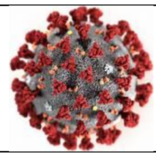
National COVID-19 Science Task Force (NCS-TF)



Type of document: Response to questions	
In response to request from: FOPH (Brigitte Meier)	**Date of request:** 17/04/2020
Expert groups involved: Data and modelling	**Date of response:** 21/04/2020
Contact person: Sebastian Bonhoeffer, Julien Riou (julien.riou@ispm.unibe.ch), Christian Althaus (christian.althaus@ispm.unibe.ch), Melissa Penny (melissa.penny@unibas.ch)	
Comment on planned updates : NA	

Title: Response to questions from FOPH 17th April 2020

Summary of request/problem

The FOPH raised five specific questions regarding the epidemic dynamics of COVID-19 in Switzerland

Executive summary: NA

Main text

Q1: What effect did the measures taken by the Swiss government have on the development of the epidemic curve?

All analyses of Swiss data known to the expert group “Data and modelling” agree that transmission decreased considerably between 17th March and the 19th of April (Appendix A). From the data, we observe a decrease in the number of diagnosed cases that began towards the end of March with a delayed decrease in numbers of daily hospitalisations, ICU admissions and fatalities (Q2). Current estimates of the effective reproduction number (R_e, the average number of new cases generated by each case in the current state of the population) from the data directly or via models are all below 1., thus indicating a decreasing trend in transmission and an expected continued decrease in number of daily new cases. This reduction in R_e can be attributed to the measures taken by the Swiss government after March 17, and confirmed by the models. If control measures continue to be applied with the same level of effectiveness, case numbers are expected to continue to decrease. Recent mobility data indicate potential lockdown fatigue, so we may expect a slight increase in R_e in the short term that may or may not become evident in the case data.

Q2: How would estimate the time lag between measures taken by the Swiss government and effect on case, hospitalization and death numbers?

Different time lags are at play here due to reporting, and due to epidemiological and intervention dynamics. Overall, we expect changes to control measures (relaxing or tightening) to have lags of approximately

1) 10-13 days before we observe effects on confirmed cases;
2) 13-16 days before we observe effects on hospital admissions;
3) 3 weeks before we observe effects on numbers of deaths.

These lags are firstly due to a delay in effect of the control measure due to the time needed to implement them (between 2 and 4 days according to analyses). Secondly, due to the incubation period we expect a further 5 days before there would be a reduction in the number of cases with onset of symptoms. Thirdly, due to testing and reporting delays (on average 4.7 +/- 0.14 days from disease onset to testing). Further delays are then at play due to disease progression: for new hospitalisations (on average 6.0 +/- 0.23 days from disease onset to hospitalisation), for new ICU admissions (0.93 +/- 0.07 days from hospitalisation to ICU admission) and for deaths (7.2 +/- 0.76 days from ICU admission to death or 10 +/- 0.75 days from hospitalisation to death among those not admitted to the ICU). Time delays for individuals that were reported to die outside of hospitals are less clear and require further investigation.

These durations were estimated by ISPM Bern from the data provided by the FOPH (Appendix B) and further confirmed with time-series analysis by Swiss TPH (Appendix C). Further analysis by EPFL suggests that a delay of 3 weeks is necessary to detect a change in the trends of deaths with sufficient power after a change in transmission.

Q3: How do you interpret the data regarding the number of new infections, patients hospitalized and deaths? What are the trends?

Our previous report (27th March) indicated several biases resulting from delays in reporting including fewer results at weekends thus there is a weekly pattern in the trends of confirmed cases.

All analyses in Appendix A confirm R_e is below 1 and thus transmission is decreasing. Time-series analysis by Swiss TPH (Appendix C) of daily confirmed cases and fatalities, further confirms consistent downward trends since 1st April and thus clear impact due to the control measures implemented since mid-March.

The confirmed cases from 14th to 16th April in the most recent data provided by FOPH could be interpreted that the daily number of new cases is stabilising. These data include delays in reporting due to Easter and/or a potential effect of Easter behavioural changes on transmission. However, based on the time-series analysis of the FOPH data we forecast in the four days following 16th April there would be likely decreases in the daily numbers of deaths, but with an uncertain trend for cases over the same period (large confidence intervals). With similar time-series analysis on data obtained from OpenZH [1] (which include data up until April 19th) we forecast a *continued decreasing trend* in the number of new cases per day.

We recommend avoiding interpreting changes to trends in the data over short periods of time (3-4 days). Data from FOPH over the period 17-20th April will confirm if there was increased transmission over Easter, a true stabilising trend, or a decreasing trend as observed before 14th April.

The time-series analysis, modelling, and the estimations of R_e require data to be available in real-time to interpret changes in trends, and to support interpretation of indicators for tightening or relaxing of measures.

Q4: What regional differences do you see in the trends, what could be an explanation?

A recent study by ISPM Bern analysed the differences in SARS-CoV-2 transmission across NUTS-2 regions in Switzerland. By assuming a mortality of 0.5-3% of all infected individuals, this study estimated about 1.2% (0.8-1.9) of the Swiss population was likely infected by April 10, with important differences by region: estimates of the attack rate (i.e. the proportion of the population affected) are higher in Ticino (4.1% [2.6-6.5]) and Région Lémanique (i.e. Geneva, Vaud and Valais, 2.3% [1.4-3.6]) than in other regions (1% or lower) (Appendix B). Conversely, estimates of the effective reproductive number were lower in Ticino and Région Lémanique than in other regions, while always remaining below 1. This may reflect higher compliance to control measures in areas more heavily affected by the epidemic.

Q5: What would you say about the relationship between cases, hospitalization and deaths with regards to the tests?

We did not understand the intended meaning of this question. Based on our interpretation, we analysed the proportion of individuals with a positive test that ended up in hospital (Appendix B) . When fewer than 2,000 tests were performed per day, an effect of preferential ascertainment of severe cases can be seen. When more than 2,000 tests a day are performed, this effect was less pronounced. To date, data suggests that with higher testing positivity can be interpreted as proportional to incidence.

Unresolved issues

Statistical and model-based analyses supporting our responses are dependent on the timely availability of data. For the most part, the contributing groups have based their conclusions on FOPH data up to 16th April (as provided on the 17th April). Additional data [1] allowed further interpretation of recent trends until 19th April or to resolve reporting delays in the FOPH database compared to cantonal data.

Despite inherent and possibly unavoidable delays in reporting at a federal level, daily real-time release of data from FOPH would be *immensely valuable* and would allow regular updates of these analyses, including estimates of R_e and assessment of indicators for the relaxing and tightening of control measures. For example, it seems that the data on the BAG dashboard was more up to date over the weekend than the data that we obtained. Additional detail on the number of negative tests (by canton, age, sex) would further improve our understanding of the influence of testing on the observed trends.

References

[1] https://github.com/openZH/covid_19

Appendices

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

Appendix B - Analysis of SARS-CoV-2 transmission in Switzerland stratified by region

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Compartmental model linking test positivity, hospital admissions, ICU admissions and deaths by NUTS-2 region. The model is fitted with MCMC to individual data on 25,659 cases of SARS-CoV-2 infection until April 10, provided by the FOPH on April 17, 2020. Important features of the model include: asymptomatic and presymptomatic transmission; accounting for the varying number of tests performed each day; decrease in transmission after the implementation of control measures on March 17 using a logistic switch function; progression in care using delays estimated from the data (and propagating uncertainty); and a hierarchical structure by region (using a random-effect on transmission).

Figure B1. Time delays between events: onset of symptoms to test, onset to hospitalisation, onset to death, hospitalisation admission to ICU admission, hospitalisation to death, and ICU admission to death.

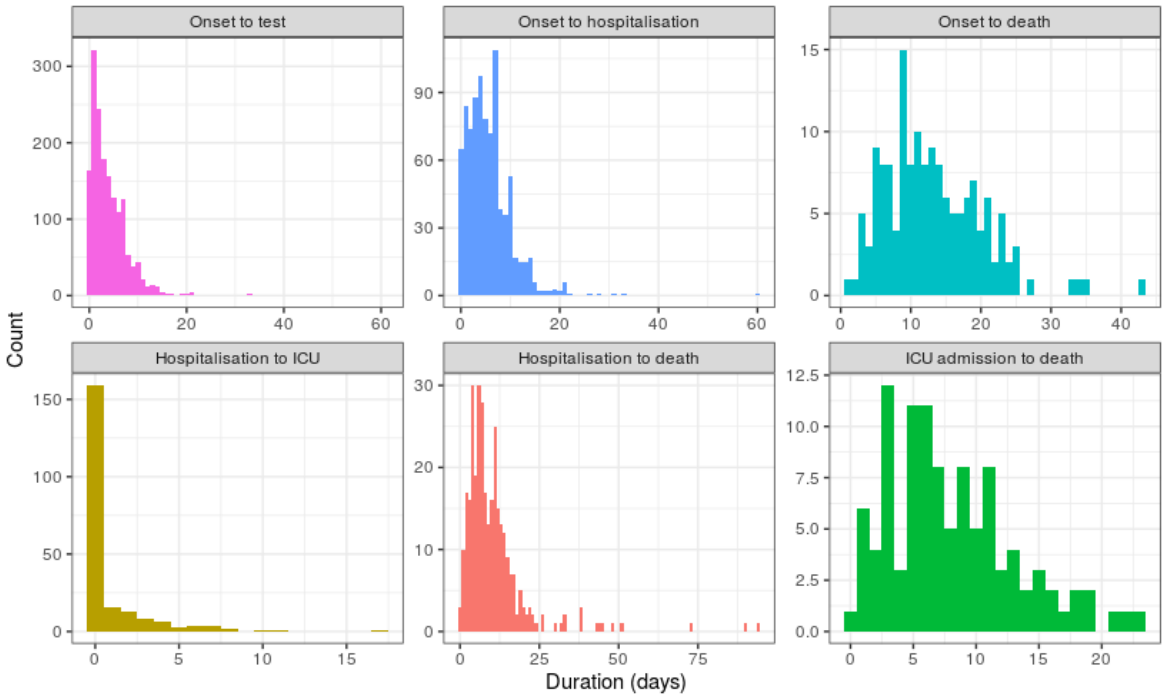


Figure B2. (A) Number of tests performed each day. (B) Proportion of individuals tested on each day that end up being hospitalised according to the total number of tests performed on that day. We observe that when fewer than 2000 tests are performed in a day, the proportion of positive cases that are hospitalised raises, suggesting that testing is focused on more severe cases.

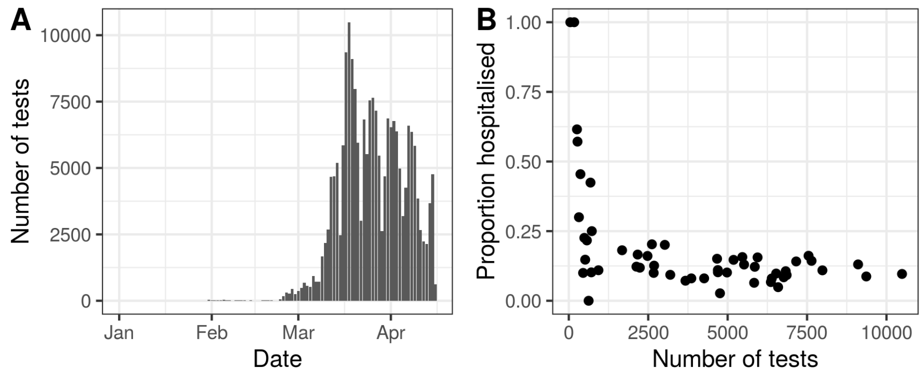
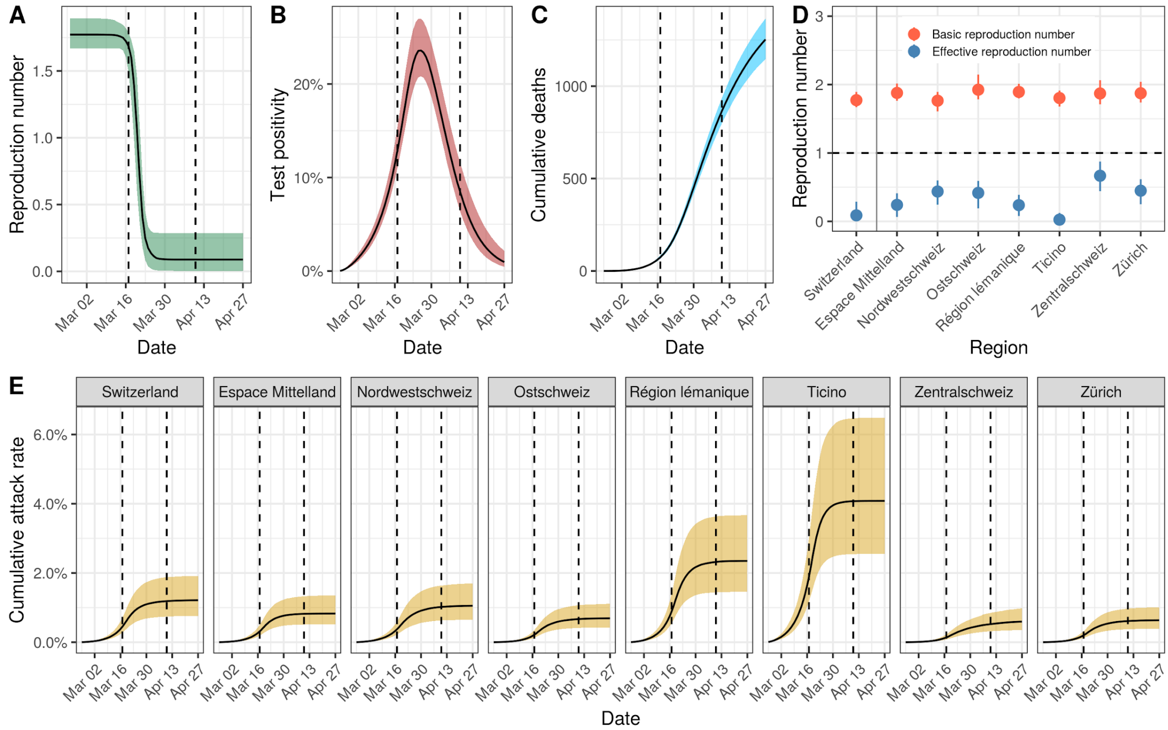


Figure B3. (A) Predicted decrease of the reproduction number after the implementation of control measures on March 17. (B) Evolution of test positivity. (C) Cumulative deaths. (D) Predicted basic reproduction number and effective reproduction number by region. (E) Estimated cumulative attack rate in Switzerland and by region based on a total mortality of symptomatics of 0.5-3%.



Appendix C - Time-series analysis to monitor and forecast the SARS-CoV-2 outbreak in Switzerland

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Analysis of trends and forecast of daily cases and deaths

Auto-regressive integrated moving average (ARIMA) models were fitted to smoothed, log-transformed time series of daily reported cases and deaths obtained from the data from FOPH (Fig. C3) and OpenZH (Fig. C4). Data was released by FOPH on April 17th, 2020 (with entries until April 16th). OpenZH data are from the Specialist Unit for Open Government Data Canton of Zurich (OpenZH(1)). The models were used to forecast future cases and fatalities over the next 4 days and to estimate the lags between measures and their effects.

Using a dynamic programming algorithm (*2*) which estimates structural change points in regression models, we estimated the lag time between measures taken by the Swiss government and their effect on case and death numbers. Analysis on both datasets from FOPH (Fig. C1) and OpenZH (Fig. C2) on the cases and death numbers yielded the following estimates on lags:

- 14 - 16 days before we observe effects on confirmed cases
- 19 - 22 days before we observe effects on numbers of deaths

Based on the analysis for the FOPH data, we observe a clear impact in the trend analysis of the FOPH data due to the control measures implemented mid-March (Fig. C3). We forecast over the period 17-20th April we are likely to see a decrease in daily numbers of deaths. We predict a potential stabilizing trend for cases over the next four days following 16th April. However, we note the last three days of the data set 14-16th April include delays in reporting since Easter. We expect data for 17-20th April from FOPH to confirm if there was increased transmission over Easter, a true stabilizing trend, or a decreasing trend as observed before 14th April.

We performed the same ARIMA analysis on the smoothed time series data obtained from OpenZH (Fig. C4) with data until April 19th. We predict a continued decreasing trend in the number of new cases per day, and a stabilizing trend in the number of deaths.

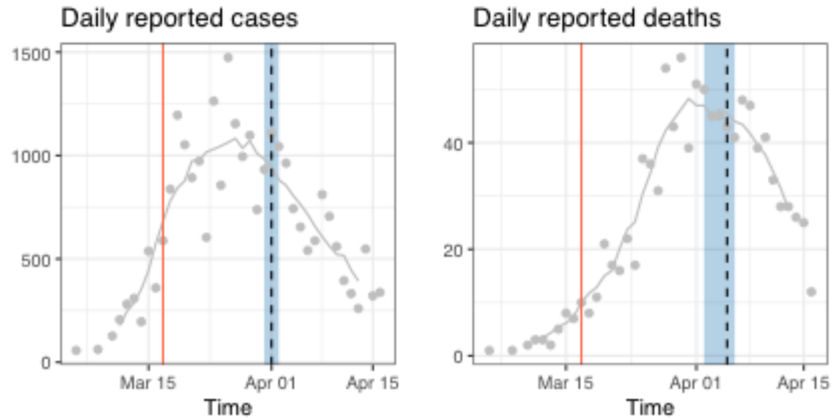

Figure C1: Estimated lag time between measures taken by the Swiss government on the 17th of March (date marked with orange line) and their effect on case and death numbers provided by FOPH. The estimated breakpoint corresponding to the beginning of the decreasing trend is displayed with the dotted line together with the estimated 95% confidence interval (blue shaded area).

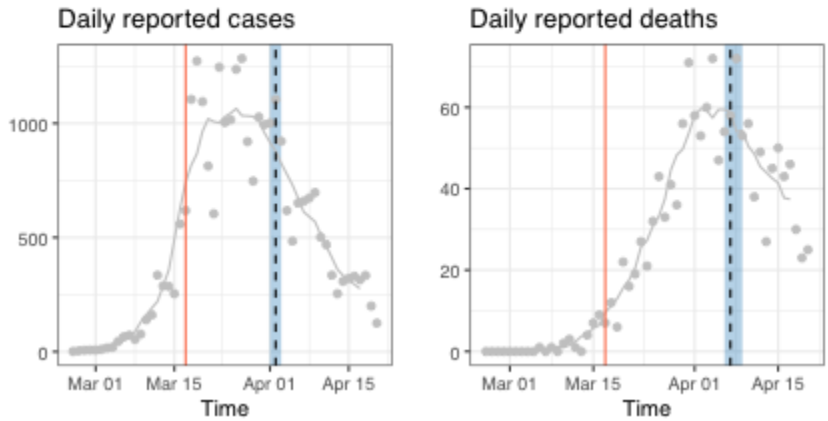

Figure C2: Estimated lag time between measures taken by the Swiss government on the 17th of March (date marked with orange line) and their effect on case and death numbers provided by OpenZH. The estimated breakpoint corresponding to the beginning of the decreasing trend is displayed with the dotted line together with the estimated 95% confidence interval (blue shaded area).

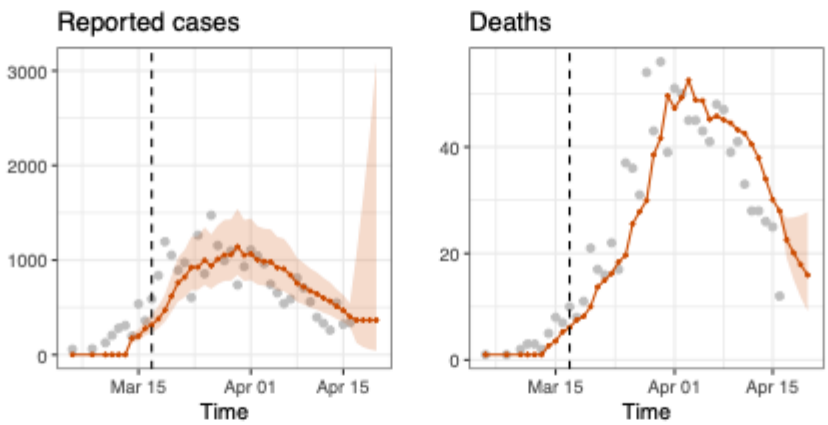

Figure C3: Results of fitting an ARIMA model to the smoothed time series of daily reported entries for new cases (left) and fatalities (right) until April 16th provided by FOPH. The model fits are shown with the orange curve along with the 95% confidence interval (orange ribbon). Forecasts are also displayed for the period April 17th - April 20th.

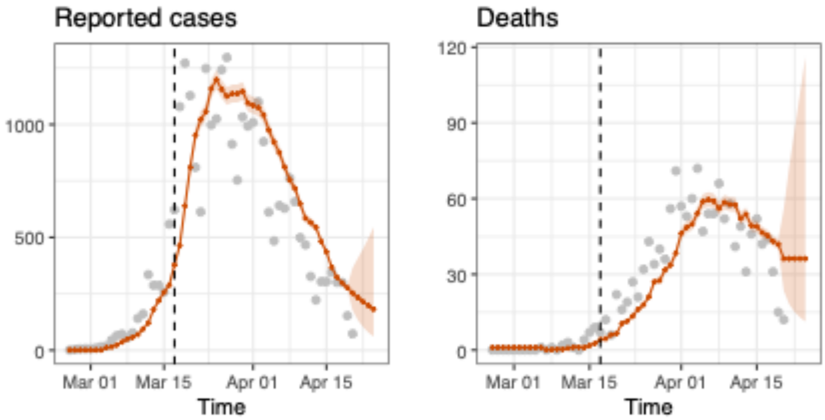

Figure C4: Results of fitting an ARIMA model to the smoothed time series of daily reported entries for new cases (left) and fatalities (right) until April 19thprovided by OpenZH. The model fits are shown with the orange curve along with the 95% confidence interval (orange ribbon). Forecasts are also displayed for the period April 20th - April 23th.

References

1. https://github.com/openZH/covid_19
2. J. Bai, P. Perron, Computation and analysis of multiple structural change models. Journal of applied econometrics 18, 1-22 (2003).