The Mathematics and Statistics of Infectious Disease Outbreaks

Michael Höhle[1]

[1]Department of Mathematics
Stockholm University, Sweden

L5: Estimation of the effective reproduction number[1]

Stockholm University

[1]LaMo: 2020-06-27 @ 10:00:04

Overview

Outline

Basic Reproduction Number

- In the previous lectures we have considered the **basic reproduction number** R_0, which was defined[2] as

$$R_0 = \beta/\gamma S(0)$$

- R_0 is the mean number of direct offspring one infectious case generates in a *completely susceptible population without intervention measures*
- However, once an epidemic unfolds susceptibles are depleted. Furthermore, interventions or behavioral changes aim at reducing β, γ or the amount of susceptibles ($\rightarrow$ vaccination).
- In order to assess public health interventions the basic reproduction number is not useful (Delamater et al., 2019).

[2] β was the infectious contact rate, γ the mean duration of the infectious period and $S(0)$ is the number of susceptibles at time zero ($S(0) \approx N$).

Effective Reproduction Number (1)

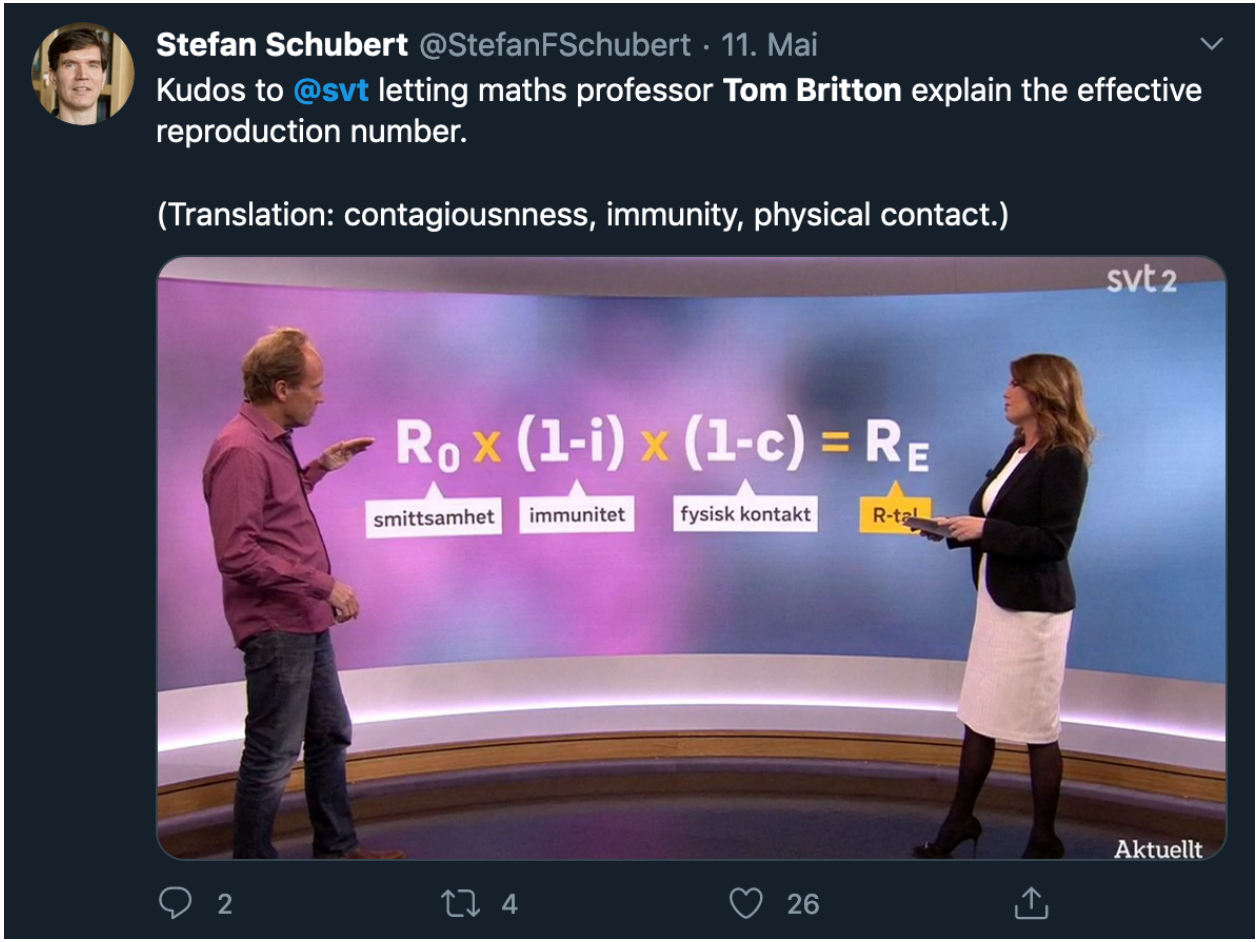
- We define the time-varying effective reproduction number $R(t)$ as a time varying quantity denoting be the average number of secondary cases generated at at calendar time t
- If contact and recovery rates do not vary with time we get

$$R(t) = R_0 \times \frac{S(t)}{S(0)}$$

- Interventions could be reflected by extending this to

$$R(t) = (1 - c(t)) \times R_0 \times \frac{S(t)}{S(0)}$$

Effective Reproduction Number (2)



Effective Reproduction Number (3)

- The derivations in this lecture will follow Fraser (2007), who does not explicitly consider depletion of susceptibles
- Let the **transmissibility** function $\beta(t, \tau)$ be a function of calendar time t and time since infection τ
- Dependence on τ could, e.g., be due to time-dependence of viral shedding in the host, but also changes in contact behaviour after infection, depletion of susceptibles
- Renewal equation

$$I(t) = \int_0^\infty \beta(t, \tau) I(t - \tau) d\tau \tag{1}$$

Effective Reproduction Number (4)

- Case reproduction number

$$R_c(t) = \int_0^\infty \beta(t+\tau, \tau) d\tau$$

  Interpretation: Average number of individuals an infected at time t can expect to infect

- Instantaneous reproduction number

$$R(t) = \int_0^\infty \beta(t, \tau) d\tau$$

  Interpretation: Average number of individuals an infected at time t is expected to infect should conditions remain unchanged

Effective Reproduction Number (5)

- Assuming the factorization

$$\beta(t,\tau) = \phi_1(t)\phi_2(\tau),$$

Fraser (2007) shows that by assuming $\int_0^\infty \phi_2(\tau)d\tau = 1$ we get

$$\beta(t,\tau) = R(t)w(\tau) \tag{2}$$

- Here $w(\tau)$ denotes the distribution of the new infections as a function of time since infection, i.e. the generation time distribution.

Effective Reproduction Number (6)

Inserting (2) into (1) yields:

- Instantaneous reproduction number

$$R(t) = \frac{I(t)}{\int_0^\infty I(t-\tau)w(\tau)d\tau}$$

- Case reproduction number

$$R_c(t) = \int_0^\infty R(t+\tau)w(\tau)d\tau$$

Discretised Instantaneous Reproduction Number (1)

- If only discrete observations for time intervals $t_i \equiv [t_i, t_{i+1})$ are available, then one would use a discretized version of the instantaneous reproduction number

$$R(t_i) = \frac{I_i}{\sum_{j=0}^{n} w_j I_{i-j}}$$

- Note: the $0 \leq w_i \leq 1$ now denote the probability mass function of a discretized version of the generation time, i.e. $\sum_{i=0}^{n} w_i = 1$.

Discretised Instantaneous Reproduction Number (2)

- Casting this into a distributional framework, e.g.,

$$I_i | I_{i-1}, I_{i-1}, \ldots \sim Po\left(R(t_i) \times \sum_{j=0}^{n} w_j I_{i-j}\right)$$

  allows the consideration of $R(t_i)$ as a parameter to be estimated in a statistical model
- This also allows the construction of confidence intervals or credibility regions for $R(t_i)$.

Smoothed Instantaneous Reproduction Number

- Estimate $R(t)$ using discrete data is subject to fluctuations and it is therefore in general not recommended to just use one time point (Cori et al., 2013)
- Suggested improvement: Compute instantaneous reproduction number over an interval of τ days as follows

$$R_\tau(t_i) = \frac{\sum_{k=i-\tau+1}^{i} I_k}{\sum_{k=i-\tau+1}^{i} \sum_{j=0}^{n} w_j I_{k-j}}$$

- Note that this is slightly difference from just using the mean of the τ computed $R(t)$ values, i.e.

$$\overline{R}_\tau(t) = \frac{1}{\tau} \sum_{k=i-\tau+1}^{i} R(t_{i-k})$$

Superspreading (1)

- So far we have considered the *mean* number of offspring one infectious case generates
- This view ignores the variability in the offspring distribution, e.g., the larger the variation, the greater the probability of extinction
- The SIR continuous time Markov chain, i.e. the stochastic SIR model with constant infectious contact and recovery rates, leads to an geometric offspring distribution

Superspreading (2)

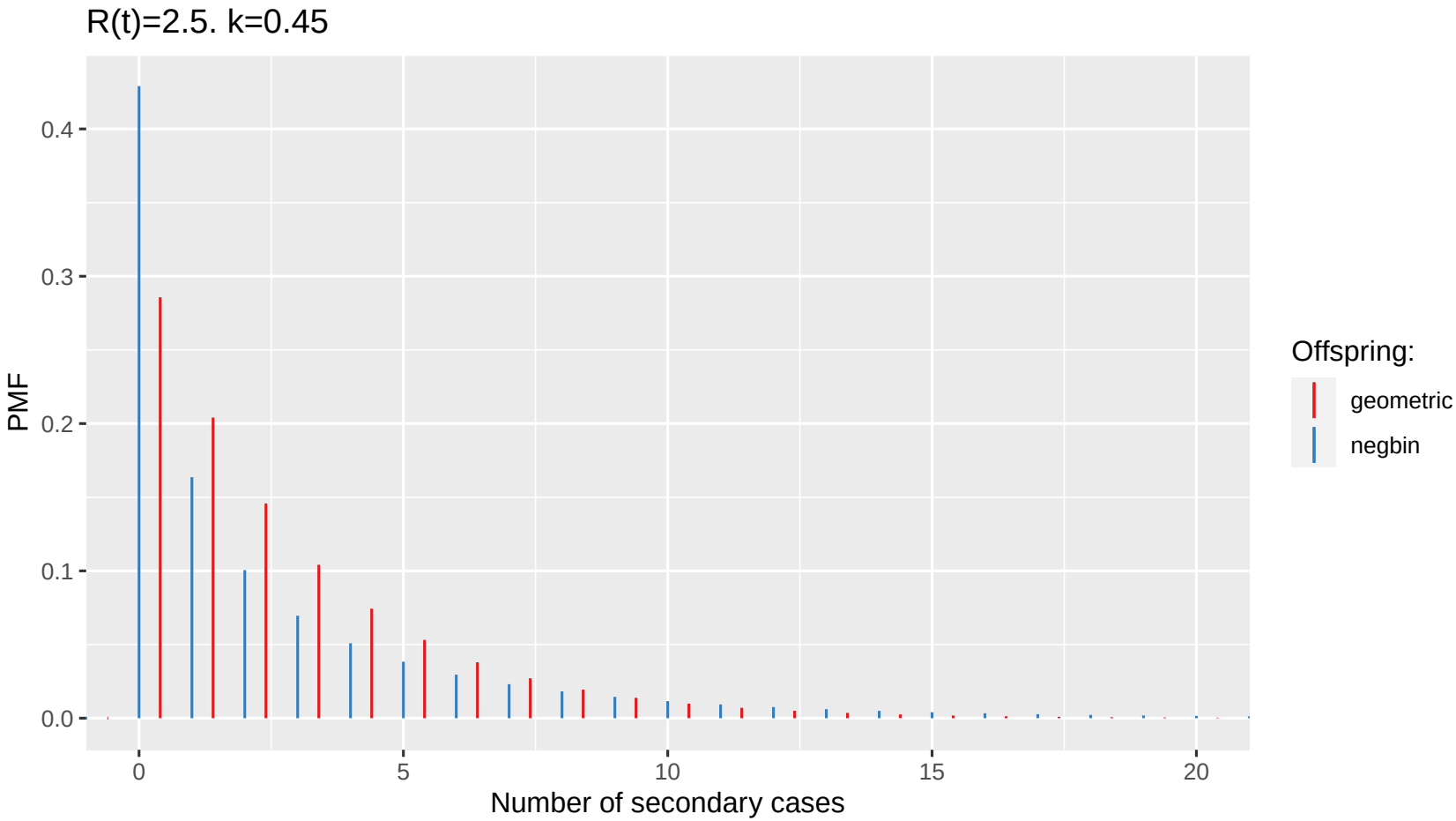
Exercise 5.1

Assume that once infected an individual is infectious for $D \sim \text{Exp}(\gamma)$ time units, i.e. the mean duration is $1/\gamma$. While being infectious individuals have infectious contacts at the rate β, i.e. the number of infectious contacts during $D = d$ time units is $C|D = d \sim \text{Po}(\beta \times d)$. Show that that for a random infected individual, the number of secondary infections is geometrically distributed. What is the mean of this distribution?
Hint: Derive the marginal distribution of C by $f_C(c) = \int f_{C|D}(c|d) f_D(d) dd$.

Superspreading (3)

- Lloyd-Smith et al. (2005) analyse that the 2002-2004 SARS-CoV-1 epidemic was driven by a small number of events where one case directly infected a large number of secondary cases, whereas many other cases did not infect any secondary cases
- This means that the offspring distribution has a larger variance than, e.g., implied by the geometric distribution
- Lloyd-Smith et al. (2005) therefore suggest the the negative binomial distribution) with mean $R(t)$ and over-dispersion parameter k, as a more flexible offspring distribution.
- If we can identify settings where super-spreading occurs, one can reduce the mean number of offspring substantially

Superspreading (3)



Outline

Outbreak simulation (1)

- Consider a growth model and denote by y_t the expected number of new symptom onsets we observe on day t.
- Let $(w_1, \ldots, w_M)'$, denote the probability mass function of the serial interval distribution, i.e. $P(GT = i) = w_i$ for $i = 1, 2, \ldots, M$.
- Assume that the expected number of cases can be described by the homogeneous linear difference equation

$$y_t = \sum_{i=1}^{M} R_c(t-i) w_i y_{t-i}, \quad t = 2, 3, \ldots$$

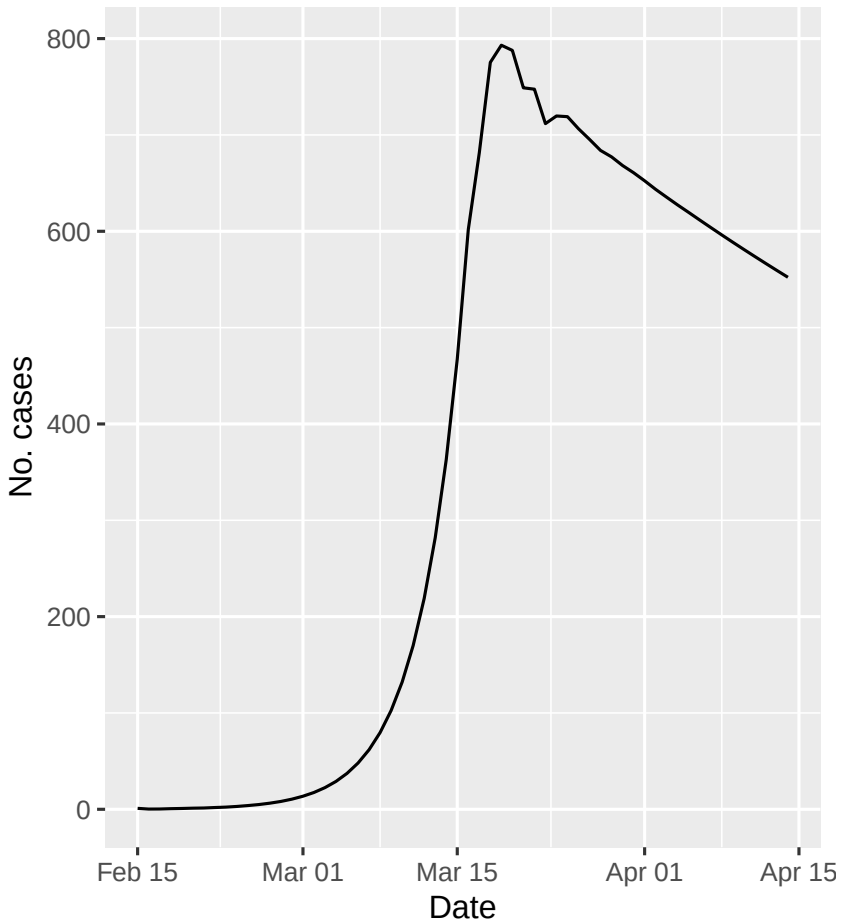
- Note: We use the case reproduction number and ignore terms on the RHS when $t - M \leq 0$.

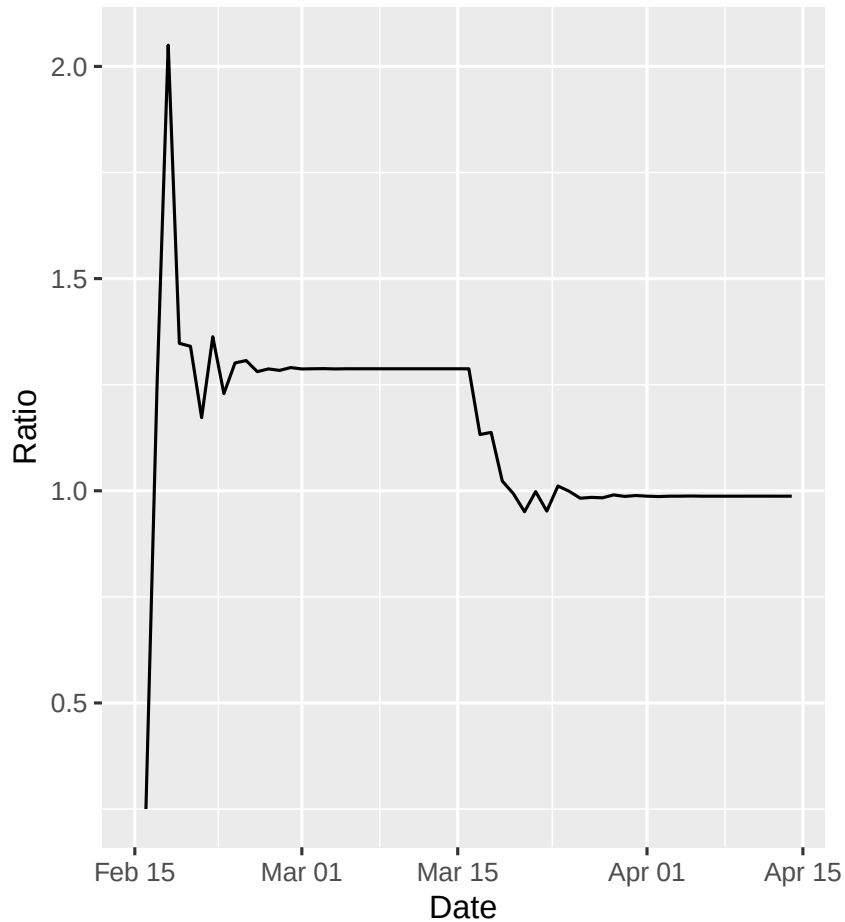
Outbreak simulation (2)

- Somewhat arbitrarily we fix $y_1 = 1$ and conceptually denote by $t = 1$ the 15th of February 2020 in calendar time.
- To simulate a COVID-19 like outbreak with lockdown type intervention we use

$$R_e(t) = \begin{cases} 2.5 & \text{if } t \leq \text{2020-03-15} \\ 0.95 & \text{otherwise} \end{cases}$$

Outbreak simulation (3)





EpiEstim (1)

- An implementation of the instantaneous reproduction estimate is available in the R package `EpiEstim` (Cori et al., 2013)
- Input is a ‘data.frame‘ containing the column ‘dates‘ and ‘I‘ (for the incidence each day)
- It also computes credibility regions for $R(t)$ and allows one to address uncertainty in the estimation of the serial interval

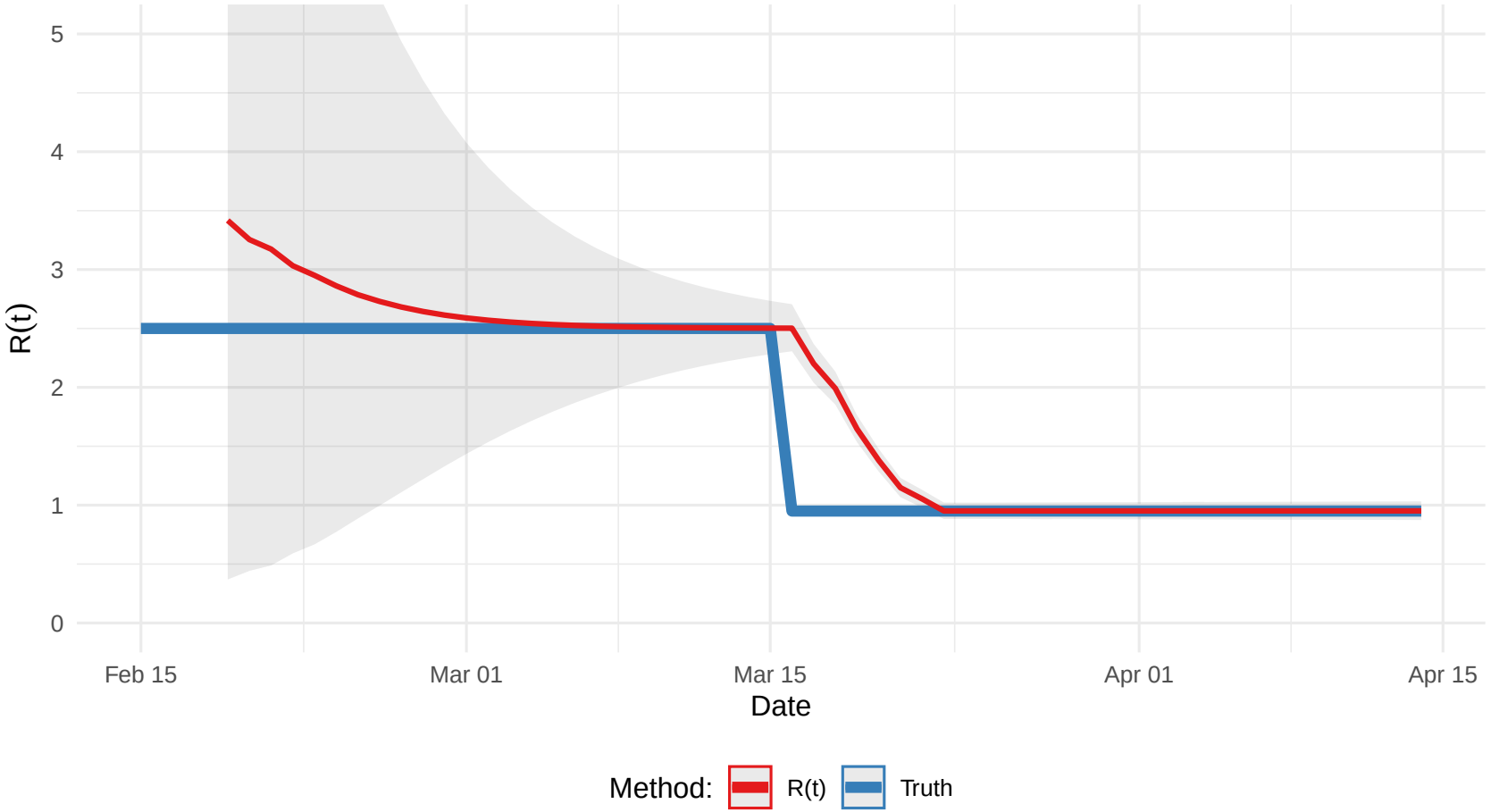
EpiEstim (2)

```
library(EpiEstim)
# Rename data.frame columns to names handled by the EpiEstim pkg.
out_epiestim <- out %>% rename(I = y, dates = Date) %>% select(dates, I)

# Estimate the instantaneous reproduction number
res <- EpiEstim::estimate_R(out_epiestim, method = "non_parametric_si",
                            config=make_config(si_distr=GT_obj$GT,
                                               t_start=2:nrow(out_epiestim),
                                               t_end=2:nrow(out_epiestim))
)

# Convert result to a data.frame
rt_irt_df <- data.frame(Date=res$dates[res$R$t_end],
                        R_hat=res$R$`Mean(R)`,
                        lower=res$R$`Quantile.0.025`,
                        upper=res$R$`Quantile.0.975`,
                        Method="R(t)")
```

EpiEstim (3)


5
4
3
2
1
0
R(t)
Feb 15
Mar 01
Mar 15
Apr 01
Apr 15
Date
Method:
R(t)
Truth

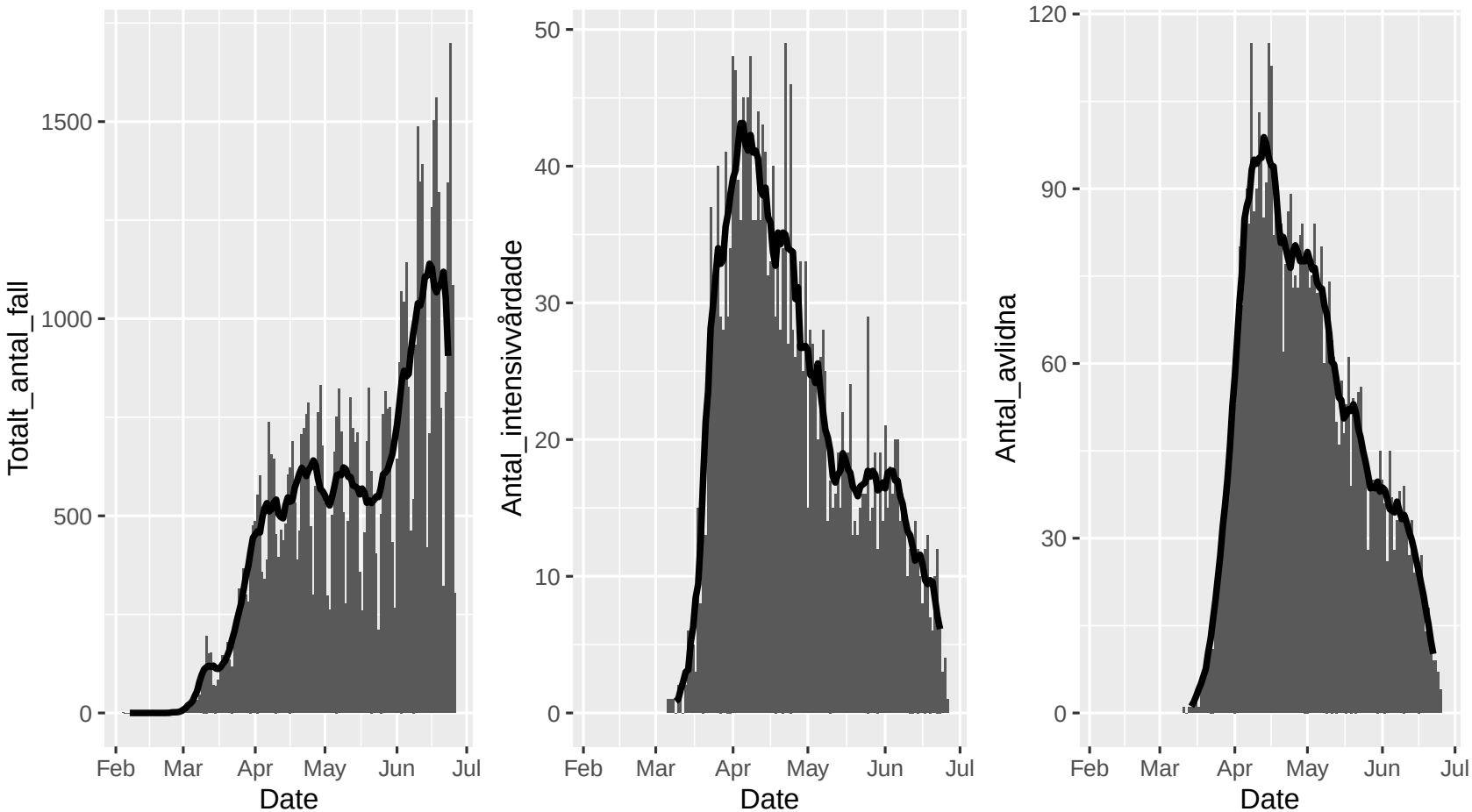
Outline

R(t) for Sweden

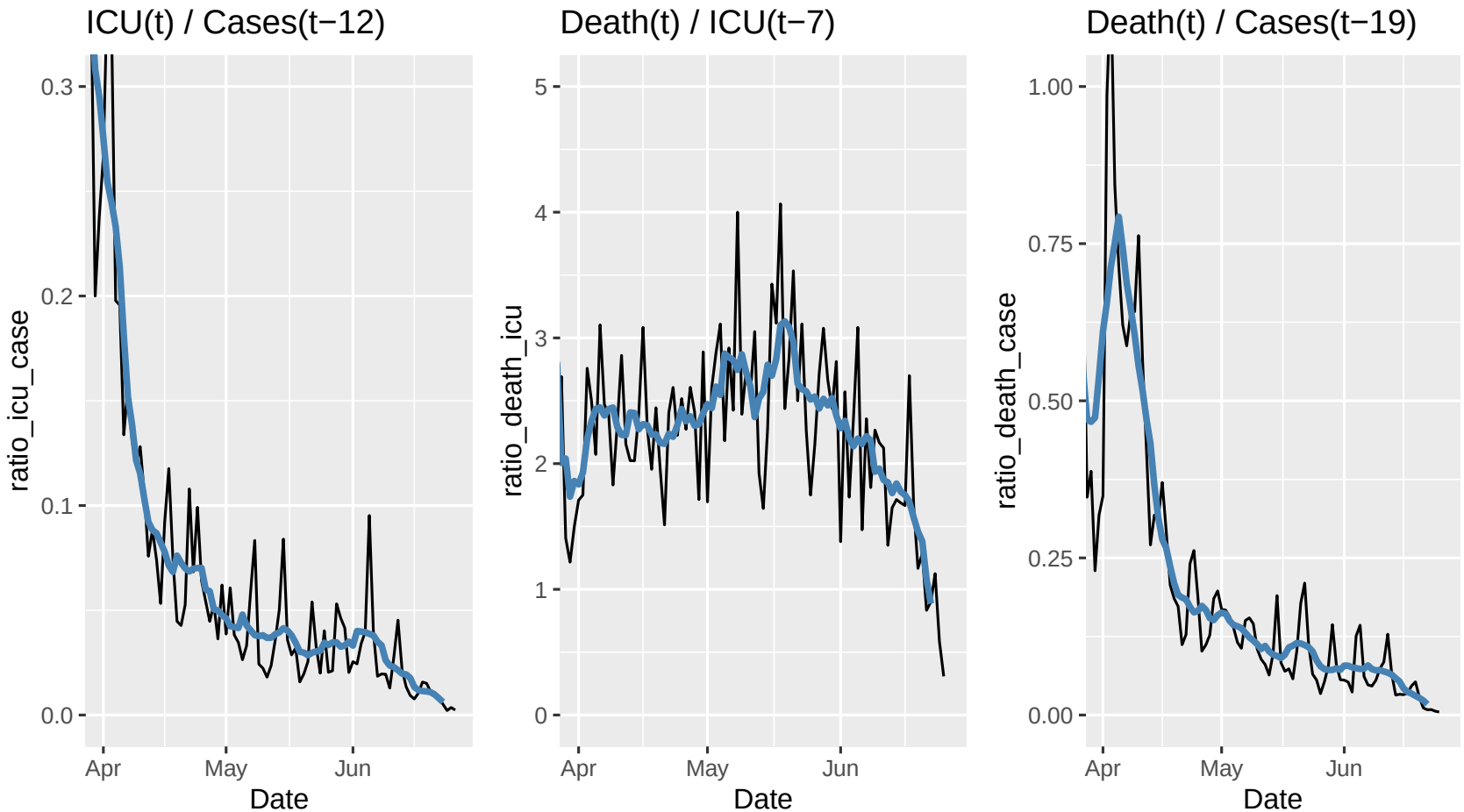
- Aim: Produce a crude $R(t)$ for Sweden based on the daily number of new cases as reported by Folkhälsomyndigheten
- In order to do so, we first look a bit closer at the data as of 2020-06-27

Totalt_antal_fall	Antal_intensivvårdade	Antal_avlidna
65137	2407	5268

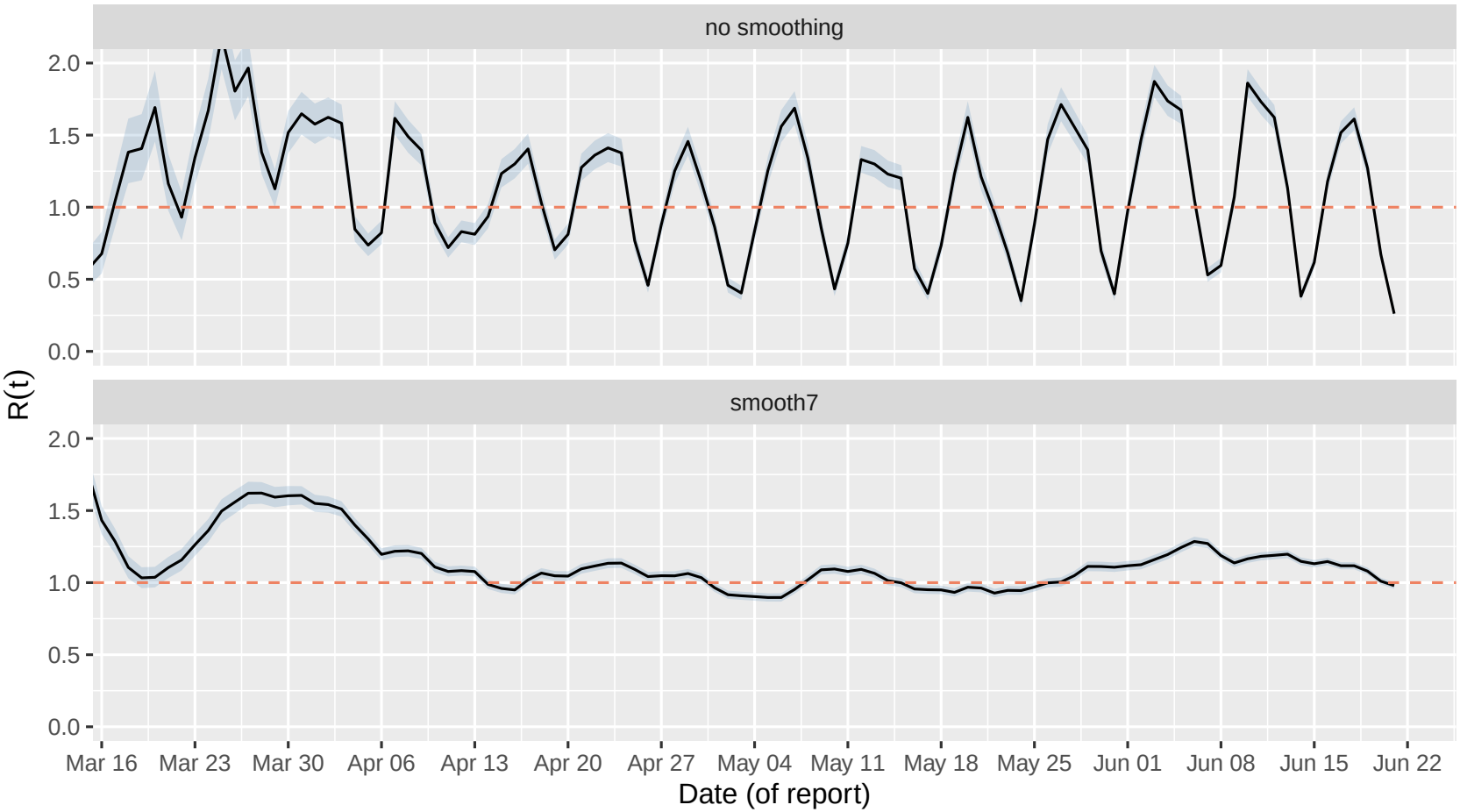
COVID-19 Time Series for Sweden (1)



COVID-19 Time Series for Sweden (2)



Coarse $R(t)$ Estimate (1)



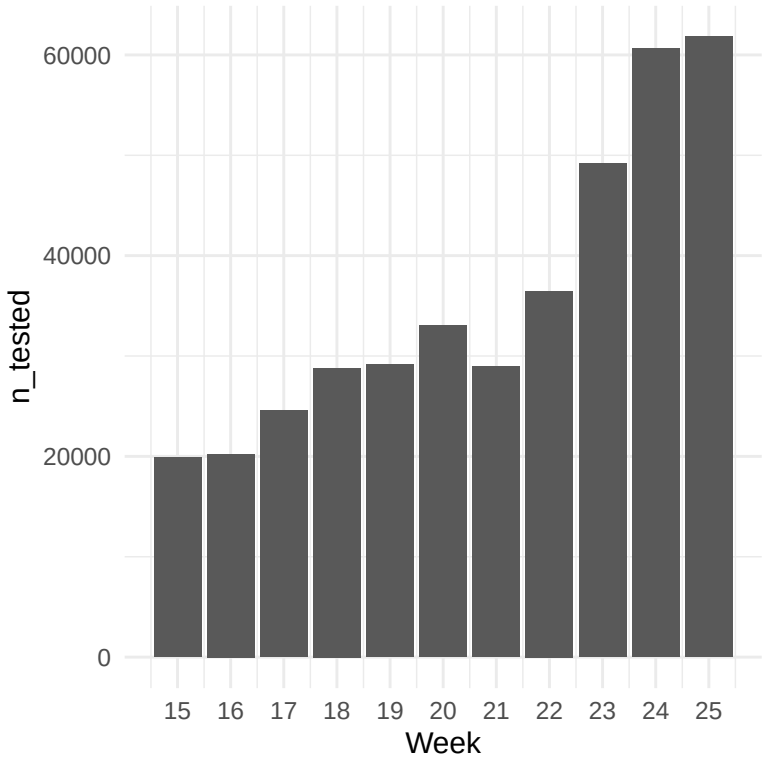
Coarse $R(t)$ Estimate (2)

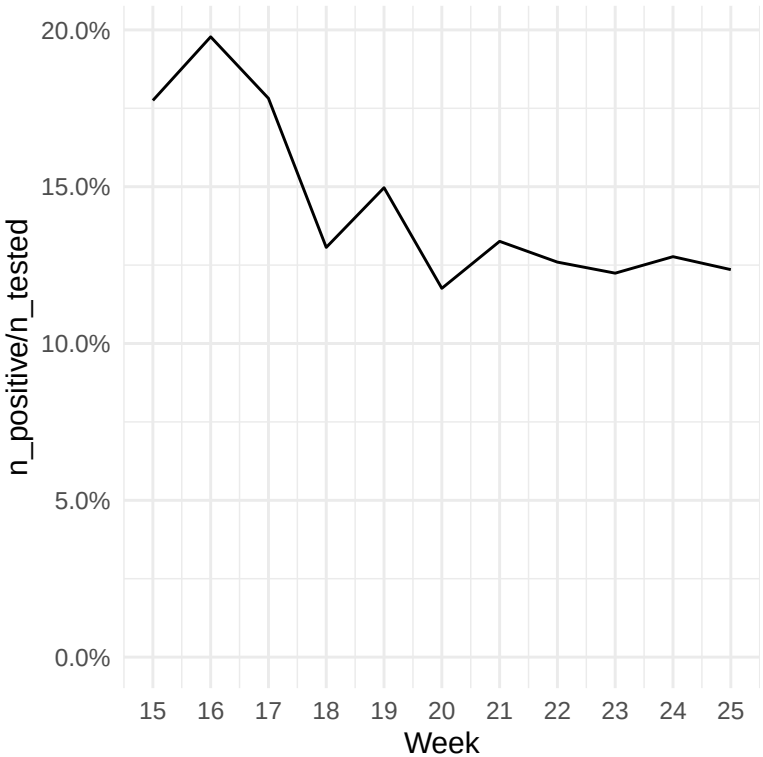
Limitations:

- All cases are considered as community transmissions, but
  - there is an increase in the overall number of tests
  - some settings are tested more pro-actively than others (e.g. hospital staff)
  - imported cases are ignored (negligible from mid March)
- Serial interval
  - The analysis used an estimate from Nishiura et al. (2020) with mean 4.8 days and a standard deviation of 2.3 days
  - Difference between generation time and serial interval (infection vs. symptom onset $\rightarrow$ Tom's lecture).
  - However, in this coarse analysis the event is actually "Day of report".
  - No specific Swedish serial interval available and no estimation uncertainty considered

Coarse $R(t)$ Estimate (3)

- More detailed analysis can be found in the regularly updated report by the Swedish Folkhälsomyndigheten
- Development in the number of test per week:



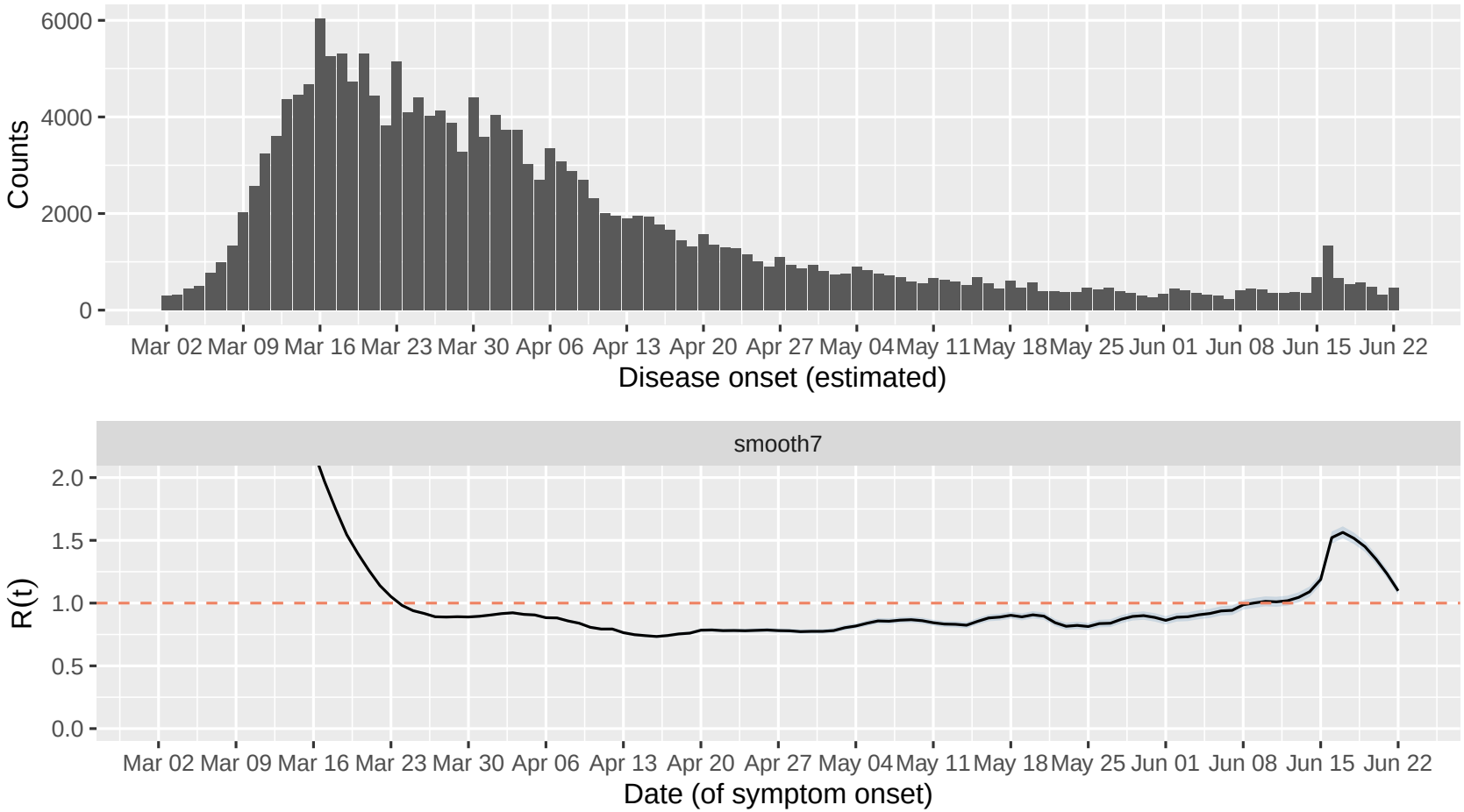


Coarse $R(t)$ Estimate (4)

- $R(t)$ always needs context, e.g., the absolute number of (reported) cases.
- The implication of $R(t) = 1.3$ is very different when you have 10,000 cases or when you have 100.
- Especially when the case number is low, spikes due to outbreaks can lead to large $R(t)$ fluctuations
- Be very careful when using $R(t)$ graphs to assess interventions!

Outline

Similar $R(t)$ Estimate for Germany[3]



[3] Note: Official estimate is computed a little differently.

Exercise

Exercise 5.2

Assume a generation time of exactly 4 days. Derive a direct expression for the 7-day smoothed instantaneous reproduction number estimator in this special case.
Compute the corresponding $R(t)$ estimate for the Swedish time series of reported cases using this generation time through an own function. Modifying the call to EpiEstim so it uses this point generation time distribution instead. Compare the results.

Outline

Outlook

- Not discussed in this lecture: COVID-19 analyses need to look at age groups, because of the strong age dependence in, e.g, mortality
- Good overview preprint about pitfalls when estimating R(t) by Gostic et al. (2020)
- Site estimating COVID-19 R(t) for countries around the world:

`https://epiforecasts.io/covid`

Literature I


Cori, Anne, Neil M. Ferguson, Christophe Fraser, and Simon Cauchemez (2013). "A New Framework and Software to Estimate Time-Varying Reproduction Numbers During Epidemics". In: *American Journal of Epidemiology* 178.9, pp. 1505–1512. DOI: 10.1093/aje/kwt133. eprint: http://aje.oxfordjournals.org/content/178/9/1505.full.pdf+html. URL: http://aje.oxfordjournals.org/content/178/9/1505.abstract.


Delamater, P. L., E. J. Street, T. F. Leslie, Y. T. Yang, and K. H. Jacobsen (2019). "Complexity of the Basic Reproduction Number (R_0)". In: 25.1, p. 1. DOI: 10.3201/eid2501.171901.


Fraser, Christophe (Aug. 2007). "Estimating Individual and Household Reproduction Numbers in an Emerging Epidemic". In: *PLOS ONE* 2.8, e758.

Literature II


Gostic, Katelyn M et al. (Jan. 2020). "Practical considerations for measuring the effective reproductive number, Rt". In: *medRxiv*, p. 2020.06.18.20134858. DOI: 10.1101/2020.06.18.20134858.


Lloyd-Smith, J. O., S. J. Schreiber, P. E. Kopp, and W. M. Getz (2005). "Superspreading and the effect of individual variation on disease emergence". In: *Nature* 438.7066, pp. 355–359. DOI: 10.1038/nature04153.


Nishiura, Hiroshi, Natalie M. Linton, and Andrei R. Akhmetzhanov (Apr. 1, 2020). "Serial interval of novel coronavirus (COVID-19) infections". In: *International Journal of Infectious Diseases* 93, pp. 284–286. ISSN: 1201-9712. DOI: 10.1016/j.ijid.2020.02.060. (Visited on 04/12/2020).