Consensus report by expert panel[1] of Swiss TPH, ISPM Bern, ETH Zurich and the ETH Domain COVID-19 Taskforce of March 27, 2020

Executive Summary

At 3 PM yesterday the Federal Office of Public Health (FOPH) shared line-listed data of the confirmed daily COVID-19 cases in Switzerland by canton, age and sex, and the daily number of negative tests for the whole country. The FOPH asked the academic community to address four questions. The expert panel undertook descriptive analyses and modelling to address the questions, to which we provide answers below.

Question 1. How should the epidemic curve be interpreted? Increasing, decreasing, stable trend?

The data provided are not themselves the epidemic curve, which would include all SARS-CoV-2 infections, but rather only the confirmed COVID-19 cases. The main difficulty in making inferences is the intrinsic biology of the virus, which means that the confirmed cases today reflect transmission 2-3 weeks ago. Furthermore, due to delays in updating the number of reported cases, the last three days should be interpreted with caution.

From the observed data, it is too early to infer either the trend of the epidemic curve or the magnitude of the effect of the control measures implemented since 13 March. A transmission model, developed for this report, also shows that, with the available data, the future trajectory of the epidemic in Switzerland is still uncertain. The uncertainty implies that we need to be prepared for the continued growth of the epidemic. Addition of data from new cases in the immediate future will considerably improve our ability to predict the effectiveness of the interventions and of the final size of the epidemic.

Question 2. Do you think that the data allow to evaluate the effect of the measures taken, and if so, how? If not why?

The data shared by FOPH are a vital information source that should make it possible to estimate the intervention effectiveness, but this will require at least a week’s more data. Additional parameters, including more complete data on the date of onset of symptoms in confirmed cases, would make it possible to estimate the trends with more confidence and to determine the impact of the control measures sooner. Variations in testing rates may be masking some of the trends in the data. These trends would be clearer if the numbers of negative test results were available disaggregated by canton and ideally, age and sex. The analysis by canton indicates that the most intense outbreaks are in a small number of cantons and that, in much of Switzerland, it might still be possible to avert a major outbreak by intensive

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case finding, contact tracing and isolation, if this strategy is implemented very soon with a state-of-the-art information system.

Question 3. What can be learned from the data despite these quality problems?
Data collection and curation is clearly challenging, and we are unsure what specific quality problems are referred to here. Despite the inevitable noise in the data and delays in reporting, our initial analyses highlight several important trends:

- The rate of confirmed cases per 10,000 population varies substantially by canton.
- The average age of confirmed cases has increased as the epidemic has developed. This trend is compatible with a pattern of initial cases being imported or detected by contact tracing, and later cases being ascertained in the clinic, when community transmission became established.
- The mean age of confirmed cases has remained constant since March 3, implying that eligibility criteria in the later increase in testing did not expand.
- There is evidence for an age-gender interaction. In younger age groups, women account for a larger proportion of confirmed cases, and in the older age groups confirmed cases are predominantly male. This pattern cannot be further interpreted without data on the distribution of testing by age and sex.
- The proportion of tests with a positive result appears to be increasing. This pattern is consistent with incomplete ascertainment in case detection. This is of concern because of the potential for continued transmission, despite social distancing measures.

Question 4. What would be your reply if you were asked how this epidemic will evolve in the near future? Especially with regard to the capacities in the medical system?
The observed data and model predictions show that future course of the epidemic remains uncertain. We must prepare for the case where the epidemic grows to levels that will severely strain the capacity of our health system. The panel currently lacks data on which to base judgements on the adequacy of the supply of ICU beds, ventilators, protective clothing, or trained and uninfected staff. The question does not specify which capacities are referred to.

Disclaimer: The answers to the four questions are based on interpretation of descriptive analyses and modelling that were conducted under extreme time pressure. The findings of the analyses are subject to change. Changes in the findings could affect the interpretation.

Main Report

Background on panel assembly and structure of the report

At 3 PM on March 26th, Brigitte Meier from the Federal Office of Public Health (FOPH) shared line-listed data of the confirmed daily COVID-19 cases in Switzerland, from 24/02/2020 - 25/03/2020, by canton, age and sex, and data summarizing the daily number of negative tests for the whole country. These data were shared with a request for feedback sent both to the mailing list of the Swiss School of Public Health (SSPH+) and the ETH Domain COVID-19 Taskforce. At 6 PM an additional variable was added to a subset of the data; the date of onset of symptoms. The deadline for feedback was 9 AM on March 27.

An ad-hoc panel of experts from ETH Zurich / ETH Domain COVID-19 Taskforce, Swiss Tropical and Public Health Institute (Swiss TPH), and the Institute of Social and Preventive Medicine, University of Bern (ISPM Bern) met in a virtual space to provide timely feedback on the shared data, and considered responses to the questions from FOPH.

This document is the response of this panel to the questions raised by Brigitte Meier, structured as follows: in part 1 (pages 3-10), we present preliminary analyses and modelling of the data provided by FOPH, highlighting some key insights from these data. All data analyses were carried out by the team at ISPM Bern. In part 2 (pages 11-13), we address each of the four questions posed by the FOPH, based on the limited analyses that we were able to conduct in the short time frame. A short outlook is provided.

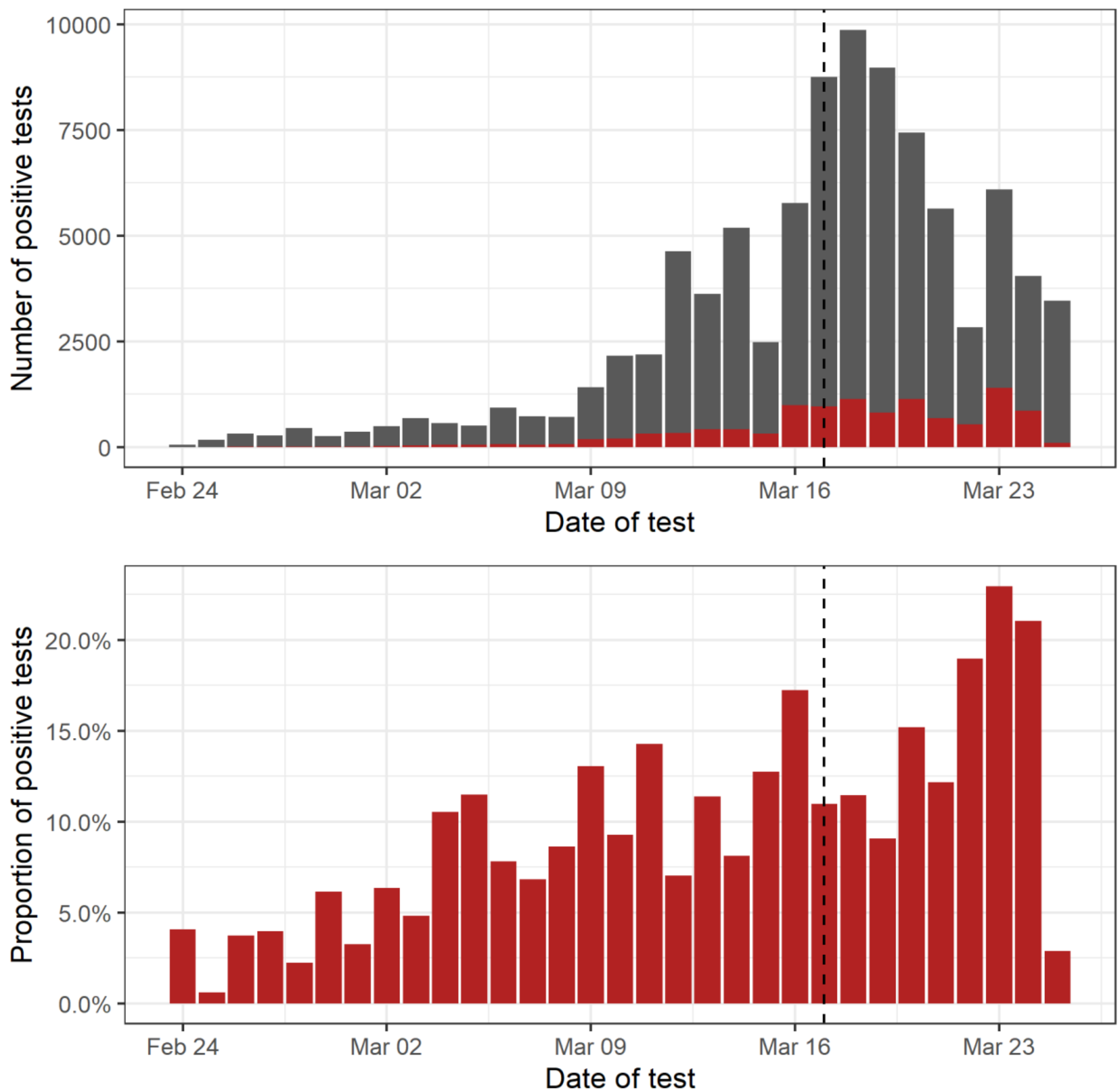
Part 1. Descriptive analyses

The data comprised two parts, confirmed positive tests and negative tests. The original individual line-listed dataset for confirmed cases with five variables: date of test (Falldatum), date of reporting (Eingangdatum), canton, age and sex. The data summarize 11,207 cases. The data were generally complete, with few missing data for sex (457 cases; 4.1%) or age (35; 0.3%). The additional variable, date of symptom onset, was available for 1130 cases (10.0% of all cases).

Note: the observed reported data are a subset of the true case count as the percentage of reported cases for Switzerland has been estimated at 38% (28% - 51%) (https://cmmid.github.io/topics/covid19/severity/global_cfr_estimates.html).

Figure 1 shows the numbers of reported cases of COVID-19 over time, in relation to the number of SARS-CoV-2 tests. The daily number of tests peaked on March 18, 2020. The continuing increase in the proportion of positive tests, even after the daily number of tests has decreased, suggests that testing is reaching the target groups, but does not identify all cases.

Figure 1. Top panel: numbers of reported cases (positive SARS-CoV-2 test result) and number of negative results by date of test. Bottom panel: test positivity by date of test



The SARS-CoV-2 epidemic in Switzerland varies geographically, with the four cantons of VD, TI, ZH and GE accounting for 58% of cases. Several cantons have fewer than 50 cases (AR, GL, NW, OW, SH, UR). Figure 2a and Figure 2b show that, while the numbers of confirmed COVID-19 cases are highest in VD, GE, TI and ZH, the rate of cases per 10,000 is the highest in TI, BS, GE, VD. The cantonal data appear to show different trends in case numbers (Figure 2a) and rates per 10,000 population (Figure 2b), although the instability in the daily rate is noted. For example, rates appear to show continuing daily increases in cantons BS, GE, TI but not in BE, BL or OW (Figure 2b). In-depth interpretation of these data would require data on the daily number of tests done in each canton.

Figure 2a. Number of reported COVID-19 cases by date of test and canton

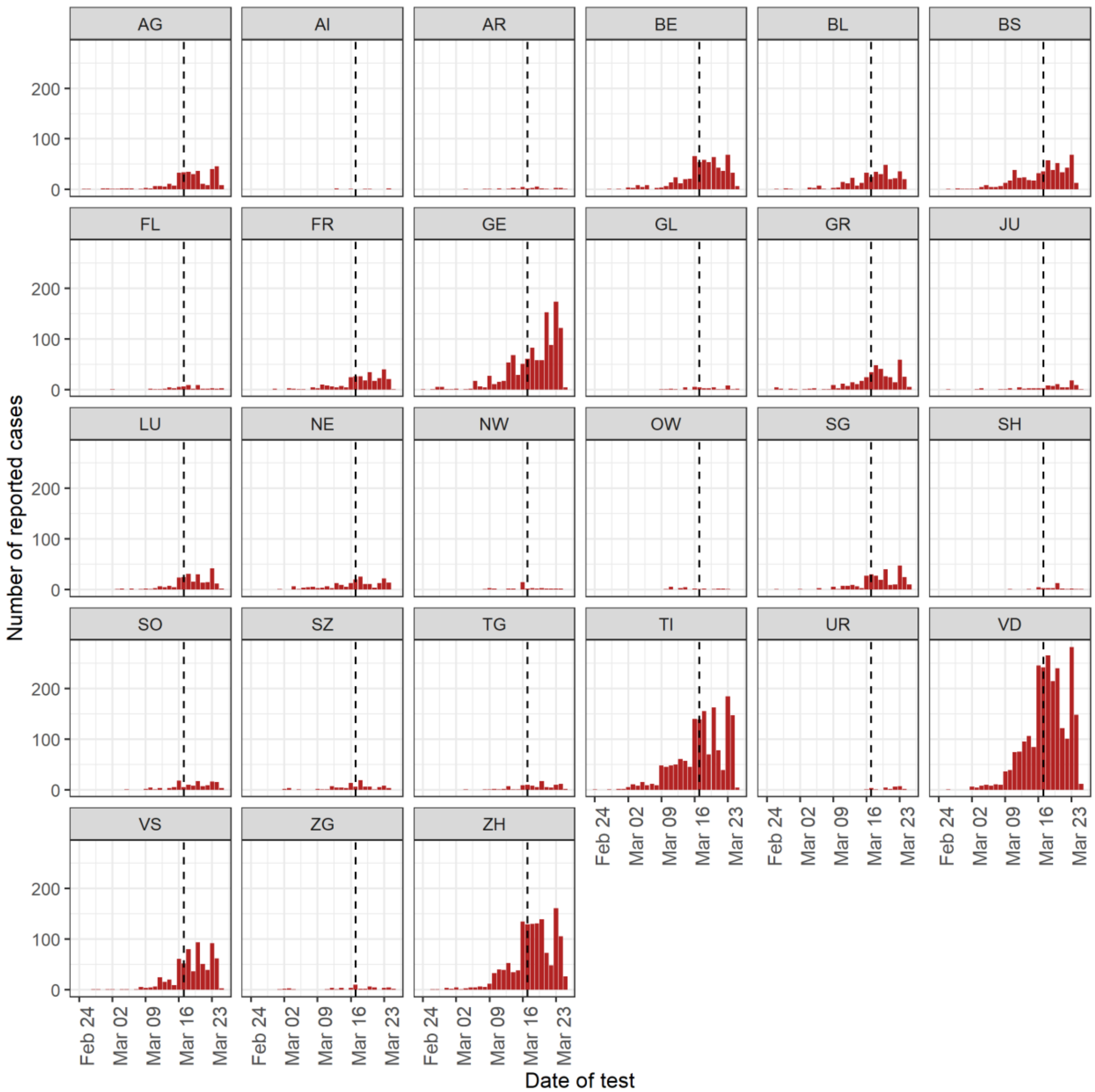


Figure 2b. Rate per 10,000 of reported COVID-19 cases, by date of test and canton

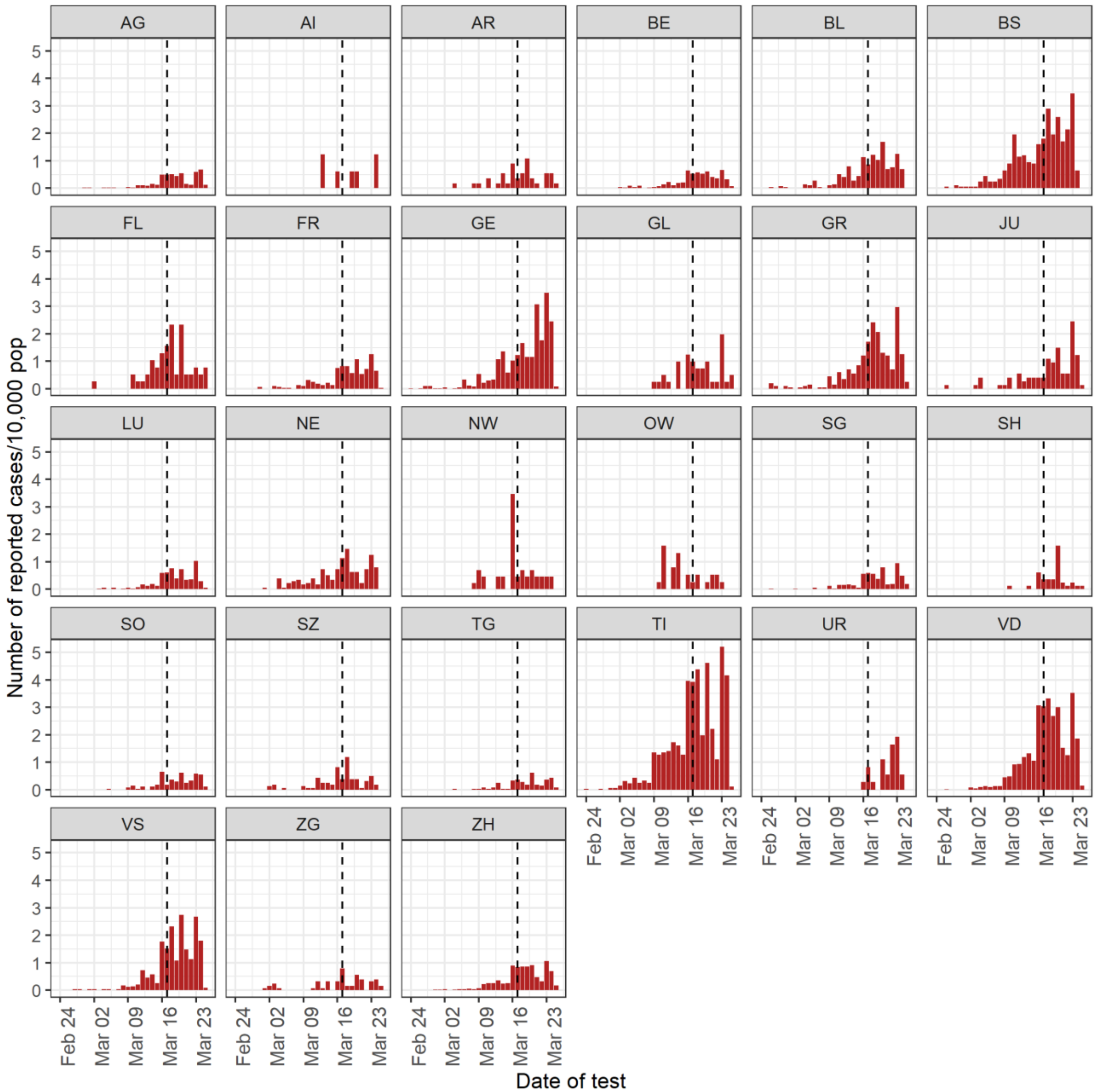
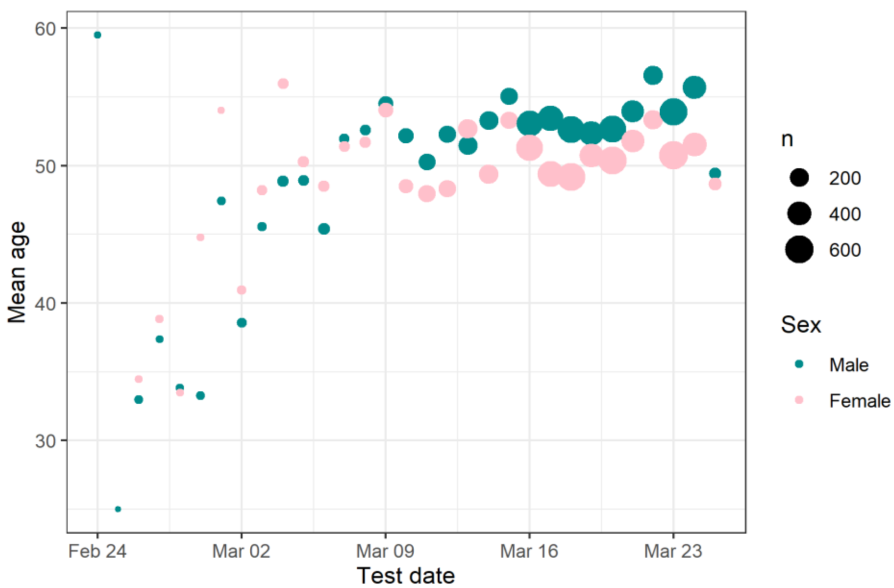


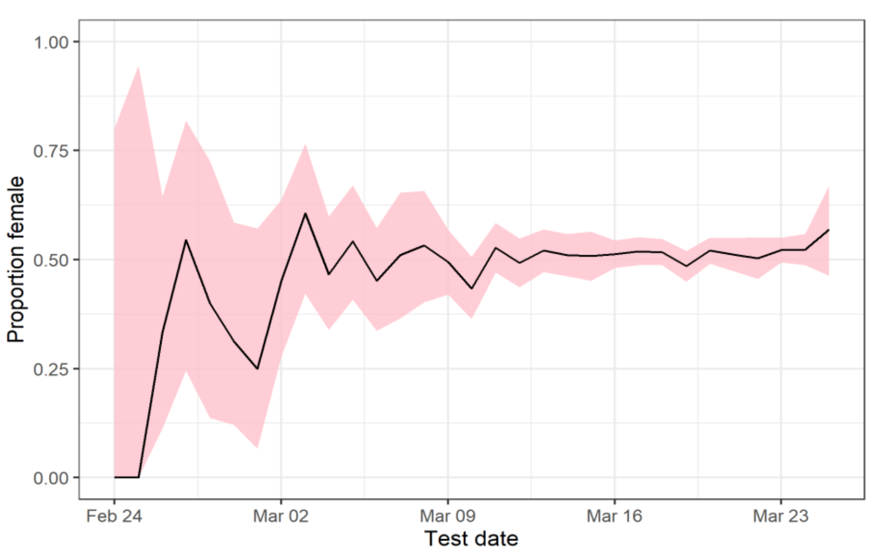
Figure 3 and Figure 4 give insights about the way that the epidemic in Switzerland has evolved over time by demographic characteristics of the cases. In general the earliest cases were in younger adults, presumably either returning travellers or their immediate contacts (Figure 3). The mean age of cases over time increases, with the men being older, on average than the women.

Figure 3. Mean age of reported COVID-19 cases by sex and date of test



As community transmission has become established, the mean age of reported cases has increased. The proportion of female cases has stabilized around 0.5 from the beginning of March onwards (Figure 4).

Figure 4. Proportion of female cases of reported COVID-19 cases by date



The analysis by canton shows a correlation between the rate per 10,000 and the mean age (Figure 5). The lower the rate the lower the mean age, again indicating that earlier in the epidemic more younger people are affected than later on, when the epidemic grew and the infection established itself in the general population.

Figure 5. Scatterplot of the cumulative number of reported cases per 10,000 population versus mean age

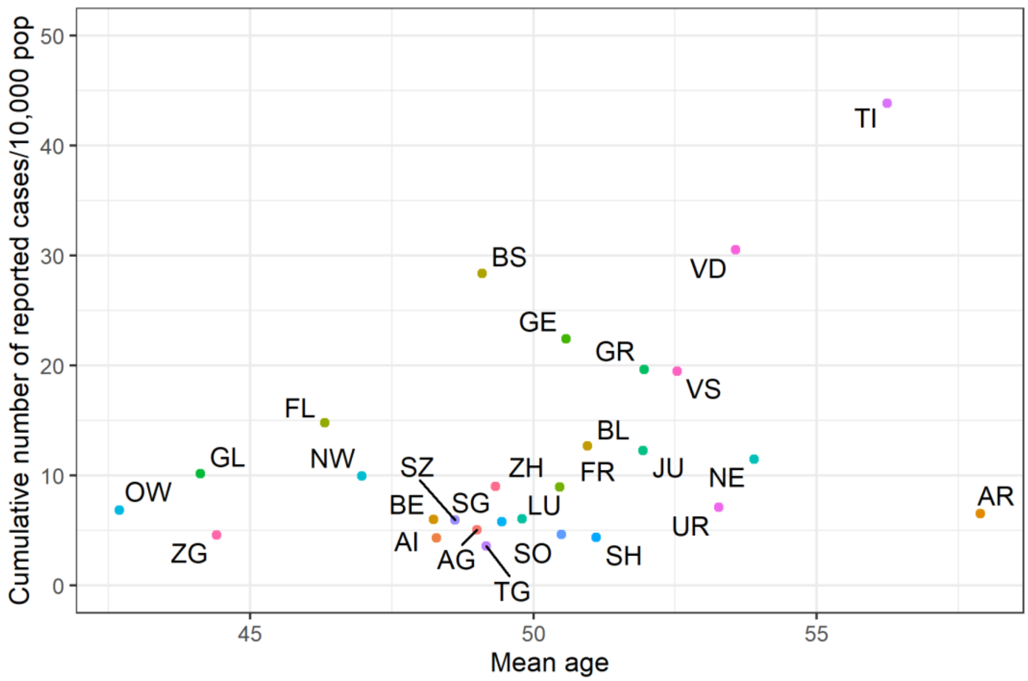
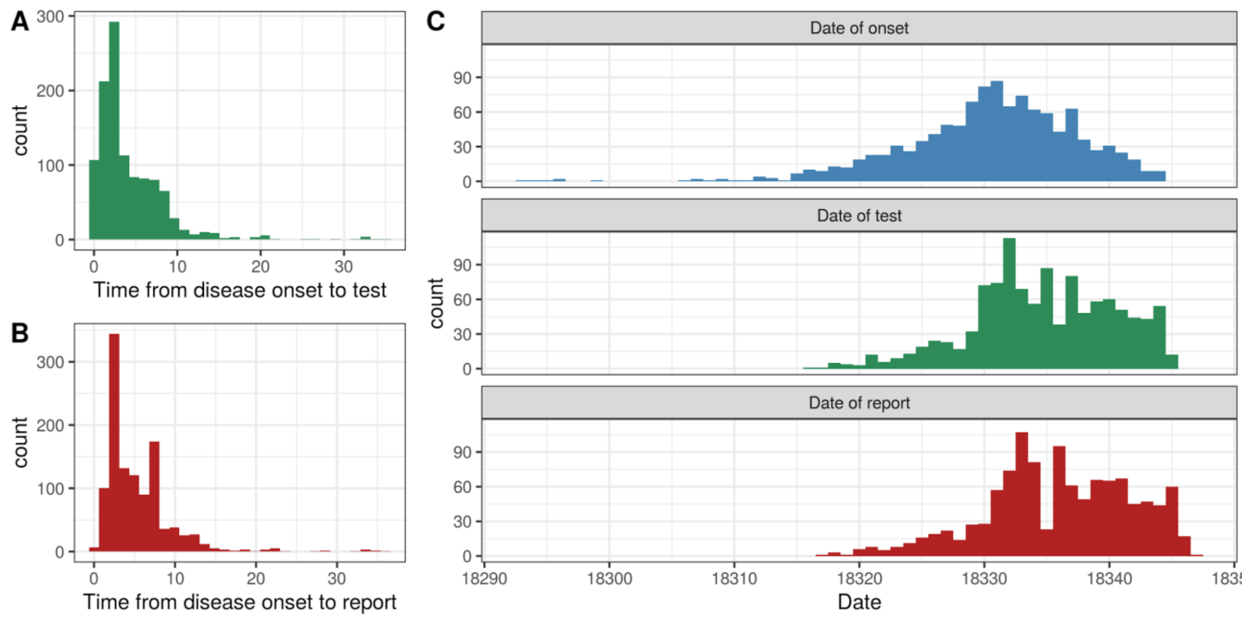


Figure 6 shows the analysis of the subset of cases with information on the date of onset. For this subset, the delay between reported symptom onset and reported date of test is quite short, median 3 days (interquartile range 1-6 days). The median delay from testing to reporting is 1 day (1-2 days).

Figure 6. Analysis of subset with information on date of onset (N=1130). Panel A shows the distribution of days from disease onset to positive test; Panel B the distribution of days from disease onset to reporting of the case. Panel C shows the dates of onset (blue), testing (green) and reporting (red).



Transmission model

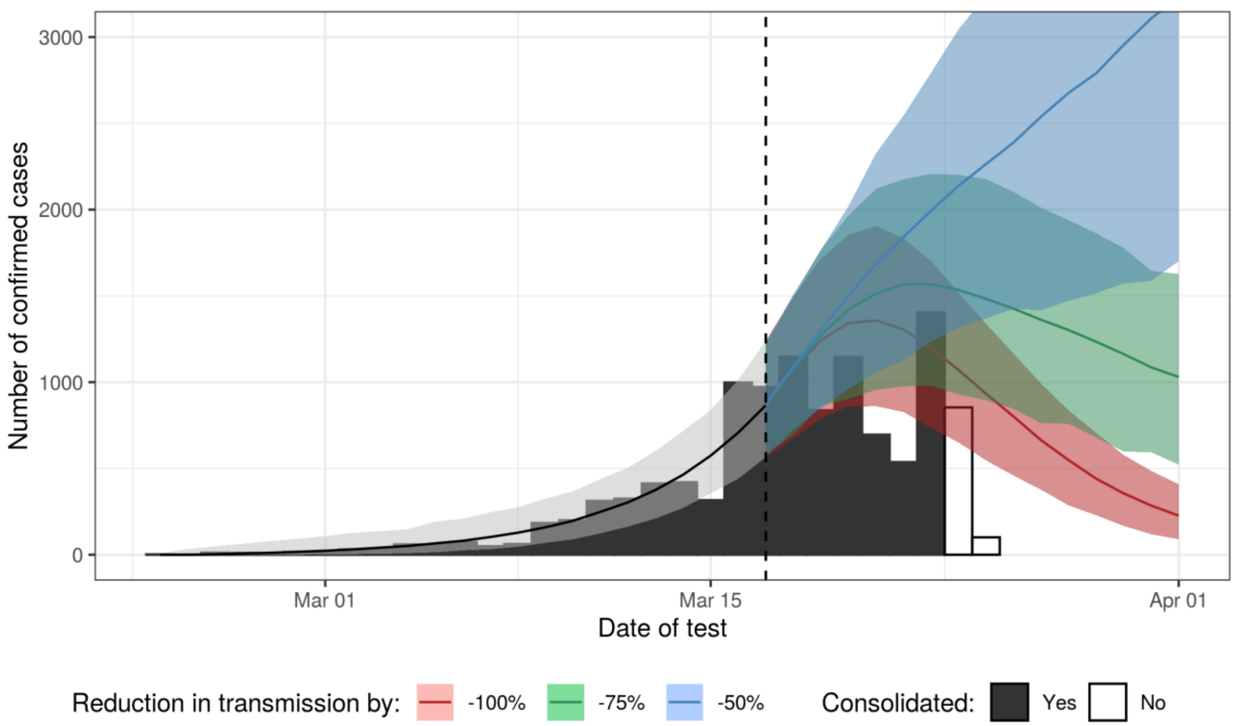
We developed the first preliminary version of a transmission model, based on the data provided by FOPH. Following a classic compartmental modelling approach, we divided the population into four groups: ‘susceptible’, ‘exposed’, ‘infectious’ and ‘recovered’. Equations determine how many people move between compartments as time passes. We account for the delay between infection and the first symptoms (date of disease onset) and between the first symptoms and being tested for SARS-CoV-2 (date of test). Fitted to the Swiss data until March 17th, the date of implementation of the control measures, the model allows predictions to be made on the course of the epidemic after this point, assuming different hypothetical scenarios for the effectiveness of control measures. Model predictions rely upon several assumptions: control measures were immediately effective, the proportion of cases that are identified and reported is stable in time, and the influence of past immunity to SARS-CoV-2 infection in the Swiss population on transmission is still negligible.

In Figure 7, we simulate three hypothetical scenarios, with a reduction of transmission by 100% (i.e. no more transmissions from March 17, when federal social distancing measures were strengthened, in red), reduction by 75% (in green) or reduction by 50% (in blue). The broken vertical line shows the date of the implementation of the strengthened measures on March 17.

It is not possible to say, at this date, which of the three hypothetical scenarios is most likely. The areas around the predicted number of cases (the red, green and blue areas) indicate the degree of uncertainty around these predictions. The uncertainty interval shows that all three hypothetical scenarios are compatible with the data on confirmed cases. Delay in reporting is another source of uncertainty in the interpretation of the number of confirmed cases: the open bars in Figure 7 indicate the number of confirmed cases likely affected by reported delays - these numbers may increase by today or tomorrow.

If the transmission of SARS-CoV-2 was interrupted completely by the strengthened social distancing measures, this will become evident by a decrease in the number of confirmed cases in the coming days. The downturn in the number of confirmed cases will probably become evident early in April if the transmission was reduced by 75%. Under the scenario of a 50% reduction of transmission, the number of cases will continue to increase.

Figure 7. Transmission model showing the expected evolution of the number of cases (bars with darker shading differentiating consolidated cases), assuming that the strengthened social distancing measures reduced transmission by 100% (red curve), 75% (green curve) or 50% (blue curve) from March 17th.



Part 2. Responses to the questions posed to panel

Question 1. ***How should the epidemic curve be interpreted? Increasing, decreasing, stable trend?***

We emphasize that the data provided are not themselves the epidemic curve, which would include all infections. The data available are only the confirmed cases. In our view, it is too early to infer either the trend of the epidemic curve or the magnitude of the effect of the control measures implemented since 17 March. The main difficulty in making inferences is the intrinsic biology of the virus, which means that the confirmed cases today reflect transmission 2-3 weeks ago. This period comprises the delay of 5-6 days after infection (mean incubation period 5-6 days, range 1-14 days) to the onset of symptoms [3], the estimated median delay of 3 days (interquartile range 1-6) from the onset of symptoms to swab to the reporting date recorded in the database, the median delay of 1 day (interquartile range 1-2) from the swab until confirmation (Figure 6), and finally the lag in isolation of symptomatic cases. Furthermore, due to delays in updating the number of reported cases, the last three days should be interpreted with caution. In China, where there was full lockdown, the time from onset to reporting of confirmed cases decreased from 12 days (range 8-18 days) at the start of the outbreak down to 3-5 days (range 1-9 days) at the end.

The model fitted by Julien Riou and Anthony Hauser of ISPM Bern (Figure 7) indicates considerable uncertainty in the future trajectory because we expect similar numbers of cases during the next few days regardless of the reduction in the contact rate achieved by the measures (see areas in red, green and blue covering the next few days). The resulting uncertainty implies that we need to be prepared for the continued growth of the epidemic, especially given the trends observed in other countries with varying control measures. Addition of data about cases reported in the immediate future will considerably improve our ability to model and predict the effectiveness of the interventions and of the final size of the epidemic.

Question 2. ***Do you think that the data allow to evaluate the effect of the measures taken, and if so, how? If not why?***

As explained above, the data shared by FOPH represents an important information source that should make it possible to estimate the intervention effectiveness once a longer time series of the same kinds of data is accrued, but this will require at least a week's more data. Additional parameters, including date of onset of symptoms in confirmed cases, could make it possible to estimate the trends with more confidence and to determine the impact of the control measures sooner. Some of the trends in the data are perhaps being masked by variations in testing rates. These trends would be clearer if the numbers of negative test results were available disaggregated by canton and ideally, age and sex. The analysis by canton indicates that the most intense outbreaks are quite local and that in much of Switzerland it might still be possible to avert a major outbreak by contact tracing if this is implemented very soon with a state-of-the-art information system.

Question 3. ***What can be learned from the data despite these quality problems?***

It is not the quality of the data, but rather the latent periods inherent in the epidemiology that limit the inferences that can be made from these data. Given the extraordinary conditions under which the data were assembled, curation was inevitably a challenge, and we are unsure what specific quality problems are referred to here. We have commented on the implications of temporal variation in the testing rate in the previous paragraph. Despite the noise and delay in reporting, our initial analyses highlight several important trends on transmission dynamics

1) There is substantial inter-cantonal variation in the rate of increase of confirmed cases.
2) The average age of confirmed cases increased as the epidemic developed, probably because many of the initial cases were detected by contact-tracing while later cases were ascertained in the clinic, leading to an overall age distribution closer to that of severe cases. Inferences about age dependence in susceptibility to infection cannot be made in the absence of an age breakdown of the negative test results.
3) The flatter age distributions in the larger urban centres, in comparison to TI, also very likely result from the role of a young urban population in establishing and maintaining transmission (see Appendix Figure A1),
4) The mean age has not changed since the 3rd March implying that the change in the criteria for testing after 13 March did not change the mean age of the confirmed cases.
5) There is an age-gender interaction in the incidence. In younger age groups, there are more women among confirmed cases (% women in the 20-29 age group), and in the older age groups, confirmed cases are predominantly men).
6) WHO stresses the key importance of testing to estimate the extent of the epidemic in each country [2]. Analyses of test results should be used to underpin decisions on when to intensify or relax control measures and the testing results are invaluable in providing clear evidence of very substantial inter-cantonal variation in the epidemic growth rate. Underreporting is probably substantial and increasing testing would provide much better indications of the progression of the epidemic. Unfortunately, the currently available testing results exhibit various biases resulting from delays in reporting (e.g. fewer results at weekends, differential delays in reporting of negative results), and are clearly a highly unrepresentative sample. Clinical diagnosis clearly has poor specificity (physicians have difficulty identifying which patients to test) so case detection depends on testing as many cases of uncertain diagnosis as possible. As testing capacity has increased, we were hoping that the proportion of tests with a positive result would decline, with tests being increasingly used to diagnose uncertain cases, rather than for confirmation of severe cases only. This has not happened. The proportion of tests with a positive result has remained more or less constant, consistent with little or no change in the proportion of cases that are detected. This is of serious concern because the control of the epidemic may ultimately depend on tracing an increasing proportion of contacts.

Question 4. ***What would be your reply if you were asked how this epidemic will evolve in the near future? Especially with regard to the capacities in the medical system?***

The future course of the epidemic remains highly uncertain (Figure 7), implying that we must prepare for the case where the epidemic grows to levels that will severely strain our health system, but it is unclear exactly which capacities are referred to in Q4. The panel currently lacks data on which to base judgements on the adequacy of the supply of ICU beds, ventilators, protective clothing, or trained and uninfected staff. The capacity for testing (see Q3 above) is the other critical element of the health care system and the extent to which this may be constrained by supply chain or human resource issues, such as lack of reagents, or insufficient numbers of functioning laboratories is unclear.

Outlook

The panel very much appreciated the opportunity to analyse the data, and our preliminary analysis and models will be further updated in the coming days. Daily updating of these data will enable us to improve our estimates, as would additional data types, including:

- Date of onset of symptoms for all confirmed cases
- Disaggregation of negative test results by age, sex and canton.

Any finer temporal or spatial disaggregation of these data would improve the capacity to analyse the epidemic curve. While we acknowledge the difficulties in compiling additional kinds of data at short notice, the assessment and planning of control measures and clinical interventions would benefit from the sharing of any information on:

- the criteria used to decide whether to test in each canton or centre at each time.
- the supply chain for tests (how many tests were available where on which date) and whether there are any known limits on testing owing to lack of laboratory capacity or consumables.
- the numbers of ICU beds operating, their locations at different times, and if there are critical human resource issues (e.g. staff falling sick).

References

1. Real-time modelling and projections of the COVID-19 epidemic in Switzerland. URL: https://ispmbern.github.io/covid-19/swiss-epidemic-model/
2. WHO laboratory testing strategy recommendations for COVID-19: https://apps.who.int/iris/bitstream/handle/10665/331509/WHO-COVID-19-lab_testing-2020.1-eng.pdf
3. World Health Organization. Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19). URL: https://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf