Analysis of HFMD Transmissibility Among the Whole Population and Age Groups in a Large City of China

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Background: Hand-Foot-and-Mouth-Disease (HFMD) has been widely spread in Asia, and has result in a high disease burden for children in many countries. However, the dissemination characteristics intergroup and between different age groups are still not clear. In this study, we aim to analyze the differences in the transmissibility of HFMD, in the whole population and among age groups in Shenzhen city, by utilizing mathematical models.

Methods: A database that reports HFMD cases in Shenzhen city from January 2010 to December 2017 was collected. In the first stage, a Susceptive-Infected-Recovered (SIR) model was built to fit data of Shenzhen city and its districts, and $R_{eff}$ was used to assess transmissibility in each district. In the second stage, a cross-age groups SIR model was constructed to calculate the difference in transmissibility of reported cases among three age groups of EV71 virus: 0–3 years, 3–5 years, and over 5 years which was denoted as age group 1, 2, and 3, respectively.

Results: From 2010 to 2017, 345,807 cases of HFMD were reported in Shenzhen city, with peak incidence in spring and autumn in Shenzhen city and most of its districts each year. Analysis of the EV71 incidence data by age group revealed that age Group 1 have the highest incidence ($3.13 \times 10^{-7}$–$2.31 \times 10^{-4}$) while age group 3 had the lowest incidence ($0.354 \times 10^{-5}$). The differences in weekly incidence of EV71 between age groups were statistically significant ($t_{12} = 7.563, P < 0.0001; t_{23} = 12.420, P < 0.0001; t_{13} = 16.996, P < 0.0001$). The $R^2$ of the SIR model Shenzhen city population-wide HFMD fit for each region was $> 0.5$, and $P < 0.001$. $R_{eff}$ values were $> 1$ for the vast majority of time and regions, indicating that the HFMD virus has the ability to spread in Shenzhen city over the long-term. Differences in $R_{eff}$ values between regions were judged by using analysis of variance (ANOVA) ($F = 0.541, P = 0.744$). $S_iR_j - S_jR_i$ models between age groups had $R^2$ over 0.7 for all age groups and $P < 0.001$. The $R_{eff}$ values between groups show that the 0–2 years old group had the strongest transmissibility (median: 2.881, range: 0.017–9.897), followed by the over 5 years old group (median: 1.758, range: 1.005–5.279), while the 3–5 years old group (median: 1.300, range: 0.005–1.005) had the weakest transmissibility of the three groups. Intra-group transmissibility was strongest in the 0–2 years age group (median: 1.787, range: 0–9.146),
frequently affects young children (10), with outbreaks reported in Malaysia, Japan, Singapore, Vietnam, and Cambodia (2–4). HFMD has a high disease burden in Asia, with 358,764 cases of HFMD in Japan each year (5). Also, it remains a major health problem for children in China, affecting more than 2 million children each year. Especially, Guangdong Province has been one of the most severely affected provinces (6). The annual incidence of HFMD in Guangdong Province exceeds 30 cases in every 10,000 people and case number has accounted for approximately 15% of the total number of cases in China in recent years (7). In addition, Shenzhen city had the highest number of HFMD cases among 143 cities in mainland China between 2009 and 2014 (8).

HFMD is a viral disease that has received great attention in the last two decades because of its high incidence rate in the pediatric population. The clinical presentation of HFMD is characterized by fever and a blistering rash, mostly on the hands, feet and oral mucosa (9). The disease is generally mild and self-limiting, but neurologic and cardiopulmonary-related complications may occur in disease outbreaks (10). Among all common febrile and rash illnesses (11), HFMD has remained the one that most frequently affects young children (12, 13). A series of analyses have shown that children younger than 5 years old are more likely to develop HFMD and that it is more likely to accumulate in younger children (14–16).

The main pathogens of HFMD infection are enterovirus 71 (EV71) and coxsackievirus A16 (CVA16) (14, 17), and EV71 infection is particularly the main viral subtype causing severe and fatal cases (12).

However, the mechanism by which EV71 causes severe central nervous system complications is still unclear. It is suggested that this may be due to a combination of pathologic immune response and direct viral action, but there is no effective treatment and no biomarker that can be used as an early warning of severe HFMD. In terms of vaccines, Asian countries that have experienced a history of HFMD infection and pandemics are actively developing vaccines as a preventive measure. Among them, a vaccine for EV-A71 in China has been available in 2016 (9, 10), and a bivalent EV-A71 / CVA16 vaccine should enter clinical trials in the near future (13). The research of Joseph T. Wu et al. showed that the cost of routine EV71 vaccination is cost-effective in China (15). However, it is promoted as a class II vaccine in China, causing some limitations in terms of immunization coverage.

Currently, many mathematical models have also been applied to the study of HFMD, such as the application of Bayesian spatio-temporal models to analyze the factors influencing HFMD and the effects of interventions (16, 18, 19), the application of lagged nonlinear models to assess the effects of meteorological factors on incidence (20, 21), SIR models (22–24), SEIR models (25), SEILR models (26), and other models (27, 28) are also used in the study of HFMD. In addition, some scholars have also focused on the differences in HMFD between different age groups (29, 30). It indicates that the existing studies related to HFMD still focus mostly on spatial and temporal variation (11, 31), the expression of overall epidemiological characteristics and the relationship between meteorological factors and the incidence of HFMD, while there is a lack of studies targeting the analysis of EV71 virus by age groups.

In this study, we assumed that there is variability in the transmissibility among the major pathogens of HFMD and variability and possible interaction in the transmission of EV71 virus among different age groups. Based on this hypothesis, we collected data on reported HFMD cases in a city with a high prevalence of HFMD in China (Shenzhen city), grouped the cases by age according to their basic information, and then used a seasonally adjusted SIR model to calculate transmissibility of different pathogens among different age groups, and further investigated the magnitude of all-virus transmissibility of HFMD in Shenzhen city. Besides, in this paper, we studied for the first time the characteristics of the transmission pattern of HFMD among different age groups in the whole population, established a transmission model of EV71 virus transmission among different age groups, and analyzed the reasons for the differences between groups.

**MATERIALS AND METHODS**

**Data Collection**

In this study, we collected HFMD cases from January 2010 to December 2017 in Shenzhen city, Guangdong Province, including the number of reported cases and deaths per day, age, sex, exposure history, date of onset, and severity of disease, and obtained basic information on the population of Shenzhen city, including the year-end resident, birth rate and death rate, by searching the Shenzhen city Statistical Yearbook 2010–2017.
Between 2010 and 2017, the population exceeded 12 million, and the average birth rate was 18.63 per 1,000 (range: 16.41/1,000–21.46/1,000) and the median death rate was 7.32 per 1,000 (range: 6.19/1,000–9.72/1,000). When we come to the Population Composition of Shenzhen city, the number of people in each age group increased linearly from 2014 to 2017, but the composition ratio remained stable: the 0–2 years old group remained stable around 95.22% (range: 95.22–95.23%), the 3–5 years old group remained stable around 2.16% (range: 2.161–2.165%) and the over 5 years old group remained stable around 2.61% (range: 2.609–2.613%)

The population of the 0–2 years old group was 281,240 thousand, 297,156 thousand, 310,928 thousand and 327,383 thousand from 2014 to 2017 respectively. The population of the over 5 years old group remained stable around 95.225% (range: 95.222–95.230%).

Shenzhen city is a large city located in the south of the coastal area of Guangdong Province, China. Shenzhen city has a southern subtropical monsoon climate with long summers and short winters, mild climate, abundant sunshine and rainfall, and an annual average temperature of 23.0°C. The climate is strongly influenced by the monsoon, with “warm temps” and humid weather in spring, high temperatures and rain in summer, little rain in fall with drought and often typhoons, and short and dry winters with little rain (32). Overall, it is a city with long summers and short winters, strongly influenced by the monsoon climate.

Model Introduction

SIR Model

Based on the transmission mechanism of HFMD and the type of case report data, the Susceptible -Infectious -Removed (SIR) model was used (Figure 1).

In this model, \(S\) denotes susceptible individuals, \(I\) denotes infectious individuals, \(R\) denotes recovered individuals and \(N\) denotes the total population size. The parameters \(br\), \(dr\), \(f\), \(\beta\) and \(\gamma\) refer to the natural birth rate of the population, the mortality rate of HFMD, the relative transmission rate and the relative recovery rate, respectively.

\[
\begin{align*}
\frac{dS_i}{dt} &= brN - \beta S_i I_i - drS_i \\
\frac{dI_i}{dt} &= \beta S_i I_i - \gamma I_i - (dr + f)I_i \\
\frac{dR_i}{dt} &= \gamma I_i - drR_i \\
N &= S + I + R
\end{align*}
\]

**SIR-Model**

Considering the interactions between age groups, we created the age group SIR model (Figure 2).

We set 0–2 years old as age group 1; 3–5 years old as age group 2; and over 5 years old as age group 3.

\[
\begin{align*}
\frac{dS_1}{dt} &= br_1 N - \beta_{11} S_1 I_1 - \beta_{21} S_1 I_2 - \beta_{31} S_1 I_3 - \beta_{33} S_1 I_3 \\
\frac{dI_1}{dt} &= \beta_{11} S_1 I_1 + \beta_{21} S_1 I_2 + \beta_{31} S_1 I_3 - \gamma' I_1 \\
\frac{dR_1}{dt} &= \gamma' I_1 \\
\frac{dS_2}{dt} &= -\beta_{22} S_2 I_2 - \beta_{12} S_2 I_1 - \beta_{32} S_2 I_3 \\
\frac{dI_2}{dt} &= \beta_{22} S_2 I_2 + \beta_{12} S_2 I_1 + \beta_{32} S_2 I_3 - \gamma' I_2 \\
\frac{dR_2}{dt} &= \gamma' I_2 \\
\frac{dS_3}{dt} &= -\beta_{33} S_3 I_3 - \beta_{13} S_3 I_1 - \beta_{23} S_3 I_2 - drS_3 \\
\frac{dI_3}{dt} &= \beta_{33} S_3 I_3 + \beta_{13} S_3 I_1 + \beta_{23} S_3 I_2 - \gamma' I_3 - drI_3 \\
\frac{dR_3}{dt} &= \gamma' I_3 - drR_3 \\
N &= S_1 + S_2 + S_3 + I_1 + I_2 + I_3 + R_1 + R_2 + R_3
\end{align*}
\]
Parameter Estimation

As shown in Table 1, there are eight parameters ($\beta_1$, $\gamma$, $br$, $dr$, and $f$).

1) The propagation coefficient among individuals in the SIR model is set to $\beta$. $\beta = 0.340609$ is obtained by fitting the reported data of Shenzhen city.

2) The parameters $br$, $dr$, and $f$ (33) were calculated based on finding the Shenzhen city Yearbook and the collected data. The annual $br$ and $dr$ values were collected; the weekly values of the two parameters were calculated; and the weekly $br$ and $dr$ values were $0.000352$ (range: $0.000330–0.000383$) and $0.0000129$ (range: $0.0000127–0.0000187$). The references give the susceptibility of the population and the likelihood of the population and the infectiousness of the population were 0.67, 0.4, and 0.433, respectively.

3) The age group SIR model in which $f_1$, $f_2$, and $f_3$ denote the disease and death rates in the three age groups 0–2 years, 3–5 years, and over 5 years, respectively, were taken as $0.0003$. $\beta_{11}$ denotes the transmission coefficient among individuals in age group 1; $\beta_{22}$ denotes the transmission coefficient among individuals in age group 2 minus; $\beta_{12}$ denotes the transmission coefficient from individuals in age group 1 to individuals in age group 2; $\beta_{13}$ denotes the transmission coefficient from individuals in age group 1 to individuals in age group 3; and $\beta_{14}$ denotes the transmission coefficient from individuals in age group 1 to individuals in age group 2 minus. Propagation coefficient from individuals within age group 1 to individuals in age group 3; $\beta_{21}$ denotes the propagation coefficient from individuals within age group 2 to individuals in age group 1 minus; $\beta_{23}$ denotes the propagation coefficient from individuals within age group 2 to individuals in age group 3; $\beta_{31}$ denotes the propagation coefficient from individuals within age group 3 to individuals in age group 1; and $\beta_{32}$ denotes the propagation coefficient from individuals within age group 3 to individuals in age group 2. The $R_{eff}$ subscript corresponds to the same age group object.

4) According to the seasonal cyclic pattern of the incidence data, they were divided into 18 segments, and $\beta$ were fitted separately within and between each age group.
Indicators of Transmission Capacity

The basic reproduction number is an important parameter to determine whether the disease is epidemic or not, which refers to the number of new cases expected to be directly transmitted by one infectious agent in the susceptible population during its transmission period. Effective reproduction number ($R_{eff}$) was set as the evaluation index, i.e., the basic reproduction number among the population. The calculation process of the $R_{eff}$ equation can be seen whereupon:

Step 1: Divide the derivatives of all infected compartments into two parts: the first part represents the transformation between non-new compartments.

$$\frac{d}{dt} \begin{pmatrix} I_1 \\ I_2 \\ I_3 \end{pmatrix} = \begin{pmatrix} I_1 (1 - I_2 I_3) \\ I_2 (1 - I_1 I_3) \\ I_3 (1 - I_1 I_2) \end{pmatrix} - \begin{pmatrix} I_2 \gamma \\ I_3 \gamma \\ I_1 \gamma \end{pmatrix}$$

$$F = \mathcal{F} - \mathcal{V}$$

Step 2: Taking the derivatives of the vectors $\mathcal{F}$ and $\mathcal{V}$ with respect to the variable $[I_1, I_2, I_3]$, respectively, yields the corresponding Jacobi matrices $\mathcal{F}$ and $\mathcal{V}$:

$$\mathcal{F} = \begin{pmatrix} S_1 \beta_{11} & S_1 \beta_{12} & S_1 \beta_{13} \\ S_2 \beta_{21} & S_2 \beta_{22} & S_2 \beta_{23} \\ S_3 \beta_{31} & S_3 \beta_{32} & S_3 \beta_{33} \end{pmatrix}$$

$$\mathcal{V} = \begin{pmatrix} \gamma \\ 0 \\ 0 \end{pmatrix} - \begin{pmatrix} \gamma dr + \gamma \\ 0 \\ 0 \end{pmatrix}$$

and further calculate the $\mathcal{V}^{-1}$:

$$\mathcal{V}^{-1} = \begin{pmatrix} \gamma & 0 & 0 \\ 0 & \gamma dr + \gamma & 0 \\ 0 & 0 & \gamma dr + \gamma \end{pmatrix}$$

Step 3: Calculate the next generation matrix $M = \mathcal{F} \cdot \mathcal{V}^{-1}$. The elements in row $j$ and column $i$ of the matrix $M$ are the $R_{eff,i,j}$ of the intergroup interactions. The result of the calculation of $R_{ij}$ can be obtained by replacing $S_i := N_i$ into the equation.

$$M = \begin{pmatrix} \frac{S_1 \beta_{11}}{\gamma} & \frac{S_1 \beta_{12}}{\gamma} & \frac{S_1 \beta_{13}}{\gamma} \\ \frac{S_2 \beta_{21}}{\gamma} & \frac{S_2 \beta_{22}}{\gamma} & \frac{S_2 \beta_{23}}{\gamma} \\ \frac{S_3 \beta_{31}}{\gamma} & \frac{S_3 \beta_{32}}{\gamma} & \frac{S_3 \beta_{33}}{\gamma} \end{pmatrix}$$

The elements in row $j$ and column $i$ of the matrix $M$ are the $R_{eff,i,j}$ of the intergroup interactions. The result of the calculation of $R_{ij}$ can be obtained by replacing $S_i := N_i$ into the equation.

Step 4: $R_0$ is defined as the maximum eigenvalue of $M$, whereupon:

$$R_0 = \lambda_{max}(M)$$

The analytic expressions for the eigenvalues of the matrix $M$ are particularly complex. The following approach is taken for this purpose.

1) First calculate the value of $R_{ij}$ and then the maximum eigenvalue of the numerical matrix $M$.
2) Use the definition method to calculate the overall $R_0$.

$$R_0 = \sum_{j=1}^{n} P(x_0 \in N_j) \sum_{i=1}^{n} R_{ij}$$

Software Introduction

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) ran model coefficients estimated by curve fitting to the data and simulated the effects of the intervention. SPSS 13.0 (IBM Corp., Armonk, NY, USA) was used for statistical testing, with t-tests used to calculate differences between age groups and $R^2$ used to assess curve fitting.

RESULTS

Epidemiological Features

From 2010 to 2017, 345,807 cases of HFMD were reported in Shenzhen city, including 129,812 cases in Baoan District, 26,377 cases in Luohu District, 24,008 cases in Futian District, 23,009 cases in Nanshan District, 136,832 cases in Longgang District, and 5,769 cases in Yantian District. Among them, 233,895 cases were 0–2 years old, 98,911 cases were 3–5 years old, and 16,071 cases were over 5 years old. Among them, 16 cases died, and the mortality rate was 0.0059%.

Analyzing the incidence data of Shenzhen city from 2010 to 2017, the median incidence rate was 5.26/100,000 people. The lowest incidence rate was 0.11/100,000 people in week 4 of 2011; the highest incidence rate was 45.10/100,000 people in week 39 of 2017. From the spatio-temporal distribution map (Figure 3), it can be seen that the burden of HMFD in Shenzhen city gradually increased from 2010 to 2017, and the increase in incidence rate was mainly concentrated in Baoan and Longgang districts, among which Longgang district had a more obvious trend of rising first and then decreasing. In addition, after 2013, the burden of disease in Nanshan District, Futian District, Luohu District, and Yantian District differed significantly from Baoan District and Longgang District, and there were also slight fluctuations during the period.

By analyzing the weekly reported case data, there are approximately two epidemic cycles per year, alternating seasonally from spring to summer and from summer to autumn. Except for 2013, Shenzhen city and most of its districts had peak incidence in both spring and autumn, especially in Luohu and Yantian districts, where the peak incidence in spring tended to be higher than that in autumn (Figure 4). Among the districts, Baoan, Longgang and Yantian had higher incidence rates, with Longgang having the highest incidence rate (1.28 × 10^{-2}–7.53 × 10^{-4}) and Futian having the lowest incidence rate (0–2.75 × 10^{-4}). In 2017, Baoan district had the highest incidence rate in Shenzhen city, with an incidence rate of 87.36/100,000 people. The differences in incidence rates among districts were statistically significant as calculated by ANOVA ($F = 65.006$,
FIGURE 3 | The Map of HFMD burden distribution in Shenzhen city.

FIGURE 4 | Fitting results for HFMD incidence rates in Shenzhen city and its districts.
Analysis of the incidence data by age group also revealed a peak in spring and autumn, with a significantly higher peak in spring than in autumn. Incidence rates were the highest ($3.13 \times 10^{-7}$ to $2.31 \times 10^{-4}$) in group 1 (the 0–2 years age group) and the lowest ($0.354 \times 10^{-5}$) in group 3 (the over 5 years age group), with the incidence in group 1 being 10.02 times higher than that in the group 3 (Figure 5). The differences in weekly EV71 prevalence between age groups were statistically significant ($t_{12} = 7.563, P < 0.0001; t_{23} = 12.420, P < 0.0001; t_{13} = 16.969, P < 0.0001$). The composition ratio of the three age groups did not change significantly during 2014–2017, and the median composition ratio of group 2 was 65.267% (59.654–74.922%), the median composition ratio of group 2 (the 3–5 years group) was 29.875% (20.385–33.895%), and the median composition ratio of group 3 was 5.197% (4.155–6.452%), all fluctuating within a certain range.

**Model Fitting Effect**

**SIR Model**

First, we fitted the SIR model for the weekly incidence of population-wide HFMD in Shenzhen city and each sub-district. In the fitting process, segments were fitted to the data. According to the seasonal characteristics of HFMD, each peak period was divided into a segment, with an average of 2–3 segments per

**TABLE 2 | The $P$ values of multiple comparisons for different districts (LSD).**

| Comparison groups | Baoan district | Futian district | Nanshan district | Yantian district | Luohu district | Longgang district |
|-------------------|----------------|----------------|------------------|-----------------|----------------|------------------|
| Baoan district    | 0              |                |                  |                 |                |                  |
| Futian district   | 0              | 0              |                  |                 |                |                  |
| Nanshan district  | 0              | 0.0002         | 0                |                 |                |                  |
| Yantian district  | 0              | 0.7209         | 0                | 0               |                |                  |
| Luohu district    | 0              | 0.0006         | 0                | 0.7404          | 0.0020         |                  |
| Longgang district |                |                |                  |                 | 0.7404         | 0.0020           |

$\alpha = 0.05$. 

**FIGURE 5 | Fitting results for EV71 incidence rates by age group.**

Reported incidence (per 10,000 individuals): $R^2:0.818, P < 0.0001$

Reported incidence (per 10,000 individuals): $R^2:0.715, P < 0.0001$

Reported incidence (per 10,000 individuals): $R^2:0.726, P < 0.0001$
year in Shenzhen city. The results of fitting for population-level HFMD in each district of Shenzhen city were good, with $R^2 > 0.5$ and $p < 0.001$ for all districts (Figure 4). The quartiles of reported incidence in Shenzhen city were $P_{25} = 1.78 \times 10^{-5}$, $P_{50} = 5.26 \times 10^{-5}$, $P_{75} = 1.19 \times 10^{-4}$. The total incidence reported in Shenzhen city had an increasing trend year by year, with the highest peak in 2017 ($4.51 \times 10^{-4}$), while the remaining districts showed a trend of increasing and then decreasing trend, except for Futian and Nanshan districts.

$S_i|R_i-S_i|R_j$ Model

We also developed the $S_i|R_i-S_i|R_j$ model to fit the HFMD incidence data between age groups in Shenzhen city for 0–2 years, 3–5 years, and over 5 years of age for transmissibility. As can be seen from the fitted curves (Figure 5), the fit was good among the age groups. The fitted $R^2$ values for each group are listed in the listed fit effect table, and it can be seen that $R^2$ is over 0.7 for all age groups, and $p < 0.001$ for all (Table 3). The quartiles for age group 1 were $P_{25} = 1.08 \times 10^{-5}$, $P_{50} = 3.17 \times 10^{-5}$, $P_{75} = 6.58 \times 10^{-5}$, age group 2 were $P_{25} = 4.98 \times 10^{-6}$, $P_{50} = 1.23 \times 10^{-5}$, $P_{75} = 2.62 \times 10^{-5}$, and age group 3 were $P_{25} = 8.26 \times 10^{-7}$, $P_{50} = 2.26 \times 10^{-6}$, $P_{75} = 4.97 \times 10^{-6}$. The transmission coefficients $\beta$ for each age group at each time period were obtained by fitting, and the fitting results are shown in Table 4.

Assessment of Transmissibility

The calculated $R_{eff}$ values of Shenzhen city and each district are shown in Figure 6, and it can be seen that the $R_{eff}$ values for most of the time are > 1, indicating that the HFMD virus were likely to continue spreading in the long term.

The median $R_{eff}$ of Shenzhen city was 4.001 (Interquartile range [IQR]: 0.021–8.929), with $R_{eff}$ values <1 in the second cycle of 2011; the median $R_{eff}$ for Baaoan was 4.069 (IQR: 2.096–10.139), with $R_{eff}$ values all over 1; the median $R_{eff}$ of Longgang District was 4.126 (IQR: 2.935–8.922), with $R_{eff}$ values all over 1 and a gradual upward trend from 2010 to 2016; the median $R_{eff}$ of Luohu District had a median $R_{eff}$ of 4.298 (IQR: 1.730–9.314), with $R_{eff}$ values over 1; the median $R_{eff}$ of Nanshan District was 3.939 (IQR: 1.937–8.002), with $R_{eff}$ values all over 1; the median $R_{eff}$ of Futian District was 4.777 (IQR: 2.924–11.105), with a decreasing trend of $R_{eff}$ over 1; the median $R_{eff}$ in Yantian District was 5.131 (IQR: 1.730–9.314), with $R_{eff}$ over 1. $R_{eff}$ values were slightly <1, indicating that HFMD will continue to be prevalent in Shenzhen city and its districts but will not cause a major outbreak. The differences in $R_{eff}$ values between districts were not statistically significant ($F = 0.541, P = 0.744$) by Analysis of Variance (ANOVA).

### Table 3: The $P$ values and fitted $R^2$ values for each group.

| Age groups          | $R^2$  | $P$     |
|---------------------|--------|---------|
| 0–3 years old group | 0.818  | <0.0001 |
| 3–5 years old group | 0.715  | <0.0001 |
| >5 years old group  | 0.726  | <0.0001 |

### Table 4: The weekly transmission coefficients $\beta$ for each age group.

| Year | Weeks | $\beta_{11}$ | $\beta_{22}$ | $\beta_{33}$ | $\beta_{12}$ | $\beta_{13}$ | $\beta_{21}$ | $\beta_{23}$ | $\beta_{31}$ | $\beta_{32}$ |
|------|-------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|
| 2010 | 1–8   | 0.222        | 0.245        | 0.020        | 0.000        | 0.015        | 0.097        | 0.030        | 0.003        |             |
| 2011 | 1–5   | 0.018        | 0.096        | 0.009        | 0.015        | 0.190        | 0.000        | 0.045        | 0.005        |             |
| 2012 | 1–8   | 0.260        | 0.221        | 0.129        | 0.000        | 0.023        | 0.157        | 0.011        | 0.052        | 0.436        |
| 2013 | 1–5   | 0.118        | 0.161        | 0.018        | 0.000        | 0.044        | 0.025        | 0.197        | 0.000        |             |
| 2014 | 1–8   | 0.079        | 0.069        | 0.048        | 0.001        | 0.021        | 0.004        | 0.001        |             |             |
| 2015 | 1–10  | 0.001        | 0.001        | 0.000        | 0.000        | 0.000        | 0.000        | 0.000        | 0.000        | 0.001        |
| 2016 | 1–23  | 0.127        | 0.008        | 0.007        | 0.009        | 0.006        | 0.248        | 0.015        | 0.006        | 0.456        |
| 2017 | 1–27  | 0.043        | 0.055        | 0.001        | 0.050        | 0.020        | 0.151        | 0.005        | 0.006        | 0.076        |
| 2017 | 27–53 | 0.000        | 0.018        | 0.001        | 0.026        | 0.004        | 1.036        | 0.016        | 0.002        | 0.007        |

The results of the cross-age groups SIR model calculations showed that the 0–2 years age group had the strongest transmissibility (Median[M]: 2.881, IQR: 0.017–9.897), followed by the over 5 years age group (M: 1.758, IQR: 1.005–5.279), while the 3–5 years age group (M: 1.300, IQR:0.005–1.005) had the weakest transmissibility among the three groups.

The $R_{eff}$ for the 0–2 years age group had the largest value in the first half of 2010, followed by a peak in late 2013 and then a gradual decrease; the $R_{eff}$ for the 3–5 years age group fluctuated within a certain range and had the largest value in the second half of 2017. $R_{eff}$ values for the over 5 years age showed an increasing and then decreasing trend, peaking at the end of 2013 (Figure 7A).

Intra-group transmissibility was strongest in the 0–2 years age group ($R_{eff}$: M: 1.787, IQR = 0–9.146), followed by that of Group 1 to Group 2 ($R_{eff12}$: M = 0.287, IQR = 0–1.988) and finally Group 1 to Group 3 ($R_{eff13}$: M = 0.287, IQR = 0–1.988 median: 0.287, range: 0–1.988). The $R_{eff}$ for this intra-group showed a significant decreasing trend during the survey years, and Group 1 to Group 2 showed a trend of increasing before decreasing $R_{eff}$ and peaked in 2014.

The transmission in the 3–5 years age group was the highest in the intra-group (median: 0.627, range: 0.005–2.928) and Group 2 to Group 1 (median: 0.497, range: 0–4.617), and the lowest in the Group 2 to Group 3 (median: 0.060, range: 0–0.590); where the intra-group transmissibility of this age group showed a decreasing trend in $R_{eff}$ year by year.
In the over 5 years age group, the $R_{\text{eff}}$ from Group 3 to Group 1 was the largest and perennially over 1 (median: 1.217, range: 1.000–2.619), followed by Group 3 to Group 2 (median: 0.063, range: 0–3.412), while intra-group transmission (median: 0.104, range: 0–1.260) was the smallest; where the $R_{\text{eff}}$ from Group 3 to Group 2 showed a trend of rising and then falling and peaked in the second half of 2015, and the intra-group transmission of this age group rose yearly until 2014 peaked and then fell and tended to zero (Figure 7B).

**DISCUSSION**

Analysis and observation of the reported incidence of HFMD in Shenzhen city revealed that the incidence rate of HFMD in Shenzhen city is higher than the national-level incidence rate (34, 35), which may be due to the fact that Shenzhen city is a coastal city with a hot and humid climate and a high population density, conditions that favor the reproduction and spread of the virus. In addition, the incidence of HFMD in Asian subtropical countries...
is characterized by distinct peaks in spring and autumn (36), and the incidence data reported in Shenzhen city are consistent with the double peak at this latitudinal. In this study, we found that the number of reported cases in Shenzhen city increased over time, and the increased incidence suggests that the HFMD pathogen is still spreading in the city. In addition, we found that the four districts with the lowest incidence rates (Nanshan District, Futian District, Luohu District, and Yantian District) also had the top four GDP per capita in Shenzhen city, while the two districts with higher incidence rates had relatively lower GDP per capita in the city’s ranking (33). The economic level affects the local sanitation and, therefore, HFMD, as it is an intestinal infectious disease.

There are some limitations in this paper. In terms of model selection, in the past, we also chose the SEIAR model for simulation when cases were reported in a daily reported data (23, 37). However, it is rather unfortunate that exposed and asymptomatic populations were not introduced into the model because of the inability to obtain more precise units of incidence data due to the reporting of HFMD month-based data in Shenzhen. Meanwhile, the SIR model had stronger stability and avoided the problem of parameter identifiability than SEIAR (38). In addition, for the setting of susceptible individuals, we set all patients before 2010 to be susceptible. This is because HFMD was only incorporated into the infectious disease management system in China in 2008, and thus data on the recovered population are not available. The proportion of patients before that time is very small compared to the 10 million population in Shenzhen, so we believe that the effect is weak. The omission of this population may have an impact on the results of the age group component of the study, which needs to be discussed in further studies in future.

The results of the goodness-of-fit tests revealed that our model fitted the reported data well, which means that our modeling procedure has good validity and the model can be used to calculate the transmission rate of each pathogen.

In terms of the overall pattern, $R_{eff}$ was $>1$ in Shenzhen city most of the time and in all administrative district, indicating that HFMD is still prevalent in the city and the disease burden remains serious, requiring attention and prevention and control concerns, whilst $R_{eff}$ in Longgang district showed a gradual upward trend from 2010 to 2016. This may be due to the fact that Longgang, as a newly developed administrative region, has experienced rapid growth in population size and density in recent years, whereas the development of health care resources has failed to match the rate of population growth, leading to a rise in the transmissibility of HFMD. In contrast, the $R_{eff}$ values in other districts experienced ups and downs between 1 and 11 with no significant trend.

When comparing the $R_{eff}$ of the three age groups, it is clear that EV71 is most transmissible in the 0–2 years old group, while the $R_{eff}$ of the 3–5 years old group is perennially lower than the other two groups. This may be due to the relatively high concentration of activities in the community among infants aged 0–2 years. Therefore, the proportion of infants and young children in the exposed population is also higher, leading to more disease transmission in this age group, and also to a greater $R_{eff}$ of EV71 in the 3–5 years and the over 5 years group.

The 3–5 years age group should show a greater transmissibility due to increased socialization, while the smaller $R_{eff}$ may be due to certain hygienic habits developed after school. Also, today's society shows concern for the disease and the parents and kindergarten teachers give more hygiene protection. The higher $R_{eff}$ in the over 5 years old group compared to the previous group may be related to the older age group of EV71 in recent years, leading to an increased exposure rate. It can be seen that the transmission coefficient of HFMD for children in the 3–5 years group started to increase year by year in 2016. The greater contribution of transmission of the 3–5 years group to the transmission of the 0–3 years group may also be related to the comprehensive two-child policy launched in 2015.

After the launch of the HFMD vaccine in 2016, it is observed that the $R_{eff}$ also declined in the city and in all districts except Yantian District. The results of the TSIR model developed by JT. Wu et al. similarly suggest that a mass EV-A71 vaccination program for infants and young children might significantly reduce the overall burden of HFMD (22). In our study, differences in the transmission capacity of different age groups for around this time point could be observed. However, the peak in the number of cases after the launch of the vaccine in the autumn of 2017 was significantly higher than in previous years, which may be due to the significant increase in the number of children after the introduction of the two-child policy, resulting in an increase in the number of HFMD cases, and may also account for the higher values of $\beta_{21}$ in the second-stage fitting results in 2017.

In summary, we estimate that the disease burden of HFMD in Shenzhen city is severe with varying disease trends across districts. There is variability in transmission in different age groups, all of which are slightly weaker, respectively, relative to the overall picture. In addition, vaccination efforts have been effective, but prevention and control of HFMD caused by enterovirus such as Cox A16 and others need to be further strengthened.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

AUTHOR CONTRIBUTIONS

PL, JR, TC, and YN made substantial contributions to conception and design. PL, QL, JR, TC, and YN collected the data and conceived the experiments. PL, QL, YW, FX, JR, ZL, and YN conducted the experiments and analyzed the results. JH, PL, JR, BD, LL, CL, WL, FX, TY, and YW involved in the visualization of the results. PL, JR, SY, CL, YN, and YW wrote the manuscript. QL, JR, PL, TC, and YN revised it critically for important intellectual content. All authors approved the final manuscript and agreed to be accountable for all aspects of the work.

FUNDING

This study was partly supported by the Bill & Melinda Gates Foundation (INV-005834).
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