ORIGINAL ARTICLE

Serial interval and time-varying reproduction number estimation for COVID-19 in western Iran

F. Najafi[1], N. Izadi[2], S.-S. Hashemi-Nazari[3], F. Khosravi-Shadmani[4], R. Nikbakht[5] and E. Shakiba[6]

1) *Department of Epidemiology, Research Centre for Environmental Determinants of Health, Kermanshah University of Medical Sciences, Kermanshah,* 2) *Student Research Committee, Department of Epidemiology, School of Public Health and Safety, Shahid Beheshti University of Medical Sciences,* 3) *Prevention of Cardiovascular Disease Research Center, Department of Epidemiology, School of Public Health and Safety, Shahid Beheshti University of Medical Sciences, Tehran,* 4) *Research Centre for Environmental Determinants of Health, Health Institute, Kermanshah University of Medical Sciences, Kermanshah,* 5) *Department of Biostatistics, Faculty of Health, Mazandaran University of Medical Sciences, Sari and* 6) *Research Centre for Environmental Determinants of Health, Kermanshah University of Medical Sciences, Kermanshah, Iran*

Abstract

There is no report on the serial interval (SI) of coronavirus disease 2019 (COVID-19) in Iran, the present report aims to estimate the SI and time-varying R of COVID-19 in western Iran. In this study, there were 1477 confirmed, probable and suspected cases of severe acute respiratory syndrome coronavirus 2 for Kermanshah from 22 February to 9 April. The close contacts of the confirmed cases were identified using telephone follow up of patients and their contacts. The SI distribution was used as an alternative. We fitted different models using the clinical onset dates of patients with their close contact (infector–infectee). Also, we applied a 'serial interval from sample' approach as a Bayesian methodology for estimating reproduction number. From 22 February to 29 March, 247 COVID-19 cases were confirmed by RT-PCR. Close contact between 21 patients (21 infector–infectee pairs), including 12 primary cases and 21 secondary cases, was confirmed. The mean and standard deviation of the SI were estimated as 5.71 and 3.89 days. The R varied from 0.79 to 1.88 for a 7-day time-lapse and ranged from 0.92 to 1.64 for a 14-day time-lapse on raw data. Also, the R varied from 0.83 to 1.84 for 7-day time-lapse and from 0.95 to 1.54 for a 14-day time-lapse using moving average data, respectively. It can be concluded that the low reproduction number for COVID-19 in Kermanshah province is an indication of the effectiveness of preventive and interventive programmes such as quarantine and isolation. Consequently, continuing these preventive measures is highly recommended.

Keywords: Coronavirus disease 2019, Iran, Serial interval, Time-varying reproduction number, Generation time
Original Submission: 5 May 2020; **Revised Submission:** 4 June 2020; **Accepted:** 9 June 2020
Article published online: 14 June 2020

Corresponding author: N. Izadi, Department of Epidemiology, School of Public Health and Safety, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
Corresponding author: S-S. Hashemi-Nazari, Prevention of Cardiovascular Disease Research Center, Department of Epidemiology, School of Public Health and Safety, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
E-mails: neda.izady@yahoo.com **(N. Izadi),** saeedh_1999@yahoo.com **(S.-S. Hashemi-Nazari)**

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is rapidly spreading around the world, and the number of confirmed and suspected cases is increasing worldwide. Therefore, estimating the epidemiological measures of coronavirus disease 2019 (COVID-19) is important in assessing the extent of epidemic transmission, predicting the future trends and designing control measures. Various studies have modelled

https://doi.org/10.1016/j.nmni.2020.100715

the transmissibility of this virus [1,2]. This research has focused on calculating the basic reproduction number (R0) using the serial interval (SI) and intrinsic growth rate or using Markov Chain Monte Carlo (MCMC) methods [2,3].

The SI is defined as the time duration between symptom onset in the primary case (infector) and symptom onset in the secondary case (infectee), and indicates the interval between the two infected patients [4]. R_0 and time-varying reproduction number (R_t) are also indices of the transmissibility, which indicates the average number of new infections caused by an infected case in a naive population over the period of the epidemic. The distribution of SI is a key input for determining the R_0 [5]. For $R_0 > 1$, the number of patients is likely to increase and for $R_0 < 1$, the transmission is likely to disappear. The basic reproduction number is a key concept in the epidemiology of infectious diseases and indicates the risk that an infectious agent will spread [6]. This number can vary based on geographical areas and the number of close contacts of people with each other. There is no report on the SI of COVID-19 in Iran, the present report aims to estimate the SI and time-varying R of COVID-19 in western Iran, where the epidemic did not become severe and so was different from the northern and central parts of Iran.

Methods

Data source

After confirming the epidemic of COVID-19 in Iran, data on patients with COVID-19 (confirmed, probable and suspected cases) for real-time RT-PCR tests, chest CT scans or clinical symptoms were collected by two different sections: public health sectors and emergency units of all selected hospitals. Public health sectors are responsible for massive phone screening programmes supervised by the Deputy of Health in the Ministry of Health and Medical Education in Iran. The emergency units of selected hospitals are referral centres for those who are in more serious condition. For the purpose of this study, we linked the data from both public health section (which are collected and stored for all districts by the Disease Control Unit of the Health Deputies) and the hospitals of each province. Public health data include the characteristics of every individual who is tested regardless of the result. The data cover both inpatient and outpatient cases. Such data include all information regarding province, district, age, sex, date of symptom onset, hospital admission, whether bedridden, discharge or death date, infection severity, symptoms (cough, fever, shortness of breath, headache, runny nose), chronic diseases history, travel history, history of other treatments, close contacts with other people and with those who have confirmed COVID-19. We defined a confirmed case as an individual with a positive real-time RT-PCR result. A probable case met the clinical criteria with close contact with a confirmed case of confirmed COVID-19 in the 14 days before the onset of symptoms or who had a positive lung CT scan diagnosed by a radiologist. Any person meeting the clinical criteria without any laboratory or radiological diagnostic criteria was defined as a possible case. In Kermanshah province, from 22 February 2020, the information on confirmed, probable and suspected cases of Coronavirus was registered daily.

In this study, there were 1477 confirmed, probable and suspected cases of SARS-CoV-2 for Kermanshah from 22 February to 9 April, of which the close contacts for confirmed cases were identified using telephone follow up of patients and their contacts. Then, we extracted the count of daily infection and the information about symptom onset in primary cases (infector) and secondary cases (infectee) from the Integrated Health System and calculated the duration to symptom onset. In addition, we used the moving average smoothing with span 5 (i.e. 2, 1, 2) for daily confirmed, probable and suspected cases.

Statistical analysis

Generation time—SI. To estimate the reproduction number, we need to determine the SI, a proxy of the generation time, which was defined as the interval between clinical onset in the initial case and secondary case [5]. As the COVID-19 generation time distribution is unknown, the SI distribution was used as an alternative in this study. We fitted different models (log normal, Weibull and Gamma) using the clinical onset dates of patients with their close contact (infector–infectee) by 'est.GT' function in R0 package, and the best distribution was determined for the SI. Then, using the distribution of the SI, time-varying R0 by Bayesian approach was used to estimate the R0 for Kermanshah province.

Estimation of the reproduction number by time-varying method. The time-varying method is a likelihood-based method for estimating effective reproduction number that uses pairs of cases to obtain the relative likelihood p_{ij}—the probability that infection i at time t_i has been infected by infection j at time t_j. The relative likelihood p_{ij} is calculated with the formula

$$p_{ij} = \frac{N_i w(t_i - t_j)}{\sum_{i \neq k} N_i w(t_i - t_k)}$$

used for calculating reproduction number in which w represents the generation time distribution. Therefore, the effective reproduction number can be obtained by averaging Rj ($R_j = \sum_i p_{ij}$)

over all infections that had the same symptom onset date with the formula:

$$R_t = \frac{1}{N}\sum_{t_j=t} R_j$$

In addition, confidence intervals for R_t are calculated by 5000 simulations [7].

We used the 'EpiEstim' package to estimate an effective reproduction number of COVD-19 given the incident case counts data of Kermanshah by the time-varying method. In the 'EpiEstim' package, estimation of reproduction number by the time-varying method can be done by various approaches for SI which are non-parametric, parametric, uncertain SI, SI from data and SI from sample. In the present study, we applied an SI from sample approach as a Bayesian methodology for estimating reproduction number that uses the METROPOLIS algorithm to obtain MCMC samples and the Gelman–Rubin statistic to assess convergence of MCMC samples. A credible interval is an alternative to the confidence interval in the Bayesian setting, so we report the credible interval of R_t because we were using a Bayesian approach. Data analysis was performed using the R0 and EpiEstim packages in R 3.6.3 software.

Sensitivity analysis. Sensitivity analysis was performed for the robustness of the R_0 estimations by different SI distributions. For this purpose, different SI were applied to show how reproduction number changed with various SI.

Results

COVID-19 epidemic curve in Kermanshah province

From 22 February to 9 April, 1477 COVID-19 cases described as confirmed, probable and suspected by the PCR test and chest CT scan were recorded in Kermanshah province. The epidemic curve for COVID-19 shows two successive waves. The first wave increased from 22 February to 22 March, then decreased; the second wave increased from 23 March to 9 April (Fig. 1). The doubling time, i.e. the period required for the number of cases in the epidemic to double was 9.66 days (95% CI 7.35–14.08 days) for the first wave and 13.82 days (95% CI 8.94–30.38 days) for the second wave.

SI for COVID-19

From 22 February to 29 March, 247 COVID-19 cases were confirmed by RT-PCR test. Close contact between 21 patients (21 infector–infectee pairs), including 12 primary cases and 21 secondary cases, was confirmed. The Weibull distribution provides the best fit for the SI of the COVID-19 outbreak in Kermanshah. The mean (μ) and standard deviation (SD) of the SI were estimated as 5.71 and 3.89 days, respectively (Fig. 2).

Time-dependent effective reproductive number (R_t) for COVID-19

From 22 February to 9 April, 1477 COVID-19 confirmed, probable and suspected cases, identified by RT-PCR, chest CT scan and clinical diagnosis by physician, were recorded in Kermanshah province.

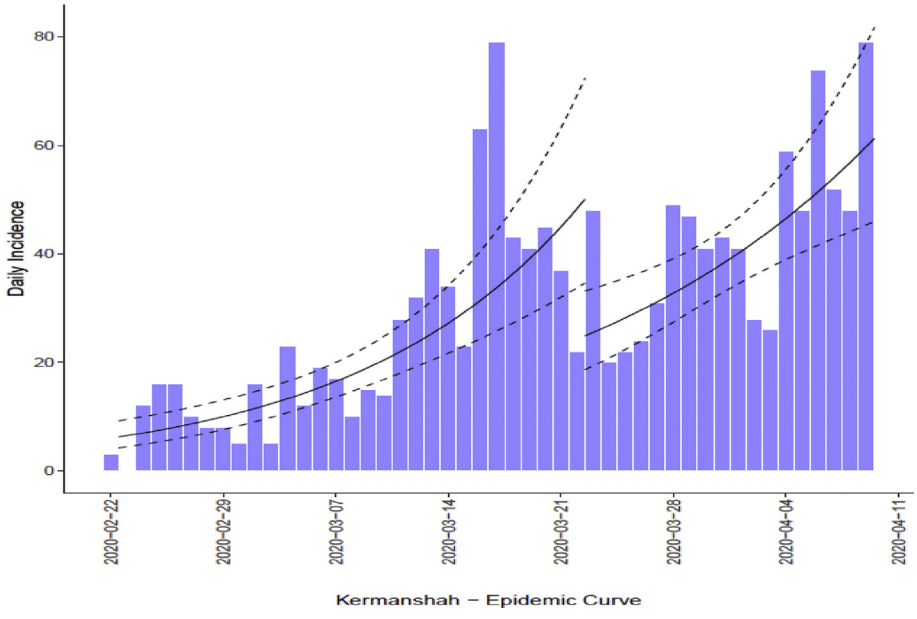

FIG. 1. The epidemic curve of COVID-19 from 22 February to 9 April 2020 in Kermanshah, Iran.

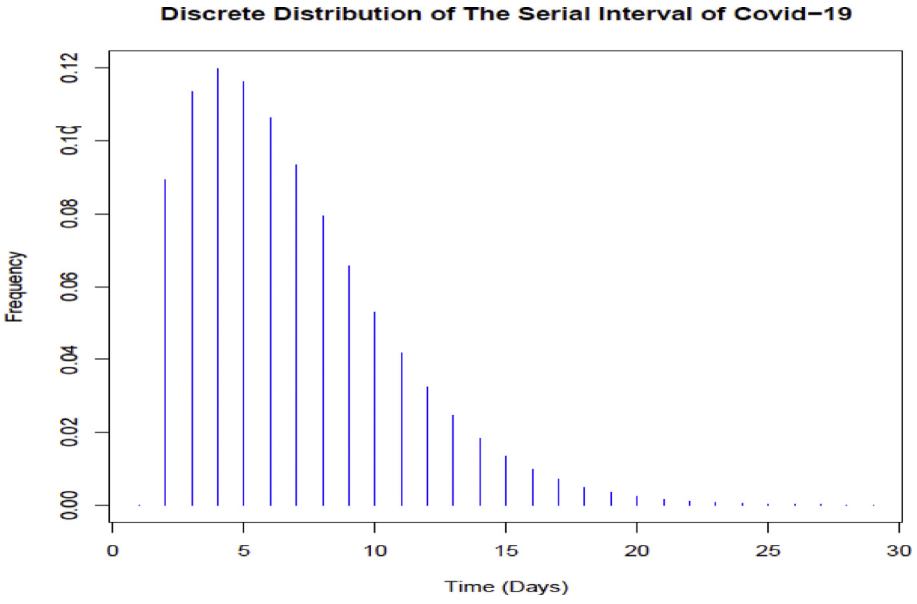

FIG. 2. The distribution of serial interval of COVID-19 in Kermanshah, Iran.

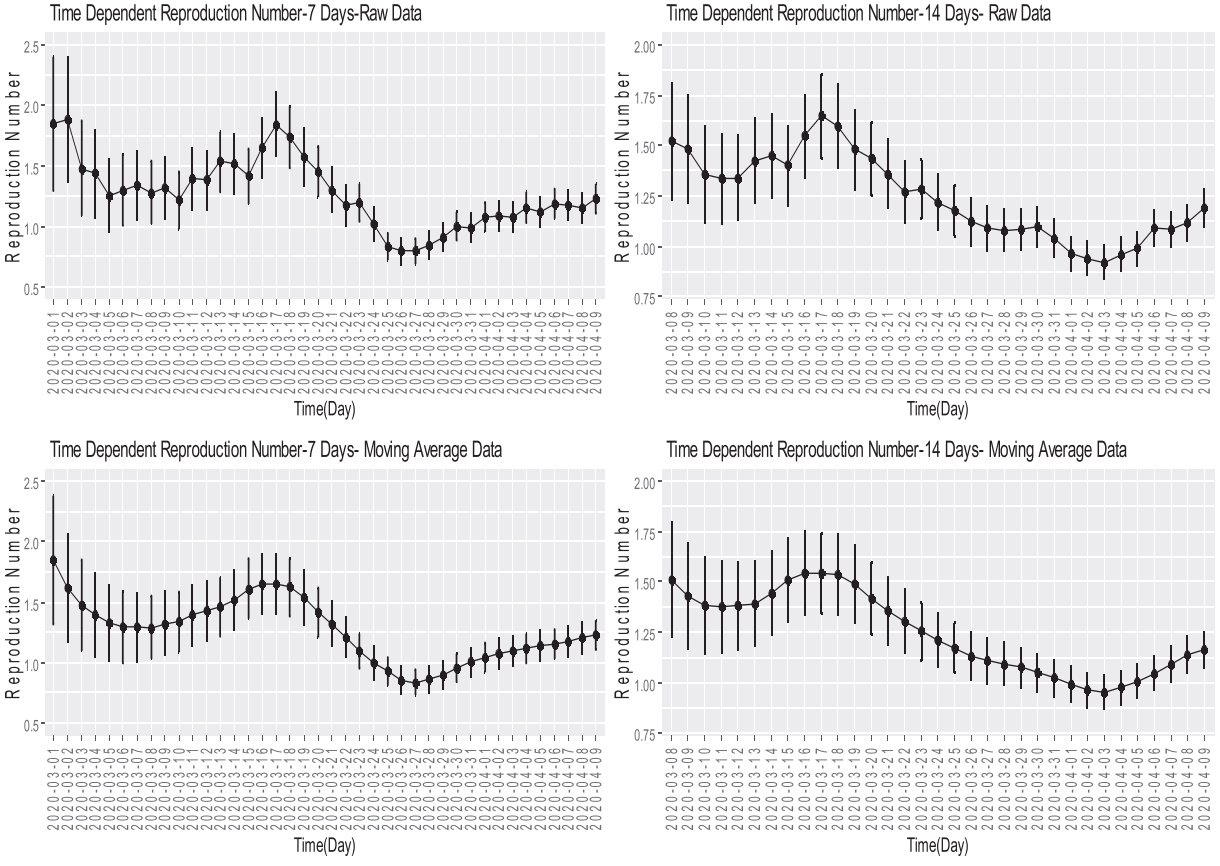

FIG. 3. The time-varying reproduction number (95% CI) of COVID-19 in Kermanshah, Iran (using the Markov Chain Monte Carlo method and for 7-day and 14-day time lapse on raw data (top row) and 7-day and 14-day time lapse on moving average (smooth data) data (bottom row)).

According to Fig. 2, the reproduction number varied from 0.79 to 1.88 for the 7-day time-lapse days and from 0.92 to 1.64 for the 14-day time-lapse on raw data. In comparison, the reproduction number varied from 0.83 to 1.84 for 7-day time-lapse and from 0.95 to 1.54 for the 14-day time-lapse using moving average data (smooth data). In addition, time-varying R on the raw and smooth data decreased and then increased in April for both 7- and 14-day time-lapses.

For the 7-day time-lapse, time-varying R ranged from 1.84 to 0.99 and from 1.07 to 1.22 for 1–31 March and 1–9 April, respectively, for raw data. Using smoothed data the time-varying R varied from 1.84 to 0.95 and from 1 to 1.22 for 1 to 31 March and 1–9 April, respectively (Fig. 3, left column). For the 14-day time-lapse the time-varying R ranged from 1.52 to 0.99 and from 1.08 to 1.19 for 8 March to 5 April and 6–9 April, respectively, using raw data; but from 1.51 to 1 and 1.04 to 1.16 for 8 March to 5 April and 6–9 April, respectively, for smoothed data (Fig. 3, right column).

Sensitivity analysis for reproduction number

We performed a sensitivity analysis to determine the effect of changes in SI on the reproduction number in two different time-lapses, 7 days and 14 days. For the 7-day time-lapse, the estimated values of reproduction number for COVID-19 were robust as the SI parameters changed (Fig. 4, top row). In addition, the impact of different SI on R values for the second time-lapse (14 days) was also robust (Fig. 4, bottom row).

Discussion

Serial interval, incubation interval and basic reproduction number are important parameters to show the shape and form of an epidemic curve. The results of this study showed that the mean and median of SI for COVID-19 were 5.71 and 4.75 days, respectively. As far as we know, this is the first report on SI from Iran, one of the ten countries with the highest number of reported cases of COVID-19. A study showed that the mean SI in 468 confirmed Chinese cases (with 59 infector–infectee pairs) was 3.96 days [6]. Other studies estimated the mean SI to be 4.6 days [8] and 4.2 days [9] in Japan and China, respectively. Also, a systematic review study by Park et al. indicated the SI for COVID-19 to be 4–8 days [10]. Generally, different studies suggest that the SI is shorter than the incubation period for COVID-19. This may be indicative of pre-symptomatic

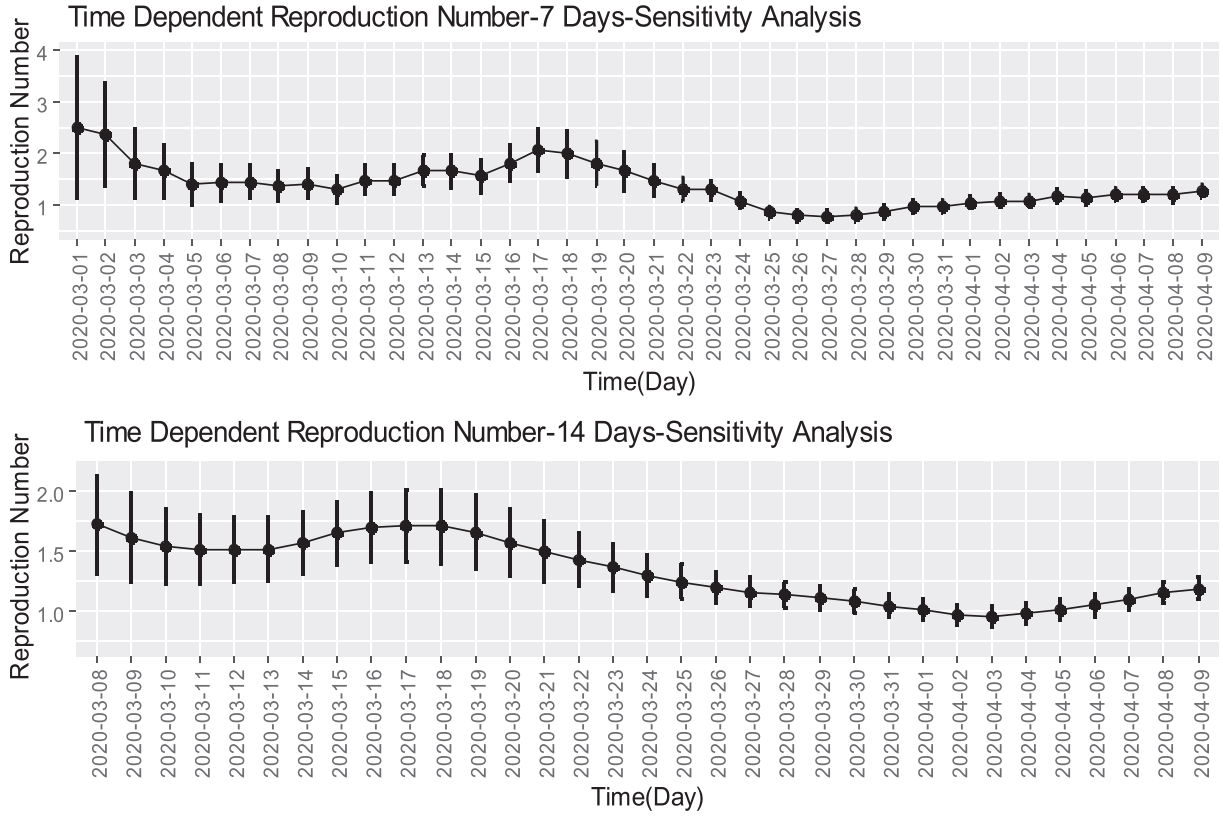

FIG. 4. Sensitivity analysis for time-varying reproduction number (95% credible interval) of COVID-19 in Kermanshah, Iran. (Using the Markov Chain Monte Carlo method and for 7-day time-lapse (top row) and 14-day time-lapse (bottom row) on raw data).

transmission; and therefore, further attention should be centred on preventive efforts. In fact, the present study showed that the SI for COVID-19 in western Iran was longer compared with reports from elsewhere. This may be a result of preventive interventions, training and better mitigation policies in Iran, which has limited person-to-person transfer. Of course, SI can change over time, space and situation [6].

In fact, the SI for SARS-CoV-2 was shorter than that of SARS-CoV and longer than that of influenza virus, which was consistent with results of other studies conducted in this area [11,12]. Different studies have shown that the SI for SARS-CoV and MERS-CoV are 8.4 and 8–13 days, respectively [13,14]. Such characteristics contribute to the more rapid transmission of SARS-CoV-2 than the other coronaviruses; therefore, contact tracing must compete against the rapid replacement of case generations [10].

In addition, the reproductive number for COVID-19 was lower than was found in the other studies. Given that the SI is an important factor when calculating the reproduction number and considering that our study showed a longer SI, the rate of spreading in this disease is slower and, therefore, the reproductive number will also be lower [9].

WHO has estimated the range of COVID-19 R0 to be 1.4–2.5; however, some studies have calculated this number to be higher and, consequently, the pace of spread to be faster. For instance, a review study found the average R0 to be 3.2 [6]; whereas, another study reported this number to be 2.28 [15]. It seems that the estimation of reproductive number is highly dependent on the method used. Plus, one of the reasons behind this difference might be different time-periods in which the estimations have taken place. Needless to say, R0 in the early stages of an epidemic is higher than in the following stages. One of the strengths of this study is that time-frames are included in the estimation of R0.

Conclusion

It can be concluded that the low reproduction number for COVID-19 in Kermanshah province is an indication of the effectiveness of preventive and interventive programmes such as quarantine and isolation. Consequently, continuing these preventive measures is highly recommended.

Funding

This study was supported by Kermanshah University of Medical Sciences grant number 990066. The funding agency did not play any role in the planning, conduct and reporting or in the decision to submit the paper for publication.

Conflicts of interest

The authors declare that they have no competing interests.

Author contributions

FN, NI, SSHN contributed to the study concept and design, acquisition, analysis and interpretation of data, drafting of manuscript. FKhSh contributed to drafting of the manuscript, RN contributed to the analysis and interpretation of data, and ESh contributed to the study concept and design.

Acknowledgements

We are grateful to all those researchers who helped us to conduct this study.

References

[1] Chen T-M, Rui J, Wang Q-P, Zhao Z-Y, Cui J-A, Yin L. A mathematical model for simulating the phase-based transmissibility of a novel coronavirus. Infect Dis Poverty 2020;9:1–8.
[2] Wu JT, Leung K, Leung GM. Nowcasting and forecasting the potential domestic and international spread of the 2019-nCoV outbreak originating in Wuhan, China: a modelling study. Lancet 2020;395(10225):689–97.
[3] Zhao S, Musa SS, Lin Q, Ran J, Yang G, Wang W, et al. Estimating the unreported number of novel coronavirus (2019-nCoV) cases in China in the first half of January 2020: a data-driven modelling analysis of the early outbreak. J Clin Med 2020;9:388.
[4] Svensson A. A note on generation times in epidemic models. Math Biosci 2007;208:300–11.
[5] Du Z, Xu X, Wu Y, Wang L, Cowling B, Ancel Meyers L. Serial interval of COVID-19 among publicly reported confirmed cases. Emerg Infect Dis 2020;26(6):1341–3.
[6] 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 13;27(2):taaa021.
[7] Cori A, Ferguson NM, Fraser C, Cauchemez S. A new framework and software to estimate time-varying reproduction numbers during epidemics. Am J Epidemiol 2013;178:1505–12.
[8] Nishiura H, Linton N, Akhmetzhanov A. Serial interval of novel coronavirus (2019-nCoV) infections. Int J Infect Dis 2020;93:284–6.
[9] You C, Deng Y, Hu W, Sun J, Lin Q, Zhou F, et al. Estimation of the time-varying reproduction number of COVID-19

outbreak in China. Inter J Hygiene Environ Health 2020;228: 113555.
[10] Park M, Cook AR, Lim JT, Sun Y, Dickens BL. A systematic review of COVID-19 epidemiology based on current evidence. J Clin Med 2020;9:967.
[11] Lipsitch M, Cohen T, Cooper B, Robins JM, Ma S, James L, et al. Transmission dynamics and control of severe acute respiratory syndrome. Science 2003;300(5627):1966–70.
[12] Vink MA, Bootsma MCJ, Wallinga J. Serial intervals of respiratory infectious diseases: a systematic review and analysis. Am J Epidemiol 2014;180:865–75.
[13] Assiri A, McGeer A, Perl TM, Price CS, Al Rabeeah AA, Cummings DA, et al. Hospital outbreak of Middle East respiratory syndrome coronavirus. N Engl J Med 2013;369:407–16.
[14] Cowling BJ, Park M, Fang VJ, Wu P, Leung GM, Wu JT. Preliminary epidemiological assessment of MERS-CoV outbreak in South Korea, May to June 2015. Euro Surveill 2015;20(25):7–13.
[15] Zhang S, Diao M, Yu W, Pei L, Lin Z, Chen D. Estimation of the reproductive number of novel coronavirus (COVID-19) and the probable outbreak size on the Diamond Princess cruise ship: a data-driven analysis. Int J Infect Dis 2020;93:201–4.