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Modeling the initial transmission dynamics of influenza A H1N1 in Guangdong Province, China

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SUMMARY

Background: The novel influenza A H1N1 (2009) virus, identified in mid-2009, spread rapidly in Guangdong Province. The accurate estimation of epidemiological parameters is of vital significance in decision-making for coping with pandemic influenza.
Methods: We used influenza A H1N1 epidemic data from local cases in Guangdong Province, China, in conjunction with a complex SEIR model (susceptible, exposed, infectious, recovered) to estimate the basic reproduction number. The transmission rate was obtained by fitting the model to the cumulative number of local daily infected cases using the nonlinear ordinary least squares method. The latent period and duration of infectiousness were obtained from the published literature, and the proportion of symptomatic infected cases was obtained from the serological survey conducted by the Center for Disease Control and Prevention of Guangdong Province. We determined the variance of model parameters via a simulation study.
Results: The model was in keeping with the observed epidemic data (coefficient of determination = 0.982). The basic reproduction number was estimated preliminarily to be $R_0 = 1.525$ (95% confidence interval 1.448–1.602), with the possible range of true R_0 being 1.30–1.85. We estimated the transmission rate β to be between 0.390 and 0.432.
Conclusions: With the help of the serological survey, useful estimates of key epidemiological parameters for the influenza A H1N1 outbreak in Guangdong Province were obtained. The sensitivity analysis suggests that different latent periods and infectious periods, which specify different mean durations of generation time, have a significant impact on R_0. Our proposed model and findings provide a relevant contribution towards understanding the characteristics of influenza A H1N1 in Guangdong Province.

1. Introduction

The influenza A H1N1 virus, a new influenza virus, was first identified in April 2009 in Mexico and the USA, and a pandemic was declared by the World Health Organization (WHO) on June 11, 2009. The first confirmed case of pandemic influenza A H1N1 in Guangdong Province was recorded on May 18, 2009 in Guangzhou, in a traveler who had returned from the USA and Canada. The first local case in Guangdong was notified on May 30, almost 2 weeks after the first case was confirmed. Following preliminary tests carried out by the Center for Disease Control and Prevention of Guangdong Province (CDC), it was revealed that effective contact with an infectious individual was the only path for the transmission of the influenza A H1N1 virus. As this virus is highly infectious, it was essential that the government put in place strategies to mitigate and control the disease in the face of uncertainty.

For a new infectious disease, working out the epidemiological parameters can help in decision-making. A key parameter for any novel infectious disease is the basic reproduction number (R_0), defined as the average number of secondary cases generated by a single primary case during its entire period of infectiousness in a completely susceptible population.[1] R_0 directly determines the growth rate of an epidemic and the final number of infected people, and is a predominant factor to be considered in optimal strategy-making. The estimation of the basic reproduction number is problematic and has gained much attention, and a few methods have been proposed to estimate R_0. One method relies on the distribution of the generation interval and the observed epidemic growth rate to estimate R_0.[2] Specifically, the shape of the generation interval distribution determines the formula for

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estimating R_0. Another method uses the sequential Bayesian procedure of the stochastic SIR (susceptible, infectious, recovered) model, which assumes homogeneous mixing of the population, to estimate the posterior probability distribution of the effective reproduction number. This method has recently been applied to the real-time monitoring of emerging infectious diseases,[3] via a Bayesian inference scheme. The third method proposes a structured epidemic model (e.g., SIR and SEIR (susceptible, exposed, infectious, recovered) model), which demands homogeneous mixing between individuals, to calculate R_0. The strength of this type of method is that they originally assume a detailed structure which complies with the realistic representation of transmission dynamics of pandemic influenza A H1N1 (e.g., asymptomatic infection) and qualify the effects of intervention strategies (e.g., vaccination) in the future. In addition, a previous study based on a SEIR model concluded that estimates of the reproductive number were not affected by age-specific transmission rates and case-fatality proportions in the pandemic influenza of 1918 in Geneva, Switzerland.[4]

In Guangdong Province the available epidemiological information (e.g., the mixing matrix among age groups, the vector of susceptibility by age) is not sufficient to validate a detailed age-structured deterministic compartmental model for the transmission of pandemic influenza. Furthermore, we have a limited knowledge of the precise shape of the generation interval distribution in Guangdong Province and so cannot estimate R_0 using the intrinsic growth rate. Thus, in the estimation procedures, we must rely on a complex SEIR model within broader model assumptions. Under the condition of understanding epidemiological mechanisms that characterize the influenza dynamics, the complex SEIR model is a more effective and reliable approach to estimating R_0 preliminarily, especially in the initial phase of an epidemic.[5] Besides, during the early epidemic period, the proportion of asymptomatic and partially infectious cases may be difficult to estimate because of difficulties in identification. Therefore, it is crucial to take into account the accurate serological estimation of the proportion of asymptomatic cases in estimating R_0 via the complex SEIR model.

In this study, a compartmental model was constructed to approximately predict or reproduce the dynamics of the influenza A H1N1 virus in the population of Guangdong Province. It is important to mention that few previous researchers have constructed the dynamic model for notifications of individuals with influenza A H1N1 virus in Guangdong Province for parameter estimation. In this study, the transmission dynamics in the initial phase of influenza were modeled using a compartmental model accounting for the known possibility of limited transmission from the exposed class. Furthermore, an estimation of the basic reproduction number (R_0) for pandemic influenza A H1N1 was made with the data from initial reports of laboratory confirmed pandemic influenza A H1N1. Some of the model parameters were estimated via nonlinear ordinary least squares (NOLS) fitting.

2. Materials and methods

2.1. Data collection

We collected individual-level data of laboratory confirmed cases of pandemic influenza A H1N1 in Guangdong, with the reported date of diagnosis between May 18 and June 30, 2009. This cutoff was chosen because the first wave occurred in June 2009 and the strategy of individual-level reporting of cases in Guangdong Province underwent major modifications after this date (Figure 1). The data were obtained from the Integrated Public Health Information System of the Province, a system that incorporates data provided by medical units engaged in the investigation of pandemic influenza A H1N1. Through the Public Health Information System it was found that effective isolation and tracking strategies were adopted for imported cases after the first case was confirmed. In order to analyze transmission dynamics in the local cases, the number of imported cases was eliminated from the total number.

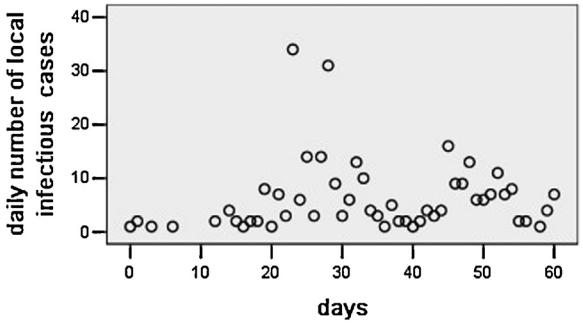

Figure 1. Daily number of symptomatic infectious notifications.

2.2. Epidemic model

In this study, pandemic influenza A H1N1 in Guangdong Province, China was modeled using a compartmental model based on a more complex SEIR model.[6–8] In this model for the transmission dynamics of pandemic influenza (Figure 2), individuals are classified as susceptible ($S(t)$), exposed ($E(t)$), symptomatic infectious ($I(t)$), asymptomatic and partially infectious ($A(t)$), and recovered ($R(t)$). It is assumed that individuals who have been infected first go into a latent (exposed) stage, during which they may have a low level of infectivity. In addition, our model includes two additional properties. Firstly, some proportion of the latent individuals never develop symptoms but go directly from the latent class to the asymptomatic and partially infectious class and then to the recovered class. Secondly, the time-scale of the epidemic is much faster than characteristic times for demographic processes. In our model, the rate at which susceptible individuals in contact with the virus progress to the latent stage is given by $\beta(qE(t) + I(t) + A(t))/N(t)$, β being the transmission rate and q a reduction factor in the transmissibility of the exposed class. Moreover, the total population size at time t is given by $N(t) = S(t) + E(t) + I(t) + A(t) + R(t)$. A proportion $0 < p < 1$ of exposed individuals progress to infectious class $I(t)$ at the rate δ and the rest $(1 - p)$ go to the asymptomatic and partially infectious class $A(t)$ at the same rate. Symptomatic and asymptomatic cases progress to the recovered class at the rates γ_1 and γ_2, respectively. Finally it is considered that an individual acquires permanent immunity after recovery.

In modeling the transmission process (for the initial influenza wave), the following system of nonlinear differential equations was employed:

$$\begin{aligned}
\frac{dS(t)}{dt} &= -\beta S(t)\frac{qE(t) + I(t) + A(t)}{N(t)} \\
\frac{dE(t)}{dt} &= \beta S(t)\frac{qE(t) + I(t) + A(t)}{N(t)} - \delta E(t) \\
\frac{dI(t)}{dt} &= p\delta E(t) - \gamma_1 I(t) \\
\frac{dA(t)}{dt} &= (1 - p)\delta E(t) - \gamma_2 A(t) \\
\frac{dR(t)}{dt} &= \gamma_1 I(t) + \gamma_2 A(t) \\
\frac{dC(t)}{dt} &= p\delta E(t)
\end{aligned} \tag{1}$$

The cumulative number of symptomatic infectious notifications, our observed data, is given by $C(t)$. All parameters used in the differential equations are listed in Table 1.

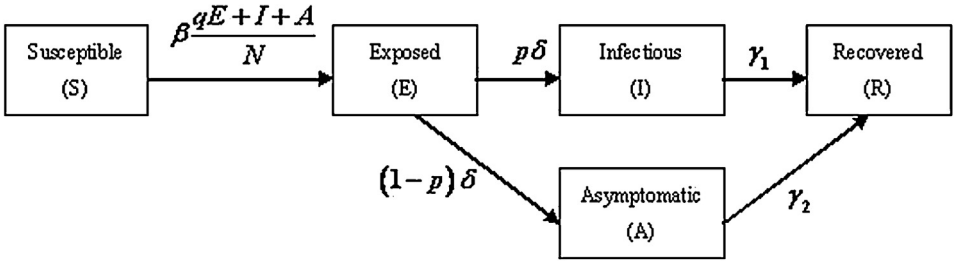

Figure 2. Flow chart of the progression of individuals in the different epidemiological classes as modeled by equation 1.

2.3. The basic reproduction number

The basic reproduction number (R_0), the expected number of secondary infections produced by an index case in a completely susceptible population, is a key factor used in estimating the transmissibility of infectious diseases. If $R_0 > 1$, it suggests that an epidemic can occur. It can be demonstrated by applying the next-generation method[9–11] to our model equations that the basic reproduction number is:

$$R_0 = \beta(q/\delta + p/\gamma_1 + (1-p)/\gamma_2) \quad (2)$$

Given the reduction factor q in the exposed class and δ, γ_1, γ_2, we can conclude that R_0 is a function of β. An estimation of R_0 is made from the data by substituting the parameters into equation 2.

2.4. Parameter estimation

In order to adjust the model to time-series data of confirmed cases of pandemic influenza A H1N1, it is necessary to set some parameter values. In our model the birth and natural death rates were ignored and the age distribution profile (shown in Figure 3) in Guangdong Province was similar to that in the province of Ontario, so the mean latent period in the exposed classes $E(t)$ was assumed to be 2.62 (95% confidence interval (CI) 2.28–3.12) days.[12] Therefore, the infected rate δ was considered to be $\delta = 1/2.62$. On the other hand, of all the cases in Guangdong Province, most symptomatic ones were characterized by mild infections and symptoms. Moreover, in a previous similar study on pandemic influenza,[8] the same rates were used to reflect recovery rates of symptomatic and asymptomatic cases. Thus, it was considered that symptomatic cases recovered at the same rate as asymptomatic cases, and the mean duration of infectiousness was fixed to $1/\gamma_1 = 1/\gamma_2 = 3.38$ days (95% CI 2.06–4.69),[12] which indicates that the duration of infectiousness might be curtailed by hospitalization or self-isolation prior to recovery. Owing to influenza virus shedding (the time during which a person might be infectious to another person) at the end of the latent period, the possibility of limited transmission from exposed class q was fixed to 1/8 in a rather crude way.[13]

According to the serological survey conducted by the Guangdong CDC, the proportion of symptomatic infectious cases p was fixed to 60.2%. The serological survey was conducted during the period January 11–24, 2010. In this cross-sectional serological survey, the serum samples, distributed across 144 residential areas, 85 streets or townships, 25 counties, and 21 cities, were collected by multistage stratified random sampling. Antibodies against the pandemic influenza A H1N1 virus were detected by hemagglutination inhibition (HI) assay, in accordance with the standards of the WHO National Influenza Center. During this period, a total of 4725 serum samples were collected from subjects who had not been vaccinated with the influenza A H1N1 vaccine. One thousand one hundred eighty-five cases were seropositive for pandemic influenza A H1N1 antibodies, including 472 asymptomatic patients ($1 - p = 39.8\%$).

The transmission rate β was estimated through NOLS fitting of $C(t,\beta,E(0))$ in model 1 to the cumulative cases of pandemic influenza A H1N1 (Figure 4). To guarantee that the global minimum of this model could be achieved, we repeated the optimization 10 times starting at randomly drawn parameter values from appropriate parameter ranges. For the NOLS fitting procedure, we used the Marquardt–Levenberg method with the line-search implemented in MODEL procedure of SAS 9.2 (SAS Institute Inc.), which analyzes models in which the relationships among the variables comprise a system of one or more nonlinear equations.

The method to generate uncertainty bounds on parameters was the calculation of bootstrap confidence intervals by generating sets of realizations of the best-fit curve $C(t)$.[14] Each realization of the $C_i(t)$ ($i = 1, 2, \ldots, m$) was generated using the increment in the real $C(t)$ from day i to day $i+1$ as the Poisson mean for the number of new case notifications observed in the i to $i+1$ interval.[8] The parameter estimation procedure (described above) was then applied to each of the 1000 simulated realizations.

Table 1
Parameter definitions in the differential equations

Parameter	Definition
β	Transmission rate
q	Relative measure of infectiousness for the class E
δ	Infected rate
γ_1, γ_2	Recovery rate for infectious and asymptomatic classes, respectively
p	Proportion of symptomatic infection

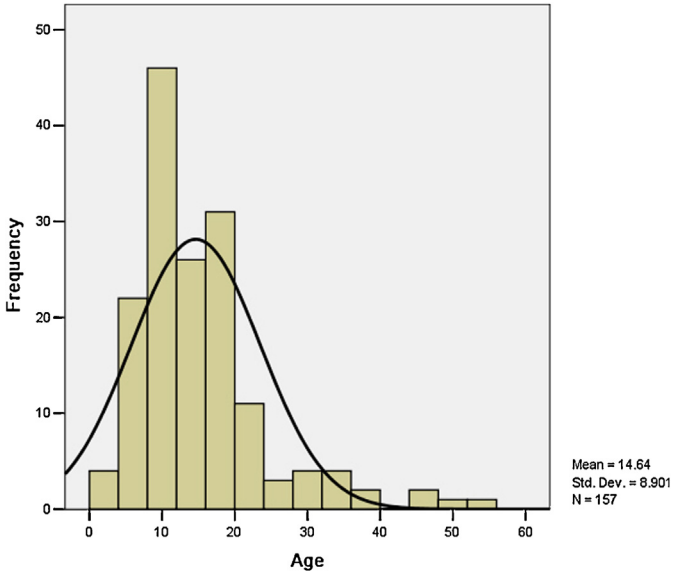

Figure 3. Age distribution of 157 laboratory-confirmed cases of pandemic influenza A H1N1 in Guangdong Province between May 18 and June 30, 2009.

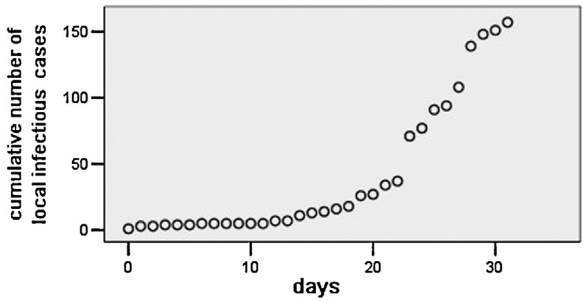

Figure 4. The cumulative number of symptomatic infectious notifications.

Table 3
Characteristics of cases of pandemic influenza A H1N1 in Guangdong Province

Demographic characteristics	*n*	Percentage
Gender		
Male	92	58.6
Female	65	41.4
Region(city)		
Guangzhou	56	35.7
Dongguan	56	35.7
Jiangmen	27	17.2
Foshan	11	7.0
Shenzhen	3	1.9
Zhuhai	3	1.9
Shantou	1	0.6

The estimation of the model requires information about epidemiological parameters of disease progression (γ_1, γ_2, δ, q). Moreover, the mean duration of the generation time reported by Tuite et al.[12] was much longer than that in other studies, so $\delta = 1/2.62$ and $1/\gamma_1 = 1/\gamma_2 = 3.38$ may not be the best choice. Thus, given that the estimates of the serial interval and R_0 are often correlated, we considered different possible combinations of epidemiological parameter values (γ_1, γ_2, δ) estimated for other strains of influenza (Table 2), which indicated different possible estimates of the serial interval of influenza A H1N1 virus infection. In other words, we changed the latent period and infectious period so as to adjust the mean generation time.

3. Results

A total of 157 laboratory-confirmed cases were included in this study. The mean age of the patients was 14.6 (standard deviation 8.9) years. The age distribution is presented in Figure 3 and the detailed demographic characteristics of the patients are presented in Table 3. Figure 3 shows that the age distribution profile of confirmed cases from Guangdong Province is similar to that in the province of Ontario.

The model employed in this study for the local influenza notifications between May 30 and June 30, 2009 in Guangdong Province, China was in conformity with the observed cumulative epidemic data (coefficient of determination = 0.982; Figure 5). The histogram of the residuals as shown in Figure 6 indicates that the normality assumption could be true.

During the early transmission of pandemic influenza A H1N1, we estimated epidemiological parameters through NOLS fitting of the model to the cumulative number of daily laboratory confirmed notifications. The resulting parameter estimates are listed in Table 4, and the best model fit to the data is shown in Figure 5. Using our expression of the basic reproduction number, it was revealed that R_0 for the initial wave in Guangdong Province = 1.525 (95% CI 1.448–1.602), consistent with most analyses of data from Mexico (R_0: 1.2–1.6)[15,16] and Vietnam (R_0: 1.5–1.6).[17]

To test the sensitivity of the assumed estimates (γ_1, γ_2, δ, q), we re-estimated R_0 several times using different combinations of parameter values from two studies reported in the literature (given in Table 2). Table 2 shows the variation of R_0 for nine different combinations. It was found that the parameters with the greatest impact on the estimated basic reproduction number were the latent period and the duration of infectiousness. When

Table 2
Sensitivity analysis with different baseline values of epidemiological parameters

Ref.	Combination of parameters	Estimated β, 95% CI	Estimated $E(0)$, 95% CI	Estimated R_0, 95% CI
12	$\delta = 1/2.62$ $\gamma_1 = \gamma_2 = 1/3.38$ $q = 1/4$	0.371 (0.353–0.389)	8.733 (5.842–11.624)	1.495 (1.422–1.568)
12	$\delta = 1/2.62$ $\gamma_1 = \gamma_2 = 1/3.38$ $q = 1/8$	0.411 (0.390–0.432)	9.191 (6.399–11.983)	1.525 (1.448–1.602)
12	$\delta = 1/2.62$ $\gamma_1 = \gamma_2 = 1/3.38$ $q = 0$	0.462 (0.438–0.486)	9.707 (6.932–12.482)	1.563 (1.483–1.643)
12	$\delta = 1/2.62$ $\gamma_1 = \gamma_2 = 1/4.69$ $q = 1/4$	0.304 (0.287–0.321)	10.044 (6.933–13.155)	1.626 (1.535–1.717)
16	$\delta = 1/3$ $\gamma_1 = 1/7$, $\gamma_2 = 1$ $q = 1/4$	0.334 (0.315–0.353)	11.070 (7.535–14.605)	1.792 (1.688–1.896)
16	$\delta = 1/3$ $\gamma_1 = 1/7$, $\gamma_2 = 1$ $q = 1/8$	0.371 (0.347–0.395)	11.686 (8.049–15.323)	1.851 (1.732–1.970)
16	$\delta = 1$ $\gamma_1 = \gamma_2 = 1/2.5$ $q = 1/8$	0.494 (0.477–0.511)	4.827 (3.217–6.437)	1.297 (1.254–1.340)
16	$\delta = 1$ $\gamma_1 = 1/4$, $\gamma_2 = 1$ $q = 1/8$	0.473 (0.453–0.493)	5.417 (3.323–7.511)	1.386 (1.327–1.445)
16	$\delta = 1$ $\gamma_1 = 1/4$, $\gamma_2 = 1$ $q = 1/4$	0.448 (0.432–0.464)	5.233 (3.380–7.086)	1.370 (1.323–1.417)

95% CI, 95% confidence interval.

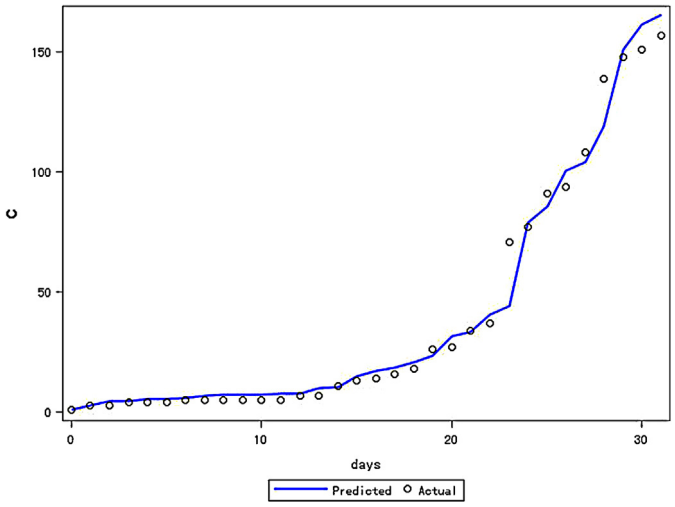

Figure 5. The best fit solution obtained by fitting $C(t)$ (solid line) in equation 1 to the cumulative number of symptomatic infectious notifications for the initial phase of the influenza A H1N1 pandemic of 2009 in Guangdong Province, China. The coefficient of determination is 0.982.

the latent period and infectious period were shortened (shown in the last three rows, Table 2), which implied the mean generation time was reduced to around 3 days, R_0 gradually decreased to around 1.3. The effect of the parameter q on the basic reproduction number of the initial phase was assessed by modifying the relative infectiousness of the exposed class. It was found that if the possibility of limited transmission from the exposed class was increased by 100%, the basic reproduction number would be reduced to 1.495.

4. Discussion

The major objective of this study was to determine whether our proposed compartmental epidemic model with homogeneous mixing could fit to the series data of pandemic influenza A H1N1 virus in Guangdong Province, China. Clearly, in view of the data currently available, the complex SEIR model provides a more practical tool for the approximate estimation of key epidemiological parameters and it seems likely that in future outbreaks, local decision-makers would be informed by the same kind of data. Thus, based on our proposed compartmental

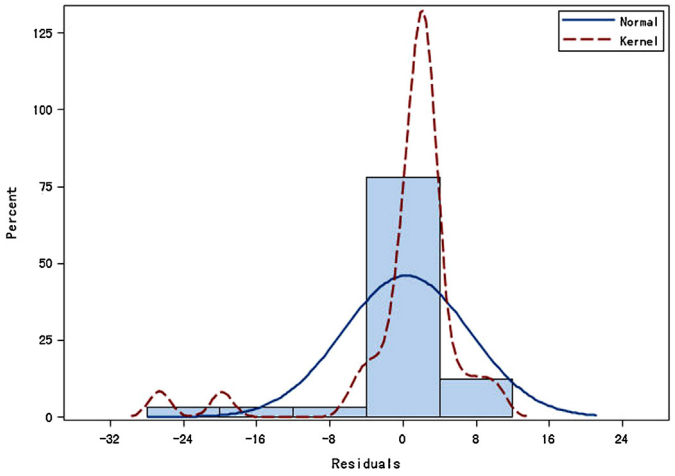

Figure 6. Histogram of residuals for the cumulative number of symptomatic infectious notifications.

Table 4
Parameter definitions and NOLS estimates for the influenza A H1N1 pandemic of 2009 in Guangdong Province, China

Parameter	Definition	Method	Estimate	95% CI
β	Transmission rate	NOLS	0.411	0.390–0.432
$E(0)$	Initial number of exposed individuals	NOLS	9.191	6.399–11.983
R_0	Basic reproduction number	-	1.525	1.448–1.602

95% CI, 95% confidence interval; NOLS, nonlinear ordinary least squares.

epidemic model, the history of daily case reports in Guangdong Province is informative to estimate the basic reproduction number and is also helpful in explaining the characteristics of influenza A H1N1 in Guangdong Province. In addition, with the help of the basic reproduction number estimated from our proposed model, we can give the Guangdong CDC valuable information about the progression and likely size of a disease outbreak. Furthermore, by utilizing the information concerning the ranges of the calculated transmission rate and basic reproduction number, we suggest that the Guangdong CDC should classify the common infectious diseases and establish corresponding emergency response plans and utilize them to assist in prioritizing prevention services. This means that the intensity of interventions will correspond to changes in R_0 and β. However, our model has some limitations in the following aspects. First, our model described above is homogeneous with respect to the age structure, which may have some impact on accurately estimating R_0. Second, our estimation of the epidemiological parameter values from the published literature may be a little biased. Finally, owing to limitations of the surveillance system, we do not have enough information and other datasets to check our estimates, hence we have just discussed the possible range of R_0.

On the basis of the data from the initial confirmed symptomatic cases of pandemic influenza A H1N1, our estimates demonstrate that the differences between the characteristics of this novel influenza virus in Guangdong Province and those of other regions are not significant. Our preliminary estimate of R_0 for the initial stage is similar to that reported in the USA[18] and in Shaanxi Province, China,[19] but lower than the values of R_0 reported in Japan[20] and New Zealand.[21]

Our analyses show that potentially biased estimation of the epidemiological parameter values (γ_1, γ_2, δ) can overestimate or underestimate the true basic reproduction number to some degree. Therefore, it is essential that the public health agencies of Guangdong Province continue to collect high-quality epidemiological data to guarantee the accurate estimation of epidemiological parameter values. On account of calculating R_0 with different combinations of epidemiological parameter values, we have full reason to believe that the possible range of R_0 in Guangdong is from 1.30 to 1.85 (shown in Table 2). In the meantime, Table 2 also implies that different combinations (γ_1, γ_2, δ) specify different mean durations of the generation time; thus we should be careful in using the range of latent period and the mean duration of infectiousness when calculating R_0. On the other hand, a reduction in the value of the relative infectiousness of the exposed class (q) could not result in the undue fluctuation of R_0. This can be explained by the fact that R_0 is robust to variation in the parameter q.

As with normal seasonal influenza, pandemic influenza A H1N1 in Guangdong Province showed a large proportion of mild or asymptomatic infections, similar to other regions affected by the influenza A H1N1 epidemic. Our model enables us to evaluate the impact of the proportion of asymptomatic infections on epidemiological parameter R_0. However, as the epidemic progressed, necessary interventions or mitigation strategies (e.g., social

distancing) could have been implemented to control the epidemic and considerably reduce the final size of the epidemic.[22,23] Moreover, public concern over the pandemic might have influenced population behavior or medical practices, resulting in a significant reduction in the observed reproduction number. Therefore, our R_0 could be lower than the true value for pandemic influenza A H1N1 in Guangdong Province, China. In addition, imported cases were removed from the calculations, which could have led to an overestimate of the true R_0, as too much transmission was assigned to local cases.[24]

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