Impact of cross-border-associated cases on the SARS-CoV-2 epidemic in Switzerland from June to September 2020

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Abstract

Introduction: In Switzerland, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) epidemic grew from a few dozen confirmed cases to several hundred cases per day during summer 2020. During this time, holiday travel without quarantine or having tested negative for SARS-CoV-2 was largely allowed. Travels to higher incidence countries might lead to more SARS-CoV-2 cases. The impact of potential cross-border-associated cases (imports) on the national epidemic dynamics remained unclear. Our objective was to assess the impact of imports on the SARS-CoV-2 epidemic in Switzerland during summer 2020.
Method: We analysed individual data on confirmed SARS-CoV-2 cases reported by the Swiss Federal Office of Public Health (FOPH) from 1 June to 30 September 2020. We used a stochastic branching process model that accounts for super-spreading of SARS-CoV-2 to simulate epidemic trajectories in absence and presence of cross-border-associated cases.
Results: From June to September 2020, a total of 23,199 SARS-CoV-2 cases were reported in Switzerland. For 12,259 (53%) of these cases, the most likely country of exposure was available and 3,304 (27%) declared that exposure was most likely abroad. Assuming that all cases were infected locally (no imported cases), we estimated the effective reproduction number $\mathcal{R}_e$ above the critical threshold of one (1.08, 95% credible interval, CI: 1.04-1.11). In contrast, we estimated $\mathcal{R}_e$ to 0.84 (95% CI: 0.81-0.87) if imports were taken into account.
Discussion: In Switzerland, imports have had a considerable impact on the national dynamics and can explain the growth of the SARS-CoV-2 epidemic during summer 2020.

1 Introduction

At the beginning of 2020 the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spread to many countries around the world, which shortly afterwards led to the SARS-CoV-2 pandemic.[1] Since then many have been aiming to minimise the SARS-CoV-2 cases and associated deaths. In spring 2020, cross-border-associated cases were most likely responsible for many local outbreaks around the wolrd.[2] With a high number of introductions, i.e., cross-border-associated cases, the local effective reproductive number $\mathcal{R}_e$ was likely overestimated.[3] The $\mathcal{R}_e$ represents the average number of secondary cases per infectious case in a population with a given state of susceptibility and particular measures of prevention and control in specific place excluding new introductions. Thus, cross-border-associated cases, i.e., new introductions, should not effect the (local) $\mathcal{R}_e$. For summer 2020, the impact of such cross-border-associated cases in Switzerland remained largely unknown.

After unprecedented measures - closure of public institutions, leisure facilities, schools and universities, mandatory home office and closing of borders - in April and May 2020, Switzerland and other European countries reopened their borders allowing for travel. Switzerland reopened borders on 15 June 2020 to countries of the Schengen area.[4] With 8,5 millions citizens Switzerland is a relatively small country in the heart of Europe with borders to Germany, France, Italy, Austria and Liechtenstein. Thus, many different countries were easily visited by the Swiss and conversely, many citizens from other countries might visited Switzerland. Between June and September, 2020, the Swiss Federal Office of Public Health (SFOPH) reported a slow increase in the number of reported SARS-CoV-2 cases from a few dozen per day to several hundreds.

In the absence of travel restrictions, cross-border-associated cases are to be expected.[2] A phylogenetic analysis showed the of cross-border-associated cases.[6] In summer 2020, the SARS-CoV-2 variant, 20E (EU1), that most likely originated in Spain spread multiple times to several other countries including Switzerland.[6] It revealed failures in travel control during the pandemic, e.g. there were travels to higher incidence countries without adequate contact tracing and containment.[6]

Previously, stochastic branching process models were used to find trajectories that were consistent with surveillance data.[7, 8] It helped to determine epidemiological parameters such as the $\mathcal{R}_e$ or the over-dispersion parameter.[7, 8] In this study, we used a stochastic branching process model to find the most plausible trajectories of the summer 2020 epidemic in Switzerland. We analysed reported SARS-CoV-2 cases and the most likely country of their exposure, i.e., where they had been the last 14 days before they got tested or began to have symptoms. Then we selected epidemic trajectories that were consistent with data reported by the SFOPH. We quantified the impact of cross-border-associated cases on the local SARS-CoV-2 incidence and $\mathcal{R}_e$ in Switzerland between June and September 2020.

2 Method

2.1 Data

We analysed surveillance data of the SARS-CoV-2 epidemic in Switzerland from 1 June to 30 September 2020. For the purpose of this study, we used individual data on positive cases reported by the SFOPH. Data included for each case: age, sex, date of diagnosis or registration, and the most likely country of exposure, i.e., a country where they had been within the last 14 days before they got tested or began to have symptoms. We considered the 23 most frequently reported countries of exposure including Switzerland. Other countries (mentioned less than ten times) were grouped to 'others'. We grouped individuals into three categories based on their age: <21 years, 21-64 years and >64 years.

2.2 Inferring growth rates and $\mathcal{R}_e$

We fitted a negative binomial generalised linear model to the daily number of reported cases of SARS-CoV-2 infections y starting on 1 June to 30 September 2020:

$$\log(\mathrm{E}(y|t)) = a + rt, \tag{1}$$

where a is an intercept, r is a growth rate and t is the time in days. Thus, we estimated a constant growth rate r for the whole study period. Growth rate and reproductive number can be derived from each other taking into account the generation time, i.e. time between the infection of a primary case and one of its secondary cases.[11, 12, 9] This approach assumes that acquired immunity was minimal during the period of interest, and that the reporting rate was stable. We assumed a gamma distributed generation

time with shape α and rate β, leading to the relation:

$$\mathcal{R}_e = (1 + \frac{r}{\beta})^{\alpha}. \quad (2)$$

For SARS-CoV-2, a mean generation time of $\mu = 5.2$ days with a standard deviation of $\sigma = 1.72$ was reported.[13] Parameters α (gamma shape) and β (gamma rate) were given by μ and σ as $\frac{\mu^2}{\sigma^2}$ and $\frac{\mu}{\sigma^2}$, respectively.

2.3 Epidemic simulations

We simulated epidemics for 1 June to 30 September 2020 using a stochastic branching process model that accounts for super-spreading in transmission of SARS-CoV-2.[8] The branching process was based on a negative-binomial distribution for the distribution of secondary cases, with a mean of $\mathcal{R}_e$ and over-dispersion parameter k. The generation time for each transmission event was sampled from a gamma distribution as described in the previous section.

Within our branching process model we considered different values for $\mathcal{R}_e$, for k and for the seed – the number of infectious individuals during the week preceding the start of the simulation (Table 1). We considered a wide range of values for $\mathcal{R}_e$, from 0.5 to 1.5. For k, we considered values between 0.49 and 0.5 as estimated from contact tracing data in India[14], and in sensitivity analyses we also considered values of 0.1 and 1.[15] For the seed, we used the estimate of the intercept ($\exp(a)$ in equation 1) with its 95% confidence interval, resulting in values of 12 to 33 cases per day (this corresponds to 94 to 222 cases from 25 to 31 May 2020, where the SFOPH reported 126 cases in Switzerland this week).

The simulations proceeded as follows. Firstly, we simulated 10^5 epidemic trajectories with the branching process model, randomly sampling parameter values in each iteration, except for the number of cross-border-associated cases that was fixed to 0. These trajectories only accounted for local transmission. We removed trajectories leading to a cumulative incidence over 10^6 (43 times more than the 23,199 cases reported over the period). Secondly, we considered cross-border-associated cases. In a baseline scenario with no cross-border-associated cases, the trajectories were kept as such. In other scenarios, cross-border-associated cases were added to each trajectory according to the date of test. Cross-border-associated cases were equally likely to transmit, initiating new branches of local transmission as all other cases (Figure 1d). The SFOPH reported 3,354 of such cases during the study period, but the information on the country of exposure was missing for 10,940 out of 23,199 (47%). We thus considered three different scenarios for the total number of cross-border-associated cases: 3,354 (actual reports), 5,050 (assuming 2/3 of cases with missing exposure were exposed abroad) and 7,573 (assuming 3/2 of cases with missing exposure were exposed abroad).

2.4 Inference

Following the principles of approximate Bayesian computation (ABC), simulated epidemic trajectories were rejected when the cumulative incidence and final incidence fell outside of a predefined range.The predefined range for cumulative incidence and final incidence were constructed using SFOPH reports on confirmed cases. We used the fitted negative binomial model to obtain 95% prediction intervals of (1) the cumulative incidence of all reported cases from 1 June to 30 September 2020, and (2) the final incidence from 24 to 30 September 2020 divided by 7.

All analyses were preformed using *R* *v*.4.0 with following packages `MASS, MCMCglmm, doParallel, foreach, lubridate, reshape2, ggplot2, ggpubr, grid, gridExtra` .[16, 17]

3 Results

In total 23,199 cases were reported to the SFOPH between 1 June to 30 September 2020 (Table **??**). Of them, 13,929 (48%) were female and 14,985 (52%) were male. For nine individuals the gender was not known. For 12,259 (53%) cases the most likely country of exposure was reported. Of them, 3,304 (27%) reported an exposure abroad (Table **??**); Figure 1). Of all exposures that were likely to have happened abroad, 1,562 (44%) were female and 2,000 (56%) were male. The peak of reported cross-border-associated was on 6 September 2020 with 105 cases (Figure 1c,d).

The study population was 34 (interquartile range (IQR): 24-50) years and individuals that had an exposure abroad were 31 (IQR: 23-48) years (Table **??**). Individuals who reported that Switzerland was the only country they had visited within the last 14 days were 35 (IQR: 24-51)

Table 1: Prior distributions of the parameters used to simulate the epidemic trajectories.

Parameter	Description	Values considered	Sampling strategy
$\mathcal{R}_e$	Effective reproductive number	0.5 - 1.5	10^5 uniformly distributed
k	Over-dispersion parameter	0.49 - 0.52	10^5 normally distributed*
n	Seeds	12 - 32 per day	for 7 days before simulation start
I	Imports	0; 3359; 5050; 7573	four scenarios**

years. Different age categories were more likely to visit some countries during summer (Table **??**); Supplementary Figure 2). At the beginning of June 2020, none of the 21 countries with at least a dozen returnees with a SARS-CoV-2 infection between June and September was on the list where returnees had to do quarantine. In July 2020 the list was including five countries of 21 countries. In August and September 3 respectively 10 additional countries were added to the list. End of September 5 of 21 countries had not been on the list during summer.

Beginning of June 2020 Switzerland had an incidence of 0.17 per 100,000 citizens (3 cases) and at the end of September 5.36 (540 cases; Figure 2c). The latter was also the maximum value during the time of interest. Accordingly, there was an increase of cases during the summer months. Assuming a constant growth, we estimated an epidemic growth rate of 0.03 (95%-confidence interval (CI): 0.02-0.03) per day and a $\mathcal{R}_e$ of 1.15 (95%-CI: 1.14-1.16) for June to September 2020. We estimated the 95%-CI of cumulative incidence of 17,019 to 30,533 cases for the period from 1 June to 30 September 2020 (23,199 cases were reported by the SFOPH; Figure 1a). For the final incidence the 95%-CI laid between 93 to 762 cases for the last day. The mean of the reported cases for the last week was 338 cases per day.

With the branching process model we simulated epidemics using different number of cross-border-associated cases. Overall, 12,884 of $4*10^5$ (3.22%) trajectories were within the 95%-CI of the expected cumulative incidence and final incidence. The basic model assumed no new introductions which was not the case for the Swiss epidemic and thus, $\mathcal{R}_e$ was an over-estimation. Accounting for new introductions required to re-evaluate the intensity of local transmission, i.e. the value of $\mathcal{R}_e$, to match the observed dynamics of SARS-CoV-2 in summer 2020. Assuming no introductions, 126 (0.13%) trajectories were within the 95%-CI of the expected cumulative incidence and final incidence. The $\mathcal{R}_e$ was 1.08 (95%-CI: 1.04-1.11; which was lower than the $\mathcal{R}_e$ derived from the calculation2.2; Figure 1ab; Supplementary Figure 1). The basic branching process model was then extended with three scenarios, i.e., 3,359, 5,050, 7,573 introductions of cross-border-associated cases. In extended models, all cases, i.e., cross-border-associated cases and local cases, were equally likely to transmit SARS-CoV-2. For 5,050 introductions, corresponding to an extrapolation of 3,304 cross-border-associated cases, 9,197 (9.29%) trajectories were within the 95%-CI of the expected cumulative incidence and final incidence (Table **??**; Figure 1). These 9,291 trajectories had a $\mathcal{R}_e$ of 0.84 (95%-CI: 0.81-0.87) (Figure 1ab; Supplementary Figure 1). For 3,359 and 7,573 introductions, corresponding to an extrapolation of 3,304 cross-border-associated cases and a multiplication with 2/3 and 1.5, 2,878 (2.88%) and 589 (0.59%) trajectories were within the 95%-CI of the expected cumulative incidence and final incidence (Table **??**; Figure 1). Needs to be revised with a new prior distribution 0f 0.5-1.5: These 2,878 and 589 trajectories had a $\mathcal{R}_e$ of 0.91 (95%-CI: 0.88-0.93) and $\mathcal{R}_e$ of 0.80 (95%-CI: ¡0.80-0.82) (Figure 1ab; Supplementary Figure 1). To be noted, we were not able to estimate a $\mathcal{R}_e$ below 0.80.

4 Discussion

The SARS-CoV-2 epidemic in Switzerland grew from a few dozen confirmed cases per day in early June 2020 to several hundred by the end of September 2020. Ignoring cross-border-associated cases a constant $\mathcal{R}_e$ was above one for the time of interest. In summer 2020, however, around a quarter of cases that had been reported by the SFOPH were cross-border-associated cases. We also found that different age groups were exposed to the SARS-CoV-2 in different countries abroad. With our stochastic branching process we showed that the local epidemic had a $\mathcal{R}_e$ below one, i.e. a value below the critical threshold. At the end of summer 2020, the reported cases stabilised (also in simulations if $\mathcal{R}_e < 1$). Thus, cross-border-associated cases and their local spread was one of the leading forces that led to several hundred

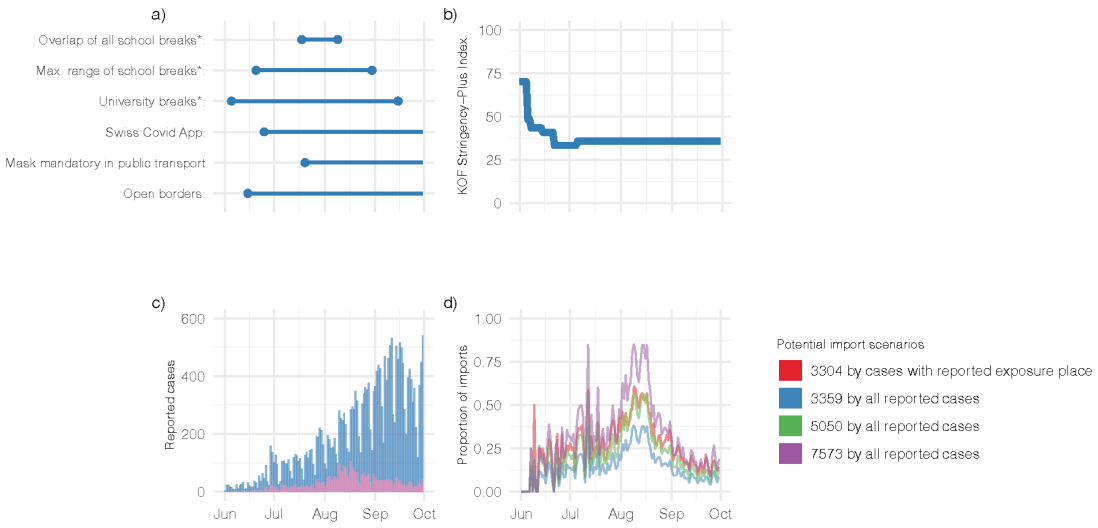

Figure 1: The Swiss SARS-CoV-2 epidemic in summer 2020: a) Five major events that might influenced the Swiss epidemic from 1 June to 30 September, 2020. b) The KOF stringency plus index records the stringency of COVID-19 policy measures in Switzerland over time. The values range from 0 (= no measures) to 100 (= full lockdown) (see here). c) All reported cases per day (blue) and 3,304 cross-border-associated cases (pink). d) Three cross-border-associated scenarios, i.e., 3,359, 5,050, and 7,573, that were evaluated in the branching process model. The SFOPH reported 3,304 cross-border-associated cases and 53% reported cases the most likely country of exposure. ∗Official breaks of universities and schools might vary for different subjects and between different schools and cantons, respectively. More details on quarantine measures in Table **??** and here.

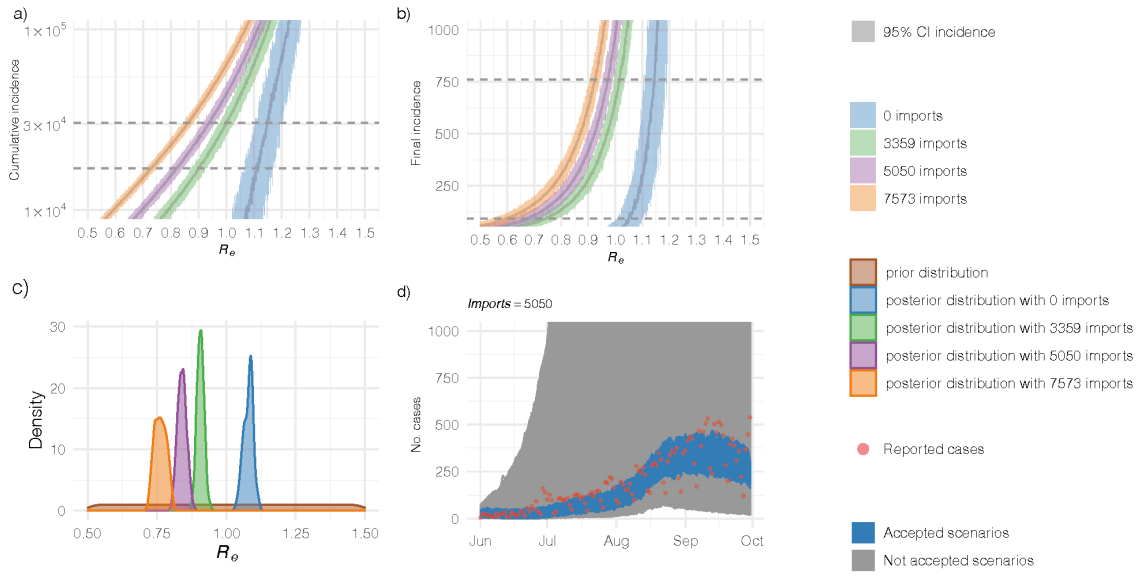

Figure 2: Impact of cross-border-associated cases on the local epidemic. a) Curves represent 95%-CI and median of simulated cumulative incidence with zero, 3,359, 5,050, and 7,573 cross-border-associated cases; expected 95%-CI of cumulative incidence during 1^{st} June to 30^{th} September 2020. b) Curves represent 95%-CI and median of simulated final incidence with zero, 3,359, 5,050, and 7,573 cross-border-associated cases; expected 95%-CI of final incidence on 30^{th} September 2020. c) Prior and posterior distribution of $\mathcal{R}_e$ with zero, 3,359, 5,050, and 7,573 cross-border-associated cases. d) Branching trajectories with 5,050 cross-border-associated cases that were within the 95%-CI of final incidence and cumulative incidence. The 95%-CI of the $\mathcal{R}_e$ of accepted simulations was: 0.84 (95%-CI: 0.81-0.87). Abbreviations: CI, credible interval; R_e, the reproductive number

cases per day within three months, i.e., by the end of September 2020. Consequently, the effect of cross-border-associated cases cannot be ignored in understanding and regulating a local epidemic (during a pandemic).

Our method has several limitations that need to be addressed. In our stochastic branching process, we did not account for a seasonal effect of the SARS-CoV-2, different restrictions carried out, social contact pattern or age-related mixing patterns. With our model, we were not interested to simulated single transmission chains. Our stochastic branching process was calibrated to assess the impact of cross-border-associated cases on an epidemiological, i.e. population-based, level. Stochastic effects were showed to play an important role in determining parameters in epidemics.[7, 8] The resulted trajectories represented the Swiss epidemic and ignored geographical differences, i.e. cantons. We found no evidence of relevant geographical differences of cross-border-associated cases (Supplementary Figure 3). Our approach assumed a constant growth rate over the summer period and ignores immunity, which we consider acceptable during this low prevalence and incidence time: The SFOPH reported 30,883 cases before 1 June and 23,199 more until 30 September, 2020. Moreover, growth rates, can be calculated for different intervals, e.g., one week or months and adjusted for different factors, after sensitivity analysis we assumed a constant growth rate without any adjustment. A constant growth rate and $\mathcal{R}_e$ was more compatible to calculate the overall impact of cross-border-associated cases.

We assumed that cross-border-associated cases transmit as likely as local cases. However, different quarantine rules applied for different countries. Our assumption is justified as we parameterised and validated our model using reported cases. These were tested positive and thus obligated to do quarantine. More sophisticate models adding different scenarios of further transmission might be useful to guide policy making. One might investigate the delay of reporting of not cross-border-associated cases and different degrees of complying quarantine better than local cases and to differences in the probability of being tested.

We validated simulated trajectories on well reported data. However, it is unlikely that all SARS-CoV-2 cases in Switzerland had been tested, but in Switzerland all cases tested have been reported to the SFOPH. Studies reported about a two-fold (or more) underreporting of SARS-CoV-2 infections.[18, 19] [The degree of under-ascertainment was not evaluated for the Swiss surveillance data. Thus, we focused on reported cases as it represents the Swiss epidemic well. Moreover, there is a delay of infection to testing and reporting. We ignored this delay for all cases. Thus, our simulations reflected the day of testing and reporting and not the start of infection. During the time of the study, testing was free and mandatory for symptomatic cases, but not for asymptomatic cases. However, if they had contact with a positive person they were required to do quarantine and test themselves. The contact tracing was provided either by infectees themselves, through authorities or the Swiss Covid app (launched on 15 June 2020).[20]

As our study period covered summer months only, seasonality had no influence. However, people were more active during summer than during winter and probably more optimistic about the pandemic (mostly at the end of summer 2020), which most likely resulted in more physical contacts than before. Tracking contact patterns, i.e., behaviour, can give a more rapid assessment of the impact of physical distancing measures than routine epidemiological surveillance.[21] Unfortunately, social contact patterns or age-related mixing patterns are missing for this time period in Switzerland. Such information of a representative study population, like established by the CoMix study, is needed to better understand the social dynamics.[22] This highlights the importance of implementing and following up the CoMix study and other studies. Our study indicates that to understand the spread of SARS-CoV-2 age-related mixing patterns need to be known. However, close contact alone is not responsible for SARS-CoV-2 transmission. Some transmission cluster were linked to crowded indoor spaces which underlines the possibility of aerosol (and droplet) transmission.[23]

Our study design was appropriate for our research question. Nevertheless, there is a need of analyses that include several more variables, such as age-related mixing patterns and seasonal changes. These would help to more precisely forecast future outbreaks and pandemics. From our findings travel strategies might be derived, including mandatory quarantine and test strategies for the coming summer 2021. Also in other countries, travel and resulting new introduction had a strong impact on the local epidemic.[1, 2, 6] Most likely (global) herd immunity will not be achieved in the summer 2021, so existing mea-

sures such as testing and physical distancing remain important to keep the incidence low. In addition, there is still uncertainty about asymptomatic cases.[24, 25] Studies found the proportion of asymptomatic cases to be 17% (or 20%) and 1/4 less transmissible.[26, 25, 27] It could be an option to test all people that cross borders and give them the option of reduced quarantine for negative cases.[28] Mandatory quarantine and testing might reduce the willingness to travel as it keeps awareness of the SARS-CoV-2 pandemic high and includes extra effort and expenses. Travel mobility might be reduced, and cross-border-associated cases and their local spreading might be minimised through testing and mandatory quarantine. Here we need to emphasised that one case might lead to an outbreak thus population based surveillance including reporting of countries of exposure and viral sequence data is crucial for appropriate measures.[1] Worbey highlighted the need to detect new introduction and transmission clusters early through routine, massive, sequence based approaches — not months or years later, when clinical symptoms have accumulated.[1]

Switzerland is a relatively small country with few million citizens, but due to its location (and its wealth) there is a high potential for travel which might have a huge impact on the epidemic. Quantifying the role of imports on the national dynamics of SARS-CoV-2 epidemics requires further investigation. However, in Switzerland, cross-border-associated cases have had a considerable impact on the national dynamics and could explain the growth of the SARS-CoV-2 epidemic during summer 2020. Our results underline the importance of improved surveillance for international travellers in order to better control the spread of SARS-CoV-2.

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6 Author contributions

MLR, EBH, JR, NAR, and CLR conceived the study and contributed to the analysis of the results. MLR performed the analysis and wrote the first draft of the manuscript. NH gave important inputs for the analysis and interpretation. All authors read and approved the final manuscript.

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8 Reference

References

[1] Worobey M, Pekar J, Larsen BB, Nelson MI, Hill V, Joy JB, et al. The emergence of SARS-CoV-2 in Europe and North America;370(6516):564–570. Available from: https://www.sciencemag.org/lookup/doi/10.1126/science.abc8169.

[2] Russell TW, Wu JT, Clifford S, Edmunds WJ, Kucharski AJ, Jit M. Effect of internationally imported cases on internal spread of COVID-19: a mathematical modelling study;6(1):e12–e20. Available from: https://linkinghub.elsevier.com/retrieve/pii/S2468266720302632.

[3] Roberts MG, Nishiura H. Early Estimation of the Reproduction Number in the Presence of Imported Cases: Pandemic Influenza H1N1-2009 in New Zealand;6(5):e17835. Available from: https://dx.plos.org/10.1371/journal.pone.0017835.

[4] Council F. Coronavirus: Switzerland to reopen its borders with all EU/EFTA states on 15 June;. Bern, Switzerland. Available from: https://www.admin.ch/gov/en/start/documentation/media-releases.msg-id-79365.html.

[5] Neher RA, Dyrdak R, Druelle V, Hodcroft EB, Albert J. Potential impact of seasonal forcing on a SARS-CoV-2 pandemic. Available from: https://doi.emh.ch/smw.2020.20224.

[6] Hodcroft EB, Zuber M, Nadeau S, Crawford KHD, Bloom JD, Veesler D, et al. Emergence and spread of a SARS-CoV-2 variant through Europe in the summer of 2020. Available from: http://medrxiv.org/lookup/doi/10.1101/2020.10.25.20219063.

[7] Althaus CL, Low N, Musa EO, Shuaib F, Gsteiger S. Ebola virus disease outbreak in Nigeria: Transmission dynamics and

rapid control;11:80–84. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1755436515000341.

[8] Riou J, Althaus CL. Pattern of early human-to-human transmission of Wuhan 2019 novel coronavirus (2019-nCoV), December 2019 to January 2020;25(4). Available from: https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2020.25.4.2000058.

[9] Svensson A. A note on generation times in epidemic models;208(1):300–311. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0025556406002094.

[10] Federal Office of Public Health. Coronavirus: Situation in Switzerland;. Available from: https://www.bag.admin.ch/bag/en/home/krankheiten/ausbrueche-epidemien-pandemien/aktuelle-ausbrueche-epidemien/novel-cov/situation-schweiz-und-international.html.

[11] Wallinga J, Lipsitch M. How generation intervals shape the relationship between growth rates and reproductive numbers;274(1609):599–604. Available from: https://royalsocietypublishing.org/doi/10.1098/rspb.2006.3754.

[12] Krauer F, Gsteiger S, Low N, Hansen CH, Althaus CL. Heterogeneity in District-Level Transmission of Ebola Virus Disease during the 2013-2015 Epidemic in West Africa;10(7):e0004867. Available from: https://dx.plos.org/10.1371/journal.pntd.0004867.

[13] Ganyani T, Kremer C, Chen D, Torneri A, Faes C, Wallinga J, et al. Estimating the generation interval for coronavirus disease (COVID-19) based on symptom onset data, March 2020;25(17). Available from: https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2020.25.17.2000257.

[14] Laxminarayan R, Wahl B, Dudala SR, Gopal K, Mohan B C, Neelima S, et al. Epidemiology and transmission dynamics of COVID-19 in two Indian states;370(6517):691–697. Available from: https://www.sciencemag.org/lookup/doi/10.1126/science.abd7672.

[15] Taube JC, Miller PB, Drake JM. An open-access database of infectious disease transmission trees to explore superspreader epidemiology [preprint];. Available from: http://medrxiv.org/lookup/doi/10.1101/2021.01.11.21249622.

[16] R Core Team. R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing;. Available from: https://www.R-project.org/.

[17] Venables WN, Ripley BD. Modern applied statistics with S. 4th ed. Statistics and computing. Springer;. OCLC: ocm49312402.

[18] Li R, Pei S, Chen B, Song Y, Zhang T, Yang W, et al. Substantial undocumented infection facilitates the rapid dissemination of novel coronavirus (SARS-CoV-2);368(6490):489–493. Available from: https://www.sciencemag.org/lookup/doi/10.1126/science.abb3221.

[19] Wu SL, Mertens AN, Crider YS, Nguyen A, Pokpongkiat NN, Djajadi S, et al. Substantial underestimation of SARS-CoV-2 infection in the United States;11(1):4507. Available from: http://www.nature.com/articles/s41467-020-18272-4.

[20] Salath M, Althaus C, Anderegg N, Antonioli D, Ballouz T, Bugnon E, et al. Early evidence of effectiveness of digital contact tracing for SARS-CoV-2 in Switzerland. Available from: https://doi.emh.ch/smw.2020.20457.

[21] Jarvis CI, Van Zandvoort K, CMMID COVID-19 working group, Gimma A, Prem K, Klepac P, et al. Quantifying the impact of physical distance measures on the transmission of COVID-19 in the UK;18(1):124. Available from: https://bmcmedicine.biomedcentral.com/articles/10.1186/s12916-020-01597-8.

[22] Coletti P, Wambua J, Gimma A, Willem L, Vercruysse S, Vanhoutte B, et al. CoMix: comparing mixing patterns in the Belgian population during and after lockdown;10(1):21885. Available from: http://www.nature.com/articles/s41598-020-78540-7.

[23] Tang S, Mao Y, Jones RM, Tan Q, Ji JS, Li N, et al. Aerosol transmission of SARS-CoV-2? Evidence, prevention

and control;144:106039. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0160412020319942.

[24] Nogrady B. What the data say about asymptomatic COVID infections;587(7835):534–535. Available from: http://www.nature.com/articles/d41586-020-03141-3.

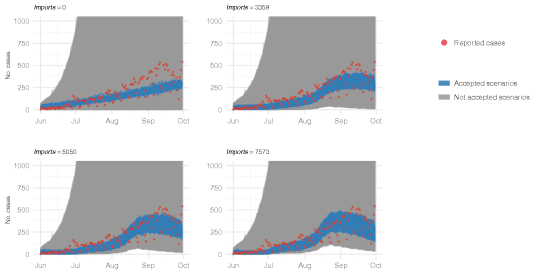
[25] Buitrago-Garcia D, Egli-Gany D, Counotte MJ, Hossmann S, Imeri H, Ipekci AM, et al. Occurrence and transmission potential of asymptomatic and presymptomatic SARS-CoV-2 infections: A living systematic review and meta-analysis;17(9):e1003346. Available from: https://dx.plos.org/10.1371/journal.pmed.1003346.

[26] Byambasuren O, Cardona M, Bell K, Clark J, McLaws ML, Glasziou P. Estimating the extent of asymptomatic COVID-19 and its potential for community transmission: Systematic review and meta-analysis;5(4):223–234. Available from: https://jammi.utpjournals.press/doi/10.3138/jammi-2020-0030.

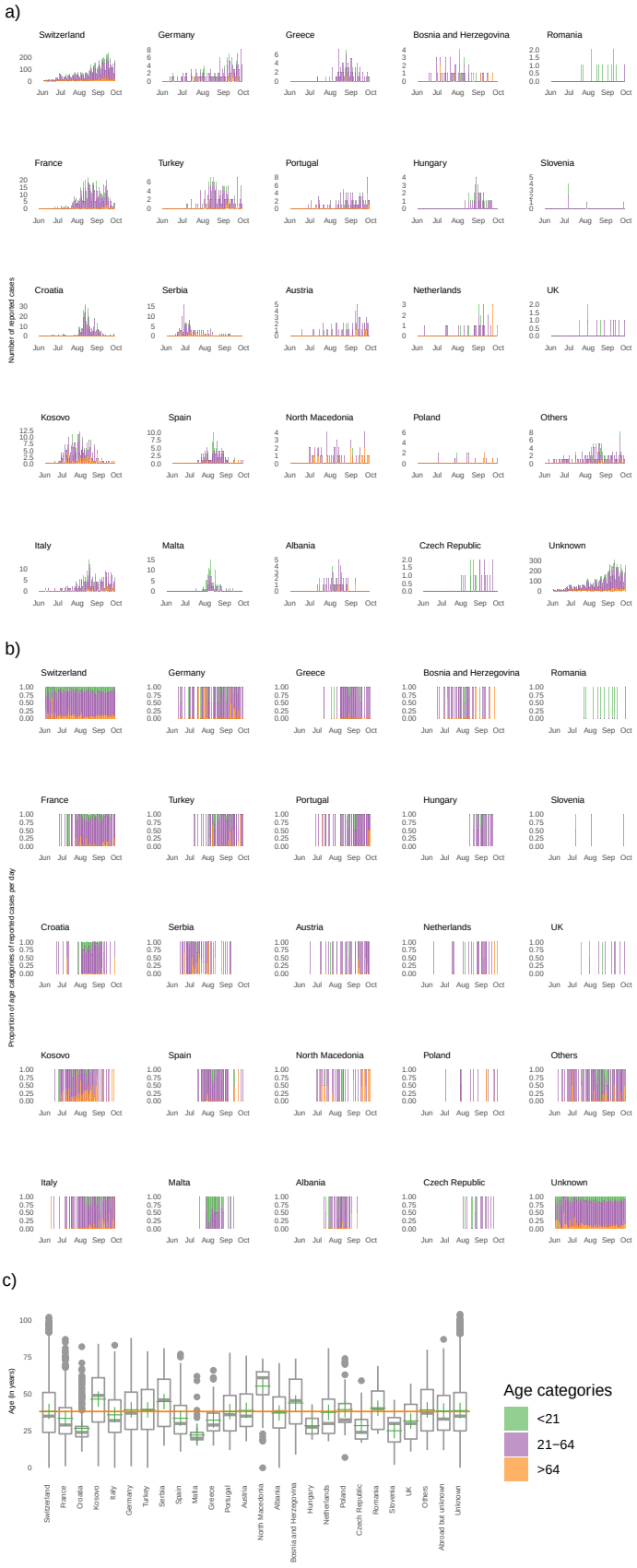
[27] Bi Q, Lessler J, Eckerle I, Lauer SA, Kaiser L, Vuilleumier N, et al.. Household Transmission of SARS-CoV-2: Insights from a Population-based Serological Survey [preprint];. Available from: http://medrxiv.org/lookup/doi/10.1101/2020.11.04.20225573.

[28] Ashcroft P, Lehtinen S, Angst DC, Low N, Bonhoeffer S. Quantifying the impact of quarantine duration on COVID-19 transmission;10:e63704. Available from: https://elifesciences.org/articles/63704.

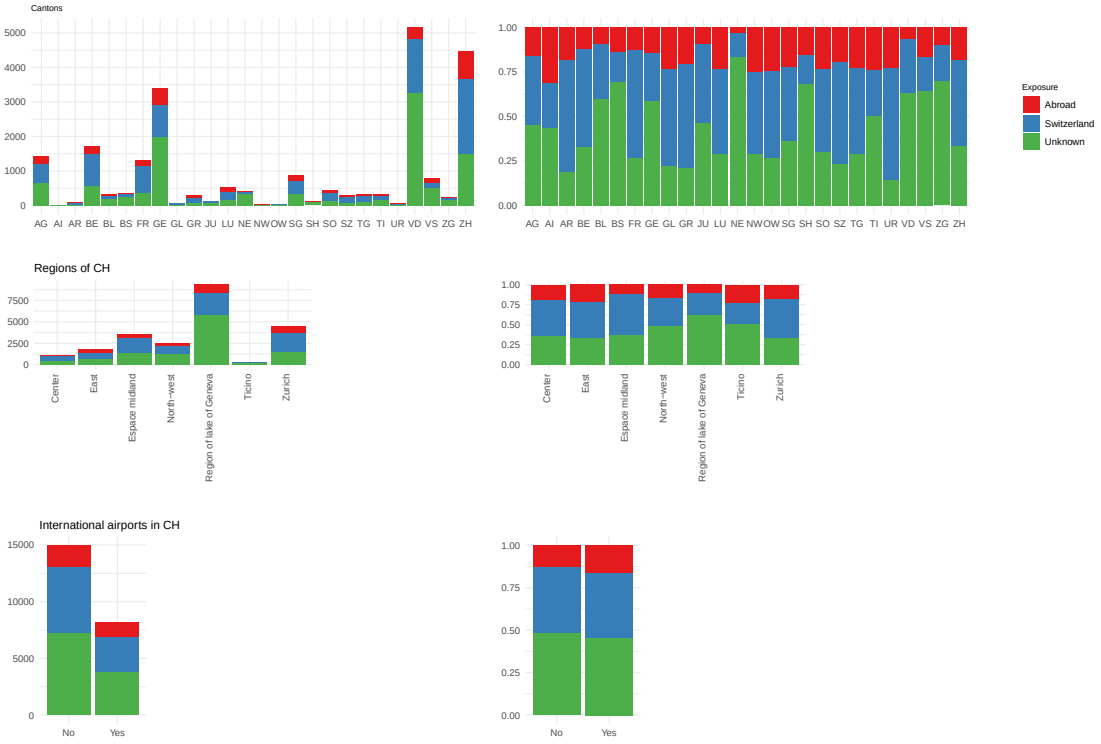
I will add again the ttest for age and different cross-border-associated cases. I will add a sensitvity analysis with k=0.1 and 1.



Supplementary Figure 1: Impact of cross-border-associated cases on the local epidemic: Branching trajectories with 0, 3,359, 5,050, and 7,573, cross-border-associated cases that were within the 95%-CI of final incidence and cumulative incidence. Abbreviations: CI, credible interval; R_e, the reproductive number



Supplementary Figure 2: Reported cases and the most likely country of exposure. a) number of reported cases and fraction of different age groups. b) proportion of all cases and proportion of different age groups. c) Age distribution for reported cases according to the most likely country of exposure. + represents the mean of the age in the corresponding group, the horizontal line is the mean of the age of all cases that were exposed only in Switzerland.



Supplementary Figure 3: Place and region of residency regarding reported exposure places