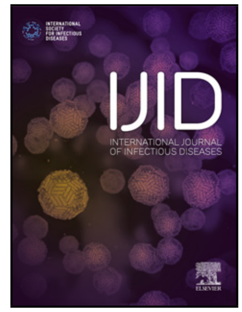
Journal Pre-proof



Monitoring Transmissibility and Mortality of COVID-19 in Europe

Jing Yuan, Minghui Li, Gang Lv, Z. Kevin Lu

PII: S1201-9712(20)30182-X

DOI: https://doi.org/10.1016/j.ijid.2020.03.050

Reference: IJID 4056

To appear in: *International Journal of Infectious Diseases*

Received Date: 13 March 2020

Revised Date: 18 March 2020

Accepted Date: 20 March 2020

Please cite this article as: { doi: https://doi.org/

TITLE PAGE

Monitoring Transmissibility and Mortality of COVID-19 in Europe

Authors: Jing Yuan, Ph.D.; [1]* Minghui Li, Ph.D.;[2]* Gang Lv, MD;[3] Z. Kevin Lu, Ph.D.[4]

Affiliations

1. Department of Pharmacy Practice & Administration, Rutgers University; 160 Frelinghuysen Road – Suite 417, Piscataway, New Jersey 08854 USA
2. University of Tennessee Health Science; 881 Madison Avenue, Room 219, Memphis, Tennessee, 38163 USA
3. The Eighth Medical Center of People's Liberation Army General Hospital, Beijing China
4. University of South Carolina; 715 Sumter Street, CLS Building 311, Columbia, South Carolina, 29208 USA

*Contributed equally

Corresponding author:

Z. Kevin Lu, PhD

Associate Professor

Address: 715 Sumter Street, CLS Building 311

Columbia, SC 29208

Phone Number: 803-777-2653

Fax Number: (803) 777-2820

Email Address: lu32@email.sc.edu

Highlights

• As of 10 March 2020, Italy has reported 9,172 COVID-19 cases with 463 deaths.

• We reported real-time reproductive numbers (R(t))and case fatality rate in in selected European countries (Italy, France, Germany, and Spain) by 9 March 2020.

• The R(t) was greater than 2 in the selected European countries, indicating the outbreak will continue.

Abstract

Objectives: As a global pandemic is inevitable, real-time monitoring of transmission is vital for containing the spread of COVID-19. The main objective was to report real-time effective reproduction numbers (R(t)) case fatality rate (CFR).

Methods: Data were mainly obtained from WHO website, up to 9 March 2020. R(t) was estimated by exponential growth rate (EG) and time dependent (TD) methods. “R0” package in R was employed to estimate R(t) by fitting the existing epidemic curve. Both naïve CFR (nCFR) and adjust CFR (aCFR) were estimated.

Results: In EG method, R(t) was 3.27 [3.17-3.38] for Italy, 6.32 [5.72-6.99] for France, 6.07 [5.51-6.69] for Germany, 5.08 [4.51-5.74] for Spain. With TD method, the R value for March 9 was 3.10

[2.21-4.11] for Italy, 6.56 [2.04-12.26] for France, 4.43 [1.83-7.92] for Germany, and 3.95 [0-10.19] for Spain.

Conclusions: This study provides important findings on an early outbreak of COVID-19 in Europe. Due to the recent rapid increase in new cases of COVID-19, real-time monitoring of the transmissibility and mortality in Spain and France is a priority

Keywords: COVID-19; effective reproduction numbers; Control; Europe

TEXT

Background

The continued outbreak of coronavirus disease 2019 (COVID-19) in Europe is a significant public health concern. Several European countries have reported imported cases of COVID-19 from Italy, the epicenter in Europe. Local transmission of COVID-19 has been confirmed in certain European countries. As of 10 March 2020, confirmed cases of COVID-19 have reached 10,000 in Italy, exceeded 1,000 in Spain, France, and Germany, and grew quickly in other European countries.(1) In terms of deaths caused by COVID-19, more than 800 were reported in Italy, approximately 50 were reported in Spain and France, but only 3 were reported in Germany. Based on the diversity in the number of infected cases and deaths, European and local authorities should adopt country-specific measures to prevent onward transmission of COVID-19.

Working with the World Health Organization (WHO), the European Centre for Disease Prevention and Control (ECDC) has provided several recommendations to national and regional authorities in Italy to contain the further spread of COVID-19. Italian governments have locked down its northern region of Lombardy, where several clusters of COVID-19 cases were found, on 8 March 2020 and extended the lockdown to the whole country on 9 March 2020. Spain, France, and Germany also announced different measures aiming at stopping the rapid spread of COVID-19. The adoption of time-sensitive prevention and control measures depends on real-time monitoring on the transmissibility and mortality of COVID-19 in each country.

Current evidence on the transmissibility and mortality of COVID-19 has been focused on China.(2) Little attention has been paid to European countries. Given the rapid increase of COVID-19 in Europe, it is urgent to understand the transmissibility and mortality in key European countries to guide the implementation of prioritized prevention and control measures. The real-time reproduction number (R(t)), defined as the number of secondary cases one case would produce over the course of the outbreak, is useful to monitor the transmissibility of COVID-19 over time.(3) Therefore, R(t) calculates the effective reproduction number when immunity intervention measures are implemented. By contrast, the basic reproduction number (R_0) is the reproduction number when no immunity from past exposures or vaccination, nor any deliberate intervention in disease transmission has been carried out. As a result, it is more appropriate to use R(t) to monitor the real-time transmissibility when public measures are in place. The case fatality rate (CFR) can be used to measure the mortality rate.

Methods

Data Source

Data were obtained from daily laboratory-confirmed cases of COVID-19, made publicly available by WHO on the Coronavirus disease (COVID-2019) situation reports since 14 January 2020.(1) Beginning on 21 January 2020 WHO released reports on the daily and cumulative number of COVID-19 cases at the provincial level in China and at the country level outside of China. For this analysis, we used data up to 9 March 2020. From 20 February 2020 and onwards, local transmission has been observed in selected European countries (**Figure 1**).

Estimates of effective reproduction number (R(t))

To estimate R(t) values, we employed two statistical methods:

1. Exponential growth rate (EG) method. The reproduction number is computed as the transformation of exponential growth rate, which was estimated by fitting a Poisson regression model over the exponential growth stage of an outbreak, under the assumption of a gamma distribution of generation time. (2-3)

2. Time-dependent (TD) method. It calculates real-time effective reproduction numbers by averaging overall transmission networks that are compatible with the observed epidemic curve.(3) TD method employs a Bayesian statistical framework, which allows real-time estimation by taking into account yet-unrecorded cases before the end of the outbreak. TD method is well-suited to account for imported cases in the early outbreak.(6)

In the abovementioned methods, generation time (GT), measured by the onset time lag between primary and secondary cases, is required but cannot be easily obtained. Here, we assumed the GT is equal to the incubation period, which was estimated to be 5.8 days (standard deviation [SD]=2.6),(7) based on previous research. We also used the assumption of 4 days (SD = 2.4) in the sensitivity analysis.(8) The R0 package, an R-language coded statistical package, was carried out to estimate the reproduction numbers of COVID-19.(11) As shown in Appendix Figure 1, TD method provides a good fit for epidemic curve.

Estimates of case fatality rate (CFR)

During the early outbreak, naïve CFR (nCFR), the ratio of reported deaths to cases, tends to underestimate the true CFR because final outcomes are unknown for some cases.(9) By accounting for the time interval [T] between case confirmation to death, we can, therefore, obtain a more accurate estimate of the denominator for the CFR.(10) Two alternative approaches were used to estimate the CFR in real-time:

1. nCFR = D(t)/C(t); division of the number of cumulative deaths by the number of cumulative cases at time t.
2. aCFR = CFR3=D(t)/C(t-interval); division of the number of cumulative deaths by the number of cumulative cases at time (t-T). Here, T is the average time from case confirmation to death. We assumed 1, 3, and 5 days due to the lack of data.

Results

In EG method, we have tested all possible combinations of begin and end dates that might yield a good fit. For Italy, the period starting on 23 February and ending on 9 March yielded the best fit for exponential growth, with daily growth rate r=0.21 (**Table 1**). The corresponding R(t) was 3.27 [3.17-3.38] for T1; 2.30 [2.25-2.35] for the T2. For France, the epidemic curve for the period 23 February and 9 March yielded the best fit for exponential growth, giving r=0.36. The corresponding R(t) was 6.32 [5.72-6.99] for T1 and 3.60 [3.37-3.85] for T2. For Germany, the period between 21 February and 9 March led to best fit with r=0.34 and corresponding R(t) was 6.07 [5.51-6.69] for T1 and 3.50 [3.28-3.74] for T2. For Spain, the period starting on 19 February and ending on 9 March yielded the best fit, giving r=0.30. The corresponding R(t) was 5.08 [4.51-5.74] for T1 and 3.11 [2.86-3.37] for T2. Overall, there were slight differences in the goodness of fit (R^2) and estimated R(t)across possible combinations of the testing period.

With TD method, all two generation intervals yielded similar trends of R(t) values with time (**Figure 2**). For Italy, from 27 February and onwards, R(t) values were in the range of 2-4. The R value for March 9 was 3.10 [2.21-4.11] for T1 method and 2.23 [2.05-2.42] for T2 method. For France, R values ranged between 4.5-6.5, and were 6.56 [2.04-12.26] for T1 method and 4.24 [3.16-5.40] for T2 method. For Germany, R(t) values were decreased from 8 to 4, and were 4.43 [1.83-7.92] for T1 method and 2.86 [2.23-3.57] for T2 method. For Spain, R values were in the range of 3-7. The R value for March 8 was 3.95 [0-10.19] for T1 method and 2.75 [1.66-3.87] for T2 method. Zero cases were reported on 2 March for France, 1 March for Germany, 2 March for Spain, corresponding R(t) for those dates were zero.

As of 9 March 2020, there were 366 deaths in Italy, 19 in France, and 10 in Spain, respectively. No death was reported in Germany. nCFR for Italy was 4.96 %, 1.70% for both France and Spain. The magnitude of CFRs depended on the calculation methods: aCFR yielded a higher estimate (**Figure 3**).

Discussion

Based on different models, the reproduction numbers in Italy, Spain, France, and Germany were all higher than 2, indicating that the outbreak of COVID-19 will continue. More strict prevention and control measures are recommended in these countries to slow the spread of COVID-19. Currently, the effects of lockdown in Italy remain unknown. Quarantining Hubei Province, including the epicenter Wuhan City, has found to be effective in slowing the rapid increase in new cases of COVID-19. Continued monitoring of new cases of COVID-19 reported in Italy is greatly needed to better assess the effects of lockdown within Italy. The quarantine of Hubei Province also prevented the transmission of COVID-19 in other areas of China and worldwide.

Active surveillance of new cases of COVID-19 reported in other European countries can help European and local authorities to better understand the effects of lockdown outside Italy.

The mortality rate of COVID-19 in Italy was higher than in China.(12) The higher mortality rate can be attributed to the ongoing nature of the outbreak, different age distributions of the population, and different treatment strategies. The epidemic in Italy started in Lombardy and using the entire Italy tend to underestimate the burden of Lombardy. Although this study focused on R(t)s at country level, we also calculated the Rt of Lombardy, which ranged from 6.39 (6.13-6.65) to 3.26 (2.70-3.86), suggesting that Lombardy is a higher-epidemic province. Continued monitoring of deaths caused by COVID-19 in Italy is required to better care patients. The mortality rates of COVID-19 in Spain and France were lower than in China but higher than in most other countries. New cases of COVID-19 reported in Spain and France increase skyrocketing recently. Real-time monitoring of deaths related to newly confirmed cases of COVID-19 is of significance in Spain and France. European and local authorities should investigate and learn from Germany on how to remain a low mortality rate.

There are several limitations to keep in mind when interpreting the results. First, due to limited laboratory capacity, the actual epidemic may not be reflected by counts of laboratory-confirmed cases reported. Second, the estimation of the reproduction number is heavily dependent on generation time, which may be hard to obtain in an early outbreak. Third, fitting the real-life epidemic curve to the statistical model is challenging. Fourth, the constant assumption of CFR may be violated if a new treatment emerges or more mild cases are identified over the course of the epidemic.

Conclusion

To summarize, this study provides important findings on an early outbreak of COVID-19 in Europe. The ECDC should monitor the transmissibility and mortality in European countries to prevent the transmission and reduce the death of COVID-19. If a rapid increase in cases of COVID-19 is found in any country, the ECDC should work closely with the WHO to visit that country and provide recommendations and support control and prevention efforts. Special attention should be paid to Italy to understand the effects of the country lockdown on the spread of COVID-19 both within and outside Italy. Due to the recent rapid increase in new cases of COVID-19, real-time monitoring of the transmissibility and mortality in Spain and France is a priority. Even though the outbreak of COVID-19 is still an important concern in Germany, it is beneficial to learn on measures related to the low mortality rate. Other European countries should continue to prepare for and respond to COVID-19 and learn from Italy, Spain, France, and Germany on relevant prevention and control measures.

Author Contributions:

Concept and design: Yuan J, Li M, Lu ZK

Acquisition, analysis, or interpretation of data: Yuan J, Lu ZK, Lv G, Li M

Drafting of the manuscript: Yuan J, Lu ZK, Lv G, Li M

Critical revision of the manuscript for important intellectual content: Yuan J, Lu ZK, Lv G, Li M

Statistical analysis: Yuan J, Li M

Administrative, technical, or material support: Lu ZK

Supervision: Lu ZK

Funding Source: This research did not receive any funding.

Ethical Approval: This research does not involve human subjects. It is not required to obtain Institutional Review Board (IRB) approval.

Conflict of Interest: We declare no conflict of interest.

Reference

1. WHO. No Title [Internet]. Coronavirus Disease 2019 (COVID-19): situation report. 2020. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports
2. Liu Y, Gayle AA, Wilder-Smith A, Rocklöv J. The reproductive number of COVID-19 is higher compared to SARS coronavirus. J Travel Med. 2020;
3. Wallinga J, Teunis P. Different epidemic curves for severe acute respiratory syndrome reveal similar impacts of control measures. Am J Epidemiol. 2004;160(6):509–16.
4. Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time. Lancet Infect Dis. 2020;
5. Obadia T, Haneef R, Boëlle P-Y. The R0 package: a toolbox to estimate reproduction numbers for epidemic outbreaks. BMC Med Inform Decis Mak. 2012;12(1):147.
6. Cauchemez S, Boëlle P-Y, Donnelly CA, Ferguson NM, Thomas G, Leung GM, et al. Real-time estimates in early detection of SARS. Emerg Infect Dis. 2006;12(1):110.
7. Linton NM, Kobayashi T, Yang Y, Hayashi K, Akhmetzhanov AR, Jung S, et al. Incubation Period and Other Epidemiological Characteristics of 2019 Novel Coronavirus Infections with Right Truncation: A Statistical Analysis of Publicly Available Case Data. J Clin Med. 2020;9(2):538.
8. Guan W, Ni Z, Hu Y, Liang W, Ou C, He J, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;
9. Kucharski AJ, Edmunds WJ. Case fatality rate for Ebola virus disease in west Africa. Lancet. 2014;384(9950):1260.

10. Nishiura H, Klinkenberg D, Roberts M, Heesterbeek JAP. Early epidemiological assessment of the virulence of emerging infectious diseases: a case study of an influenza pandemic. PLoS One. 2009;4(8).

11. Delamater PL, Street EJ, Leslie TF, Yang YT, Jacobsen KH. Complexity of the basic reproduction number (R0). Emerg Infect Dis. 2019;25(1):1.

12. WHO. Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19) [Internet]. Available from: https://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf

Figure Legends

Figure 1. Epidemic curve of the outbreak of COVID-19 in selected European countries (Italy, France, Germany, and Spain)

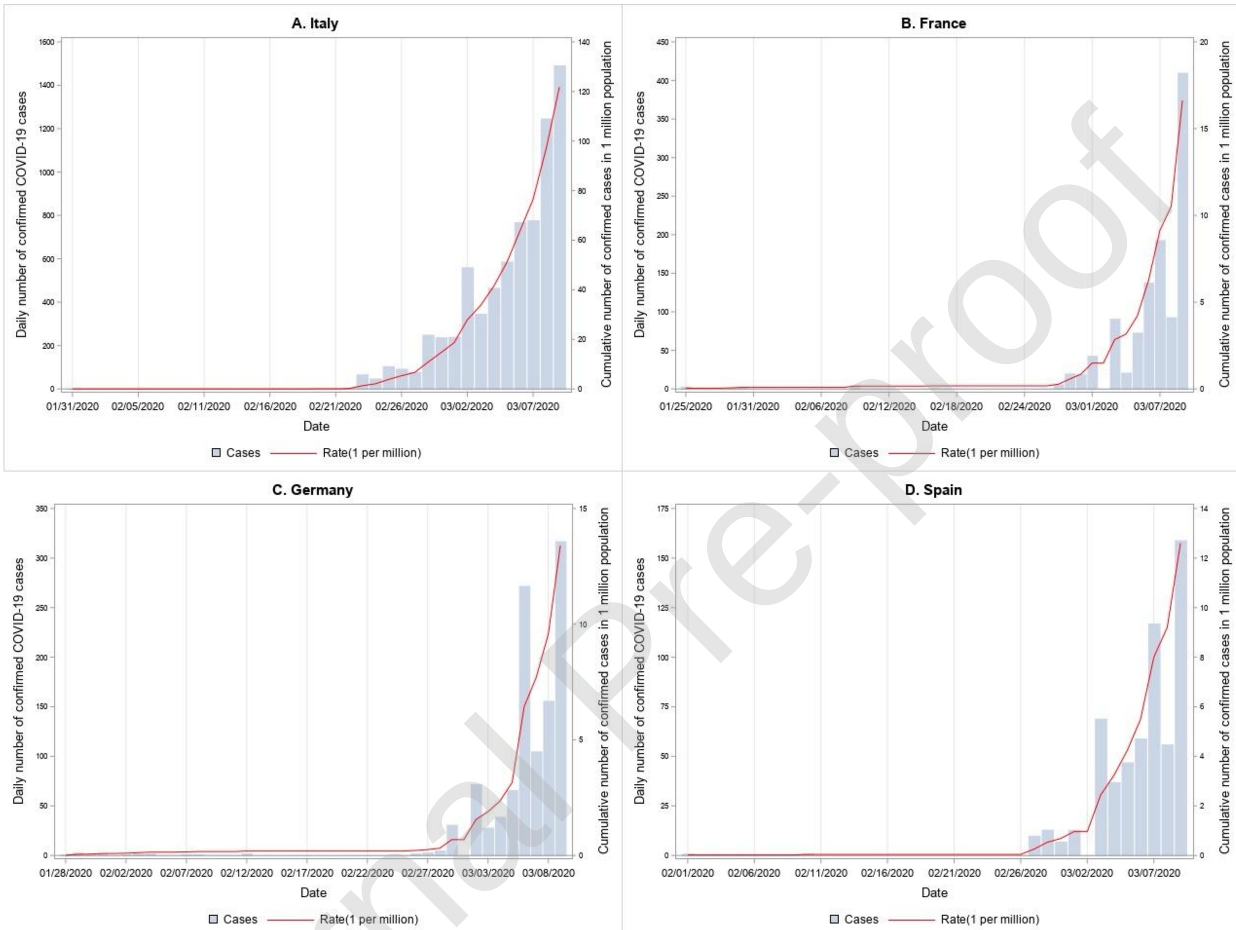


Figure 2. Estimates of the real-time R values in the COVID-19 outbreak in selected European countries (Italy, France, Germany, and Spain), calculated with TD method

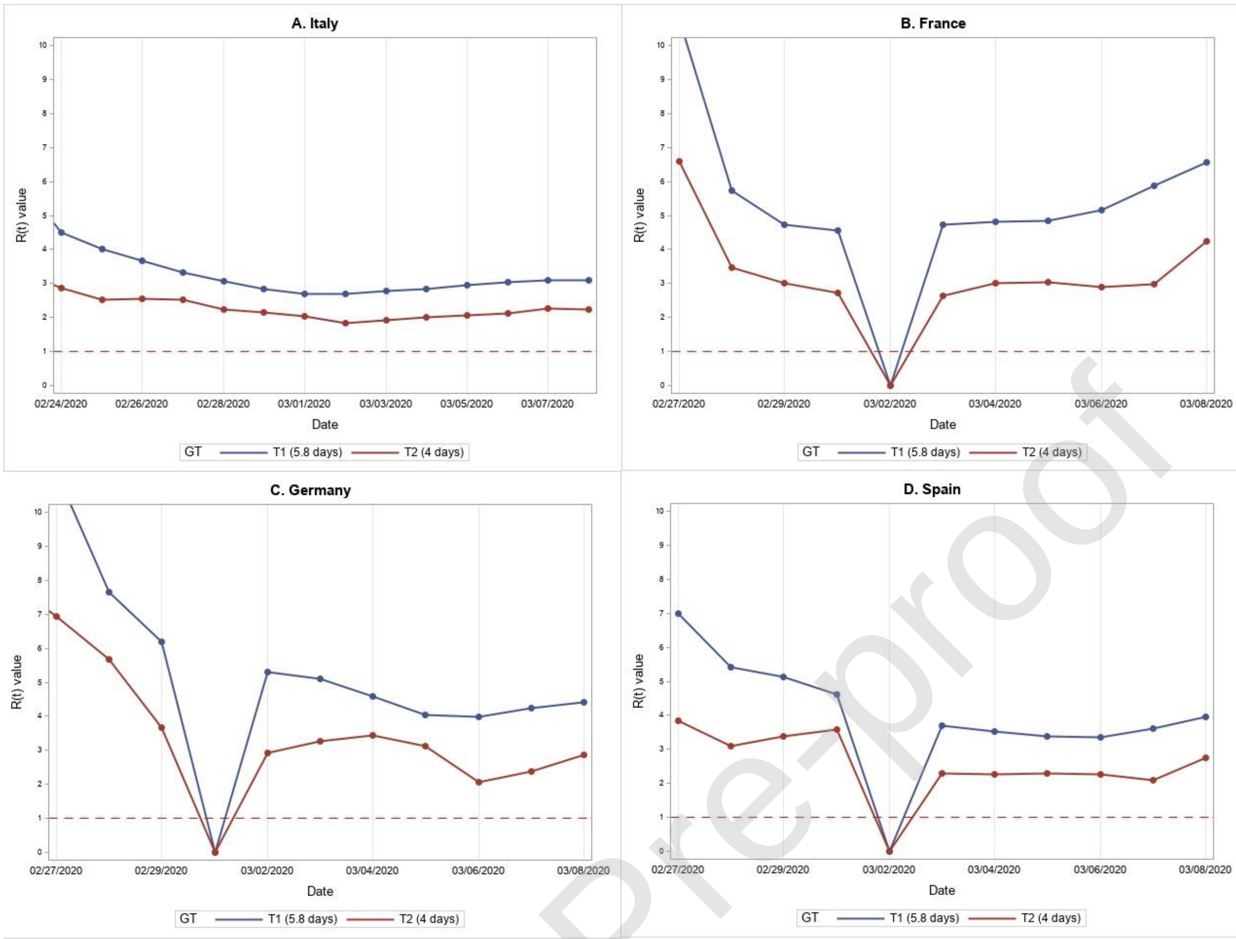


Figure 3. Real-time estimates of case fatality rate (CFR) from three different methods in selected European countries (Italy, France, Germany, and Spain)

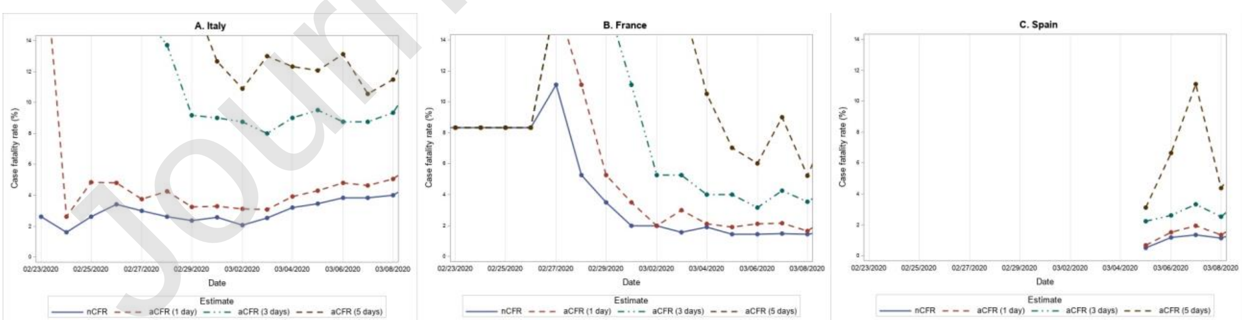


Table 1. Epidemic growth rates and corresponding reproduction number estimated with EG method

Country	Start date (m/d/y)	End date (m/d/y)	R^2	Growth rate (/day)	T1 (GT=5.6 days)			T2 (GT=4 days)		
					R (t)	95% CI		R (t)	95% CI	
Italy	**02/23/2020**	**03/09/2020**	**0.952**	**0.21**	**3.27**	**3.17**	**3.38**	**2.30**	**2.25**	**2.35**
	02/22/2020	03/09/2020	0.949	0.21	3.36	3.26	3.47	2.35	2.30	2.40
	02/24/2020	03/09/2020	0.947	0.21	3.28	3.17	3.40	2.31	2.25	2.36
	02/25/2020	03/09/2020	0.941	0.21	3.22	3.11	3.34	2.28	2.22	2.33
	02/26/2020	03/09/2020	0.934	0.21	3.24	3.12	3.36	2.28	2.23	2.34
	02/23/2020	03/07/2020	0.933	0.21	3.22	3.10	3.34	2.28	2.22	2.33
	02/22/2020	03/07/2020	0.930	0.21	3.33	3.21	3.46	2.33	2.27	2.39
	02/24/2020	03/07/2020	0.925	0.21	3.23	3.10	3.36	2.28	2.22	2.34
France	**02/23/2020**	**03/09/2020**	**0.833**	**0.34**	**6.32**	**5.72**	**6.99**	**3.60**	**3.37**	**3.85**
	02/24/2020	03/09/2020	0.821	0.34	6.24	5.64	6.91	3.57	3.33	3.82
	02/25/2020	03/09/2020	0.808	0.34	6.12	5.52	6.79	3.52	3.29	3.78
	02/23/2020	03/07/2020	0.807	0.37	6.96	6.03	8.05	3.84	3.49	4.24
	02/26/2020	03/09/2020	0.792	0.33	5.96	5.36	6.62	3.46	3.22	3.72
	02/24/2020	03/07/2020	0.791	0.36	6.81	5.88	7.90	3.79	3.43	4.18
	02/27/2020	03/09/2020	0.774	0.32	5.73	5.15	6.40	3.37	3.13	3.63
	02/25/2020	03/07/2020	0.773	0.35	6.60	5.68	7.68	3.71	3.35	4.11
Germany	**02/21/2020**	**03/09/2020**	**0.836**	**0.34**	**6.07**	**5.51**	**6.69**	**3.50**	**3.28**	**3.74**
	02/22/2020	03/09/2020	0.827	0.33	6.02	5.46	6.64	3.48	3.26	3.72
	02/23/2020	03/09/2020	0.817	0.33	5.95	5.40	6.57	3.46	3.24	3.70
	02/21/2020	03/07/2020	0.772	0.39	7.65	6.65	8.83	4.10	3.73	4.51
	02/21/2020	03/08/2020	0.772	0.33	6.01	5.36	6.75	3.48	3.22	3.77
	02/22/2020	03/07/2020	0.758	0.39	7.58	6.58	8.76	4.07	3.70	4.49
	02/22/2020	03/08/2020	0.758	0.33	5.94	5.29	6.69	3.45	3.19	3.74
	02/23/2020	03/07/2020	0.742	0.38	7.48	6.48	8.66	4.03	3.66	4.45
Spain	**02/19/2020**	**03/09/2020**	**0.844**	**0.30**	**5.08**	**4.51**	**5.74**	**3.11**	**2.86**	**3.37**
	02/19/2020	03/07/2020	0.842	0.36	6.63	5.60	7.89	3.72	3.32	4.18
	02/20/2020	03/09/2020	0.836	0.30	5.04	4.47	5.70	3.09	2.85	3.36
	02/20/2020	03/07/2020	0.833	0.35	6.58	5.56	7.84	3.70	3.30	4.16
	02/21/2020	03/09/2020	0.827	0.29	5.00	4.42	5.66	3.07	2.83	3.34
	02/21/2020	03/07/2020	0.823	0.35	6.52	5.49	7.78	3.68	3.28	4.14
	02/22/2020	03/09/2020	0.817	0.29	4.94	4.36	5.60	3.05	2.80	3.32
	02/22/2020	03/07/2020	0.811	0.35	6.44	5.41	7.70	3.65	3.24	4.11

*All combinations of dates have been tested for a better model fit.