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Monitoring transmissibility and mortality of COVID-19 in Europe

Jing Yuan[a,1], Minghui Li[b,1], Gang Lv[c], Z. Kevin Lu[d,*]

[a] Department of Clinical Pharmacy, Fudan University School of Pharmacy, 826, Zhangheng Road, Shanghai 201203, China
[b] University of Tennessee Health Science Center, 881 Madison Avenue, Memphis, TN 38163, USA
[c] The Eighth Medical Center of the People's Liberation Army General Hospital, Beijing, China
[d] University of South Carolina, 715 Sumter Street, CLS Building 311, Columbia, SC 29208, USA

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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 of this study was to report the real-time effective reproduction numbers ($R(t)$) and case fatality rates (CFR) in Europe.
Methods: Data for this study were obtained mainly from the World Health Organization website, up to March 9, 2020. $R(t)$ were 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 the naïve CFR (nCFR) and adjusted CFR (aCFR) were estimated.
Results: With the EG method, $R(t)$ was 3.27 (95% confidence interval (CI) 3.17–3.38) for Italy, 6.32 (95% CI 5.72–6.99) for France, 6.07 (95% CI 5.51–6.69) for Germany, and 5.08 (95% CI 4.51–5.74) for Spain. With the TD method, the R value for March 9 was 3.10 (95% CI 2.21–4.11) for Italy, 6.56 (95% CI 2.04–12.26) for France, 4.43 (95% CI 1.83–7.92) for Germany, and 3.95 (95% CI 0–10.19) for Spain.
Conclusions: This study provides important findings on the 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.

Introduction

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 March 10, 2020, confirmed cases of COVID-19 had reached 10 000 in Italy, had exceeded 1000 in Spain, France, and Germany, and were growing quickly in other European countries (No Title, 2019). In terms of deaths caused by COVID-19, more than 800 had been reported in Italy and approximately 50 in each of Spain and France, but only three had been 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 locked down the northern region of Lombardy, where several clusters of COVID-19 cases had been found, on March 8, 2020; this lockdown was extended to the whole country on March 9, 2020. Spain, France, and Germany have also announced different measures aimed at stopping the rapid spread of COVID-19. The adoption of time-sensitive prevention and control measures depends on real-time monitoring of 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 (Liu et al., 2020). Little attention has been paid to European countries. Given the rapid increase in COVID-19 in Europe, it is urgent to understand the transmissibility and mortality in key European countries in order 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 (Wallinga and Teunis, 2004). 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

* Corresponding author.
E-mail address: lu32@email.sc.edu (Z. K. Lu).
[1] Jing Yuan and Minghui Li contributed equally.

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immunity from past exposures or vaccination, or any deliberate intervention in disease transmission has occurred. 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 the WHO in the 'Coronavirus disease (COVID-2019) situation reports' since January 14, 2020 (No Title, 2019). Beginning on January 21, 2020, the 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, data up to March 9, 2020 were used. Local transmission has been observed in selected European countries from February 20, 2020 and onwards (Figure 1).

Estimates of the effective reproduction number (R(t))

Two statistical methods were employed to estimate $R(t)$ values: the exponential growth rate (EG) method and the time-dependent (TD) method.

In the EG method, the reproduction number is computed as the transformation of the exponential growth rate, which is 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 (Wallinga and Teunis, 2004; Liu et al., 2020).

The TD method calculates real-time effective reproduction numbers by averaging overall transmission networks that are compatible with the observed epidemic curve (Wallinga and Teunis, 2004). The 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. The TD method is well-suited to account for imported cases in the early outbreak (Cauchemez et al., 2006).

With the methods mentioned above, the generation time (GT), measured by the onset time lag between primary and secondary cases, is required; however this cannot easily be obtained. Here, it was assumed that the GT is equal to the incubation period, which was estimated to be 5.8 days (standard deviation (SD) 2.6 days) based on previous research (Linton et al., 2020). We also used the assumption of 4 days (SD 2.4 days) in the sensitivity analysis (Guan et al., 2020). The R0 package, an R-language coded statistical package, was used to estimate the reproduction numbers of COVID-19 (Delamater et al., 2019). As shown in Supplementary Material Figure S1, the TD method provides a good fit for the epidemic curve.

Estimates of the case fatality rate (CFR)

Early in an outbreak, the naïve CFR (nCFR) – the ratio of reported deaths to cases – tends to underestimate the true CFR because final

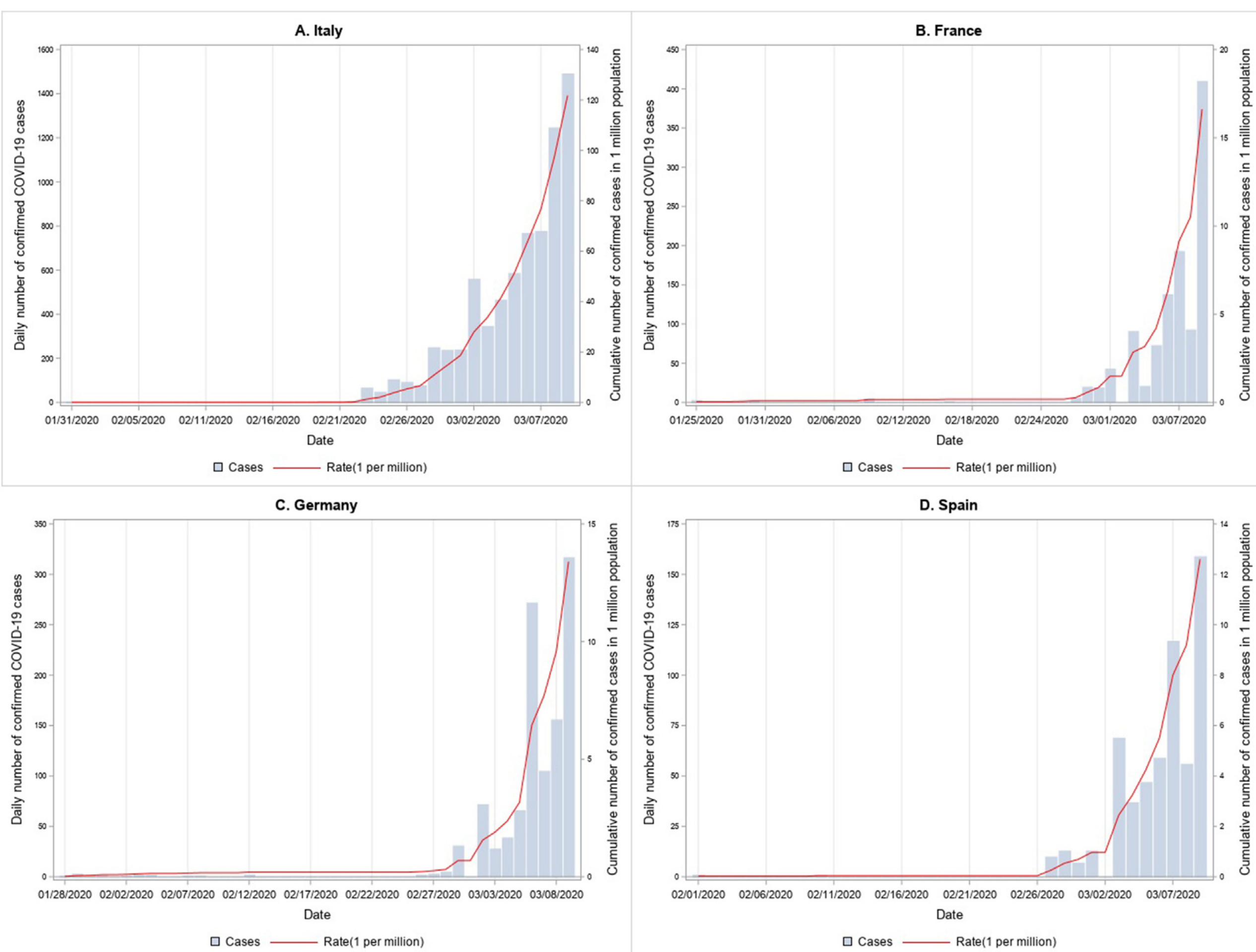

Figure 1.

outcomes are unknown for some cases (Kucharski and Edmunds, 2014). By accounting for the time interval (T) between case confirmation and death, we can, therefore, obtain a more accurate estimate of the denominator for the CFR (Nishiura et al., 2009). Two alternative approaches were used to estimate the CFR in real-time, the nCFR and the adjusted CFR (aCFR)), as described below.

- nCFR = $D(t)/C(t)$; division of the number of cumulative deaths by the number of cumulative cases at time t.
- aCFR = CFR3 = $D(t)/C(t\text{-interval})$; 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

With the EG method, all possible combinations of begin and end dates that might yield a good fit were tested. For Italy, the period starting on February 23 and ending on March 9 yielded the best fit for exponential growth, with daily growth rate r = 0.21 (Table 1). The corresponding $R(t)$ was 3.27 (95% confidence interval (CI) 3.17–3.38) for T1 and 2.30 (95% CI 2.25–2.35) for T2. For France, the epidemic curve for the period February 23 to March 9 yielded the best fit for exponential growth, giving r = 0.36. The corresponding $R(t)$ was 6.32 (95% CI 5.72–6.99) for T1 and 3.60 (95% CI 3.37–3.85) for T2. For Germany, the period between February 21 and March 9 led to the best fit, with r = 0.34; the corresponding $R(t)$ was 6.07 (95% CI 5.51–6.69) for T1 and 3.50 (95% CI 3.28–3.74) for T2. For Spain, the period starting on February 19 and ending on March 9 yielded the best fit, giving r = 0.30. The corresponding $R(t)$ was 5.08 (95% CI 4.51–5.74) for T1 and 3.11 (95% CI 2.86–3.37) for T2. Overall, there were slight differences in the goodness of fit (R (Liu et al., 2020)) and estimated $R(t)$ across possible combinations of the testing period.

With the TD method, all two-generation intervals yielded similar trends in $R(t)$ values with time (Figure 2). For Italy, from February 27 and onwards, $R(t)$ values were in the range of 2–4. The R value for March 9 was 3.10 (95% CI 2.21–4.11) for the T1 method and 2.23 (95% CI 2.05–2.42) for the T2 method. For France, R values ranged between 4.5 and 6.5, and were 6.56 (95% CI 2.04–12.26) for the T1 method and 4.24 (95% CI 3.16–5.40) for the T2 method. For Germany, $R(t)$ values were decreased from 8 to 4, and were 4.43 (95% CI 1.83–7.92) for the T1 method and 2.86 (95% CI 2.23–3.57) for the T2 method. For Spain, R values were in the range of 3–7. The R value for March 8 was 3.95 (95% CI 0–10.19) for the T1 method and 2.75 (95% CI 1.66–3.87) for the T2 method. Zero cases were reported on March 2 for France, March 1 for Germany, and March 2 for Spain; corresponding $R(t)$ for those dates were zero.

As of March 9, 2020, there had been 366 deaths in Italy, 19 in France, and 10 in Spain. No death had been reported in Germany. The nCFR for Italy was 4.96%, while it was 1.70% for both France and Spain. The magnitude of the CFR depended on the calculation method: the 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

Table 1
Epidemic growth rates and corresponding reproduction numbers estimated by exponential growth rate (EG) method[a]

Country	Start date (m/d/y)	End date (m/d/y)	R (Liu et al., 2020)	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

GT, generation time; $R(t)$, real-time effective reproduction number; CI, confidence interval.
[a] All combinations of dates have been tested for a better model fit.

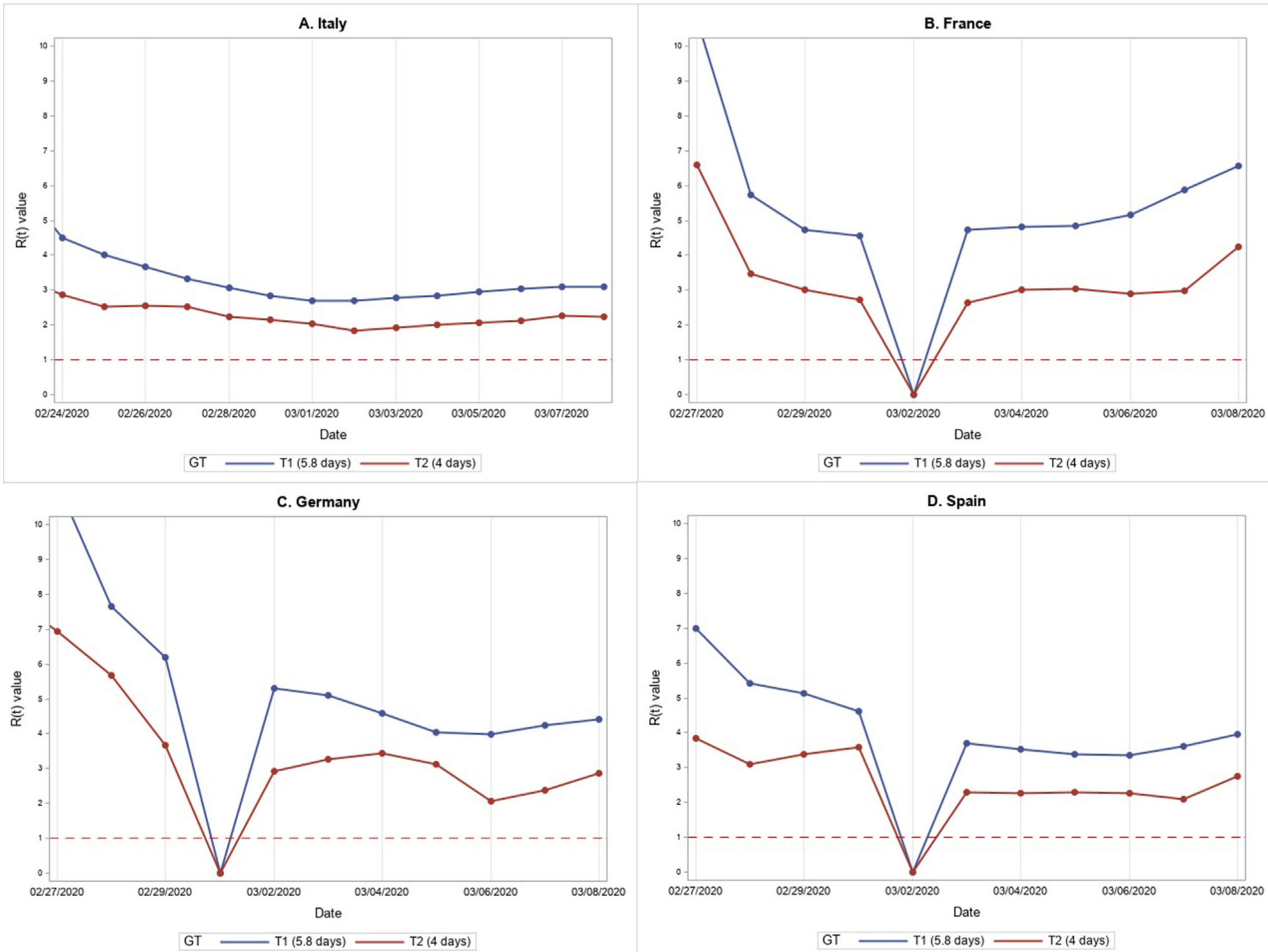

Figure 2.

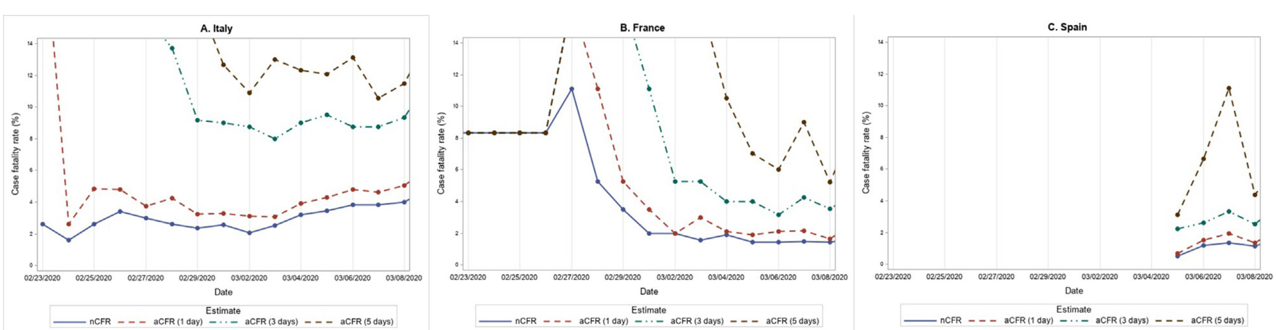

Figure 3.

remain unknown. Quarantining Hubei Province, including the epicenter Wuhan City, has been 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 could help European and local authorities to better understand the effects of lockdown outside Italy.

The mortality rate of COVID-19 in Italy was found to be higher than that in China (WHO and WHO, 2019). The higher mortality rate could 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 country of Italy will tend to underestimate the burden in Lombardy. Although this study focused on $R(t)$ at the country level, we also calculated the $R(t)$ for Lombardy, which ranged from 6.39 (95% CI 6.13–6.65) to 3.26 (95% CI 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 for patients. The mortality rates of COVID-19 in Spain and France were found to be lower than that in China but higher than those in most other countries. New cases of COVID-19 reported in Spain and France have recently been skyrocketing. 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 maintain a low mortality rate.

There are several limitations to keep in mind when interpreting the results of this study. 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 the generation time, which may be difficult to obtain early in an 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.

To summarize, this study provides important findings on the early outbreak of COVID-19 in Europe. The ECDC should monitor the transmissibility and mortality in European countries to prevent transmission and reduce death from 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, in addition to supporting control and prevention efforts. Special attention should be paid to Italy in order 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. Although the outbreak of COVID-19 is still an important concern in Germany, it would be beneficial to understand the 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, and/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, and/or material support: Lu ZK. Supervision: Lu ZK.

Declarations

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Ethical approval: This research did not involve human subjects. Obtaining institutional review board (IRB) approval was not required.

Conflict of interest: We declare no conflict of interest.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ijid.2020.03.050.

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