Epidemiological characteristics of hand, foot and mouth disease reinfection in Guangzhou, Southern China from 2012 to 2017

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Keywords: Hand, Foot and mouth disease; Enterovirus; Reinfection; Epidemiology

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Abstract

Background: Hand, foot and mouth disease (HFMD) is a common infectious disease that occurs mostly in infants and children. Reinfection is not uncommon because of the limited cross-protection from infections of different enterovirus. This study was to investigate the epidemiological characteristics and its influential factors of HFMD reinfection in Guangzhou. Methods: Data on HFMD patients aged ≤5 years from 2012 to 2017 were extracted from surveillance system. Descriptive epidemiology method was adopted to analyze the characteristics of populations and time. Influential factors of reinfection were assessed using the logistic regression model. Results: Of 369,054 HFMD patients, 11,321 patients were classified as reinfection, corresponding to a rate of 3.07%. The reinfection rate in male was higher than in female (χ2=60.11, P<0.001). The reinfection rate in patients ≤1 year was 3.86%, which showed a downward trend with age (Z=37.37, Ptrend<0.001). The highest reinfection rate was observed in the scattered children (3.38%), followed by nursery care children and others (χ2=514.75, P<0.001). Besides, higher risk of reinfection was detected among those who were male, lower age group and other enteroviruses infection compared with their respective counterparts. Seasonality was illustrated according to the number of reinfections peaked from April to July. Time intervals curves revealed the number of reinfections gradually increased after 13 months from the initial infection. Conclusions: These results indicated that male ≤4 years, especially those lived scattered and infected with other enteroviruses were more likely to be reinfection. Administrations need to be alert to signs of HFMD reinfection. Effective interventions should be imposed on these high-risk children in time.

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Background

Hand, foot and mouth disease (HFMD) is a common childhood illness caused by various enteroviruses. Generally, the disease is mild and self-limiting, with common symptoms including fever, painful sores in the mouth and a rash with blisters on hands, feet and buttocks. However, severe symptoms such as meningitis, encephalitis and polio-like paralysis may occur[1]. The most common causative pathogens are coxsackievirus A16 (CoxA16) and enterovirus 71 (EV71), with the latter accounting for the majority of severe and fatal HFMD[2]. HFMD is widespread in the Asian-Pacific region, such as Japan, Singapore, Vietnam, Taiwan and Hong Kong[3]. As one of the most affected countries, China reported 10,717,283 HFMD cases from May 2008 to June 2014, with 3,046 deaths and a fatality rate of 0.03%[4]. Morbidity increased from 146.6/100,000 population in 2015 to 149.4/100,000 population in 2018 and peaked in 2016 at 178.2/100,000 population. The incidence of HFMD also varies geographically[5, 6], with most cases occurring in large, densely populated cities. The situation is more serious in Guangzhou, where the incidence was 4 times higher than the national average[7]. Guangzhou is one of the top 3 cities in terms of the total number of HFMD cases reported[8]. Thus, HFMD represents a growing public health threat to children and social development.

The first inactivated EV71 vaccine for preventing HFMD became commercially available in China in 2015[9]. Although the EV71 vaccine showed a >90% protective effect against EV71-related HFMD[10, 11], reinfection can occur because of the lack of cross-protection against other viral subtypes. From 2008 to 2015, 398,010 out of an estimated 820,000 HFMD patients were diagnosed as reinfection cases in China[12]. The prevalence of HFMD reinfection in different regions has been estimated, with the reinfection rate ranging from 0.10% to 12.68%[13]. For example, 8,960 patients (2.02%) were confirmed to have reinfection in Anhui province and the annual reinfection rate increased each year from 2008 to 2013[14]. Furthermore, a cohort study reported the reinfection rate was 3.15% in Fujian province; patients were mainly infected twice, with the cumulative number of up to five reinfections[15].

Nevertheless, few large-scale epidemiological studies have been carried out on HFMD reinfection in Guangzhou, the capital of Guangdong province. Considering that children aged ≤5 years represent a high-risk population of HFMD[16], this study aims to describe epidemiological characteristics for HFMD reinfection and examine the relationship between reinfection in patients aged ≤5 years and influential factors.

Methods

Surveillance data

HFMD (mild/severe) is a collection of laboratory-confirmed cases (EV71/CoxA16/other enteroviruses) and clinically diagnosed cases (unknown enteroviruses) that are considered notifiable diseases in China. Once diagnosed, cases must be reported to the web-based China Information System for Disease Control and Prevention (CISDCP) within 24 h according to the guidelines for the prevention and control of HFMD (2009 edition)[17], which was published by the Chinese Ministry of Health. Daily count data for HFMD patients aged ≤5 years covering the period 2012–2017 were obtained from CISDCP. Patients' name, sex, age, date of birth, detailed address, group classification, case classification, date of onset, laboratory results, severity, parents' names and contact number were also collected from the system. Non-resident cases were excluded. In addition to passive surveillance of infectious diseases, the local Centers for Disease Control offices also conducted regular active surveillance to reduce misreporting and underreporting rates. The Ethics Committee of Guangzhou Center for Disease Control and Prevention (GZCDC) approved this study.

Screening criteria

The following definitions were used in this study. Single infection: only one infection between 2012 and 2017; multiple infections during this period but within 14 days after the first onset.

Reinfection: at least two infections during this period; the infections with the same patient's name, date of birth and contact information. If only one item is similar, then the infection can be verified by other items such as parents' names or address; the interval between the two infections was ≥15 days[18]. The initial infection refers to the first infection of the reinfected patient; the secondary infection refers to the second infection of the reinfected patient.

Statistical analysis

The reinfection rate was calculated as follows:

$$\text{Reinfection rate} = \text{number of reinfections} / \text{number of reported infections} \times 100\,\%.$$

The median and interquartile range (IQR) were used for statistical description of measurement data, and count data were presented as rate and proportion. The chi-squared test or Fisher's exact test was used to compare differences between groups. The Cochran–Armitage trend test was applied to analyze the relationship between reinfection rate and age. A multivariate logistic regression model was employed to evaluate the correlation between influential factors and HFMD reinfection. Patient screening and statistical analyses were performed using SAS V9.4 (SAS Institute, Cary, NC, USA). Statistical significance was defined as $P<0.05$.

Results

General characteristics

In total, 369,054 HFMD patients aged ≤5 years were included in analyses. Of these, 11,321 patients had repeatedly suffered from HFMD (3.07%), including 10,934 (2.96%) patients who had histories of two infections, 376 (0.10%) patients who had histories of three infections and 11 (0.003%) patients who had histories of four infections. Nearly 5.91% (1,154/19,526) of patients have showed HFMD reinfection among laboratory-confirmed cases, and other enteroviruses was the highest reinfection prevalent (6.36%). Twenty-eight single infection patients progressed to severe HFMD. No severe patients were identified among reinfection cases.

The reinfection rate was significantly higher in males (3.24%) than in females (2.79%) (P<0.001). Reinfection rates were also age-specific. Patients aged <4 years (96.54%) accounted for the majority of reinfection cases [median age: 2 years (IQR=1,3)]. The reinfection rate of patients aged 1 year was the highest (3.86%) and declined with increasing age (P_{trend}<0.001). More reinfection cases (3.38%) occurred in scattered children than those in nursery care children (1.75%) and other (0.81%) children (P<0.001). No significant difference in the case severity rate between reinfection and single infection patients was found (P>0.05, Table 1).

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Seasonal distributions and time interval

The highest HFMD reinfection rate was reported in 2013 (4.49%), whereas the lowest rate was reported in 2017 (0.20%, data not shown). As expected, the number of initial infections peaked from April to July each year, while a smaller autumnal peak (around September) was evident in 2012–2015. The lowest number of patients was seen in February. The seasonal distributions of initial, secondary and single infections were similar (Figure 1).

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Figure 1. Seasonal distributions of reinfections and single infections

The median time interval of patients infected twice was 13 months (IQR=10,21). In patients infected thrice, the median time intervals of the antecedent two infections and the latter two infections were 12 months (IQR=8,15) and 13 months (IQR=10,21), respectively. Likewise, in patients infected four times, the median time intervals between adjacent infections was 7 months (IQR=4,19), 7 months (IQR=4,17) and 12 months (IQR=2,16) in order. Reinfections were more likely to occur in the next epidemic season for all age groups. The first peak in the time interval between initial and secondary infections was 13 months, followed by 25 months and 37 months (Figure 2). For patients aged 1, 2, 3, 4 and 5 years, reinfection rates within 2 years were 78.56%, 84.52%, 91.36%, 100% and 100%, respectively.

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Figure 2. Time intervals between initial infections and secondary infections in different age groups

Virus subtype of HFMD reinfection

A total of 1,832 HFMD reinfection were classified as laboratory diagnosed, of which 1,154 patients had initial infection and 678 patients had secondary infection. Laboratory results were available for both initial and secondary infections in 301 patients with reinfection. The median age was 2 years for seven patients who were infected with EV71 twice, and the median time interval between infection and reinfection was 11 months. In addition, three patients were infected with CoxA16 twice. For patients infected with different enteroviruses between the initial infection and the secondary infection, statistically significant differences in virus types of HFMD reinfection infection were recognized (P<0.001, Table 2).

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The proportion of patients diagnosed with EV71-associated HFMD as the secondary infection (24.34%; OR=1.37, 95%CI=1.07–1.75) was higher than that in the single infection group (19.45%; OR=1.23, 95%CI=1.04–1.46) and the initial infection group (14.56%) (Table 3).

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Multivariate analysis of influential factors for reinfection

Multivariate analysis indicated that the reinfection risk was higher among males compared with females (OR=1.18, 95%CI=1.14–1.23). The risk of reinfection was also 17.95-fold higher in patients aged 2 years than those aged 5 years (95%CI=12.57–25.64). Notably, the OR of reinfection in patients aged ≤1 year reached 20.65 (95%CI=14.46–29.48). Interestingly, patients with other enteroviruses had a higher risk of reinfection than those with EV71 infection HFMD (OR=1.21, 95%CI=1.02–1.44) (Table 4).

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Discussion

We conducted a retrospective study to explore the epidemiological characteristics of HFMD reinfection and its associations with influential factors. The results revealed that the HFMD reinfection rate of patients aged ≤5 years in Guangzhou from 2012 to 2017 was 3.07%. This finding was consistent with that reported in Jiang et al.'s study (3.17%)[19], and the rate in Guangzhou was higher than that in Wuhan (1.93%)[18] and lower than that in Wuxi (6.01%)[20]. This difference in HFMD reinfection rates may be attributed to variation in geographical regions and time spans. Previous studies have hinted that a highly dense population is a risk factor for spread of HFMD[21], similar to dengue fever[22] and influenza[23].

The population density in Guangzhou amounted to 1,950 people/square kilometers in 2017, ranking in the top 10 most populated cities in China[24]. Consequently, densely populated areas such as Guangzhou should be closely monitored for HFMD infection.

The results obtained from our study and Chen et al.'s study were comparable[14], with a higher reinfection rate in males than in females. It is possible that males are more likely to be exposed to pathogens because of their high activity[25]. Additionally, it may be related to children's immune constitution[26]. However, the susceptibility of males aged ≤1 year to HFMD reinfection remains to be further studied.

A systematic review has demonstrated that the antibody level against EV71 or CoxA16 dramatically increased among children aged 1–4 years[27]. Zhang et al. believed that the immune level to enterovirus would accordingly increase with increasing age[28]. Our results also clarified that younger children have a greater likelihood of HFMD reinfection. It is necessary to remind younger children to maintain healthy habits, especially good hand washing practices[29].

The present study discovered that scattered children were more prone to HFMD reinfection. A similar finding has also been noticed in Huainan[30]. These findings are somewhat contrary to the general belief that nursery care children have more contact with each other and should have a higher risk of reinfection[31]. Possible reasons are that most scattered children are young and have poor self-care ability. For instance, because these children are accustomed to sucking their fingers, reinfection may readily occur through the fecal-oral route[32]. Moreover, scattered children lack effective early detection methods, such as morning examination.

Remarkably, findings of a seasonal pattern with the peak from April to July are consistent with the findings obtained in Yang et al.'s study[33], which examined the effects of humidity on HFMD reinfection. Relative humidity is associated with elevated risks of HFMD reinfection[33]. Adverse effects of relative humidity are generally long term. A humid environment has been reported to promote survival of HFMD-related virus[34]. A relatively small number of reinfections were identified in February, which coincided with the school holiday season, reducing contact opportunities among susceptible children. These results agreed with those of Eames et al.[35], who suggested the association between holidays and disease epidemics.

More importantly, the median time interval of HFMD reinfection was 13 months. It can be speculated that initially infected patients recovered from the infection at the peak of the epidemic, and then became infected with another virus in the next peak month, resulting in reinfection. In this study, single infection included both patients initially infected before 2012 and patients reinfected after 2017. Therefore, the actual reinfection rate is likely higher than reported, which may also explain the seasonal distribution curve of the lower peak for secondary infection in 2012 and initial infection in 2017.

Laboratory results in patients whose pathogens were detected in two infections support the notion that limited cross-protection against different virus subtypes occurs after natural infection, which is in agreement with observations from the EV71 vaccine study[36] and a modeling study of natural

infections[37]. One reason underlying EV71 reinfection is that patients have been infected with the variant EV71 genogroup successively. At present, the EV71 genogroup reported in most regions of China is C4a/C4b[38], but there are also reports of EV71 B genogroup causing disease[39]. Thus, the current EV71 vaccine may not provide cross-protection between genogroups, allowing for reinfection.

Interestingly, a relatively higher reinfection rate was observed for other enteroviruses compared with EV71. Recently, studies have shown that other enteroviruses have replaced EV71 and CoxA16 as predominant pathogens of HFMD in mainland China, although it is unclear if this is consistent throughout China[6]. Additionally, other enteroviruses have been responsible for HFMD outbreaks in Europe[40, 41]. These studies provided strong evidence of other enteroviruses as new and important causes of reinfection, thus highlighting the necessity of comprehensive surveillance of HMFD infections caused by other enteroviruses in addition to EV71 and CoxA16 in the future.

In this study, although patients were more susceptible to EV71 during single infection, patients were at greater risk of contracting EV71 during secondary infection than in initial infection if secondary infection occurred. Patients infected with EV71 have increased risk for severe HFMD reinfection[12]. This indicates that severe risk of secondary infection may be higher. However, few severe cases were observed, which requires further verification.

While we characterized HFMD infection over a longer period in this study, there are some limitations that must be discussed. First, influential factors for HFMD include hygiene and social contacts, but we failed to collect this information completely. Second, the results are not representative enough to be extended to other regions.

Conclusions

In summary, our present study sheds light on the latest epidemiological characteristics of HFMD reinfection in Guangzhou, China. The HMFD reinfection rate was 3.07% from 2012 to 2017. The data suggested that sex, age and case classification have a significant effect on HFMD reinfection. Targeted health education programs and interventions must be developed to reduce the HFMD reinfection rate in susceptible populations.

Abbreviations

HFMD: Hand, foot, and mouth disease; CoxA16: Coxsackievirus A16; EV71: Enterovirus 71; IQR: Interquartile range; CI: Confidence interval; OR: Odds ratio

Declarations

Ethics approval and consent to participate

The study approval was obtained from The GZCDC Ethics Committee (Grant No.: 2017014) and this study got the permission of use these data from GZCDC.

Consent for publication

Not applicable.

Availability of data and material

The data that support the findings of this study are available from the Chinese Centre for Disease Control and Prevention but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available.

Competing interests

The authors declare that they have no competing interests.

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Authors’ contributions

ZX analyzed data and wrote the manuscript. WH and LTG conceived and designed the study and revised the manuscript. CC and ZXN contributed data collection and helped supervise the data quality. All authors read and approved the final manuscript.

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Tables

Due to technical limitations, the tables are only available as a download in the supplemental files section.

Figures

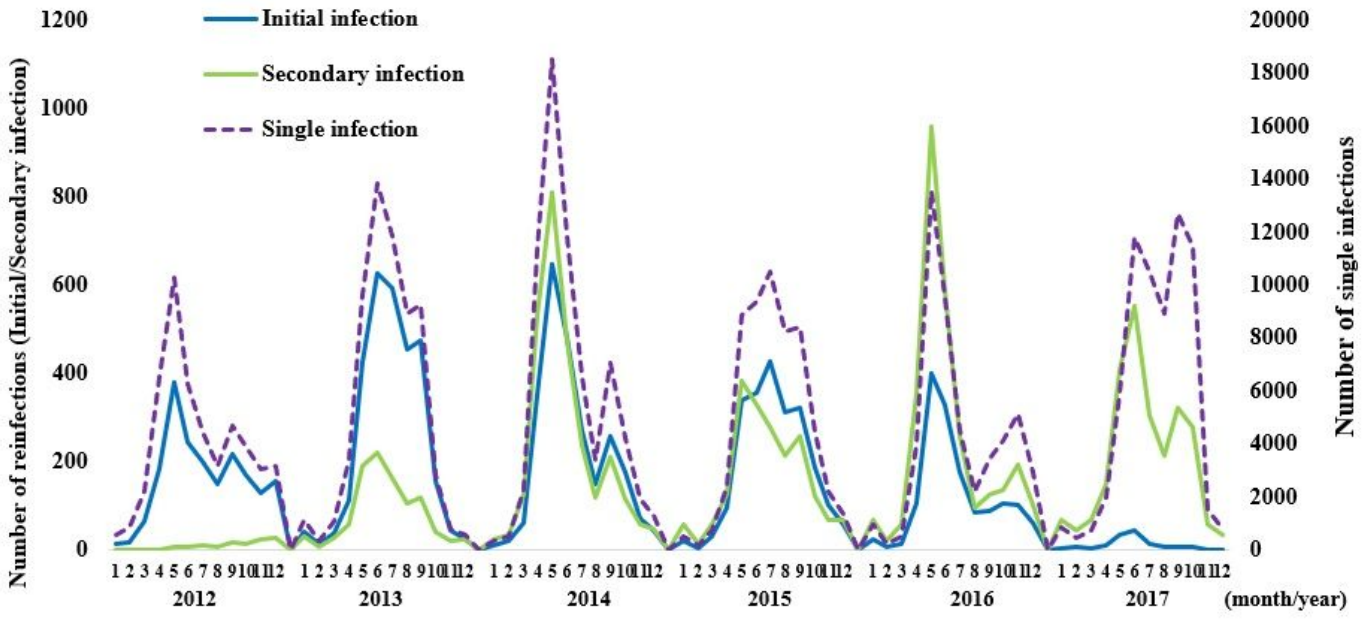

Figure 1. Seasonal distributions of reinfections and single infections

Figure 1

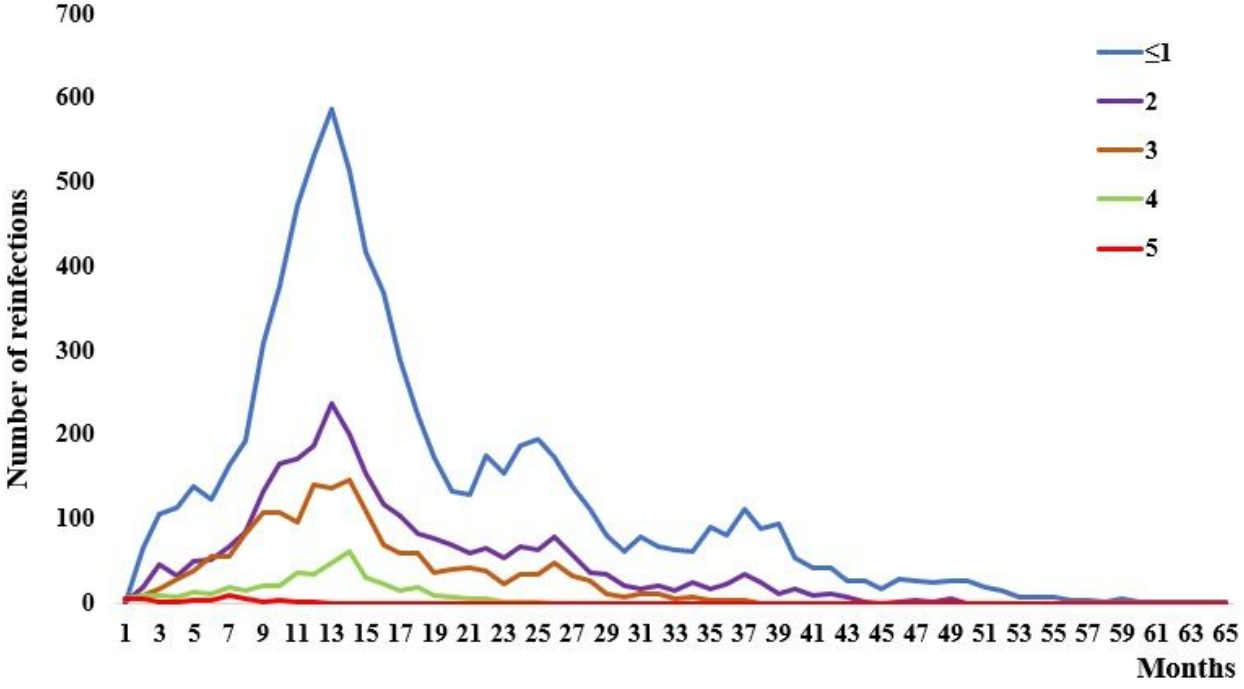

Figure 2. Time intervals between initial infections and secondary infections in different age groups

Figure 2

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Tables.pdf