European Commission

JRC TECHNICAL REPORT

Effective Reproduction Number Estimation from Data Series

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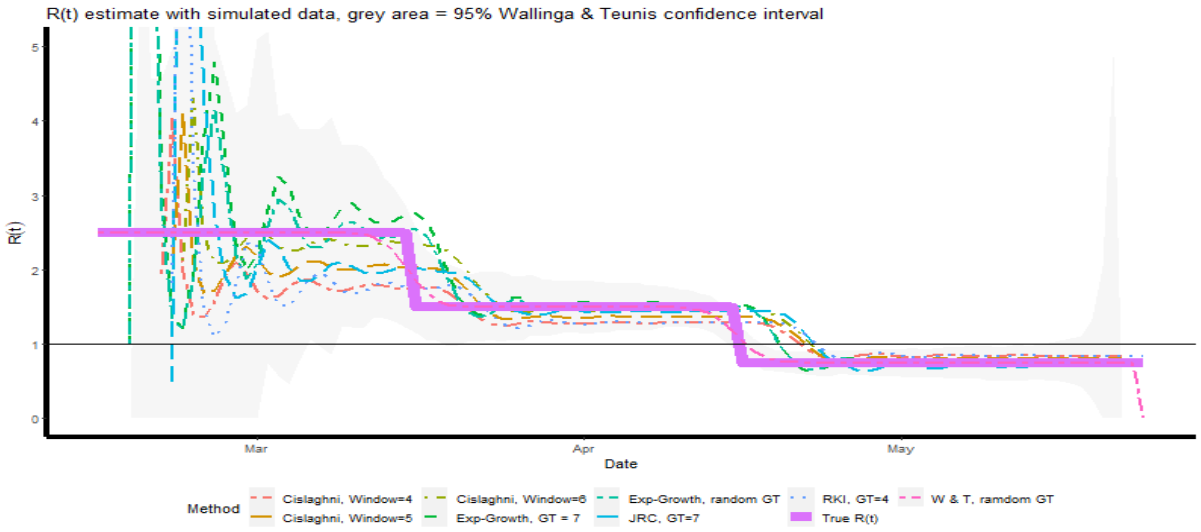

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Abstract

The COVID-19 pandemic spreading determined the need for several countries to define methods to show the current status of the spreading in each country, in each region or even in each municipality. During the initial expansion phase, it was important to establish which was the growth rate and after the introduction of containment measures to provide a method to understand the effectiveness of the implemented measures. In the current phase of de-escalation there is a great interest in understanding when it is necessary to reintroduce containment measures on the basis of the possibility of resurgence of the spread. The objective of this Technical Note is to consider a selection of these methods to highlight merits and issues and apply them for a number of actual cases.

1 Introduction

The COVID-19 pandemic spreading determined the need for several countries to define methods to show the current status of the spreading in each country, in each region or even in each municipality. During the initial expansion phase, it was important to establish which was the growth rate and after the introduction of containment measures to provide a method to understand the effectiveness of the implemented measures. In the current phase of de-escalation there is a great interest in understanding when it is necessary to reintroduce containment measures on the basis of the possibility of resurgence of the spread.

In its communication on a roadmap for lifting of COVID-19 containment measures, the Commission proposes to develop EU level tools as well as guidelines, both for public health and the economic response.

According to the recent European Communication on Tourism, the following is mentioned:

The ECDC, in cooperation with Member States and the Joint Research Centre, is developing and will continuously maintain a map18 of the level of COVID-19 transmission at sub-national level. Member States are invited to provide data in order to ensure that this map is complete and up to date [1,2].

To assess and monitor the growth rate of an outbreak, its transmission potential and effects of interventions a common metric used is estimating the reproduction number. The reproduction number describes how many persons an infectious individual will in average infect in a certain population. The reproduction number is used in many contexts and it has several definitions and symbols to describe it.

This Technical Note will address both basic reproduction number and the effective reproduction number.

The basic reproduction number describes how many persons an infectious person infects totally in average during his or her time being infectious in a population where nobody is assumed to have any protection against the disease. Thus, it describes in most situations what happens if a new disease enters a population. The basic reproduction number is in this study mentioned as R_0. Other common symbols used are r0 and R.

The effective reproduction number describes how many persons an infectious person infects totally in average during his or her time being infectious in a population where some individuals can have protection against the disease. This value thus describes how much infection can be spread at different timepoints depending on the immunity of the population. The effective reproduction number in this study is mentioned as R(t) where t denotes time. Other common used symbols are Reff, R., R*, reff, R0, R0(t) and Rt. As some of the common used symbols coincide with symbols used for the basic reproduction number R_0 it is therefore of great importance to clearly understand the meaning what the symbol in different studies describes.

Basic reproduction number R_0 and effective reproduction number R(t) are used in several applications in epidemiology and public health decision making. They are the crucial factors to make estimates of the herd immunity, i.e. how large proportion of a populations needs to be protected to prevent a large outbreak. This is applied in establishing national childhood vaccination programs such as for rubella and measles, where R_0 and R(t) provides estimates of minimal needed vaccination coverage to

prevent larger outbreaks in a population. If for example vaccination coverage rates are reducing, it is possible to monitor the value of R(t) to see when it reaches critical value of not having anymore herd immunity in the population. This approach of R(t) is thus important in public health policy making for then reacting and for example campaign for increasing the vaccination coverage.

For past outbreaks like SARS in 2002 and swine flu in 2009 R(t) calculations were applied in many areas. At the beginning of the outbreak it is a tool to provide input if the outbreak can be contained at the source of if it is expected to spread globally. It gives also input into preparedness and response planning, knowing the value of R(t) and possible reduction on contacts through school closure, social distancing etc. can give estimates on their effectiveness on the handling of the outbreak.

In the context of COVID-19 the estimation and use of R_0 and R(t) has thus a large field of utilization for public health policy making and for estimating needed lockdown measures in the population. At the early stage of the outbreak, estimates for R_0 were made by various research groups; later when it was detected in EU Member States several countries started producing R(t) estimates on their national or regional data.

The importance to get harmonized R(t) numbers at national level for all EU Member States is also to gather information on how different lockdown and social distancing measure have affected the transmission rate , thus giving valuable insight for other EU MS to estimate the effect of introducing the intervention in their country.

The Communication also indicates that the Member States are invited to provide data to ECDC and JRC in order to compile a table of R(t) estimates.

Having access to necessary data for performing R_0 and R(t) estimates for countries or regions could then be a possible approach to make EU MS wide estimates of the quantities. There is although another complication in this process, namely that there is a wide range of analytical methods to make the R0 and R(t) estimate. And these methods can also give a different value on R_0 or R(t). It is therefore crucial to make an overview of a selected number of available methods and know what specific data is needed, assumption made and the output generated by each one. The objective of this Technical Note is to consider a selection of these methods to highlight merits and issues and apply them for a number of actual cases.

2 Methodology

2.1 Reproduction number definition

At the introduction section the definition of R_0 and R(t) were given in words. In this section R0 is also described by equations.

The basic reproduction number, denoted R_0, is the expected number of secondary infections caused by a single infectious case over the course of their infectious period, in an otherwise fully susceptible population.

The definition of R0 is defined as

$$R_0 = \tau\, c\, d \qquad (1)$$

Where τ is the transmission probability per contact, c is the contact rate (number of contacts between individuals per unit time) and d is the length of the infectious period.

In the initial phase of the epidemic, the reproduction number characterizes the exponential growth rate in fully susceptible. The change of new cases (dI/dt) is expressed by:

$$\frac{dI}{dt} = \frac{R_0}{d}\frac{S}{N}I - \frac{1}{d}I \qquad (2)$$

Where S is the number of susceptible people, I is the number of Infectious people, N is the total population size. In the initial phase of the epidemic, S is almost identical to N and so S/N is approximated by 1, which means that the solution of the above equation is (I_0 denoting number of infectious persons at the beginning of the outbreak):

$$I = I_0 e^{(R_0-1)t/d} \quad (3)$$

During the period of free circulation of the virus, the three quantities of equation (1) are constant; therefore the only way to contain the spread is to act on the product τ c which means to reduce the transmission probability (τ) by social distancing measures such as stay at home or the contact rate (c) by the means of protective equipment, prophylactic or vaccination interventions.

For estimating effective reproduction number R(t) no unique way exists. In principle R(t) could be seen as R_0 and multiplying if with contact reduction factor f and $\frac{S}{N}$.

$$R(t) = R_0 f(t)\frac{S}{N}$$

The parameter f in this case could reflect reductions in contacts and also for example non-pharmaceutical interventions like use of masks.

If R(t) is reduced the curves are bended and the number of new cases can decrease. Therefore R(t) that is the reproduction number during the course of the epidemic that may decrease or increase as a function of the prevention and control measures proposed and adopted on the population.

A broad array of methods exists for estimating R_0 and R(t). For a broad review on differences between R0 and R(t) and several methods are presented in Heffernan et al . One of the major conclusions of the paper is that the methods used to calculate R_0 utilizing incidence data (number of reported new cases per day) can show different results depending on the method. Owing to the usual limitations in using real data, the authors note that the models typically used during outbreaks are simple, deterministic and non-structured.

In this report we will concentrate on the most used methods for R_0 and R(t) estimation and also compare with some methods that have been recently developed by some EU MS during the COVID-19 outbreak.

2.2 Additional needed assumptions and input values

The previous section mentioned that for estimating R(t) no "golden standard" method exists. It is more depending on how to define the R(t), this can be built on what (statistical) model structure to use, what epidemiological features it should include and what kind of data is available.

Several methods utilize epidemiological quantities such as incubation period (time from infection until developing symptoms), serial interval (i.e. time between onset of symptoms between the infector and the infectee in a transmission chain of infections) and generation time (i.e. time between persons becoming infected in a chain of infections). These quantities are sometimes assumed to be constant or to have a certain assumption on its statistical distribution. For a in depth review of difference between serial time and generation time and their effect on R(t) estimates are available in [3, 4].

Other assumptions on the calculation of R(t) is that there is no change on the coverage of the reported data, i.e. more cases detected because of increased testing or changing places where tests are performed. There are some methods available to account for this but they rely on several assumptions.

For input values in this paper, the value of the generation time when constant is 7 days. For methods where a random distribution can be used, gamma distribution with mean 6.6 days and variance 1.5 is applied as used in [5] using data from [6].

A recent study [7] found mean 5.2 and standard deviation 1.7 for Singapore data, and mean 3.95 days and standard deviation 1.5 for Tianjin in China for generation time. There is thus a variation on its estimate.

2.3 Availability and coverage of the data

A general difficulty in analysing epidemiological data is the fact that the quality or coverage of the data is not everywhere and all the time the same. Data on COVID-19 can be published regularly by EU MS, but it does not always include information on date of confirmation of the case, thus analysis are most often based on the day the data was reported and not the date the infection was confirmed. In addition, there can be delays for example that cases during weekends are reported first the following week. Sometimes there can be a change on testing policies. this means that sometimes only information from severe cases are reported and at some other time periods also community spread data is reported.

The above mention factors together with other driving factors, can in some cases lead to that a number of cases are accumulated and examined all together. This can create

spikes in the daily cases which then are reflected in the estimation of R(t). Some methods try to compensate for this problem by smoothing in advance the curves, but still some oscillations can remain which are not due to the dynamic of the epidemic but to the method of data collection.

In these conditions the precise estimation of R(t) should be done carefully, considering all the various aspects.

2.4 Analysis of the methods selected

2.4.1 Method 1: Systrom Method

Kevin Systrom developed a method [8] which is a modified version of a solution to estimate real-time using a Bayesian approach [9]. While this methods estimates a static value, a script in python is developed by Systrom to produce also its error estimates utilizing Gaussian noise to estimate R(t) [8].

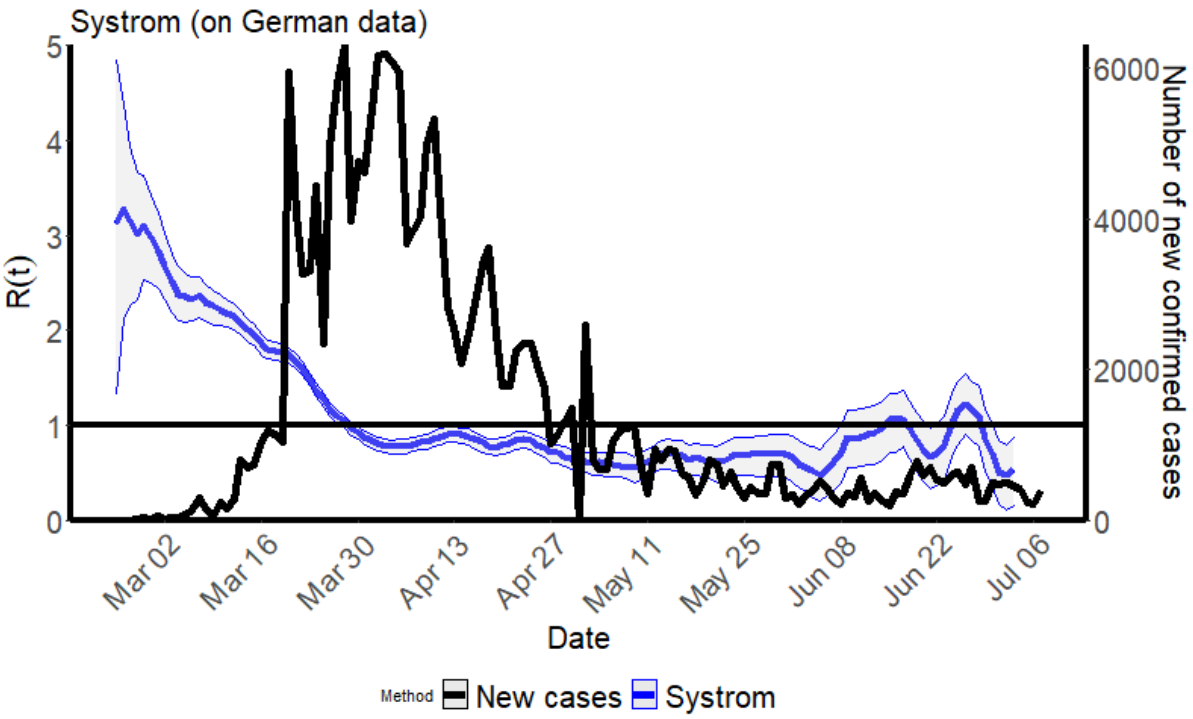

Figure 1 - R(t) determined with K. Systrom method. Shaded area is the 95% confidence interval

2.4.2 Method 2: Cislaghi method

This is a method that is in use in some regions in Italy (e.g. Emilia Romagna) [10] for a quick method to obtain R(t) The method stems from the fact that every d days the number of cases is increasing by a factor R(t), the number of days depends on the incubation period d, between 4 and 5. So the ratio between the number of new cases of day y and the number of new cases at day y-d. The ratios are performed on the smoothed curves from a moving average of 5 days, to avoid daily strong variations. The same procedure is repeated for 4, 5 and 6 days.

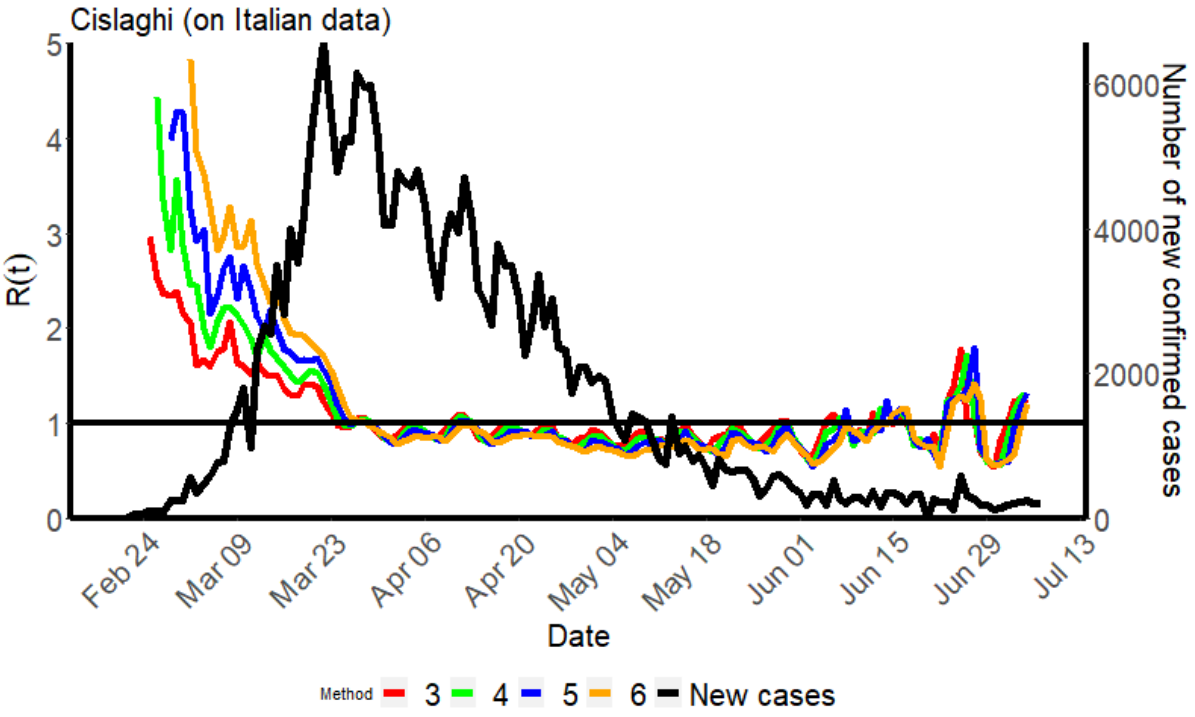

Figure 2 – R(t) determined with Cislaghi method

It is interesting to note that at the beginning there are differences between the various days considered but with the time the differences are smaller and smaller. This can be explained that the estimation of R starts when the epidemic is growing or has many infectious persons in the population. Taking then ratios of person infected different days will create more variation on the estimates than when there are less infectious persons in the population. This is the case when R(t) if reducing in size.

2.4.3 Method 3: JRC Method

According to equation (1) and its solution (3), it is possible to take the natural logarithm of the above equation on both sides for 2 characteristic times t_1 and t_2.

$$\log(I_1) = \log(I_0) + (R(t) - 1)t_{1/\mathrm{d}}$$

$$\log(I_2) = \log(I_0) + (R(t) - 1)t_2/d$$

Taking the difference between the two equations above, it is possible to solve for R(t):

$$R(t) = \frac{(\log(I_2) - \log(I_1))}{t_2 - t_1}\mathrm{d} + 1$$

In order to verify that this method to determine the R(t) is correct we have imposed various changes of the R(t) to a SIR model and estimated the corresponding values of I and the value obtained respects the imposed values of R(t). Currently d is applied with a value of 7 days.

The application to the Germany case provides the following result.

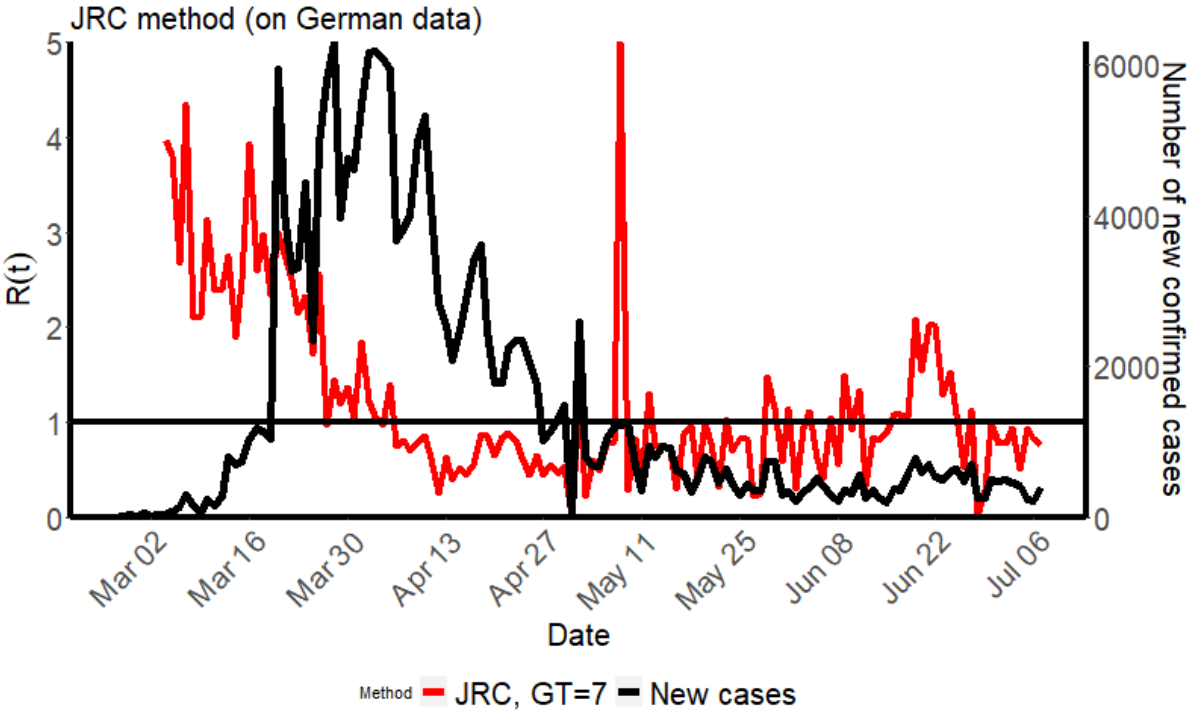

Figure 3 – R(t) estimated with the JRC Method

Method 4: Robert Koch Institute method

This is a method assuming a constant generation time of four days[11]. The effective reproduction number R(t) is calculated as the sum of new reported cases during four consecutive days divided by the sum of new reported cases during four consecutive days prior to the days used in the denominator. As an illustration, considering the first eight days of the reported epidemic for Germany are the following:

1	2	3	4	5	6	7	8
63	28	41	64	138	239	156	107
			196				640
							R(t) for day 8: 640/196=3.04

R(t) for day 8: 640/196=3.04

The application to the whole epidemic is shown in the following plot. The first plot represents the cases in Germany is:

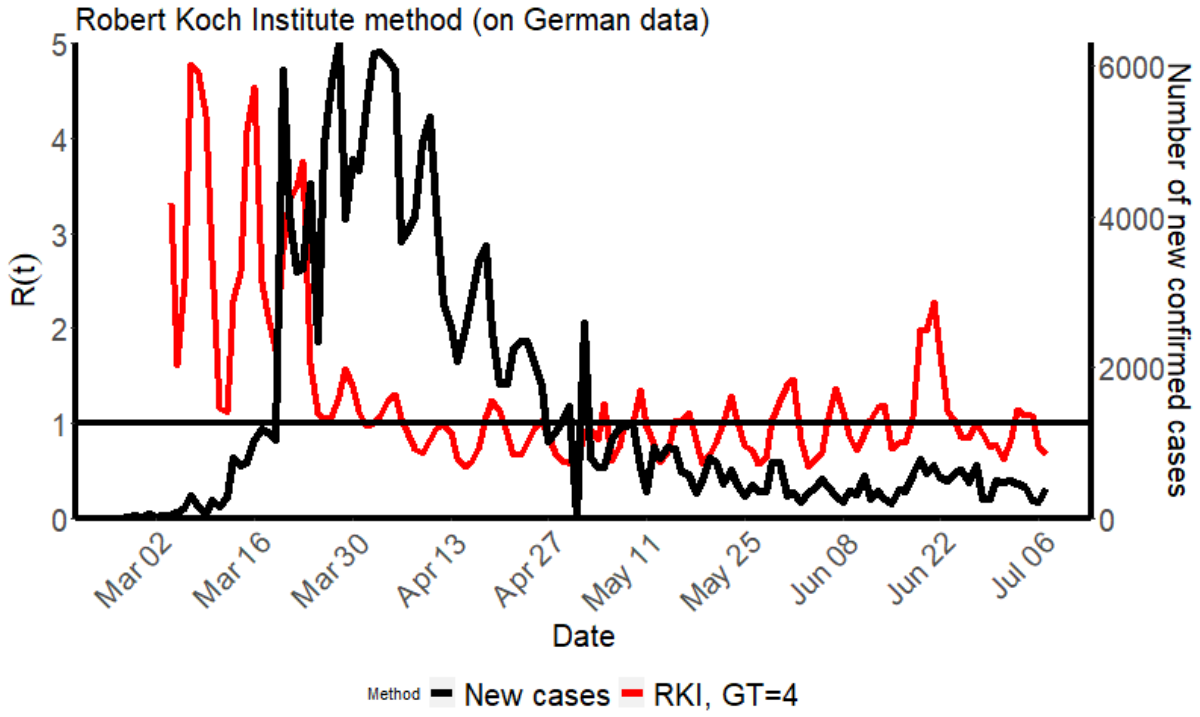

Figure 4 – R(t) obtained with RKI method

A slightly different method, obtained as the RKI method but using a period of 14 days and subperiods of 7 days, is also included in the estimations of Annex 1, and is named 7days method.

2.4.4 Method 5: Exponential growth / Wallinga & Lipsitch method

From epidemic modelling theory it is known that the reproduction number R(t) can be written as

$R(t) = 1 + rT$, where r is the growth rate of the outbreak and T the mean generation interval[12]. From this a pointwise estimate of *R(t)* can be derived by looking at a short time interval, for COVID-19 one week interval should be sufficient.

Wallinga and Lipsitch developed a method how to calculate R(t) when the generation time has a random distribution and not only a constant value[13]. The reproduction number R(t) can then be calculated as R(t)=1/ M(-r) where r is the growth rate and M(-r) the moment generating function to the assumed generation time distribution. By making additional assumptions on the random distribution describing the growth of the outbreak also the variance of R(t) can be calculated[13].

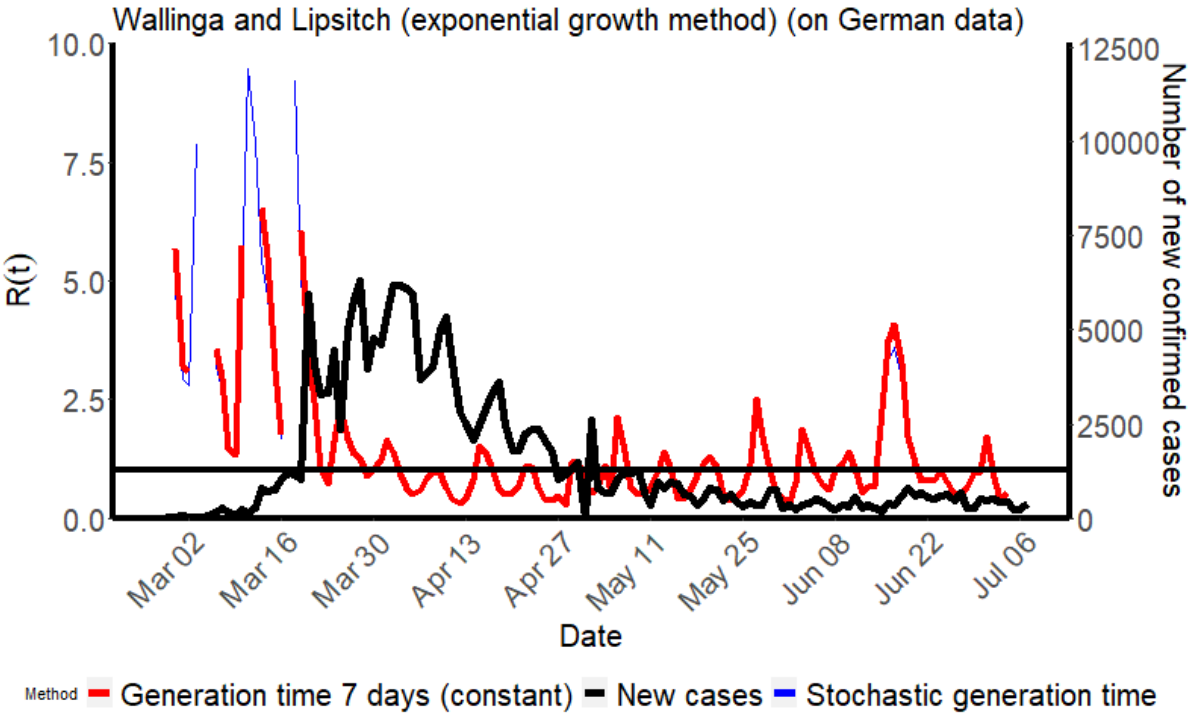

Figure 5 – R(t) estimated with Wallinga and Lipsitch method

Method 6: Wallinga & Teunis method

This method uses a different approach, mainly differing by not only looking at number of new cases each day. The principle is to look at an infectious individual who get infections day , by assuming a random distribution w(t) on the generation time, what is the probability p_{ij} that an individual i got infected at time j [14]. This approach and possible infection chains grow very rapidly into millions why the authors developed a likelihood based estimator that utilizes the daily number of reported infections to come to a similar solution. The approach is also able to provide exact confidence intervals on the effective reproduction number R(t), thus no numeric method is needed to estimate the confidence intervals.

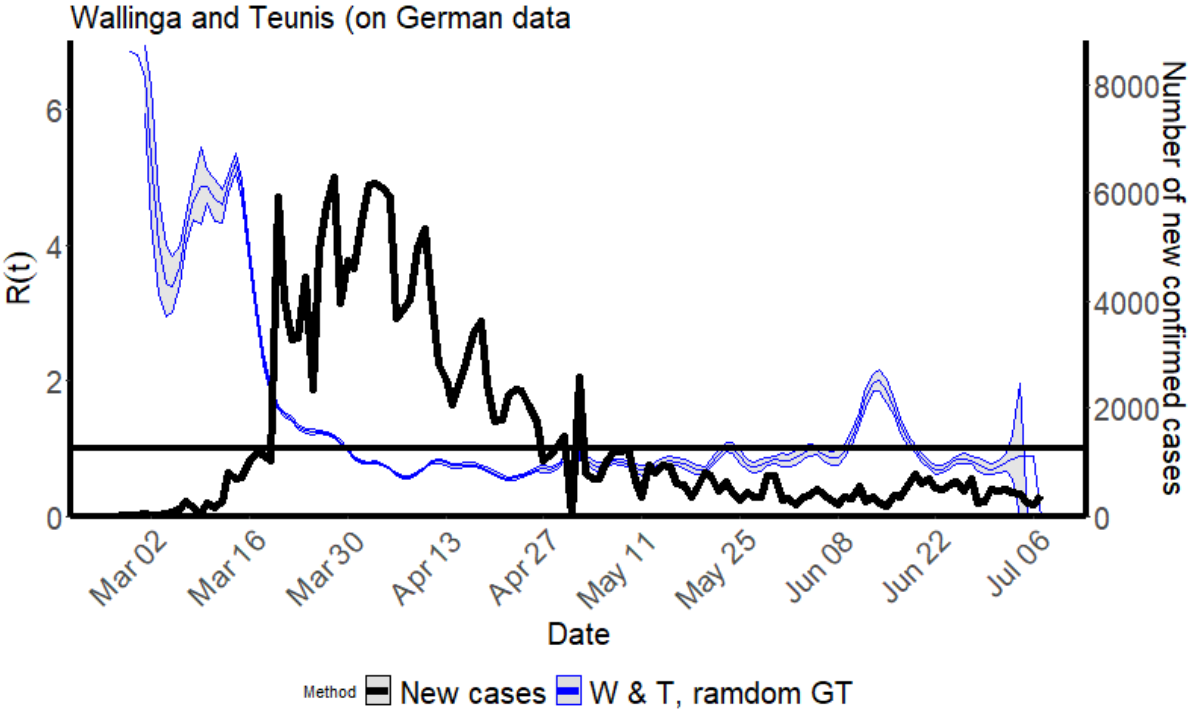

Figure 6 – R(t) estimated with Wallinga and Teunis method, shaded are is the 95% confidence interval of R(t)

2.5 Results and discussion

To test how the different methods act on data, two approaches will be done, first to test on country data and second on a simulated data set. The simulated dataset will be made with a R(t) value that will change value at specified datapoints. Using this pre-known value of R(t) the expected number of daily new cases will be generated. This will thus create a dataset where the true value of R(t) is known at each timepoint and can be used as a reference value to compare with what the different methods estimate as the true value.

The simulated dataset, will utilize daily know values of R(t) together with a known value of generation time a gamma distribution with mean 6.6 days and variance of 1.5 to generate the expected number of new cases during a hypothetical outbreak. It is calculated with methodology from epidemic modelling utilizing a deterministic solution to the difference equation.

2.5.1 Different assumptions in deriving effective reproduction number R(t)

To make a comparison on the different methods, the underlying methodology needs to be investigated. The different assumptions are listed under each method description. The methods can in general be put into two main types, based on an underlying assumption on the epidemic spread or assuming that the epidemic is spread with a constant value on generation time or the incubation period. For methods utilizing an underlying assumption on the epidemic spread are JRC method, Wallinga & Lipsitch, Systrom and Wallinga & Teunis method. Methods not using any underlying epidemic model and just assuming the number of new cases will reproduce with a constant value on the generation time or incubation time are the Robert Koch institute method and the Cislaghi method.

The methods based on an underlying epidemic spread/model understanding give an scientific based background to what is calculated and they also give a proof of how the effective reproduction number R(t) is derived. This approach also adds the possibility to add random distribution on different parameters used in the model and their fluctuation can be considered in the estimation process.

The methods based purely on assuming a constant value on the generation time or incubation time, can still work as an estimate of the effective reproduction number R(t). As they are not based on a model for epidemic spread it is although not scientifically shown that the result gained is actually R(t) or some other quantity. This approach also makes less possibilities to investigate effects of random variations on quantities such as incubation time, serial time and the generation time.

2.5.2 Basic Reproduction estimates based on modelled data

Apply a model with changing values on R(t) at two specific intervals and constant in the rest of the period. The incidence takes the form indicated in the figure below.

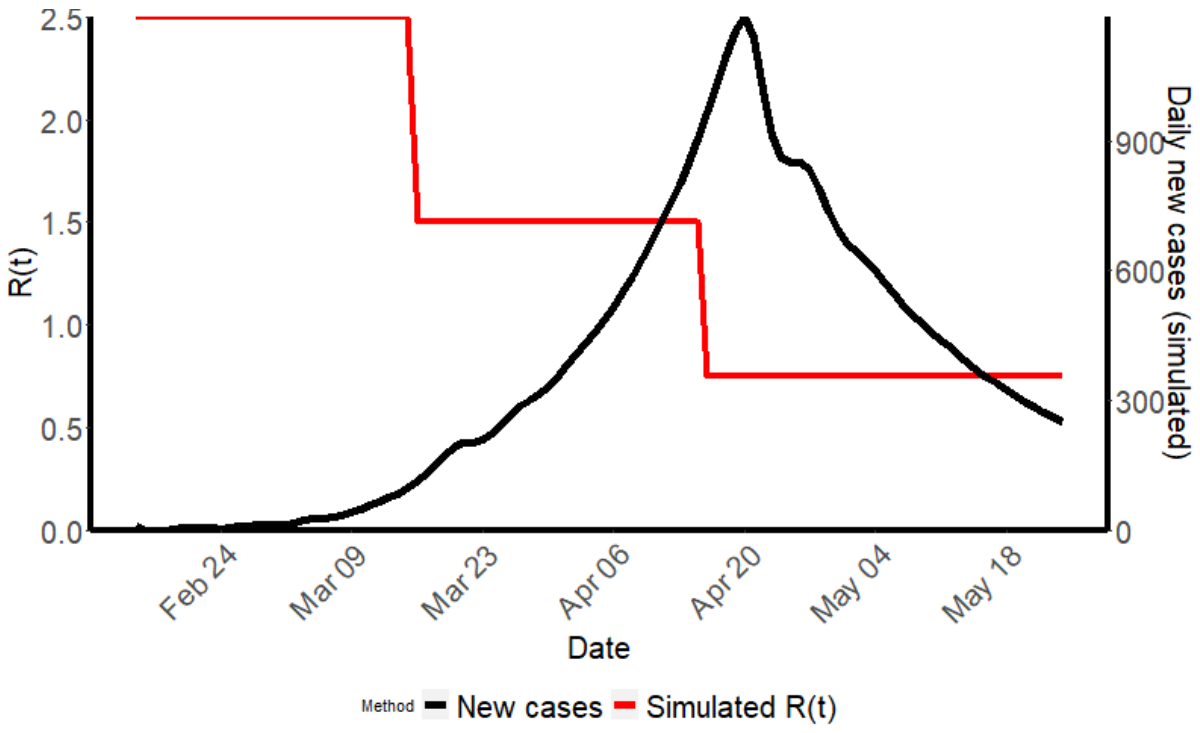

Figure 7 - Simulated epidemic curve

Applying the various methods described in the previous chapters, the result is indicated in the following figure. The pink curve represents the imposed R(t) and the various curves are the result when the methods are applied to the simulated epidemic of the figure above

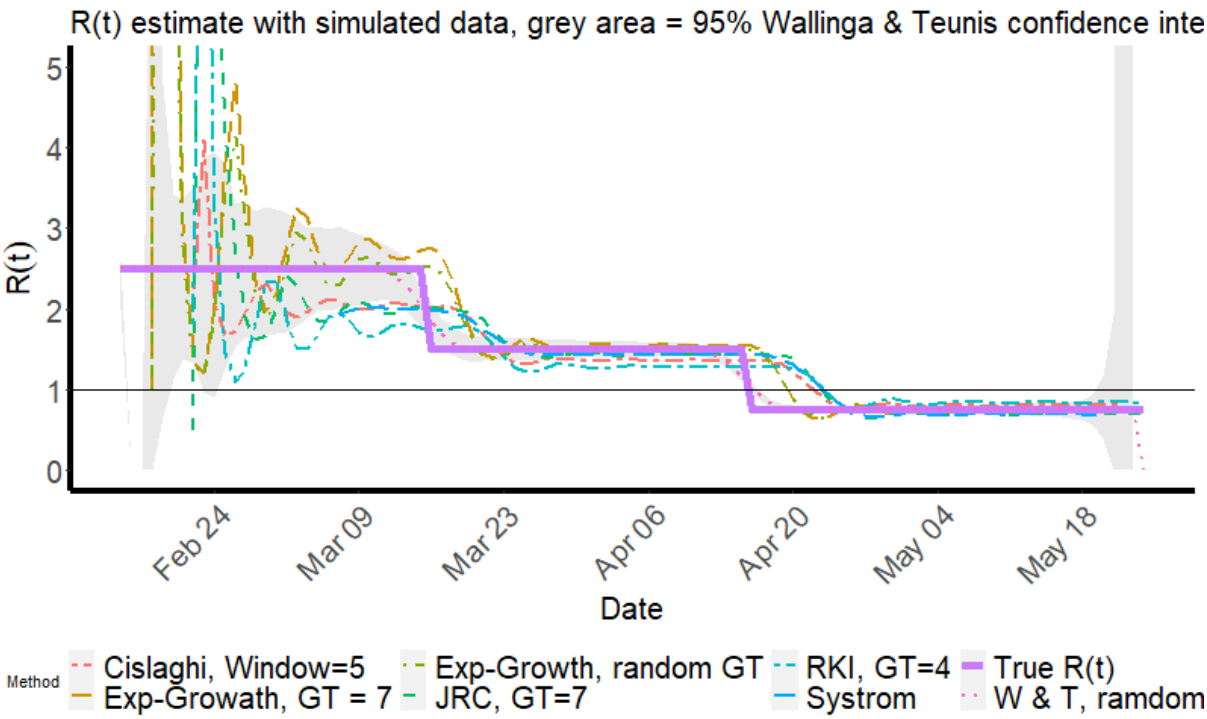

Figure 8 - Estimated R(t) applying the simulated epidemic

In general all methods tend provide a qualitative correct trend even if some methods are faster in the sudden changes. Please check in chapter 2.5.4 for the discussion on the results.

2.5.3 Applying different methods on simulated data

Utilizing the simulated dataset, used at 2.5.2 the R(t) is calculated using each method.

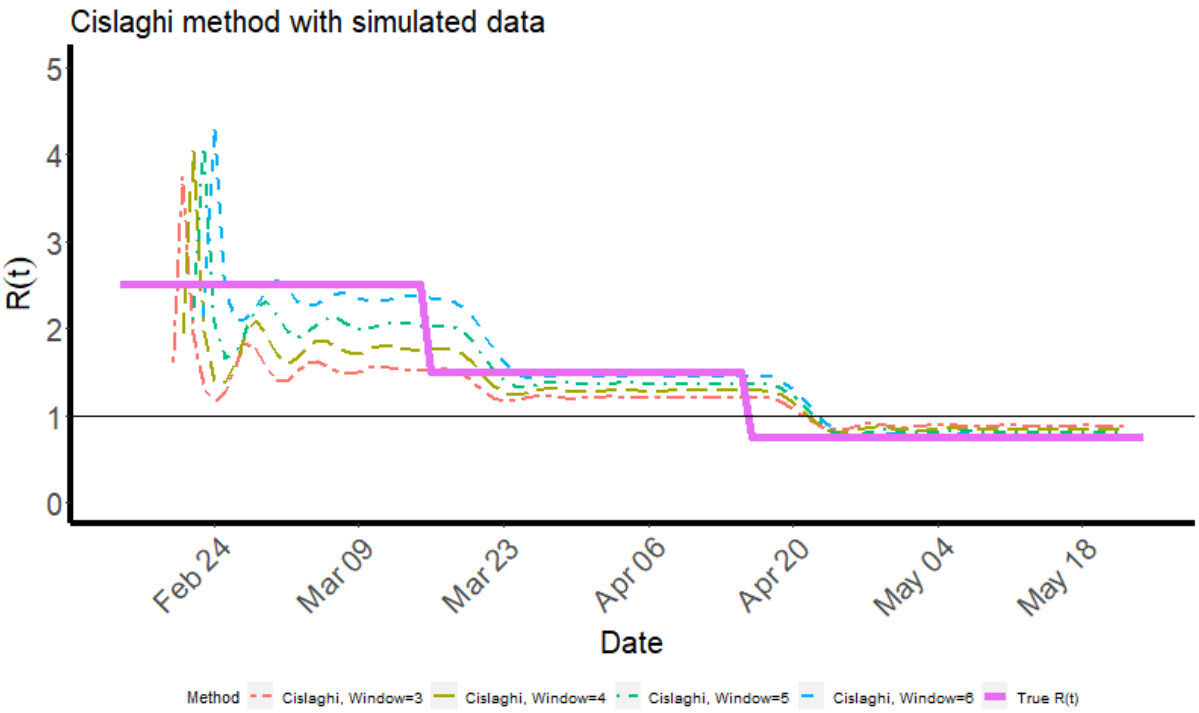

Figure 9 – R(t) estimates from simulated data with Cislaghi method

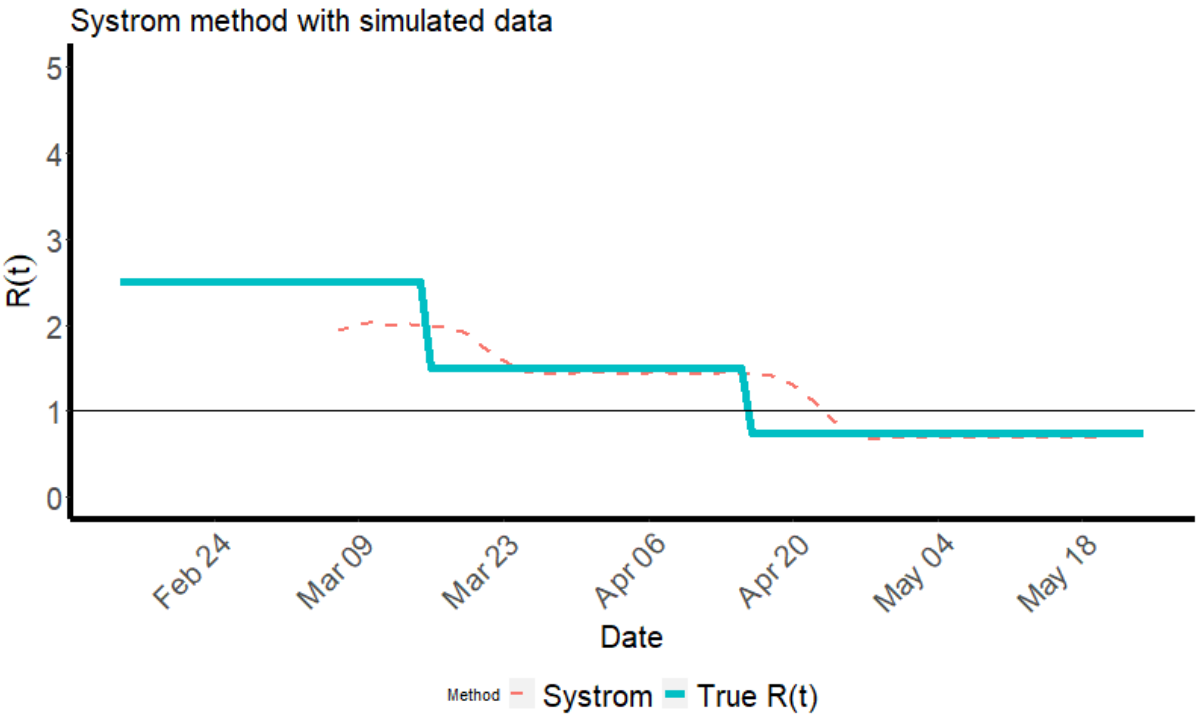

Figure 10- R(t) estimates from simulated data with Systrom method

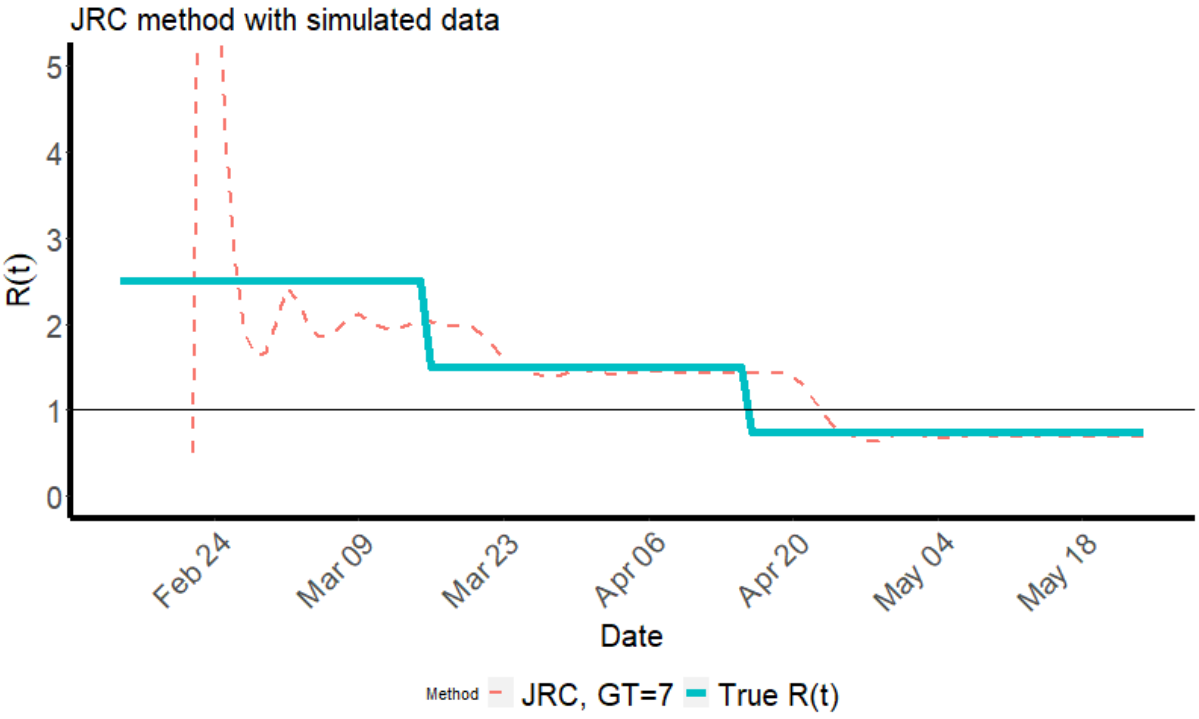

Figure 11– R(t) estimates from simulated data with JRC method

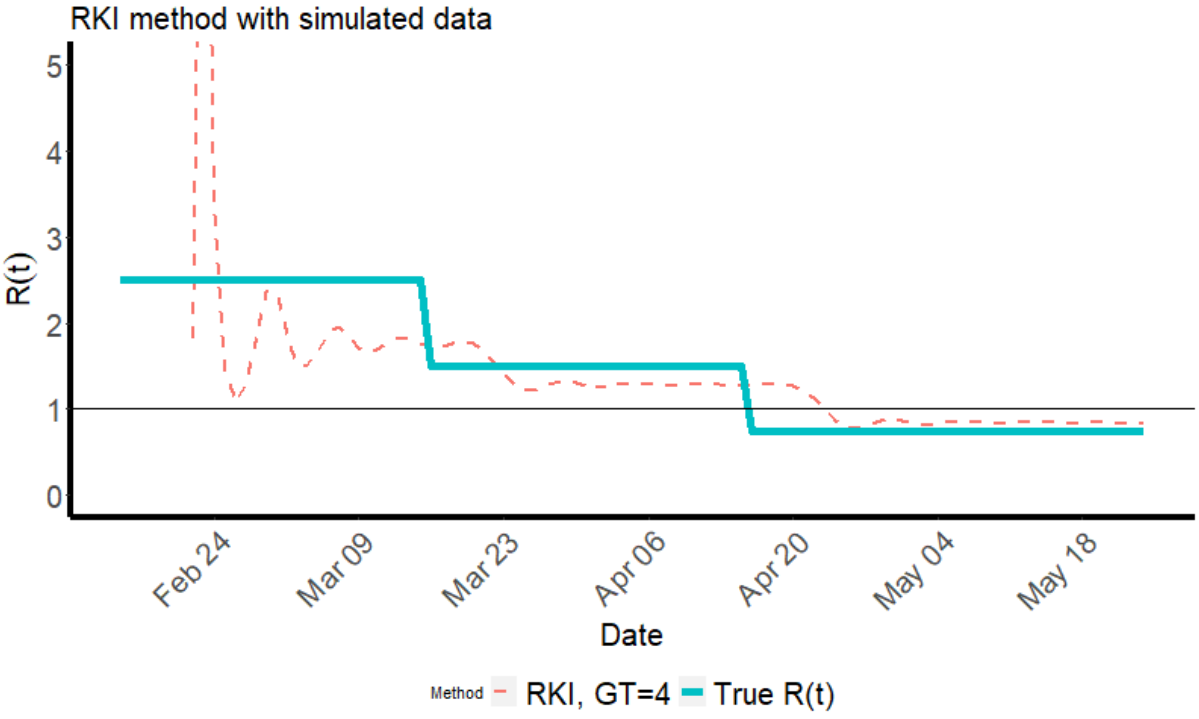

Figure 12- R(t) estimates from simulated data with RKI method

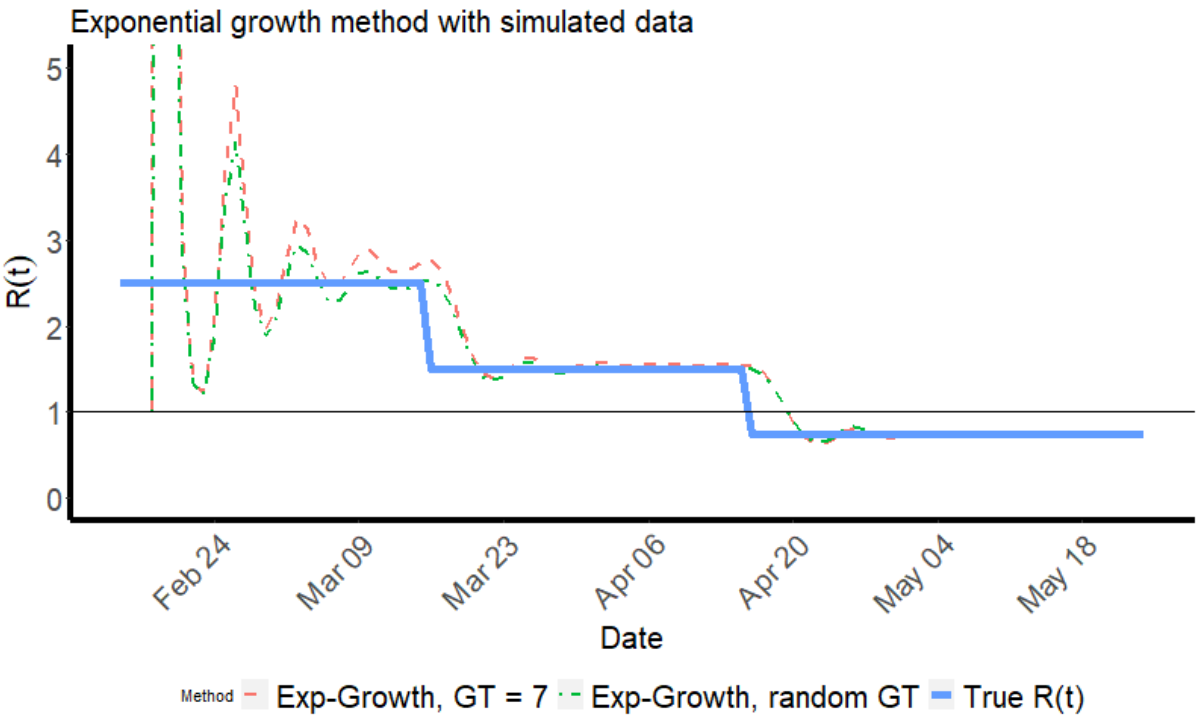

Figure 13 - R(t) determined with exponential growth method

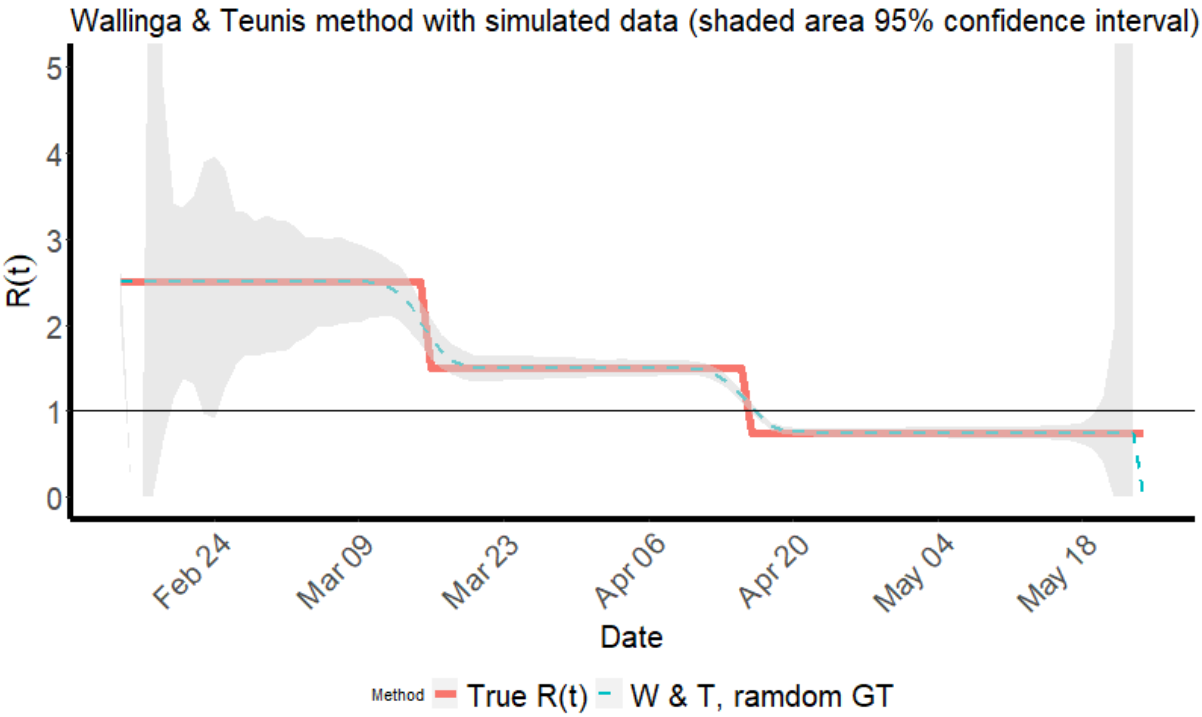

Figure 14 - R(t) determined with Wallinga & Teunis method

2.5.4 Applying different methods on country data

Utilizing data of daily number of new reported cases based on day of reporting is illustrated in a selected number of countries (Italy, Germany, Sweden, Austria and Poland)

or the input values, a generation time of fixed value of 7 days is used or a gamma distribution with mean 6.6 days and variance of 1.5. For the RKI method a generation time of four days is applied. The grey area on the graph is the 95% confidence interval for the Wallinga-Teunis method. In Annex 1 all the EU countries values are shown.

Please check in chapter 2.5.5 for the discussion on the results.

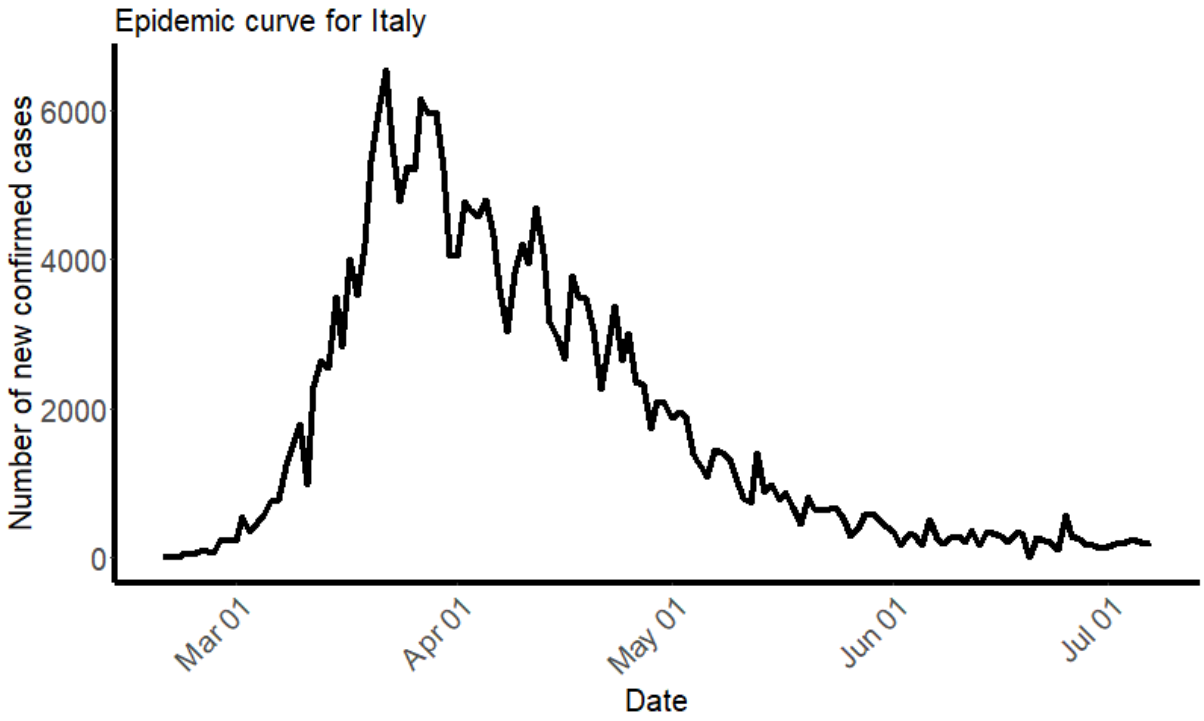

Figure 15 - Epidemic curve for Italy

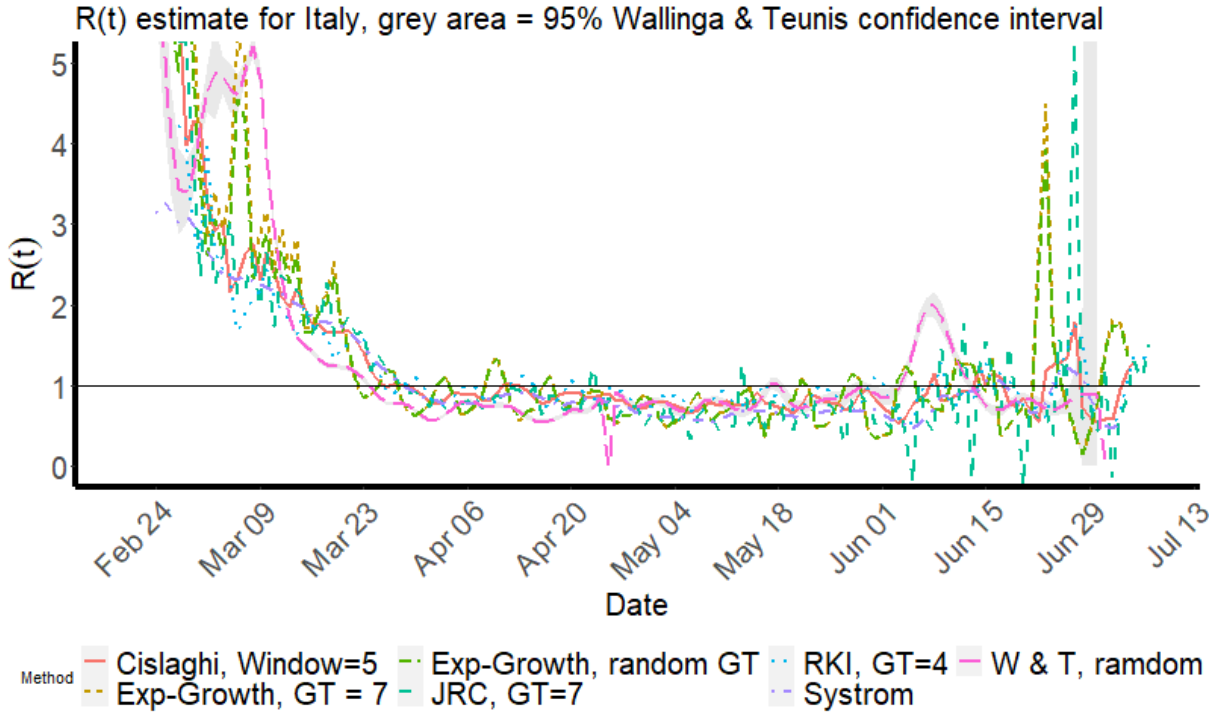

Figure 16 - R(t) determined with all the methods for Italy

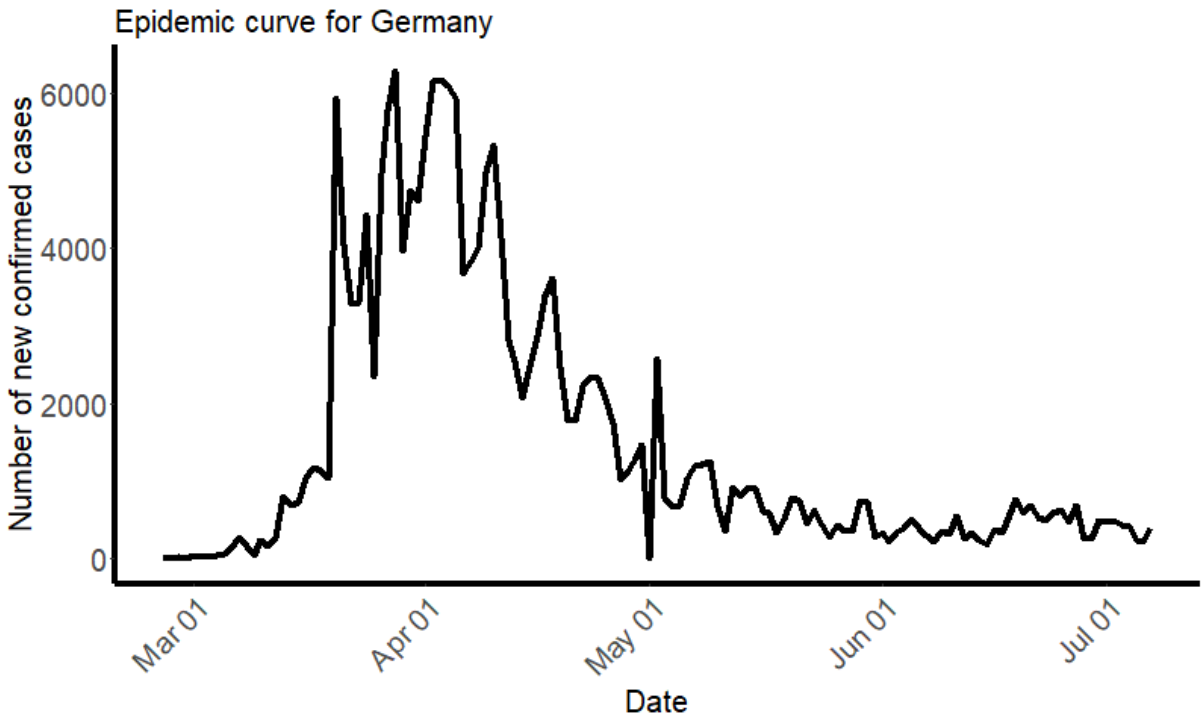

Figure 17 - Epidemic curve for Germany

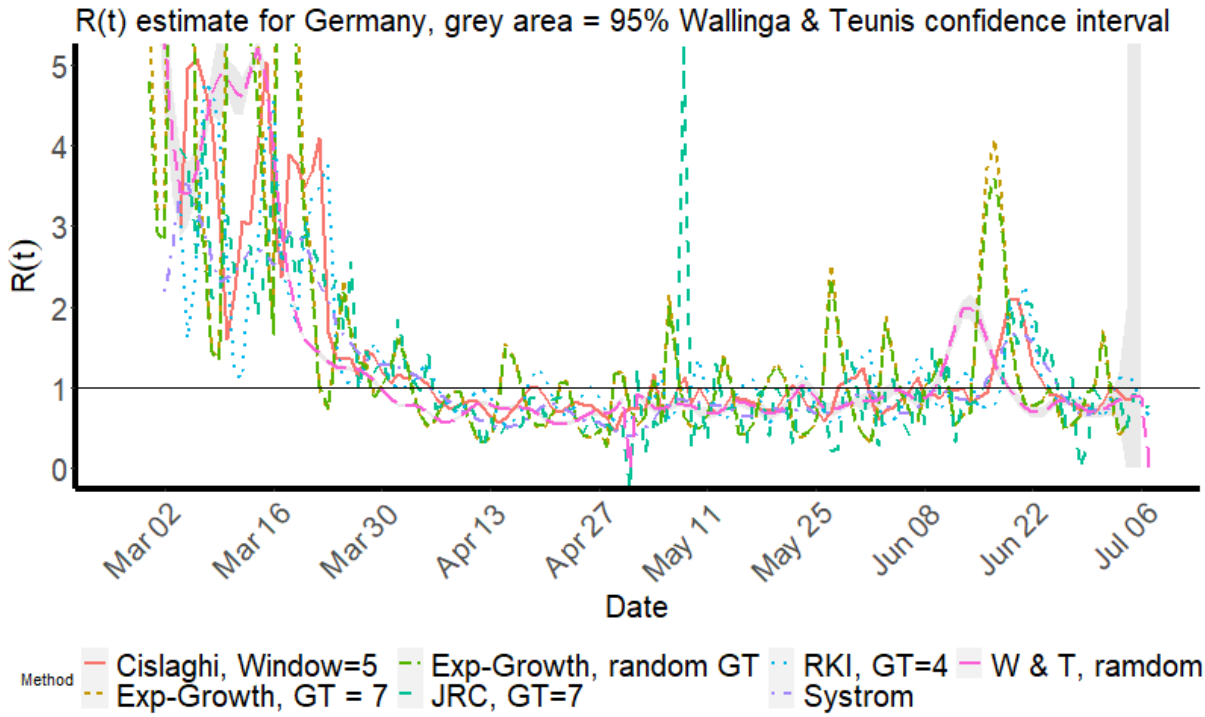

Figure 18 - R(t) determined with all the methods for Germany

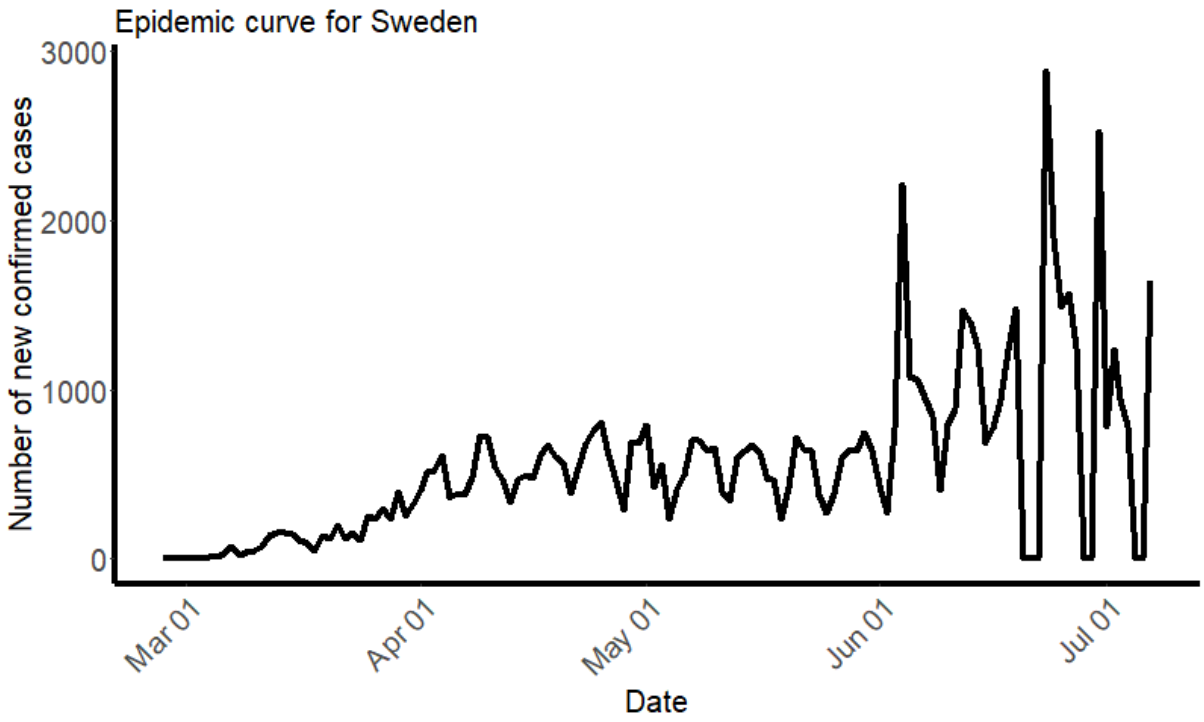

Figure 19 – Epidemic curve for Sweden

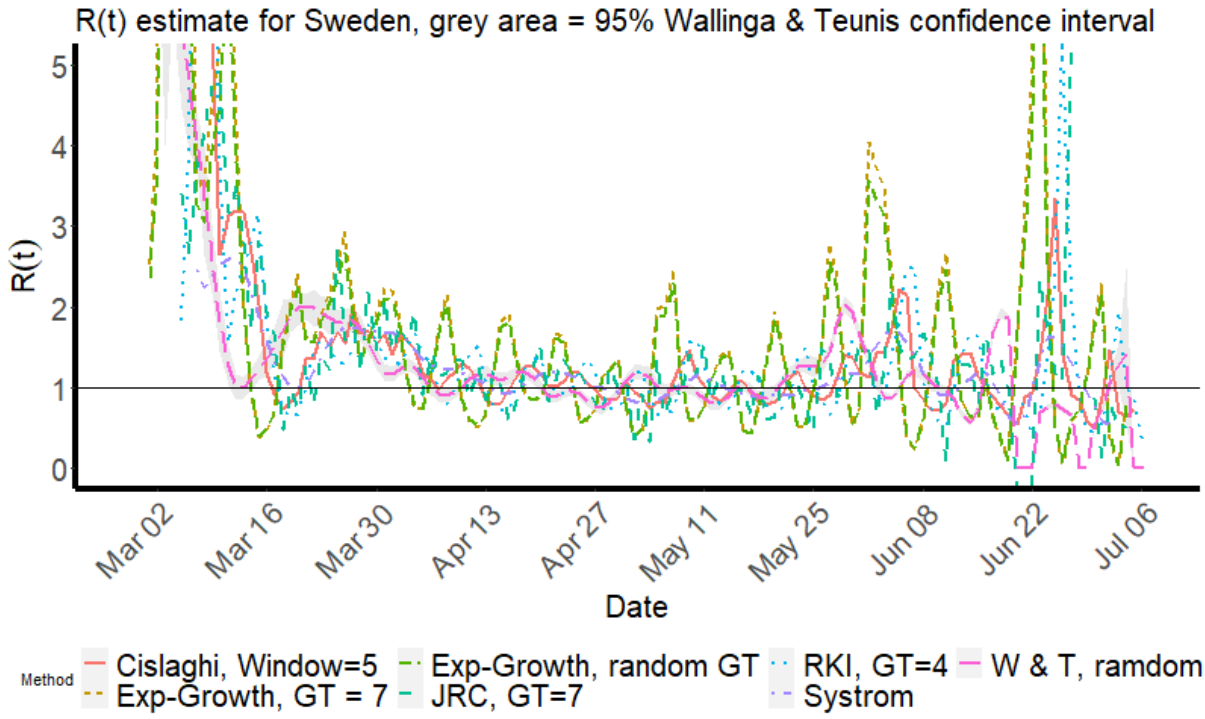

Figure 20 - R(t) determined with all the methods for Sweden

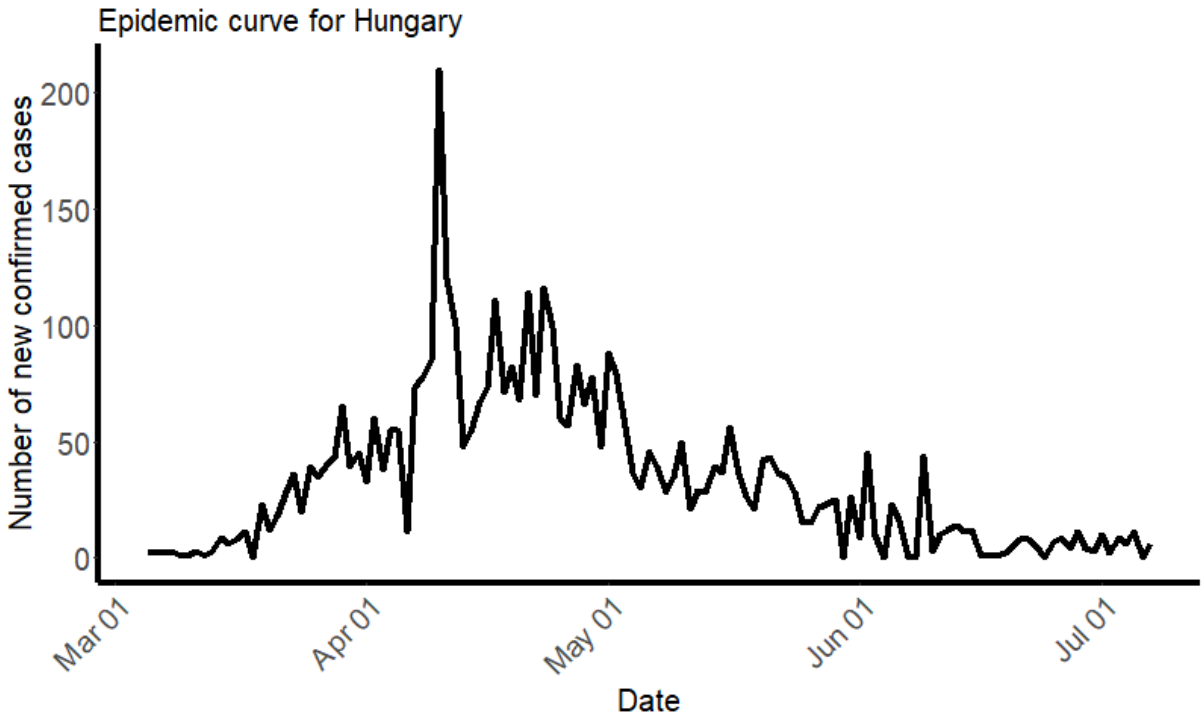

Figure 21 - Epidemic curve for Hungary

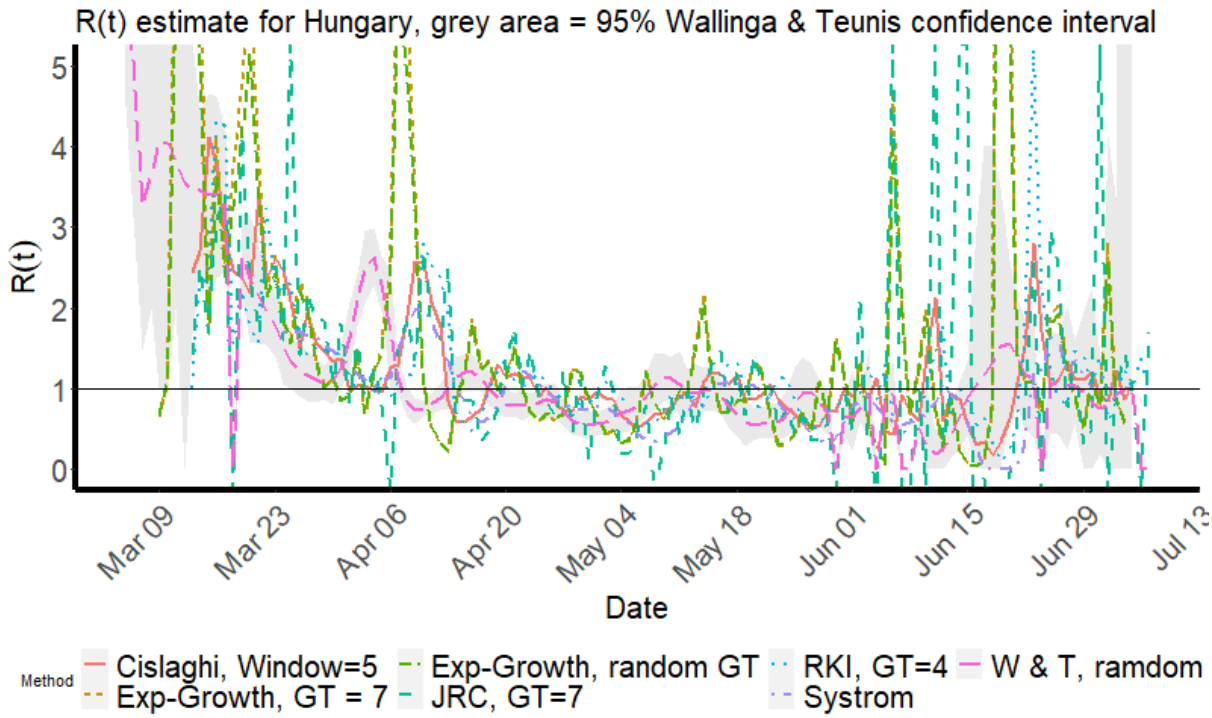

Figure 22 - R(t) determined with all the methods for Hungary

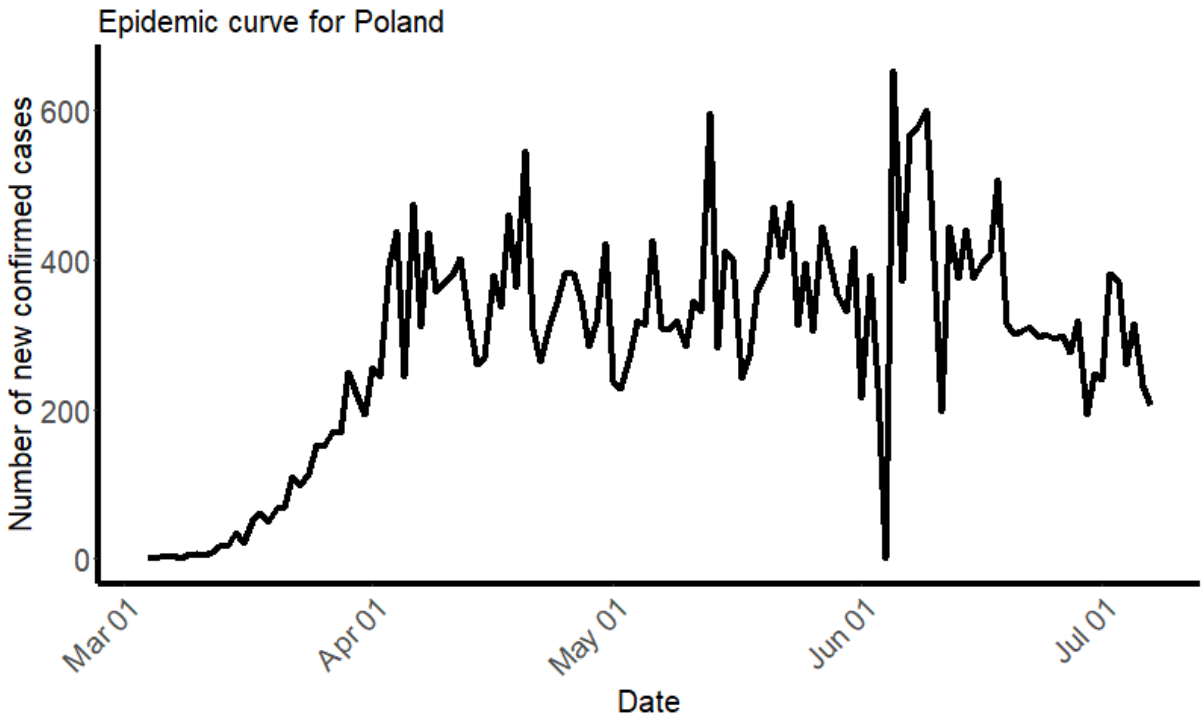

Figure 23 - Epidemic curve for Poland

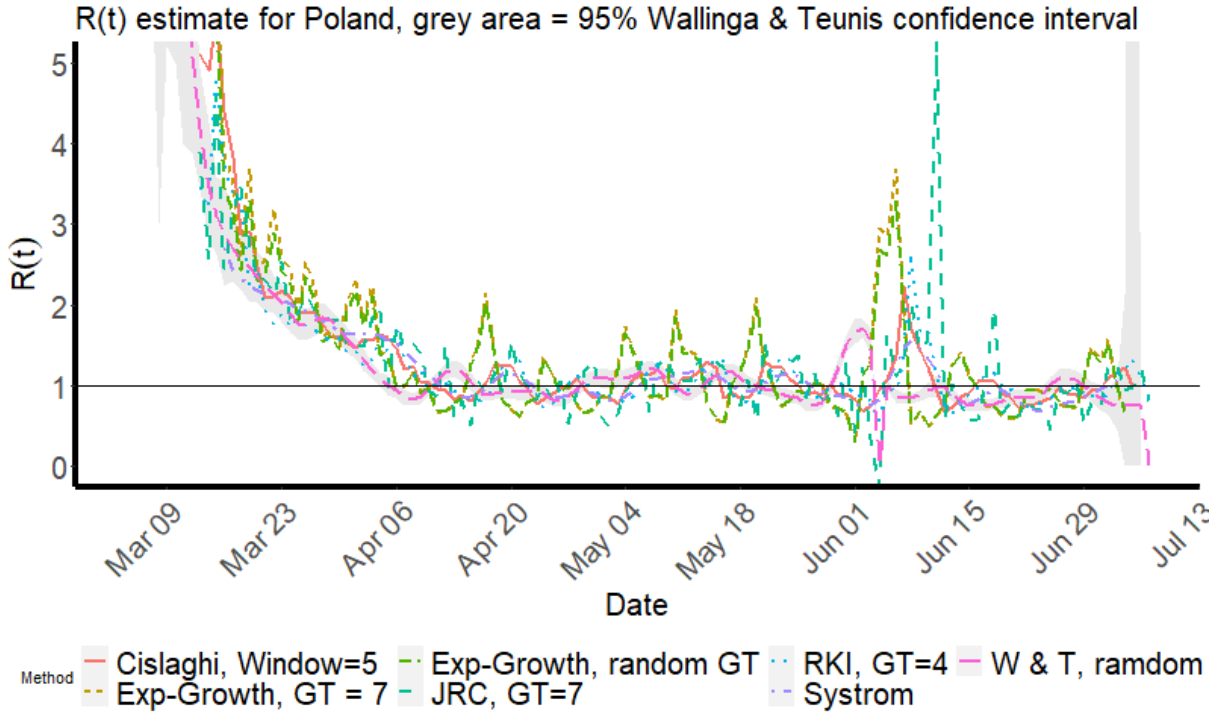

Figure 24 - R(t) determined with all the methods for Poland

2.5.5 Differences between the methods

From both simulated and real data examples, it is illustrated that the effective R(t) estimates gathered from different methods differ less when R(t) value is lower. This is a logical consequence of the fact that with a higher R(t) value more cases are generated and larger numbers will as a consequence show bigger differences between the methods. There is also a larger variation on the daily R(t) estimates for the same methods for higher R(t) values, this is largely an artifact of the assumptions especially on the length of the incubation or generation time estimates.

For the illustration using simulated data, there is no delay assumed between the change of R(t) and the cause of changing the R(t). In reality introducing a non pharmaceutical intervention, the societies behaviour is not always immediate but can take days if not even weeks before it is fully implemented. Our simulation study makes an immediate change on R(t) as the aim is to compare how different methods can detect the change on real R(t) by analysing daily case data.

Methods like the Robert Koch Institute and Cislaghi have a clear bias, for R(t) values above one it underestimates R(t) while for R(t) values below one it overestimates R(t).

The methods vary on how fast they react to the changes on the real R(t) value. The simulation approach shows that most methods make a rather good estimate about one week after the change in the R(t) value. The Walling-Teunis shows a reduction already before the R value was reduced. This is explained by the use of a random distribution on the generation time. As Wallinga-Teunis makes the R(t) estimate based on number of new cases and how many they could infect during the generation time, the length of that can be over two weeks long due to variation. This can have the effect that if R(t) value is changed, cases being infectious before the R(t) value changed and still infectious after the R(t) change will count into the R(t) estimate before the change. This can lead to the fact, that by applying Wallinga-Teunis method, the R(t) estimate thus is being affected already before the real R(t) value changed. Thus this method is in many cases among the fastest detecting the change of R(t).

For the situation in which effective R(t) can be below one, still several methods shows a variation on their daily estimation, mostly depending on the number of cases reported during the data interval used to the R(t) estimate.

Apart of having the estimate on R(t) also the uncertainty of R(t) is crucial. For all methods uncertainty intervals can be calculated. There are differences on how to estimate those intervals; the Wallinga-Lipsitch and Wallinga-Teunis approach also produces confidence intervals for the estimate, which can be derived from mathematical formulas. For other methods confidence intervals by simulation methods could be applied, this approach is not performed in this report.

2.5.6 Effects of epidemiological parameters

All methods depend on certain assumptions on the incubation time, serial time or generation time. Incubation time has a clear definition and is easiest to make estimates from data. The drawback with incubation time is that it will not take into account when a person is infectious after becoming infected, this is more addressed by serial time and generation time.

Serial time and generation time estimates vary as mentioned at the beginning of the paper. These estimates also vary during an outbreak i.e. observing generation time at the beginning or the peak of the epidemic, will give different values, as described in [4]. This implies that to make accurate R(t) estimates also good estimates or serial time or generation time is needed. To make these estimates more accurate only data on reported number of cases a certain day is not enough. Data on contact tracing to get very accurate information about the start of the infection would be necessary. EU Member States could perform these estimates by having access to more detailed data from cases.

3 Conclusions

The report covers a number of methods that are widely used for R(t) estimation. These can be used in order to establish the reproduction number from the published national and subnational data.

The methods presented here are data driven, based on the number of daily cases to make an estimate of R(t). There are other approaches such as model driven approaches, where a model is developed to predict the spread of the disease and from the model the R(t) value is extracted. This can sometimes be close to the data driven R(t) estimate. But in cases where for example many asymptomatic cases exist the model driven R(t) can differ from the data driven. Those methods have not been analysed in this report.

The quality of the estimation depends strongly on the quality of the reported data in terms on quantity, timings and representativeness of the reported information. There can also be irregularities in data, such as reporting delays for different reasons as well as testing policy changes. These can result in that the data coverage is not the same for each day.

The compilation of overall tables and maps for all member states should be done, as much as possible, using a method that best fits the data availability in the Member state. It can thus be either data driven or model driven. Important is that the R(t) estimate is well founded and have an epidemiological meaning. In addition it would be important to use a standard methodology for all EU MS. The standard method could also be used to check qualitatively the national R(t) estimates: even if the estimates are not exactly the same, they should have similar trends over time.

If this is not possible, due to the willingness of Member States to provide their own quantities, a mechanism for collecting the final daily estimation from the Member States at subnational level should be implemented to allow data introduction and validation before the publication is performed.

The application of such methodology to EU27 could allow

- Development of national and subnational maps of transmission
- Development of tables
- Inclusion in the daily Factsheets

The vast array of methods in this paper shows that the effective reproduction number R(t) can be estimated in several different ways. In addition, several countries produce their own R(t) estimates. Some of these numbers are not coming with information how they were calculated. In this paper we include the method from Germany, Robert Koch Institute as their method is explained. Other countries like Luxembourg, France, Netherlands and Italy also have information on how the R(t) is calculated. Other countries like Sweden, Finland, Belgium produce R(t) estimates but do not provide exact information on how it is derived.

This paper can be used to highlight different methods to use for R(t) estimation. It also gives EU MS the possibility to then compare how their own estimate compares to an existing method. Apart from this input from EU MS is needed on how their methods work, some countries might have developed another method due to availability of some other data, these methods could be very relevant for other countries. A review of available methods would be useful for making R(t) estimates and their comparison more fruitful.

All the programs used to calculate the R(t) values are contained at this repository online:

https://github.com/ec-jrc/COVID-19/tree/master/programs/ReprNumber

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Errata-Corrige
Respect to the first version that was published in May 2020, the following corrections have been done, thanks to prof. Stefano Stefani who pointed out the errors in some of the pages and who we strongly thank.

Section 2.1, equation 3

Errata: $I = I_0 e^{(\frac{R_0}{d}-1)t}$ (3)

Corrige: $I = I_0 e^{(R_0-1)t/d}$ (3)

11th line from below, the contact trace c is wrongly indicated as transmission probability

Par 2.4.3

Errata:

$$\log(I_1) = \log(I_0) + (\frac{R(t)}{d} - 1)t_1$$
$$\log(I_2) = \log(I_0) + (\frac{R(t)}{d} - 1)t_2$$

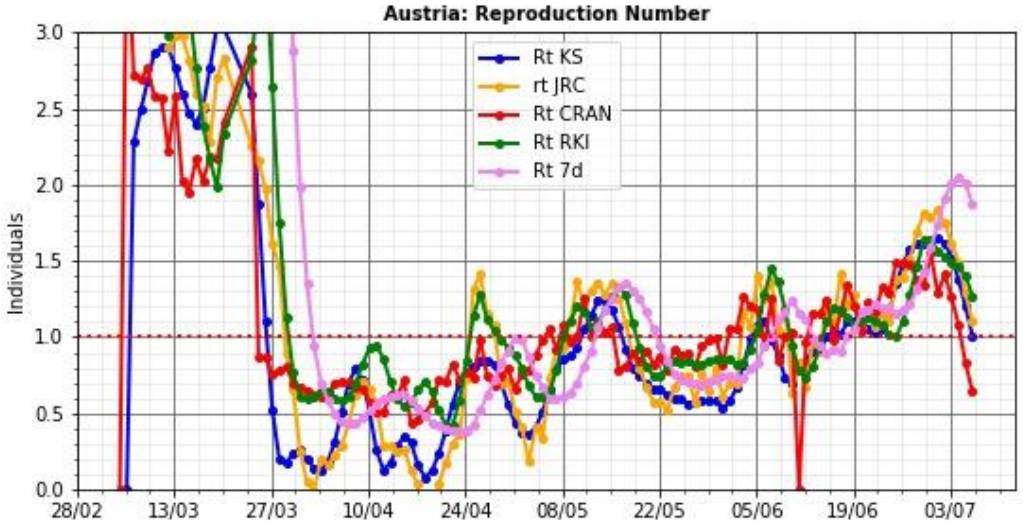
Corrige:

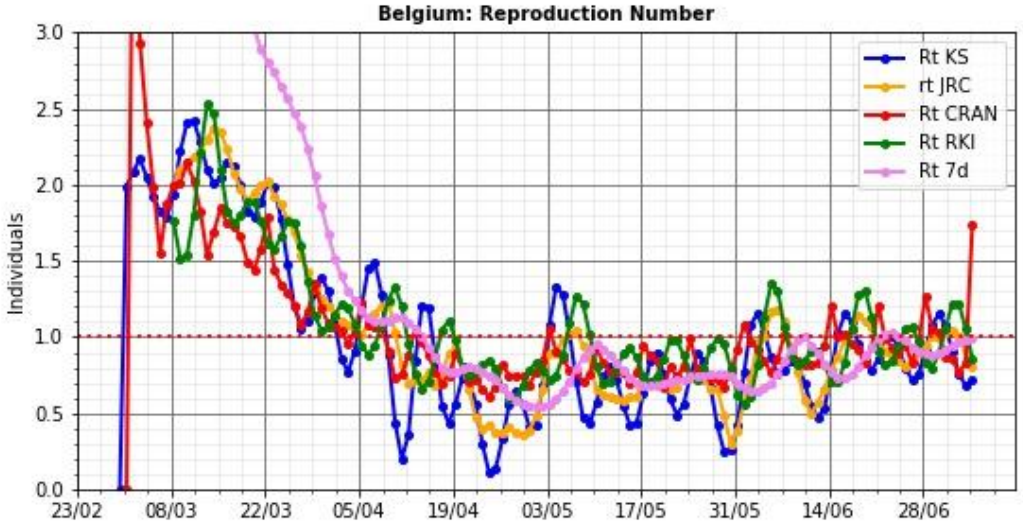
$$\log(I_1) = \log(I_0) + (R(t) - 1)t_{1/\mathrm{d}}$$
$$\log(I_2) = \log(I_0) + (R(t) - 1)t_2/d$$

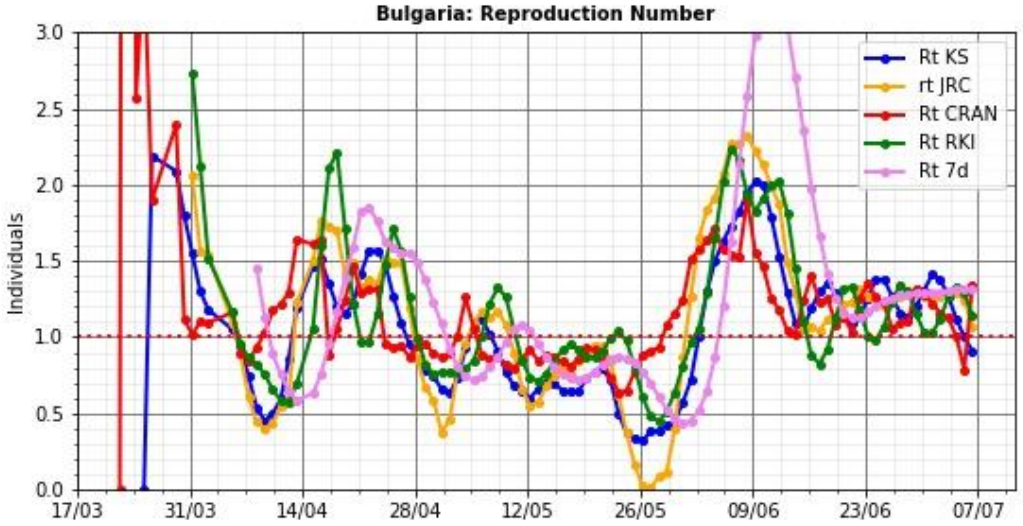
List of figures

Annexes

Annex 1. Effective reproduction number estimated with 5 methods as of 8 Jul 2020 for EU27 countries



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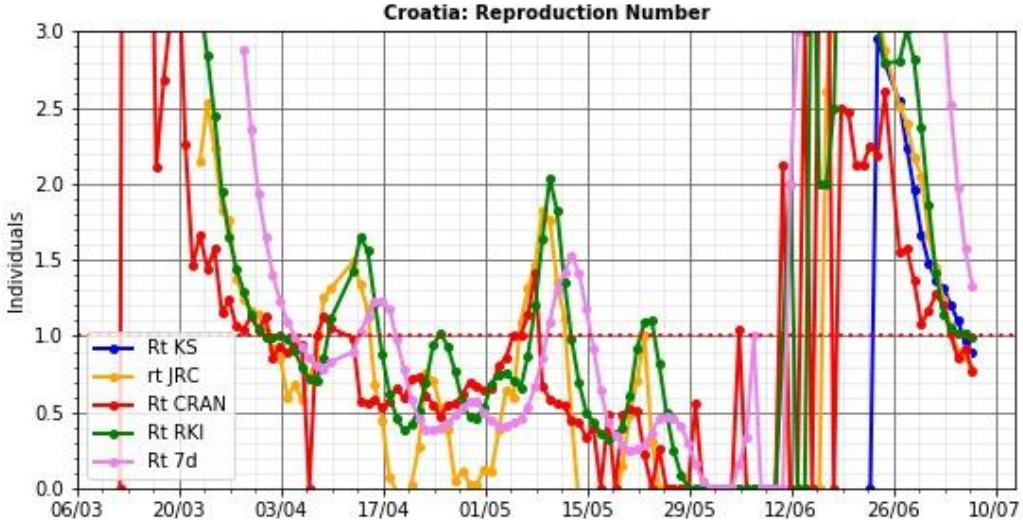
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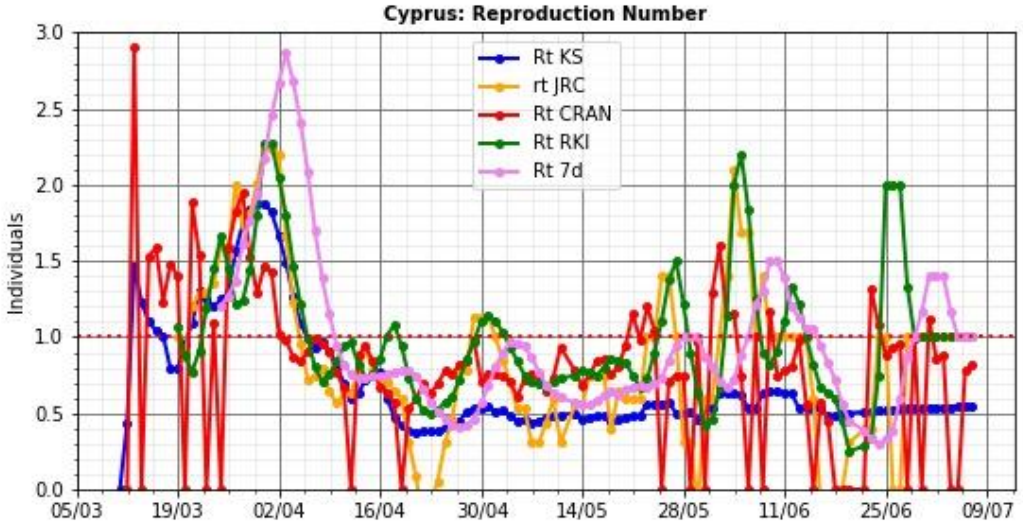
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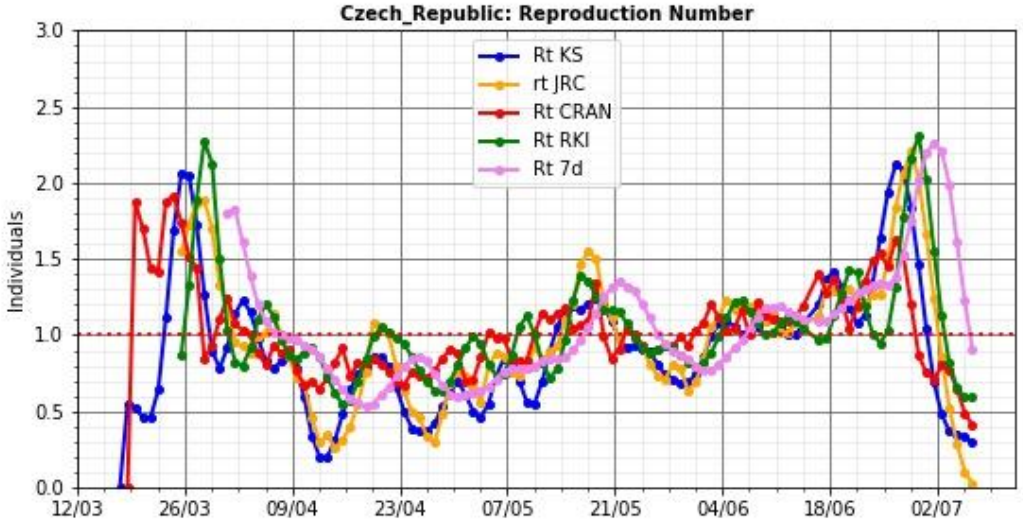
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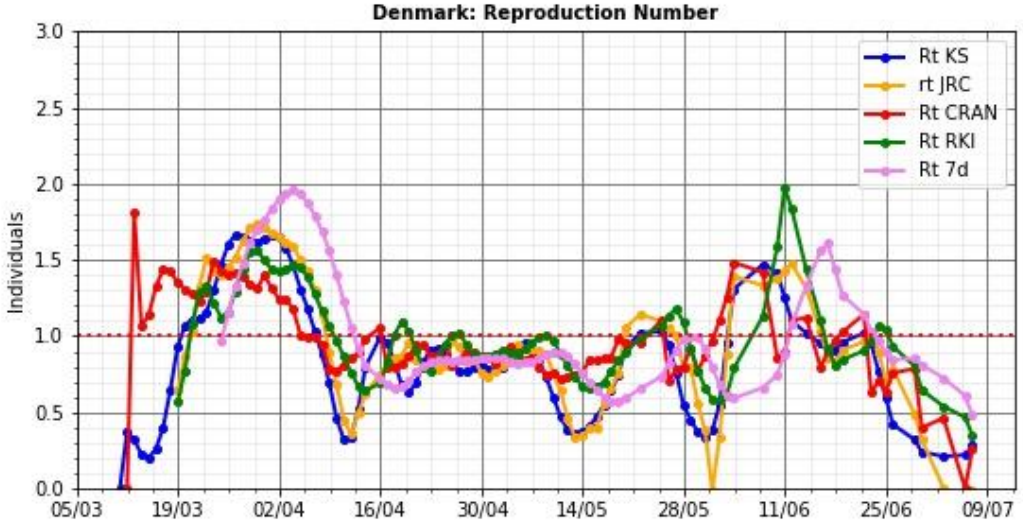
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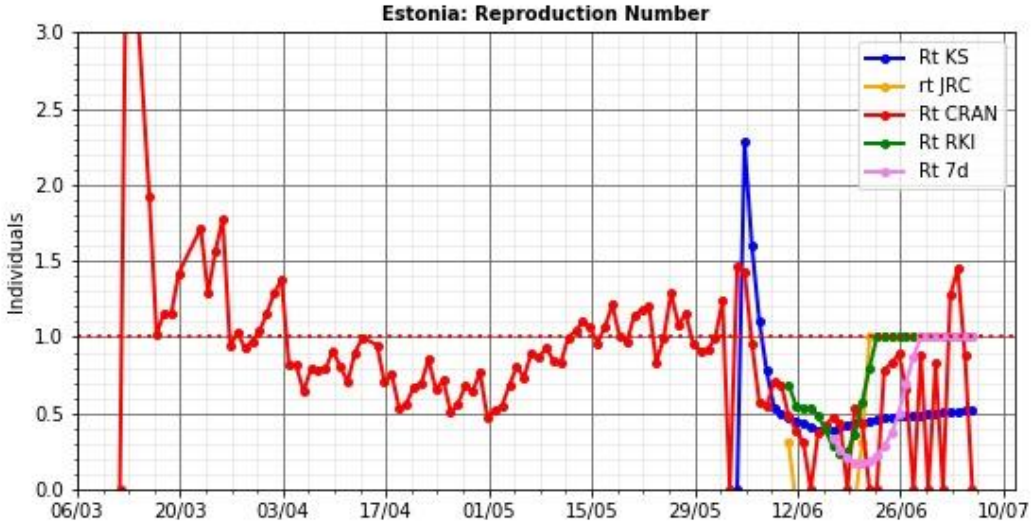
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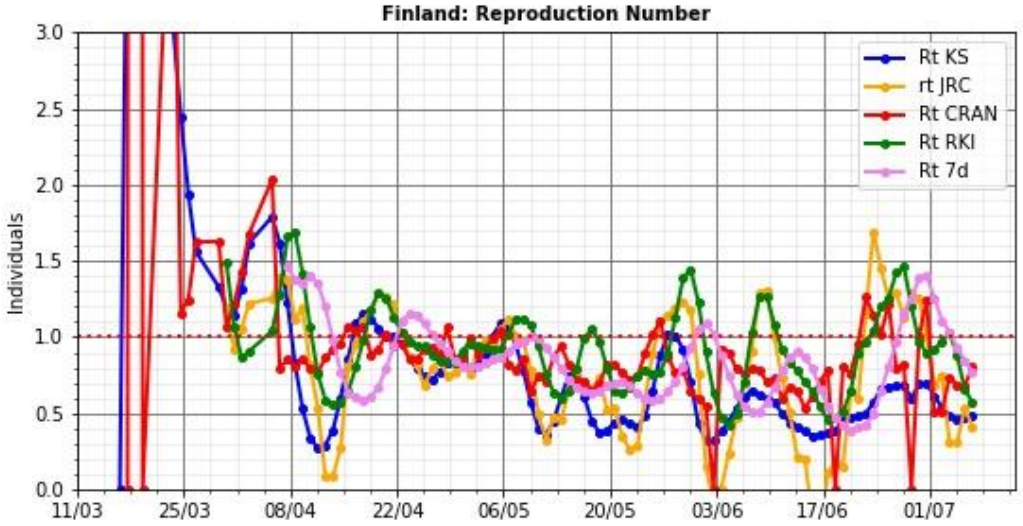
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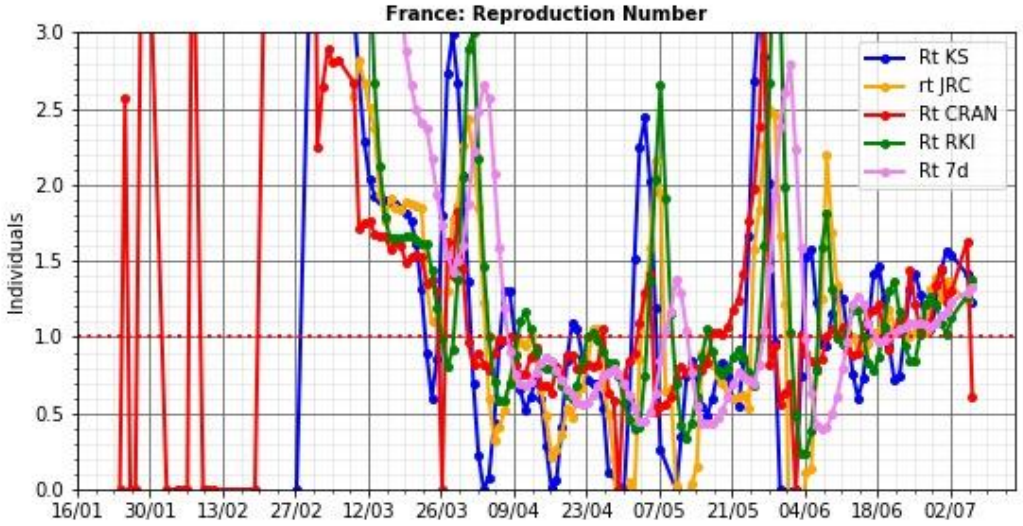
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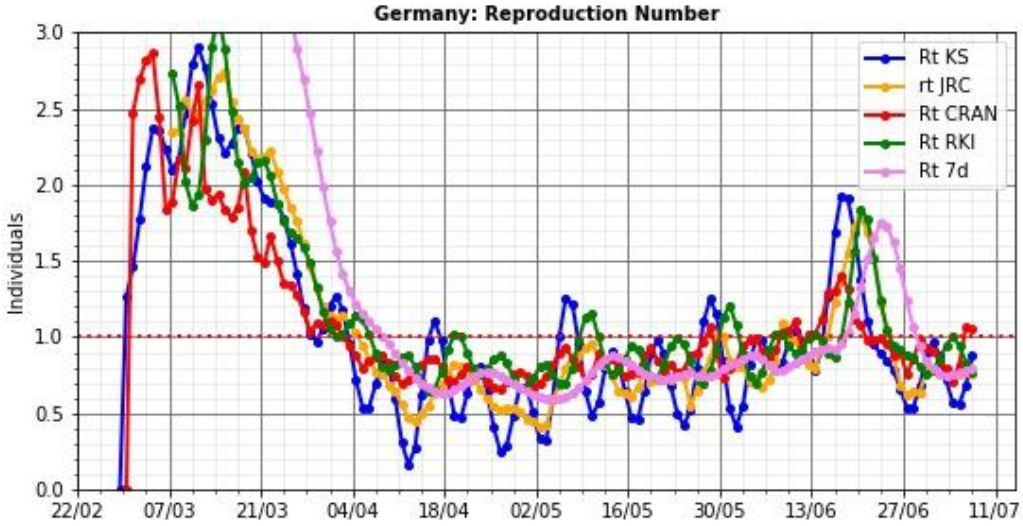
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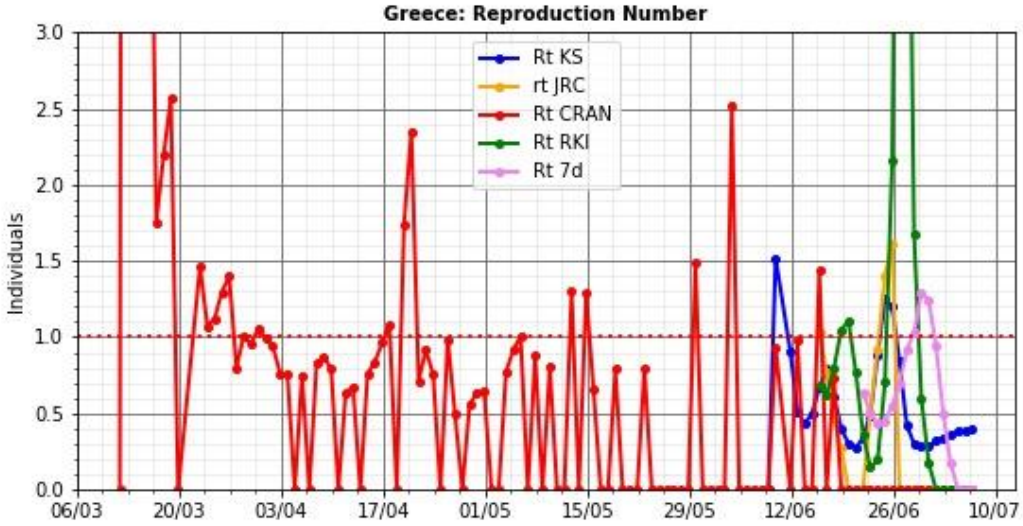
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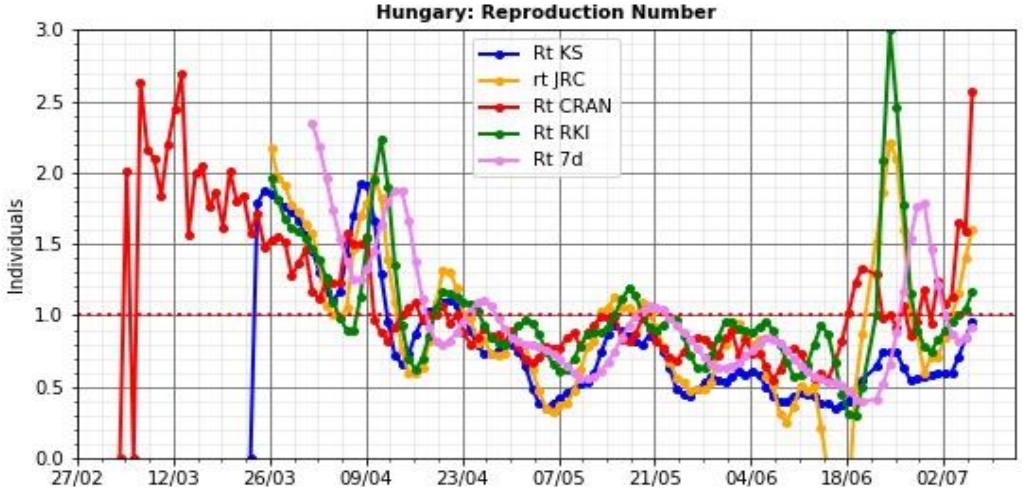
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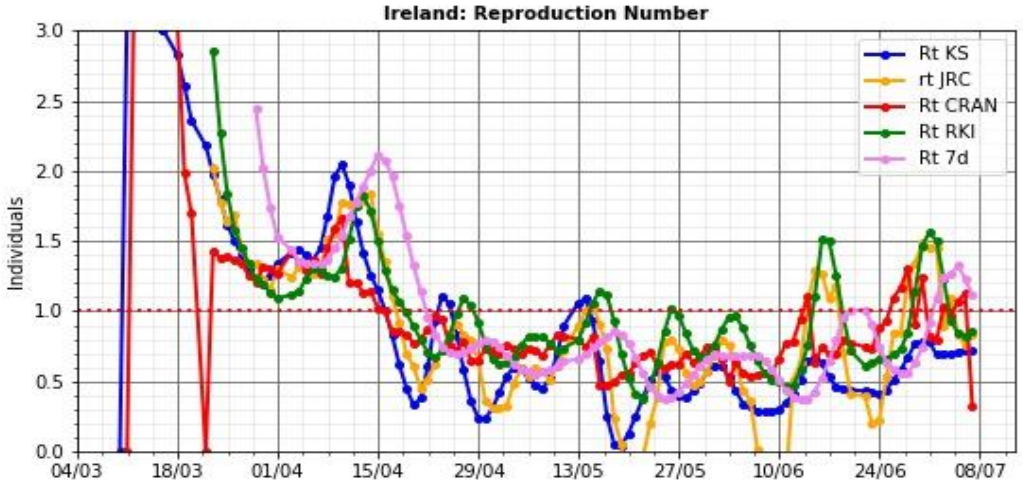
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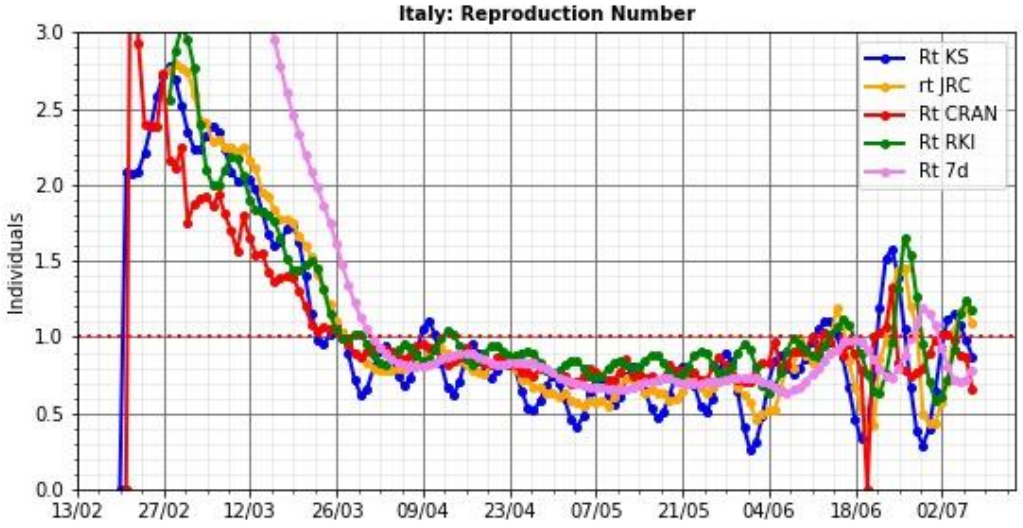
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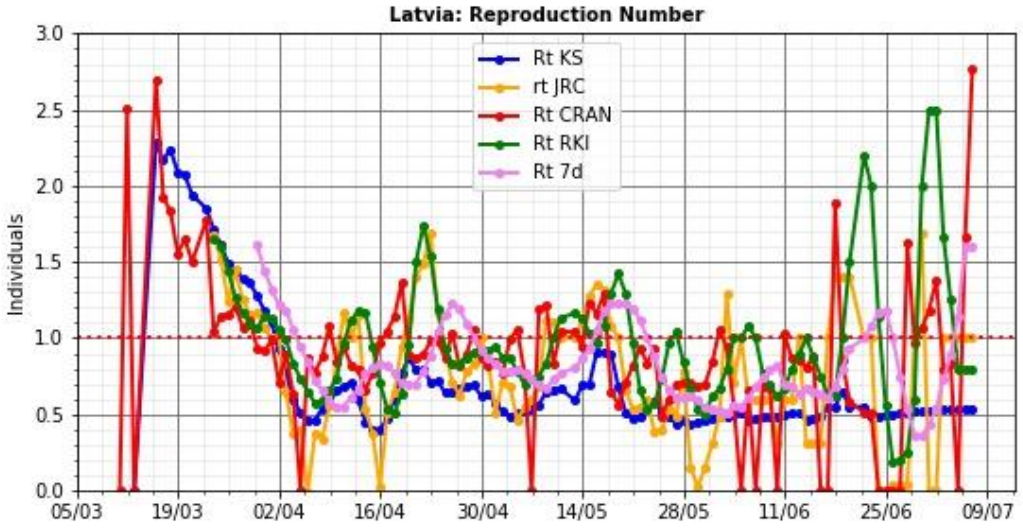
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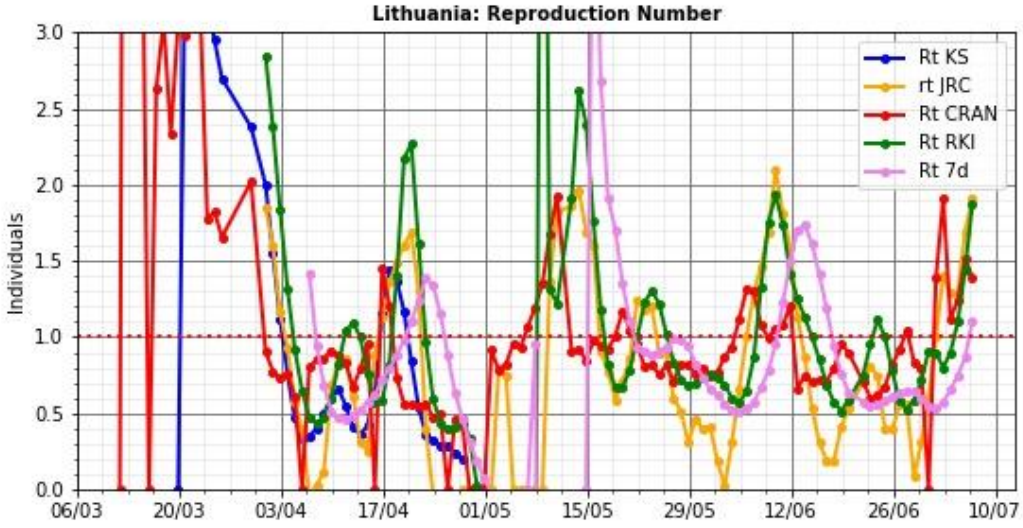
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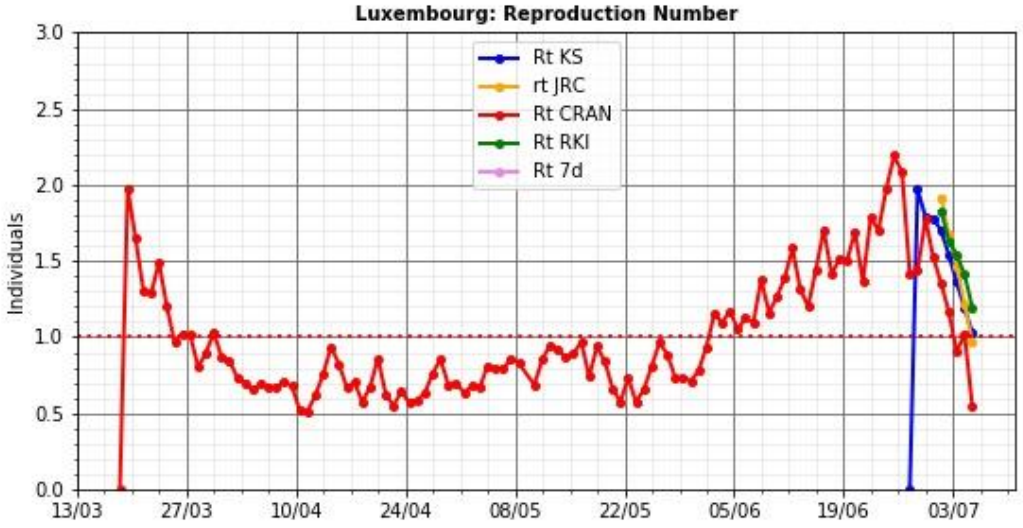
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22/05
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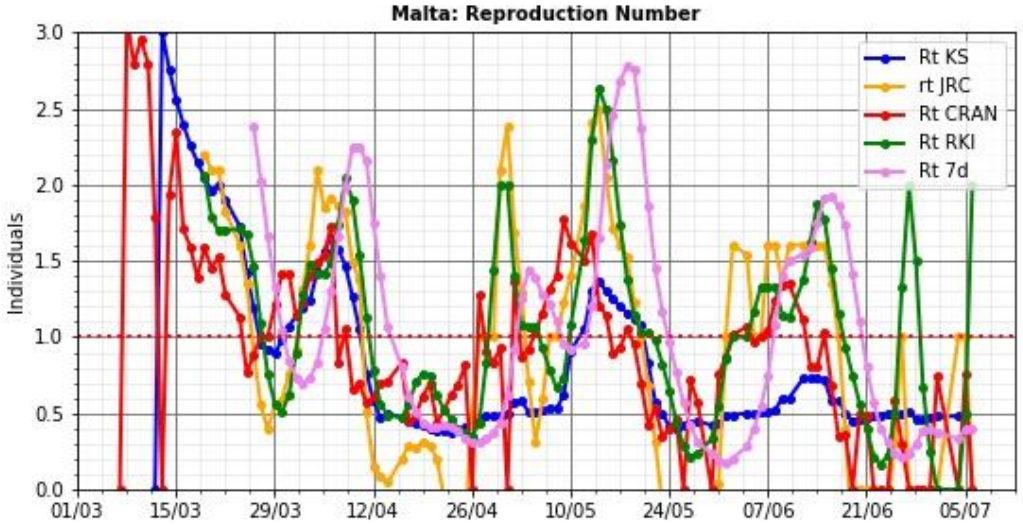
19/06
03/07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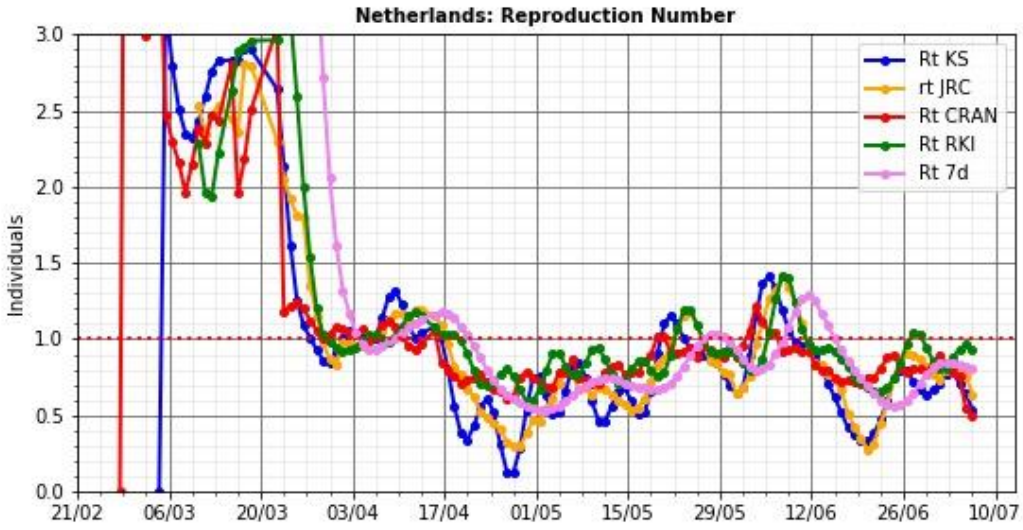
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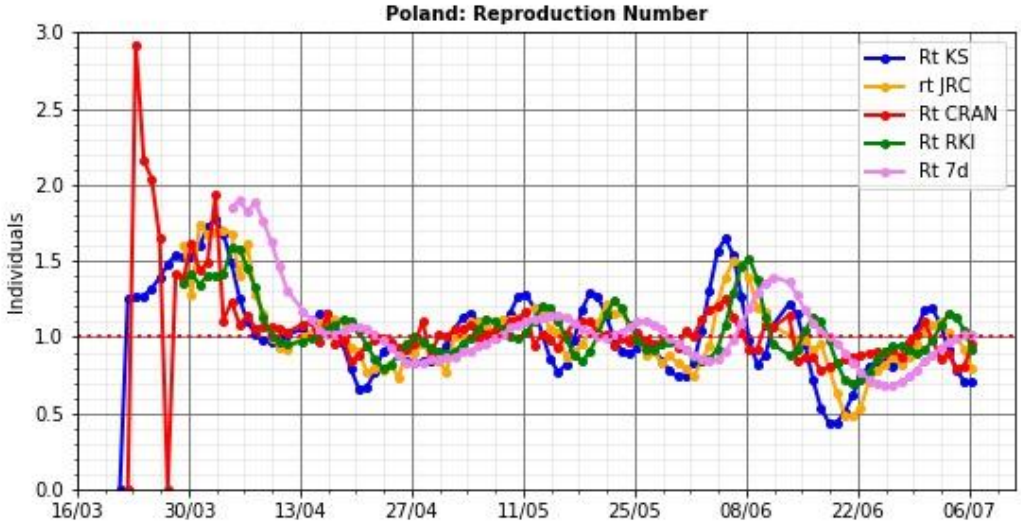
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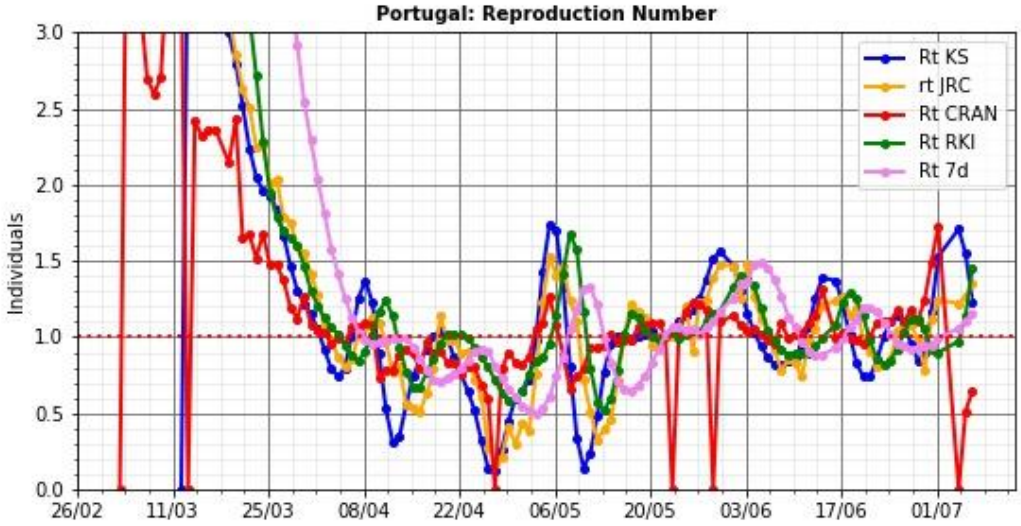
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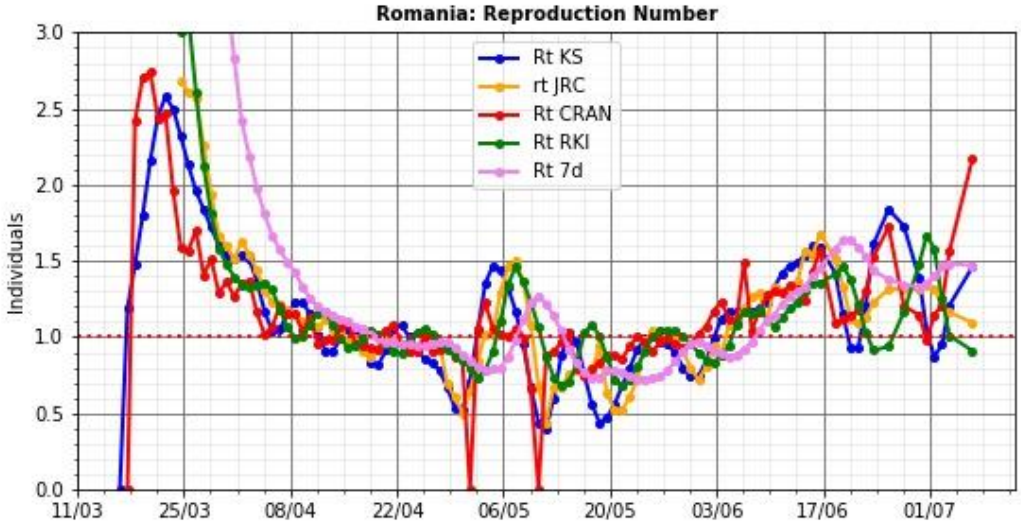
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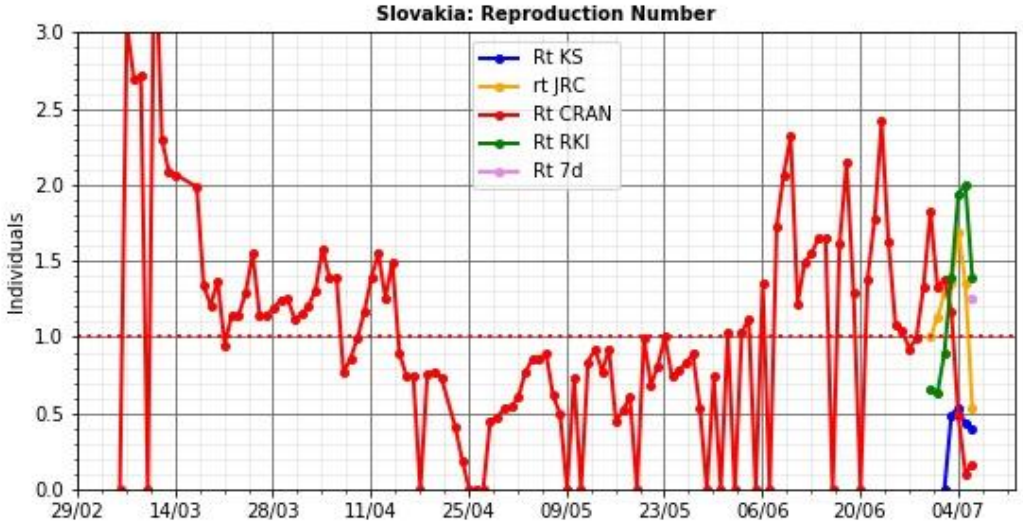
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14/03
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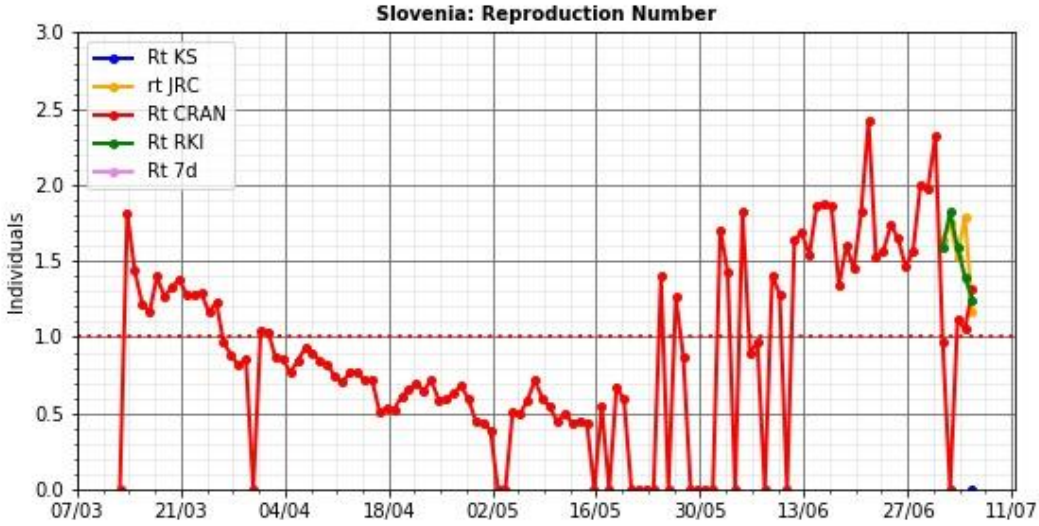
04/07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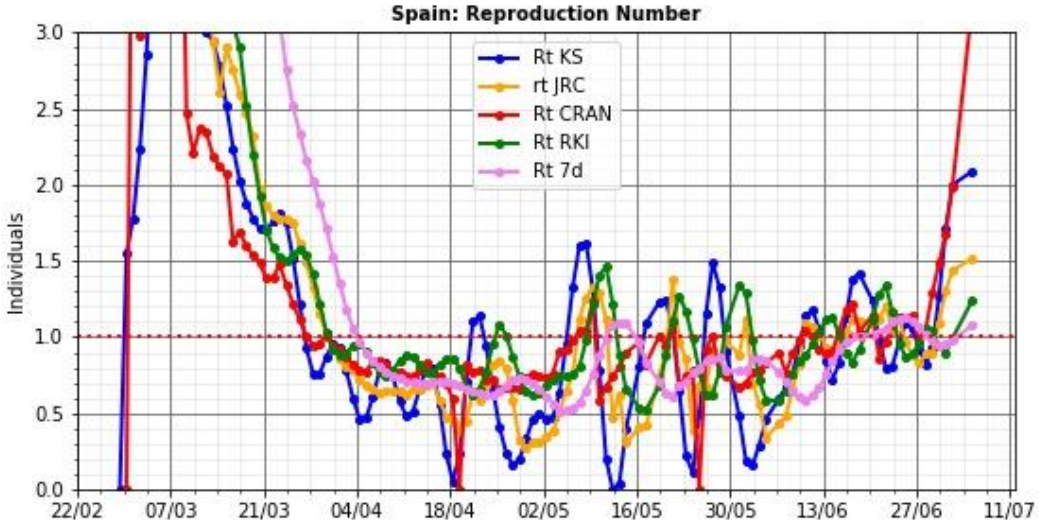
11/07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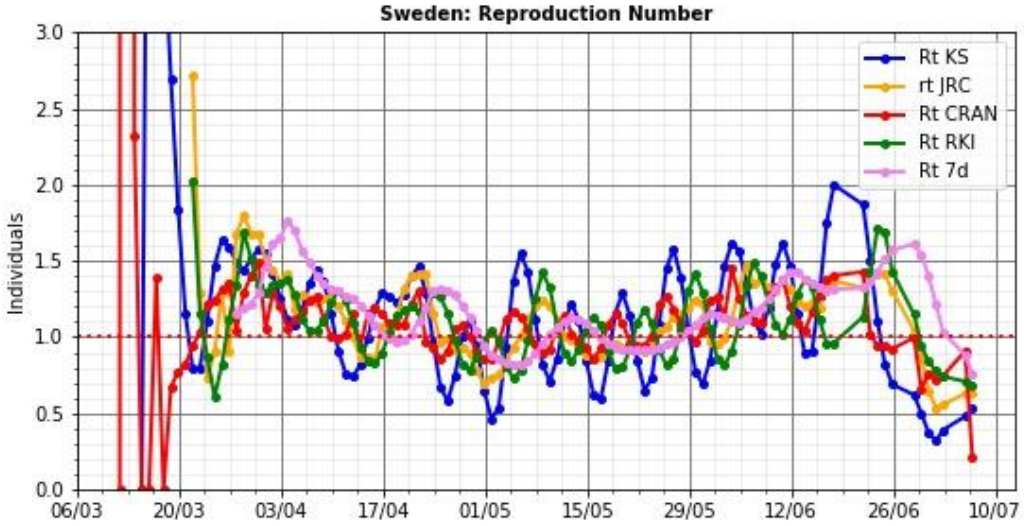
11/07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1.0
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06/03
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17/04
01/05
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10/07

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