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Estimating the reproductive number and the outbreak size of SARS-CoV-2 in Slovenia

Ocena stopnje reprodukcije okužbe in deleža okuženih z virusom SARS-CoV-2 v Sloveniji

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Abstract

Background: We estimate the impact of non-pharmaceutical interventions implemented to slow-down the SARS-CoV-2 epidemic in Slovenia. The main measures of interest are the reproductive number in time and the total number of infected individuals.

Methods: We apply a recently proposed Bayesian model, which is built using most recent data for 12 (model A) or 10 European countries (model B, Spain and Italy excluded).

Results: The reproductive number estimate after the lock-down equals 0.6, with the whole 95% credible interval remaining below 1 [0.3–0.9]. By excluding Italy and Spain from the model (model B), the estimated reproductive number increases to 0.8 (95% credible interval [0.5–1.2]). The estimated proportion of infected individuals in Slovenia is below 1% (0.53 [0.23–1.01]% in model A and 0.66 [0.26–1.45]% in model B). Thus, it is our opinion that the official number of confirmed cases underestimates the true one approximately by a factor of 10.

Conclusion: The results indicate that the interventions were successful, with the reproductive number being below 1. We believe it is sensible to keep the current set of interventions for at least 2 more weeks, as we expect that this will ensure at least 5 additional weeks before the need to reinitiate lock-down.

Izvleček

Izhodišče: Članek ocenjuje vpliv uveljavljenih ukrepov za obvladovanje epidemije okužbe z virusom SARS-CoV-2 na stopnjo reproduciranja okužbe z virusom in ocenjuje delež okuženih v Sloveniji.

Metode: Uporabljen je Bayesov model, ki predpostavlja enako učinkovitost ukrepov v različnih državah in je zgrajen na podlagi podatkov o številu umrlih za 12 (model A) oz. 10 evropskih držav (izločeni Španija in Italija, model B).

Rezultati: Ocenjena stopnja reproduciranja virusa v Sloveniji po sprejetih ukrepih je 0,6; pod 1 je celoten 95-odstotni interval kredibilnosti [0,3–0,9]. Če pri gradnji modela izločimo Italijo in Španijo (model B), je ocena stopnje reproduciranja v Sloveniji po sprejetih ukrepih 0,8 (95-odstotni interval kredibilnosti [0,5–1,2]). Ocenjeni delež okuženih v Sloveniji je manjši od enega odstotka (0,53 [0,23–1,01] % pri modelu A in 0,66 [0,26–1,45] % pri modelu B), uradno število potrjenih primerov pa podcenjuje dejansko število za približno faktor 10.

Zaključek: Dosedanji sprejeti ukrepi so bili uspešni, saj menimo, da je trenutna stopnja reproduciranja virusa SARS-CoV-2 pod 1. Pri sproščanju ukrepov je smiselno počakati vsaj 2 tedna, saj ocenjujemo, da to pomeni vsaj dodatnih 5 tednov zamika do ponovnih zaostritev.

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1 Introduction

The novel coronavirus SARS-CoV-2 has spread rapidly across the globe. One of the key reasons for its rapid spread is the high reproductive number (R_t). The R_t value is the average number of people that an individual infects during the course of their infectiveness, with t standing for the calendar time, as R_t can change (due to interventions, weather, etc.). With $R_t < 1$, the number of new cases declines. With $R_t > 1$, the number of new cases increases until the pandemic reaches its peak, at which point the number of new cases starts to decline because of the obtained collective immunity. The estimate of R_0, the basic reproductive number, differs for the SARS-CoV-2, and is around 3 (1-7). Such a high reproductive number means an exponential rise in the number of cases, leading to a fast increase in the number of people who require hospital and ICU treatment. Due to limited capacities of the healthcare system, this can quickly lead to a state when it is no longer possible to provide care to everyone in need.

Slovenia, similar to numerous other countries around the world, has adopted certain nonpharmaceutical interventions for reducing the reproductive rate of the infection. Among others, on 10 March 2020, the government enacted the prohibition of organising closed events with over 100 people in attendance; from 16 March 2020 on, all preschools and schools closed, and on that same date, all public transportation was stopped; from 20 March 2020, there has been a prohibition of public gatherings. It is essential to assess the effect of these NPIs on R_t. In their recent study, Flaxman et al. studied the impact of non-pharmaceutical interventions on R_t for 11 European countries, including Italy, Spain, France, Austria and Sweden (Slovenia was not included), and showed that after the introduction of NPIs, R_t decreased from the initial value of 3.87 (median for all 11 countries) to 1.43 (range from 0.97 for Norway to 2.64 for Sweden (7), whereby they took into account the data until 28 March 2020.

Standard R_t assessment is based on the number of infected individuals, which is not appropriate for SARS-CoV-2, as this data is severely underestimated. The number of confirmed cases strongly depends on the strategy and methodology of testing, which differs between countries and the stage of the epidemic. Therefore, these differences do not allow for a direct comparison of the epidemic between countries in a given time period. Flaxman et al. used the data on the number of the deceased as the basis for their R_t assessment. These data are among the most valuable and reliable information which can be compared between countries (7). Bayesian model was used to assess the infection cycle to the detected cases of death.

In this article, we will also include Slovenia into the proposed model in order to estimate the actual number and the share of those infected with the SARS-CoV-2 and evaluate the effect of the adopted NPIs on R_t. Below, we will first provide a short presentation of the methodology used, then present the key results and conclusions.

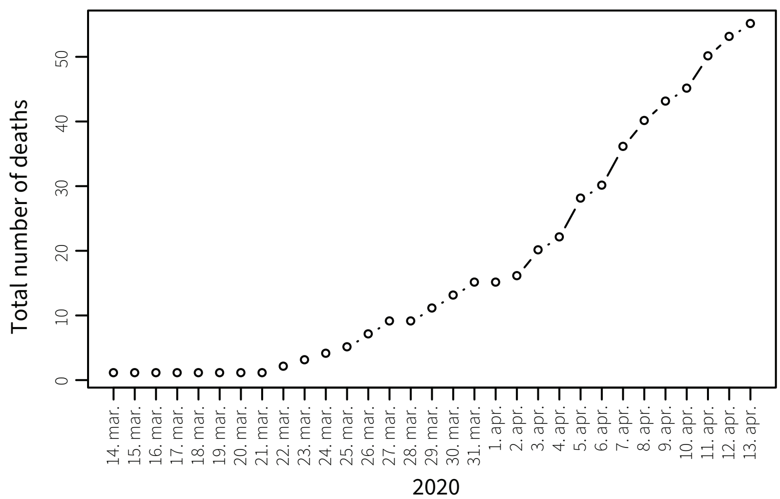

Figure 1: Total number of deaths in time in Slovenia.

2 Methods

Data on the number of deaths for Slovenia was obtained from Sledilnik COVID-19 [https://covid-19.sledilnik.org/]. Data for other countries was obtained from the ECDC website (8). We analysed the obtained data up to and including 13 April 2020. The cumulative number of deaths for Slovenia over this period is shown in Figure 1.

The used model was thoroughly presented by Flaxman et al. in detail (7); here, we only sum up some of the key characteristics.

The model is assessed with data on the number of deaths for 12 countries (besides Slovenia, the analysis also includes Austria, Belgium, Denmark, France, Italy, Germany, Norway, Spain, Sweden, Switzerland, and United Kingdom). The data on the number of deceased on a particular day is taken into account, with the first day of the analysis being set to 30 days before there were 10 deceased in a country; this excludes the impact of patients who were infected outside of their home country. The key assumptions are that the NPIs have a similar effect on R_t across all 12 countries, and that the effectiveness of a given NPI does not change over time. This way, we can estimate the model by using the data from several countries, thereby obtaining more precise estimates. We point out that countries with more deaths, for example Italy and Spain, have a bigger impact on estimates, and they were also the first to adopt the NPIs. Because of the bigger number of infections in these two countries, it is also possible that the data on the number of deceased is less reliable or has changed in different ways than in other countries (9-10). In order to verify the impact this has on the results for Slovenia, we repeated the analysis by not taking into account these two countries (model B).

To ensure comparability of different NPIs between countries, we classified the NPIs in 5 groups in the same way as the Flaxman et al. study (7) (Table 1). By specifying the dates of NPIs, we defined the intervals for which we assessed the R_t: R_0 value before the NPIs were first introduced (before 9 March 2020), R_1 being the estimate between the first two NPIs (from 9 March 2020 to 10 March 2020) etc. The value from the last introduced NPI (20 March 2020) to the date of the analysis (13 April 2020) is denoted as R_4. The model assumes that the values are constant within the intervals and are interpreted as average values on this interval.

When setting the dates of the NPIs for Slovenia, our basic principle was to find the dates that most fit the definition in the Flaxman et al. study (7). In appendix (6.1), we explained the selection of the dates for Slovenia. It is clear that certain NPIs were

Table 1: The dates that NPIs were introduced in Slovenia, as defined in the Flaxman et al. study (7).

Measure	Date
Self-isolation	9. 3. 2020
Public events banned	10. 3. 2020
School closure	16. 3. 2020
Social distancing	16. 3. 2020
Complete lock-down	20. 3. 2020

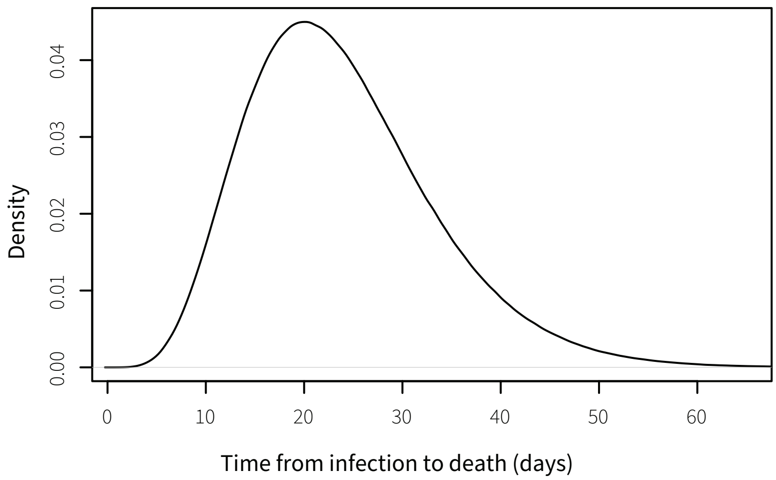

Figure 2: Assessed distribution of time from infection to death for the deceased.

not completely equal in all countries, and they also differ by how they were named. We believe that the classification in Table 1 is as coherent as possible to the NPIs in other countries.

Alternatively, 30 March could also be considered as the start of the so-called *complete lockdown*, when Slovenia implemented the limitation of movement outside of individual's municipalities. This option is discussed as model C, and the results are provided in Appendix (6.3). By this we assume that Slovenian NPIs on 20 March were not as strict as in other countries. What's more, this model does not permit a jump to this date, as there was no similar in-between NPI in other countries. Due to this inability to compare with other countries, Slovenia could have a possible significant limitation to the model: the model used cannot answer the question if the two periods differ, [20 March –30 March] and [30 March – 13 April] or by how much.

The key parameters in the model are infection fatality rate (*ifr*) and the distribution of time from infection to death, which connect the number of deaths with the number of cases, thereby allowing us to estimate R_t. We used the same approach for estimating the time from infection to death as Flaxman et al., and assumed that the distribution of time from infection to death is the same in all countries, i.e., with a median value of 23.9 days (7), Figure 2.

Flaxman et al. have calculated ifr_m, m = 1, …, 11 for each of the 11 countries. The mean *ifr* value, i.e., the mean assumed probability of death among the infected for the 11 countries, is 0.954% (a range from 0.792% for Norway to 1.153% for France). The *ifr* value was estimated based on past studies and taking into account the age structure of the population and the contacts between individuals from different age groups in individual countries (7). Due to the lack of such data for Slovenia, the *ifr* calculation could not be performed using the same approach, so we set *ifr* for Slovenia as: [1] mean ifr_m, [2] maximum ifr_m, [3] minimum ifr_m.

In addition, we examined the forecast curves of repeated growth of the number of infected and dead after NPIs would be loosened. For this purpose, we assumed different estimated values of the number of infected and R_t after the loosening of the NPIs (marked with R_5). Because the time to repeated growth completely depends on the assumed value of R_5, we mainly focused in this part of the analysis on the effect of the so-called *delay*, before the NPIs were be loosened. This is from the end of our analysis (13 April) to the date when the first NPIs were loosened. This value made it possible to estimate the number of weeks until growth curves surpass some critical values (arbitrarily set at 500 newly infected or 5 deaths per day). Just like before, we assumed the estimated value of R_4 to remain the same for the duration of the so-called *delay* until the first loosened NPIs and a constant value of R_5 across the whole interval after the loosening.

We performed the analysis using the software R (R version 3.6.3) (11)) and the rstan package (12). In our results, we report the mean of the a posteriori distribution with accompanying 95% credibility intervals (CI) in square brackets, i.e., the interval that includes 95% of the estimated a posteriori distribution of the parameter.

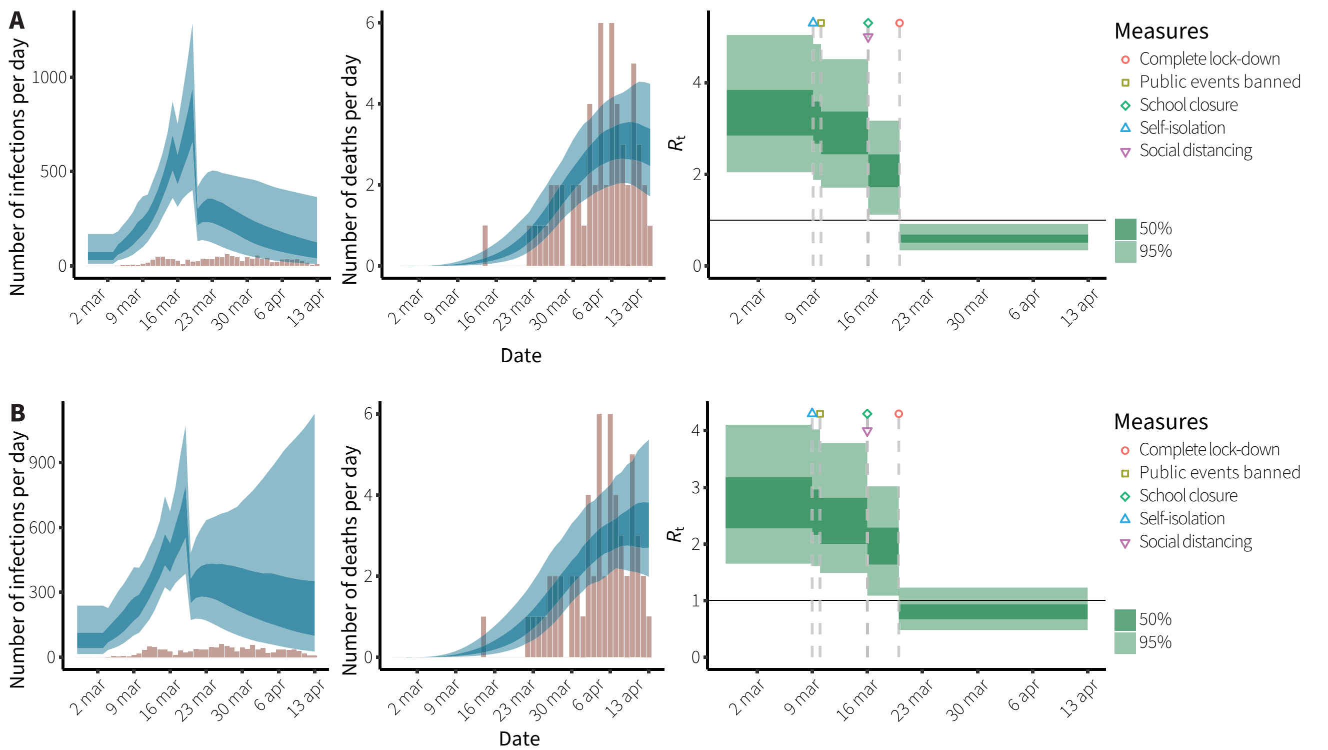

Figure 3: Estimates for Slovenia.
Left image: forecasted and actual number of new cases per day. Middle image: forecasted and actual number of deaths per day. Right image: R_t at adoption of different NPIs. Up: model A includes all countries. Below: model B does not include Italy and Spain. All estimates are made while taking into account the mean ifr_m.

3 Results

For Slovenia, we estimate that with regard to the medium scenario (mean ifr_m), the basic reproductive number before the adopted NPIs equalled 3.4 [2.0–5.0] (which is the lowest estimated value, and is equal to that estimated for Sweden: 3.4 [2.6–4.6], the highest estimated value applies to Belgium: 6.9 [5.6–8.7], and was reduced after all NPIs were adopted to 0.6 [0.3–0.9] (the lowest estimated value for Slovenia and Norway: 0.6 [0.4–0.9], the highest estimated value for Sweden: 2.1 [1.6–2.5], Figure 3A (right), Table 2. In model B, which was built without taking into account Italy and Spain, the final estimated reproductive number equals 0.8; however, there was less data, so the credibility interval is expectedly broader ([0.5–1.2], Figure 3B, Table 2). The R_t estimates are somewhat higher, when we consider the minimum ifr_m, and somewhat lower, when we consider the maximum ifr_m (Table 2 and Figure 6 in the appendix).

The estimated (cumulative) share of infected for Slovenia according to different scenarios is presented in Table 3. According to the medium scenario (mean ifr_m) we estimate that the share of infected in Slovenia is 0.5% [0.2–1.0] (lowest estimated value for Slovenia and Norway: 0.5% [0.3–0.9], highest estimated value for Sweden: 12.9% [6.2–24.9]). The estimated data on the number of cases indicates that the official number of confirmed cases is underestimated by approximately a factor of 10. Using different ifr_m estimates for Slovenia does not have a significant impact on the results; in line with the expectations, the estimate is higher if ifr_m is lower and vice-versa. The results are also not signifi-

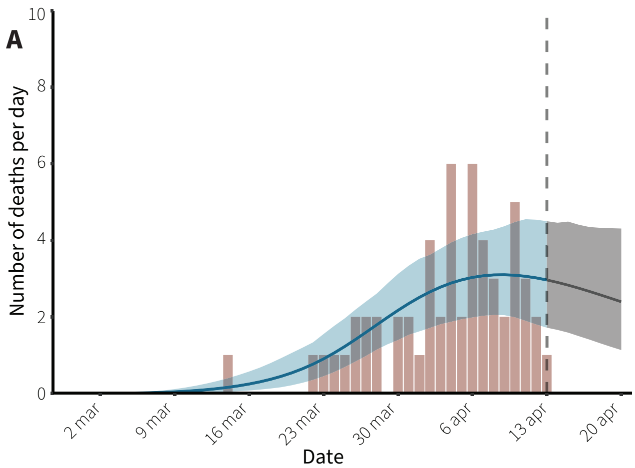

Figure 4: The actual (red columns) and the forecasted number of deaths (blue curve) for Slovenia, taking into account mean ifr_m (model A: includes all countries, model B: Italy and Spain excluded).

cantly affected by the exclusion of Spain and Italy from the analysis; model B has somewhat higher estimates of the share of infected; however, the difference at no point exceeds 0.2 percentage point.

The actual number and the forecasted number of deaths for Slovenia for the reviewed period is depicted in Figure 4 by the model used, along with the forecasted number of deaths for the 7 days following the final date of the analysis. In both models, we can notice an agreement between the actual number and the forecasted number of deaths, and in model B, the forecast for the next 7 days is somewhat more pessimistic. Using different estimates of ifr_m has very little effect on the results (Figure 7 in the appendix).

Figure 5 shows an example of the growth curves with the assumption that after the NPIs are loosened, R_t increases to R_5 = 1.5. We can notice that the curves are approximately parallel and that putting off loosened NPIs (so-called *delay*) by each additional week means approximately 2.5 weeks longer until a critical value is reached; we arbitrarily set 500 newly infected or 5 deaths per day as the critical values. For lower assumed values of R_5, the distance between the curves is somewhat longer, with R_5 = 1.25 it is already at 4 weeks (in the more pessimistic model B it is on average a week shorter and only increases with longer delays).

Table 2: Estimated R_t (mean and [95 % CI]) at the adoption of various NPIs for Slovenia according to different scenarios.

Model	Scenario ifr_m	R_0	R_1	R_2	R_3	R_4
A	mean ifr_m	3.4 [2.0-5.0]	3.2 [1.9-4.8]	2.9 [1.7-4.5]	2.1 [1.1-3.2]	0.6 [0.3-0.9]
	maximum ifr_m	3.4 [1.9-5.1]	3.2 [1.8-4.8]	2.9 [1.6-4.5]	2.1 [1.1-3.5]	0.6 [0.3-0.9]
	minimum ifr_m	3.6 [2.1-5.1]	3.3 [2.1-4.8]	3.1 [1.8-4.5]	2.2 [1.1-3.3]	0.6 [0.4-0.9]
B	mean ifr_m	2.8 [1.7-4.4]	2.6 [1.6-4.0]	2.4 [1.5-3.8]	2 [1.1-3.0]	0.8 [0.5-1.2]
	maximum ifr_m	2.7 [1.6-4.1]	2.6 [1.5-3.8]	2.4 [1.3-3.7]	1.9 [1.0-3.0]	0.8 [0.4-1.2]
	minimum ifr_m	3 [1.9-4.4]	2.8 [1.8-4.2]	2.6 [1.5-4.0]	2.1 [1.3-3.3]	0.9 [0.5-1.3]

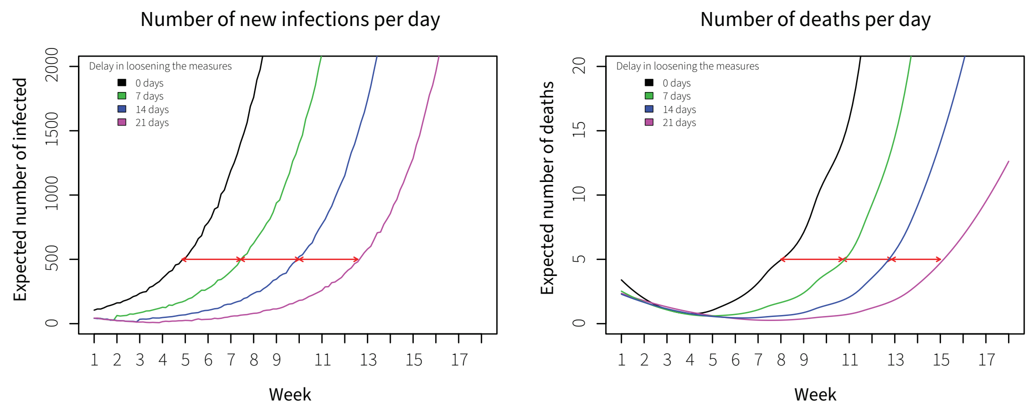

Figure 5: Forecast increase in the number of infected and deceased after the NPIs are loosened (assumed $R_5 = 1.5$). Red arrows mark the distance between the curves when crossing the 500 new infected per day or 5 deceased per day thresholds.

4 Discussion and conclusions

Our calculations show that the NPIs for limiting the spread infection in reviewed countries were successful, as we estimate that the current reproductive number of the infection in Slovenia is below 1, regardless of the model used. With model A (taking into account all 12 countries) 1 is not included in the 95% credibility interval, while in model B, where we intentionally included less data (by excluding Italy and Spain), the upper limit of the 95% credibility interval is above 1.

When interpreting these results, it must be emphasised that they are based on a very strong assumption that the effectiveness of the NPIs in Slovenia was the same as in other countries. Here we could be concerned whether the estimated decline of R_t for Slovenia is not just an artefact of the model, as the data for Slovenia for assessing the model has less weight because of the small number of deaths. With this in mind, we conducted sensitivity analysis in which we exponentially increased the number of deaths in Slovenia for the total reviewed period. The estimated R_t was still decreasing in accordance with the assumption of the model; however, both the initial R_t and the R_t after the final NPIs, were at significantly higher levels (above 3), from which we can conclude that the model is sensitive enough.

Table 3: The estimated (cumulative) share (%) of infected for Slovenia according to different scenarios.

Model	Scenario ifr_m	Mean [95 % CI]
A	mean ifr_m	0.53 [0.23-1.01]
	maximum ifr_m	0.45 [0.20-0.88]
	minimum ifr_m	0.66 [0.31-1.22]
B	mean ifr_m	0.66 [0.26-1.45]
	maximum ifr_m	0.53 [0.20-1.12]
	minimum ifr_m	0.83 [0.34-1.77]

We can note from our results that the impact of excluding Spain and Italy from the analysis is negligible. In this case, our estimates of R_t before the NPIs are lower, and after the NPIs they are higher than if all countries were to be taken into account. This can be the result of the fact that the nature of the pandemic and the effectiveness of the NPIs in Spain and Italy were different than elsewhere, or that it can be merely a reflection of a different phase of the epidemic in these two countries with regard to the rest.

Both models provide similar forecasts regarding the number of deaths for the next 7 days after 13 April, with the forecasts of model B being somewhat more pessimistic. In the period between 14 April and 18 April, we had on average 3 deaths per day (in these 5 days the daily number of deceased were 1, 5, 0, 5 and 4; this data is not final and is subject to change), which is in line with the forecasts of both models. Because of the small absolute numbers in Slovenia, random variation is larger, and it takes longer to be able to differentiate between random variability and actual trends. Therefore, even when taking into account the data on the number of deceased for the period between 14 and 18 April (not included in the model), it is currently not possible to conclude which model fits the data better. Because of the short time that passed in most countries between the adoption of different NPIs, this analysis is not sufficient to evaluate the effect of any individual NPIs, but merely their cumulative effect. It can present a potential problem to assume that an effect of a NPI on R_t is immediate. We verified the effect of this assumption by adding another *artificial NPI* (10 days for a full lockdown); however, this did not have a significant impact on the result.

We also tested the alternative option, where we assumed a full lockdown only on 30 March (model C, more detailed results in appendix, Figure 8). When interpreting these results, one has to understand the limits of the model. The absence of a spike after the NPIs on 20 March is a consequence of the model and not its estimate, while the strong impact of the fact that in other countries the reproductive number did not meaningfully decline without a total lockdown should also be taken into account. Model C can provide reasonably high estimate of the reproductive number (1.54; 95% CI [1–2.28]) for the period between 16 and 30 March. The model then attempts to correct this high estimate and bring it in line with the actual number of deceased because of the great downward leap and a very low value in the last interval (R_4 = 0.47; 95 % CI [0.29–0.79]). Despite this low final value, the estimate of the total number of infected is significantly higher in model C than in model A, and very similar to model B, with the forecasts of the number of deceased in the following days also being very similar.

The data on the cumulative share of the infected (0.53% and 0.66% considering model A and model B or C, respectively) shows that in Slovenia we are still very far from achieving herd immunity. At the same time, the number of potentially infected individuals is relatively high, and therefore we can expect that if NPIs were partially loosed, this would lead to another increase in the virus reproductive number and thereby in the number of infected. If the new reproductive number (R_5) is similar to the one before the NPIs, then current NPIs were pointless, as the number of newly infected will achieve the highest values within a week. If the roll-out of loosening NPIs would be slower, the key question is, how long it is sensible to persist until the NPIs start to be loosened, so that the time until the need to re-intensify the NPIs can be as long as possible. Our results show that every additional week of the so-called delay in the loosening the NPIs (which increases the reproductive number to R_5 = 1.5) extends the period until a critical level is reached by approximately 2.5 weeks, and with a lower R_5 value, this time is further extended.

We can conclude that the current NPIs have an effective impact on slowing down the course of the epidemic. Based on the model, it seems that it is sensible to persist with the NPIs for at least a few weeks. It is currently impossible to assess the impact of loosening the NPIs, as this data is not yet available.

In this light, it is especially interesting to monitor and compare data with the Swedish experiment, where the adopted NPIs are significantly milder. According to our estimates, the virus reproductive number in Sweden after all the implemented NPIs is approximately 2. Consequently, the estimated share of infected in Sweden (12.9%)

is the highest among the 12 countries that were included in the analysis. How much of this is an artefact of the model, cannot be estimated at this time (similarly to the model C), because the official data on the infected is not usable. Time will tell which of the paths will be more successful in the long run.

5 Acknowledgment

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6 Appendix

6.1 Explanation of selected dates of NPIs

The listed dates of implementations of NPIs from Table 1 were chosen in accordance with the definitions that were given in the Flaxman et al. study (7), page 14. The appropriate dates for Slovenia are as follows (Figure 6):

- 9 March is the date when strict instructions for self-isolation of those with symptoms for SARS-CoV-2 came into effect, and the infrastructure for testing potential cases across the country was already established (13);
- On 10 March, all public events in closed spaces for more than 100 people were banned (and in open spaces, for more than 500 people) (14);
- On 16 March, all primary and secondary schools in Slovenia were closed (15);
- On 16 March, the NPI was implemented instructing the population to avoid personal contact as much as possible, with most shops and services closing down and most work to be done remotely, along with a stop to public transportation services (16);
- On 20 March, the prohibition of public gatherings, meaning that in public, people can only move individually, and only if they have urgent business, and for exceptions listed in the ordinance (16).

6.2 Results of models A and B while taking into account the lowest and the highest value of ifr_m

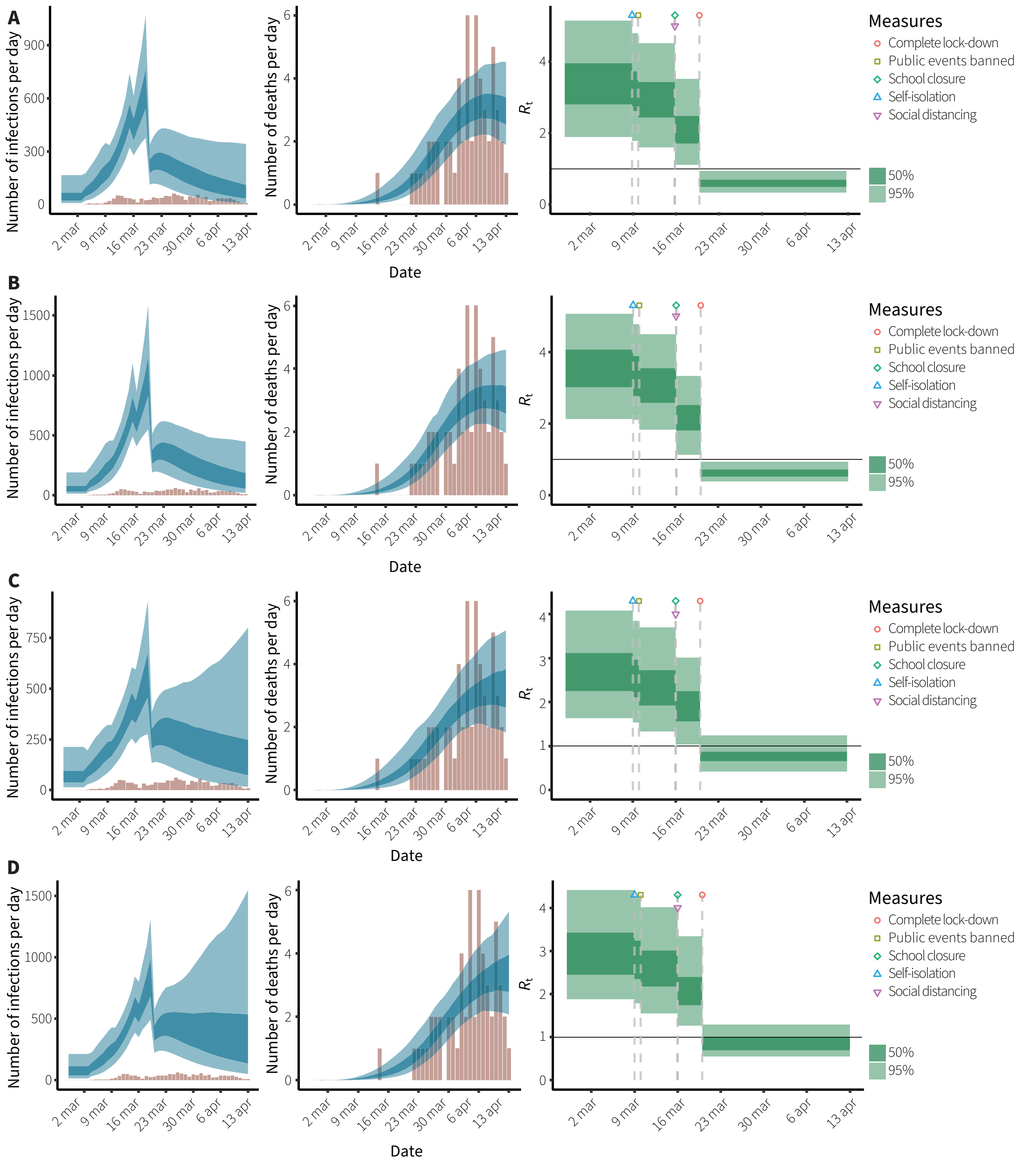

Figure 6: Estimates for Slovenia.

Left image: forecasted and actual number of new cases per day. Middle image: forecasted and actual number of deaths per day. Right image: R_t at the adoption of different NPIs for Slovenia in different scenarios (A: all countries while taking into account the maximum ifr_m, B: all countries while taking into account the minimum ifr_m, C: excluding Italy and Spain, while taking into account the maximum ifr_m, D: excluding Italy and Spain while taking into account the minimum ifr_m).

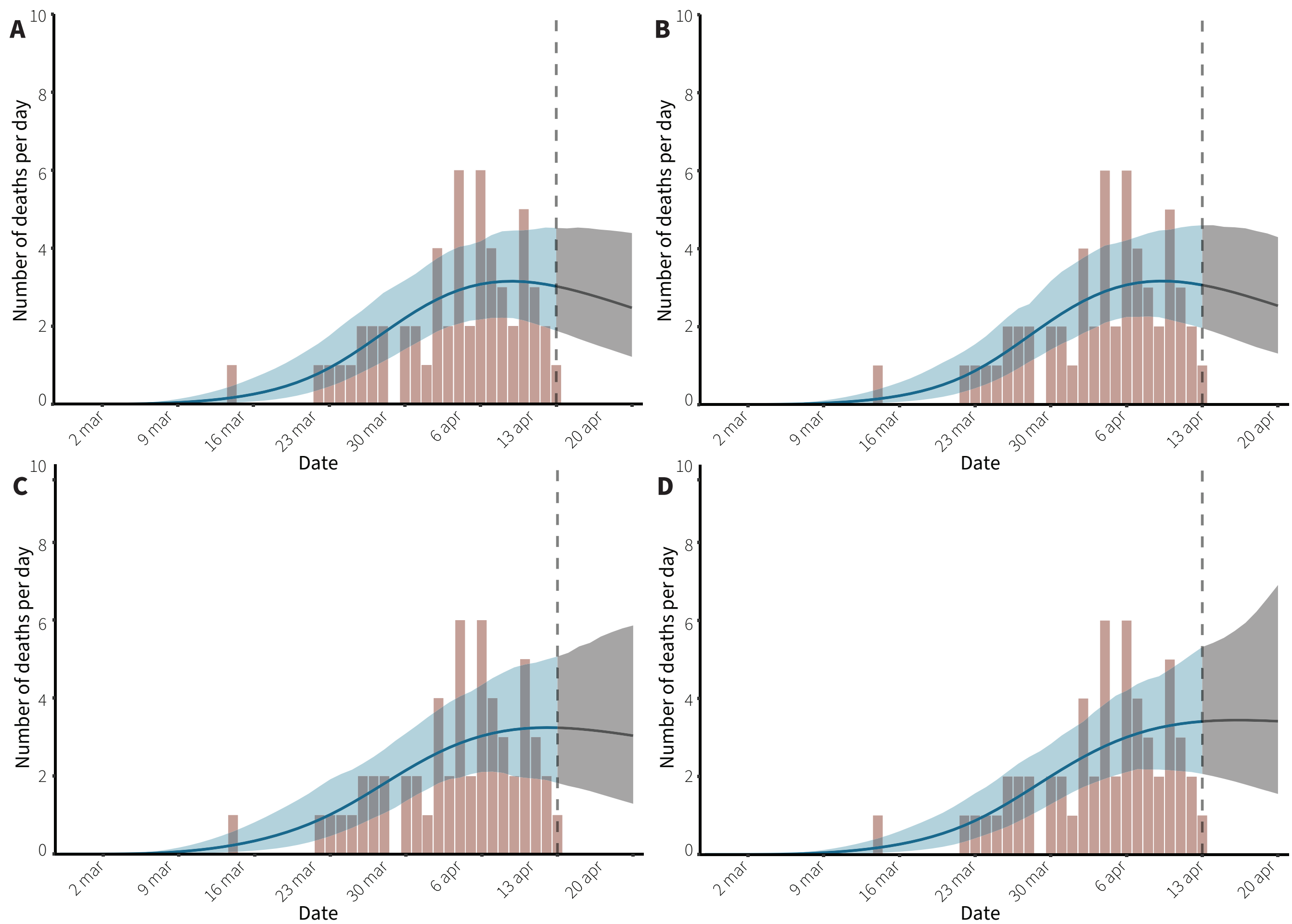

Figure 7: Actual and forecast number of deaths for Slovenia under different scenarios.
A: all countries while taking into account the maximum ifr_m, B: all countries while taking into account the minimum ifr_m, C: excluding Italy and Spain, while taking into account the maximum ifr_m, D: excluding Italy and Spain while taking into account the minimum ifr_m).

6.3 Results of model C (complete lockdown only on 30 March, 12 countries mean value of ifr_m)

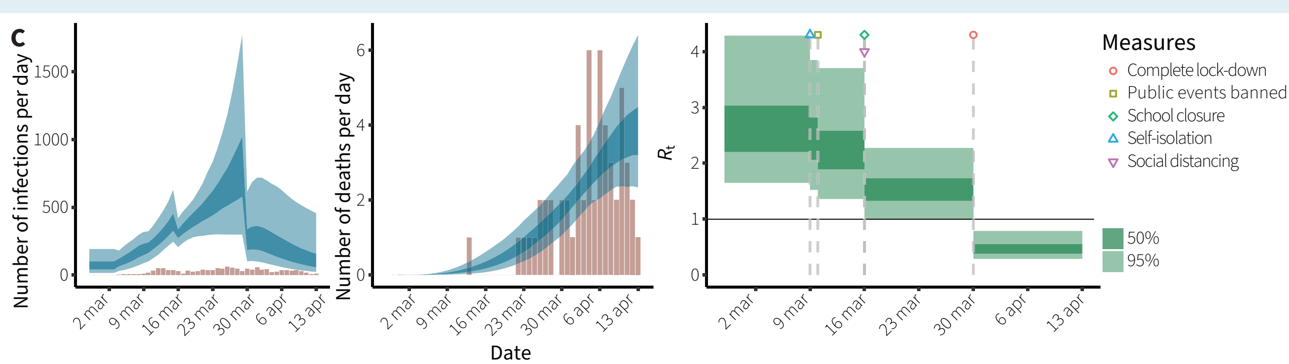

Figure 8: Estimates for Slovenia under the model C.
Left image: forecasted and actual number of new cases per day. Middle image: forecasted and actual number of deaths per day. Right image: R_t with the adoption of different NPIs for Slovenia.

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