Retrospective modelling of epidemics using historical mortality data

Katarina Matthes

University of Zurich

Outline

- Excess mortality (spatial context)
- Reproduction number

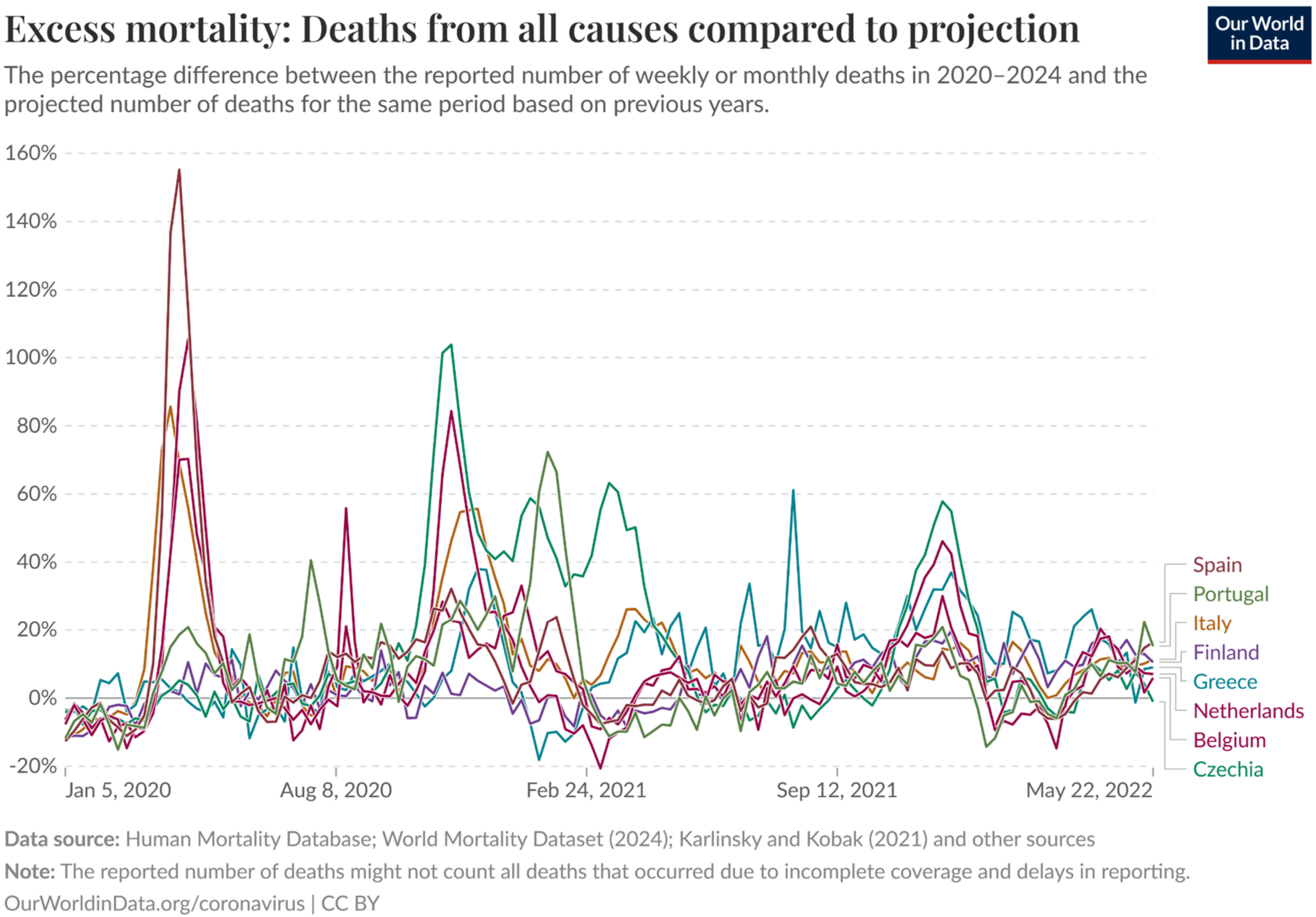
Aim: To give an introduction and overview of this methods.

Codes and presentation:

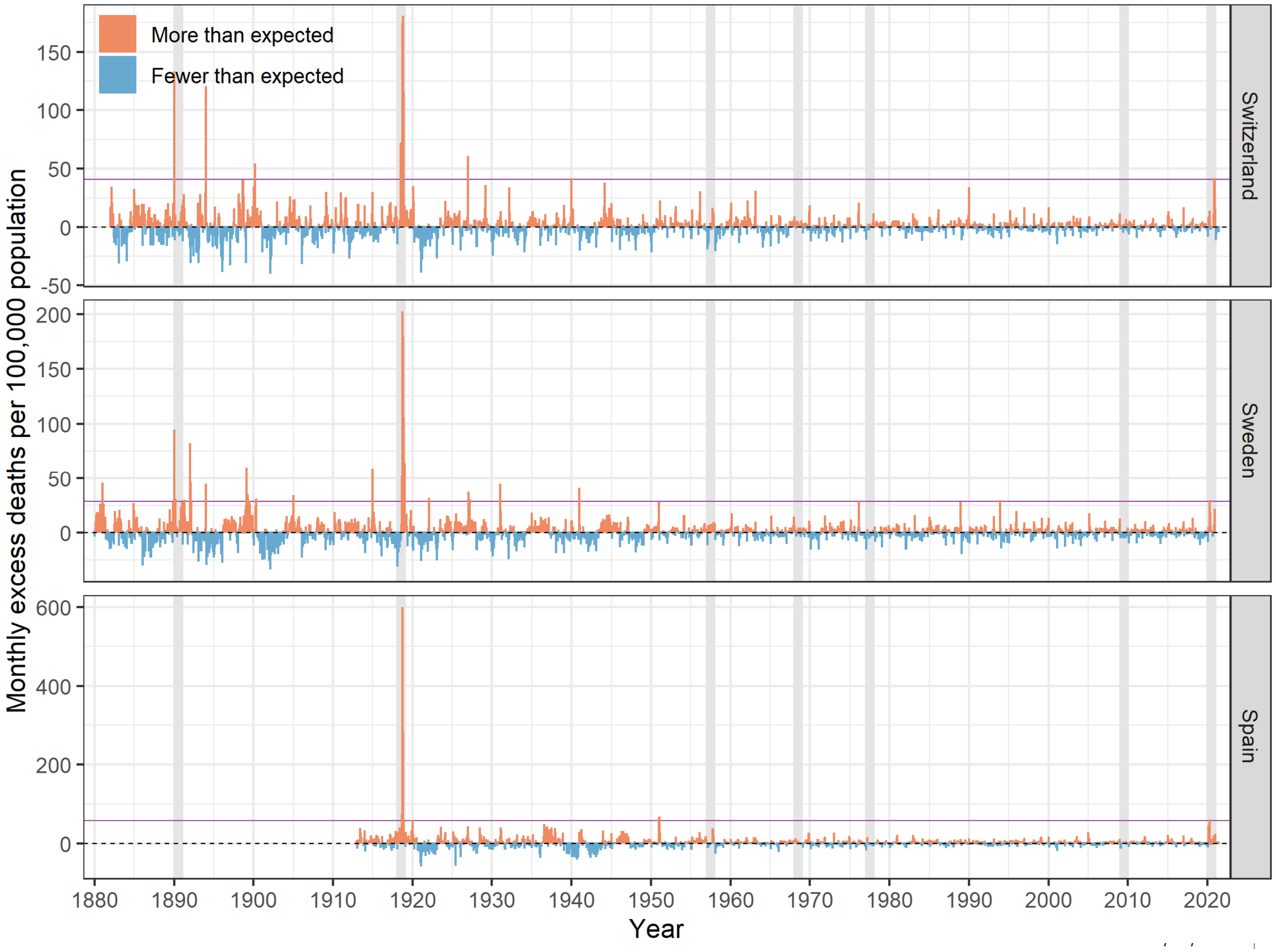
https://github.com/KaMatthes/Greatleap_lecture

Excess mortality

Since Covid-19 the concept of "excess death" become widely known

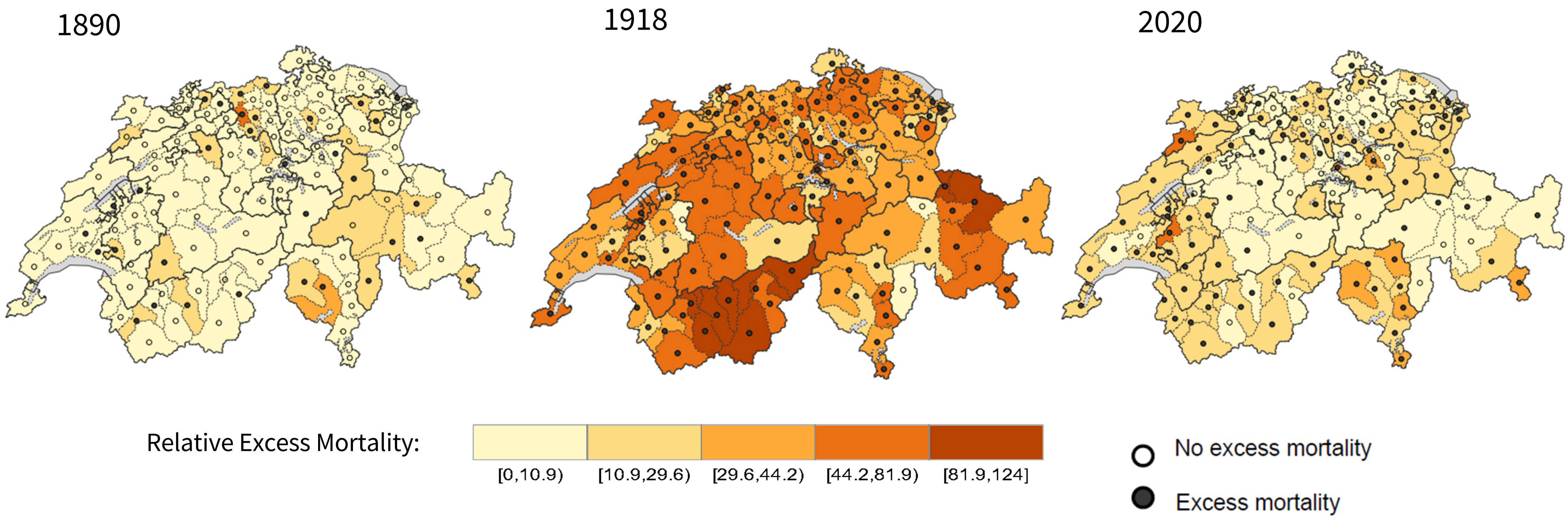


Comparison with other pandemics and countries



Staub, Panczak, Matthes, Floris, Berlin, Junker, Weitkunt, Mamelund,Zwahlen, Riou **Historically High Excess Mortality During the COVID-19 Pandemic in Switzerland, Sweden, and Spain.** Ann Intern Med.2022; doi:10.7326/M21-3824

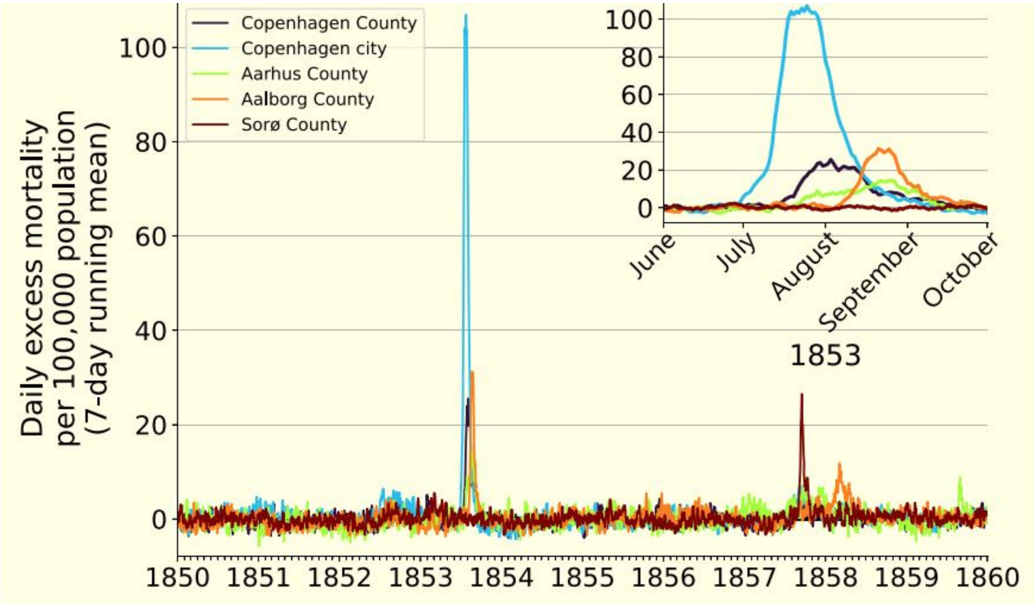
Spatial comparison with other pandemics



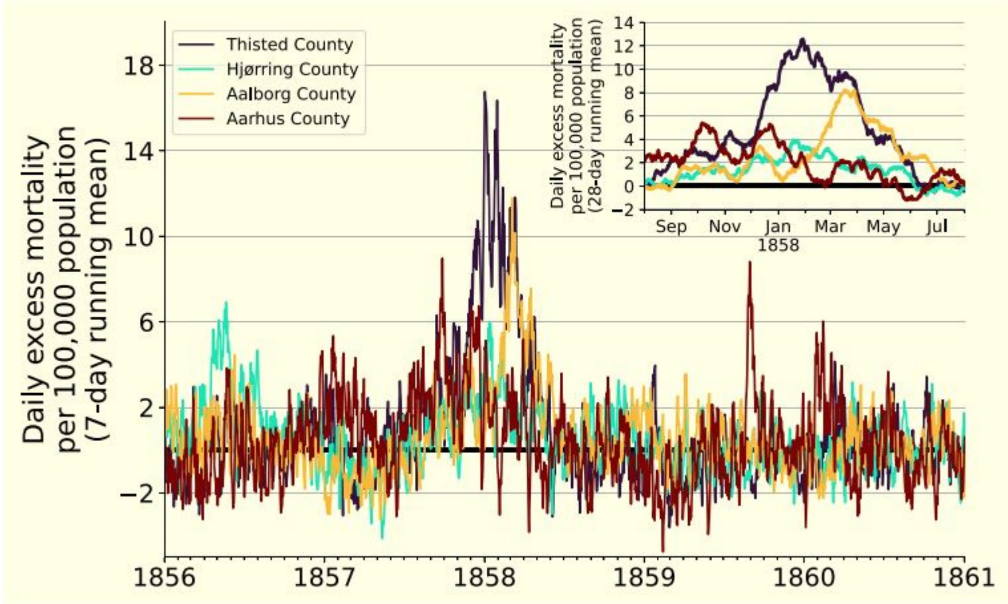
Matthes, Floris, Merzouki, Junker, Weitkunat, Rühli, Keiser, Staub,
Spatial pattern of all cause excess mortality in Swiss districts during the pandemic years 1890, 1918 and 2020,
Spatial and Spatio-temporal Epidemiology, 2024,100697, https://doi.org/10.1016/j.sste.2024.100697.

Epidemic diseases from the 19th century

Cholera epidemic



Scarlet fever epidemic



Pedersen, Ingholt, Van Wijhe, Andreasen, Simonsen, **Identifying signature features of epidemic diseases from 19th century all-cause mortality data,** American Journal of Epidemiology, https://doi.org/10.1093/aje/kwae187

Why estimate excess mortality?

What are the advantages of estimating the overall excess mortality?

- Estimates of the total burden of the event
- Accounts for both the direct and indirect impacts
- Independent of cause-of-death reporting
- Overcome the issue of death misclassification
- Comparable across regions, time, age groups, SES groups, etc.

And disadvantages?

- May underestimate epidemic deaths (because some causes of death decrease during epidemics)
- May overestimate epidemic deaths (indirect deaths are also included)
- Requires a baseline mortality -> strongly depends on the statistical model

Excess mortality - concept

excess deaths = observed death counts – expected death counts

The actual number of deaths

What would be expected considering that an specific event did not occur?
“counterfactual” death numbers

Estimation, using statistical models

Relative excess death:

P-score = excess death / expected death

How to estimate the baseline?

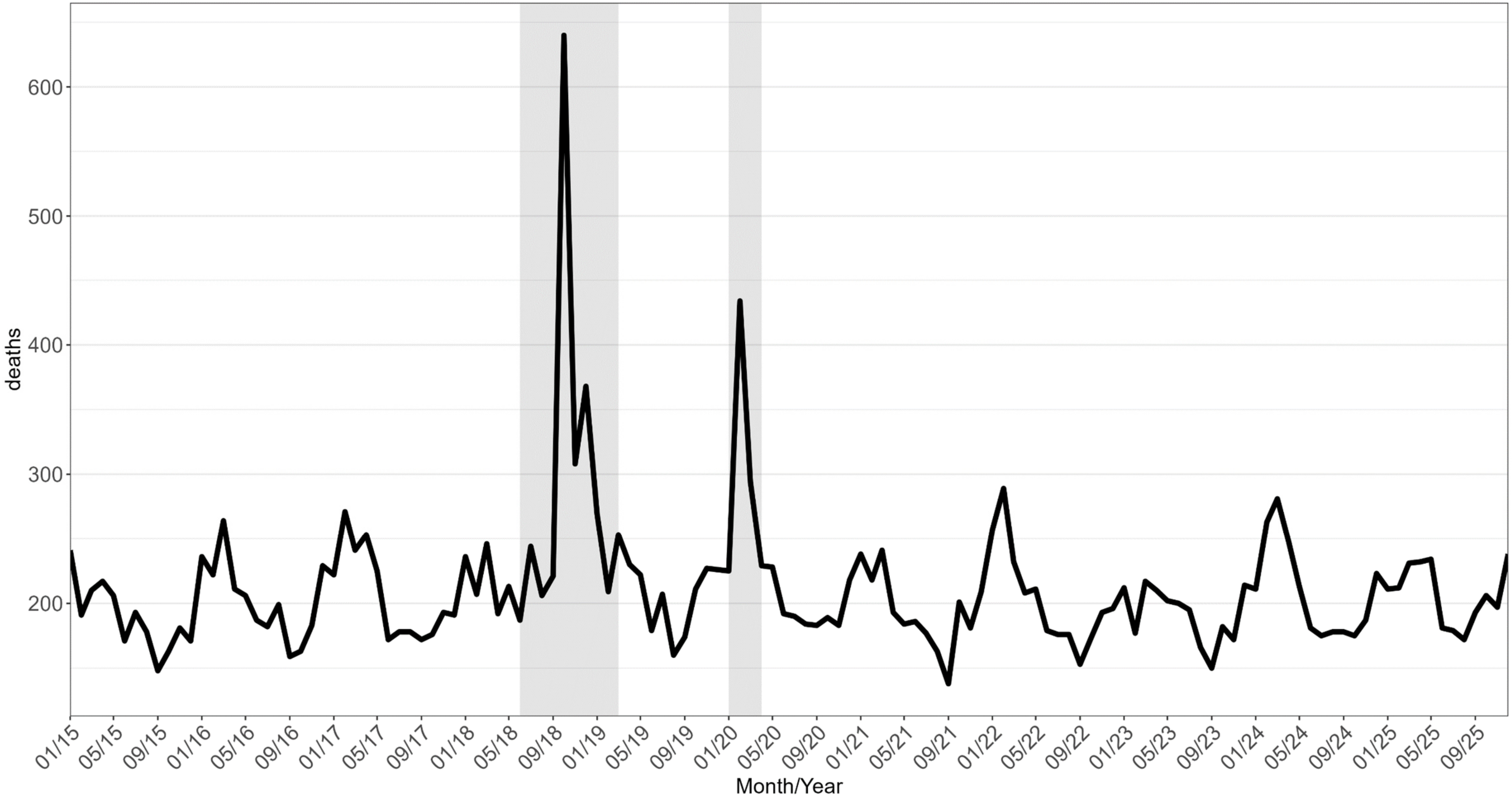
Expected death: The hypothetical or “counterfactual” total death numbers

Requires to build a counterfactual scenario (baseline):

- We need a statistical model
- Which one? Not an easy answer
- Whole workshop about it organized by Hampton Gaddy and Eric Schneider

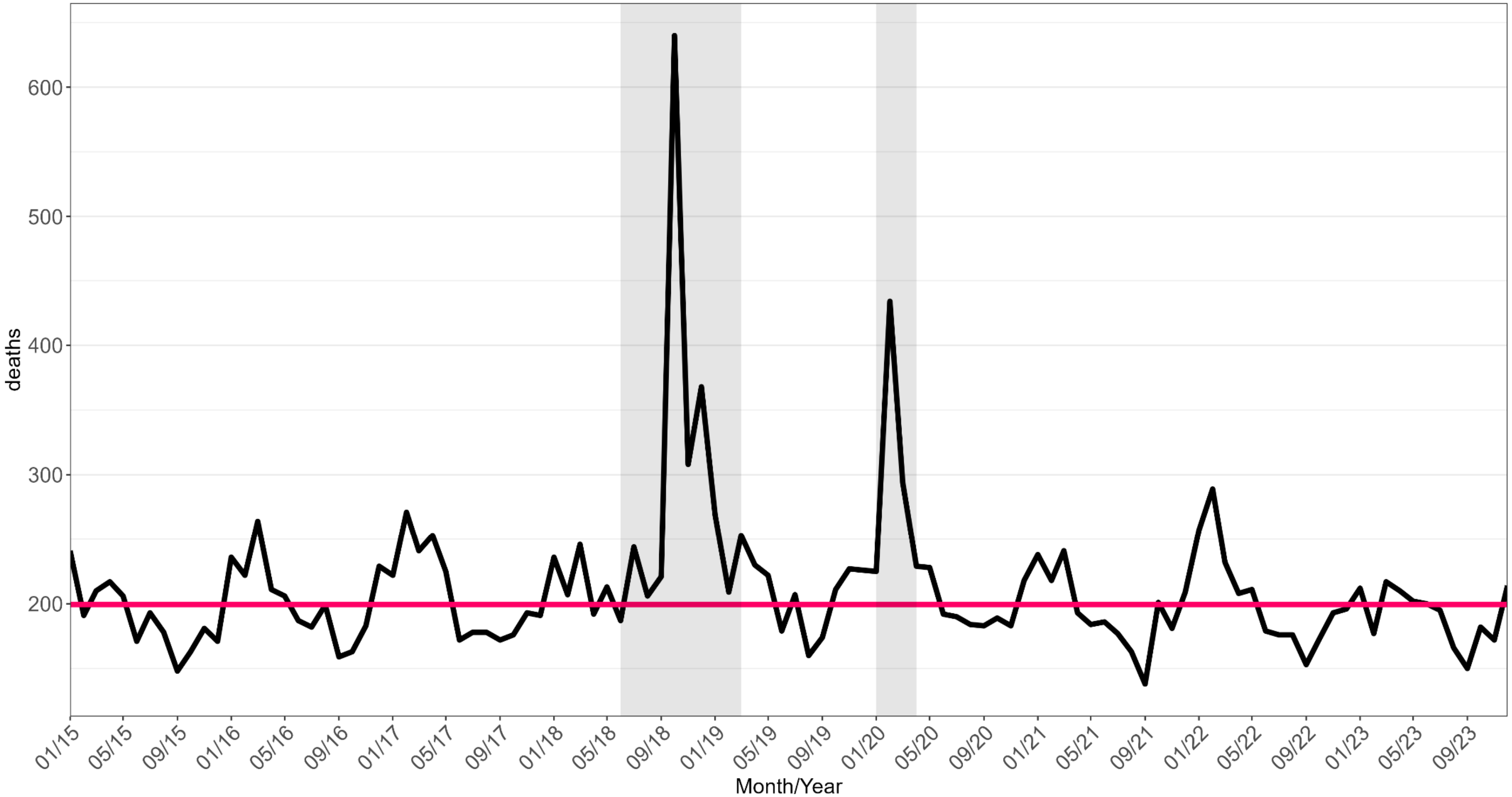
  One epidemic, many estimates (1EME): 21.5- 22.5.2026 London
- Comparison papers: Schöley (2021), Nepomuceno et al. (2022), Wakenfield & Knutson (2025)

1918-1920 Pandemic in Zurich, monthly deaths data



Baseline estimation - average over the whole training period

Training period: 3 years before and after, excluding pandemic months (grey areas)

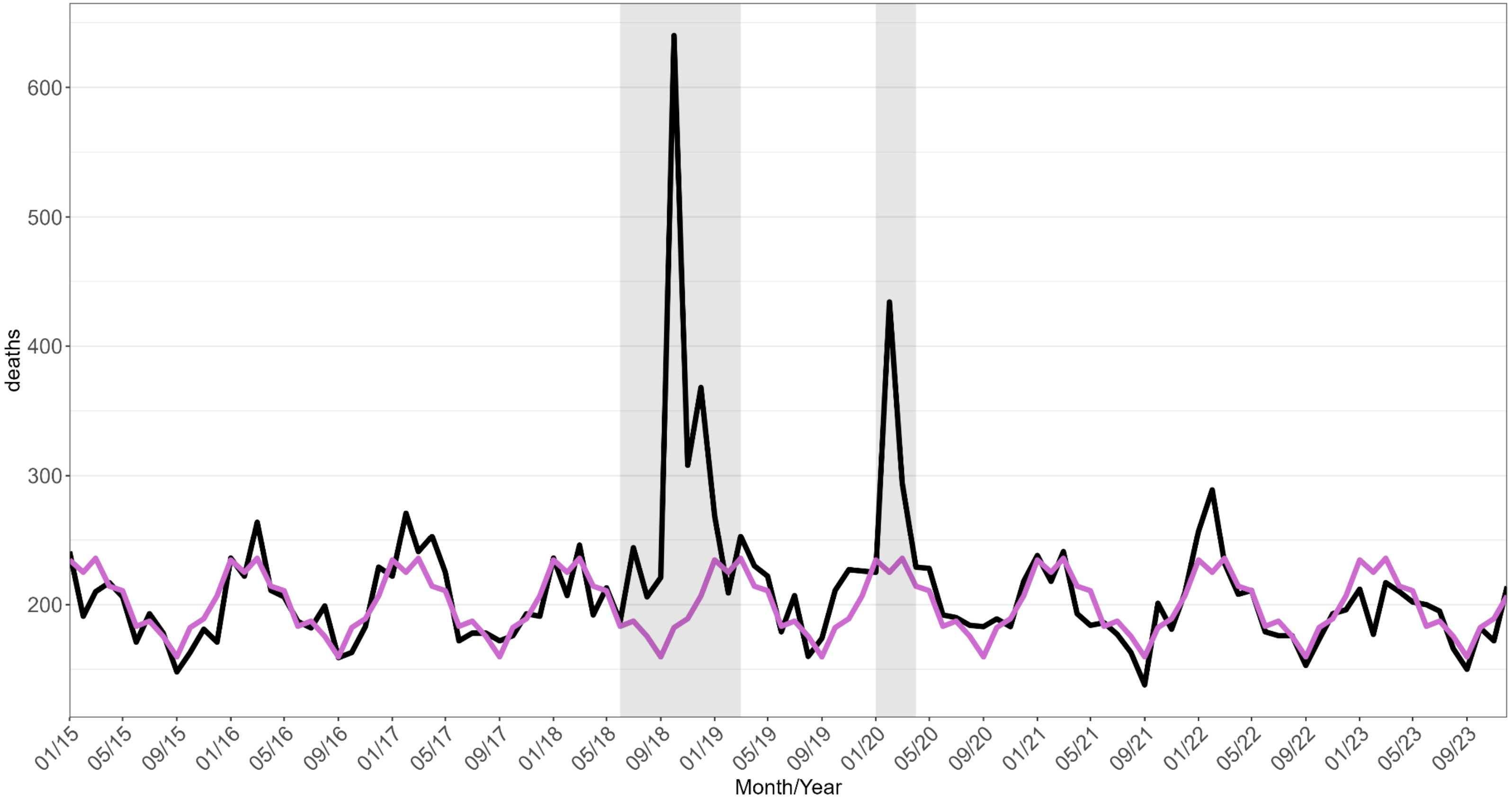


- Average death over the whole period by excluding pandemic month
- Don't use it – easy but too simple

Why is this approach too simplistic?

Baseline estimation – monthly specific average

Training period: 3 years before and after, excluding pandemic months (grey areas)

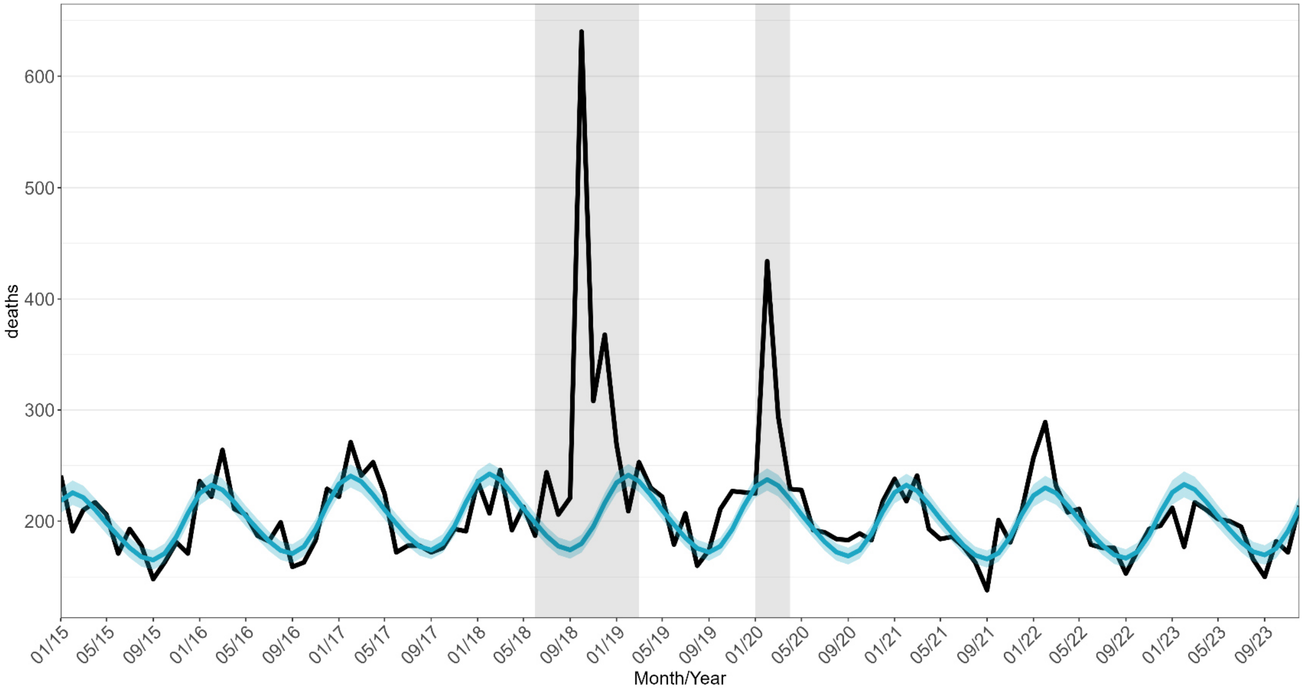


- Average death by month excluding pandemic month
- No trend included

Much better! But what is still a problem?

Estimate the baseline – Serfling model

Training period: 3 years before and after, excluding pandemic months (grey areas)



Fit monthly deaths in a Poisson model that accounts for:

- Secular trends
- Seasonality
- Changes in population over time

To avoid overdispersion (varianz > mean):

- Quasi- Poisson
- Negative Binomial

$$log(deaths_t) = \underbrace{\beta_0 + \beta_1 t}_{\text{Secular trend}} + \underbrace{\beta_2 \sin\left(\frac{2\pi t}{period}\right) + \beta_3 \cos\left(\frac{2\pi t}{period}\right)}_{\text{First harmonic}} + \underbrace{\beta_4\, sin\left(\frac{4\pi t}{period}\right) + \beta_5\, cos\left(\frac{4\pi t}{period}\right)}_{\text{Second harmonic}} + \underbrace{\log(population)}_{\text{Population}}$$

Period:
Monthly data = 12
Weekly data = 52

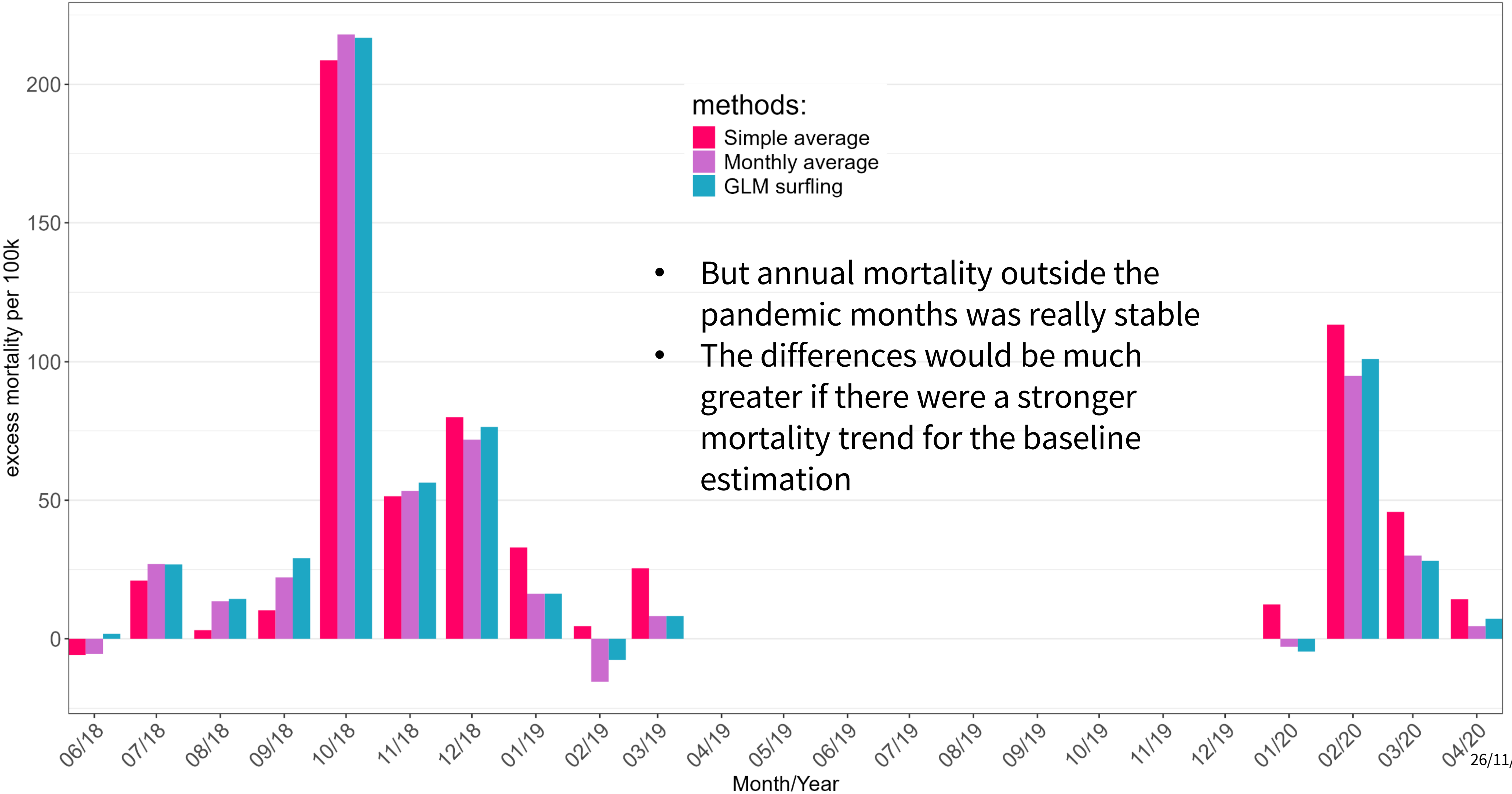
Secular trend

First harmonic (annual cycle) main seasonal variation captures winter–summer seasonality (big yearly pattern)

Second harmonic (semi-annual cycle) captures additional smaller peaks more complex seasonal patterns

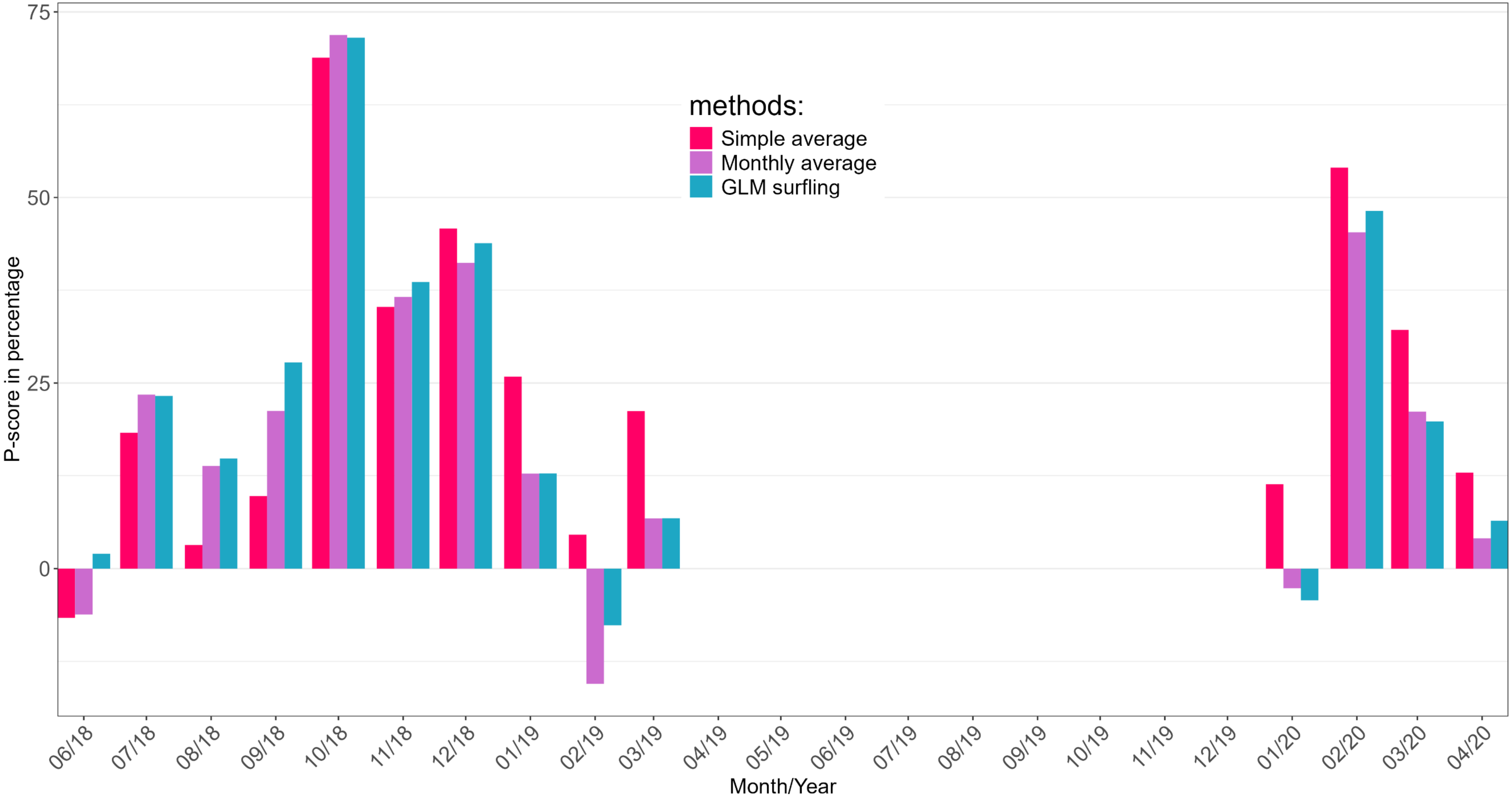
Population

Comparison of excess deaths



- But annual mortality outside the pandemic months was really stable
- The differences would be much greater if there were a stronger mortality trend for the baseline estimation

P-score


methods:
Simple average
Monthly average
GLM surfling
P-score in percentage
75
50
25
0
06/18
07/18
08/18
09/18
10/18
11/18
12/18
01/19
02/19
03/19
04/19
05/19
06/19
07/19
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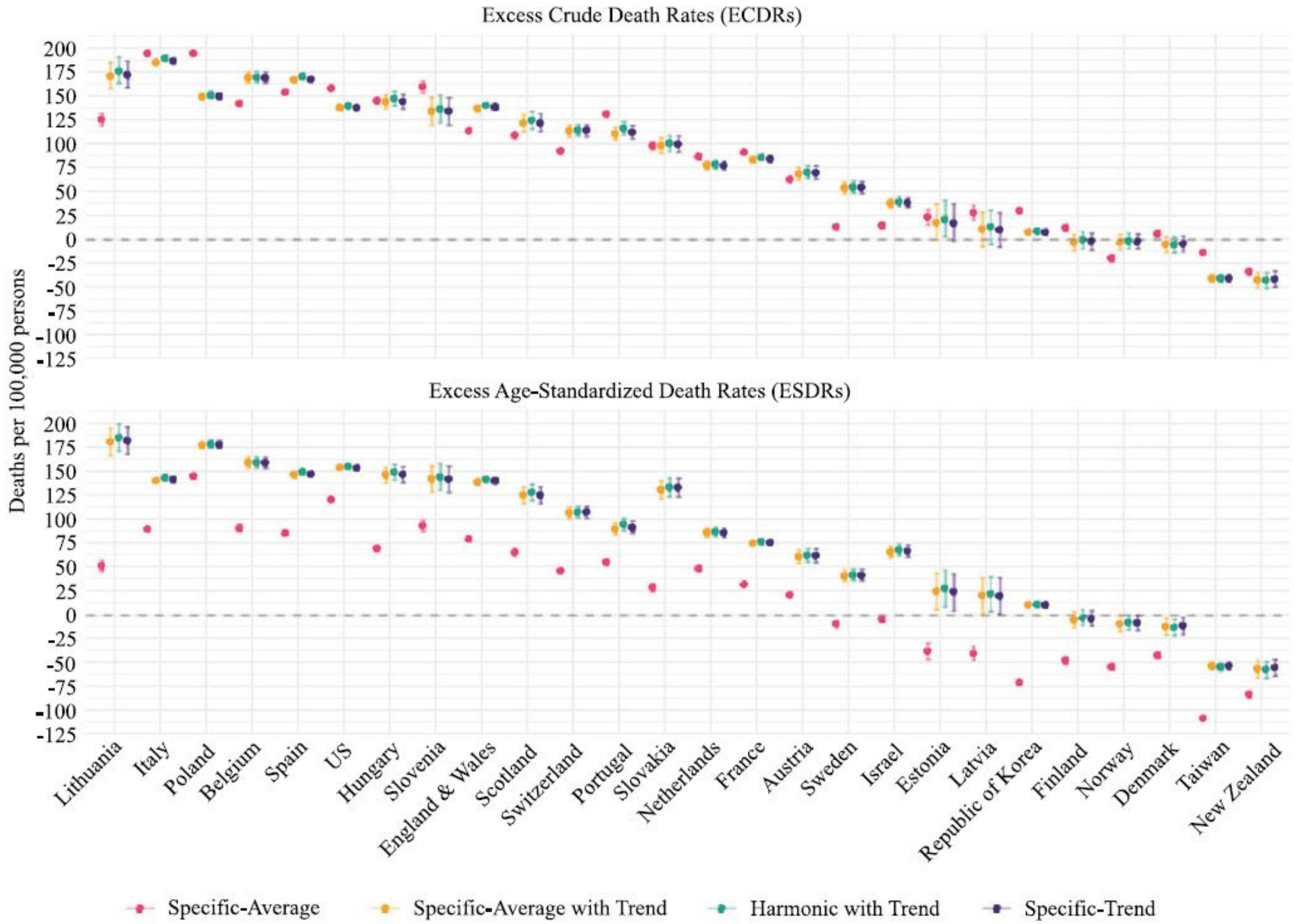
09/19
10/19
11/19
12/19
01/20
02/20
03/20
04/20
Month/Year

Comparison - methods

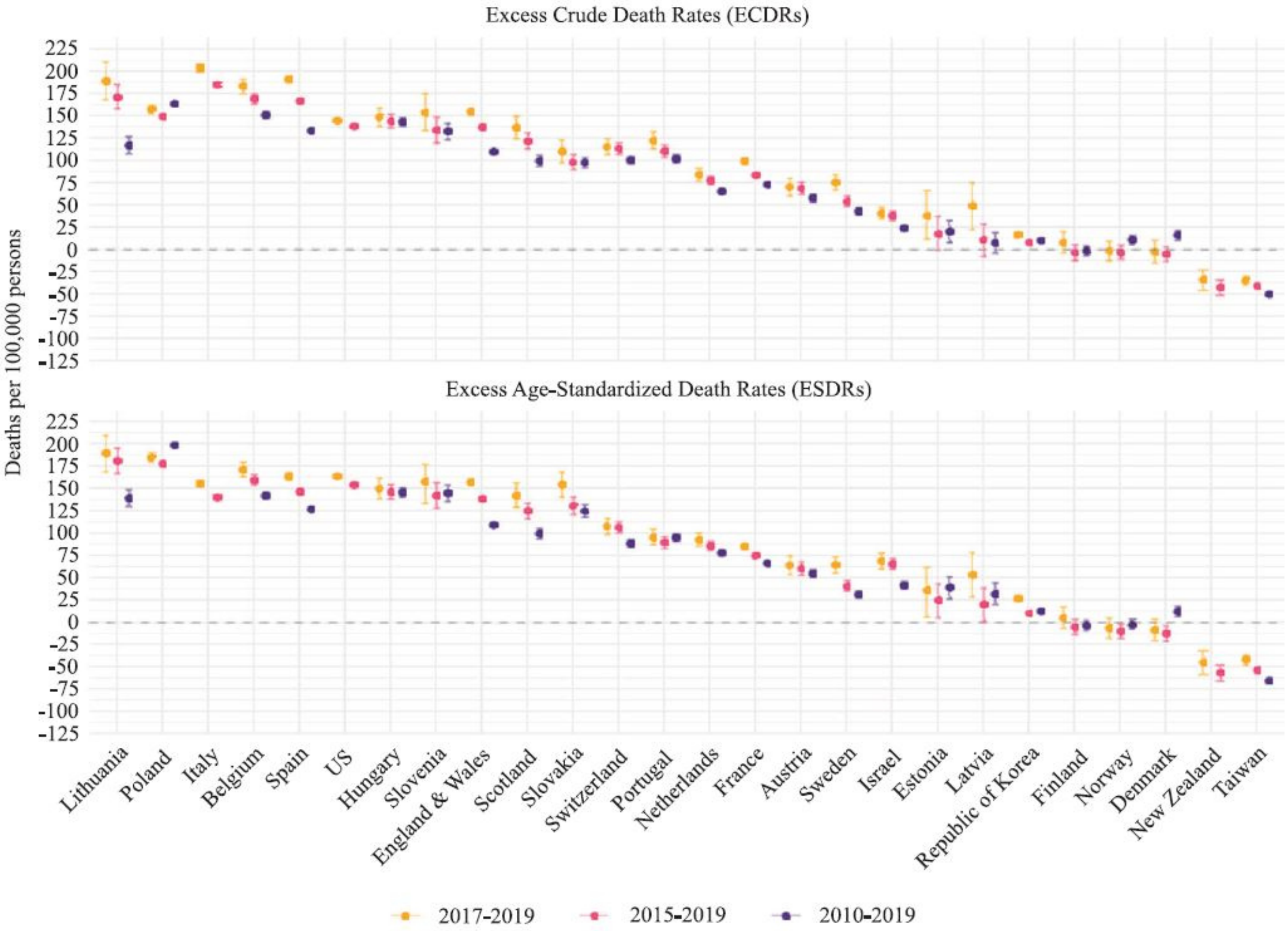


Specific-Average method:

- Underestimate the excess death
- Don’t use it

Nepomuceno, M.R., Klimkin, I., Jdanov, D.A., Alustiza-Galarza, A. and Shkolnikov, V.M. (2022), **Sensitivity Analysis of Excess Mortality due to the COVID-19 Pandemic**. Population and Development Review, 48: 279-302. https://doi.org/10.1111/padr.12475.

Comparison – reference period

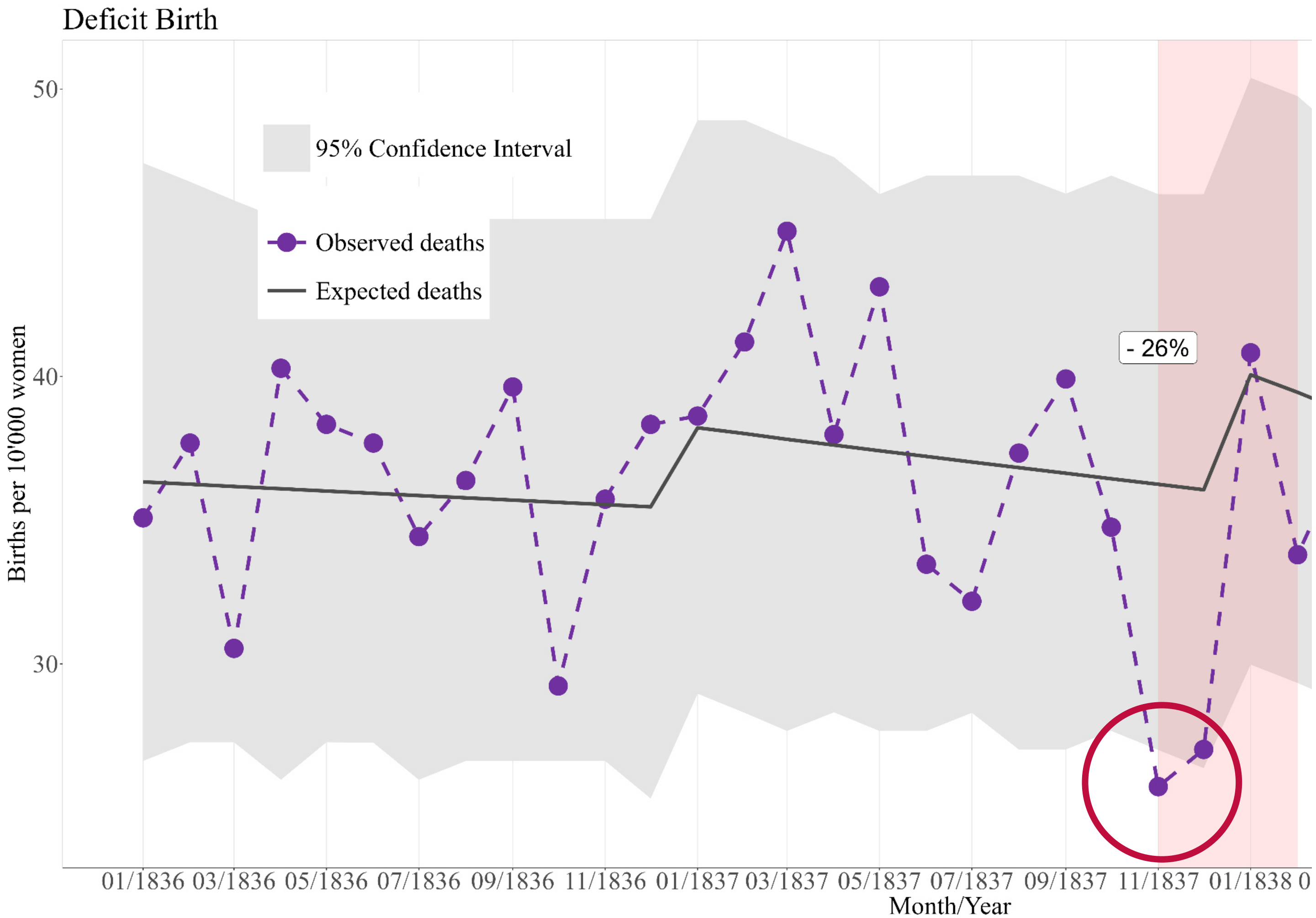


The choice of the reference period can affect excess mortality estimates:

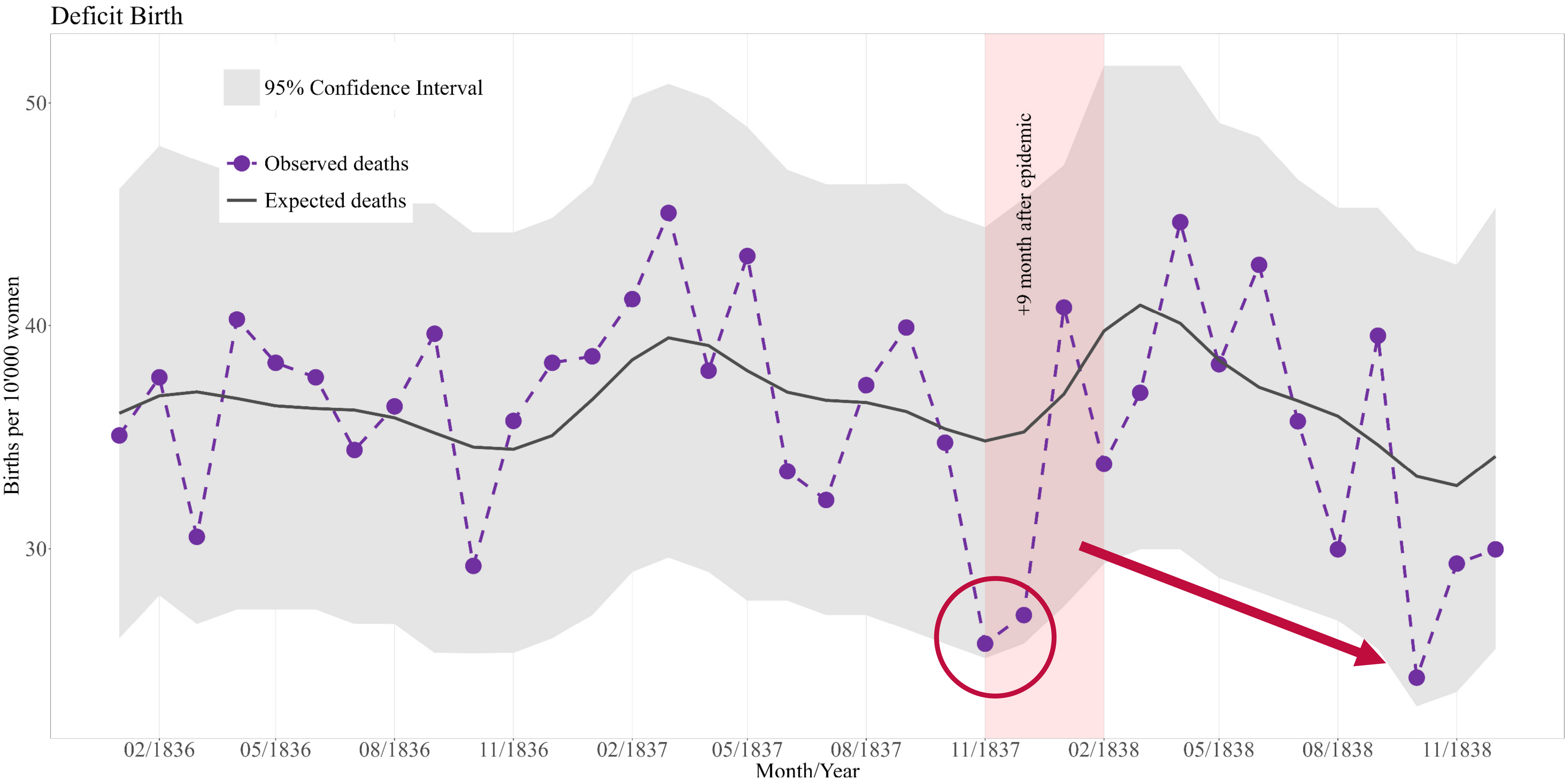
- Some previous epidemic/crisis years may be included
  - Increased baseline
- Mortality decline is not linear in the last years
  - Baseline different for 5 or 10 years

Nepomuceno, M.R., Klimkin, I., Jdanov, D.A., Alustiza-Galarza, A. and Shkolnikov, V.M. (2022), **Sensitivity Analysis of Excess Mortality due to the COVID-19 Pandemic**. Population and Development Review, 48: 279-302. https://doi.org/10.1111/padr.12475.

Comparison – including years after?

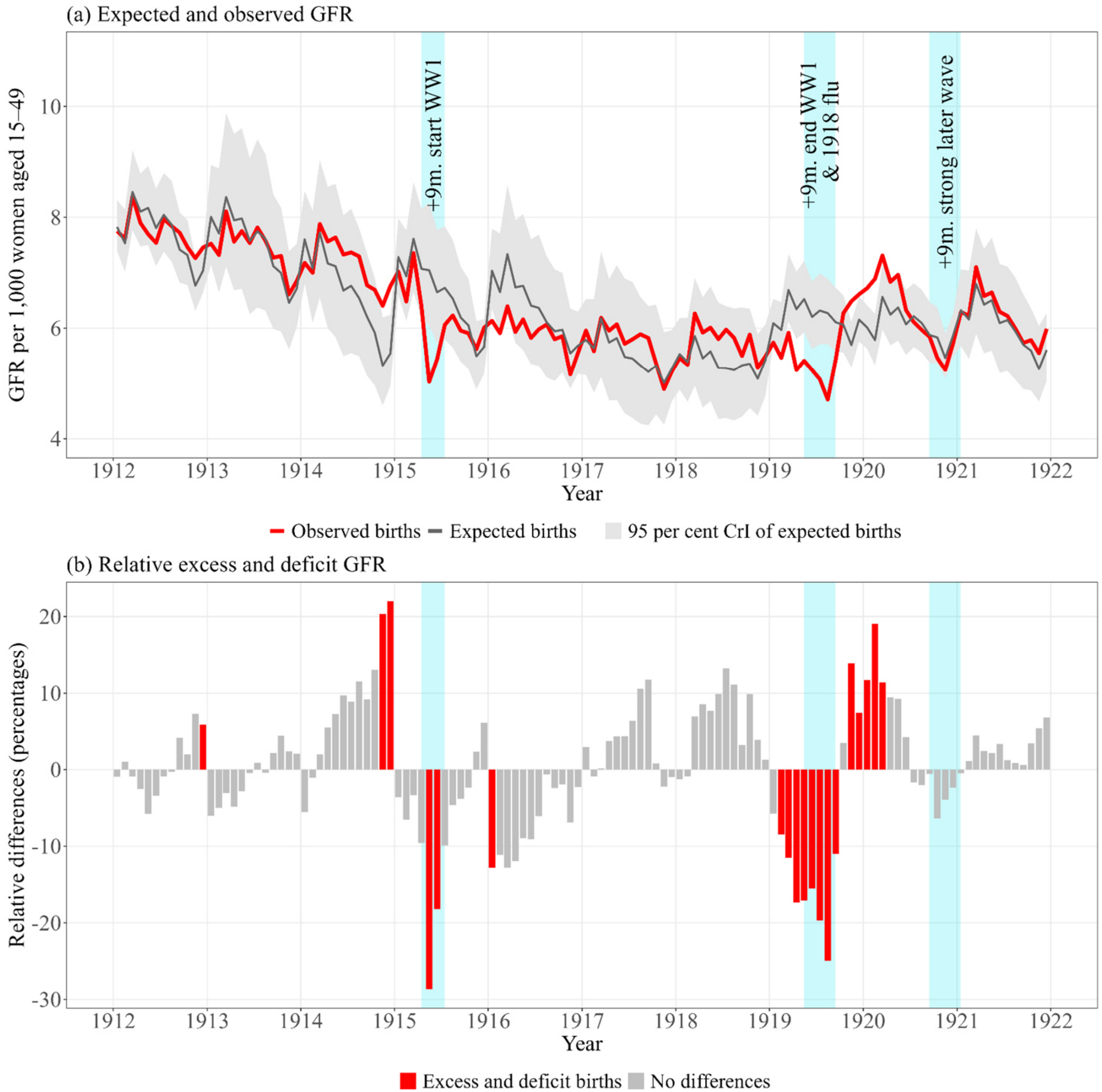


Comparison – including years after?



Other application

Excess and deficit birthrate



Matthes, Le Vu & Staub (2025). **Fertility dynamics through historical pandemics and COVID-19 in Switzerland, 1871–2022.** *Population Studies*, *79*(3), https://doi.org/10.1080/00324728.2025.2462291

Excess mortality - summary

How many years to include in the baseline?

- Depending on the trend, research question and also available data
- Using historical data and if data after the event is available, include also years after the event

Weekly, monthly or annual data?

- Depending on the event and your research question
  - For short events like heat wave weekly data is the better option, monthly or annual data will probably blur the effect
  - For epidemics with high mortality, monthly or even annual data will be sufficient
- But always check: Enough number of deaths per week or month?

Excess mortality - summary

What about the model?

- Use models which include the trend and population, when using weekly or monthly data include the seasonality
- Include also years after the event to consider possible trends

What about the seasonality?

- Should be included by using weekly or monthly data -> mortality depends on seasonality
- Use surfling model or flexible approaches like cyclic splines (GAM models)

What should be considered as crisis period ? Which particular periods should be excluded?

- The event itself, with high mortality
- Maybe also following years -> still effect of event
- Nonnormal conditions such as conflicts or extreme weather events

Excess mortality - summary

There are a lot more methods to estimate excess mortality:

- GAM model - General additive models (often used), includes splines, more accurate for example if mortality trend is not linear
- Bayesian methods
- etc…

Excess mortality – in a spatial context

What needs to be considered by estimating spatial excess mortality for high spatial-(temporal) resolution?

- Small population and small number of deaths can lead to high uncertainties
- Spatial and temporal correlations
- Statistical methods that account for spatial dependencies to get more robust and accurate estimates

Excess mortality – In a spatial context

Disease mapping framework

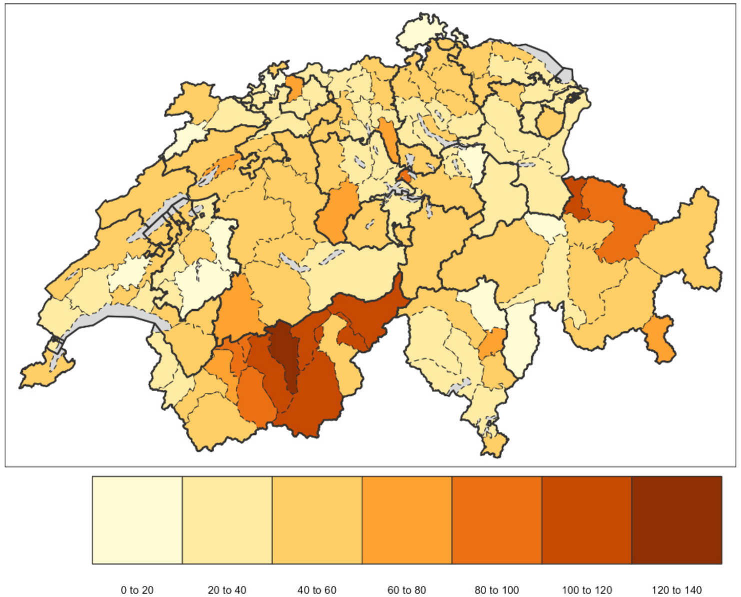
- Bayesian disease mapping
- GAM spatial mapping

That would need an extra lecture to go deeper into the methods!

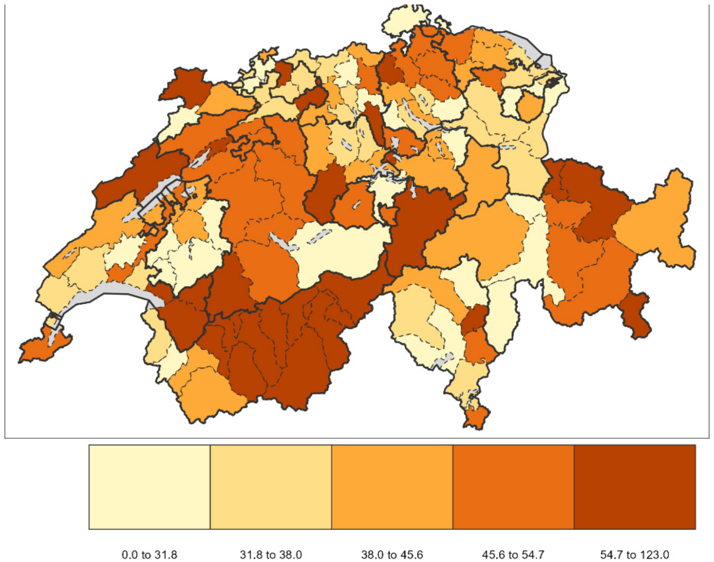
Important for now: Please consider spatial methods when estimating excess mortality for high spatial resolutions

Spatial excess mortality – How to show?

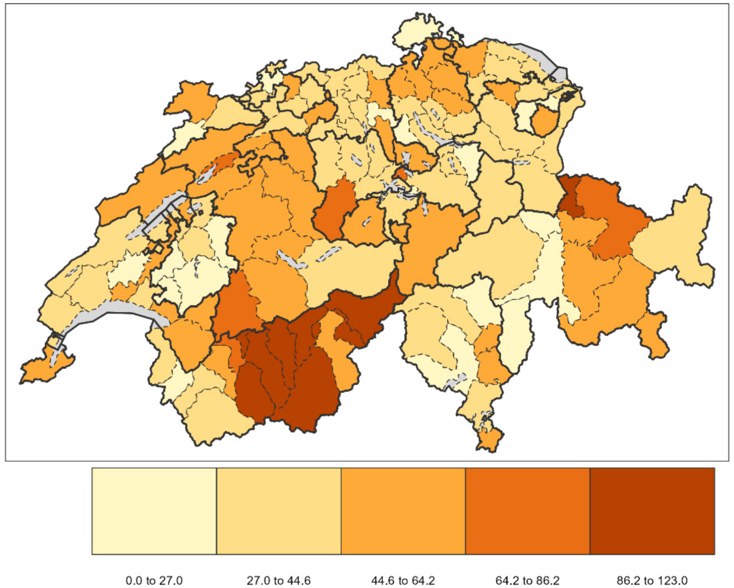
pretty



quantile



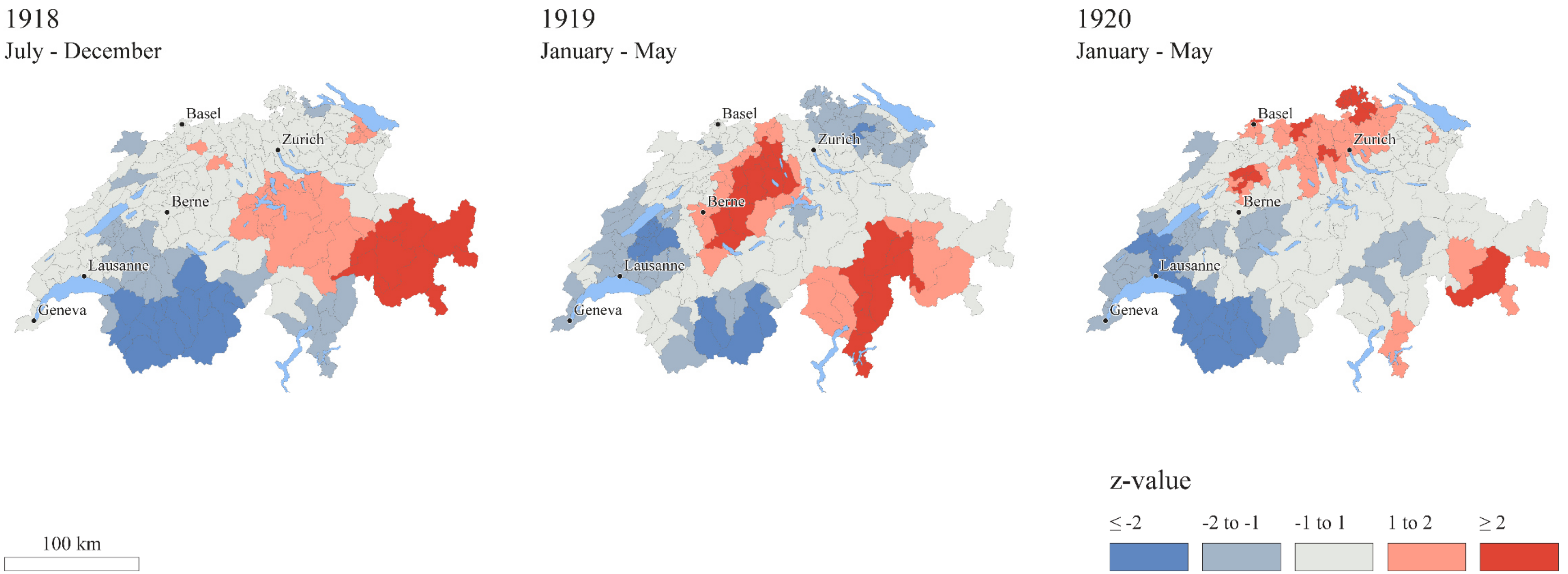
jenks



- Jenks natural breaks: data cluster method

Spatial excess mortality – Cluster?

Gi* statistic: Gives z-value
- greater than 2 indicate significantly rates
- less than -2 indicate significantly lower rates



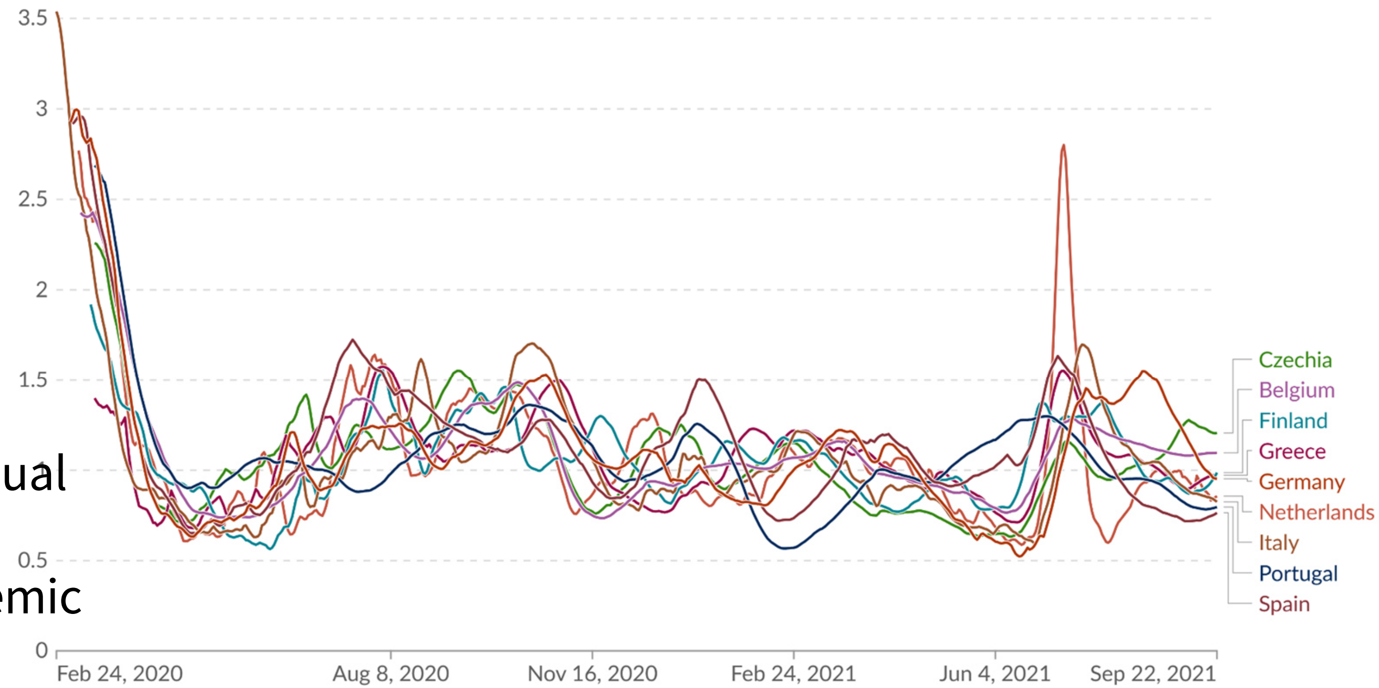
Reproduction number (transmissibility)

Since Covid-19 the concept of "Reproduction numbers " become widely known

What does it show?

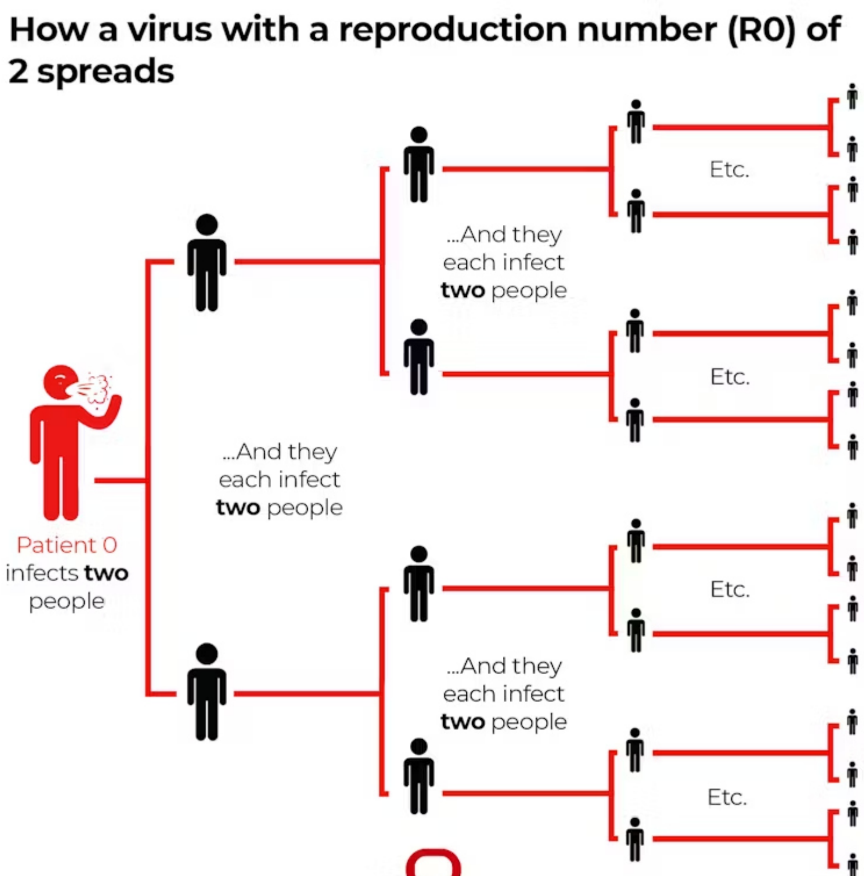
- average number of new infections caused by a single infected individual

- > 1 = exponential increase -> epidemic
- 1 = stable transmission
- < 1 = decrease of cases



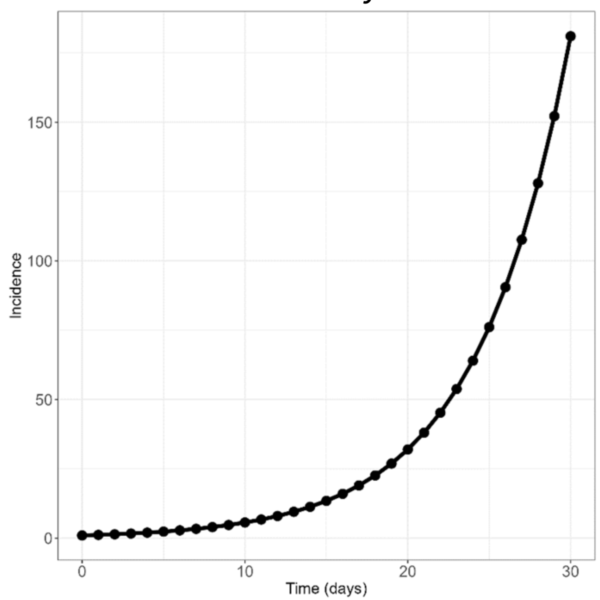
Data source: Arroyo-Marioli F, Bullano F, Kucinskas S, Rondón-Moreno C (2023)

Basic reproduction number (R0) - exponential growth

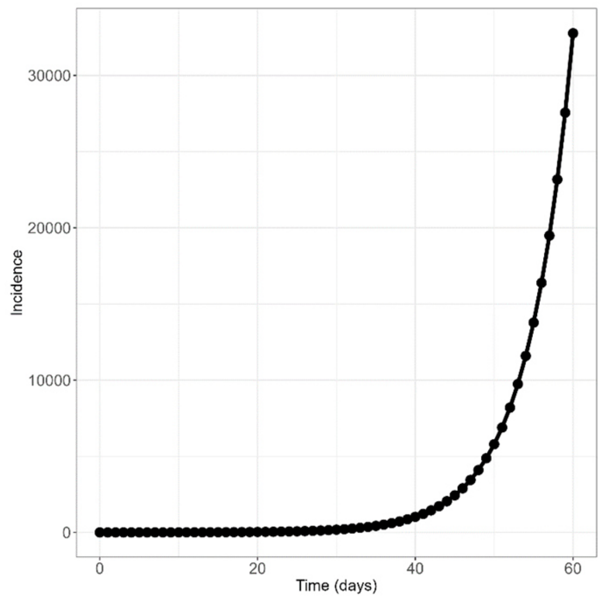


Assumption:
Generation time: *time from primary infection to second infection = 4 days*

After 30 days



After 60 days



Every 4 days, the figures are doubled

https://theconversation.com/r0-how-scientists-quantify-the-intensity-of-an-outbreak-like-coronavirus-and-predict-the-pandemics-spread-130777

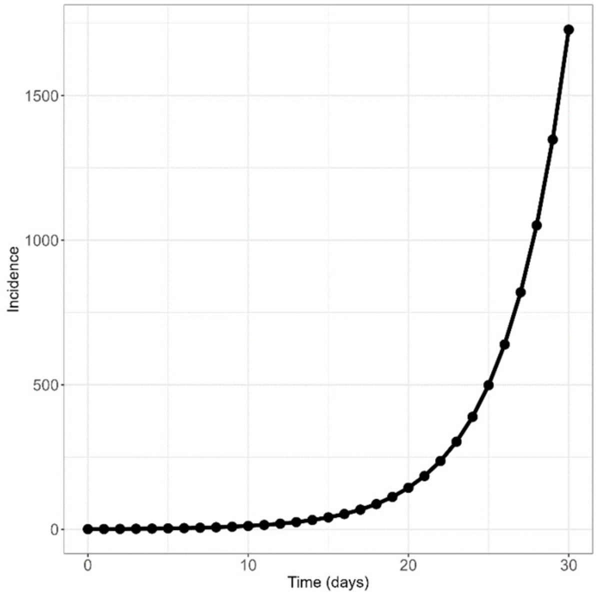
R0 for other infection diseases

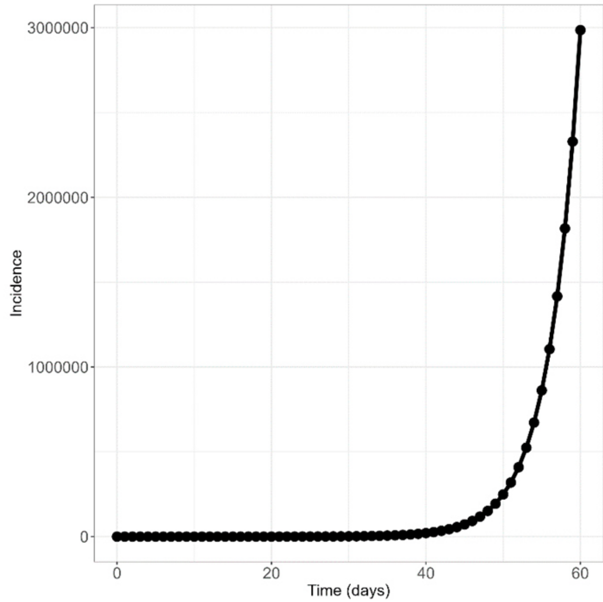
Disease	Reproduction number R0
Ebola, 2014	1.51 to 2.53
H1N1 Influenza, 2009	1.46 to 1.48
Seasonal Influenza	0.9 to 2.1
Measles	12 to 18
MERS	around 1
Polio	5 to 7
SARS	<1 to 2.75
Smallpox	5 to 7
SARS-CoV-2 (causes COVID-19)	1.5 to 3.5

https://theconversation.com/r0-how-scientists-quantify-the-intensity-of-an-outbreak-like-coronavirus-and-predict-the-pandemics-spread-130777

Measles

Assumption:
Generation time: = *10 days, R0 = 12*



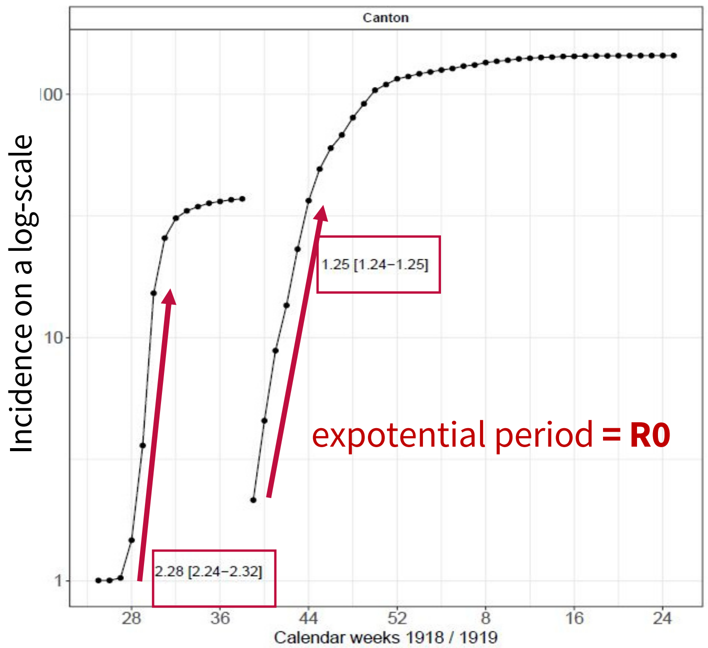


Every 2.73 days, the figures are doubled

Basic (R0) vs effective (Re) reproduction number

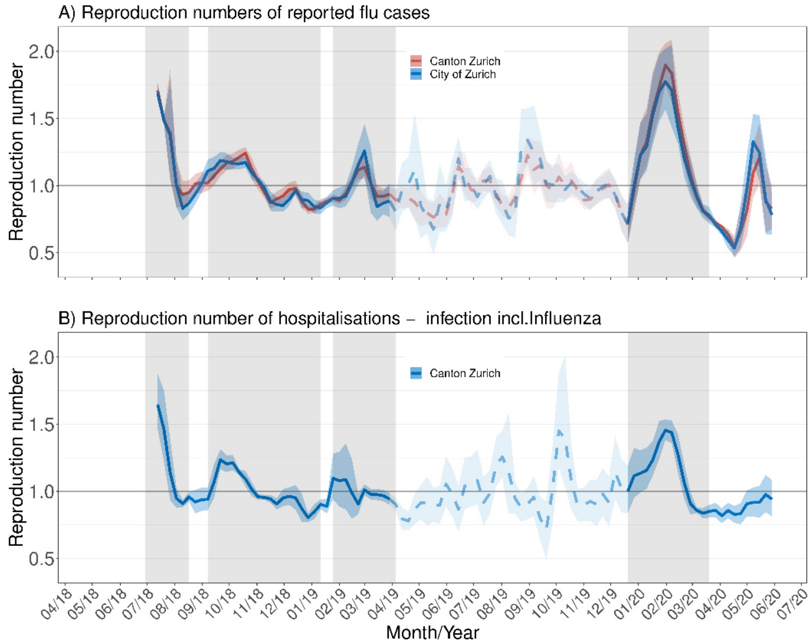
R0 = at start, no immunity, no interventions
Re (also Rt) = changes over time, interventions, immunity

R0 = only the exponential period



Staub, Jüni, Urner, Matthes et al. **Public Health Interventions, Epidemic Growth, and Regional Variation of the 1918 Influenza Pandemic Outbreak in a Swiss Canton and Its Greater Regions**. Ann Intern Med.2021;doi:10.7326/M20-6231

Re over a time period



Ziegler, Matthes, Middelkamp, SchuenemannAlthaus, Staub, **Retrospective modelling of the disease and mortality burden of the 1918–1920 influenza pandemic in Zurich, Switzerland**, Epidemics, 2025,https://doi.org/10.1016/j.epidem.2025.100813.

How and why to use with historical death data?

- Excess mortality to estimate R
- Cause-specific deaths to estimate R
- Often no morbidity data and if not reliable or underestimated
- Undestand transmissibility of past epidemics
- Quantify effectiveness of interventions
- Differences in region

1918-1919 pandemic in England and Wales using death data

Table 2. Reproduction number (R) estimates for the autumn and winter 1918–1919 pandemic waves with 95% CIs for England and Wales, at three different spatial scales and using different assumptions about the generation interval.

	3-day generation interval			6-day generation interval		
	administrative units ($N^a = 305$)	counties ($N^a = 62$)	national ($N^a = 1$)	administrative units ($N^a = 305$)	counties ($N^a = 62$)	national ($N^a = 1$)
autumn wave	1.40 (1.38, 1.42)	1.36 (1.33, 1.39)	1.39 (1.36, 1.43)	1.86 (1.82, 1.90)	1.76 (1.69, 1.83)	1.84 (1.75, 1.92)
winter wave	1.35 (1.33, 1.37)	1.33 (1.31, 1.36)	1.39 (1.29, 1.49)	1.74 (1.70, 1.78)	1.71 (1.66, 1.76)	1.82 (1.61, 2.05)

Chowell, Bettencourt, Niall, Alonso and Viboud, **The 1918–1919 influenza pandemic in England and Wales: spatial patterns in transmissibility and mortality impact**, Proc. R. Soc. 2008http://doi.org/10.1098/rspb.2007.1477

1889/90 pandemic in Madrid using death data

Table 2
Mean estimates and the corresponding 95% confidence intervals for the effective reproduction number during the early growth phase of the 1889–1890 influenza pandemic in Madrid, Spain

Estimates	3-Day generation interval	4-Day generation interval
Reproduction number	1.3 (1.2–1.3)	1.4 (1.3–1.5)
Growth rate, r	0.22 (0.12–0.39)	
Deceleration of growth parameter, p	0.90 (0.80–1.0)	

We assumed a generation interval that follows a gamma distribution with a mean of 3 or 4 days and variance of 1.

Ramiro, Garcia, Casado,Cilek, Chowell, **Age-specific excess mortality patterns and transmissibility during the 1889–1890 influenza pandemic in Madrid, Spain**, Annals of Epidemiology,2018, https://doi.org/10.1016/j.annepidem.2017.12.009.

Estimation of reproductive number - intrinsic growth rate

Assumptions: Take it from the literatur

- Mean generation time μ in days for example:
  - Influenza μ = 3 days
  - Measles μ = 10 days
- Standard deviation (sd) σ of the generation time for example:
  - Influenza σ = 1 days
  - Measles σ = 3 days

Model generation time:

- Generation time is gamma distributed:

  shape: $\frac{\mu^2}{\sigma^2}$

  rate: $\frac{\mu}{\sigma^2}$

Model reproduction number: $$R_t = (1 + \frac{r_t}{rate})^{shape}$$

R = reproduction number

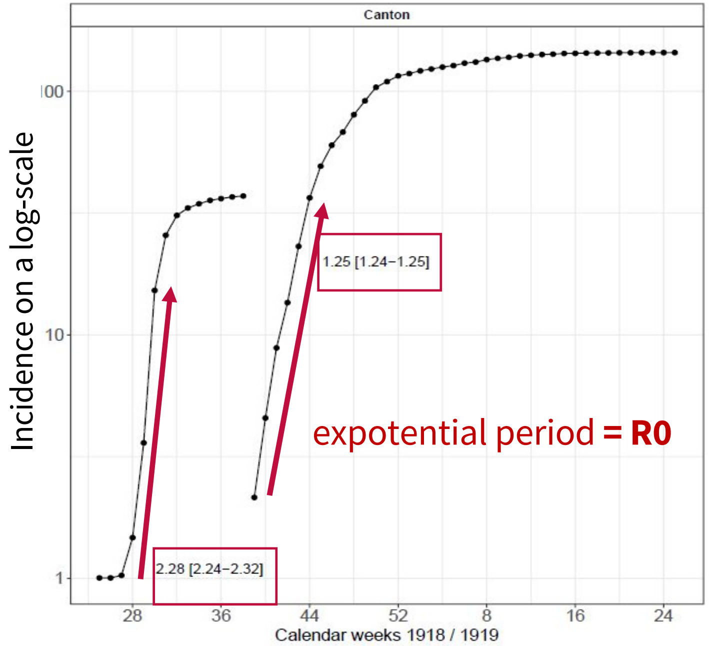
r = growth rate → needs to be modeled, we will use a quasi poisson model (overdispersion)

$$\log(death) \sim \beta_o + r_t$$

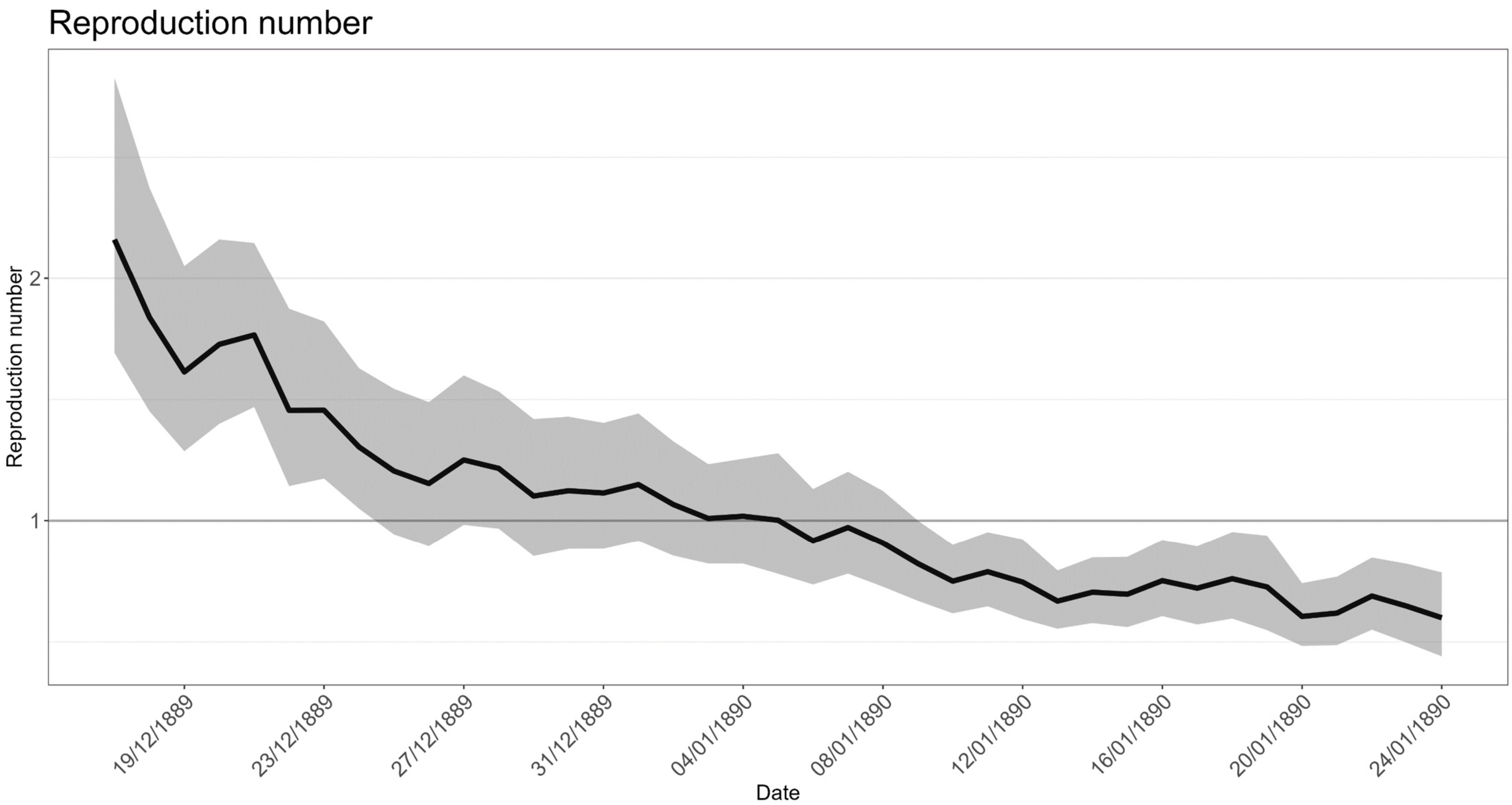
- define how many days should be include in your model to estimate r

R0 = same model

- define longest epidemic period consistent with exponential growth



Estimation of reproductive number - intrinsic growth rate



Let your data speak!

Literature

Excess mortality:

- Wakefield and Knutson (2025), Excess Mortality Estimation, Annu. Rev. Stat. Appl, Vol. 12:45-68 https://doi.org/10.1146/annurev-statistics-112723-034236
- Nepomuceno et al. (2022), Sensitivity Analysis of Excess Mortality due to the COVID-19 Pandemic. Population and Development Review, 48: 279-302. https://doi.org/10.1111/padr.12475
- Schöley (2021), Robustness and bias of European excess death estimates in 2020 under varying model specifications medRxiv 2021.06.04.21258353; https://doi.org/10.1101/2021.06.04.21258353
- Shkolnikov et al. (2022) What should be the baseline when calculating excess mortality? New approaches suggest that we have underestimated the impact of the COVID-19 pandemic and previous winter peaks ,SSM - Population Health Volume 18,101118, https://doi.org/10.1016/j.ssmph.2022.101118

Spatial Exess mortality in a Bayesion framework:

- Konstantinoudis et al. (2023), A framework for estimating and visualising excess mortality during the COVID-19 pandemic. ArXiv [Preprint]. https://doi.org/10.48550/arXiv.2201.06458

Reproduction number:

- Wallinga Lipsitch (2007), How generation intervals shape the relationship between growth rates and reproductive numbers*Proc. R. Soc. B.*274599–604, http://doi.org/10.1098/rspb.2006.3754