

Estimation of the transmission risk of 2019-nCov and its implication for public health interventions

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Summary

Background: Since the emergence of the first pneumonia cases in Wuhan, China, the novel coronavirus (2019-nCov) infection has been quickly spreading out to other provinces and neighbouring countries. Estimation of the basic reproduction number by means of mathematical modelling can be helpful for determining the potential and severity of an outbreak, and providing critical information for identifying the type of disease interventions and intensity.

Methods: A deterministic compartmental model was devised based on the clinical progression of the disease, epidemiological status of the individuals, and the intervention measures.

Findings: The estimation results based on likelihood and model analysis reveal that the control reproduction number may be as high as 6.47 (95% CI 5.71-7.23). Sensitivity analyses reveal that interventions, such as intensive contact tracing followed by quarantine and isolation, can effectively reduce the control reproduction number and transmission risk, with the effect of travel restriction of Wuhan on 2019-nCov infection in Beijing being almost equivalent to increasing quarantine by 100-thousand baseline value.

Interpretation: It is essential to assess how the expensive, resource-intensive measures implemented by the Chinese authorities can contribute to the prevention and control of the 2019-nCov infection, and how long should be maintained. Under the most restrictive measures, the outbreak is expected to peak within two weeks (since January 23rd 2020) with significant low peak value. With travel restriction (no imported exposed individuals to Beijing), the number of infected individuals in 7 days will decrease by 91.14% in Beijing, compared with the scenario of no travel restriction.

Keywords: coronavirus; infection management and control; travel restriction; mathematical model; SEIR model

Research in context

Evidence before this study

Coronaviruses occasionally lead to major outbreaks, with reproduction numbers ranging from 2.0 to 4.9. Currently, a fourth large-scale outbreak is occurring and spreading from Wuhan, Hubei province, China, to neighbouring provinces and other countries. There is a dearth of epidemiological data about the emerging coronavirus, which would be of crucial importance to design and implement timely, *ad hoc* effective public health interventions, such as contact tracing, quarantine and travel restrictions.

Added value of this study

In this study, we adopted a deterministic model to shed light on dynamics transmission of the novel coronavirus and assess impacts of public health interventions on infection. We found that the basic reproduction number could be as high as 6.47 (95% CI 5.71-7.23), which seems consistent with the opinion that the virus has gone through at least three-four generations. Furthermore, according to our model, the outbreak, under the most restrictive measures, is expected to peak within two weeks (since January 23rd 2020) with significant low peak value.

Implications of all the available evidence

Our investigation has major practical implications for public health decision- and policy-makers. The rather high reproduction number seems to suggest that the outbreak may be more serious than what has been reported so far, warranting effective, strict public health measures aimed to mitigate the burden generated by the spreading of the new virus.

Introduction

Coronaviruses are enveloped, single-stranded, positive-sense RNA viruses belonging to the family of *Coronaviridae*.¹ They cause generally mild respiratory infections, even though occasionally lethal. Since their discovery and first characterization in 1965,² three major, large-scale outbreaks have occurred, caused by emerging, highly pathogenic coronaviruses; namely, the “Severe Acute Respiratory Syndrome” (SARS) outbreak in 2003 in mainland China,³ the “Middle East Respiratory Syndrome” (MERS) outbreak in 2012 in Saudi Arabia,^{4,5} and the MERS outbreak in 2015 in South Korea.^{6,7} These outbreaks have resulted in more than 8,000 and 2,200 confirmed SARS and MERS cases, respectively.⁸

Recently, a fourth outbreak has occurred in Wuhan, capital city of the Hubei province and the seventh largest city in the People’s Republic of China.⁹⁻¹¹ Since December 12th 2019, when the Wuhan Municipal Health Commission reported 27 cases of viral pneumonia including 7 critically ill cases, the pneumonia outbreak has received considerable global attention. A novel coronavirus was identified as the causative agent by the Chinese authorities on January 7th 2020, and on January 10th 2020 the World Health Organization (WHO) has designated the novel coronavirus as 2019-nCoV. On the same day, the WHO has released a wide range of *interim* guidance for all countries on how they can get prepared for coping with this emergency, including how to monitor for potentially infected people, collect and test samples, manage patients, control and mitigate the burden generated by the infection in health centers, maintain the right drug supplies, and effectively communicate with the lay public regarding the new virus.¹²

By the morning of January 23rd 2020, more than 571 confirmed cases with 17 deaths have been reported in other parts of the mainland China, and in various countries including South Korea, Japan, Thailand, Singapore, Philippines, Mexico and the United States of America. The transmission potential, often measured in terms of the basic reproduction number, the outbreak peak time, value and duration under current and evolving intervention measures, remain unclear, and warrant further investigation.

On January 20th 2020, the Chinese government has revised the law provisions concerning infectious diseases to add the 2019-nCoV as class B agent. Public health officials have announced a further revision to classify the novel virus as class A agent. Some non-pharmaceutical interventions (NPIs), including intensive contact tracing followed by quarantine of individuals potentially exposed to the disease, isolation of infected, symptomatic individuals, were implemented, but their effectiveness during the early stage is questionable. Quantifying the effectiveness of these interventions is of crucial importance for Wuhan as well as for other cities in their preparedness and rapid response to the importation of infected cases.

With the arrival of Spring Festival, massive traveling is expected to mobilize a large segment of the population, by which the novel coronavirus may be broadly reseeded. Extreme, unprecedented measures have been taken, for example, on January 23rd 2020 when the Chinese authorities introduced travel restrictions affecting five cities (Wuhan, Huanggang, Ezhou and Chibi and Zhijiang), effectively shutting down the movement of more than 40 million people. However, how these expensive and resource-intensive measures can contribute to the prevention and control of the infection in these cities and other parts of the country, and how long these travel restrictions should be maintained remain to be determined.

In the context of a novel coronavirus affecting a naïve population, estimation of the basic reproduction number is important for determining the potential and severity of an outbreak, and

providing critical information for designing and implementing disease outbreak responses in terms of the identification of the most appropriate, evidence-based interventions and mitigation measures and the determination of the intensity of such programs in order to achieve the maximal protection of population with the minimal interruption of social-economic activities.⁸

As recognized by the WHO,¹³ mathematical models, especially those timely, play a key role in informing evidence-based decisions by health decision- and policy-makers. To the best of our knowledge, only two mathematical models have been so far publicly released – a Bats-Hosts-Reservoir-People transmission network model and a returning traveler study aimed to compute underestimated coronavirus cases.^{14,15} No study has focused on the practical implications of public health interventions and measures. Therefore, the present study was undertaken to fill in this gap of knowledge.

Methods

Data

We obtained data of laboratory-confirmed 2019-nCov cases of in mainland China from the WHO situation report, the National Health Commission of the People's Republic of China and the Health Commission" of Hubei Province.¹⁶⁻¹⁹ Data information includes the cumulative number of reported cases, the cumulative number of cured cases and the number of death cases, shown in Figure 1(a). The data were released and analyzed anonymously. Since the identification of the 2019-nCov on January 10th 2020, some cases were ruled out and the cumulative number of reported cases per day was 41 from January 10th to January 15th 2020. To obtain the relatively reliable data we use the exponential growth law to deduce the number of reported cases per day from December 31st 2019 to January 10th, 2020 (called dataRev1) or from January 10th to 15th (called dataRev2) based on the 41 cases on that date, as shown in the Figure 1 (a).

The model

Here, we propose a deterministic SEIR compartmental model based on the clinical progression of the disease, epidemiological status of the individuals, and the intervention measures (Figure 2). We parameterize the model using data obtained for the confirmed cases of 2019-nCov in mainland China, and estimate the basic reproduction number of the disease transmission. By inferring the effectiveness of intervention measures including quarantine and isolation (Figure 1 (b)), we estimate the required effectiveness of these interventions in order to prevent the outbreak.

More in detail, we investigate a general SEIR-type epidemiological model, which incorporates appropriate compartments relevant to interventions such as quarantine, isolation and treatment. We stratify the populations as susceptible (S), exposed (E), infectious but not yet symptomatic (pre-symptomatic) (A), infectious with symptoms (I), hospitalized (H) and recovered (R) compartments, and further stratify the population to include the quarantined susceptible (S_q), isolated exposed (E_q), and isolated infected (I_q) compartments.

With contact tracing, a proportion, q , of individuals exposed to the virus is quarantined. The quarantined individuals can either move to the compartment E_q or S_q , depending on whether they are effectively infected or not,²⁰ while the other proportion, $1 - q$, consists of individuals exposed to the virus who are missed from the contact tracing and move to the exposed compartment E once effectively infected or stay in compartment S otherwise. Let the transmission probability be β and the contact rate be constant c . Then, the quarantined individuals, if infected (or uninfected), move

to the compartment E_q (or S_q) at a rate of βcq (or $(1 - \beta)cq$). Those who are not quarantined, if infected, will move to the compartment E at a rate of $\beta c(1 - q)$. The infected individuals can be detected and, then, isolated at a rate of d_I and can also move to the compartment R due to recovery. The transmission dynamics is governed by the following system of equations:

$$\begin{aligned} S' &= -(\beta c + cq(1 - \beta))S(I + \theta A) + \lambda S_q, \\ E' &= \beta c(1 - q)S(I + \theta A) - \sigma E, \\ I' &= \sigma E - (\delta_I + \alpha + \gamma_I)I, \\ A' &= \sigma(1 - \varrho)E - \gamma_A A, \\ S_q' &= (1 - \beta)cqS(I + \theta A) - \lambda S_q, \\ E_q' &= \beta cqS(I + \theta A) - \delta_q E_q, \\ H' &= \delta_I I + \delta_q E_q - (\alpha + \gamma_H)H, \\ R' &= \gamma_I I + \gamma_A A + \gamma_H H, \end{aligned}$$

where ' is the derivative with respect to time, and the other parameters are summarized in Table 1.

Model-based method for estimation

Given the model structure with quarantine and isolation (Figure 2), we use the next generation matrix^{21,22} to get an expression for the control reproduction number when control measures are in force as follows:

$$R_c = \left[\frac{\beta \varrho c(1 - q)}{\delta_I + \alpha + \gamma_I} + \frac{\beta c \theta (1 - \varrho)(1 - q)}{\gamma_A} \right] S_0.$$

We use the Markov Chain Monte Carlo (MCMC) method to fit the model, and adopt an adaptive Metropolis-Hastings (M-H) algorithm to carry out the MCMC procedure. The algorithm is run for 100,000 iterations with a burn-in of the first 70,000 iterations, and the Geweke convergence diagnostic method is employed to assess convergence of chains.

Likelihood-based method for estimation

We employ the likelihood-based method or generation interval-informed method of White and Pagano,²³ using the following formula:

$$L(R_c, p | N) = \prod_{t=1}^T \frac{\exp(-\phi_t) \phi_t^{N_t}}{\Gamma(N_t + 1)}$$

where $\phi_t = R_c \sum_{j=1}^k p_j N_{t-j}$ and k is the maximum value of the serial interval (chosen as $k = 6$ here) and $\Gamma(x)$ is the gamma function. $N = \{N_0, N_1, \dots, N_T\}$, where N_j denotes the total number of cases on day j and T is the last day of observations. p_j is the probability function for the generation interval on day j . We assume that the generation interval follows a gamma distribution with mean E and variance V . Since the generation interval of the 2019-nCov is undetermined, we investigate the sensitivity of R_c to different E values ranging from 2 to 8 days (given in Table 2).

Simulation

The population of Wuhan is around 11,081,000 inhabitants¹⁸, hence, we set $S(0) = 11,081,000$. By January 10th 2020, 2 patients recovered and were discharged from the hospital leading to $R(0) = 2$; and 739 individuals were quarantined leading to $S_q(0) = 739$. We set $H(0) = 1$, corresponding to that the reported confirmed case on January 10th 2020 is 1. The quarantined

individuals were isolated for 14 days, thus $\lambda = 1/14$. According to WHO,²⁴ the incubation period of 2019-nCoV is about 7 days, hence $\sigma = 1/7$.

Results

Likelihood-based estimates

Likelihood-based estimation of R_c during the outbreak for Wuhan gives a mean value of 6.39 with mean and variance of generation time of 6 and 2 days on the basis of a revised data series (dataRev 1). The reproduction number based on likelihood-based estimation ranges from 1.66 to 10 and it follows from Table 2 that R_c is sensitive to changes in mean generation intervals. Fitting to the other revised data series (dataRev 2) gives a mean value of 6.32 with mean and variance of generation time of 6 and 2 days. Note that the estimates of R_c on two time series agree well, and consequently two revised data series are feasible to be used to fit the proposed dynamics transmission model. In the following sections of the manuscript, we choose the revised data set (dataRev 1) to fit the proposed model.

Model-based estimates

Fitting the model without considering asymptomatic infections to the data of hospital notification for confirmed 2019-nCoV cases (dataRev 1), we estimate the mean control reproductive number as $R_c=6.47$ (95% CI 5.71–7.23), and other parameter estimations are reported in Table 1. Note that mean estimations on R_c for the likelihood method are within the 95% confidence interval of the model-based estimates (Table 2).

Using the estimated parameter values, we predict the trend of 2019-nCoV infection. Under the current intervention (before January 22nd 2020), the number of infected individuals ($I(t)$) is expected to peak on around March 10th 2020 with a peak size of 1.63×10^5 infectious individuals.

To examine the possible impact of enhanced interventions on disease infections we plot the number of infected individuals ($I(t)$) and predicted cumulative number of reported cases with varying quarantine rate q and contact rate c . This analysis shows that reducing contact rate persistently decreases the peak value but may either delay or bring forward the peak, as shown in Figure 3 and Table 3. More in detail, it shows that increasing quarantine rate q by 10 times or 20 times will bring forward the peak by 6.5 days or 9 days, and lead to reduction of peak value in the number of infected individuals by 87% or by 93%. This indicates that enhancing the quarantine and isolation following contract tracing and reducing contact rate can significantly lower the peak and reduce the cumulative number of predicted reported cases (Figure 4).

Considering the spreading of the virus (Figure 5) and to examine the impact of the travel restriction on other cities such as Beijing, we initially calculate the number of imported individuals who are in exposed status from Wuhan to Beijing per day, denoted by $I_{me}(t)$. According to our model we get the fraction that is exposed on $E(t)/N$ before January 22nd 2020: approximately 40,000 persons from Wuhan to Beijing via trains (around 37,000) and flights (around 3,000),²⁵ then we have

$$I_{me}(t) = 40000 * E(t)/N$$

that is, the imported exposed individuals are 40 individuals on January 22nd 2020. We found that with travel restriction (no imported exposed individuals to Beijing), the number of infected individuals in 7 days will decrease by 91.14% in Beijing, compared with the scenario of no travel restriction, while, given no travel restriction, the number of infected individuals in 7 days will

decrease by 88.84% only if we increase the quarantine rate by 100 thousand time, as shown in Figure 6A. This means that the effect of travel restriction of Wuhan on 2019-nCov infection in Beijing is almost equivalent to increasing quarantine by 100-thousand baseline value. It follows from Figure 6B that with travel restriction, the number of cumulative individuals in 7 days will significantly decrease (by 75.70%) in Beijing, compared with the scenario of no travel restriction.

Discussion

Based on the 2019-nCov case data until January 22nd 2020, we have estimated the basic reproduction numbers using different methods (likelihood-based and model-based approaches). The mean control reproduction number was estimated as high as 6.47 (95% CI 5.71–7.23), in comparison with the values of the SARS epidemic ($R_0=4.91$) in Beijing, China, in 2003,²⁶ and MERS in Jeddah ($R_0=3.5-6.7$) and Riyadh ($R_0=2.0-2.8$), Kingdom of Saudi Arabia, in 2014.²⁷ This implies the potential of a very serious epidemic unless much swift public health interventions are implemented.^{28,29}

On the other hand, such high reproduction number seems to be consistent with the opinion that the virus has gone through at least three-four generations of transmission.²⁴

Note that the series interval is an essential factor affecting the accuracy of likelihood function estimation. According to the current report, the incubation period of Wuhan patients with coronavirus pneumonia is about 2 to 15 days. We then assume that the series interval follows the gamma distribution with varying mean and variance, which allows us to examine the influence on the reproduction number. With the distribution of series interval with mean 6 days and variance 2 days, the likelihood-based estimation on the reproduction number is consistent with the model-based estimation. It shows that long series interval induces great reproduction number, and hence more new infections, which further confirms that the epidemic may be more serious than what has been reported until now.¹⁵

Based on the reported data, we have estimated that the number of people who were identified through contact tracing and quarantined were 5,897 on January 22nd 2020. In comparison with the total population size of Wuhan, the effort of close contact tracing and quarantine was insufficient and appears to have limited impact in terms of reducing the number of infected cases and/or slowing down the epidemic. The contour plot of $R_c=1$ gives the threshold values of contact rate and quarantine rate for a city to avoid an outbreak. This high threshold rate of quarantine puts extremely high requirement for the city's public health infrastructure and its citizen's adherence to personal protective and public health interventions including reduction of transmission-effective contacts, separation and restriction during the quarantine. Such a high level of quarantine rate and reduction of contact is possible only when the number of imported cases from the epicenter is minimal, speaking in terms of the value of the travel restriction.

A strict travel restriction to the city of Wuhan is expensive and resource-consuming, imposing substantial challenge to the decision- and policymakers and the city's resilience. In conclusion, our simulations show that the appropriate duration of this travel restriction depends on a combination of effective quarantine and reduction of contact within the city.

Tables.

Table 1: Parameter estimates for 2019-2020 Wuhan pneumonia in China.

Parameter	Definitions	Estimated mean value	Std	Source
c	Contact rate	14.781	0.904	MCMC
β	Probability of transmission per contact	2.1011×10^{-8}	1.1886×10^{-9}	MCMC
q	Quarantined rate of exposed individuals	1.8887×10^{-7}	6.3654×10^{-8}	MCMC
σ	Transition rate of exposed individuals to the infected class	1/7	–	24
λ	Rate at which the quarantined uninfected contacts were released into the wider community	1/14	–	18,19
ϱ	Probability of having symptoms among infected individuals	0.86834	0.049227	MCMC
δ_I	Transition rate of symptomatic infected individuals to the quarantined infected class	0.13266	0.021315	MCMC
δ_q	Transition rate of quarantined exposed individuals to the quarantined infected class	0.1259	0.052032	MCMC
γ_I	Recovery rate of symptomatic infected individuals	0.33029	0.052135	MCMC
γ_A	Recovery rate of asymptomatic infected individuals	0.13978	0.034821	MCMC
γ_H	Recovery rate of quarantined infected individuals	0.11624	0.038725	MCMC
α	Disease-induced death rate	1.7826×10^{-5}	6.8331×10^{-6}	MCMC
Initial values	Definitions	Estimated mean value	Std	Source
$S(0)$	Initial susceptible population	11081000	–	18
$E(0)$	Initial exposed population	105.1	35.465	MCMC
$I(0)$	Initial symptomatic infected population	27.679	11.551	MCMC
$A(0)$	Initial asymptomatic infected population	53.839	25.25	MCMC
$S_q(0)$	Initial quarantined susceptible population	739	–	data
$E_q(0)$	Initial quarantined exposed population	1.1642	0.20778	MCMC
$H(0)$	Initial quarantined infected population	1	–	data
$R(0)$	Initial recovered population	2	–	data

Table 2: Estimation for the basic reproduction number for 2019-nCov in Wuhan, China.

R_0	V=2 (dataRev1)	V=3 (dataRev1)	V=2 (dataRev2)	V=3 (dataRev2)
E=2	1.4546	1.6560	1.4545	1.6554
E=3	1.7459	1.7155	1.7456	1.7145
E=4	2.5828	2.4462	2.5815	2.4427
E=5	3.9893	3.7134	3.9802	3.6956
E=6	6.3901	5.8303	6.3164	5.7304
E=7	10	9.2564	9.6409	8.7299
E=8	10	10	10	10

E: mean value of Gamma distribution, V: Deviation of Gamma distribution

dataRev1: [1 2 3 4 6 9 12 20 28 41 45 62 121 198 291 440 571];

dataRev2: [1 2 3 4 6 9 12 20 28 41 41 41 41 41 41 45 62 121 198 291 440 571];

Table 3: The effects of travel restrictions on the peak time and peak value.

Parameter	c	c	$0.8c$	$0.5c$	$0.3c$	$0.1c$
Peak Time		19.3 days	22.6 days	33.8 days	61.3 days	3.4 days
Value of I at peak time		1.63×10^5	1.5×10^5	1.15×10^5	6.68×10^4	2.42×10^3
Parameter	q	q	$5q$	$10q$	$15q$	$20q$
Peak time		19.3 days	15.1 days	12.8 days	11.4 days	10.3 days
Value of I at peak time		1.63×10^5	3.76×10^4	1.98×10^4	1.38×10^4	1.08×10^4

Note that, the baseline values are $(c, q) = (14.78, 1.88 \times 10^{-7})$.

Figures.

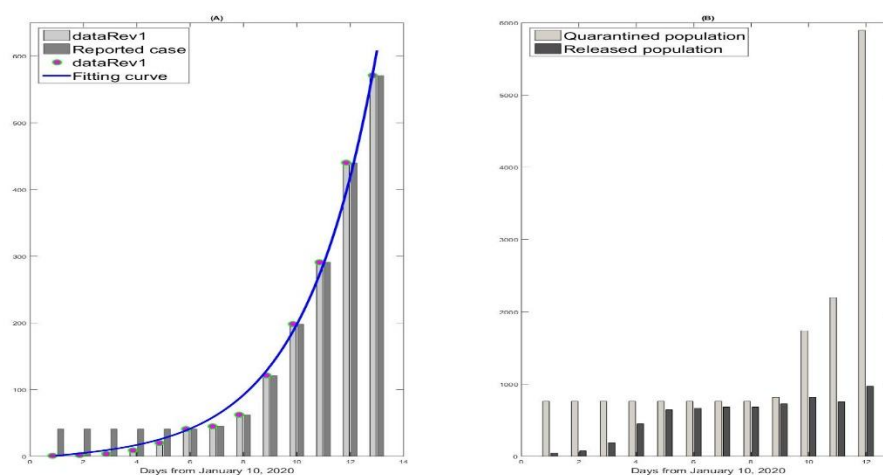


Figure 1: Cumulative diagnoses and revised case data (dataRev1) in mainland China are shown in (A), and cumulative quarantined/released populations are shown in (B).

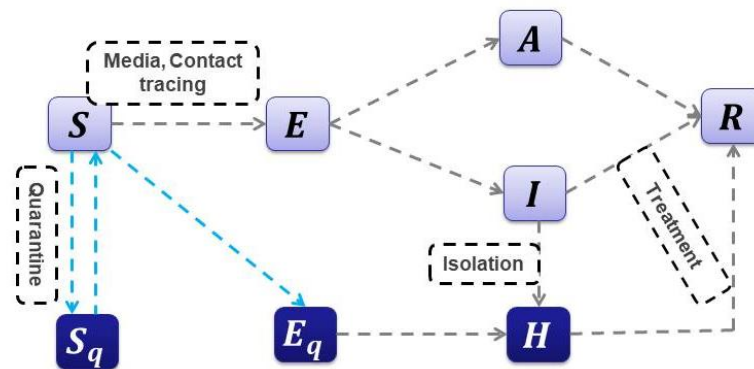


Figure 2: Diagram of the model adopted in the study for simulating the 2019-nCov infection. Interventions including intensive contact tracing followed by quarantine and isolation are indicated.

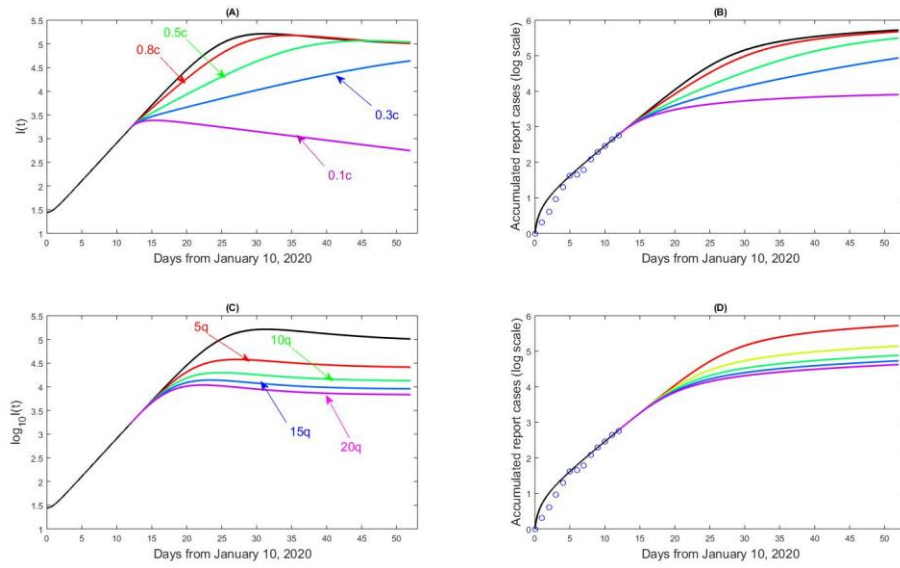


Figure 3: Sensitivity analyses with respect to contact rate c (A-B), and quarantine rate q (C-D) on the log number of infected individuals and cumulative reported cases.

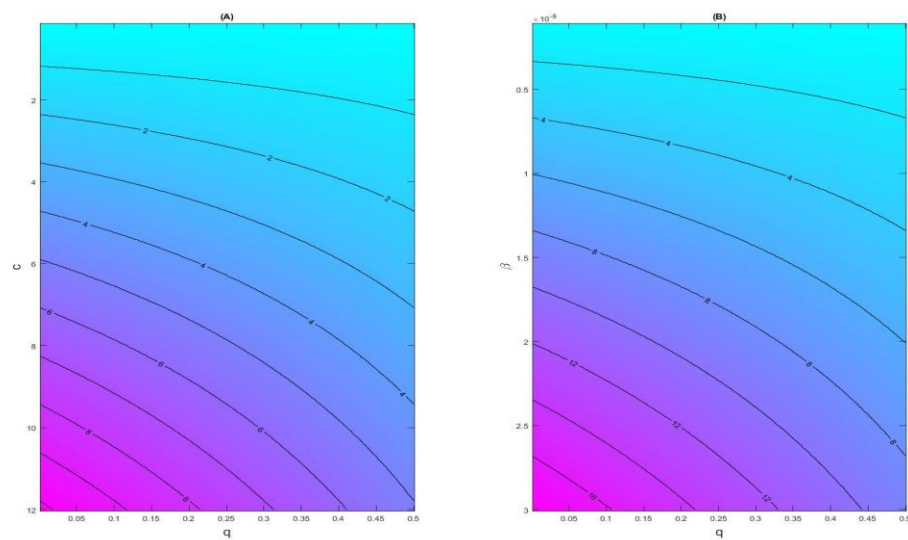


Figure 4: Contour plot of R_c with parameter of baseline transmission probability and the contact rate c (A) or the quarantine rate q (B).

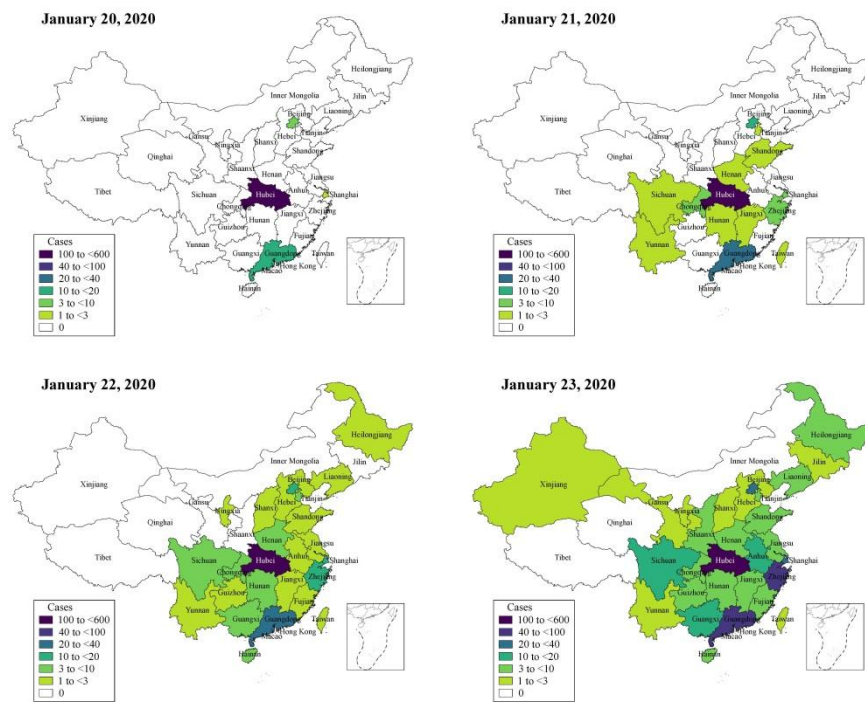


Figure 5: Heat-map showing the spreading of Coronavirus infection..

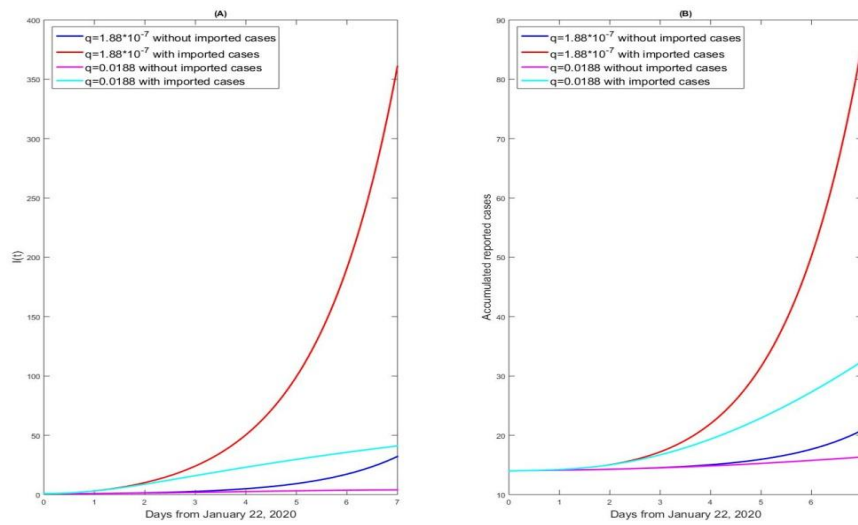


Figure 6: The effects of travel restrictions in Hubei Province on the Coronavirus disease in Beijing city.

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Contributors

S.T., Y.X. and J.W. conceived and designed the study. B.T., X.W., Q.L. and S.T. analyzed the data, carried out the analysis and performed numerical simulations, N.L.B. conducted the literature review. All authors participated in writing and reviewing of the manuscript.

Declaration of interests

All authors declare no competing interests.

Data sharing

All data utilized in the present investigation are publicly available.

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