

Epidemiological analysis of asymptomatic coronavirus disease 2019-infected individuals in the community based on an individual-based model

Zuiyuan Guo

Center for Disease Control and Prevention in Northern Theater Command

Dan Xiao (✉ danxiaoepi@163.com)

Beijing Tiantan Hospital

Research Article

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Abstract

Background: Asymptomatic coronavirus disease 2019 (COVID-19)-infected individuals (AIs) is a special group that differs from COVID-19 patients. This will provide us with a deeper understanding on the impact of AIs on the epidemic and a theoretical basis to establish more precise prevention and control measures to control this disease.

Methods: We established an individual-based computer model to simulate the occurrence, infection, discovery, quarantine, and quarantine release (recovery) of AIs or patients within the community. The model was used to explore the effects of measures such as active tracing, laboratory testing, active treatment, and home quarantine on the epidemic.

Results: Given the condition that $R_0=1.2$, when a case of imported AI was reported in the community, the implementation of measures reduced the number of AIs and patients by 62.2% and 62.4%, respectively. The number of undetected AIs and patients peaked at 302 d of the epidemic, reaching 53 and 20 individuals, respectively.

Conclusion: The implementation of sustained active tracing, laboratory testing, active treatment, and home quarantine can significantly reduce probability of disease outbreak and block the spread of the COVID-19 epidemic caused by asymptomatic infected individuals in the community.

1 Introduction

In 2020, the coronavirus disease 2019 (COVID-19) epidemic has continued to spread throughout the world.[1, 2] According to the World Health Organization statistics, as of April 22, 2020, there have been 2.48 million confirmed cases of COVID-19, including almost 170,000 deaths.[2] In April 2020, China was able to successfully control the spread of the epidemic, and the number of new daily cases has essentially dropped to single digits.[3] Nevertheless, there are still asymptomatic COVID-19-infected individuals (AIs) in the population; as of April 22, 984 AIs remain under medical observation in China.[4]

In this study, AIs refer to those who often experience mild, limited or no symptoms and hence go unrecognized, but showed positive COVID-19 test results of respiratory tract and other specimens.[5] Surveillance data from China showed that there is a sustained occurrence of second-generation cases among the close contacts of AIs and that AIs can cause clustered outbreaks.[6-12] Studies with small sample sizes have shown that the viral load in the respiratory tract specimens of AIs did not differ significantly from those of confirmed cases.[6] Some experts believe that even though pathogenic nucleic acids can be detected in the respiratory tract specimens of AIs, due to the absence of clinical symptoms, such as coughing and sneezing, they have a lower chance of viral shedding compared with patients who have confirmed cases.[6]

The findings of the above mentioned studies suggest that AIs carry transmission risks. The first factor is the covertness of transmission. As AIs do not exhibit clear symptoms or signs, it is difficult to detect

these individuals in the population, which can lead to problems in preventing transmission. The second factor is the subjectivity of symptoms. Individuals with mild or atypical symptoms may think that have not been infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Hence, they will not take the initiative to seek medical help and are difficult to detect in routine clinical work. The third factor is the limitations of detection. Due to the presence of a testing window period, it is difficult to identify all Alls using nucleic acid and serological tests. The existing Alls in China have been primarily identified through active screening of individuals who had close contacts with confirmed cases, retrospective investigation of infection causes among patients, screening of individuals exposed to clustered outbreaks, and active testing of personnel in high-risk areas. However, identifying Alls remains a challenge.[13]

A number of epidemiological studies evaluating patients with COVID-19 have been published,[14-17] while only few studies on Alls have been conducted.[18] As Alls experience mild or no clinical symptoms, it is not possible to include the discovery and isolation of Alls as one of the leading measures for epidemic prevention and control in clinical practice.[13] Therefore, some Alls are not usually included in the prevention and control of the epidemic, thus increasing the difficulty and uncertainty in identifying and managing this group. Questions such as the role played by Alls in epidemic transmission, whether Alls can cause the sustained presence of COVID-19 in the population, and whether the management measures for Alls adopted by China can effectively curb the spread of the epidemic are all of great significance for a more profound understanding of the transmission mechanisms underlying the COVID-19 pandemic and for guiding the government in taking more precise measures to prevent and control the epidemic.

Based on the epidemiological characteristics of Alls, an individual-based stochastic computer model was established in this study to simulate the spread of the epidemic within the community, which incorporated some of the prevention and control measures adopted by China in response to Alls, in order to quantitatively analyze the impact of Alls on the development trends of the epidemic and to theoretically evaluate the effectiveness of the interventional measures. In addition, we want to explore consistent solution programmes during a regular epidemic, not only emergency prevention and control measures in case of an outbreak, because in the real world, non-special and urgent strict control measures may be the normal state of society.

2 Methods

2.1 Preconditions

The following preconditions were specified for model establishment: 1. The outbreak occurred within a closed community of 3,300 households and approximately 10,300 residents. The number of family members varied from 1 to 7, and followed a Poisson distribution with a mean of 3. Within the period of the study, no births (immigration) and deaths (emigration) were reported in the community, and the residents were generally susceptible to COVID-19. 2. All Alls and patients underwent the incubation

period, infection period, and recovery period. Both groups were not infectious during the incubation and recovery periods, and viral nucleic acid could not be detected in the respiratory tract specimens. Both groups were infectious during the infection period, and viral nucleic acid could be detected in respiratory tract specimens. 3. Patients who were diagnosed were quarantined in the hospital in order to receive appropriate treatment. Alls who were discovered were quarantined at home for 14 d. None of the current studies have provided a definite period in which the Alls become infectious; hence, the infection period of Alls was determined based on the symptomatic period of COVID–19 patients. Further, all family members of Alls were regarded as close contacts and were also quarantined for a maximum of 14 d, after which they were allowed to move freely. 4. Alls and patients developed an immunity after prolonged exposure to the virus and could not be re-infected with COVID–19. 5. The event involving the transmission from Alls or patients to susceptible persons during the infection period is a Poisson process with a rate of λ (where λ is the basic reproduction number divided by the infection period). The above parameter values and their statistical distributions are shown in Table 1.

2.2 Simulation

2.2.1 Infection

Alls and patients became sources of infection after an incubation period. They transmitted the virus to susceptible persons through daily contact with unquarantined residents in the community. We specified 6:00–18:00 each day as the time frame during which infection sources could randomly come into contact with unquarantined residents (including members of their own families), whereas between 18:00 and 6:00 the next day, infection sources could only randomly come into contact with their own family members. Once a susceptible person has been infected, they have a probability p of developing into a patient, with a basic reproduction number of R_1 , and a probability $1-p$ of developing into an All, with a basic reproduction number of R_0 .

2.2.2 Discovery

Patients were admitted to the hospital to receive treatment after the onset of illness, and their respiratory tract specimens were collected by physicians to test for COVID–19. Once the patients were diagnosed, the health department traced their infection sources and close contacts through epidemiological surveys. The infection sources and close contacts had a probability q of being traced; after that, they underwent laboratory testing for COVID–19. If the test results were negative, they were excluded. As viral nucleic acid cannot be detected in patients and Alls during the incubation and recovery periods, a proportion of people will remain undiagnosed.

2.2.3 Isolation

For cases where the infection sources or close contacts tested positive, those who showed clinical symptoms but had not received treatment were considered confirmed cases and were immediately sent to the hospital for quarantine and treatment; those who had yet to show clinical symptoms were regarded as Alls and quarantined at home and put under observation. In addition, all family members were also quarantined at home for 14 d from the time the confirmed cases and Alls were identified. During home quarantine, if another COVID-19 patients or Alls were discovered among the family members, those family members will be quarantined for another 14 d on the day of discovery. During home quarantine, none of the family members were allowed to come in contact with other residents, and only one family member was allowed to purchase their daily necessities while wearing a mask. If someone in the household was confirmed after the quarantine was lifted, then home quarantine was once again imposed based on the strategy described above. For the computer program used in the Methods section, please refer to the supplemental material.

2.3 Sensitivity analyses

We performed sensitivity analyses of five significant parameters to assess the impact on the attack rate. Partial rank correlation coefficients (PRCCs) and Latin hypercube sampling were used when performing sensitivity analyses. PRCC-LHS is an efficient and reliable sampling-based sensitivity analysis method that measures the monotonicity between a set of parameters and the model output after the removal of the linear effects of all parameters except the parameter of interest.[19, 20] Each parameter interval was divided into N smaller and equal intervals, and one sample was selected randomly from each interval.[19, 20] A standard coefficient denoting the correlation between the parameter and the model output was calculated. All analyses were conducted using MATLAB R2019a (The MathWorks, USA, 2019).

We study characteristics of COVID-19 epidemic spread in virtual environment, which is a theoretical simulated epidemiological model study. The research data are simulated by the computer, without using the real world population survey database. The parameter values needed to establish the model are partly derived from the author's inference and partly from the literatures, which are open source data (Table 1 for details).

3 Results

3.1 Epidemic caused by one case of imported All

3.1.1 Probability of community outbreak and incidence among residents

Outbreak was defined as the occurrence of more than 10 patients or more than 20 Alls within the community. There were 3,300 households within the community, and approximately 10,300 residents. Figure 1a1 shows that when $R_0 = 1.2$, $p = 0.2$, and $q = 0$, and under the conditions of an outbreak, the

median infection rate of Alls and median incidence rate of patients at 730 d of the epidemic were 0.22 and 0.06, respectively. As q increased, the infection rate and incidence rate decreased. When $q = 1$, their medians decreased to 0.01 and 0.005, respectively. Figure 1a2 shows that compared with $R_0 = 1$, when $R_0 = 1.2$, the probability of patients and Alls to cause an outbreak increases.

3.1.2 Temporal distribution of the cumulative number of new Alls and patients in the absence of interventions

Figure 1b shows that without the tracing of infection sources and close contacts and without the home quarantine of Alls, given the premise of a community outbreak, the cumulative number of Alls and patients during a community outbreak increased from almost 0 to 3,653 (25%–75% percentile [50% P]: 3,529–3,741) and 907 (50% P: 875–949), respectively.

3.1.3 Epidemic trends in the presence of interventions

Figure 1c shows that if the tracing of infection sources and close contacts and the home quarantine of Alls after detection were implemented, given the premise of a community outbreak, the number of Alls and patients increased to 1,381 (50% P: 1,092–1,620) and 340 (50% P: 272–414), respectively, when $t = 730$. In the absence of interventions, the medians of the two groups decreased by 62.2% and 62.5%, respectively. Figure 1d shows that the number of undetected Alls and patients initially increased, but eventually decreased to 0. The proportion of Alls and COVID–19 patients peaked at 302 d, reaching 53 (50% P: 27–71) and 20 individuals (50% P: 10–25), respectively. Moreover, Figure 1e shows that the number of quarantined individuals and households initially increased, but eventually decreased to 0. The peaks of the two groups appeared at 333 d, reaching 49 individuals (50% P: 26–65) and 14 households (50% P: 6–21), respectively.

3.2 Epidemic caused by 1,000 Alls in the presence of interventions

3.2.1 Temporal distribution of the number of new Alls and patients

Figure 2a shows that given the conditions of $p = 0.2$ and $q = 0.5$, when R_0 were 0.8, 1.2, and 1.6, the number of newly infected persons peaked at 13 d, 14 d, and 17 d, respectively, reaching 70 (50% P: 66–76), 81 (50% P: 74–87) and 91 individuals (50% P: 86–97). Figure 2b shows that the number of patients peaked at 13 d, 15 d, and 16 d, respectively, reaching 10 (50% P: 7–13), 16 (50% P: 13–19) and 21 individuals (50% P: 17–24), respectively.

3.2.2 Temporal distribution of the cumulative number of new Alls and patients

Figure 2c shows that when R_0 were 0.8, 1.2, and 1.6, the cumulative number of newly infected persons at 180 d of the epidemic reached 2,573 (50% P: 2,491–2,624), 3,854 (50% P: 3,766–3,933), and 4,971 individuals (50% P: 4,918–5,027), respectively. Figure 2d shows that the cumulative number of new patients at 180 d of the epidemic reached 392 (50% P: 373–408), 692 (50% P: 661–724), and 962 individuals (50% P: 933–986), respectively.

3.2.3 Temporal distribution of the number of undetected AIs and patients

Figure 2e shows that when R_0 were 0.8, 1.2, and 1.6, the number of undetected AIs in the infection period peaked within 3 d, 7 d, and 10 d of the epidemic, reaching 1,013 (50% P: 1,001–1,029), 1,173 (50% P: 1,150–1,188), and 1,391 individuals (50% P: 1,370–1,416), respectively. Figure 2f shows that the number of undetected patients in the infection period peaked at 10 d, 11 d, and 13 d of the epidemic, reaching 43 (50% P: 38–47), 66 (50% P: 60–71), and 92 individuals (50% P: 86–97), respectively.

3.2.4 Temporal distribution of the number of quarantined households and residents

Figure 2g shows that when R_0 were 0.8, 1.2, and 1.6, the number of quarantined households peaked at 20 d, 21 d, and 24 d of the epidemic, reaching 169 (50% P: 160–184), 258 (50% P: 244–269), and 345 households (50% P: 325–362), respectively. Figure 2h shows that the number of quarantined residents peaked at 20 d, 21 d, and 22 d of the epidemic, reaching 571 (50% P: 525–628), 888 (50% P: 838–924), and 1,208 individuals (50% P: 1,130–1,272), respectively.

3.3 Sensitivity analyses

In this study, sensitivity analyses of the five parameters and a continuous time series of the sum of asymptomatic infected individuals and patients each day were conducted. We took 500 samples from a uniform distribution for each parameter range. PRCCs near -1 or $+1$ indicate that the parameter has a strong negative or positive impact on the output, respectively, whereas those closer to 0 indicate less effect on the output result for that parameter (Figure 3). The results reflected that R_0 , R_1 , and p had positive effect on the model outputs; meanwhile, λ and q had a negative effect on the model outputs.

4 Discussion

4.1 Advantages of this study

Firstly, the individual-based computer model combines the covertness and infectivity of Alls who underwent preventive and control measures such as tracing, treatment, and quarantine, which made the model more compatible with the actual conditions of the epidemic prevention and control. Secondly, the model randomly assigns the parameters for the daily activities and disease characteristics of residents, as well as medical treatment according to their respective statistical distributions, which gives the model richer and more powerful analytical capabilities compared with the traditional dynamic models. Thus, the results of the model will provide more precise guidance for the government's undertakings in preventing and controlling the disease. Thirdly, there is a current lack of epidemiological studies on Alls, therefore, using computer simulations to quantitatively analyze the epidemiological distribution of Alls and patients in the population, we have provided a preliminary solution to address the international concerns of coping with Alls.

4.2 Epidemiological analysis of an outbreak caused by one case of imported All

The results in Figure 1a show that when one case of imported All is reported in a community, the probability of an epidemic outbreak decreases with the increase in parameter q . This finding reflects the fact that tracing the infection sources and close contacts of patients not only enables the early discovery of Alls and patients in the community, but also lays the foundation for the timely isolation of Alls at home and the isolation of patients for treatment. This, in turn, will reduce the probability of epidemic outbreaks and the incidence rates among residents. In addition, the probability of outbreak is related to the infection time of the imported All; that is, the earlier the infection time, the shorter the infection period in the community, and the lower the probability of an epidemic outbreak. The model randomly assigns the infection time, which ensures the objectivity of the results to a certain extent.

The results in Figure 1b and 1c show that in the absence of any intervention measures, where Alls and patients are allowed to transmit the disease in the community, about 44% of residents will be infected with COVID-19 in the event of an outbreak. In the presence of intervention measures, i.e., though the infection sources and close contacts of patients have a 50% chance of being discovered, the proportion of infected residents decreased by 62% in the event of an outbreak compared with the absence of such measures. This finding once again confirms that prevention and control measures can significantly reduce the risk of infection among the residents.

Undetected Alls and patients are the primary sources of infection during an epidemic, and understanding the temporal distribution characteristics of their numbers is of significant value to predicting the epidemic trends. Furthermore, determining the number of quarantined individuals and households will facilitate the government's rational allocation of livelihood materials and safeguard the normal daily routine of quarantined individuals. The results in Figure 1d and 1e show that the number of undetected Alls and patients, as well as the number of quarantined residents and households initially increased, but

eventually decreased to 0. This finding indicates that as long as the normalization of such measures are maintained, the epidemic will be eventually controlled.

4.3 Epidemiological analysis of an outbreak caused by 1,000 AIs

The results of Figure 2 show that the number of new and undetected AIs and patients, as well as the number of quarantined households and individuals showed a rapid initial growth, followed by a slow decline to 0. The primary cause for this trend is that the early stage of the outbreak is dominated by the community transmission of COVID-19 by patients and AIs. With the continuous tracing of patients and AIs for quarantine, the number of freely moving infection sources will not only reduce, but the transmission routes of the virus will also be eliminated, thereby gradually controlling the epidemic.

4.4 Sensitivity analyses

The results of the sensitivity analyses showed that the PRCCs of R_0 always remained close to 1, indicating that the basic reproduction number of AIs has a substantial impact on the total number of infected persons. The PRCCs of R_1 were slightly lower than those of R_0 . This may be because although R_1 was greater than R_0 , patients accounted for a smaller proportion of infected persons compared with AIs, which restricted the contribution of the number of patients to the growth in the number of infected persons. In addition, a larger p value resulted in a greater number of patients; hence, patients with greater infectivity increased number of infected persons. As q increased, the number of AIs and patients detected increased, which reduced the number of newly infected persons. The length of tracing time t^* had a relatively small effect on the total number of infected persons.

4.5 Study limitations

Firstly, the model does not take into account the investigation of individuals exposed to clustered outbreaks. This is because the design of this model is not suitable for the simulation of clustered outbreaks, and a new model must be established for such analyses. Secondly, this model does not take into account the active screening of key populations. This is because most countries do not carry out mandatory pathogenic testing of their populations; hence, this program is not universally implemented. Thirdly, AIs are still infectious during home quarantine and will infect their family members. Therefore, appropriate measures must be adopted in accordance with the national conditions of each country. Lastly, due to constraints on computing power, this model is limited to a closed community. However, during the epidemic, most countries and regions have adopted policies such as restricting movement across borders, strict home quarantine, and so on. Therefore, most regions can be considered to be relatively closed, and the results of this study are applicable to areas with epidemic outbreaks where restrictions on population movement and personnel activities have been imposed.

5 Conclusion

In summary, when one case of imported All is reported in the community, the probability of an epidemic outbreak is low. The implementation of sustained prevention and control measures can significantly reduce the risk of infection among the residents. The number of new and undetected Alls and patients will both undergo an initial increase, followed by a decrease, finally disappearing completely.

Declarations

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Competing interests

The authors declare that they have no competing interests.

Ethical Approval

The study is a theoretical epidemiological model study and does not need to be reviewed by the ethics committee. The database is provided in Table 1 that is an open source data.

Contributions

Guo ZY designed the study, analyzed the data, and wrote the manuscript; Xiao D reviewed the manuscript and provided many comments.

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Table

Table 1. Model parameters

Description	Distribution characteristics	Numerical values	Sources
Basic reproduction number of AIs (R_0)	none	0.8, 1.2, 1.6	Inferred
Basic reproduction number of patients (R_1)	Uniform distribution	4–5	Inferred according to our previous study
Probability of newly infected persons developing into patients (p)	Bernoulli distribution	0.2	Inferred according to [21]
Probability of tracing the infection sources of individuals who were in close contacts with the patients (q)	Bernoulli distribution	0.5	Inferred
The duration from the time the patient first sought medical attention until the time their infection source or close contacts have been traced (τ)	Uniform distribution	1–2	Inferred
Infection period of AIs	Uniform distribution	15–20	Inferred according to [22]
Incubation period of AIs and patients	Lognormal distribution		[23]
Infection period (time from disease onset to seeking medical attention)	Weibull distribution		[23]
Number of family members	Poisson distribution		Inferred

Figures

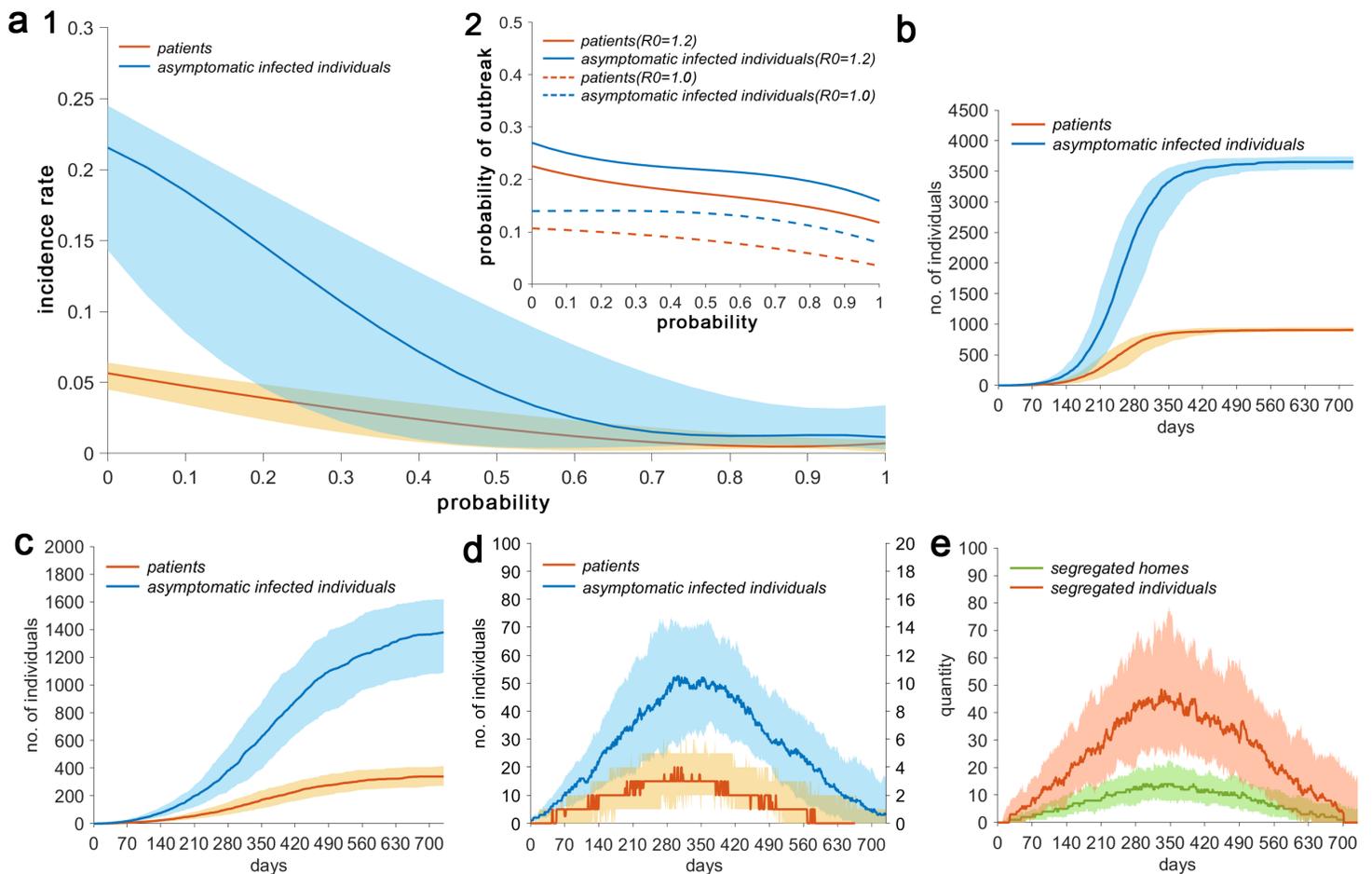


Figure 1

Transmission of an epidemic caused by one case of imported All Legends: a1 Given $R_0=1.2$, $p=0.2$, $t=730$ d, and in the presence of prevention and control measures, the effect of parameter q on the infection rate of Alls and incidence rate of patients during an epidemic outbreak (cumulative number of new Alls more than 20 or cumulative number of new patients more than 10). a2 Given $R_0=1.2$, 1.0, and in the presence of measures, the effect of parameter q on the probabilities of Alls and patients causing an epidemic outbreak. b Given $R_0=1.2$ and in the absence of any measures, the temporal distribution of the cumulative number of new Alls and patients during an epidemic outbreak. c Given $R_0=1.2$ and in the presence of measures, the temporal distribution of the cumulative number of new Alls and patients during an epidemic outbreak. d Given $R_0=1.2$ and in the presence of measures, the temporal distribution of the number of undetected Alls and patients. e Given $R_0=1.2$ and in the presence of measures, the temporal distribution of the number of quarantined households and residents during an epidemic outbreak.

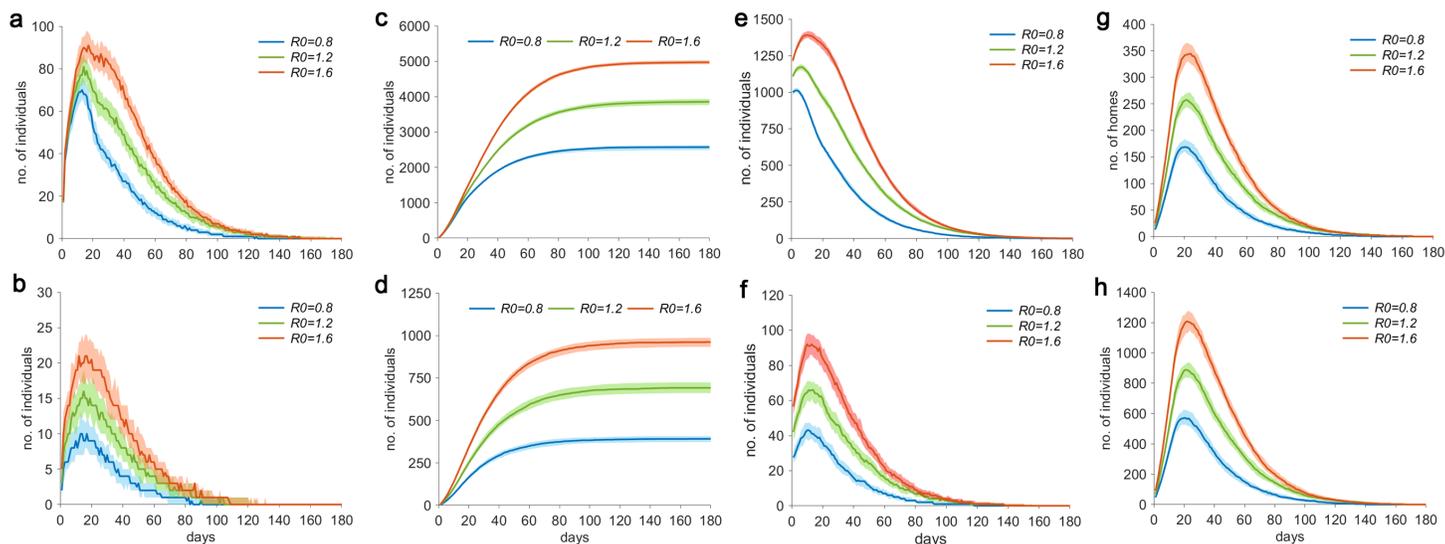


Figure 2

Given $p=0.2$, $q=0.5$, an initial number of 1,000 AIs, and in the presence of prevention and control measures, the transmission characteristics of the epidemic for different values of R_0 Legends: a Temporal distribution of the number of new AIs. b Temporal distribution of the number of new patients. c Temporal distribution of the cumulative number of new AIs. d Temporal distribution of the cumulative number of new patients. e Temporal distribution of the number of undetected AIs. f Temporal distribution of the number of undetected patients. g Temporal distribution of the number of quarantined households. h Temporal distribution of the number of quarantined residents.

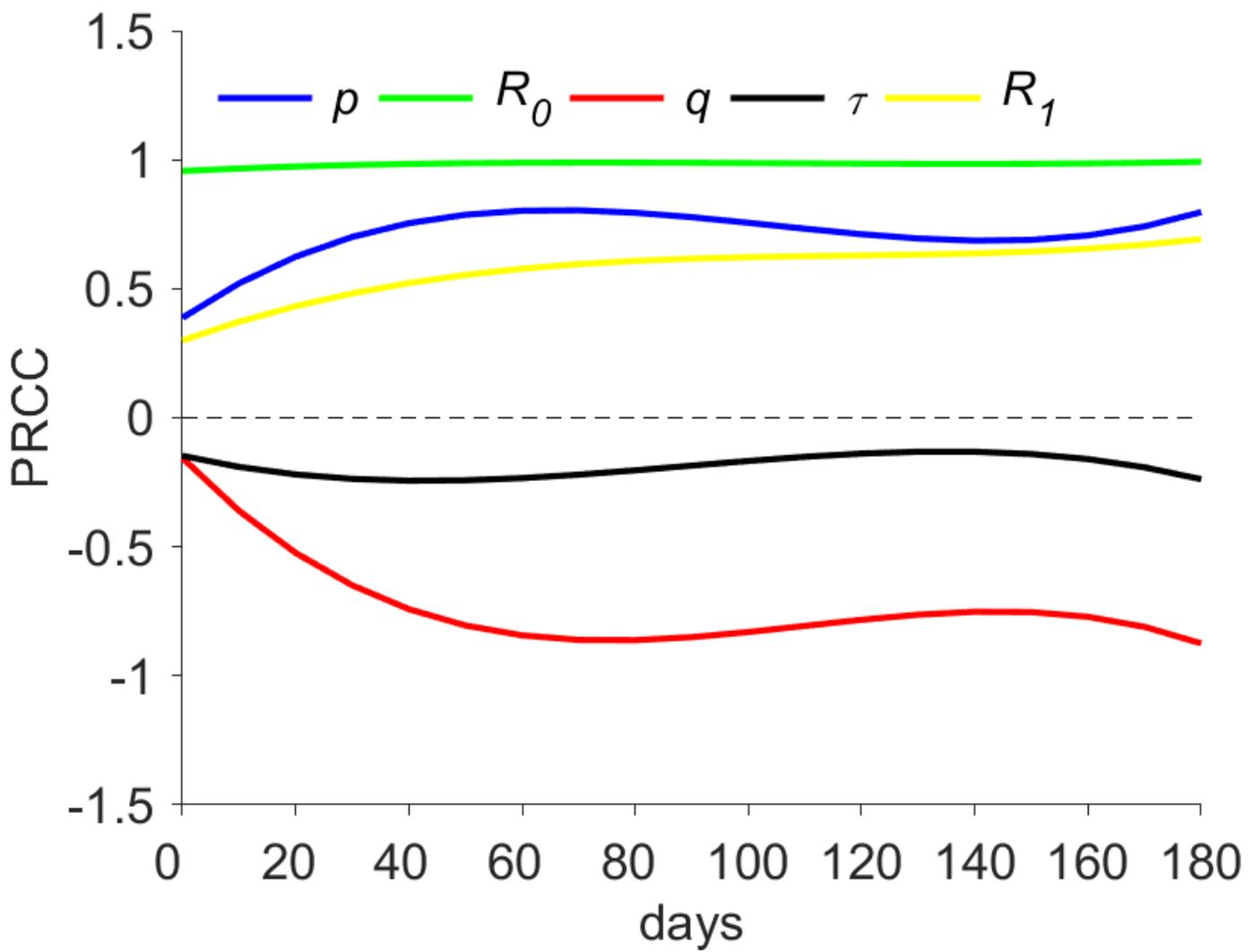


Figure 3

Results of continuous-time sensitivity analyses

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