

Epidemiological characteristics and influential factors of hand, foot and mouth disease (HFMD) reinfection in children in Anhui province

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SUMMARY

Hand, foot and mouth disease (HFMD) is an acute contagious condition caused by a spectrum of human enteroviruses. HFMD reinfection is common in the absence of cross-protection from other virus subtypes. This study focused on reinfection in children in Anhui province, China between 2008 and 2013 using surveillance system data. We classified 8960 cases as reinfected, corresponding to a rate of 2·02%. The reinfection rate was higher in boys than in girls [odds ratio (OR) 1·27, 95% confidence interval (CI) 1·21–1·32, $P < 0\cdot001$], children aged < 3 years (OR 3·82, 95% CI 3·58–4·07, $P < 0\cdot001$), and children living in rural areas (OR 1·09, 95% CI 1·04–1·14, $P = 0\cdot001$). The reinfection rate in children who were originally infected with non-enterovirus A71 (non-EVA71) enteroviruses was higher than those infected with EVA71 (OR 1·36, 95% CI 1·02–1·80, $P = 0\cdot034$). Influential factors of reinfection rate included annual incidence (β coefficient = 0·715, $P = 0\cdot002$) and the proportion of EVA71 in patients with mild HFMD (β coefficient = $-0\cdot509$, $P = 0\cdot018$). These results demonstrate that boys aged < 3 years, especially those in rural areas or regions with a lower EVA71 proportion are more prone to reinfection, and specific health education programmes should be developed to protect these susceptible populations.

Key words: Epidemiology; hand, foot and mouth disease (HFMD); re-infection.

INTRODUCTION

Hand, foot and mouth disease (HFMD) is a common acute contagious disease, particularly in children aged < 5 years. It is characterized by fever, ulcers or blisters in the mouth, and a rash on the hands, feet, or buttocks [1]. HFMD is typically a mild, self-limiting disorder; however, some patients may progress to develop severe complications such as aseptic meningitis,

neuronal pulmonary oedema, myocarditis, or even death [2–4]. While HFMD is caused by a spectrum of human enteroviruses, enterovirus A71 (EVA71) and coxsackievirus A16 (CVA16) are considered to be the major pathogens [5].

There have been widespread cases of HFMD in the Asia-Pacific region in past decades, especially in East and South East Asia including Taiwan (China), Singapore, Malaysia, Japan and mainland China [6–8]. The first case of HFMD in mainland China was reported in Shanghai in 1981, and additional cases were gradually reported in other regions [9, 10]. However, HFMD did not receive sufficient attention until two large outbreaks caused 25 deaths in Linyi city, Shandong province and

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Fuyang city, Anhui province [11, 12]. Subsequently, there was a nationwide epidemic, and HFMD was classified as a category C notifiable infectious disease by the Chinese Ministry of Health on 2 May 2008. More than 100 000 HFMD cases are reported annually through the National Infectious Disease Surveillance System of China, ranking it first among the notifiable infectious disease categories. Between 2008 and 2013, there were approximately 600 severe HFMD cases and 20 deaths annually in Anhui province. As a result, HFMD has become an important public health issue.

Lacking cross-protection from different virus subtypes, HFMD reinfection is quite common [13], which increases the prevalence of HFMD and the associated public health burden. However, few studies have focused on reinfection, which hampers the development of targeted interventions. The present investigation assessed the reinfection rate in children in Anhui province, China between 2 May 2008 and 31 December 2013 in order to summarize the epidemiological characteristics and influential factors of reinfection.

METHODS

Study samples

Since 2 May 2008, HFMD has been required to be reported as a statutorily notifiable infectious disease, with laboratory-confirmed and clinically diagnosed cases to be reported within 24 h. Data on HFMD cases from 2 May 2008 to 31 December 2013, including name, sex, age, date of birth, date of onset, current address, phone number, name of parents, reporting unit, and pathogenic results, were extracted from the National Infectious Disease Surveillance System of China by date of onset and current address.

Case definition

The diagnostic criteria of HFMD were based on the 2010 HFMD Clinic Guidelines issued by the Ministry of Health of China. A clinically diagnosed case of HFMD was defined as a patient presenting with a vesicular rash over the hands, feet, mouth, or buttocks, with or without fever. A laboratory-diagnosed case of HFMD was defined as a clinically diagnosed case with laboratory evidence including enterovirus isolation, detection of enterovirus-specific RNA, or at least a fourfold increase in the antibody titres between the acute and convalescent phases or

neutralizing antibody titres $\geq 1:256$. Patients were diagnosed as severe cases of HFMD, regardless of clinical or laboratory diagnosis, if they presented with any neurological complications (e.g. brainstem encephalitis, aseptic meningitis, acute flaccid paralysis) and/or cardiopulmonary complications (e.g. myocarditis, pulmonary oedema, shortness of breath, cardiorespiratory failure). All other patients were diagnosed with mild HFMD. A reinfected case was defined as a patient who was infected with HFMD at least twice from 2008 to 2013, and a patient who was infected with HFMD only once was identified as a non-reinfected case.

Reinfected case screening

The screening criteria for reinfected cases included (1) the same patient's name; (2) >15 days between the two infections; (3) more than one item alike among the parent's name, phone number, and current address. If only one item was alike, the information was checked with the patient's guardians.

Reinfected HFMD cases were screened using the Microsoft Excel macro program (Microsoft, USA) that automatically copies eligible case information to a file. All data were then checked manually, and if any inaccuracy was identified, the patients' guardians would be contacted to confirm the information.

Statistics

The numbers and percentages were calculated for categorical variables, and medians and interquartile ranges (IQRs) were summarized for continuous variables. The χ^2 test was applied to stratify comparisons of reinfection rate (the number of reinfected cases divided by number of probable and confirmed cases) and case-severity rate (the number of severe cases divided by number of probable and confirmed cases), and the trend χ^2 test was used to analyse the incidence trend with age. A linear regression model was used to explore the influential factors of reinfection rate in different regions. $P < 0.05$ was considered statistically significant. All statistical analyses were performed with SPSS v. 11.0 (SPSS Inc., USA).

RESULTS

General patient information

A total of 444 076 paediatric cases of HFMD were reported from 2008 to 2013 in Anhui province, of

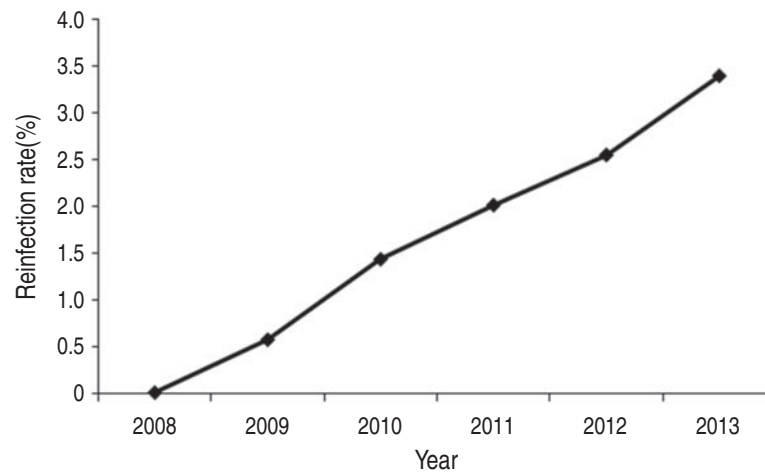


Fig. 1. HFMD reinfection rate from 2008 to 2013.

Table 1. Reinfection rate according to sex, age group, and residence

Characteristics	Reinfection (n)	Non-reinfection (n)	Reinfection rate (%)	OR (95% CI)	χ^2	P
Sex						
Male	6168	276 683	2.18	1.27 (1.21–1.32)	104.678	<0.001
Female	2792	158 433	1.73			
Age (years)*						
0	1898	35 240	5.11	3.37 (3.07–3.68)	3420.090	<0.001
1	4099	130 331	3.05	2.91 (2.68–3.16)		
2	1882	120 011	1.54	2.38 (2.19–2.59)		
3	789	75 003	1.04	2.33 (2.14–2.55)		
4	207	37 397	0.55	1.96 (1.78–2.16)		
≥5	85	37 134	0.23	1.00		
Residence						
Rural	6615	314 235	2.06	1.09 (1.04–1.14)	11.343	0.001
Urban	2345	120 881	1.90	1.00		

CI, Confidence interval; OR, odds ratio.

* Age calculated according to the primary infection.

which 8960 cases were reinfections. The reinfection rate was 2.02%, with 8752 cases infected twice, 200 cases three times, and eight cases four times. The annual reinfection rate increased each year (Fig. 1).

Population and time distribution

The reinfection rate was higher in boys than girls [odds ratio (OR) 1.27, 95% confidence interval (CI) 1.21–1.32, $P < 0.001$]. The reinfection rate decreased with age ($\chi^2 = 3420.090$, $P < 0.001$), and the reinfection rate in children aged < 3 years was higher than that of older children (OR 3.82, 95% CI 3.58–4.07, $P < 0.001$). Subjects aged < 3 years accounted for 87.94% of reinfected cases. The reinfection rate was higher in rural areas than urban

areas (OR 1.09, 95% CI 1.04–1.14, $P = 0.001$; Table 1). The seasonal distributions of primary and secondary infections and non-reinfection were similar, and the peaks occurred from May to July annually (Fig. 2).

Reinfection time interval

In cases that were infected twice, the median time interval between the infections was 11 (IQR 7–17) months, and reinfection was more likely to appear in the next epidemic season in all age groups (Fig. 3). In cases that were infected three times, the median time intervals were 9 (IQR 6–12) and 10 (IQR 5–14) months between the previous two infections and the latter two infections, respectively.

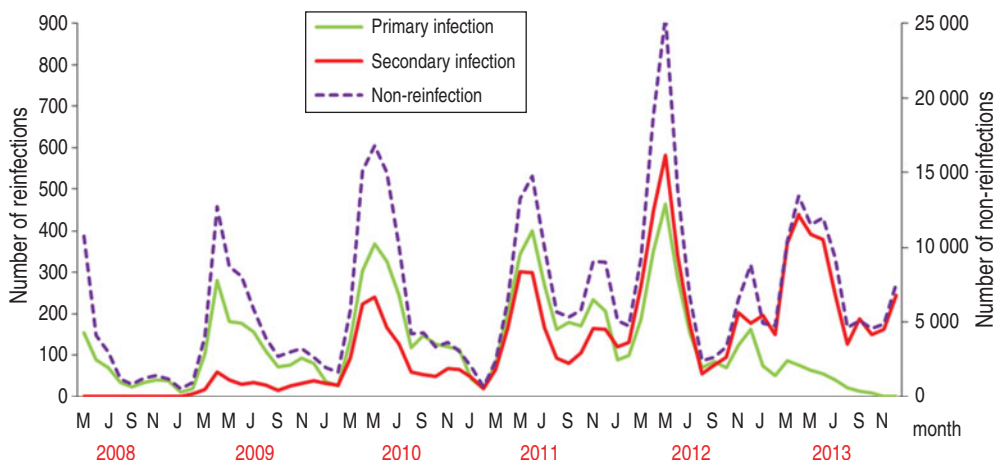


Fig. 2. Seasonal distributions of the primary and secondary infections and non-reinfection.

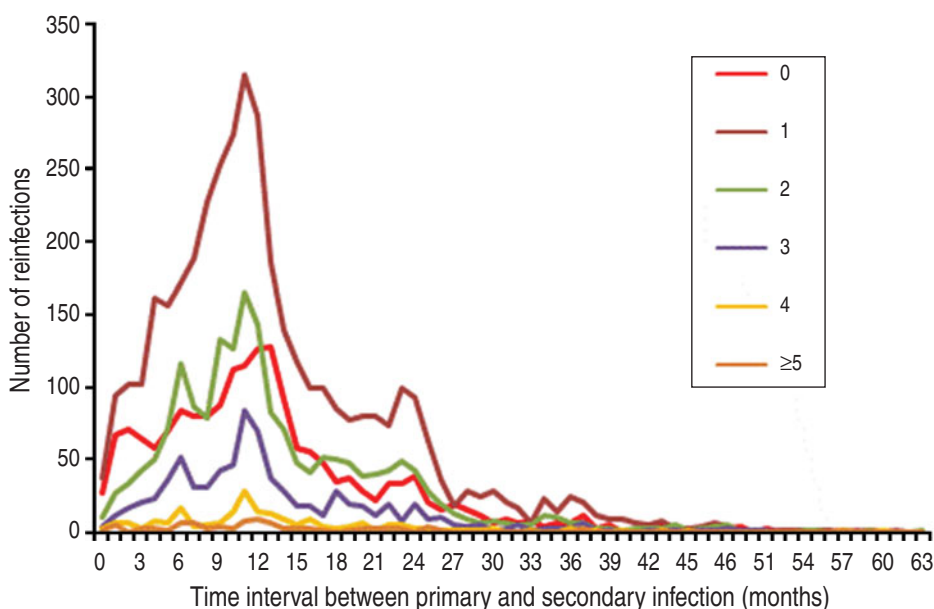


Fig. 3. Time intervals between primary and secondary infections in different age groups.

Table 2. Regression analysis of the factors correlated with reinfection rate at the city level

	Non-standard coefficient, β	Standard coefficient, β	t	P
Constant	2.143		4.328	0.001
Annual incidence	0.010	0.715	3.795	0.002
EVA71 proportion	-2.397	-0.509	-2.702	0.018

Influential factors of regional reinfection rate

A linear stepwise regression analysis was used to identify factors influencing the regional reinfection rate. It was significantly correlated with the proportion of EVA71 in laboratory-confirmed HFMD cases of mild illness (β coefficient = -0.509, $P = 0.018$) and the annual incidence of HFMD (β coefficient = 0.715, $P = 0.002$), but it was not significantly correlated with the proportion of boys or the proportion of children aged <3 years. The detailed results are listed in Table 2 and Figure 4.

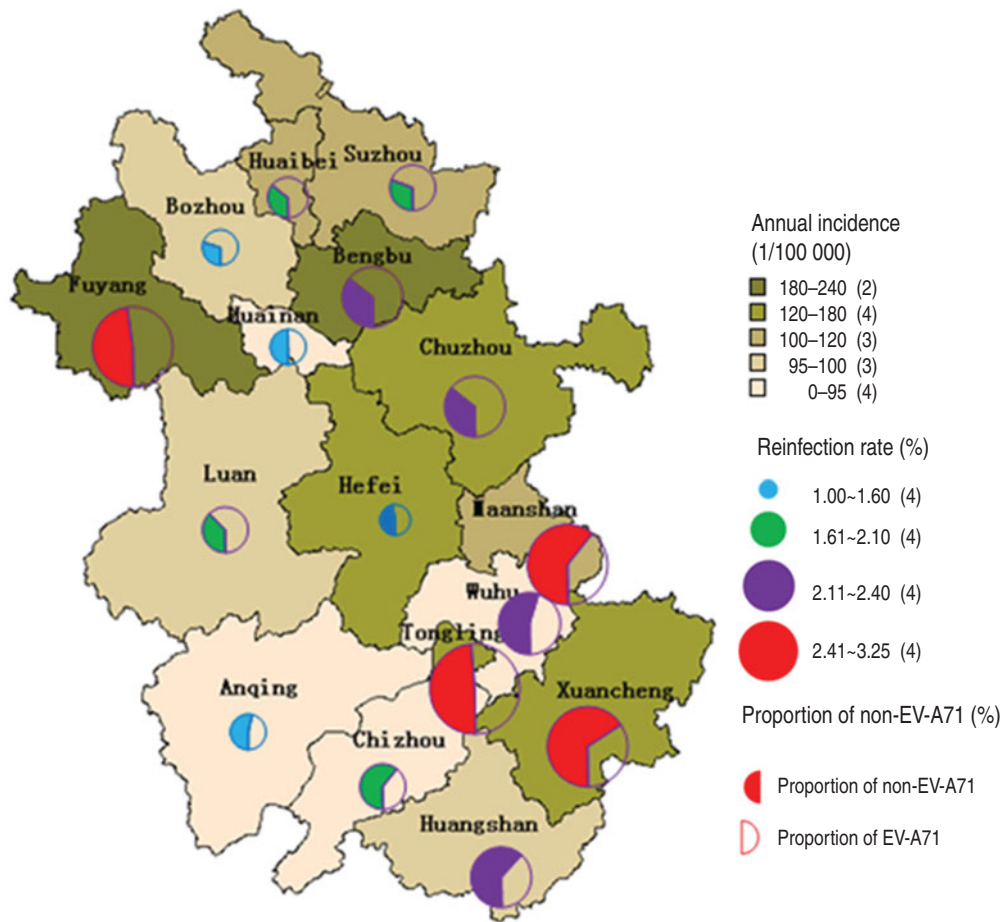


Fig. 4. Distribution of the annual incidence, proportion of non-EVA71 disease, and reinfection rate from 2008 to 2013 in Anhui province, China. The annual incidence is colour coded from pale to dark brown, and the proportion of non-EVA71 disease and reinfection rate are shown according to the area and size of circular symbols.

Table 3. Case-severity rates of reinfection and non-reinfection

Characteristics	Severe (n)	Mild (n)	Case-severity rate (%)	OR (95% CI)	χ^2	P
Reinfection	27	8933	0.30	0.55 (0.38–0.81)	9.541	0.002
Non-reinfection	2360	432 756	0.54	1.00		

CI, confidence interval; OR, odds ratio.

Clinical classification and reinfection virus subtype

Of all the reinfected cases, 88 were classified as severe, and there were no fatal cases. Of these, 27 severe cases were identified in the second infection; however, the case-severity rate for reinfection was lower than that of non-reinfection (OR 0.55, 95% CI 0.38–0.81, $P = 0.002$; Table 3).

There were 477 laboratory-confirmed reinfected cases. Of these, 223 cases were only tested in the primary infection, 246 in the reinfection, and eight

cases in both. In the mild cases that were analysed, the reinfection rate was higher in patients infected with non-EVA71 enteroviruses (OR 1.36, 95% CI 1.02–1.80, $P = 0.034$; Table 4).

Eight patients had both primary and secondary laboratory test results (Table 5), and two patients were infected with EVA71 in both infections. The first patient was a 1-year-old child who was infected in May 2012 and March 2013, and the second patient was a 3-year-old child infected in May and November 2013.

Table 4. *Reinfection rates of different virus subtypes in mild cases*

Characteristics	Reinfection (n)	Non-reinfection (n)	Reinfection rate (%)	OR (95% CI)	χ^2	P
Non-EVA71	111	4463	2.43	1.36 (1.02–1.80)	4.484	0.034
EVA71	86	4697	1.80	1.00		

CI, confidence interval; OR, odds ratio.

Table 5. *Pathogenic results in subjects whose pathogens were detected in two infections*

Primary infection	Secondary infection	Number
EVA71	EVA71	2
EVA71	CVA16	2
CVA16	Other enteroviruses	2
Other enteroviruses	EVA71	1
Other enteroviruses	Other enteroviruses	1

DISCUSSION

Children are susceptible to enteroviruses that can cause HFMD. The antibodies produced after natural infection can provide certain protection against the same virus subtype; however, they cannot provide cross-protection for other subtypes [13]. For this reason, HFMD reinfection is quite common. Our results show that the reinfection rate in Anhui province during 2008 to 2013 was 2.02%, and it increased every year.

Ji *et al.* [14] demonstrated that the seroprevalence rate of anti-EVA71 and anti-CVA16 gradually increased with age and peaked in 4-year-olds. The median time interval between reinfection was 11 months; therefore, children aged <3 years were more prone to HFMD reinfection. We found that the reinfection rate in children aged <3 years was significantly higher than that in older children, with the primary infection age of <3 years accounting for 87.94% of reinfected cases. The present results also demonstrate that the HFMD reinfection rate was higher in boys than in girls, which is in accordance with HFMD incidence outcomes [15]. A possible reason for this discrepancy is that boys are generally more mischievous and active and may therefore have more opportunities to touch objects polluted by other infected children. A difference in the consultation rate between boys and girls in rural areas may also contribute to the sex-specific difference. We observed that the reinfection rate was higher in rural areas, mainly due to the poor sanitary conditions. In summary, boys aged <3 years living in

rural areas were more susceptible to HFMD reinfection. Therefore, their parents or guardians need to be alert to signs of HFMD, even if their children were previously infected. In addition, administrations need to develop specific health education programmes to inform susceptible populations of the risk reinfection. These could include videos playing in vaccination clinics, sending text messages to guardians of children aged <3 years through the vaccination system, and handing out fliers to the guardians of HFMD patients at clinics.

There was a significant difference in reinfection rates in different cities with a maximum and minimum of 3.25% and 1.09%, respectively. Both the regional annual incidence and EVA71 proportion in mild cases were associated with the regional reinfection rate. Prior to this report, lower EVA71 prevalence rates were encouraging as they predicted lower case-severity rates and lower HFMD burden [16]. However, according to our study, the lower primary infection rate of EVA71 is associated with a higher reinfection rate. Public health authorities in areas with a lower EVA71 proportion of laboratory-confirmed cases need to promote hygiene education so that children can reduce the likelihood of reinfection.

Since the 2008 HFMD outbreak, EVA71 has been shown to be predominant in Anhui province, and it reached 51.09% in mild HFMD cases. As EVA71 was more prevalent in the environment, children infected with non-EVA71 enteroviruses tended to be reinfected with HFMD. In the present study, the reinfection rate in subjects infected with EVA71 was 1.80%, which was lower than that in those infected with non-EVA71 enteroviruses (2.43%). The case-severity rate in reinfection was also lower than that in non-reinfection. A similar phenomenon was reported for H1N1 influenza reinfection [17], and it was hypothesized that these patients had suboptimal immune protection from the primary natural infection.

HFMD has a high silent infection rate and multiple transmission routes, both of which contribute to the

relatively poor effectiveness of public health interventions, and vaccine development is a priority. In mainland China, three EVA71 vaccines have gone through phase 3 clinical trials, with a vaccine efficacy >90% [18–20]. However, there were some discrepant results throughout the trials. Chen *et al.* [21] reported that two HFMD patients were infected with EVA71 twice, and the time intervals were 7 and 15 months. In the present study, there were also two patients infected with EVA71 virus twice, and the time intervals were 5 and 10 months. There are several reasons that may explain this phenomenon. First, more than two genogroups of EVA71 viruses can occur simultaneously in an epidemic. Huang *et al.* [22] demonstrated that children infected with genogroup B or C EVA71 virus were not cross-protected against genogroup A, and genogroups A and C EVA71 viruses were found throughout China [23, 24]. Therefore, patients can be infected with different EVA71 virus genogroups. Second, individual immune system differences can cause reinfection such as host immunological defects or host sub-optimal immune responses in the primary infection. It is therefore necessary to conduct pathogen tests on reinfected cases to determine the EVA71 reinfection rate, which will provide essential data to guide EVA71 vaccine development.

The present study has several limitations. First, only 5–10% of cases were confirmed with laboratory tests, therefore very few reinfected cases had laboratory results for both infections. Second, the samples of two patients infected with the EVA71 virus in both infections could not be collected for sequence analysis.

CONCLUSION

Our results demonstrate that the HFMD reinfection rate in Anhui province was 2.02% from 2008 to 2013. The reinfection-susceptible population comprised children living in rural areas who were aged <3 years, particularly boys, and children who had been primarily infected with non-EVA71 enteroviruses. A higher incidence and lower EVA71 proportion of laboratory-confirmed cases were positively associated with regional reinfection. It is vital that administrations develop specific health education policies to inform susceptible populations and reduce the reinfection rate.

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DECLARATION OF INTEREST

None.

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