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Original Article

Risk Factors for Hand, Foot and Mouth Disease Reinfection in Qingdao, China, from 2014 to 2022

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Abstract

Background: Hand, foot and mouth disease (HFMD) is a common infection disease among children, which is caused by human enterovirus (EV) family. The absence of cross-protection against different EV sub-types, makes HFMD reinfection common. Thus, we aimed to explore the epidemiological characteristics and influencing factors of HFMD reinfection in Qingdao City.

Methods: Data on HFMD cases from 2014 to 2022 were obtained from National Infectious Surveillance System. Logistic regression analysis was used to assess the independent risk factors of HFMD reinfection.

Results: Overall, 78422 HFMD cases were enrolled. Of these, 2041 cases were classified as reinfection, corresponding to the reinfection rate of 2.60%. The median time interval between the primary infection and secondary infection was 12.75 (IQR=12.24) months. The seasonal peak of reinfection occurred from June to August each year. Multivarite logistic analysis showed that male, younger age, scattered children, severe cases, hospitalization, and EV71 infection were risk factors for HFMD reinfection. The proportion of patients infected with EV71 in the primary infection cases was higher than that in non-reinfection cases (OR=1.83, 95%CI=1.29-2.60).

Conclusion: Boys aged 5 years and below, especially those with severe cases and first infected with EV71 are more prone to reinfection. Therefore, authorities should implement targeted health education and intervention strategies to reduce the reinfection rate among vulnerable population.

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

Introduction

Hand, foot and mouth disease (HFMD) is a common contagious disease caused by human enteroviruses. The disease primarily affects children less than 5 years old, but it can affect adults as well. The major pathogens are considered to be enterovirus 71 (EV71) and coxsackievirus A16

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(CoxA16) (1). In recent years, CV-A6 has emerged as a major contributor to sporadic HFMD cases and outbreaks in numerous countries (2). HFMD is characterized by skin eruptions on the hands, feet, or buttocks and oral ulcers or blisters, with or without fever (3). Typically, HFMD presents with mild symptoms and is a self-limiting illness that lasts for 7-10 days. However, aseptic meningitis, neurogenic pulmonary edema, or even death may occur in some patients (4).

In the past decades, HFMD has been widespread among the Asian-Pacific region, especially in Singapore, Vietnam and Japan (5), causing a significant public health issue. In 1981, the first case of HFMD was reported in Shanghai, China (6). However, it did not receive sufficient attention until two large-scale outbreaks in Linyi and Fuyang City, which led to thousands of cases and 25 deaths (7, 8). Subsequently, HFMD was listed as a class C notifiable disease in China on 2 May 2008. As one of the most affected countries, China reported more than 10 million HFMD cases from May 2008 to June 2014, with 3,046 deaths and a fatality rate of 0.03% (9). The annual average child incidence rate of HFMD was 217/10,000 in Qingdao City, which is higher than the other cities in Shandong Province (10). Therefore, it is particularly important to identify related risk factors to prevent it.

In 2015, the monovalent EV71 inactivated vaccine was approved for use in China, serving as an effective tool for preventing HFMD caused by EV71 and reducing the number of severe cases. Although the EV71 vaccine and neutralizing antibodies produced after infection can provide some protection against the same EV sub-type of HFMD, they cannot prevent infection by the other different EV sub-types (11). The absence of cross-protection against virus infection by different EV sub-types makes HFMD reinfection quite common, thereby escalating the prevalence of HFMD and the associated societal health burden. Different regions have reported a high incidence of HFMD reinfection, ranging from 1.9% to 4.0% (12-14). However, these studies mainly focused on the basic epidemiological description of reinfection, and there was insufficient studies on HFMD reinfection in Qingdao City.

For these reasons, we aimed to evaluate the epidemiological characteristics of HFMD reinfection in Qingdao from 2014 to 2022, and explore the influencing factors of reinfection.

Material and Methods

Data collection

At present, laboratory-confirmed and clinical diagnosed HFMD cases should be reported to the National Infectious Surveillance System within 24 hours. Data of HFMD cases in Qingdao City from 1 January 2014 to 12 December 2022 were obtained from the National Infectious Surveillance System. The collected data consisted of basic demographics (name, sex, identification number, birth date, diagnosed date; address, telephone number, parents' name, group classification); hospitalization status (yes or no); clinical classification (severe or mild); date of onset, and death (if any); case classification (clinical or laboratory); and pathogenic results (EV71, CoxA16, or other enteroviruses).

The Ethics Committee of Qingdao Center for Disease Control and Prevention approved this study (Grant No.: 202308).

Case definitions

The diagnosis of HFMD cases was based on the guidelines for diagnosis and treatment issued by the National Health Commission of the People's Republic of China (15). A clinical diagnosed case of HFMD was defined as exhibiting a vesicular or maculopapular rash on hands, feet, mouth and/or buttocks, with or without fever. A laboratory-confirmed case of HFMD was defined as a clinical diagnosed case with one of the following laboratory evidence, which included: 1) a positive specific nucleic acid test for enteroviruses (EV71, CoxA16 or other enteroviruses); 2) isolation of EV (EV71, CoxA16 or other EV). Patients were diagnosed as severe HFMD if developed pulmonary edema, cardiorespiratory failure or any neurological complications such as aseptic meningi-

tis, brainstem encephalitis or encephalomyelitis. Otherwise,the patients were diagnosed with mild HFMD. Scattered children referred to young children who had not been sent to a nursery, daycare center, or kindergarten, but were only raised at home.

Reinfection case screening criteria

The screening criteria for reinfection cases included: 1) at least two infections during this period; 2) > 15 days between the two diagnosed date; 3) more than two items were alike among the name, birth date, unique identification number, parent's name, phone number, place of work, and current address. The information was verified with the patient's guardians if only one item was the same. Reinfection cases included two stages: primary infection and secondary infection. The primary infection referred to the first infection of the reinfected patient, while the secondary infection referred to the second infection of the reinfected patient. The patient who had only infected HFMD once was considered non-reinfection case.

Statistical analysis

We used Microsoft Excel 2010 (Microsoft, US) for data entry as well as to sort cases of reinfection and non-reinfection. Then all data entry was rechecked manually. The reinfection rate was calculated as follows:

Reinfection rate= number of reinfection cases/(number of reinfection cases + non-reinfection cases) *100%.

Categorical variables were presented as numbers and percentages. The chi-square test was used to compare differences in categorical variables between groups. Logistic regression analysis was used to assess the independent risk factors of HFMD reinfection. All statistical analyses were performed with SPSS version 21.0 (IBM Corp. in Armonk, NY, US). All testing was two-sided, and *P*-value ≤ 0.05 was considered statistically significant.

Results

General patient information

From 2014 to 2022, a total of 78422 HFMD cases were included in our study. Of these, 2041 cases were identified as reinfection and 76381 cases were identified as non-reinfection. The reinfection rate was 2.60%. Among 2041 reinfection cases, 1992 cases were infected twice (2.54%), 48 cases were infected three times (0.06%), and one case was infected four times. No deaths were reported in our study.

The reinfection rates for different groups are shown in Table 1. The reinfection rate was significantly higher in males (2.78%) than in females (2.34%) (P<0.001). The reinfection rate decreased with increasing age (P<0.001). Scattered children had a reinfection rate of 3.28%, significantly higher than other groups (P<0.001). A significant difference in reinfection rate between urban (2.82%) and rural areas was (2.51%) found (P<0.05). In severe cases and hospitalization cases, the reinfection rate was significantly higher than in their counterparts (P<0.001). Compared with other groups, more higher reinfection rate occurred in patients first infected with EV71.

Seasonal distributions and time interval

The annual reinfection rate from 2014 to 2022 was 0.27 %, 1.95%, 3.48%, 3.19%, 2.57%, 4.51%, 3.00%, 2.82%, 2.30%, respectively. The highest reinfection occurred in 2019. The seasonal distributions of primary infection, secondary infection, and non-reinfection cases were similar (Fig. 1). The seasonal peak of reinfection occurred from June to August each year.

Table 1: Reinfection rates of HFMD by different social demographic characteristics in Qingdao city

Characteristics	Total (N)	Reinfection		Non-Reinfection		χ^2	*P*
		n	%	n	%		
All cases	78422	2041	2.60	76381	97.40		
Sex						14.74	<0.001
Male	46800	1302	2.78	45498	97.22		
Female	31622	739	2.34	30883	97.66		
Age (yr)						382.11	<0.001
<1	6410	233	3.63	6177	96.37		
1~2	20523	747	3.64	19776	96.36		
2~3	12887	408	3.17	12479	96.83		
3~4	13511	383	2.83	13128	97.17		
4~5	9867	159	1.61	9708	98.39		
≥5	15224	111	0.73	15113	99.27		
Group classification						288.60	<0.001
Scattered children	49291	1617	3.28	47674	96.72		
Kindergarten children	22554	407	1.80	22147	98.20		
Students/others	6577	17	0.26	6560	99.74		
Region						5.98	0.014
Urban	22578	637	2.82	21941	97.18		
Rural	55844	1404	2.51	54440	97.49		
Clinical classification						82.77	<0.001
Severe	1178	80	6.79	1098	93.21		
Mild	77244	1961	2.54	75283	97.46		
Hospitalization status						88.80	<0.001
Yes	4560	217	4.76	4343	95.24		
No	73862	1824	2.47	72038	97.53		
Laboratory results						17.50	<0.001
Other enteroviruses	2586	65	2.51	2521	97.49		
CoxA16	1309	38	2.90	1271	97.10		
EV71	1039	48	4.62	991	95.38		
Unknown	73488	1890	2.57	71598	97.43		

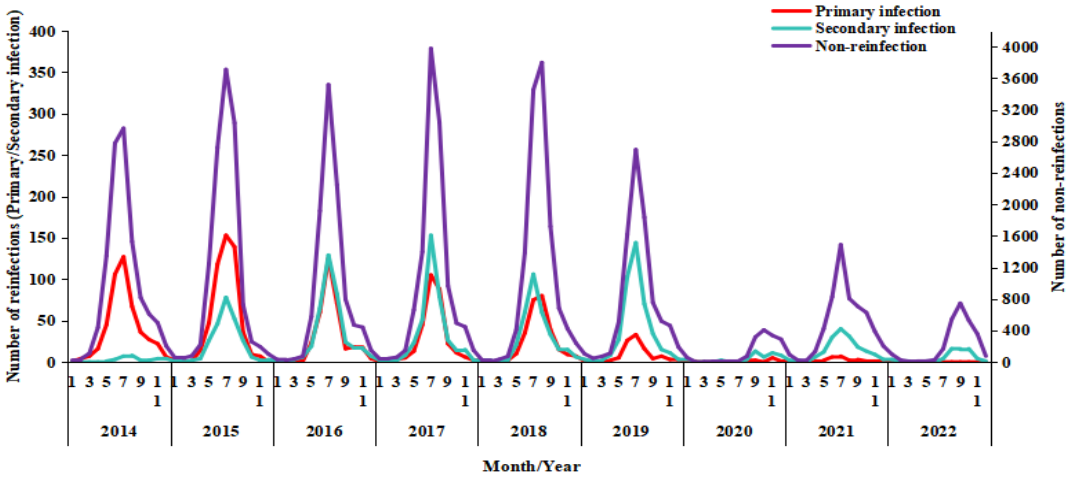

Fig. 1: Seasonal distributions of reinfections and non-reinfections

In patients who were infected twice, the median time interval between the two infections was 12.75 (IQR=12.24) months. In patients who were infected three times, the median time intervals between the 1st and 2nd infections and the 2nd and 3rd infections were 11.85 (IQR=12.56) and 13.88 (IQR=16.77), respectively. The time interval between sequential infections in patients infected four times was 3.03 months, 9.87months, and 4.47 months, respectively.

For the different age groups (<1, 1~2, 2~3, 3~4, 4~5, and ≥5 years), the proportions of cases in which the time interval between the primary and secondary infections was within 2 years were 66.52%, 60.51%, 71.57%, 69.71%, 72.33% and 59.46%, respectively.

Multivariate analysis of influential factors for reinfection

The results of univariable analysis showed that sex, age, group classification, region, clinical classification, hospitalization, and laboratory results were all significant factors affecting the risk of HFMD reinfection (Table 2).

Table 2: Logistic regression analysis results on the relationship between influential factors and HFMD reinfection

Characteristics		Univariable analysis			Multivariate analysis		
		OR	95%CI	*p*	OR	95%CI	*p*
Sex	Male	1.20	1.09-1.30	<0.001	1.22	1.11-1.33	<0.001
	Female	1.00	-		1.00	-	
Age(yr)	<1	5.14	4.09-6.45	<0.001	2.87	2.22-3.71	<0.001
	1~2	5.13	4.21-6.29	<0.001	2.92	2.31-3.69	<0.001
	2~3	4.45	3.60-5.50	<0.001	2.59	2.04-3.29	<0.001
	3~4	3.97	3.21-4.91	<0.001	2.57	2.05-3.23	<0.001
	4~5	2.23	1.75-2.85	<0.001	1.51	1.17-1.95	0.002
	≥5	1.00	-		1.00	-	
Group classification	Scattered children	13.09	8.11-21.12	<0.001	4.85	2.87-8.19	<0.001
	Kindergarten children	7.09	4.36-11.53	<0.001	3.89	2.32-6.54	<0.001
	Students/others	1.00	-		1.00	-	
Region	Urban	1.13	1.02-1.24	0.014	1.01	0.92-1.11	0.827
	Rural	1.00	-		1.00	-	
Clinical classification	Severe	2.80	2.22-3.53	<0.001	1.73	1.30-2.30	<0.001
	Mild	1.00	-		1.00	-	
Hospitalization status	Yes	1.97	1.71-2.28	<0.001	1.38	1.15-1.64	<0.001
	No	1.00	-		1.00	-	
Laboratory results [1)]	Other enteroviruses	1.00	-	0.001	1.00	-	<0.001
	CoxA16	1.16	0.77-1.74	0.475	1.29	0.87-1.94	0.225
	EV71	1.88	1.28-2.75	0.001	2.00	1.37-2.93	<0.001

[1)]The laboratory results have much missing values. Adjusted for only sex and age.

The multivariate analysis indicated that the reinfection risk was higher among males compared with females (OR=1.22, 95%CI=1.11-1.33). Compared with ≥5 years old, the reinfection risk was higher in younger age groups, with OR (95%CI) of 2.87 (2.22-3.71), 2.92 (2.31-3.69), 2.59 (2.04-3.29), 2.57 (2.05-3.23), 1.51 (1.17-1.95), for different age groups (<1, 1~2, 2~3, 3~4, and

4~5 years), respectively. Compared with students/others group, the OR (95%CI) for reinfection was 4.85 (2.87-8.19) and 3.89 (2.32-6.54) in scattered children group and kindergartens children group. Interestingly, after adjustment for potentially confounding factors, living in urban areas showed no significant reinfection risk compared to living in rural areas. Compared with the control group, the reinfection risk was higher among severe cases and hospitalization cases. In addition, compared to other enteroviruses infections, infected with EV71 was risk factor for reinfection.

Reinfection virus sub-type and clinical classification

The case-severity rate for the primary infection cases (3.92%) was higher than that in the secondary infection cases (0.15%) and non-reinfection cases (1.44%). However, the case-severity rate in secondary infection cases (0.15%) was lower than that of non-reinfection cases (1.44%). The adjusted results were shown in Table 3.

Table 3: The case-severity rate in different groups

Groups	Severe cases	Total cases	Severe rate (%)	OR (95%CI)	*p*[4]
Reinfection cases				18.10 (5.60-58.47)	<0.001[1]
Primary infection	80	2041	3.92%	2.38 (1.88-3.00)	<0.001[2]
Secondary infection	3	2041	0.15%	0.12 (0.04-0.38)	<0.001[3]
Non-reinfection	1098	76381	1.44%	1.00	

[1] The *P* value was for the primary infection group compared with the secondary infection group, [2] The *P* value was for the primary infection group compared with the non-reinfection group, [3] The *P* value was for the second infection group compared with the non-reinfection group, [4]Adjusted for sex and age

The proportion of patients infected with EV71 in the primary infection cases was higher than that in secondary infection cases (OR=2.80, 95%CI=1.24-5.76) and the non-reinfection cases (OR=1.83, 95%CI=1.29-2.60). The proportion of patients infected with other enteroviruses in the primary infection cases was lower than that in non-reinfection cases (OR=0.62, 95%CI=0.45-0.87). However, there was no statistically significant difference in the proportion of infected with CoxA16 among the groups (Table 4).

Table 4: Risk analysis of HFMD causative pathogens in different infection groups

Groups	Laboratory diagnosed	Virus subtypes								
		EV71			CoxA16			Other enteroviruses		
		n(%)	OR(95%CI)	*P*[4]	n(%)	OR(95%CI)	*P*[4]	n(%)	OR(95%CI)	*P*[4]
Reinfection cases			2.80 (1.24-5.76)	0.005[1]		0.79 (0.43-1.47)	0.469[1]		0.60 (0.34-1.07)	0.081[1]
Primary infection	151	48 (31.79%)	1.83 (1.29-2.60)	0.001[2]	38 (25.17%)	1.01 (0.69-1.47)	0.986[2]	65 (43.05%)	0.62 (0.45-0.87)	0.005[2]
Secondary infection	113	16 (14.16%)	0.61 (0.36-1.04)	0.071[3]	38 (33.63%)	1.27 (0.85-1.89)	0.238[3]	59 (52.21%)	1.08 (0.74-1.58)	0.676[3]
Non-reinfection	4783	991 (20.72%)	1.00		1271 (26.57%)	1.00		2521 (52.71%)	1.00	

[1]The *P* value was for the primary infection group compared with the secondary infection group, [2] The *P* value was for the primary infection group compared with the non-reinfection group, [3] The *P* value was for the second infection group compared with the non-reinfection group, [4]Adjusted for sex and age

Discussion

The main purpose of our study was to explore the epidemiological characteristics and influencing factors of reinfection. Our data suggested that the reinfection rate of HFMD in Qingdao City during 2014-2022 was 2.60%, with the highest rate occurring in 2019 (4.51%). Qingdao City had a higher reinfection rate than Wuhan City (1.93%) and Anhui Province (12) (2.02%), and lower than that in Wuxi City (6.01%) (16). This discrepancy may be attributed to variations in geographical location, study population, duration, and meteorological factors.

Our results showed that the males were more susceptible to reinfection, which was comparable with the study in Guangzhou (13). It was possible that males tended to be more active and energetic (17), giving them more opportunities for infection by touching surfaces contaminated with viruses. The present study revealed that the reinfection rate declined with increasing age. This may be because the prevalence of anti-EV71 and anti-CoxA16 gradual increased with age (18). In addition, with the increase of age, the immune level against enterovirus also increased accordingly (19). Thus, parents need to educate young children to maintain healthy habits, especially the habit of washing hands before meals (20).

In our study, we discovered that scattered children had a higher reinfection rate than kindergarten children. Scattered children referred to young children who had not been sent to a nursery, daycare center, or kindergarten, but were only raised at home. A similar finding had also been found in Huainan City (21). This finding contradicted the widely held belief that kindergarten children had more opportunities to be exposed to viruses and a higher risk of reinfection (22). The possible reason was that scattered children were younger and had poor hygiene habits. For example, due to their habit of sucking on their fingers, these children were more likely to be infected through fecal-oral route (23). People generally believed that rural areas had poor hygiene conditions and a higher risk of reinfection. However, we observed that the reinfection rate was higher in urban areas than rural areas, which was inconsistent with results in Anhui Province (12). This may be attributed to the high population density and increased floating population, leading to an increased risk of reinfection. In addition, living in urban areas provides better medical conditions, resulting in higher diagnostic rate.

Interestingly, our study found that the hospitalized cases and severe cases in primary infection had a higher reinfection rate than non-reinfection cases. Further analysis revealed that the primary infection group had highest case-severity rate.The results suggested that the occurrence of reinfection was related to the severity of the symptoms in the primary infection. A study of reinfection with H1N1 influenza revealed a similar phenomenon (24), and it was hypothesized that these individuals had inadequate immune defense against the primary infection.

Notably, the reinfection rate of patients initially infected with EV71 was relatively higher compared with other enteroviruses and CoxA16. Further analysis revealed that the proportion of patients infected with EV71 in primary infection cases was higher than non-reinfection patients. This indicated that patients infected with EV71 were more prone to reinfection, which was inconsistent with a study in Guangzhou (13). Therefore, further large-scale studies are still needed in the future to verify the conclusions. The proportion of patients infected with other enteroviruses in the primary infection cases was lower than that in non-reinfection cases. However, other enteroviruses have become the main pathogens of HFMD in Qingdao (25), and caused outbreak in many countries (2, 26). Thus, it is necessary to enhance the surveillance of HFMD infections caused by other enteroviruses in the future.

In addition, our study found that the seasonal peak occurred from June to August each year, which may be related to the effects of ambient temperature and humidity on HFMD (27, 28). Research showed that ambient temperature and

humidity could influence the dynamics of the infection transmission by affecting the survival and transmission of the HFMD virus in the environment (29, 30).

Nevertheless, a few drawbacks required further discussion. First, the HFMD cases of our study were mainly reported by medical institutions. There may be an under-reporting. Second, our data were obtained from the National Infectious Surveillance System, which lacks clinical and vaccine information. Third, our study was based on data from Qingdao, and these findings may not be generalizable to other cities. Therefore, further investigation need to be conducted in other regions. Lastly, and most importantly, some non-reinfection cases may actually have the possibility of reinfection outside of our study period, leading to the possibility of misclassification in this study.

Conclusion

The reinfection rate of HFMD in Qingdao from 2014 to 2022 was 2.60%. Male, younger age, scattered children, severe cases, hospitalization, and EV71 infection were risk factors for HFMD reinfection. The reinfection susceptible population comprised boys who were aged <5 years, particularly those with severe cases, and children who had been primary infected withEV71. Therefore, authorities should implement targeted health education and intervention strategies to reduce the reinfection rate among vulnerable population.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflict of Interest

We declare that we have no conflict of interest.

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