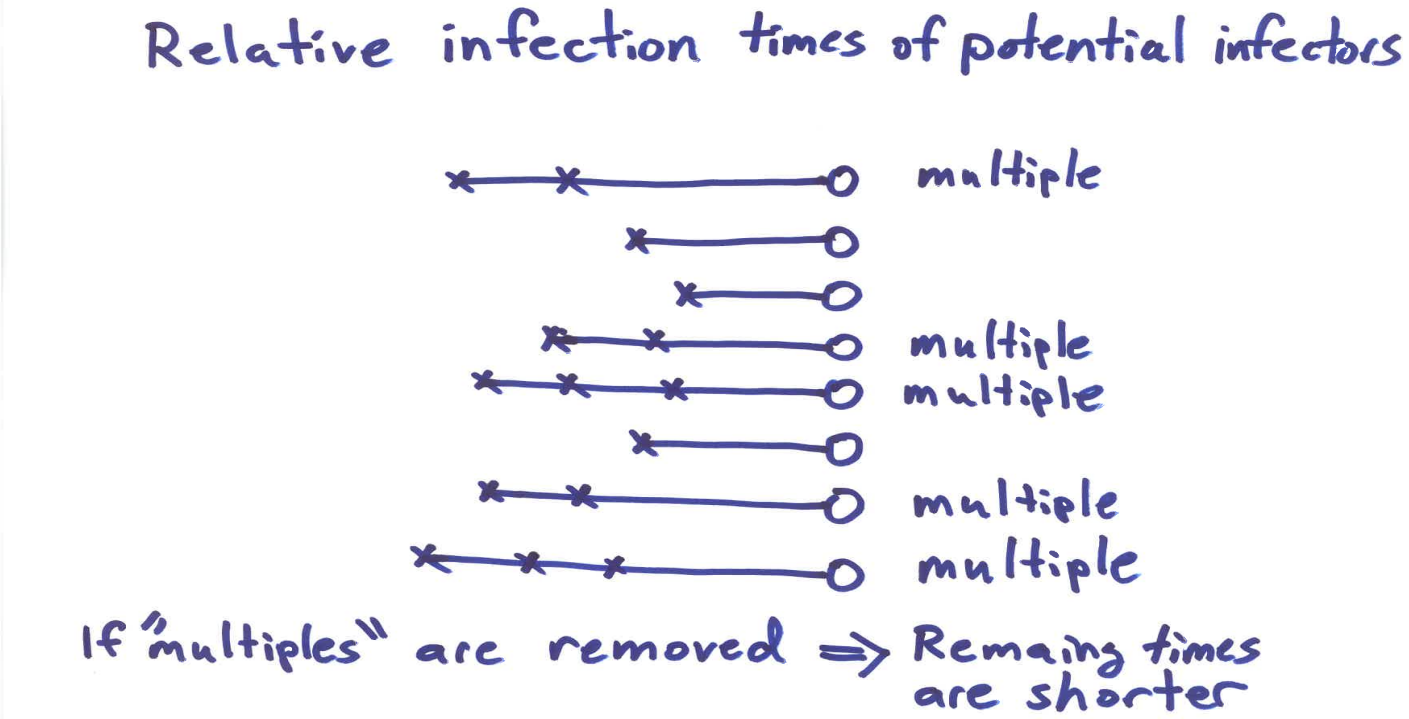
$E(S) = E(G)$, and $V(S) \geq V(G)$

(The relation holds true for all (?) epidemic models)

So, if we estimate $G \sim \{g(s)\}$ from observations on Serial intervals we will *over-predict* variance of G

Multiple exposures

Another problem when contact tracing is that sometimes there are several potential infectors (see illustration on next slide)



Multiple exposures

If observations with more than one infected are neglected, remaining intervals are biased from below.

This will also lead to *under-estimation* of $E(G)$

Conclusions: looking backwards and neglecting multiple exposures lead to **under-estimation** of $E(G)$ and observing serial intervals rather than generation intervals lead to **over-estimation** of $V(G)$

We now see how this can affect estimates of R_0

We analyse the biasing effects of these inference problems

Conclusions:

1 & 3 give shorter mean, and 2) larger variance of GTD

All three lead to R_t being **under-estimated** in the Euler-Lotka equation

For Ebola outbreak we think R was under-estimated by $\approx 25\%$

GTD also changes when preventive measures are adopted

Favero, Scalia Tomba and Britton (2022)

During covid-19 pandemic preventive measure have been enforced and we have changed behaviour:

1. Social distancing in general
2. Self-isolation upon symptoms
3. Screening - testing
4. Contact tracing diagnosed cases

All of these reduce the daily reproduction number R_t (the average number of infections made by an infected now)

But some also change the timing when infections happen, so changes the GTD

We included various preventive measures in an epidemic model and analyse its effect on the GTD

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Covid example and effect on bias

Combining preventions (added isolation, screening and CT) where we have "guessed" the amount of preventions

$R = 3.9 \ \rightarrow \ R = 1.45$ (reduction by 62%)

$E(G) = 7.4 \ \rightarrow \ E(G) = 5.8$ days (reduction by 22%)

Inferring R_t

Suppose we observe (increasing) incidence $\{I(t)\}$ for this situation ($R_t = 1.45$ and mean gen-time $E(G) = 5.8$)

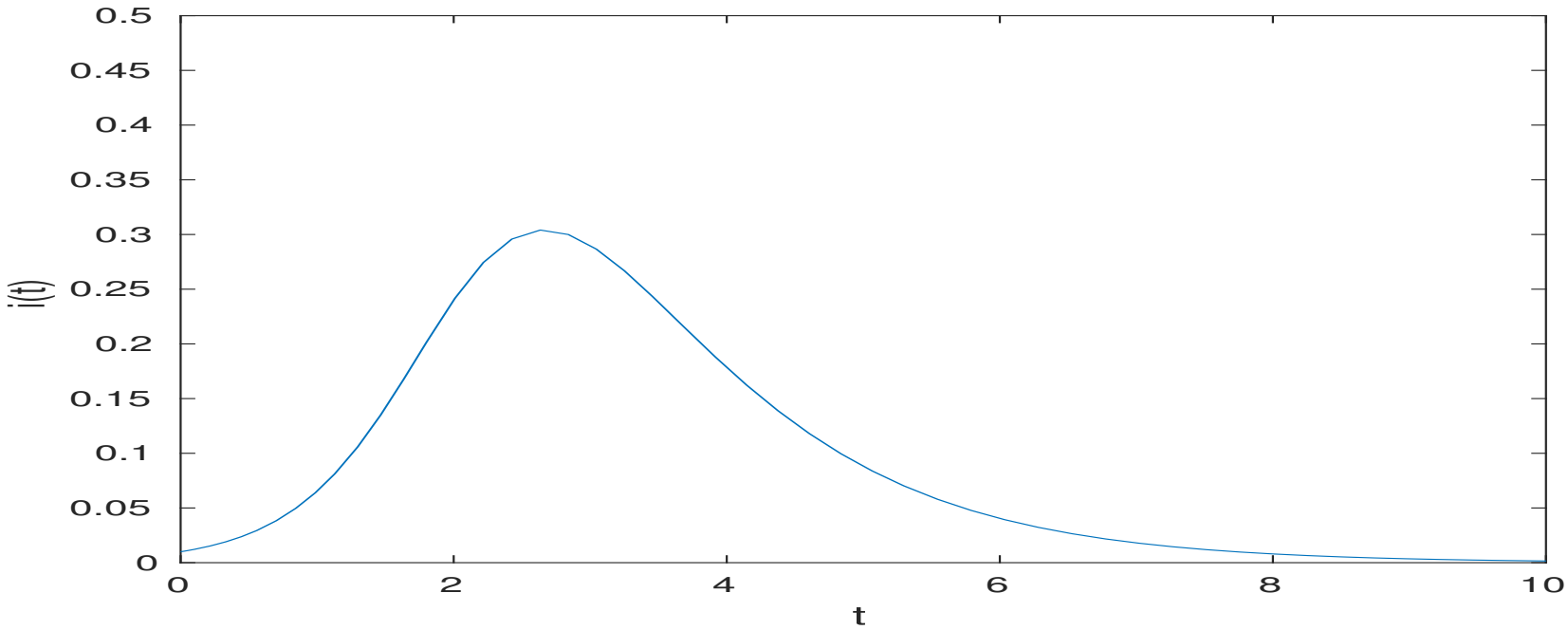
If we use this new correct GTD and apply Euler-Lotka estimating equations we get $\hat{R}_t \approx 1.45$ as it should

However, if we instead used the original/old GTD with mean 7.4 days (as most countries do!!!) we would get $\hat{R}_t \approx 1.75$, so biased from above by more than 20%

R_t-**estimates** that use early GTD-estimates are **biased from above** (or more accurately "biased away from 1")

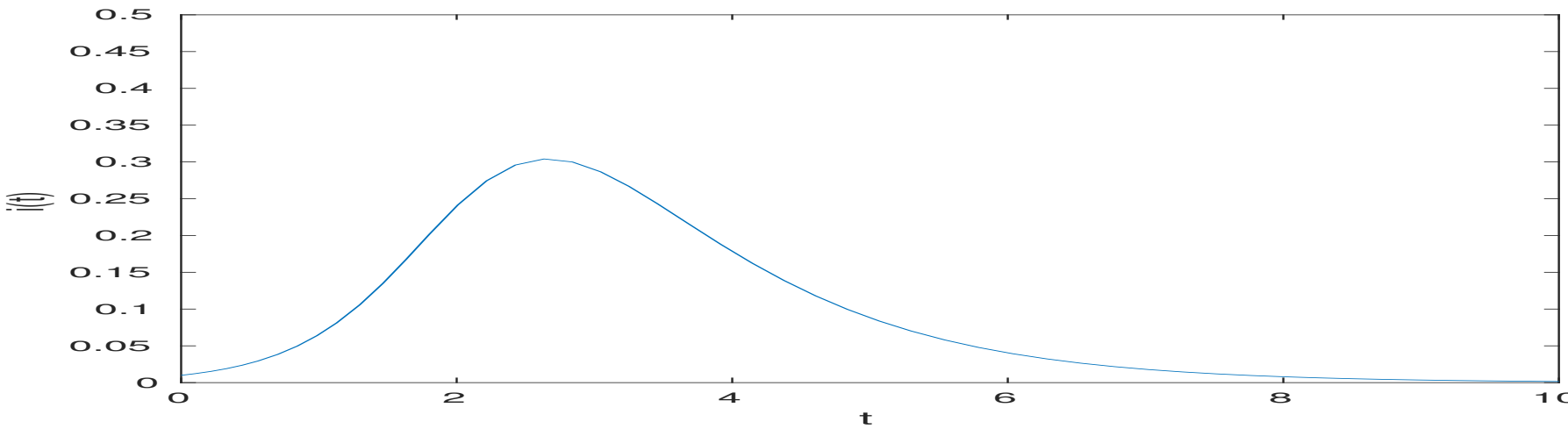
Back to: Optimizing preventions (with Lasse Leskelä)

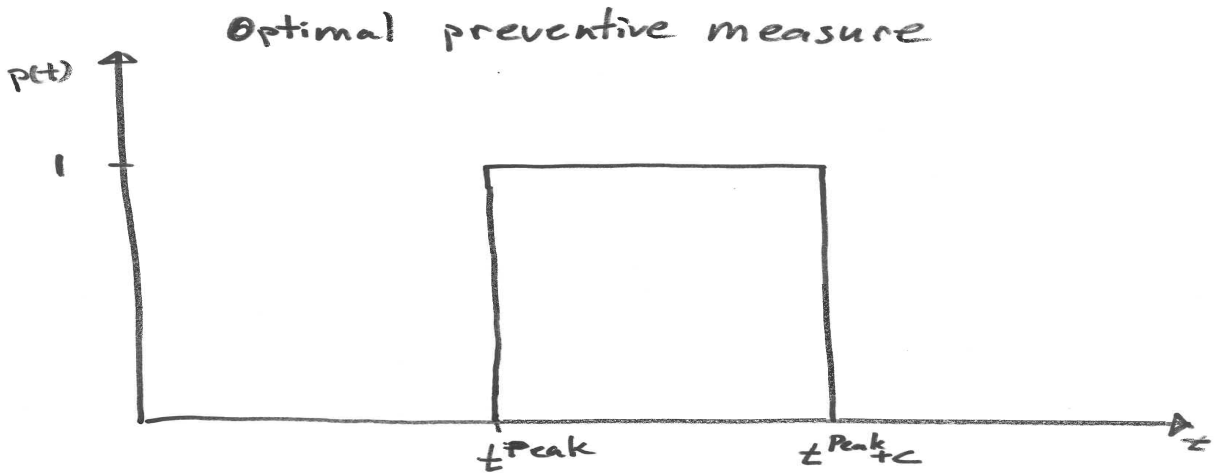
$i(t)$ when no interventions



Which prevention strategy (with $\int p(t)dt \leq c$) minimizes final epidemic size?

Best strategy: complete lockdown starting at peak





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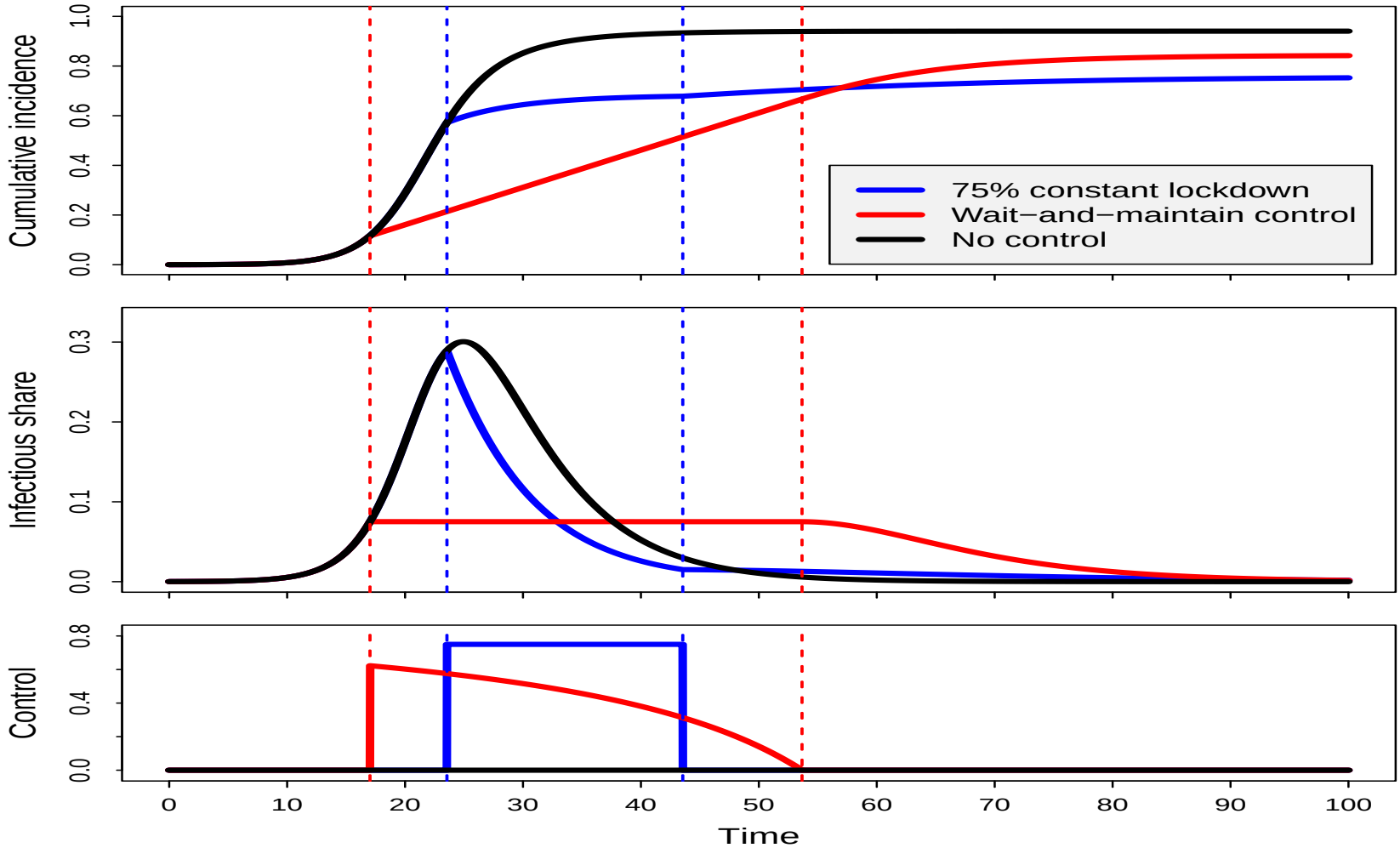
Minimizing final size vs minimizing maximum peak



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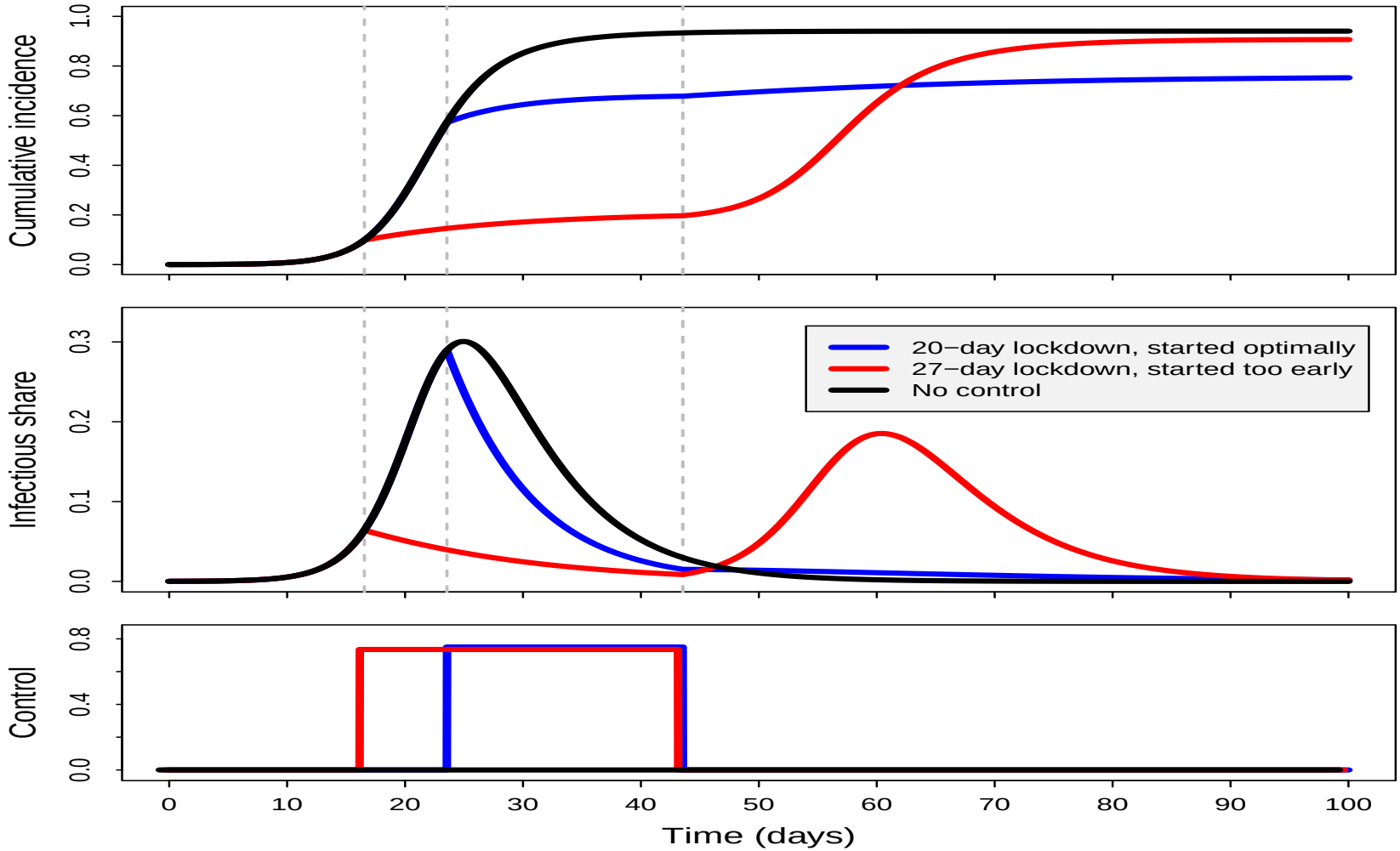
Adding prevention before optimal may **increase** final size!



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Thanks for your attention!

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