Markus Müller :: CMT/LSM :: Paul Scherrer Institut

Random Testing for a safe exit from the COVID19 lockdown

LSM Seminar, Paul Scherrer Institute, May 7 2020

Collaborators

Peter Derlet (PSI, EPF Lausanne, ETH Zürich)

Christopher Mudry (PSI, EPF Lausanne)

Gabriel Aeppli (PSI, EPF Lausanne, ETH Zürich)

Using random testing in a feedback-control loop to manage a safe exit from the COVID-19 lockdown

Online preprints:	arXiv:2004.04614
	https://www.medrxiv.org/content/10.1101/2020.04.09.20059360v2

Collaborators

Peter Derlet (PSI, EPF Lausanne, ETH Zürich)

Christopher Mudry (PSI, EPF Lausanne)

Gabriel Aeppli (PSI, EPF Lausanne, ETH Zürich)

Using random testing in a feedback-control loop to manage a safe exit from the COVID-19 lockdown

Online preprints: arXiv:2004.04614
https://www.medrxiv.org/content/10.1101/2020.04.09.20059360v2

A simple theoretical physicists' approach

To show how statistical, random sampling can save live and costs

Collaborators

Peter Derlet (PSI, EPF Lausanne, ETH Zürich)

Christopher Mudry (PSI, EPF Lausanne)

Gabriel Aeppli (PSI, EPF Lausanne, ETH Zürich)

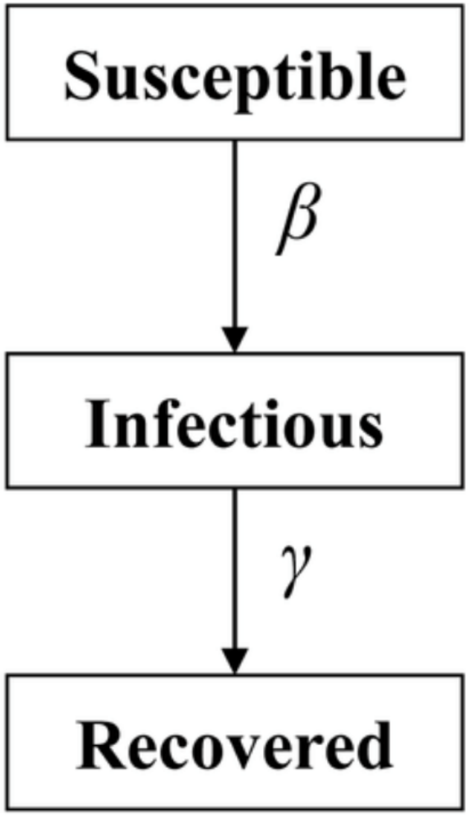
Using random testing in a feedback-control loop to manage a safe exit from the COVID-19 lockdown

Please ask questions during the talk!

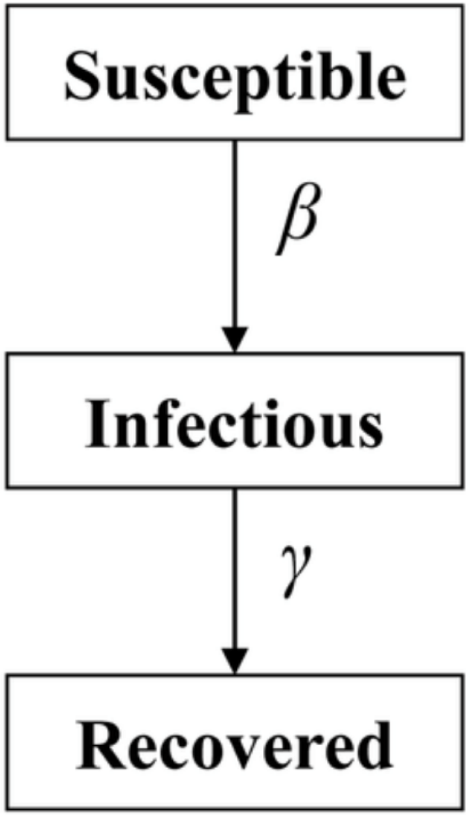
Fragen während des Vortrags sind willkommen!

Questions bienvenues pendant l’exposé!

Simplest epidemiologic model:
Global SIR model - Susceptible-infected-recovered



Simplest epidemiologic model: Global SIR model - Susceptible-infected-recovered

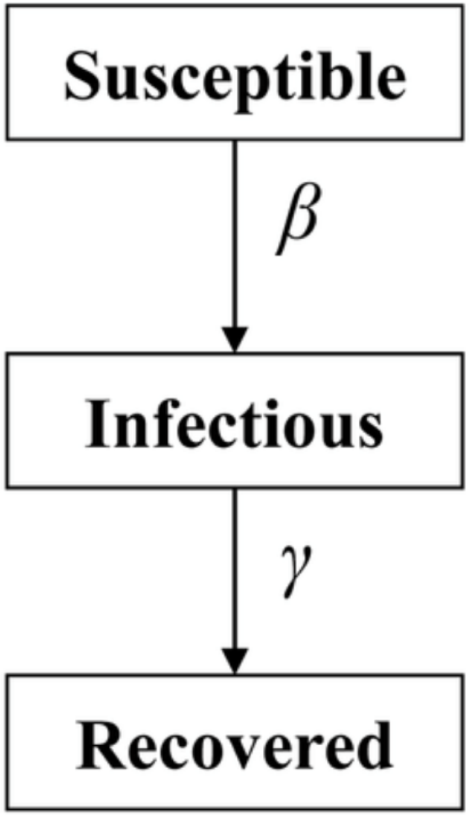


$$\frac{dS}{dt} = -\beta SI$$

$$\frac{dI}{dt} = \beta SI - \gamma I$$

$$\frac{dR}{dt} = \gamma I$$

Simplest epidemiologic model:
Global SIR model - Susceptible-infected-recovered

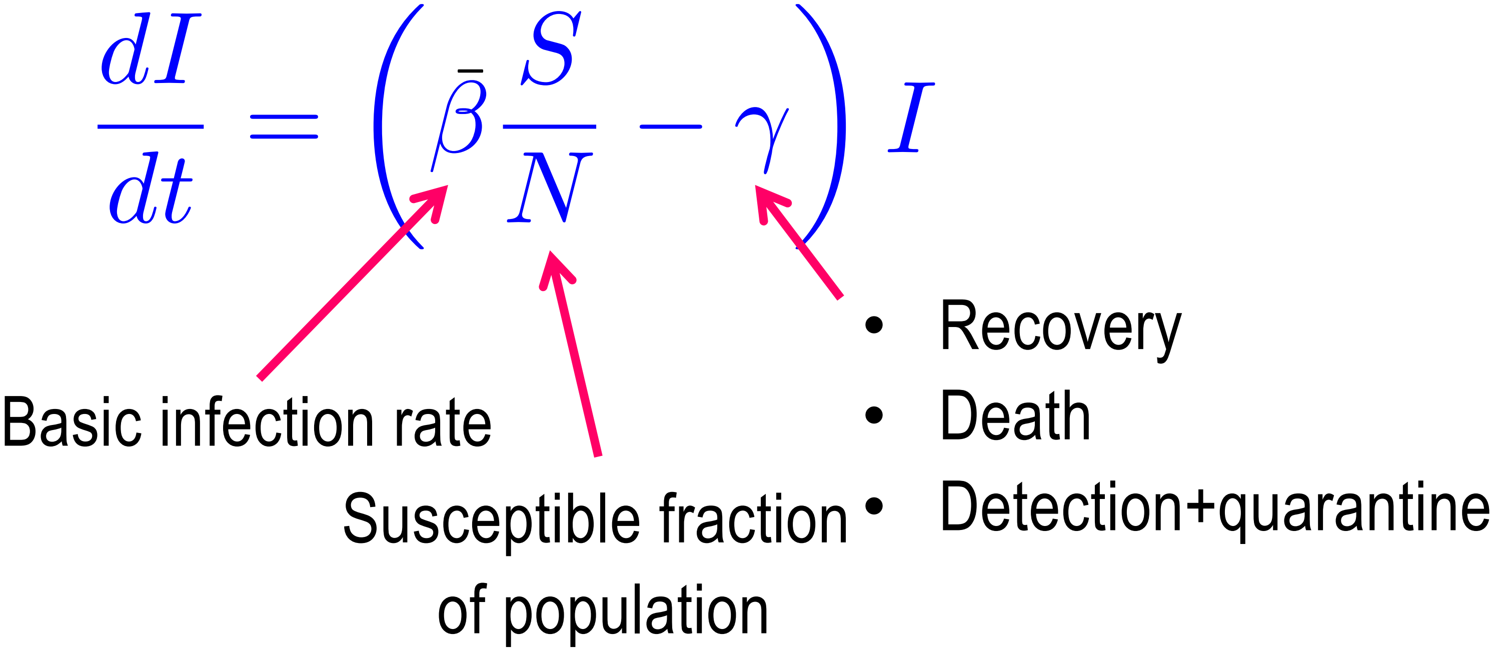


$$\frac{dS}{dt} = -\beta S I$$

$$\boxed{\frac{dI}{dt} = \beta S I - \gamma I}$$

$$\frac{dR}{dt} = \gamma I$$

SIR model (susceptible-infected-recovered)



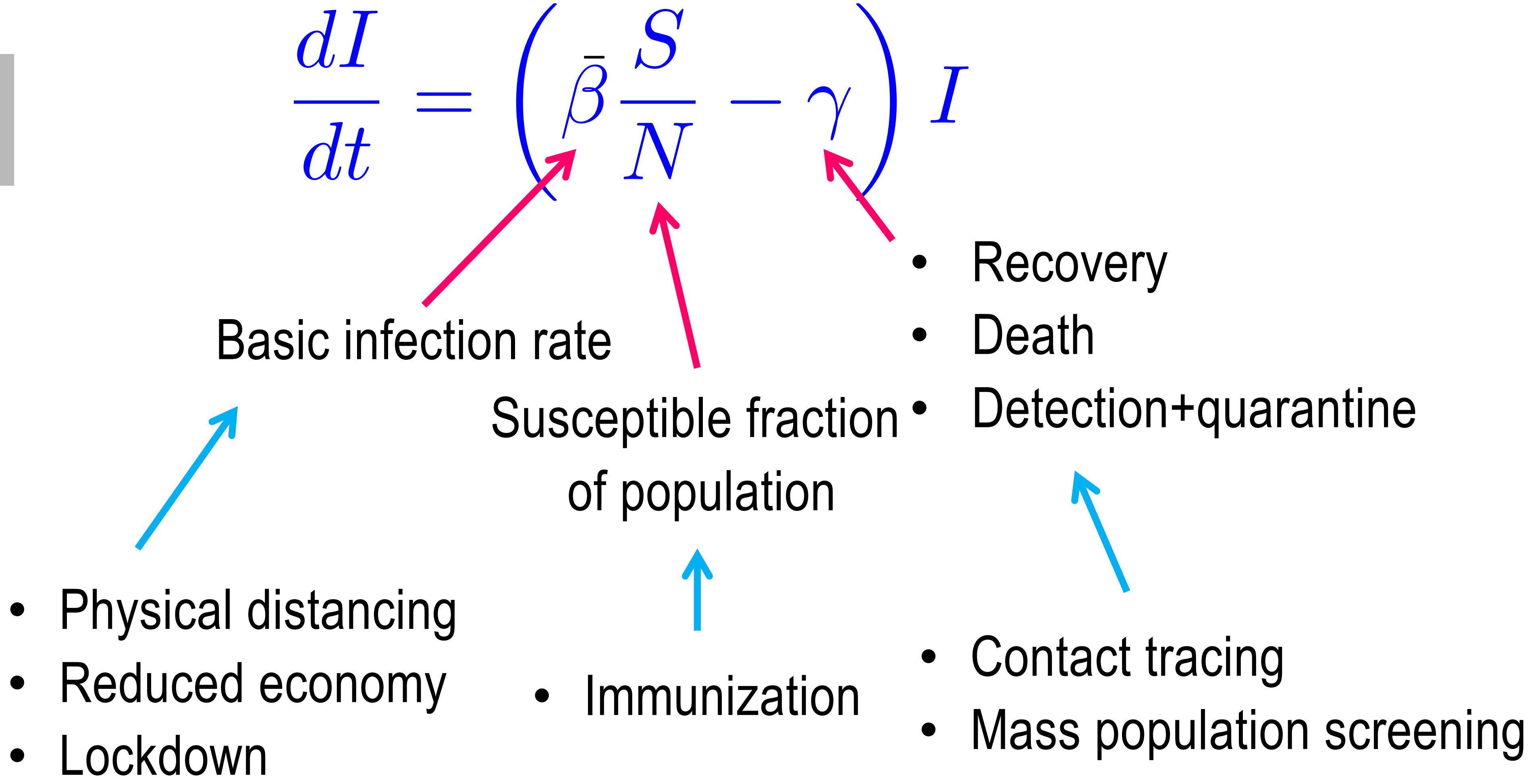
$$\frac{dI}{dt} = \left(\bar{\beta} \frac{S}{N} - \gamma \right) I$$

Basic infection rate

Susceptible fraction
of population

- Recovery
- Death
- Detection+quarantine

SIR model (susceptible-infected-recovered)



$$\frac{dI}{dt} = \left(\bar{\beta} \frac{S}{N} - \gamma \right) I$$

Basic infection rate

Susceptible fraction of population

- Recovery
- Death
- Detection+quarantine

- Physical distancing
- Reduced economy
- Lockdown

- Immunization

- Contact tracing
- Mass population screening

SIR model

$$\frac{dI}{dt} = \underbrace{\left(\bar{\beta}\frac{S}{N} - \gamma\right)}_{k(t)} I$$

Unmitigated growth rate

$$k_0 \equiv \bar{\beta} - \gamma \approx \frac{\ln 2}{3} \approx 0.23$$

Reproduction number

$$R_0 = \frac{\bar{\beta}}{\gamma} = 1 + \frac{k_0}{\gamma} \approx 3$$

$$\gamma^{-1} \approx 10$$

SIR model

$$\frac{dI}{dt} = \underbrace{\left(\bar{\beta}\frac{S}{N} - \gamma\right)}_{k(t)} I$$

Unmitigated growth rate

$$\boxed{k_0 \equiv \bar{\beta} - \gamma \approx \frac{\ln 2}{3} \approx 0.23}$$

Reproduction number $R_0 = \frac{\bar{\beta}}{\gamma} = 1 + \frac{k_0}{\gamma} \approx 3$

$\gamma^{-1} \approx 10$

Exponential explosion: $k > 0\,;\ R > 1$

SIR model

$$\frac{dI}{dt} = \underbrace{\left(\bar{\beta}\,\frac{S}{N} - \gamma\right)}_{k(t)} I$$

Unmitigated growth rate $k_0 \equiv \bar{\beta} - \gamma \approx \frac{\ln 2}{3} \approx 0.23$

Reproduction number $R_0 = \frac{\bar{\beta}}{\gamma} = 1 + \frac{k_0}{\gamma} \approx 3$

$\gamma^{-1} \approx 10$

Exponential decrease: $k < 0\,;\ R < 1$

SIR model

$$\frac{dI}{dt} = \underbrace{\left(\bar{\beta}\frac{S}{N} - \gamma\right)}_{k(t)} I$$

Unmitigated growth rate

$$k_0 \equiv \bar{\beta} - \gamma \approx \frac{\ln 2}{3} \approx 0.23$$

Reproduction number $$R_0 = \frac{\bar{\beta}}{\gamma} = 1 + \frac{k_0}{\gamma} \approx 3$$

$\gamma^{-1} \approx 10$

Stability (with least restrictions): $$\boxed{k = 0\,;\; R = 1}$$

Different ways of testing

0. Diagnostic use: patients, medical staff

Different ways of testing

1. Suppressing $k(t)$

Ferretti et al Science, March 2020

- Contact tracing (BUT: asymptomatic spread is dangerous!)
- Massive screening of entire population

2. Monitoring $k(t)$

- Measure k(t) via random sampling
- → Assess policies with minimal delay
- → Feedback and control loop to reach optimal steady state:

$$\boxed{k = 0\,;\ R = 1}$$

Different ways of testing

1. Suppressing $k(t)$

Ferretti et al Science, March 2020

- Contact tracing (BUT: asymptomatic spread is dangerous!)
- Massive screening of entire population

2. Monitoring $k(t)$

- Measure k(t) via random sampling
- → Assess policies with minimal delay
- → Feedback and control loop to reach optimal steady state:

$$\boxed{k = 0\,;\; R = 1}$$

Always use both approaches: (2) monitors the success of (1) !

Different ways of testing

1. Suppressing $k(t)$

- Contact tracing (BUT: asymptomatic spread is dangerous!)
- Massive screening of entire population

2. Monitoring $k(t)$

- Measure k(t) via random sampling
- → Assess policies with minimal delay
- → Feedback and control loop to reach optimal steady state:

$$\boxed{k = 0\,;\; R = 1}$$

Always use both approaches: (2) monitors the success of (1) !

Massive testing

Goal: Identify and quarantine infected households within a serial time → $R < 1\, ;\, k < 0$

Test every household once per 6 days!

$$N_{\text{test}} = \frac{N_{\text{Household}}}{6} \text{ daily, i.e. } \begin{array}{r} 22.000.000 \text{ (USA)} \\ 700.000 \text{ (CH)} \end{array}$$

!!

Massive testing

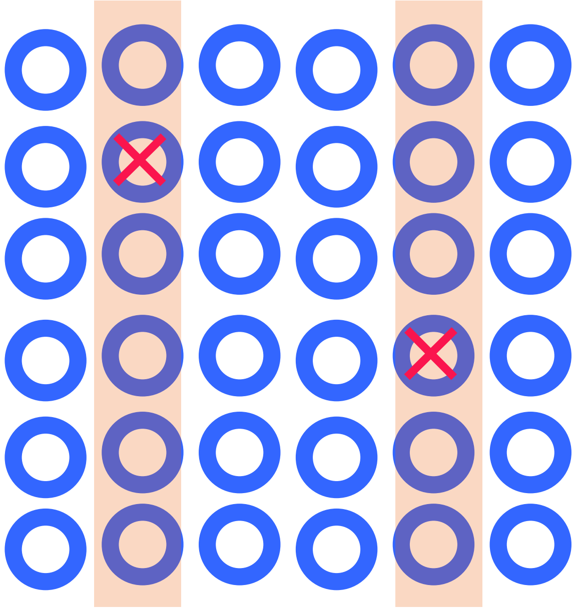
Goal: Identify and quarantine infected households within a serial time → $R < 1\,;\; k < 0$

Test every household once per 6 days!

$$N_{\mathrm{test}} = \frac{N_{\mathrm{Household}}}{6}$$ daily, i.e. $22.000.000$ (USA) 700.000 (CH) !!

How to carry out such large numbers of tests?

Testing large numbers: **Pool testing**



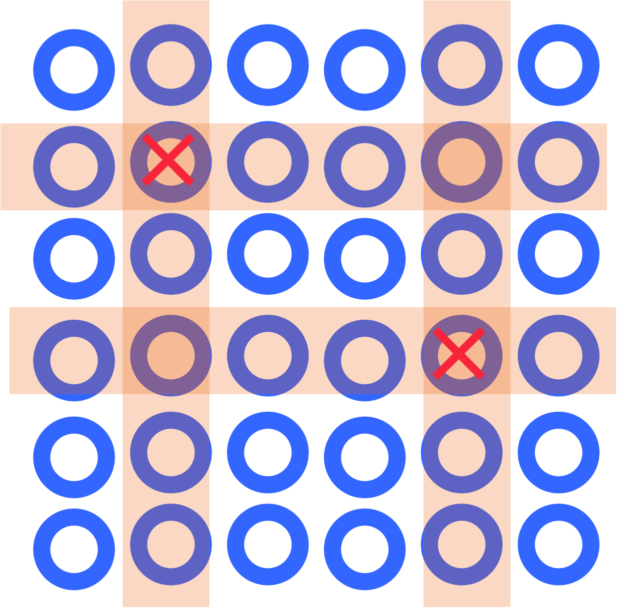
A very old idea

For COVID19, see:

R. Hanel, St. Thurner,

arxive 2003.09944

Testing large numbers: **Pool testing**



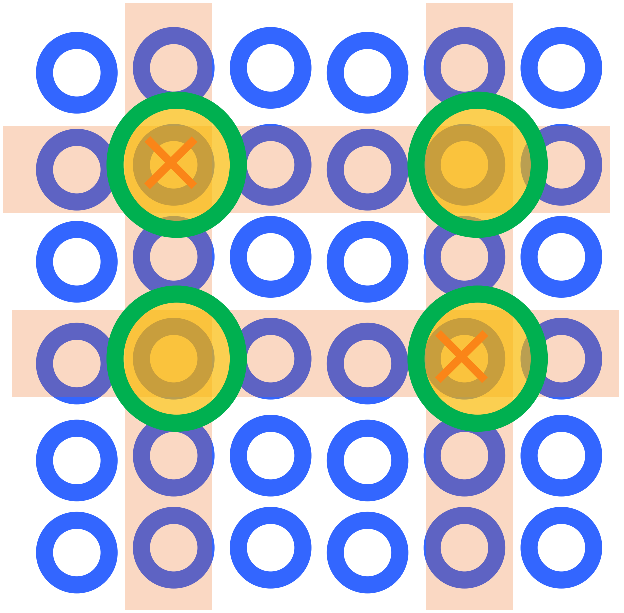
A very old idea

For COVID19, see:

R. Hanel, St. Thurner,

arxive 2003.09944

Testing large numbers: **Pool testing**



A very old idea

For COVID19, see:

R. Hanel, St. Thurner,

arxive 2003.09944

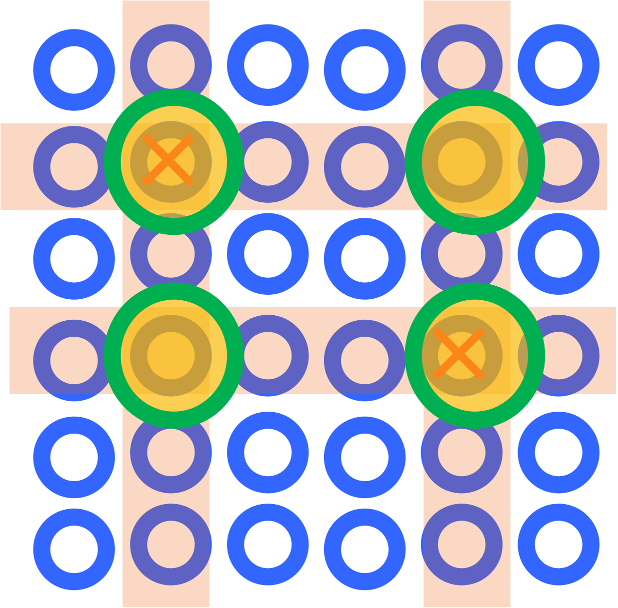
With 8 tests find the infected!

Reduction of required tests by a factor $3i_0^{2/3}$

i_0: Prevalence (infected fraction of population)

$$i_0 = 0.001 \rightarrow \frac{N_{\mathrm{PCR}}}{N_{\mathrm{test}}} = 0.03$$

Testing large numbers: **Pool testing**



Old idea; for COVID19, see:

R. Hanel, St. Thurner,

arxive 2003.09944

With 8 tests find the infected!

Reduction of required tests by a factor $3i_0^{2/3}$

i_0: Prevalence (infected fraction of population)

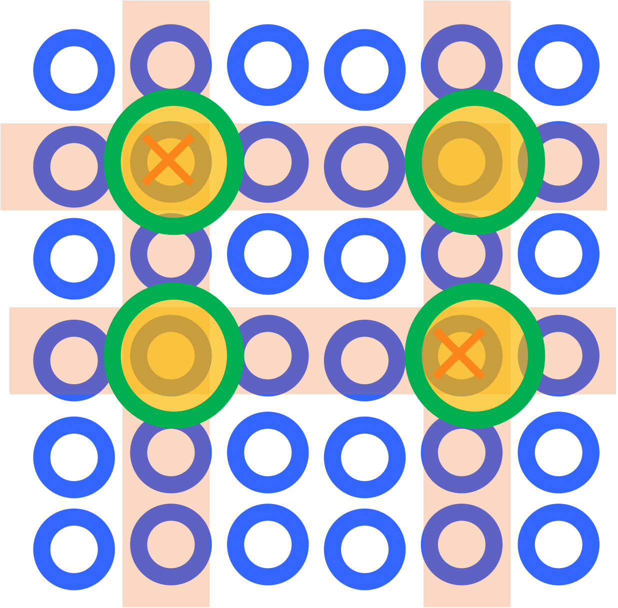
Daily PCR:

660.000 (USA)

20.000 (CH)

$$i_0 = 0.001 \rightarrow \frac{N_{\mathrm{PCR}}}{N_{\mathrm{test}}} = 0.03$$

Testing large numbers: **Pool testing**



More precise analysis / proposal:

Feasibility of COVID-19 Screening for the U.S. Population with Group Testing

P. Frazier et al, April 2020 (Cornell)

Reduction of required tests by a factor $3i_0^{2/3}$

i_0: Prevalence (infected fraction of population)

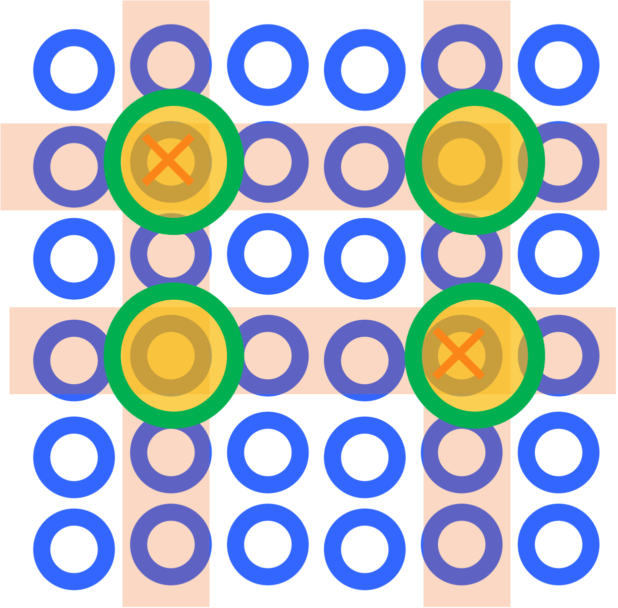
$$i_0 = 0.001 \rightarrow \frac{N_{\text{PCR}}}{N_{\text{test}}} = 0.03$$

Daily PCR:

660.000 (USA)

20.000 (CH)

Testing large numbers: **Pool testing**



BUT:

Pooling COVID19 virus is hard:

So far only pooling of small numbers of tests has worked.

Reduction of required tests by a factor $3i_0^{2/3}$

i_0: Prevalence (infected fraction of population)

$$i_0 = 0.001 \rightarrow \frac{N_{\mathrm{PCR}}}{N_{\mathrm{test}}} = 0.03$$

Daily PCR:

660.000 (USA)

20.000 (CH)

Different ways of testing

1. Suppressing $k(t)$

- Contact tracing (BUT: asymptomatic spread is dangerous!)
- Massive screening of entire population

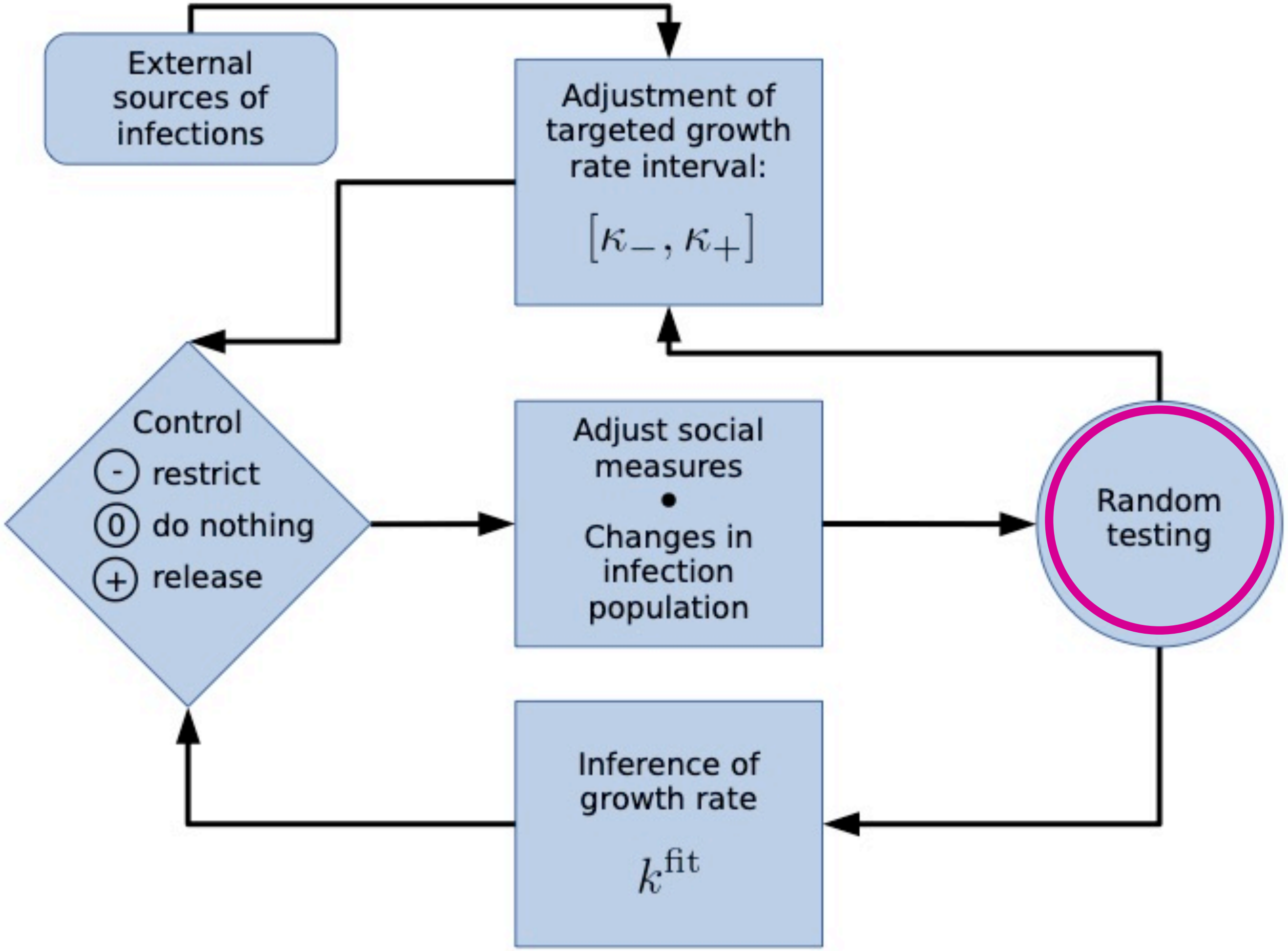
2. Monitoring $k(t)$

- Measure k(t) via random sampling
- → Assess policies with minimal delay
- → Feedback and control loop to reach optimal steady state:

$$\boxed{k = 0\,;\ R = 1}$$

Always use both approaches: (2) monitors the success of (1) !

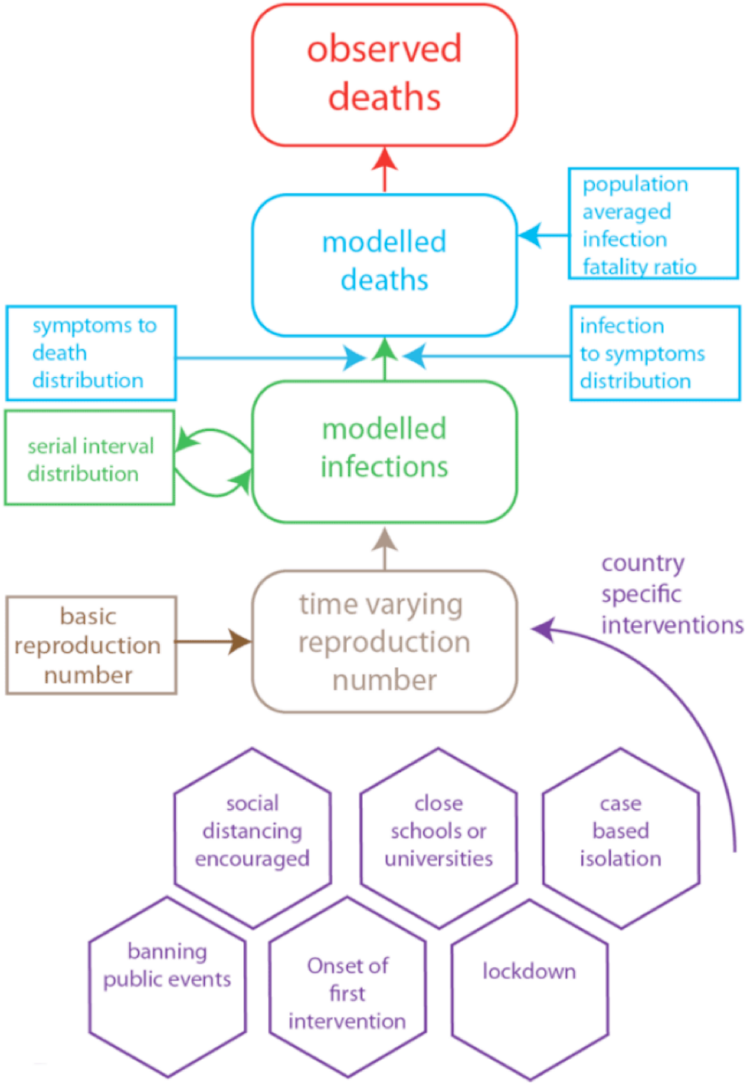
Feedback and control loop -- like a thermometer!



No representative sampling = almost blind flight

Or driving from the back seat with only rear view

Post-diction of infections from death numbers



N. Ferguson et al, Imperial College Covid19 Report No.13

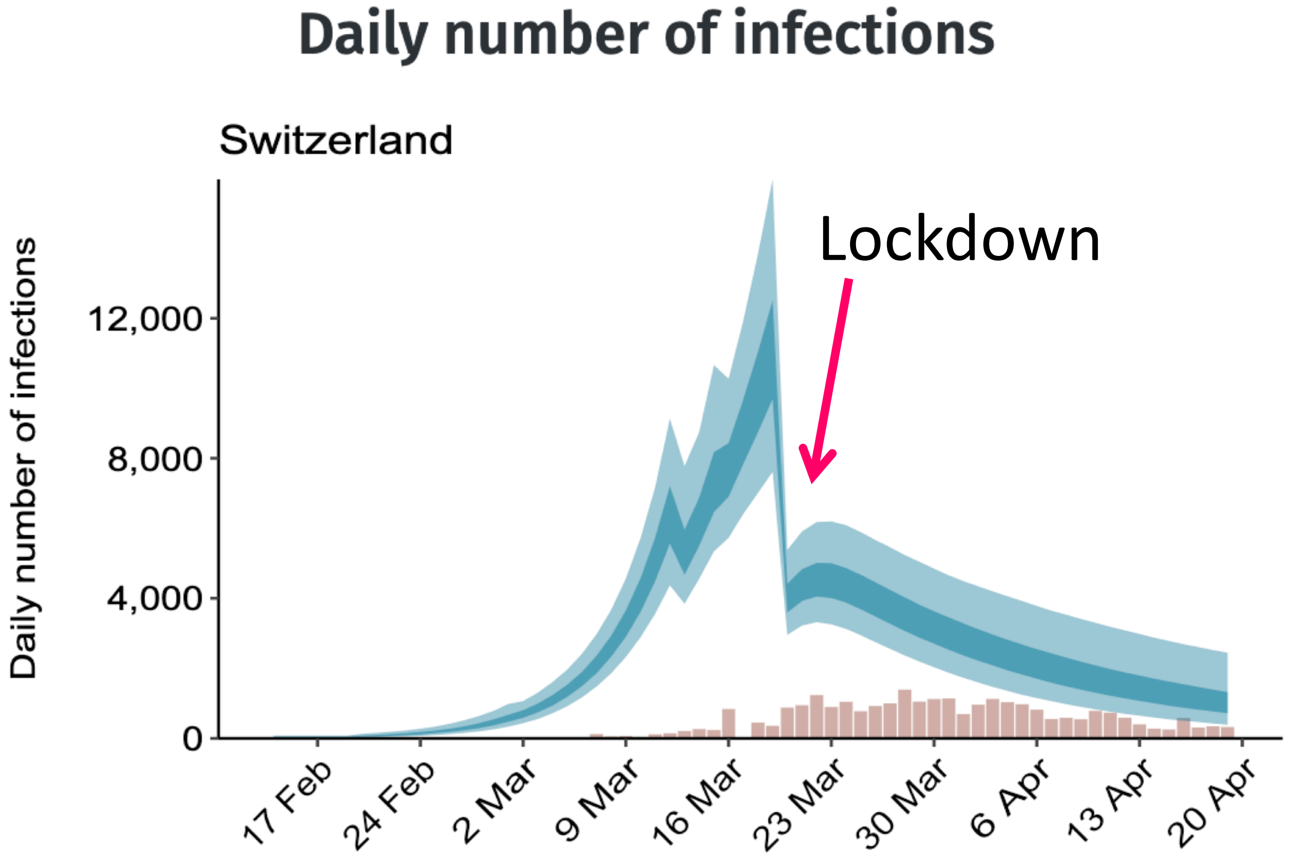
Many groups in Switzerland use similar modelling

https://mrc-ide.github.io/covid19estimates/#/

Post-diction of infections from death numbers

N. Ferguson et al, Imperial College

Covid19 Report No.13



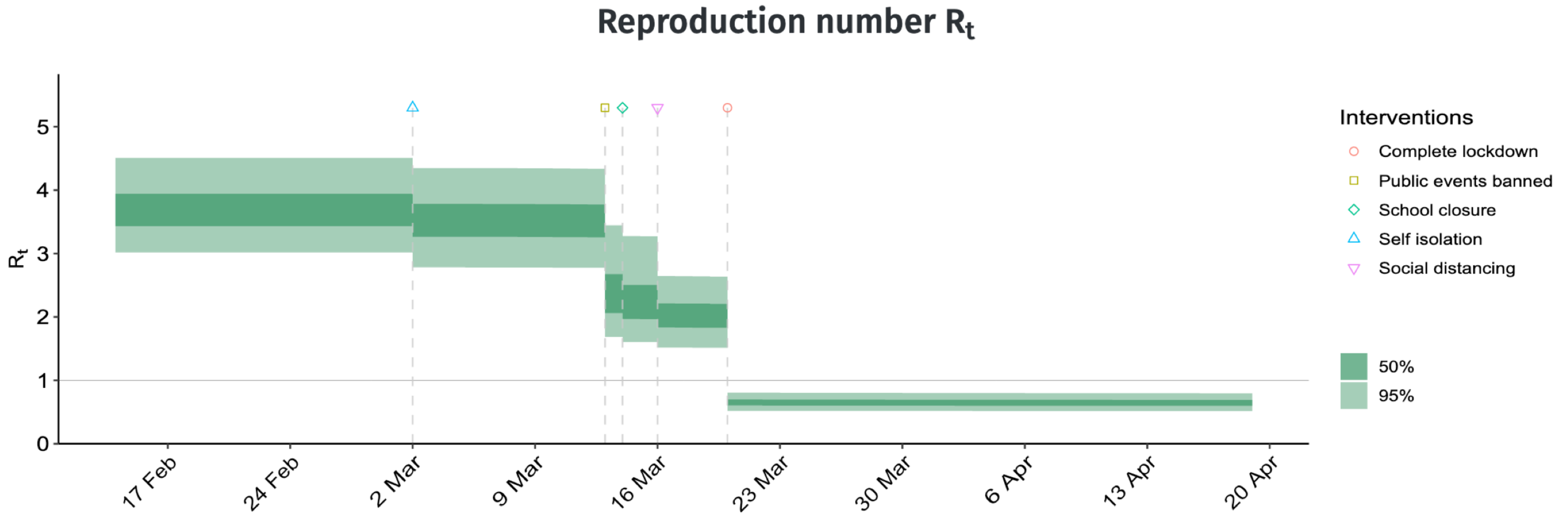
Lockdown

Daily number of infections, brown bars are reported infections, blue bands are predicted infections, dark blue 50% credible interval (CI), light blue 95% CI.

Post-diction of infections from death numbers

N. Ferguson et al, Imperial College

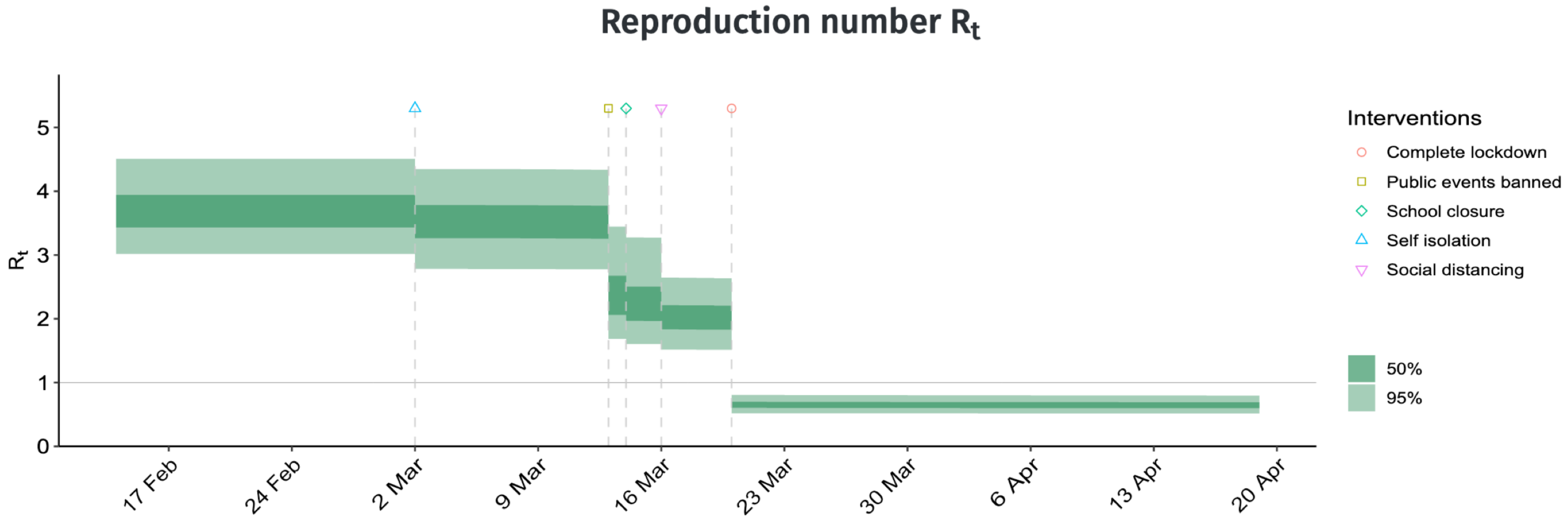
Covid19 Report No.13



Time-varying reproduction number R_t, dark green 50% CI, light green 95% CI. Icons are interventions shown at the time they occurred.

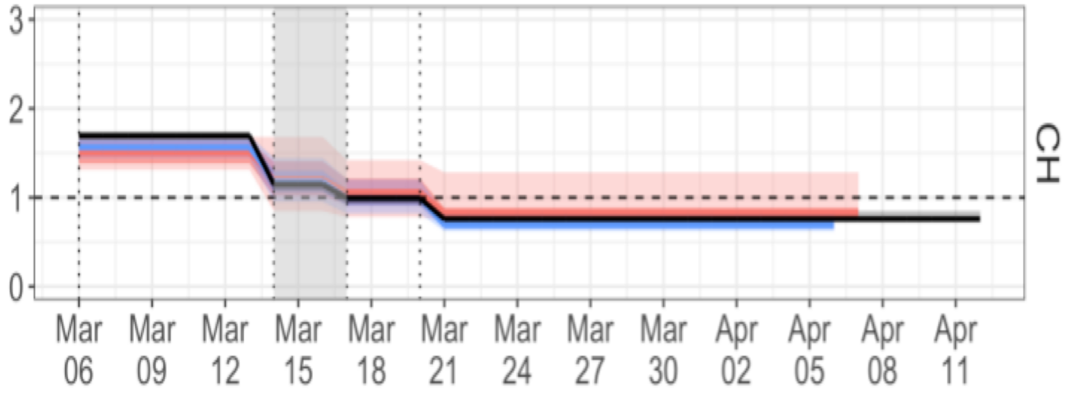
Post-diction of infections from death numbers

N. Ferguson et al, Imperial College
Covid19 Report No.13


Reproduction number R_t

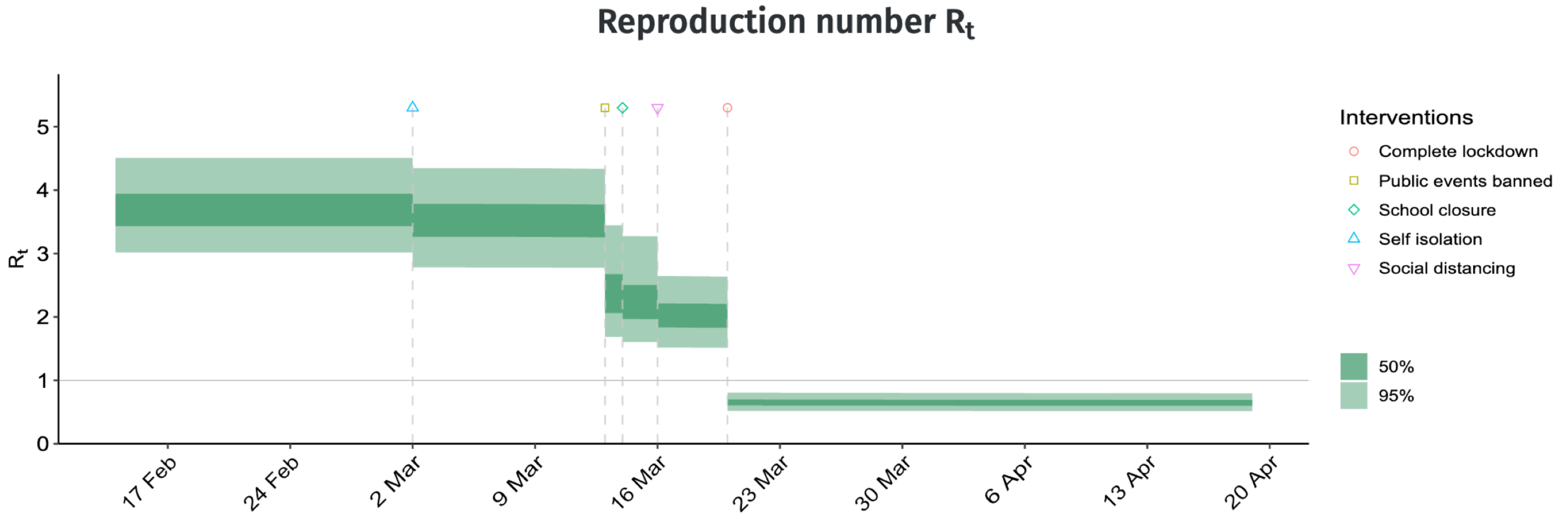
Time-varying reproduction number R_t, dark green 50% CI, light green 95% CI. Icons are interventions shown at the time they occurred.

T. Stadler, ETH
Monitoring COVID-19
Spread in Switzerland



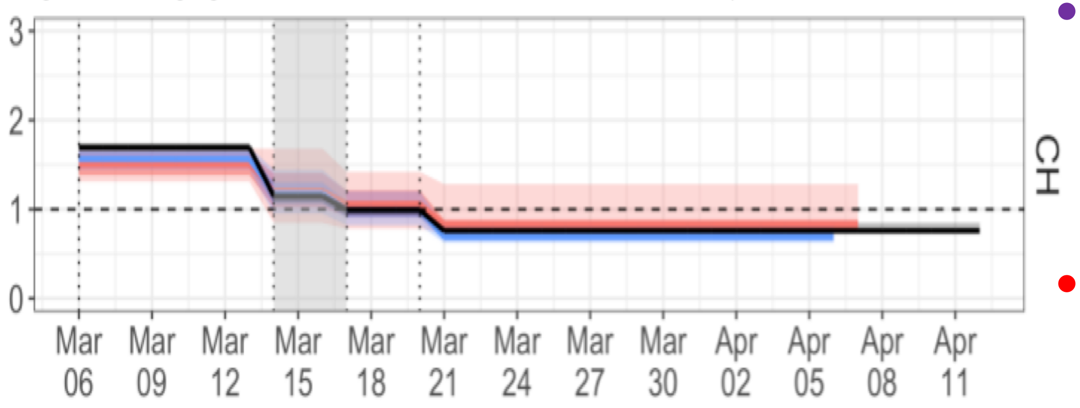
Post-diction of infections from death numbers

N. Ferguson et al, Imperial College
Covid19 Report No.13



Time-varying reproduction number R_t, dark green 50% CI, light green 95% CI. Icons are interventions shown at the time they occurred.

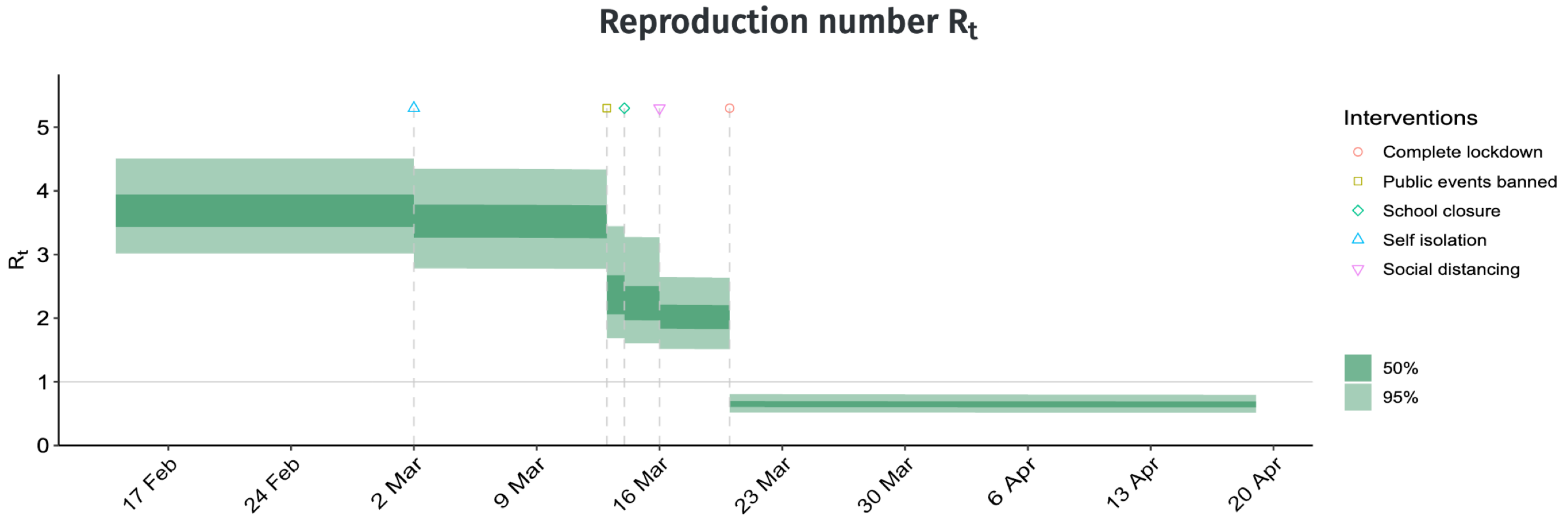
T. Stadler, ETH
Monitoring COVID-19
Spread in Switzerland



- Model-dependent results!
- **~ 14 day delay**

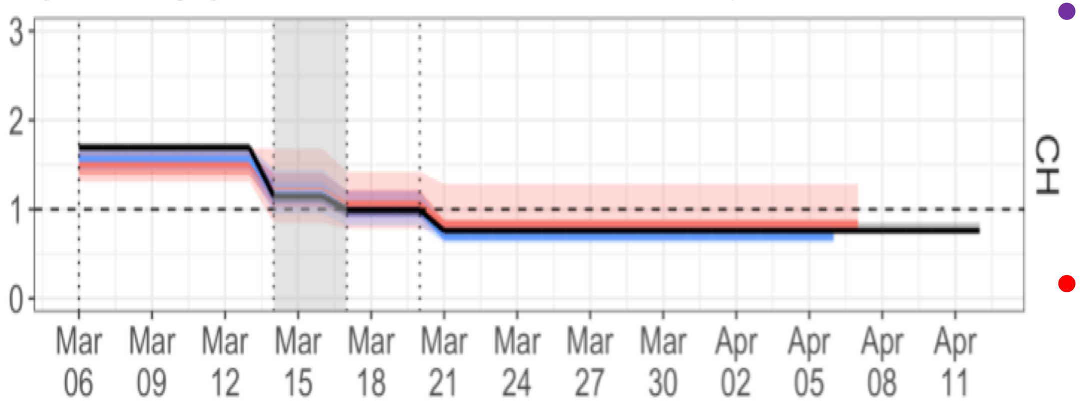
Post-diction of infections from death numbers

N. Ferguson et al, Imperial College
Covid19 Report No.13



Time-varying reproduction number R_t, dark green 50% CI, light green 95% CI. Icons are interventions shown at the time they occurred.

T. Stadler, ETH
Monitoring COVID-19
Spread in Switzerland

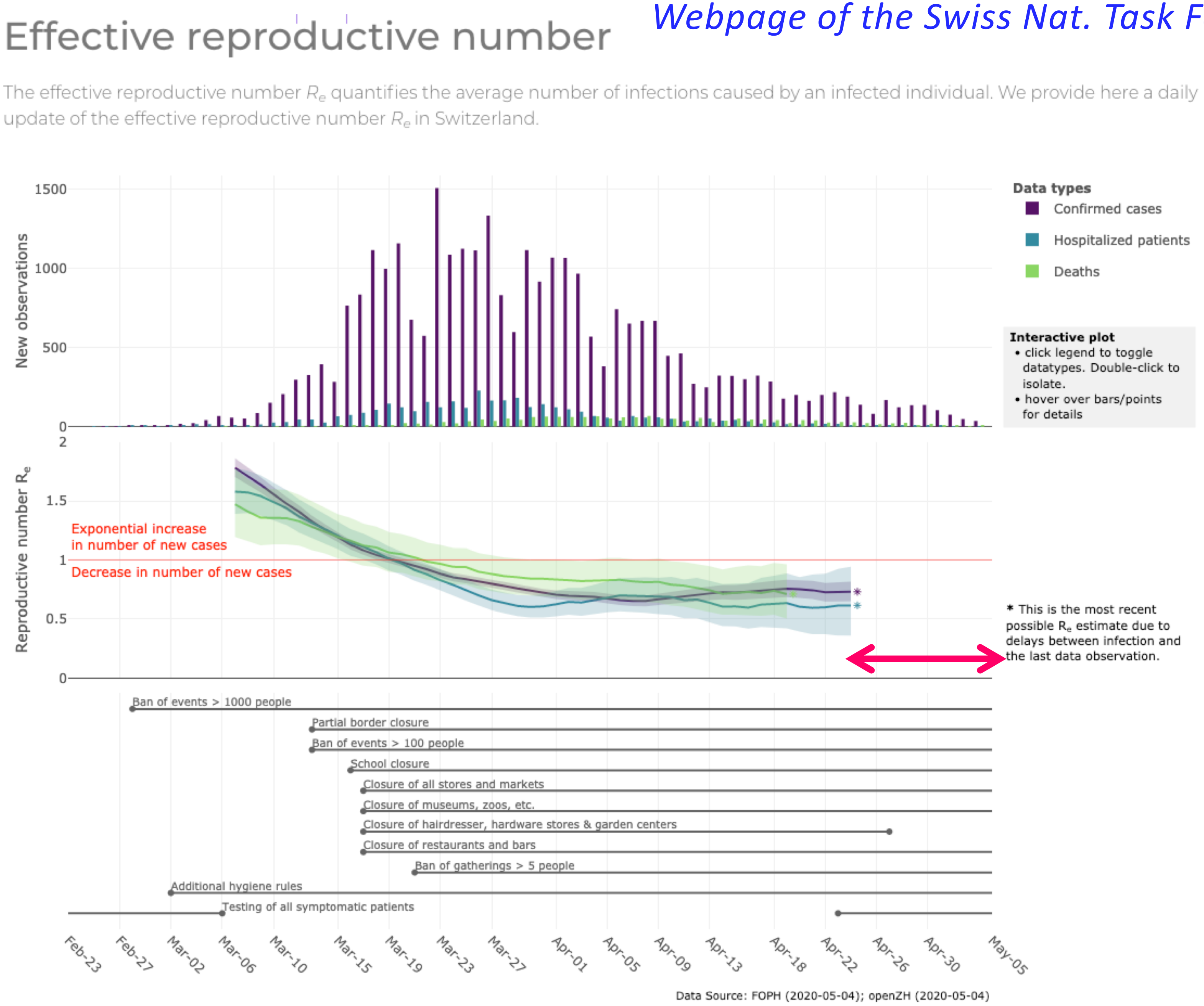


- Model-dependent results!
- **~ 14 day delay**

Undetected doubling in 3 days results in 10-30 times increase of prevalence!

Measuring the reproduction number: Status quo

Webpage of the Swiss Nat. Task Force



Effective reproductive number

The effective reproductive number R_e quantifies the average number of infections caused by an infected individual. We provide here a daily update of the effective reproductive number R_e in Switzerland.

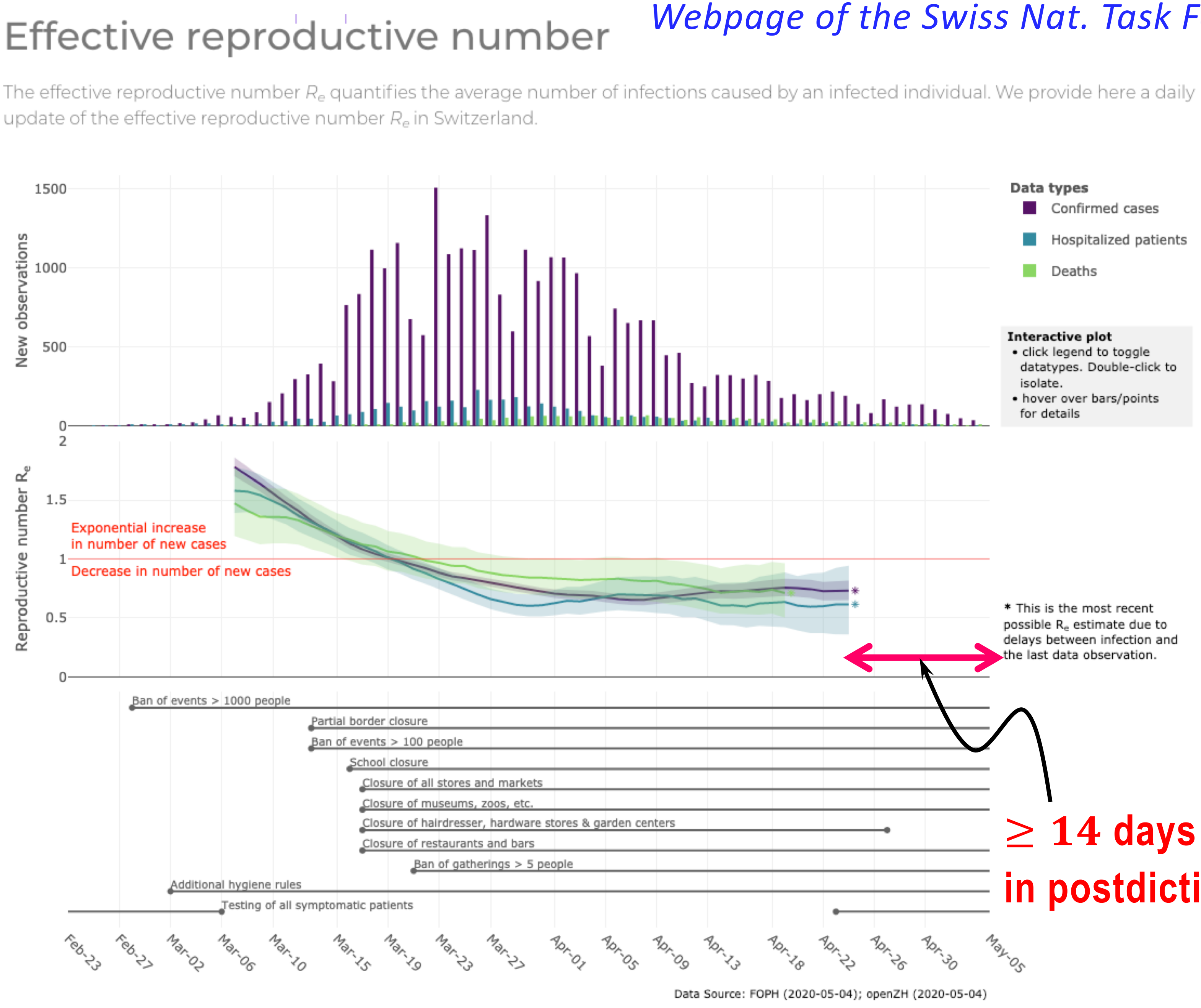
Interactive plot
- click legend to toggle datatypes. Double-click to isolate.
- hover over bars/points for details

* This is the most recent possible R_e estimate due to delays between infection and the last data observation.

Data Source: FOPH (2020-05-04); openZH (2020-05-04)

Measuring the reproduction number: Status quo

Webpage of the Swiss Nat. Task Force



Effective reproductive number

The effective reproductive number R_e quantifies the average number of infections caused by an infected individual. We provide here a daily update of the effective reproductive number R_e in Switzerland.

Interactive plot
- click legend to toggle datatypes. Double-click to isolate.
- hover over bars/points for details

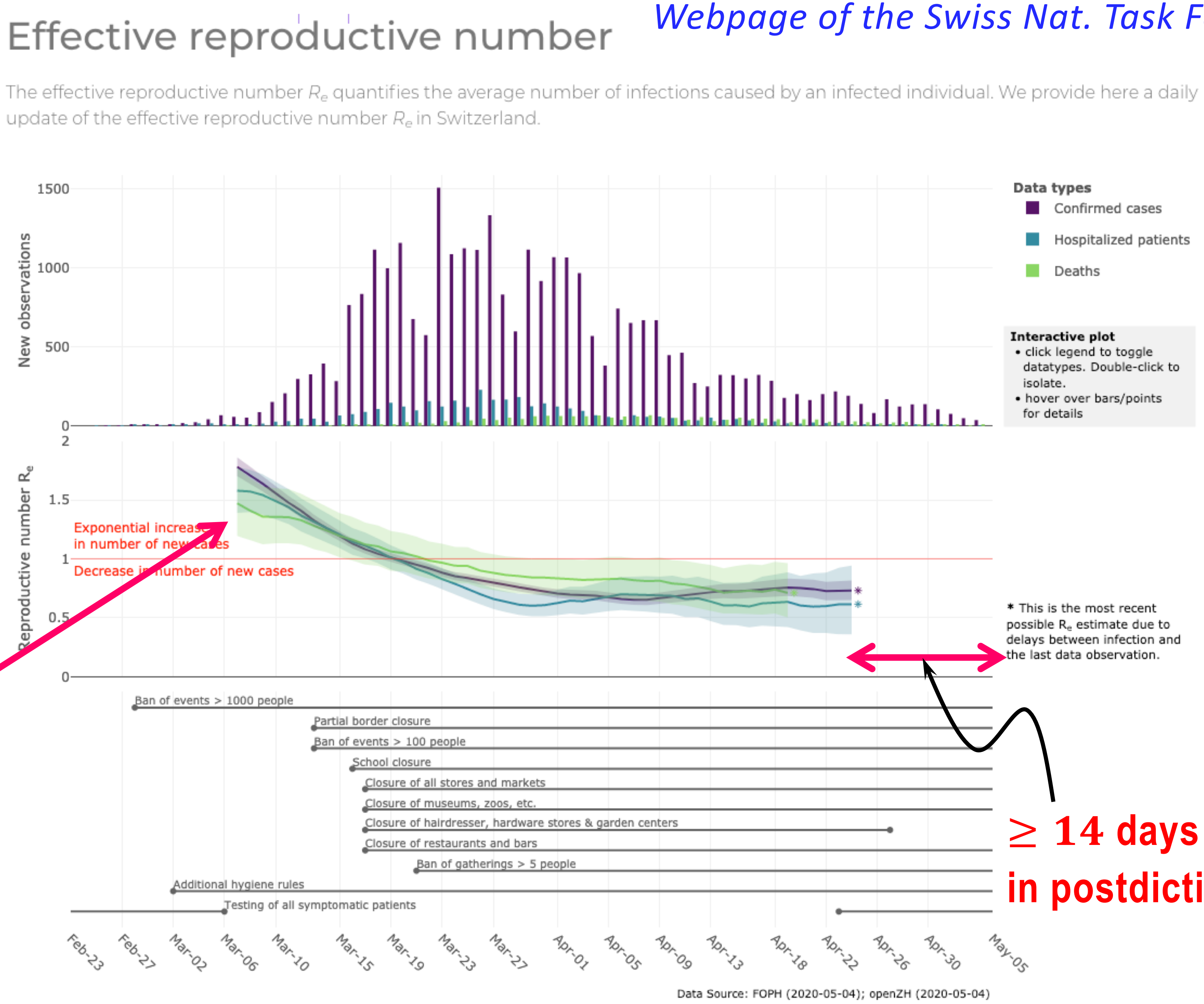
* This is the most recent possible R_e estimate due to delays between infection and the last data observation.

Data Source: FOPH (2020-05-04); openZH (2020-05-04)

≥ 14 days delay in postdiction!

Measuring the reproduction number: Status quo

Webpage of the Swiss Nat. Task Force



Effective reproductive number

The effective reproductive number R_e quantifies the average number of infections caused by an infected individual. We provide here a daily update of the effective reproductive number R_e in Switzerland.

Interactive plot

- click legend to toggle datatypes. Double-click to isolate.
- hover over bars/points for details

* This is the most recent possible R_e estimate due to delays between infection and the last data observation.

Data Source: FOPH (2020-05-04); openZH (2020-05-04)

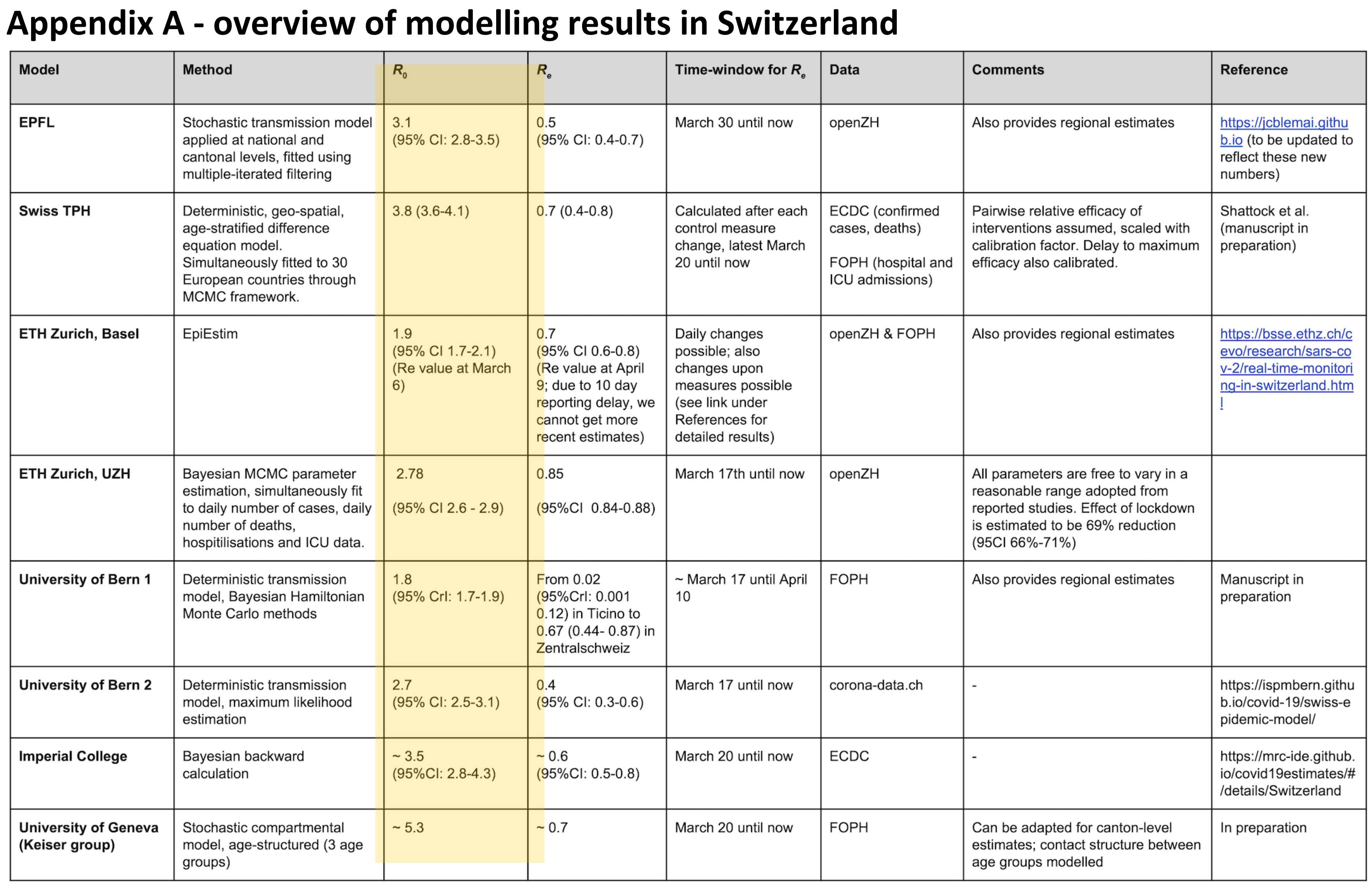
1.Depends on model / fit

2. Large uncertainty due to small numbers

$\geq$ **14 days delay in postdiction!**

Variability of models and confidence intervals

Report of the Swiss Nat. Task Force



Appendix A - overview of modelling results in Switzerland

Model	Method	R_0	R_e	Time-window for R_e	Data	Comments	Reference
EPFL	Stochastic transmission model applied at national and cantonal levels, fitted using multiple-iterated filtering	3.1 (95% CI: 2.8-3.5)	0.5 (95% CI: 0.4-0.7)	March 30 until now	openZH	Also provides regional estimates	https://jcblemai.github.io (to be updated to reflect these new numbers)
Swiss TPH	Deterministic, geo-spatial, age-stratified difference equation model. Simultaneously fitted to 30 European countries through MCMC framework.	3.8 (3.6-4.1)	0.7 (0.4-0.8)	Calculated after each control measure change, latest March 20 until now	ECDC (confirmed cases, deaths) FOPH (hospital and ICU admissions)	Pairwise relative efficacy of interventions assumed, scaled with calibration factor. Delay to maximum efficacy also calibrated.	Shattock et al. (manuscript in preparation)
ETH Zurich, Basel	EpiEstim	1.9 (95% CI 1.7-2.1) (Re value at March 6)	0.7 (95% CI 0.6-0.8) (Re value at April 9; due to 10 day reporting delay, we cannot get more recent estimates)	Daily changes possible; also changes upon measures possible (see link under References for detailed results)	openZH & FOPH	Also provides regional estimates	https://bsse.ethz.ch/cevo/research/sars-cov-2/real-time-monitoring-in-switzerland.html
ETH Zurich, UZH	Bayesian MCMC parameter estimation, simultaneously fit to daily number of cases, daily number of deaths, hospitilisations and ICU data.	2.78 (95% CI 2.6 - 2.9)	0.85 (95%CI 0.84-0.88)	March 17th until now	openZH	All parameters are free to vary in a reasonable range adopted from reported studies. Effect of lockdown is estimated to be 69% reduction (95CI 66%-71%)	
University of Bern 1	Deterministic transmission model, Bayesian Hamiltonian Monte Carlo methods	1.8 (95% CrI: 1.7-1.9)	From 0.02 (95%CrI: 0.001 0.12) in Ticino to 0.67 (0.44- 0.87) in Zentralschweiz	~ March 17 until April 10	FOPH	Also provides regional estimates	Manuscript in preparation
University of Bern 2	Deterministic transmission model, maximum likelihood estimation	2.7 (95% CI: 2.5-3.1)	0.4 (95% CI: 0.3-0.6)	March 17 until now	corona-data.ch	-	https://ispmbern.github.io/covid-19/swiss-epidemic-model/
Imperial College	Bayesian backward calculation	~ 3.5 (95%CI: 2.8-4.3)	~ 0.6 (95%CI: 0.5-0.8)	March 20 until now	ECDC	-	https://mrc-ide.github.io/covid19estimates/#/details/Switzerland
University of Geneva (Keiser group)	Stochastic compartmental model, age-structured (3 age groups)	~ 5.3	~ 0.7	March 20 until now	FOPH	Can be adapted for canton-level estimates; contact structure between age groups modelled	In preparation

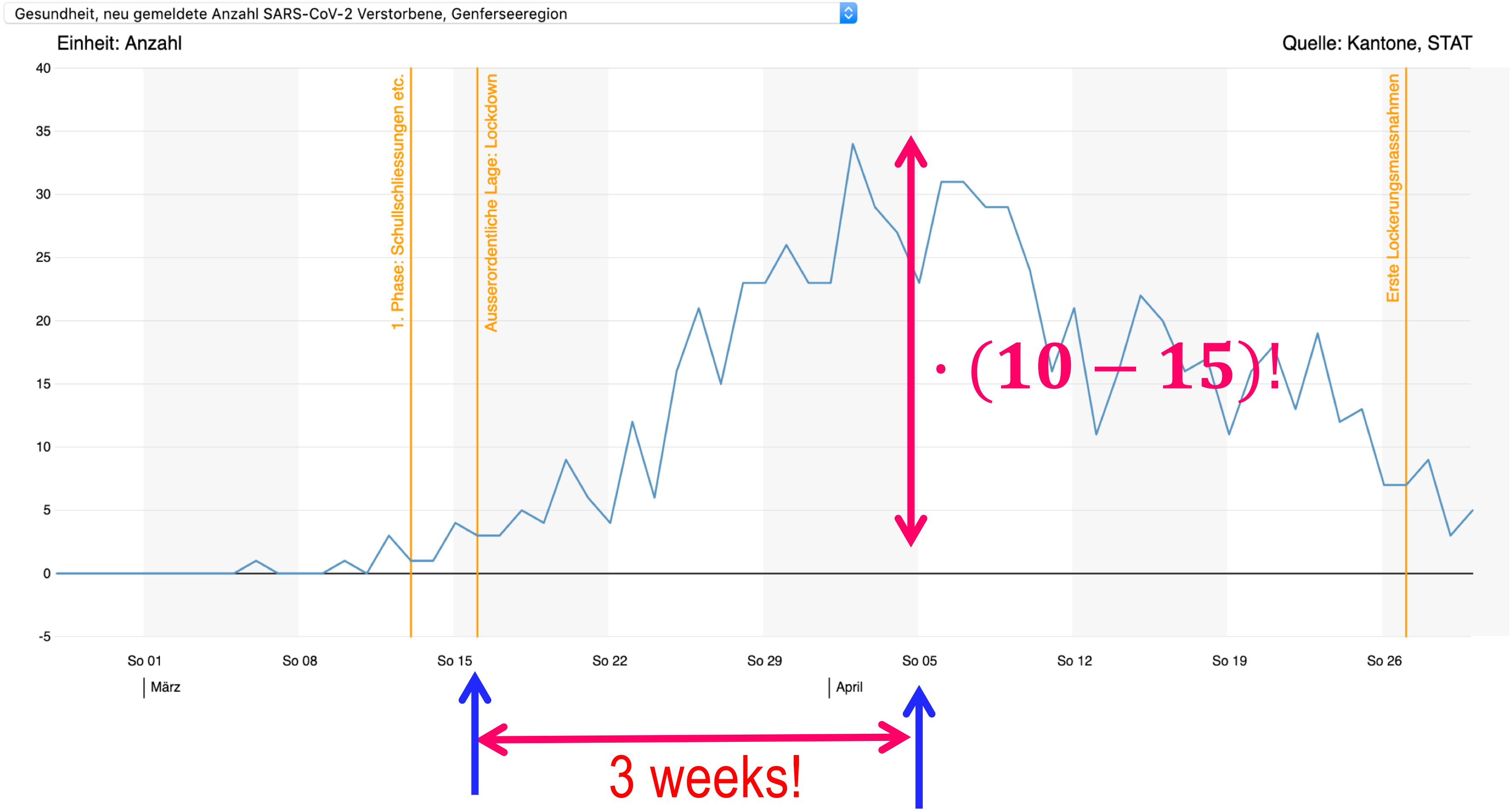
Confidence intervals of different models do not overlap!

Can we do better?

- Avoid 14 days delay
- Remove modelling uncertainty

?

Delay in death numbers (Geneva)



Gesundheit, neu gemeldete Anzahl SARS-CoV-2 Verstorbene, Genferseeregion

Einheit: Anzahl

Quelle: Kantone, STAT

$\cdot\ (10-15)!$

3 weeks!

Lockdown

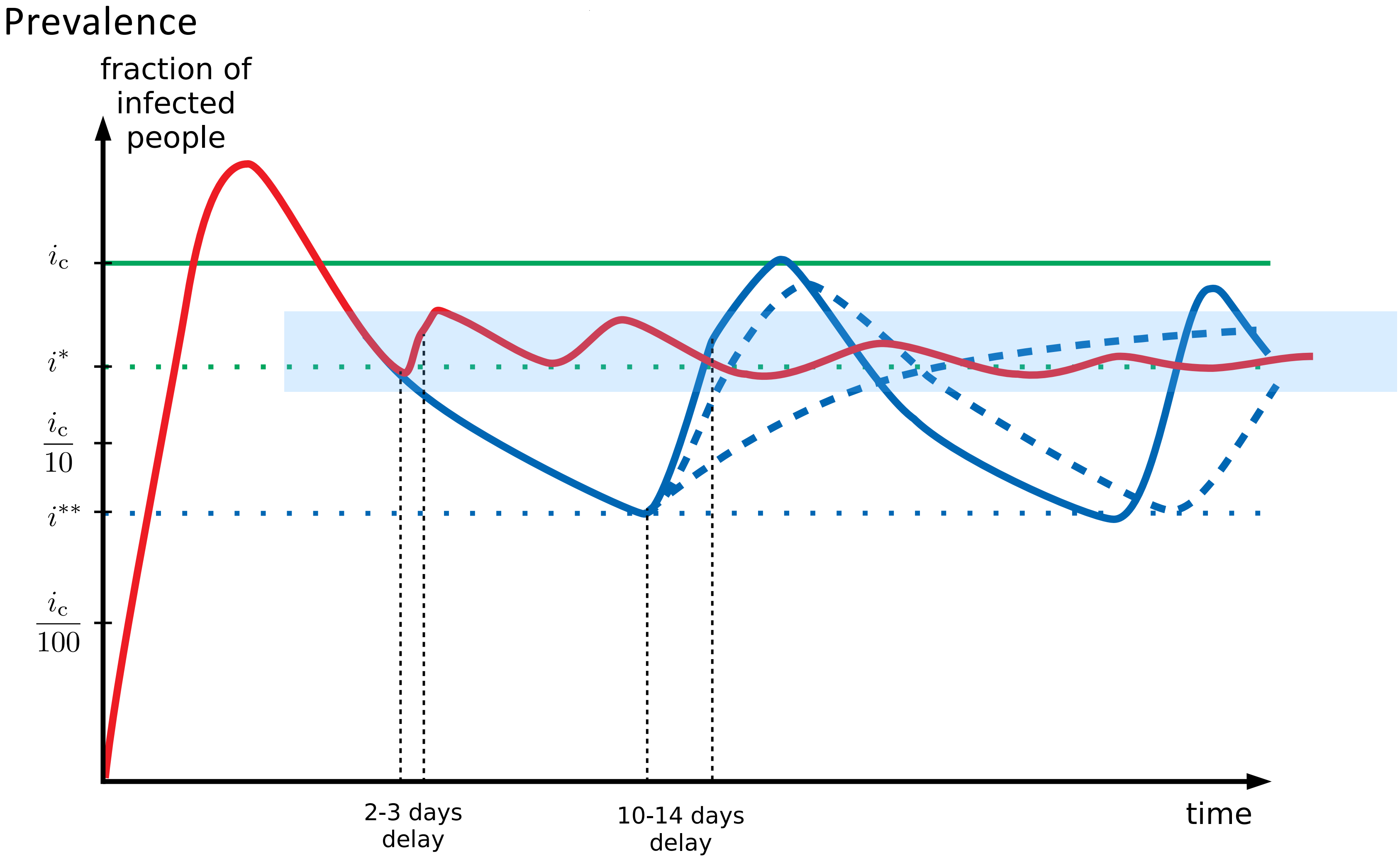
Peak in deaths

Benefit of shortend delay

Benefit of shortend delay

1. Reduce unwanted increase of prevalence

→ damps oscillations



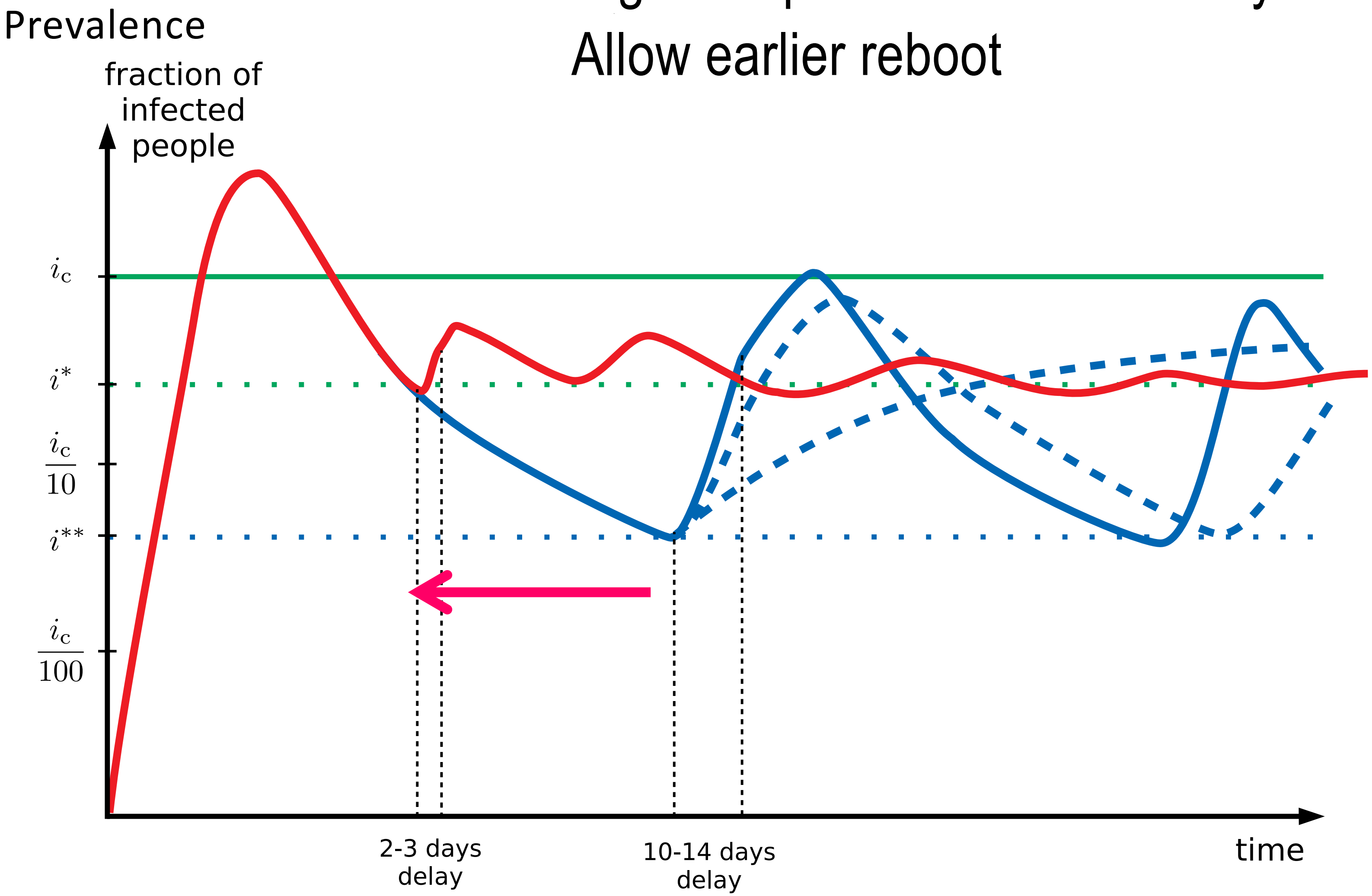
Benefit of shortend delay

1. Reduce unwanted increase of prevalence

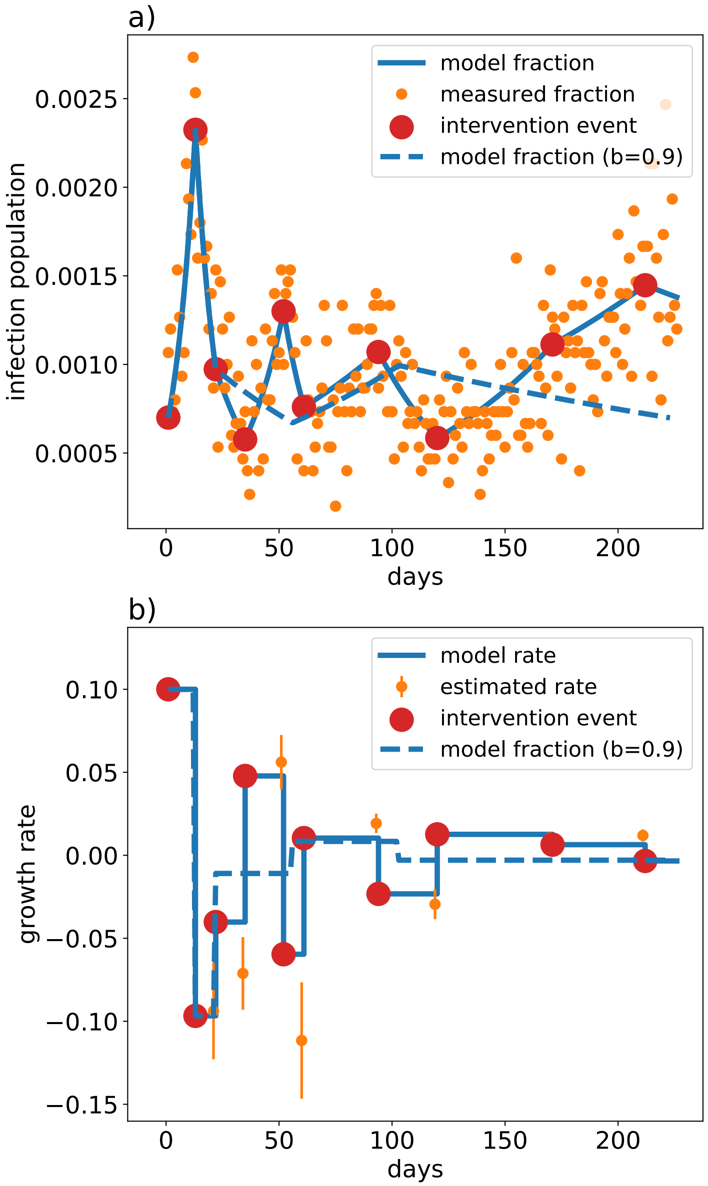
→ damps oscillations

2. If manageable prevalence is ethically acceptable:

Allow earlier reboot



Intervention strategy to reach a steady state k = 0



Assume:

k(t) is constant and jumps when policies change

Measure k(t):

- Test r people daily
- Split time interval Δt in two
- Infections detected

$$N_1 \approx r i_0 \frac{\Delta t}{2} \qquad N_2 \approx N_1 e^{k\Delta t/2}$$

→

$$k_\iota^{\text{fit}}(\Delta t) = \frac{2}{\Delta t} \ln\left(\frac{N_{\iota,2}(\Delta t)}{N_{\iota,1}(\Delta t)}\right)$$

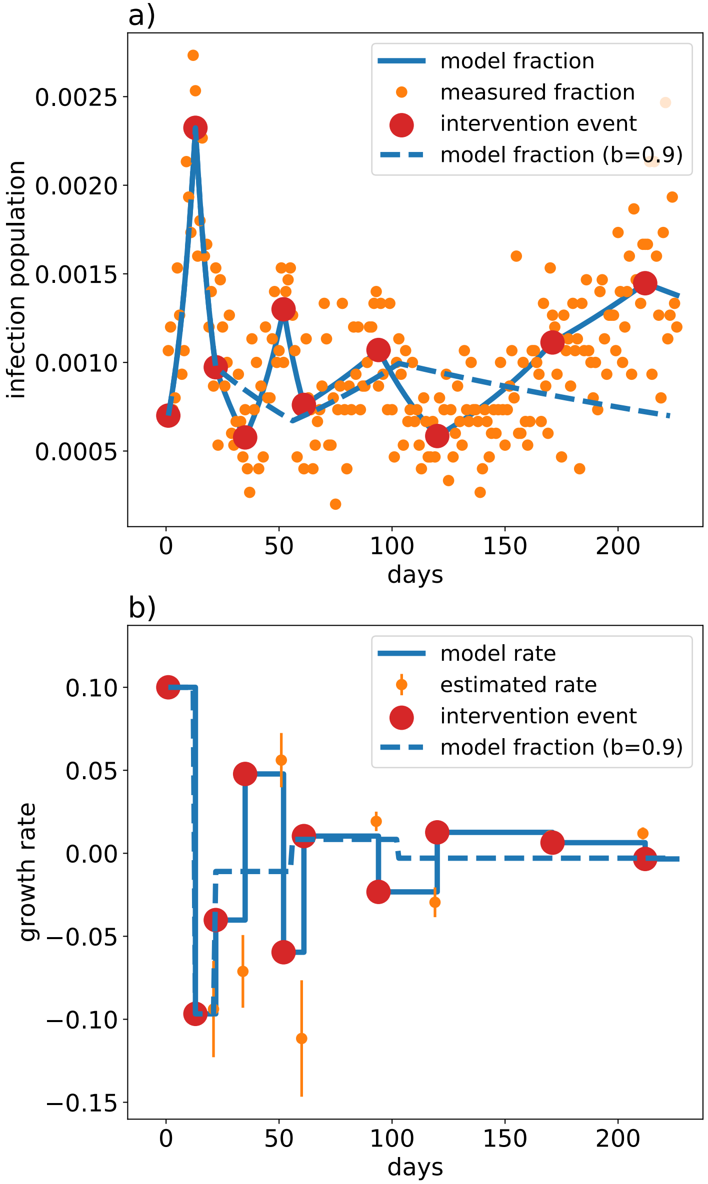
- Uncertainty:

→

$$\delta k(\Delta t) = \frac{2}{\Delta t}\sqrt{\frac{1}{N_{\iota,1}(\Delta t)} + \frac{1}{N_{\iota,2}(\Delta t)}}$$

→ Obtain quick feedback about new k

Intervention strategy to reach a steady state k = 0



Intervention strategy:

- If $k_{\text{fit}} > 3\,\delta k$: Restrict
  or $i > i_{\max}$
- If $k_{\text{fit}} < -3\,\delta k$: Release
  or $i < i_{\min}$

Convergence to $\boxed{k = 0\,;\; R = 1}$

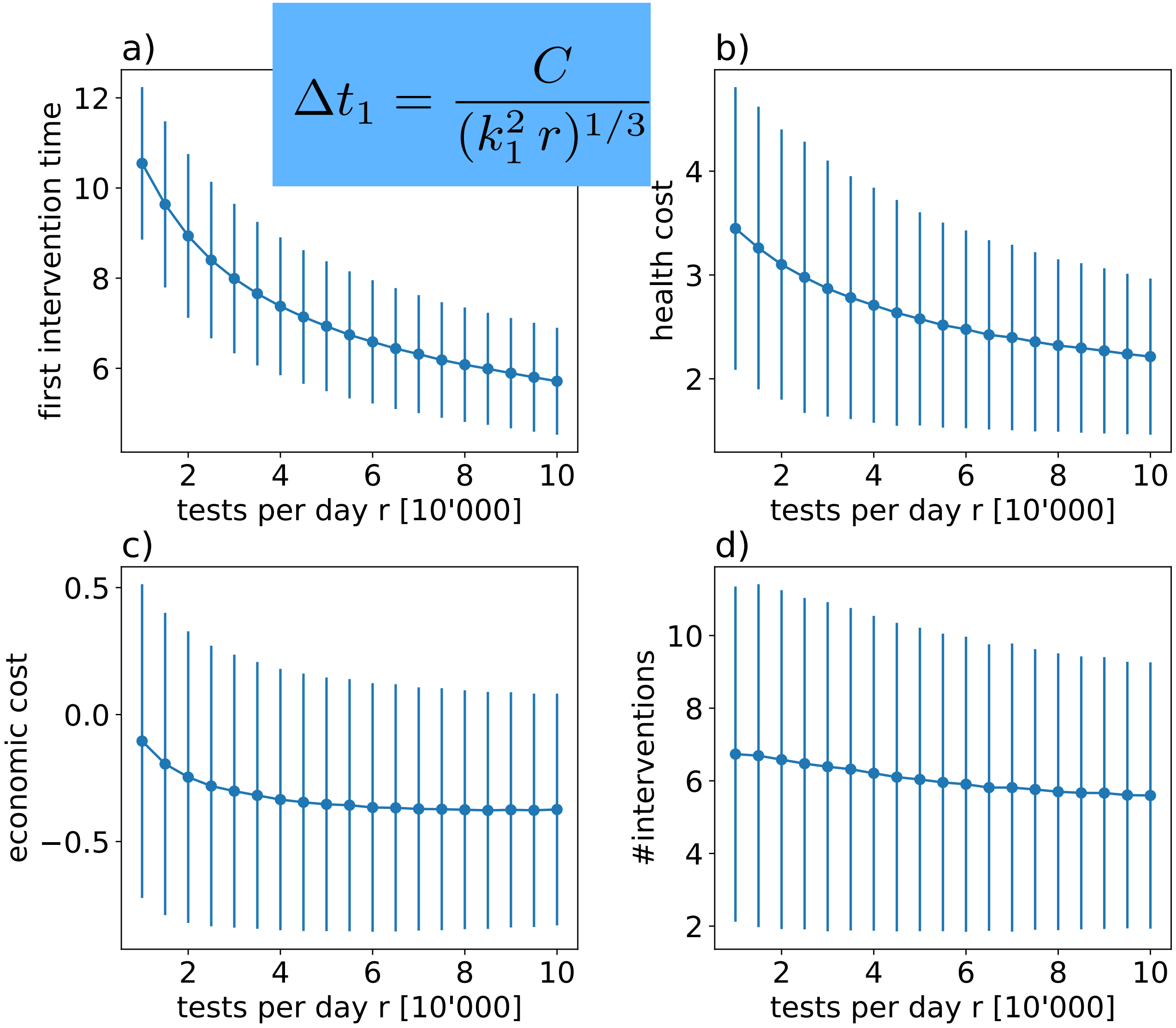
Faster & better with more daily tests r

$$r \geq 5/i_0$$

i_0 should initially be ~ ¼ of manageable threshold prevalence

More testing = better result for health, economy and politics
Win-win-win situation!

$$\Delta t_1 = \frac{C}{(k_1^2\, r)^{1/3}}$$



Concrete benefit of random testing

versus

postdiction based on symptomatic cases?

Concrete benefit of random testing

versus

postdiction based on symptomatic cases?

Most important benefit: Monitoring sudden release of restrictions:

Switzerland: 11th of May and 8th of June 2020

Concrete benefit of random testing

versus

postdiction based on symptomatic cases?

Most important benefit: Monitoring sudden release of restrictions:

Switzerland: 11th of May and 8th of June 2020

Later:
- Re-opening universities & high schools
- Re-opening borders,
- Allowing mass gatherings, concerts, festivals

Concrete benefit of random testing

versus

postdiction based on symptomatic cases?

Further benefits:

- Precise, undelayed mapping of symptomatic/asymptomatic cases
- Data allows to fix epidemiological parameters
  → improve predictability

Concrete benefit of random testing

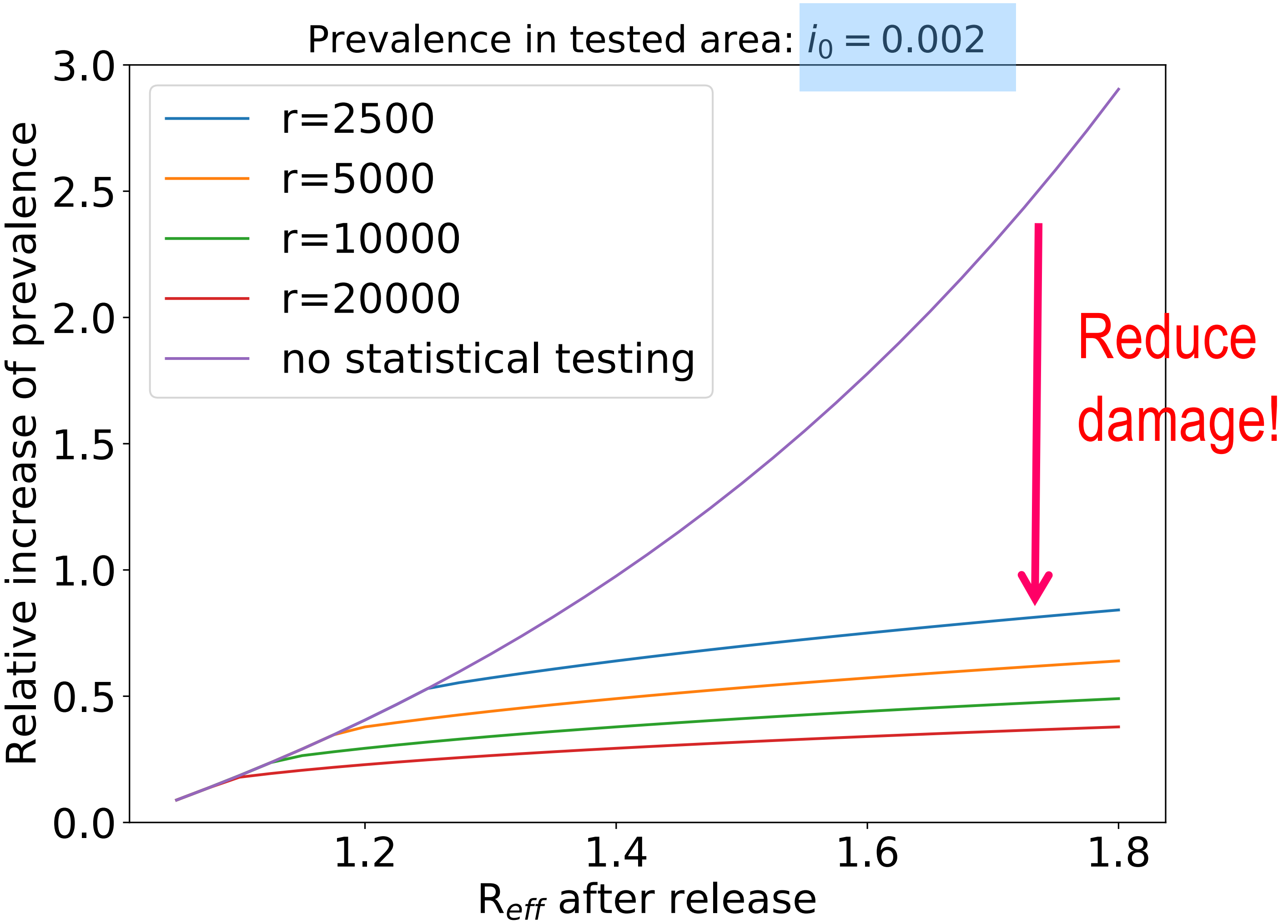
versus

postdiction based on symptomatic cases?

Direct benefits when releasing restrictions:

Like upgrade from basic health insurance to private premium insurance!

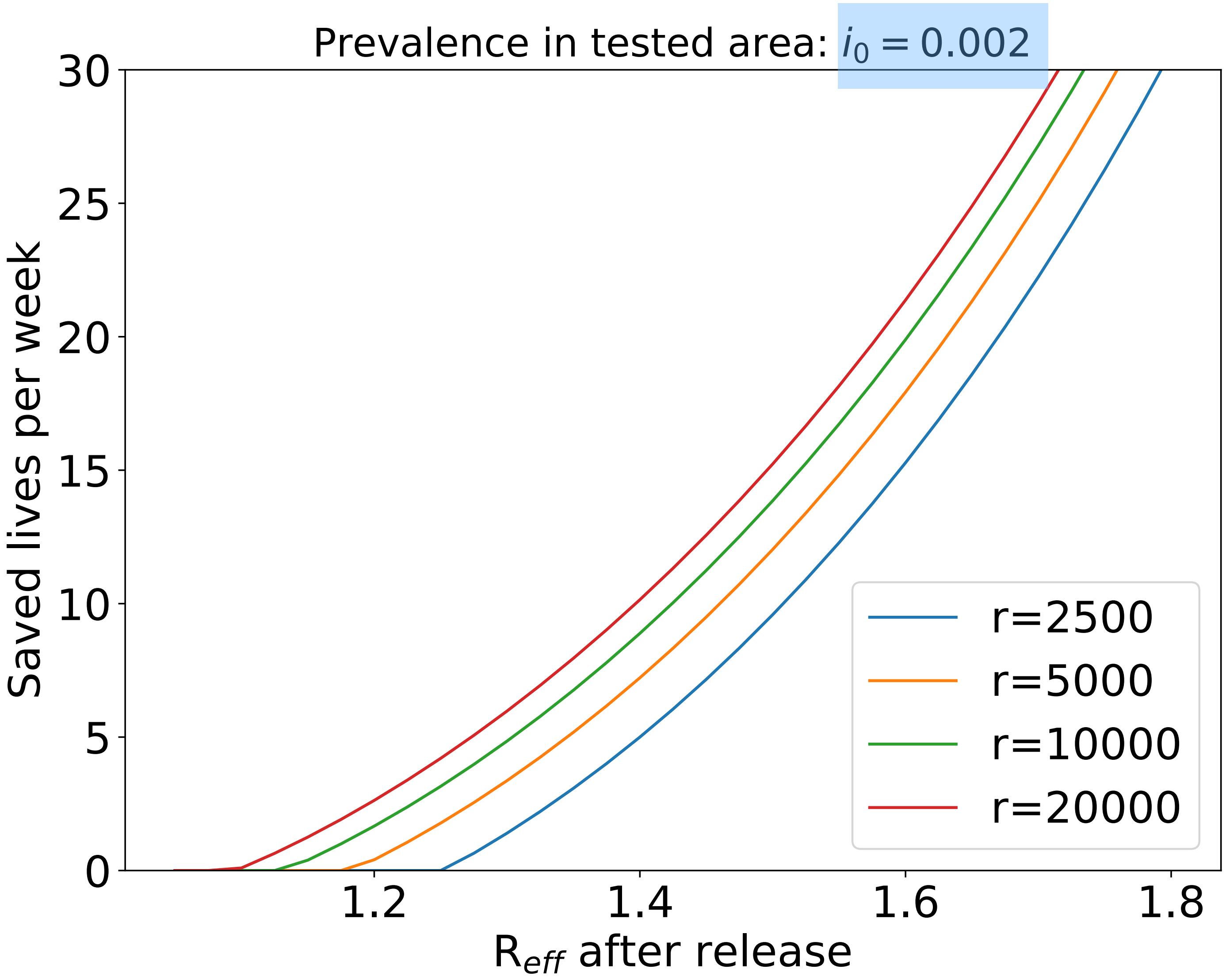
Reduced increase of prevalence after policy release



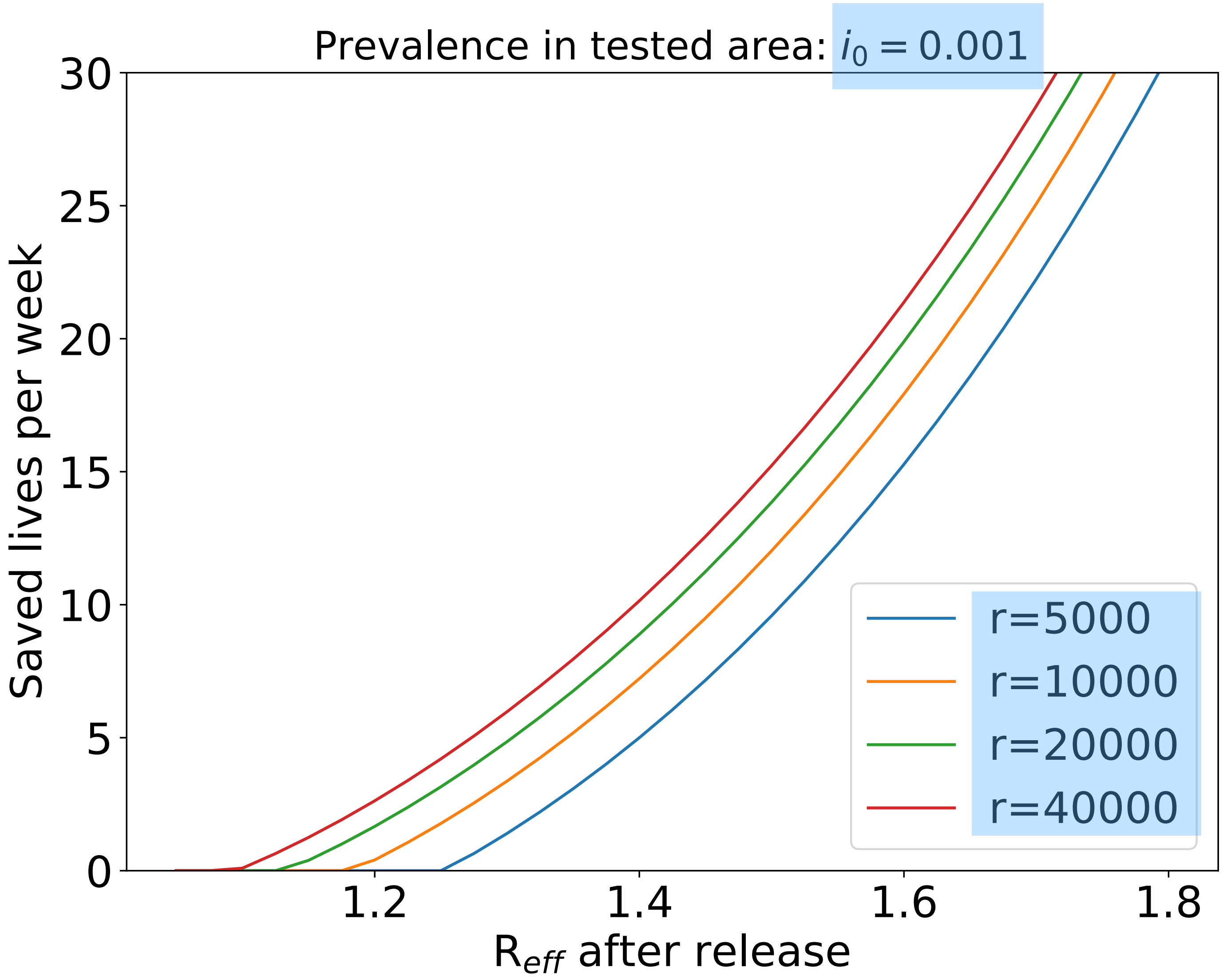
Increase of prevalence ⟷ Increase of health costs, health damage

Increase of death toll

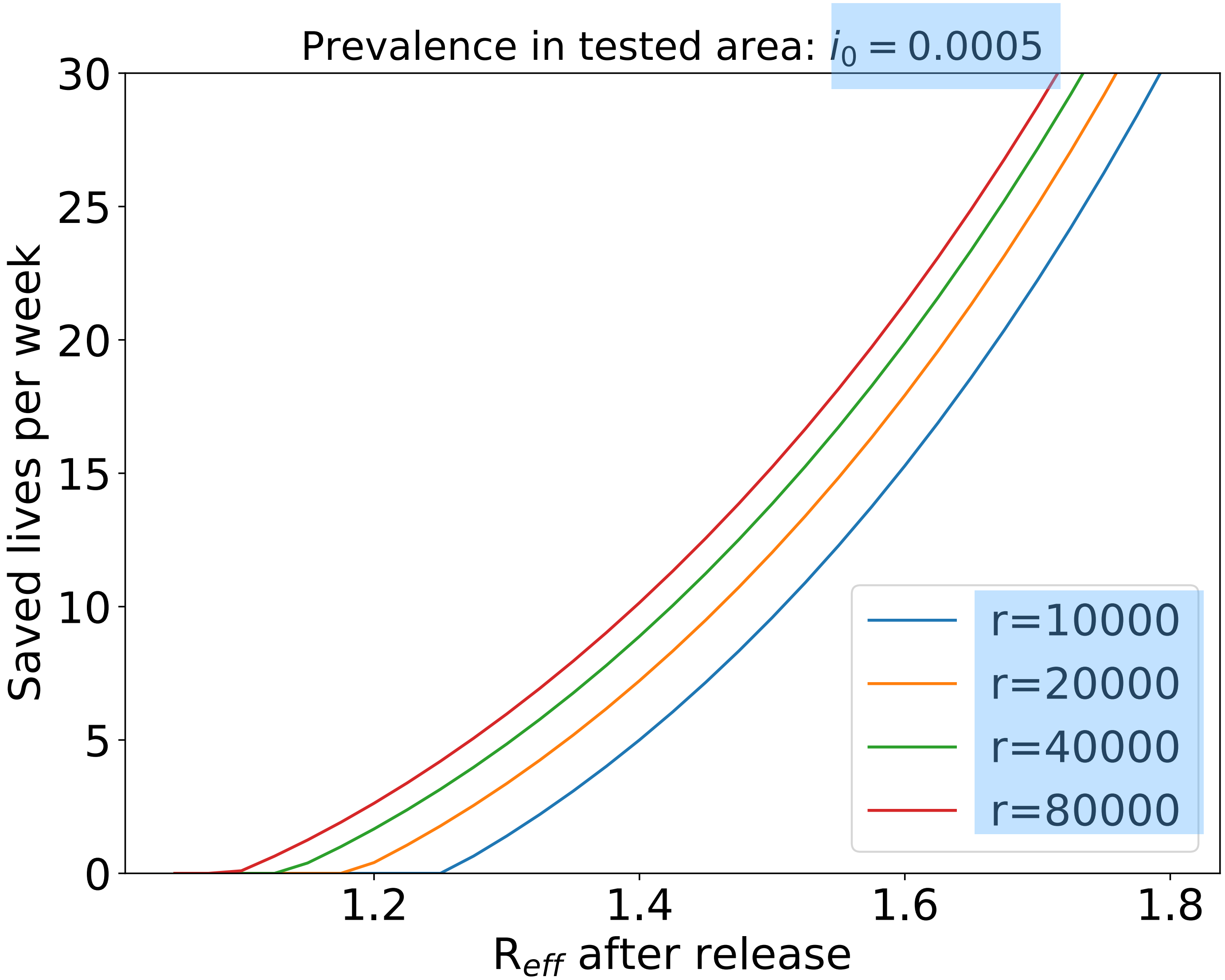
Lives saved by random testing



Lives saved by random testing



Lives saved by random testing



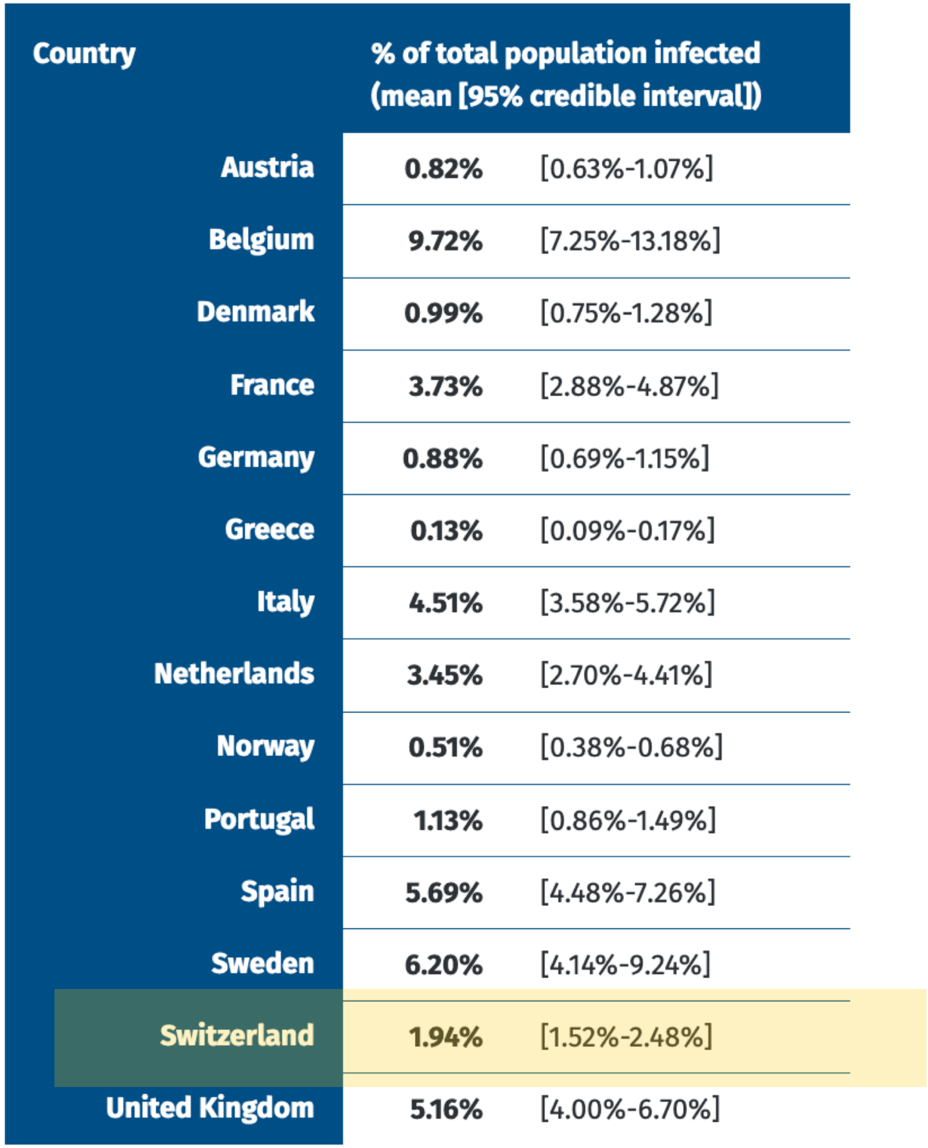
What is the current prevalence?

We don’t know!

But we can estimate it.

How many people were already infected some time?

N. Ferguson et al,
Covid19 Report No.13



Country	% of total population infected (mean [95% credible interval])	
Austria	0.82%	[0.63%-1.07%]
Belgium	9.72%	[7.25%-13.18%]
Denmark	0.99%	[0.75%-1.28%]
France	3.73%	[2.88%-4.87%]
Germany	0.88%	[0.69%-1.15%]
Greece	0.13%	[0.09%-0.17%]
Italy	4.51%	[3.58%-5.72%]
Netherlands	3.45%	[2.70%-4.41%]
Norway	0.51%	[0.38%-0.68%]
Portugal	1.13%	[0.86%-1.49%]
Spain	5.69%	[4.48%-7.26%]
Sweden	6.20%	[4.14%-9.24%]
Switzerland	1.94%	[1.52%-2.48%]
United Kingdom	5.16%	[4.00%-6.70%]

Posterior model estimates of percentage of total population infected over the course of the pandemic. Estimates as of 2020-05-02.

https://mrc-ide.github.io/covid19estimates/#/total-infected

Estimate of prevalence for the Canton of Geneva

Sero-prevalence (antibodies) tested: $SP \sim 5.5\%$

Estimate of prevalence for the Canton of Geneva

Sero-prevalence (antibodies) tested: $SP \sim 5.5\%$

→ Estimate of acute prevalence just before lockdown :

$$i_{\text{peak}} \sim (0.4 - 0.6) \cdot SP \approx 2.5 - 4\%$$

Halving time after lockdown: 8-10 days

Estimate of prevalence for the Canton of Geneva

Sero-prevalence (antibodies) tested: $SP \sim 5.5\%$

→ Estimate of acute prevalence just before lockdown :

$$i_{\text{peak}} \sim (0.4 - 0.6) \cdot SP \approx 2.5 - 4\%$$

Halving time after lockdown: 8-10 days

Estimated prevalence after 50 days of lockdown:

$$i_0 \equiv i_{\text{peak}}(2^{-6} - 2^{-5}) \approx 0.0004 - 0.0015\%$$

↔ 4-15 people in 10’000 are acutely infected

PAUL SCHERRER INSTITUT

Estimate of prevalence for the Canton of Geneva

Sero-prevalence (antibodies) tested: $SP \sim 5.5\%$

$\longrightarrow$ Estimate of acute prevalence just before lockdown :

$$i_{\mathrm{peak}} \sim (0.4 - 0.6) \cdot SP \approx 2.5 - 4\%$$

Halving time after lockdown: 8-10 days

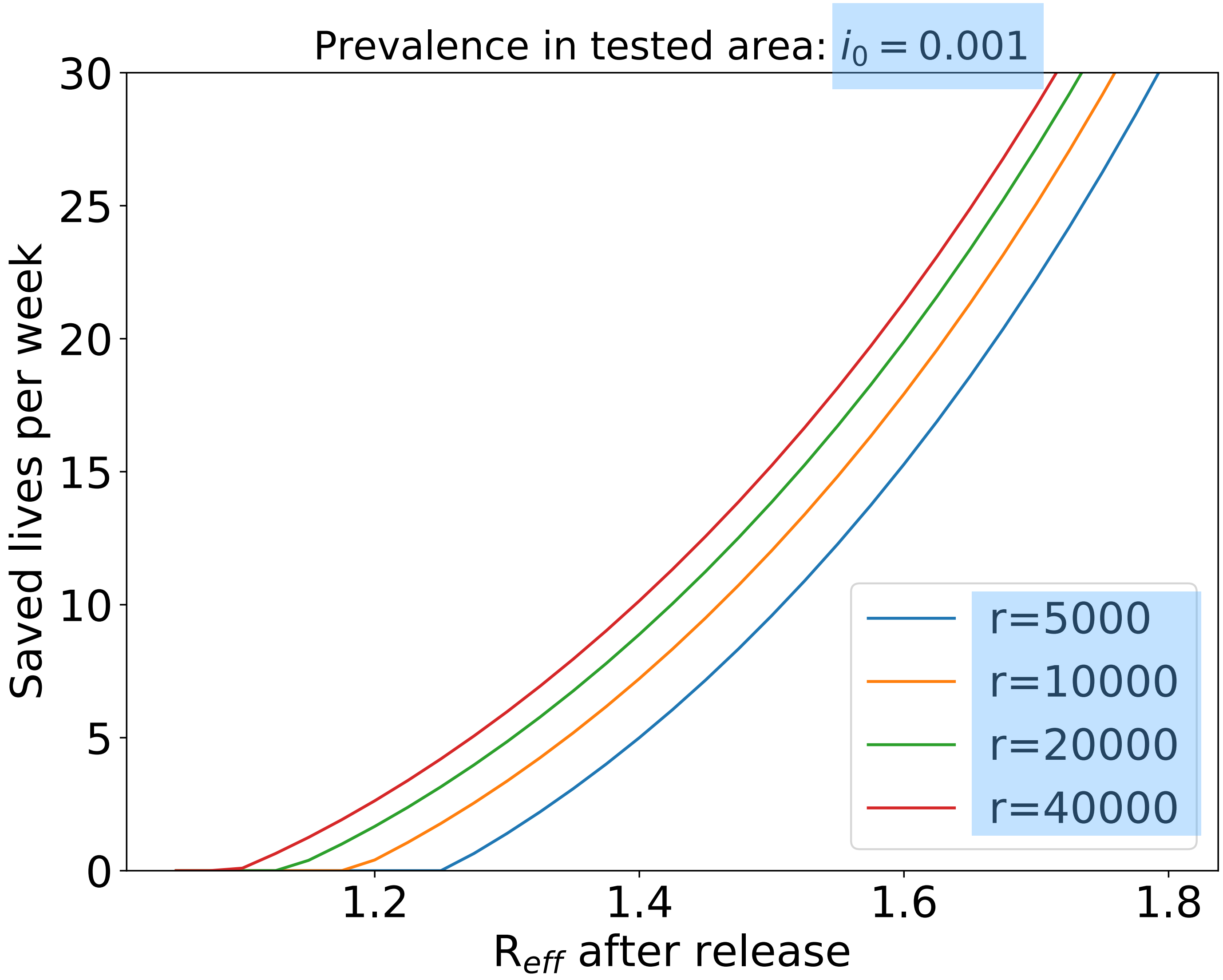
Estimated prevalence after 50 days of lockdown:

$$i_0 \equiv i_{\mathrm{peak}}(2^{-6} - 2^{-5}) \approx 0.0004 - 0.0015\%$$

$\leftrightarrow$ 4-15 people in 10’000 are acutely infected

($\leftrightarrow$ 2 people in 10’000 tested positive over last 10 days)

Lives saved by random testing



Costs

Cost per tested person

PCR analysis ~ 20 CHF

Logistics: ~ 30 CHF

- Call centers, Bureau of statistics

- Test centers, medical staff

Could be avoided
with self-tests
sent by mail
(like in the UK)
But: currently not
allowed in CH

Where to test best?

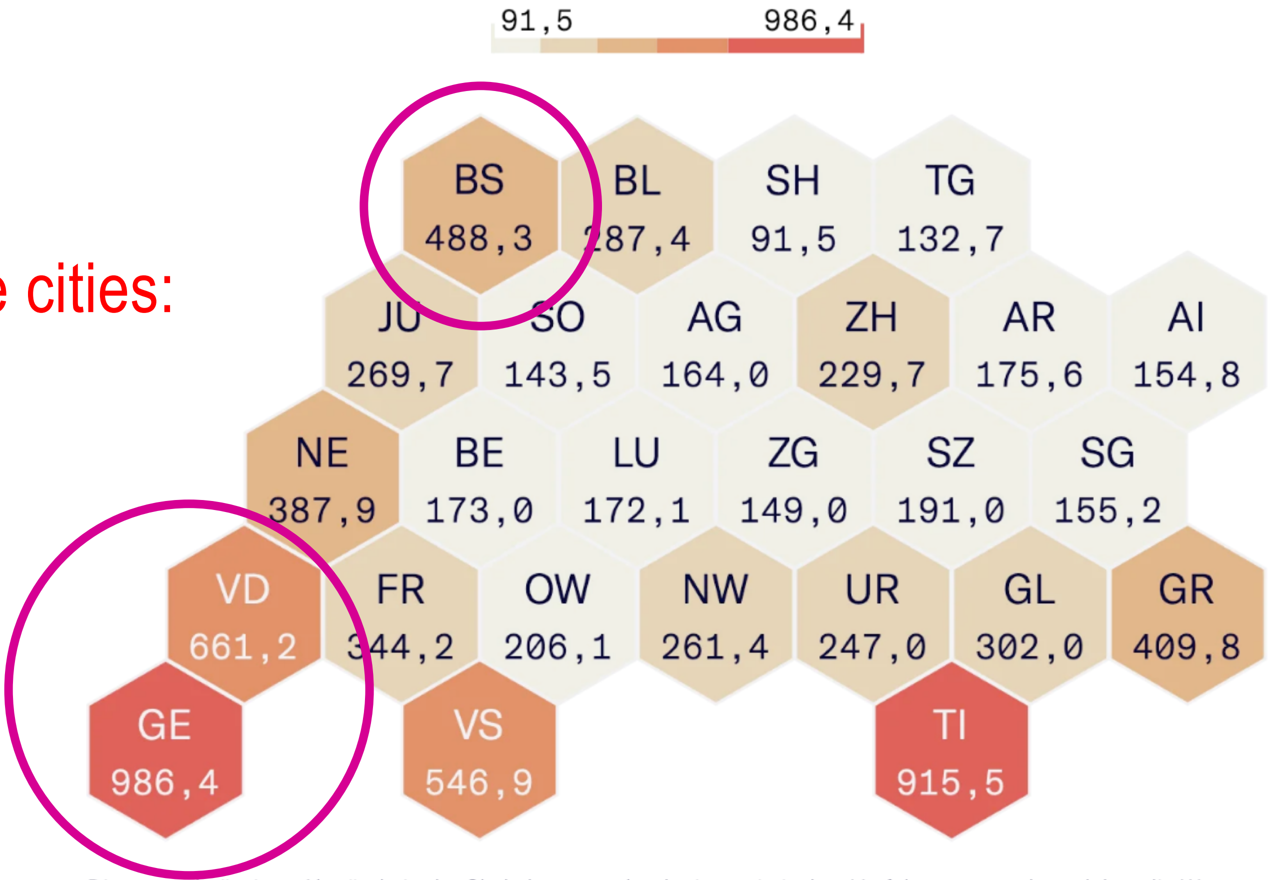
Vulnerable cities:

Geneva

Lausanne

Basel

Anzahl der Coronavirus-Fälle pro 100 000 Einwohner, nach Kanton



Die unregelmässigen Abstände in der Skala kommen durch ein statistisches Verfahren zustande, welches die Werte so in Gruppen einteilt, dass die Unterschiede zwischen den Regionen möglichst gut sichtbar werden (Jenks Natural Breaks). Stand: 4. Mai 2020, 7 Uhr

Quelle: Kanton Zürich

NZZ / brt.

Statistical sampling: Previous experience?

Earliest: Iceland (but self-selected sampling) i_0 = 0.88%

First statistically random sampling in Austria (April 11) i_0 = 0.33%

San Francisco Mission Bay:
50% of population sampled: i_0 = 2.1% ;
6% in subgroup

Just started: UK: 100’000 tested people REACT1 program

Replace randomly testing people by testing sewage water?

Statistical sampling: Test daily mixes of sewage (PCR)?

Open questions about sewage screening

Ch. Ort et al., EAWAG, Switzerland

- Validation

Proportionality of sewage signal to infection numbers?
Fluctuations due to dilution by rain, insufficient mixing?

- Calibration: translating signal into # of infected people

- Delay between infection and dectability in feces

The New York Times

Opinion

We Need Coronavirus Tests for Everyone. This Is the Next Best Thing.

Random sampling is the quickest, most feasible and most effective means of assessing the U.S. population.

By Louis Kaplow

Mr. Kaplow is a professor of law and economics at Harvard.

April 24, 2020

Outlook

- Logistics of testing? Testing sub-groups?
- Optimal tests? (Self-applied saliva tests?)
- Sewage
- → Geographic refinements:

$$\frac{dI_m}{dt} = K_{mn}(t)I_n$$

Fit matrix K and intervene regionally

Summary

- Random testing requires modest numbers of people per day
- It significantly shortens the delay in feedback and control loop

→ more efficient and faster

→ saves lives and reduces damage

- Informs about actual infection rate
  - → input & constraints for epidemiological models
  - → better forecasts

How long until the crisis ends?

- until a vaccine is found

Or

- Maintaining the infection fraction at a manageable level i_0:

~ 5-10 days

~ 0.7

$$T_{\mathrm{imm}} = f_{\mathrm{imm}} \frac{T_{\mathrm{inf}}}{i_0} \sim 1 - 2\,\mathrm{years}$$

~ 0.01 (?)

Random COVID19 testing

Saved Lives

Safe Reboot

Less Damage