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Mathematical models for devising the optimal SARS-CoV-2 eradication in China, South Korea, and Italy

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ABSTRACT

Background: Coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), spreads rapidly and has attracted worldwide attention.

Methods: To improve forecast accuracy and investigate the spread of SARS-CoV-2, we constructed four mathematical models to investigate the numerical spread of SARS-CoV-2 and eradication pathways.

Results: Using the SEIR model, and including measures, such as city closure and holiday extension policy taken by the Chinese government which effectively reduced the β value, we estimated that the β value and basic transmission R0 of SARS-CoV-2 was 0·476 / 6·66 in Wuhan, 0·359 / 5·03 in Korea, 0·400 / 5·60 in Italy. Considering medicine and vaccines, an advanced model demonstrated that the emergence of vaccines can greatly alleviate the spread of the virus. Our model predicted that 100,000 people would become infected assuming the isolation rate alpha is 0·30 in Wuhan. If quarantine measures were taken from Mar 10, 2020 and the quarantine rate of alpha was also 0·3, the final number of infected people might be 11,426 in South Korea, and 147,142 in Italy.

Conclusions: Our mathematical models propose that SARS-CoV-2 eradication depends on systematic thinking, effective hospital isolation, and SARS-CoV-2 medicine and vaccination, and some measures including city closure and holiday policy should be taken for SARS-CoV-2 eradication.

Keywords: COVID-19; SARS-CoV-2; Mathematical models; Hospital isolation.

Introduction

The outbreak of COVID-19 pneumonia in Wuhan caused by the novel coronavirus SARS-CoV-2 has drawn tremendous attention around the world (1). The current COVID-19 outbreak in China caused more than 80,424 infections of SARS-CoV-2 and over 2,984 deaths by March 4, 2020 (2). There are now more than 10,566 additional cases, in over seventy countries (3). SARS-CoV-2 has never been found in humans before and may not be as virulent as severe acute respiratory syndrome (SARS), but in humans it is highly infectious.

Coronaviruses (CoVs) are pathogens that can infect the respiratory, gastrointestinal, hepatic and central nervous systems of humans, livestock, avians, bats, mice and other wild animals (4, 5). As in the outbreaks of SARS in 2002 and Middle East respiratory syndrome (MERS) in 2012, the possibility of SARS-CoV and MERS-CoV transmission from animals to humans has been suggested (6, 7). However, there have been no effective strategies, including therapeutics and vaccines, and the best way to deal with severe CoV infections is to control the source of infection, using early diagnosis, isolation, treatments, and timely epidemic information to avoid unnecessary panic. Thus, surveillance and outbreak response management systems are urgently needed to control SARS-CoV-2 outbreaks worldwide as a framework for SARS-CoV-2 virus disease outbreak modeling.

Mathematical modeling plays an important role in understanding the complexities of infectious diseases and their control (8), and can rapidly meet the need for assessing the potential long-term impact of such a disease and offer strategies for the evaluation and prediction of the effect of possible interventions, even when available data is limited.. Typical examples are the abundance of early models for HIV (9), pandemic influenza (10, 11), bovine spongiform encephalopathy (BSE) (12), and Creutzfeldt–Jakob disease (CJD) (13). After the outbreak of SARS, mathematical models have been published (14, 15). and policy makers have learned how models can help support their decision. Based on the full genomic sequence data of this coronavirus released on January 22, 2020 (16) and SARS-CoV-2 being more than 82% identical to those of SARS-CoV and bat SARS-like coronavirus (SL-CoV) (17), COVID-19 can now be tracked in the population, and rapid and accurate mathematical models can aid epidemiologic monitoring.

To improve forecast accuracy and investigate the spread and eradication pathways of SARS-CoV-2, a mathematical model needs to take into consideration the medical condition improvements, personal protection, regulation promulgation, and other contributing factors. By considering the characteristics of SARS-CoV-2: its spread trend, local condition constraints, and economic optimization, we aimed to develop mathematical models that would provide the optimal SARS-CoV-2 virus disease eradication plan that was realistic sensible and feasible.

Methods

Characteristics of SARS-CoV-2. For feasibility and usefulness of our approach and before constructing our models, the important attributes of SARS-CoV-2 virus were summarized and included (1) origin: according to the current etiological research, the natural host may be bats; the intermediate host is currently unknown. Most patients were geographically linked to the Huanan seafood wholesale market (18); (2) transmission: the route of SARS-CoV-2 infection is direct, aerosol and contact transmissions (19). SARS-CoV-2 causing the outbreak was different from the human coronavirus previously identified, and he common ancestor of SARS/SARS-like coronaviruses is a virus similar to HKU9-1. The Susceptible period of SARS-CoV-2 is 1-14 days. (5, 20-22).

Assumptions of modeling for SARS-CoV-2 analysis. Basic assumptions are that the outbreak occurred in Wuhan. After the outbreak, the city was closed on January 23, 2020, the remaining total population of Wuhan is 9,000,000 and we assumed it remained unchanged. Basic assumptions in South Korea and Italy: (1) the reporting time of the first case in China was Dec 08, 2019, and the diagnosis time of the first case was Jan 11, 2020, with a difference of 34 days. We assumed that the actual occurrence time of the first case in other countries was 30 days earlier than the announcement time of the diagnosis; (2) In 2018, South Korea has a population of 51,640,000 and Italy has a population of 60,430,000.

Four models for the prediction of the numerical spread of SARS-CoV-2. All information of the basic considerations and assumptions of SIR, SEIR model, and advanced models considering hospital isolation, medicine and vaccine were included in the online methods. For SIR model, estimated of the β parameter sensitivity (the probability of transfer from the cultivated state to the resistant state): There was N ≈

S in the early stage of the epidemic, so:

$$\frac{dI}{dt} = \beta\frac{IS}{N} - \gamma I \approx (\beta - \gamma)I,$$

Works out as:

$$I(t) = e^{(\beta-\gamma)t}.$$

For SEIR model, we divided the total population into four groups including Susceptible (*S*), Incubation (*E*), Infected (*I*) and Removed group (*R*), and modeled SARS-CoV-2 infection as related to the number of instances of contact between susceptible and infected people times infection rate β. We can express the changing rate of the susceptible group as:

$$\frac{dS}{dt} = -\beta S\frac{I}{N}.$$

σ represents the outflow rate of the incubation group to the infected group. The changing rate of the incubation group can be expressed as:

$$\frac{dE}{dt} = \beta S\frac{I}{N} - \sigma E.$$

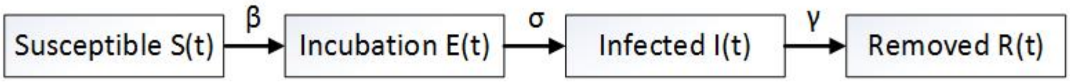
γ represents the outflow rate of the infected group to the removed group. We obtain the following equation:

$$\frac{dI}{dt} = \sigma E - \gamma I.$$

We can obtain the changing rate of the removed group. Its inflow is from the infected group at the rate of γ, and it has no outflow since it is the end of the system. Hence, we get the following equation:

$$\frac{dR}{dt} = \gamma I.$$

The whole process set out above can be displayed in the below flow chart.



Further, we made some modifications to the basic model with hospital isolations. The outflow rate of the infected group will change since part of this group will be moved to the hospital isolation group at the rate of α, and the other part will move to the removed group at the rate of γ. Hence, we have:

$$\frac{dI}{dt} = \sigma E - \gamma(1-\alpha)I - \alpha I .$$

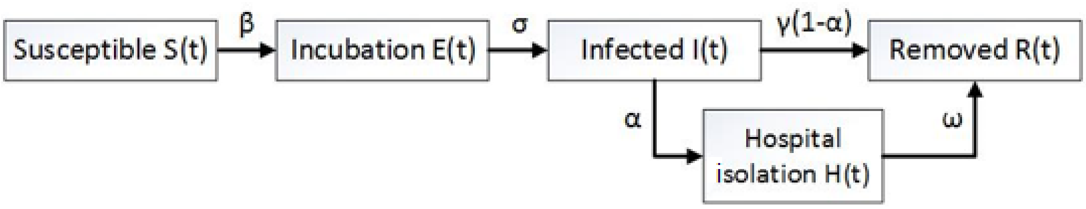
For the new hospital isolation group, its inflow is from the infected group at the rate of α; and its outflow is to the removed group at the rate of ω. We can get the changing rate of this group:

$$\frac{dH}{dt} = \alpha I - \omega H .$$

Similarly, we make some modifications to the changing rate of the removed group:

$$\frac{dR}{dt} = \gamma(1-\alpha)I + \omega H .$$

The advanced model introduced above can be displayed in the flow chart below.

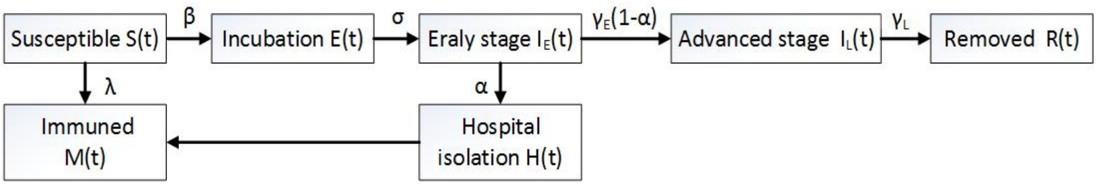


Finally, we present the differential equations system for our advanced model considering medicine and vaccine as follows:

$$\frac{dS}{dt} = -\beta S \frac{I_E + I_L}{N} - \theta S$$
$$\frac{dE}{dt} = \beta S \frac{I_E + I_L}{N} - \sigma E$$
$$\frac{dI_E}{dt} = \sigma E - \gamma_E (1-\alpha) I_E - \alpha I_E$$
$$\frac{dI_L}{dt} = \gamma_E (1-\alpha) I_E - \gamma_L I_L$$

$$\frac{dH}{dt} = \alpha I_E - \omega H$$
$$\frac{dM}{dt} = \theta S + \omega H$$
$$\frac{dR}{dt} = \gamma_L I_L \quad .$$

The model above can be displayed in the flow chart shown below.



Results

Disease review of COVID-19

Dec 8, 2019 was the first confirmed case, and the Chinese government began to continuously report it from Jan 11, 2020. As of Mar 01, 2020, Fig. 1a was the detailed epidemic trend, which includes the number of confirmed cases in Wuhan. Fig. 1b were the number of cumulative treatments and recoveries, and the number of deaths in Wuhan. As of Mar 08, 2020, Fig. 1c was the detailed epidemic trend includes the number of confirmed cases in South Korea. As of Mar 05, 2020, Fig. 1d was the detailed epidemic trend includes the number of confirmed cases in Italy. There is now a total of 90,870 reported cases of COVID-19 globally and 3,112 deaths. Outside China, 10,566 cases were reported in 72 countries and a large percentage of those cases are from South Korea and Italy. The severe situation means an accurate mathematical model needs to be established to predict epidemic trends in order to take positive and effective countermeasures. The actions these affected countries take today will be the difference between a handful and a larger cluster of cases.

Effect of SARS-CoV-2 infection rate on eradicating SARS-CoV-2

Under the optimistic estimation, the number of cases reported in only Wuhan is counted as the confirmed case recorded in Wuhan. In the modeling, according to the pessimistic estimate, it is assumed that the infection cases found in other areas are all from Wuhan. By setting different β values, the β value is selected with the minimum variance as the fitted β value:

$$\min_{\beta} \sum_{i=1}^{n} (f_i - d_i)^2$$

where f_i denotes the value of data i on the fitted curve, d_i denotes the real data value and n denotes the data size. It can be concluded that the β value in the optimistic case is 0.213 (Fig. 2a). Therefore, the fitting of infection cases under optimistic conditions is shown in Fig. 2b. A pessimistic estimate of β, we can conclude that the β value in the pessimistic case is 0.236 (Fig. 2c). Therefore, the fitting of infection cases under pessimistic conditions is shown in Fig. 2d. It can be concluded that the value of the parameter resistance (the probability of transfer from the potential state to the potential state) is between 0.213 and 0.236. We can also estimate the basic reproduction number (R0) of the novel coronavirus as:

$$R_0 = \frac{\beta}{\gamma} = \frac{0.213 \sim 0.236}{1/14} = 2.98{\sim}3.30.$$

The basic number of infections is the average number of people infected with an infectious disease that can spread to other people without intervention and without immunity. The larger the R0 number is, the more difficult it is to control the epidemic. In this modeling, we estimated that the basic transmission R0 of SARS-CoV-2 was approximately between 2.98 and 3.30.

Effect of SARS-CoV-2 government control measures on eradicating SARS-CoV-2

(1) In Wuhan: Until Feb 12, 2020 (day 67), a total of 19,558 cases were confirmed in Wuhan. That is, I (67) = 19,558 can be solved as β = 0.476. In the SEIR model, R0 of the basic reproduction number of the novel coronavirus is:

$$R_0 = \frac{\beta}{\gamma} = \frac{0.476}{1/14} = 6.66$$

It can be found that the disease starts to break out intensively around the 80th day (late Feb) and reaches its peak around the 120th day (mid-April). The changing trend of each group is shown in Fig. 2e. According to the actual number of cases in Wuhan, the epidemic curve was fitted (Fig. 3a) and β values were evaluated. For government control of intensity, under the SEIR model, we simulated that β was 0.476 (Fig. 3b). According to the above β value, we estimated that about 3,200,000 people will be infected in the whole city of Wuhan. When β decreases to 0.4, the peak infection rate drops to 3,000,000, and when β further decreases to 0.3, the peak infection rate drops to 2,500,000 (Fig. 3b).

(2) In South Korea and Italy: In the SEIR model, the basic reproduction number of the novel coronavirus in South Korea, and Italy is

$$R_0(South\ Korea) = \frac{\beta}{\gamma} = \frac{0.359}{1/14} = 5.03;$$

$$R_0(Italy) = \frac{\beta}{\gamma} = \frac{0.400}{1/14} = 5.60.$$

According to the actual number of cases in Korea and Italy, the epidemic curve was fitted (Fig. 3d, g) and β values were evaluated. For government control intensity: under the SEIR model, we simulated that β were 0.359 for South Korea (Fig. 3e) and 0.400 for Italy (Fig. 3h). According to the above β values, we estimated that about 51,640,000, 60,430,000 people would be infected in South Korea and Italy, respectively. If the government takes some measures, such as city closure policy and holiday extension policy, it can effectively reduce the beta value. In South Korea, when β drops to 0.30 or 0.20, the peak infection rate drops to 13,974,030 or 9,313,317 (Fig. 3e). In Italy, when β decreases to 0.30 or 0.20, the peak infection rate drops to 16,358,690 or 10,897,254 in Italy (Fig. 3h).

Effect of hospital isolation on eradicating SARS-CoV-2

Under different alpha ratios, we can see that with the increase in the ratio of hospital isolation, the number of infections at the highest point decreased, and the time of occurrence was later. When not isolated, approximately 3,200,000 people eventually become infected in Wuhan. When only 10% of the population is quarantined, only 1,200,000 will become infected in Wuhan. When the quarantine rate was raised further, to 20 or 30%, 400,000 or only 100,000 people would become infected (Fig. 3c), respectively, which is consistent with current number of infected people in the report, verifying that 30% of the population has been quarantined in Wuhan according to analysis of this modeling. Also, if quarantine measures were taken from Mar 10, 2020 and the quarantine rate of alpha was 0.3, the final number of infected people would be 11,426 in South Korea with a peak of 450 days (Fig. 3f) and 147,142 in Italy with a peak of 405 days (Fig. 3i).

Effect of the vaccination rate and time on eradicating SARS-CoV-2 in Wuhan.

Vaccination rate: Assuming the isolation rate alpha is 0.2, the changes in the number of infected patients under different vaccination rates (theta) are shown in Fig. 4a. Without a vaccine, at a 20% isolation rate, 400,000 people could end up being infected. If the vaccination rate is 0.005, fewer than 20,000 people will become infected. Therefore, the emergence of vaccines can greatly alleviate the spread of a virus. If a vaccine is developed within two months of the outbreak (day 60) with a vaccination rate of 0.005, the changes after that are shown in Fig. 4b; this implies that the SARS-CoV-2 virus will peak at day 150 and only 15,000 people in Wuhan will be infected. However, it will take a few months to develop a vaccine for SARS-CoV-2.

Discussion

To date, the epidemic of COVID-19 is still in a phase of rapid dispersion worldwide and this epidemic represents a clear and ongoing global health threat. It is currently uncertain whether it is possible to contain the continuing epidemic within China (23). In the early stage of a SARS-CoV-2 infection, the medical conditions are not perfect, and no effective measures have been taken. The number of infected people increases exponentially, so it is particularly critical to control the value of β. In our model, the β of South Korea is 0.359, which is the lowest among the three countries, followed by Italy, whose β is 0.4. The β of both South Korea and Italy is lower than that of China. In these three countries, the trend of R0 was consistent with β. Thus, reducing the exposure rate of β could significantly reduce the reproduction number. Next, we had estimated a R0 of 6.66 in Wuhan, which represents a relatively higher value than those so far computed (till Mar 01, 2020). In several other mathematical models which have been so far devised and released the R0 varies from 1.30 to 6.47 (table S1) (24-28). By comparing the various investigations, these different reproduction number reflecting the dynamics of transmission and case of COVID-19, fluctuating and varying over the time. Thus, we used the latest reported data (Jan 15, 2020 - Mar 01, 2020) to estimate a relatively accurate R0, which was relatively reliable in our models.

We further took hospital isolation, SARS-CoV-2 drug and vaccine into account in our models. With other parameters unchanged, the greater the α for the isolation rate in the hospital is, the later the peak is reached, and the smaller the peak size is, and the more effective it is to prevent the spread of the disease. The hospital pathway could sufficiently isolate SARS-CoV-2-infected patients from other patients to decrease infection, be more concerned about protecting doctors and nurses (29). For the penetration of vaccines and drugs, the greater the parameter theta, the earlier the peak would appear, the smaller the peak would be, and the lower the final total number of infections would be. However, scientists have still not found the effective medications and vaccines of SARS-CoV-2 (30). Finally, our simulations have shown that the control outcome depends highly on the effectiveness of the intense control effort now underway in China. Reducing the exposure rate of β and increasing the isolation rate of alpha can significantly reduce the number of infected people. The government should continue to tightly monitor the epidemic situation and must take immediate measures against it, and this includes immediate isolation of newly infected people and the city with severe cases being closed, in case there may be unexpected outbreaks in the eradication process. Regional transmission is the root of the spread of COVID-19. Local governments must have the responsibility to set a deadline for the final eradication, and the SARS-CoV-2 epidemic in China revealed that China still needs to strengthen the establishment of a rapid outbreak response strategy and health policies.

Conclusions

In summary, our mathematical model of SARS-CoV-2 infection can accurately predict the incidence and number of cases as well as the peak and end times of the epidemic and provide feasible solutions for future epidemic prevention and control, including predicting future epidemic trends and offering advice about effective control options, which emphasized that effective SARS-CoV-2 eradication must involve the active cooperation between the government, pharmaceutical companies and hospital organizations.

Ethics approval and consent to participate

Not Applicable.

Consent for Publication

Not Applicable.

Availability of data and material

The datasets generated during and/or analyzed during the current study are available in WHO (https://www.msn.com/en-gb/weather/other/coronavirus-outbreak-who-names) .

Competing interests

The authors declare no competing financial interests.

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Author Contributions

Conceived and designed the experiments: J.W., and S. J. Constructed the mathematical model, designed and carried out analyzed data: S.J. Analyzed the data: S. J., C.L., X. H., H. L., and T. W. Contributed analysis tools: S.L., C.C., X.Z. and

J.X. Wrote the manuscript: Q.L. and J.W. Revised the manuscript: J.W.

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Figure Legends

Figure 1. Review of COVID-19 in Wuhan, Republic of Korea, Iran, Italy. a: The number of confirmed cases in Wuhan, and (b) the number of cumulative cured patients and deaths in Wuhan; c: distribution of confirmed cases of COVID-19 in China; the number of confirmed cases in South Korea (d), Italy (e).

Figure 2. The SIR and SEIR models analyze the basic data of the epidemic in Wuhan. a, b: optimistic estimation; c, d: pessimistic estimation. a: The β value in the optimistic estimation; b: the infection cases in the optimistic estimation is reasonable; c: The β value in the pessimistic estimation; d: the fitting of infective cases in the pessimistic estimation: e: Trends in each group of SEIR model in Wuhan.

Figure 3. The SIR and SEIR models were used to analyze the epidemic situation in Wuhan. a: The fitted curve (blue) in Wuhan, red points represented the actual number of cases; b: SEIR model analysis of Wuhan; and c: Hospital isolation was included in the model analysis of Wuhan. Hospital isolation model with different isolation ratios, and the peak of the outbreak occurred on day 450. d: The fitted curve (blue) in South Korea, red points represented the actual number of cases; e: SEIR model analysis of South Korea; f: hospital isolation model with different isolation ratios was included in the model analysis of South Korea. The peak of the outbreak occurred on day 450. g: The fitted curve (blue) in Italy, red points represented the actual number of cases; h: SEIR model analysis of Italy; i: hospital isolation model with different isolation ratios was included in the model analysis of Italy, and the peak of the outbreak occurred on day 405.

Figure 4. Vaccination rates were included in the model analysis of Wuhan. a: SEIR model with different vaccination rates; b: the changes of SEIR model with vaccine at day 60.