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Control measures during the COVID-19 outbreak reduced the transmission of hand, foot, and mouth disease

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ABSTRACT

Control measures during the coronavirus disease 2019 (COVID-19) outbreak may have limited the spread of infectious diseases. This study aimed to analyze the impact of COVID-19 on the spread of hand, foot, and mouth disease (HFMD) in China. A mathematical model was established to fit the reported data of HFMD in six selected cities in mainland China from 2015 to 2020. The absolute difference (AD) and relative difference (RD) between the reported incidence in 2020, and simulated maximum, minimum, or median incidence of HFMD in 2015–2019 were calculated. The incidence and R_{0} of HFMD have decreased in six selected cities since the outbreak of COVID-19, and in the second half of 2020, the incidence and R_{0} of HFMD have rebounded. The results show that the total attack rate (TAR) in 2020 was lower than the maximum, minimum, and median TAR fitted in previous years in six selected cities (except Changsha City). For the maximum, median, minimum fitted TAR, the range of RD (%) is 42.20–99.20%, 36.35–98.41% 48.35–96.23% (except Changsha City) respectively. The preventive and control measures of COVID-19 have significantly contributed to the containment of HFMD transmission.

1. Introduction

Hand, foot, and mouth disease (HFMD) is an acute infectious disease caused by the Coxsackie virus and human enterovirus [1]. It usually occurs in children under five years of age. It spreads rapidly and widely, and is mainly spread through the respiratory tract, nose, mouth, and other secretions. In addition, studies have shown that close contact with patients with HFMD and long-term living in nursery institutions or schools also contributes to the spread of HFMD among children [2]. Since 2010, the number of HFMD cases and deaths has been ranked first in China’s category C infectious diseases [3]. This infectious disease not only seriously threatens the health of children, but also poses as a certain economic burden to the society and many families.

In December 2019, the coronavirus disease 2019 (COVID-19) caused by a new type of coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), began a pandemic. Countries across the globe have adopted a series of corresponding control measures to contain the spread of the epidemic. At the beginning of the outbreak, China launched a first-level response to public health emergencies as quickly as possible, and effectively controlled the transmission of COVID-19 through intervention measures such as suspension of classes and work, cancellation of gathering activities, and closed management of rural areas and communities [4–6]. Such control measures have not only suppressed the spread of COVID-19 but also limited the spread of other infectious diseases. Studies have found that during the outbreak of COVID-19, reported cases of respiratory infectious diseases such as chickenpox, influenza, and pneumonia have been significantly reduced [7–10]. At the same time, studies have shown that the prevalence of several infectious diseases that occur in paediatric primary care, such as acute otitis media (AOM), influenza and pneumonia have also been significantly reduced [11–13].

Mathematical models have been employed to forecast or simulate the transmission of infectious diseases. Researchers have used the SARIMA-SVR hybrid model to predict the incidence of HFMD in Wuhan [14], and transmission dynamics models such as susceptible – infectious – recovered (SIR) and susceptible – exposed – infectious – asymptomatic – recovered (SEIAR) to evaluate the transmissibility of HFMD [15,16]. There are significant differences in the incidence of HFMD in mainland China. The southeast coastal areas, and the east and central areas are areas with high incidence of HFMD [17], and the incidence is higher than that of the northern and inland areas. In China, since the COVID-19 outbreak, many studies have shown that COVID-19 will have a cer-
tain impact on other infectious diseases; however, no study has been published about the quantitative effect of COVID-19 on HFMD in different regions. Therefore, this study intends to use the SEIAR model to explore the impact of COVID-19 on the spread of HFMD in many cities of mainland China. This can be used in developing targeted prevention and control measures based on the difference in the incidence of HFMD.

2. Methods

2.1. Study area

Six cities (Changchun City in Jilin Province, Zhongwei City in the Ningxia Hui Autonomous Region, Yichang City in Hubei Province, Changsha City in Hunan Province, Xiamen City in Fujian Province, and Shenzhen City in Guangdong Province) were selected as the research area for this study (Fig. S1).

2.2. Date collection

This study collected the reported HFMD cases in six selected cities in mainland China from 2015 to 2020. The data included the following information: name, age, gender, current address, onset date, date of diagnosis, population classification (scattered children, children in kindergarten, students, etc.), and classification of the case (clinically diagnosed case or confirmed case).

We also collected data on reported COVID-19 cases, including locally acquired cases and imported cases of each city. This study collected various interventions in six selected cities since the emergence of COVID-19. The timeline of interventions to control the transmission of COVID-19 was collected from the official website, including the health committee and local news website of each city. Data on the number, birth rate, and death rate of the population of the six cities were collected from statistical yearbooks announced by the Statistical Bureau of the Cities.

2.3. Transmission model of HFMD

Our previous studies showed that the SIR model could be employed to simulate the weekly incidence data of HFMD [15,18,19], and the SEIAR model could be adopted to simulate the daily data of the disease [16,20,21]. In this study, the SEIAR model was developed because the daily incidence data of HFMD were used.

In the SEIAR model, individuals were classified as: susceptible (S), exposed (E), infectious and symptomatic (I), asymptomatic (A), which means infectious but not symptomatic, and recovered (R). A flowchart of the model is shown in Fig. S2.

2.4. Estimation of parameters

There were nine parameters ($\beta$, $k$, $p$, $\omega$, $\gamma$, $\gamma'$, $f$, $br$, and $dr$) in the SEIAR model. The parameter $\beta$ was time-basic and was estimated by curve fitting the model to the reported data in the six cities. We set $k = 1$, $p = 0.4423$, $\omega = 0.2$, $\gamma = 0.5$, and $\gamma' = 0.0476$, according to our previous researches [16,20]. The range of the fatality rate was 0.0001–0.0005 [22–24], with a median of 0.0003; therefore, $f = 0.003\%$. The birth rate ($br$) and mortality rate ($dr$) were collected from the statistical yearbooks announced by the Statistical Bureau of the Cities. The parameters of the SEIAR model used in our study are shown in Table 1 and Table 2.

2.5. Transmissibility of HFMD

Based on our previous studies [16,20], the effective reproduction number ($R_{eff}$) was employed to quantify the transmissibility of HFMD and was calculated using the following equation:

$$R_{eff} = \beta S \left( \frac{P}{y} + \frac{(1 - P) k}{\gamma'} \right)$$

2.6. Indicators for assessing the change of incidence

Indicators, absolute difference (AD), and relative difference (RD) were used to assess the change in the incidence, and were calculated using the following equations:

$$TAR = \frac{\text{Total number of cases in a year}}{\text{Total population of the year}}$$

$$AD = TAR_1 - TAR_2$$

$$RD = \frac{TAR_1 - TAR_2}{TAR_1} \times 100\%$$

In the equations, TAR1 refer to fitted the maximum, minimum or median total attack rate (TAR), TAR2 refer to the TAR of 2020.

2.7. Simulation methods and statistical analysis

In our study, Berkeley Madonna 8.3.18 (developed by Robert Macey and George Oster of the University of California at Berkeley. Copyright ©1993–2001 Robert I. Macey & George F. Oster) was used to fit the model with the data to calculate the parameters, while the transmissibility was calculated based on the parameters. The determination coefficient ($R^2$) was used to evaluate the goodness of fit of the model simulation. Regression analysis was used to calculate $R^2$, and was performed using SPSS software (version 21.0; IBM Corp., Armonk, NY, USA).

Data and software availability

Extra data is available by emailing to Tianmu Chen (chen_tianmu@xmu.edu.cn) on reasonable request.

3 Results

3.1. The transmission and control measures of COVID-19 in the six selected cities

The reported data show that the peak of confirmed cases of COVID-19 in the six cities is mainly concentrated at the end of January or early February 2020. With the implementation of preventive and control measures such as: controlling the source of infection, cutting off the route of transmission, and protecting susceptible groups by suspension of classes, home isolation, close all kinds of leisure and entertainment places, and wearing masks, the number of locally confirmed cases reported showed a downward trend since February, and the subsequent reported cases are mainly foreign cases from abroad (Figs. S3–S8). Xiamen and Shenzhen, which are located in coastal cities, have more imported cases.

3.2. Changes in the reported incidence of HFMD due to COVID-19 transmission

The reported incidence of HFMD in each city showed a certain degree of seasonal periodicity from 2015 to 2019. Changchun City had one epidemic peak in incidence, and the other five cities had two epidemic peaks (Fig. 1).

During the COVID-19 epidemic period in 2020, the transmission of HFMD was almost interrupted in the two northern cities. The reported incidence of HFMD in Changchun City and Zhongwei City was 0.05% and 0.13%, respectively, with no epidemic observed in 2020. The median AD and RD of the reported incidence in the two cities were 2.44% (range: 1.19–5.26%) and 1.13% (range: 0.96–1.31%), and 97.99% (range: 95.97–99.06%) and 89.68% (range: 88.07–90.97%), respectively.

The transmission state in two southern cities was different from that in the northern ones. Although the epidemic peak in spring disappeared, a smaller epidemic peak was observed in the two cities. The reported incidence of HFMD in Xiamen City and Shenzhen City was 3.63% and
Table 1
Parameter definitions and values.

| Parameter | Description | Unit | Value | Method |
|-----------|-------------|------|-------|--------|
| $\beta$   | Transmission relative rate | (individual × day)$^{-1}$ | Curve fitting |
| $k$       | Relative transmissibility rate of asymptomatic to symptomatic individuals | | References [16,20] |
| $p$       | Proportion of the symptomatic | | References [16,20] |
| $\omega$  | Incubation relative rate | Day$^{-1}$ | 0.2 | References [16,20] |
| $\gamma$ | Recovery rate of the infectious | Day$^{-1}$ | 0.07143 | Reference [16,20] |
| $\gamma'$ | Recovery rate of the asymptomatic | Day$^{-1}$ | 0.04762 | Reference [16,20] |
| $f$       | Fatality rate of HFMD cases | 1 | 0.035 | References [16,20] |
| $br$      | Birth rate | 1 | 0.0009747 | Collected data |
| $dr$      | Natural death rate of the whole city | 1 | 0.0004529 | Collected data |

Fig. 1. Curve fitting results based on the data in six selected cities, 2015–2020.

Table 2
Absolute difference (AD) and relative difference (RD) of six cities.

| City      | TAR (%) | AD    | RD (%) |
|-----------|---------|-------|--------|
| Changchun | 0.0094  | —     | —      |
| Zhongwei  | 0.0013  | —     | —      |
| Yichang   | 0.0013  | —     | —      |
| Changsha  | 0.0268  | —     | —      |
| Xiamen    | 0.0363  | —     | —      |
| Shenzhen  | 0.0861  | —     | —      |

8.61%, respectively, with no epidemic observed in 2020. The AD and RD of the reported incidence in two cities were 15.93% (range: 11.07–22.72%) and 39.74% (range: 17.75–43.21%), and 81.44% (range: 75.31–86.22%) and 82.19% (range: 67.34–83.38%), respectively.

Although Yichang City and Changsha City are located in the center of China, they have different transmission modes in 2020. The transmission of HFMD was almost interrupted in Yichang City, with a reported incidence of HFMD of 0.36%, and no epidemic was observed in 2020. The AD and RD of the reported incidence in the city were 9.05% (range: 6.12–14.80%) and 96.17% (range: 94.44–97.63%), respectively. In contrast, the first epidemic wave of Changsha City disappeared in spring, but a large epidemic wave in autumn was observed in 2020. The reported incidence of HFMD in the city in 2020 was 35.63% The AD and RD of the reported incidence in the city were −3.96% (range: −12.56–6.65%) and −12.50% (range: −54.44–15.73%), respectively.

3.3. Changes in the transmissibility of HFMD due to COVID-19 transmission

The SEIAR model fitted the reported data well. The $R^2$ values of the fitting were above 0.50, and the $P$ values were less than 0.001 in Changchun, Yichang, Changsha, Xiamen, and Shenzhen City. Although the value of $R^2$ was lower than 0.50 ($R^2 = 0.464$) in Zhongwei City, it also had a statistical significance of $P < 0.001$. 

References...
From 2015 to 2019, the median $R\text{eff}$ of HFMD in Changchun, Zhongwei, Yichang, Changsha, Xiamen and Shenzhen were 2.75 (range: 1.01–4.09), 2.56 (range: 1.08–3.82), and 3.33 (range: 0.01–8.94), 2.12 (range: 1.32–3.38), 1.71 (range: 0.14–3.55), and 3.48 (range: 1.03–7.44), respectively. The daily values of $R\text{eff}$ for the six cities are shown in Fig. 2.

It can be seen from the $R\text{eff}$ curve that after the outbreak of COVID-19, the $R\text{eff}$ of each city dropped to 0. In the second half of 2020, the $R\text{eff}$ values of the four cities of Yichang, Changsha, Xiamen, and Shenzhen City rebounded. In 2020, the $R\text{eff}$ ranges of HFMD in Changchun, Zhongwei, Yichang, Changsha, Xiamen, and Shenzhen cities are 0, 0, 0.00–5.60, 0.00–7.74, 0.00–6.94, and 0.00–7.25, respectively.

4 Discussion

In this study, we used the SEIAR model to investigate the epidemiological characteristics and transmission capacity of HFMD in six selected cities in different geographical locations in China during the COVID-19 epidemic. To the best of our knowledge, this is the first study to explore the impact of the COVID-19 epidemic in multiple regions on the incidence of HFMD and the differences among regions from the perspective of transmission dynamics.

The model fitting results showed that each city model fits well, except for Zhongwei City. The regression analysis $R^2$ values of all cities were above 0.5, and the $P$ values were all less than 0.001. The $R^2$ value of Zhongwei City was less than 0.5, which may be due to the small number of cases in Zhongwei City and the existence of more outliers.

The results showed that from 2015 to 2019, the median $R\text{eff}$ of the six cities was above 1. This indicates that six cities have the risk for HFMD transmission, and the preventive and control of HFMD should be reinforced in any period. After the outbreak of COVID-19, $R\text{eff}$ in each city dropped to 0, indicating that some preventive and control measures taken during the COVID-19 epidemic reduced the transmission ability of HFMD to a certain extent.

During the COVID-19 epidemic, local governments took a series of preventive and control measures, such as school suspension, home quarantine, closing all kinds of leisure places, wearing masks, advocating frequent hand washing, etc. These measures have not only effectively suppressed the spread of COVID-19 epidemic, but also had a certain impact on other communicable diseases such as HFMD.

Studies have shown that the fecal-oral route is an important route of transmission in HFMD. Improving hand hygiene and hygiene conditions is the main method of preventing transmission [25]; therefore, frequent hand washing effectively blocks the transmission of HFMD. To prevent transmission among high-density populations, closing schools is a common way to mitigate the spread of infectious diseases during outbreaks. A study in Singapore showed that school closures reduced the spread of HFMD in local schools [26], but the effect was small because infected children may still transmit the virus to others in amusement parks, shopping malls, and other places. Isolation or isolation of patients is an effective strategy to prevent the occurrence and spread of infectious diseases [27,28]. Home isolation, as a non-drug measure, is a key strategy for preventing the spread of HFMD [29]. During the epidemic period of COVID-19, the government, aside from suspending classes, also took other measures such as closing management in the community, isolating at home and closing all kinds of leisure places. These preventive and control measures were superimposed to control the source of infection, while frequent handwashing and wearing masks effectively blocked the transmission route. Hence, the transmission of HFMD was minimized.

The targeted strategies of COVID-19 as city lockdown and social distancing have made an essential contribution to some other communi-
cable diseases, including HFMD [30]. Our research results were similar with it, after the COVID-19 outbreak in 2020, there was a significant reduction in the incidence of HFMD of six cities. However, since the second half of 2020, when the COVID-19 epidemic was controlled, schools resumed classes, kindergartens opened, and entertainment and leisure places were reopened, the incidence and $R_g$ of HFMD increased. This indicates that the prevention and control measures taken by the government during the epidemic period effectively reduced the transmission of HFMD.

Preschool children are the primary population susceptible to HFMD [31,32]. As seen in the incidence curve of HFMD of each city in 2020, the peak incidence in Changsha City was earlier than that in Xiamen City and Shenzhen City. The reason may be that kindergartens in Changsha City resumed classes earlier than those in Xiamen City and Shenzhen City. This leads to the spread of HFMD among children in Changsha City first, hence the peak time appeared earlier. The incidence of Changsha and Xiamen City was still high in September and October, and the decreasing trend was not obvious. Since the second half of 2020, the $R_g$ in cities in the central and southern regions of China, such as Changsha, Xiamen, and Shenzhen City, had an obvious upward trend, and Changsha even exceeded the previous maximum value. This suggests that the preventive and control measures taken during the epidemic period, such as school suspension and home isolation, may lead to the rebound incidence of HFMD in cities in the central and southern regions of China. Further, the specific influencing factors and pathogenesis need to be studied further.

This study has some limitations. First, the regions selected for the study did not involve cities located in western China, so the estimation of transmission capacity, the fitting results of the epidemic curve, and the research conclusions of this research may not be applicable to these regions. Second, the cut-off period of this study is 2020, and it was found that in the second half of 2020, the incidence of HFMD had rebounded in cities in the south and central China. The question of how long this effect will last is unknown, future studies should take a longer study period to see how long the rebound effect will last after the strong control measures during the COVID-19 outbreak.

5 Conclusion

Based on the incidence data of six cities from 2015 to 2019, the SEIR model demonstrated a significant effect on the incidence of HFMD. During the period of COVID-19, the incidence and $R_g$ of HFMD decreased, and the preventive and control measures of COVID-19 contributed significantly to limit HFMD transmission.

Declaration of competing interest

The authors declare no conflicts of interest.

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CRediT authorship contribution statement

Yan Niu: Conceptualization, Writing – original draft. Li Luo: Conceptualization, Formal analysis. Jia Rui: Conceptualization, Formal analysis. Shiting Yang: Writing – original draft. Bin Deng: Formal analysis. Zeyu Zhao: Formal analysis. Shengnan Lin: Formal analysis. Jingwen Xu: Writing – original draft. Tianlong Yang: Formal analysis. Weikang Liu: Formal analysis. Peihua Li: Formal analysis. Zhuyong Yuan: Formal analysis. Chan Liu: Formal analysis. Jiefeng Huang: Formal analysis. Tianmu Chen: Conceptualization, Writing – original draft.
COVID-19 measures reduced the transmission of HFMD