China's effective control and other countries' uncharted challenge against COVID-19: an epidemiological and modelling study

Lingling Zheng

Guangzhou Women and Children's Medical Center

Qin Kang

Guangzhou Women and Children's Medical Center

Xiujuan Chen

Guangzhou Women and Children's Medical Center

Shuai Huang

Guangzhou Women and Children's Medical Center

Dong Liu

Guangzhou Women and Children's Medical Center

Weiyao Liao

Sun Yat-Sen University

Huimin Xia

Guangzhou Women and Children's Medical Center

Jinling Tang

Guangzhou Women and Children's Medical Center

Huiying Liang (✉ lianghuiying@hotmail.com)

Guangzhou Women and Children's Medical Center

Research article

Keywords: COVID-19, the serial interval, R_t , epidemic

Posted Date: June 9th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-32370/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Objective: In this study, we use the time-dependent reproduction number (R_t) to comprise the COVID transmissibility across different countries.

Methods: We used data from Jan 20, 2019, to Feb 29, 2020, on the number of newly confirmed cases, obtained from the reports published by the CDC, to infer the incidence of infectious over time. A two-step procedure was used to estimate the R_t . The first step used data on known index-secondary cases pairs, from publicly available case reports, to estimate the serial interval distribution. The second step estimated the R_t jointly from the incidence data and the information data in the first step. R_t was then used to simulate the epidemics across all major cities in China and typical countries worldwide.

Results: Based on a total of 126 index-secondary cases pairs from 4 international regions, we estimated that the serial interval for SARS-2-CoV was 4.18 (IQR 1.92 – 6.65) days. Domestically, R_t of China, Hubei province, Wuhan had fallen below 1.0 on 9 Feb, 10 Feb and 13 Feb (R_t were 0.99 ± 0.02 , 0.99 ± 0.02 and 0.96 ± 0.02), respectively. Internationally, as of 26 Feb, statistically significant periods of COVID spread ($R_t > 1$) were identified for most regions, except for Singapore (R_t was 0.92 ± 0.17).

Conclusions: The epidemic in China has been well controlled, but the worldwide pandemic has not been well controlled. Worldwide preparedness and vulnerability against COVID-19 should be regarded with more care.

Introduction

Background

The latest threat to global health is the ongoing outbreak of SARS CoV-2 (formerly 2019-nCoV) infection emerged in December 2019 in Wuhan, Hubei Province, China.[1] As of 4 March, 2020, there had been 80,422 confirmed cases including 2,984 deaths in China and over 12,668 confirmed cases in other 76 countries.[2] Local transmission outside China has been reported in both developed countries and developing countries.[3-4]

The Chinese government has instituted restrictions on population movements with an eye toward slowing the spread of this new disease, such as Wuhan and nearby cities in Hubei province lockdown approaches, large-scale quarantine,[5] public entertainment places closure, banning public gathering,[6] and mandatory wearing of masks in public places.[7] Subsequently, the number of new cases reported each day has plummeted the past few weeks. However, the opposite has happened in other countries (Fig 1). Just this past week, the number of affected countries shot up from 37 to 61 and the number of new cases reported each day are growing exponentially. Thus, whether China's current control efforts are enough or whether worldwide additional interventions are required remains an open question.

There is a proxy, however, that could help to evaluate disease progression and that have not been sufficiently explored in measuring COVID-19 transmissibility across different countries. The time-dependent reproduction number (R_t) represents the expected number of secondary cases arising from a primary case infected at time t , which changes throughout the outbreak.[8] The R_t is directly related to the type and intensity of interventions to control an epidemic. If the value of R_t is and remains >1 , a sustained outbreak is likely. While R_t is <1 , the outbreak will die out. The aim of control interventions is typically to reduce the reproduction number below one as soon as possible.

Particularly, Thompson developed a novel framework to estimate the R_t based on the approach developed by Wallinga. Rather than depending on the previous estimates of the serial interval, the distribution of which may be unavailable early in an outbreak or with significant uncertainty, this new framework allowed the direct estimation of the serial interval through integrating information from known pairs of index and secondary cases. They applied this method to data from H1N1 influenza in the USA in 2009 and 2013 Ebola virus epidemic, showing improvements of the precision and accuracy of R_t .

Objectives

In this study, we used the statistical framework of Thompson *et al.*[8] to describe and estimate the domestic and international ongoing control situation of the epidemic based on officially reported COVID case data.

Methods

Data Collection

Firstly, we collected the daily cumulative confirmed, fatal and discharge cases data from Chinese CDC's official website as of February 29, 2020.[9] Then, we collected 126 index-secondary infector-infected pairs of confirmed cases with known or coarsely reported date of symptom onset by scanning publicly available case reports from official health websites or reliable news or other published papers as of February 16, 2020 (S1 Table).[4,10] Last, we further collected the daily new confirmed cases overseas from WHO reports as of February 26, 2020.[2]

Process of Data Analysis

Epidemic curve

The epidemic curve was constructed by date of cumulative reported cases by laboratory diagnosis, cumulative reported all cases (including laboratory diagnosis and clinical diagnosis), cumulative fatal, cumulative discharge and existing cases, and key dates relating to epidemic identification.

The serial interval

The serial interval was the period of time between analogous phases of an infectious illness in successive cases of a chain of infection that is spread from person to person.[11] We performed Bayesian parametric estimation of the serial interval distribution from 126 pair data using data augmentation Markov chain Monte Carlo (MCMC). And we fitted a gamma distributed serial interval distribution offset by one day.[12] The MCMC estimation was used to a joint posterior sample data for the parameters of the gamma distribution, with the parameter set corresponding to a step in the MCMC chain.

The time-dependent reproduction number (R_t)

The time-dependent reproduction number, R_t , was an important parameter for assessing whether current control efforts were effective or whether additional interventions were required.[13] The value of R_t represented the expected number of secondary cases arising from a primary case infected at time t . This value changed throughout an outbreak. If the value of R_t was below one, the outbreak would die out. However, while R_t was larger than one, a sustained outbreak was likely. The aim of control interventions is typically to reduce the reproduction number below one.[11] We used R.N. Thompson's method to estimate disease incidence time series and serial interval data for integrating the estimation of the serial interval distribution within the estimation of R_t . [8] This allows R_t to be estimated directly not only from the most up-to-date incidence data, but also from up-to-date serial interval data.

Patient and public involvement

No patient involved.

Statistical Analysis

Analyses aimed to describe the change epidemic of COVID-19 in China and outside China. First, we described the overall epidemic curve in China. Second, 126 infector-infected pairs of confirmed cases characteristics were described, including age, gender and the relationship between infectors and the infected. We calculated the serial interval by 126 infector-infected pairs. Third, we assessed the geographical distribution of daily new confirmed cases by laboratory diagnosis across all 31 provinces in China, grouping into three regions with different outbreak levels: Wuhan city (the main epidemic area), Hubei province excluding Wuhan and other provinces in China excluding Hubei Province. And we compared the R_t among these three regions. Last, we used the same method to estimate the development of epidemics outside China, separating six groups: Japan, Singapore, South Korea, Italy, Iran (which were the five top most serious epidemic countries) and other outside countries. Data analyses were performed by the use of R software (version 3.6.0), with "EpiEstim" for estimating the serial interval and R_t .

Results

Overall epidemic trends of COVID-19

As of 29 February, 79,824 confirmed cases of COVID-19 in 32 provinces has been reported to the China CDC surveillance system, of which 2,870(3.60%) were fatal, 7,356(20.85%) were severe and 41,625(52.15%) were cured. The overall epidemic trends of NCIP were shown in Figure 1. On February 12, the cumulative reported cases split into two curves. That's because on this day new clinically confirmed cases of COVID-19 were added in Hubei Province including Wuhan. Although the existing confirmed cases have been on the rise, they had gradually flattened in recent days. In addition, the number of discharged patients also showed a gradually increasing trend, the number of fatal remained increased but slowly. Therefore, the number of existing will begin to show a downward trend soon.

Estimated the serial time

The characteristics of 126 infector-infected pairs of confirmed cases were showed in Table 1. We found out the relationship of 83 infector-infected pairs. A half of pairs were belonged to elder and junior. And nearly a third of pairs were couples. We fitted a gamma distributed serial interval offset by one day which was shown in Figure 2. The median serial time was 4.18 with IQR 1.92 to 6.65 days.

Table 1 The characteristics of 126 infector-infected pairs of confirmed cases				
Characteristic	Total	Infected	Infector	<i>P</i>
N	252	126	126	
Age(Mean±SD)	46.9±17.4	49.5±14.9	44.2±19.3	.017
Gender				
Female	99(47)	55(51)	44(42)	.17
Male	113(53)	52(49)	61(58)	
Relationship				
Couple	26(31)	-	-	-
Elders and Juniors ^a	43(52)	-	-	-
Siblings/colleagues	14(17)	-	-	-
Unknown	43			
a. The relationships of elder and Junior included parent-child, grandparent-child, law parent-child, law grandparent-child.				

Estimated R_t in three areas with varying levels of outbreak

Figure 3A compared the daily incidence in three regions with different levels of outbreaks. It explored that the number of the incidence of Wuhan City had a rapid upward trend. In the early stage, except for a sudden sharp increase on Jan 27, daily incidence had been increasing as of Feb 4. And from this day onwards, there was a flat phase of volatility. The downward trend began on Feb 11. The other two regions, Hubei Province exclude Wuhan and China exclude Hubei Province were showing roughly similar trends. They first slowly increased to a certain level and then decreased slowly, and the peaks were significantly lower than those in Wuhan.

Figure 3B revealed the R_t of Wuhan, where the epidemic of COVID-19 originate as well as the most severe epidemic, showed a dynamic change and a downward trend. And the R_t (1.06 ± 0.02) was close to one on February 13th, and dropped below one (0.96 ± 0.02) the next day. China excluded Hubei Province took the lead in dropping below one (0.99 ± 0.02) on February 9, followed by Hubei Province excluded Wuhan the next day (0.99 ± 0.02). In addition, we compared the R_t among each province in China, the results were shown in the section B of the supplement S1 File. The more detail of R_t result were shown in Table S5 (the supplement S2 File).

Estimating the foreign countries' R_t

The outbreak had spread many countries around the world, of which Japan, Singapore, Korea, Italy and Iran were the most serious. Therefore, we also analyzed the changed of the R_t in these countries as well as other overseas countries and regions to find out the international spread of COVID-19. During February 7 (0.92 ± 0.26) and February 13 (0.46 ± 0.23), the R_t in Japan were below one, which meant the COVID-19 was not spread widely. However, since February 14 the Japan's R_t showed a suddenly growth trend and even increased to 3.26 ± 0.63 on February 16. And Korea also showed the similar change of R_t with Japan, but greater than Japan's R_t . The epidemic in Singapore was slightly better. Due to less reported cases data, the estimating for R_t had a wide range, but got stable estimates in the later stages. Compared with Japan, Singapore's R_t fluctuated below two, and the current R_t showed that it had fallen to one on February 21 (0.92 ± 0.17), indicating the epidemic was under control. Another two countries (Iran and Italy) also had a fluctuating R_t , which was always greater than one (4.45 ± 0.57 and 5.40 ± 0.63 as February 26). But other overseas countries showed the R_t had fallen to one recently (0.89 ± 0.06 on February 23). (Figure 4) The more detail of result was shown in Table S6 (the supplement S2 File).

Discussion

In this study, we mainly applied Thompson's method to estimate the R_t of COVID-19 in different areas to assess the spread of the epidemic in China and oversea. We found out that the R_t in China had almost been falling below one, which mean the non-pharmaceutical intervention in China were effective. But the situation of overseas is not optimistic as $R_t > 1$, which indicated the epidemic was still in the stage of gradual spread.

As of Feb 29, almost 80,000 confirmed cases of COVID-19 in China have been reported and nearly 3,000 people have died. As we all know, Wuhan as the origin outbreak is also the most severely affected area accounting nearly 60 percent of cumulative cases nationwide in China. And the fatality rate in Wuhan is much higher than in other regions.[14] Although existing confirmed cases was still increasing the rate of increase was steadily declining. It meant the series of non-pharmaceutical interventions implemented by the Chinese Government have achieved remarkable achievement. In this study, we found daily incidence of three areas were at different levels in China. Most of the new cases still came from Wuhan. The overall daily incidence has been gradually decreasing since February 4 and the daily incidence in Hubei Province excluded Wuhan and China excluded Hubei Province was gradually approaching zero, while Wuhan was still at a relatively high level and the decline of incidence was relatively slow.

As of Feb 11, the cumulative number of reported cases in China showed a bifurcation. According to the update of “The diagnosis and treatment program of novel coronavirus pneumonia (Trial Fifth Edition)”, [15] only Hubei province added the classification of “clinical diagnosis”, that the suspected cases with clinical features of pneumonia were clinically diagnosed cases. And it was cancelled in the sixth edition a few days. That’s because the Chinese authorities considered the limited medical resources and huge number of suspected patients. During Feb 4th and Feb 10th, the daily incidences in Wuhan fluctuated around 2,000, indicating that due to limited medical resources, many suspicious patients were still waiting for diagnosis, which might result in aggravated conditions and the risk of potential outward transmission. To speed up controlling the epidemic, Chinese authorities had adopted the standard of adding clinical diagnosis. When most suspected patients are diagnosed and treated effectively, the chain of disease transmission will become clearer.

In order to find out the trend of the epidemic, we calculated the R_t in different regions in China. And we also further calculated the R_t abroad to understand the international development of the epidemic. Based on official data and published literature, we analyzed the interval time between the onset dates of 126 pairs of infected and infected cases. By fitting the Gamma distribution, we got the median serial time of COVID-19 is 4.18 days. It’s longer than Hiroshi Nishiura’s result (2.6 days), which estimated by 26 infector-infected pairs.[16] The intergenerational time obtained in this study was smaller than the estimated value of 5 clustered outbreaks in 425 cases at beginning of the epidemic. And the time was also smaller than the average incubation period of 5.2 days, which was also estimated by 425 cases at beginning.[12] We supposed that the infected person was infected before the onset of symptoms.

Then, by inputting the serial time distribution and the latest (as of February 16) the incidence of laboratory confirmed cases with 7 days as the moving time window to estimate the value of R_t .

At first, we compared the R_t among three different regions in China. We could see all R_t in three areas had downward trends, as well as had fallen below one. It meant the series non-pharmaceutical interventions implemented in China had achieved some achievement.

And Wuhan as the origin of the epidemic, which also having the majority of patients, had the different change trend of R_t . Compared with other two regions, the average R_t of Wuhan was higher and taken longer time to drop below one. In addition, as we all know, there are still over thousands accumulated cases in Wuhan, so it still has a long way to control the epidemic.

Optimistically, the contagiousness of COVID-19 in China has been well controlled. As long as strict management is maintained, the number of incidences will drop to zero soon. As of February 25, the incidence in China had dropped from thousands to hundreds, meanwhile the number of cures was also increasing.[17] Zeliang Chen et al predicted the peak incidence to be in early or middle February.[18]

Secondly, we assessed the development of the epidemic overseas. Considering the extent of the epidemic, we listed top five countries with relatively severe outbreaks, Japan, Korea, Singapore, Iran and Italy, and combined other overseas countries for R_t calculations. As of February 26, except Singapore, other four countries' R_t were still upper than one, which meant the epidemic might be growing abroad. On February 7, the Singapore government officially decided to upgrade the response level of the outbreak response system from yellow to orange in view of the discovery of several local cases in Singapore, which were unrelated to previous cases and had no history of travel to China.[19] In our study, the result showed the R_t in Singapore had fallen below to one on February 20, which meant the outbreak in Singapore had been under control. Although the other overseas countries' R_t also had fallen below to one, it didn't mean the outbreak around the world was in control. On 30 January 2020, the outbreak was declared a Public Health Emergency of International Concern by WHO. And WHO and countries have been engaged in massive preparedness activities.[20] And according to the growth rate of the worldwide new confirmed cases, there were still a trend of rapid growth, which liked the early stage of epidemic in Wuhan. We hope it should be taken more attention and learn the experience from China or Singapore.

Our study used the latest generation time and new confirmed case data at the same time, trying to estimate the R_t of each region in China and oversea, which could provide a basis for grasping the development trend of the epidemic and evaluate prevention and the interventions. But there were some limitations in our study. First, we collected the personal history of epidemiological investigation data from different publish websites to estimate the serial interval, which made bias. We hope the government might build the database to collect the history epidemiology data, what could provide more reliable information.[21-22] Second, failure to exclude imported cases in the calculation of R_t might make bias, but it could still reflect a certain epidemic situation and the effectiveness of prevention and intervention. Another limitation is that we used the time-series data of confirmed cases to calculate according to the official date of diagnosis. So, the date we estimated that the R_t went below one should be delayed by about 10~17 days (the incubation period of 7 days added days from onset to diagnosis of 10 days). Although we estimated the time when the epidemic was under control had a delay than the actual time, it could still provide information of the trend of the epidemic.

Conclusions

In conclusion, the outbreak in China has been well controlled, but the worldwide pandemic has not been well controlled. However, there is still uncertainty about what the SARS-CoV-2 virus will do worldwide and even in China after the country inevitably lifts some of its strictest control measures.

Declarations

Ethics approval and consent to participate

The Ethics Committee of Guangzhou Women and Children's Medical Center, Guangdong, China approved this study. No consent to participate was required.

Consent for publication

The author gives consent for publication of this paper.

Competing interests

All authors declare no competing interests.

Authors' contributions

L Zheng and K Qin contributed equally to this manuscript. L Zheng, K Qin conceived and designed the study. L Zheng wrote the paper. X Chen, S Huang and D Liu collected data. W Liao reviewed and edited the manuscript. H Liang guided the study.

Funding

This work is funded by the National Key Research and Development Program of China (2019YFB1404803)

Acknowledgments

We thank the data sharing from the China Centre for Disease Control and Prevention.

Reference

1. Heymann DL, Shindo N. COVID-19: what is next for public health? Lancet (London, England). 2020;395(10224):542-545. doi:10.1016/S0140-6736(20)30374-3

2. World Health Organization. Coronavirus Disease 2019 (COVID-19) Situation Report -27.
www.who.int/godata.
3. Jernigan DB. Update: Public Health Response to the Coronavirus Disease 2019 Outbreak - United States, February 24, 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(8):216-219.
doi:10.15585/mmwr.mm6908e1
4. Haider N, Yavlinsky A, Simons D et al. Passengers' destinations from China: low risk of Novel Coronavirus (2019-nCoV) transmission into Africa and South America. *Epidemiol Infect*. 2020;148:e41. doi:10.1017/S0950268820000424
5. 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;6736(20). doi:10.1016/S0140-6736(20)30260-9
6. CDC C. Strengthening community prevention and control of pneumonia outbreak caused by novel coronavirus infection.
<http://www.nhc.gov.cn/xcs/zhengcwj/202001/dd1e502534004a8d88b6a10f329a3369.shtml>.
7. Bureau C health and disease control. The Guidelines for the Protection of Different Risk Groups for Novel Coronavirus Infection and the Use of Pneumonia Masks for the Prevention of Novel Coronavirus Infection.
<http://www.nhc.gov.cn/jkj/s7916/202001/a3a261dabfcf4c3fa365d4eb07ddab34.shtml>.
8. Thompson RN, Stockwin JE, van Gaalen RD et al. Improved inference of time-varying reproduction numbers during infectious disease outbreaks. *Epidemics*. 2019;29:100356.
doi:10.1016/j.epidem.2019.100356
9. CDC C. The data of novel coronavirus (COVID-19) around the world.
<http://2019ncov.chinacdc.cn/2019-nCoV/index.html>. Published 2020.
10. Hernandez-Garcia I, Gimenez-Julvez T. Assessment of Health Information About COVID-19 Prevention on the Internet: Infodemiological Study. *JMIR Public Heal Surveill*. 2020;6(2):e18717.
doi:10.2196/18717
11. Vynnycky E, Fine PEM. Lifetime risks, incubation period, and serial interval of tuberculosis. *Am J Epidemiol*. 2000;152(3):247-263. doi:10.1093/aje/152.3.247
12. Li Q, Guan X, Wu P et al. Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus–Infected Pneumonia. *N Engl J Med*. 2020:1-9. doi:10.1056/nejmoa2001316
13. Cauchemez S, Fraser C, Van Kerkhove MD et al. Middle East respiratory syndrome coronavirus: quantification of the extent of the epidemic, surveillance biases, and transmissibility. *Lancet Infect Dis*. 2014;14(1):50-56. doi:10.1016/S1473-3099(13)70304-9
14. Guan WJ, Ni ZY, Hu Y et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med*. February 2020:NEJMoa2002032. doi:10.1056/NEJMoa2002032
15. China NH and HC of the people's R of. Novel Coronavirus Pneumonia Diagnosis and Treatment Plan (Revised Version Fifth) [].
<http://www.nhc.gov.cn/yzygj/s7653p/202002/d4b895337e19445f8d728fcdf1e3e13a.shtml>.

16. Nishiura H, Linton NM, Akhmetzhanov AR. Serial interval of novel coronavirus (2019-nCoV) infections. medRxiv. 2020:2020.02.03.20019497. doi:10.1101/2020.02.03.20019497
17. World Health Organization. Coronavirus Disease 2019 (COVID-19) Situation Report -36. 2020. https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200225-sitrep-36-covid-19.pdf?sfvrsn=2791b4e0_2.
18. Chen Z, Zhang W, Lu Y. From SARS-CoV to Wuhan 2019-nCoV Outbreak: Similarity of Early Epidemic and Prediction of Future Trends. SSRN Electron J. 2020. doi:10.2139/ssrn.3528722
19. Board S tourism. Singapore tourism board statement on coronavirus disease (covid-19) outbreak 2019ak 2019. 2020.
20. World Health Organization. Statement on the second meeting of the International Health Regulations (2005) Emergency Committee regarding the outbreak of novel coronavirus (2019-nCoV). 2020. [https://www.who.int/news-room/detail/30-01-2020-statement-on-the-second-meeting-of-the-international-health-regulations-\(2005\)-emergency-committee-regarding-the-outbreak-of-novel-coronavirus-\(2019-ncov\)](https://www.who.int/news-room/detail/30-01-2020-statement-on-the-second-meeting-of-the-international-health-regulations-(2005)-emergency-committee-regarding-the-outbreak-of-novel-coronavirus-(2019-ncov)).
21. Torous J, Jän Myrick K, Rauseo-Ricupero N et al. Digital Mental Health and COVID-19: Using Technology Today to Accelerate the Curve on Access and Quality Tomorrow. JMIR Ment Heal. 2020;7(3):e18848. doi:10.2196/18848
22. de Lusignan S, Lopez Bernal J, Zambon M et al. Emergence of a Novel Coronavirus (COVID-19); A Protocol for Extending Surveillance Used by the Royal College of General Practitioners (RCGP) Research and Surveillance Centre (RSC) and Public Health England (PHE). JMIR Public Heal Surveill. 2020;6(3). doi:10.2196/preprints.18606

Figures

Figure 1

The distribution of cumulative report cases, fatal case, discharge and exiting cases in China. Four lines showed the distribution of cumulative reported cases, cumulative reported cases by laboratory diagnosis, fatal and discharge in China. And the bar chart showed the daily exiting cases in hospital in China

Explored SI distributions

Figure 2

The distribution of serial interval time

Figure 3

The daily incidence and R_t in three areas with varying levels of China. Figure 3A showed the daily incidence in three areas with varying levels; Figure 3B showed the R_t in three areas with varying levels

Figure 4

The distribution of daily incidence and R_t in top five sever outbreak countries (excluding China) and combined other overseas countries. The histogram plots showed the daily incidence of each country; the line plots showed the R_t of each country

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [supplement8.pdf](#)
- [supplement9.pdf](#)