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Original Article

Epidemiological Characteristics of Hand, Foot, and Mouth Disease Outbreaks in Qingdao, 2009-2018

Jing Jia [1], Fei Kong [2], Xueling Xin [1], Jiwei Liang [1], Hualei Xin [1], Liyan Dong [1], *Fachun Jiang [1]

1. *Department of Acute Infectious Disease, Qingdao Centre for Disease Control and Prevention, Qingdao Institute of Prevention Medicine, Qingdao, Shandong, China*
2. *Sinopec Research Institute of Safety Engineering, Qingdao, Shandong, China*

***Corresponding Author:** Email: 792114402@qq.com

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Abstract

Background: In China, hand, foot, and mouth disease (HFMD) outbreaks have become an important issue recent years. We analyzed the epidemiological characteristics of HFMD outbreaks in Qingdao during 2009-2018, and provided evidences for prevention and control of the disease.

Methods: Data were analyzed by descriptive analysis and correlation analysis, and throat swabs were detected for enterovirus RNA using RT-PCR.

Results: Overall, 116 HFMD outbreaks were reported in Qingdao during 2009-2018, with the epidemic of the outbreaks exhibiting a decreasing tendency. The characteristics of outbreaks presented two patterns, including two-peak pattern and rural area to urban-rural fringe area to urban areas pattern. Male patients were predominant in these outbreaks. The location of the outbreaks changed from nursery to community. Non-EV71/CA16 enteroviruses were gradually becoming predominant enteroviruses serotypes. The durations of outbreaks were positively correlated with response times and the number of cases.

Conclusion: The epidemiological characteristics analysis of HFMD outbreaks could provide a scientific basis for the prevention and control the disease. Reporting and handling promptly are the keys to control epidemic outbreaks of HFMD.

Keywords: Hand; Foot; Mouth disease; Outbreak; Epidemiology

Introduction

Hand, foot, and mouth disease (HFMD) is a common intestinal infectious disease caused by viruses that belong to the Enterovirus group principally including Enterovirus 71(EV71) and Coxsackievirus A16 (CA16)(1,2). Most cases, typically characterized by fever, skin eruptions on the hands and feet, and vesicles in the mouth, are mild and self-limiting (3). Few patients infected with EV71 may develop severe complications involving neurological symptoms such as encephalitis, meningitis and even death (4, 5). Symptomatic cases mostly affect children aged 0-5 yr, but also can affect older children and adults (6). Since the first case of HFMD was described

clinically in New Zealand and Canada in 1957, HFMD have been reported globally (1, 7-10). In recent years, more than one million HFMD cases have been reported in China every year (11-13), which prompted huge public health concerns. HFMD is becoming a considerable global public health challenge.

In the last decade, there are a large number of HFMD outbreaks reported in East and Southeast Asia (14-16), which have a great impact on families and society. In China, the first large-scale HFMD outbreak was reported in Linyi, Shandong Province in 2007, led to 1149 diagnosed cases and 3 deaths (17). Subsequently, a serious outbreak was reported in Fuyang, Anhui Province in 2008, resulted in 353 severe cases and 22 deaths (18). In order to better cope with the outbreaks of HFMD, the Ministry of Health of China listed HFMD as a Class C statutory infectious disease on May 2, 2008.

Qingdao is one of the largest tourist port cities in China. The HFMD epidemic appeared an upward tendency with the incidence rates ranged from 31 in 2008 to 138 in 2018 per million person-years. Meanwhile, the HFMD outbreaks were at the front of the outbreaks of infectious diseases in Qingdao. However, no long-term and systematic epidemiological studies of HFMD outbreaks in Qingdao have been reported since 2009. Therefore, we analyzed the epidemiology of HFMD outbreaks in Qingdao, China, from 2009 to 2018.

Materials and Methods

Study subjects

All HFMD cases were notified to Qingdao Center for Disease Control and Prevention (CDC) via the National Notifiable Disease Reporting System (NNDRS) by medical practitioners. The information included gender, age, address and source was obtained by the interview. The range of time was from Jan 1, 2009 to Dec 31, 2018.

Outbreak, Region and Index definitions

According to the criteria of the 2009 guideline for the management of cluster and outbreak of HFMD (19), Individuals were defined as outbreak if they met one of the following standards: 1) 5 or more cases of HFMD in a natural village or community within 1week; 2) 10 or more cases of HFMD in a nursery or school within one week.

According to the regional and demographic characteristic, the 10 districts in Qingdao are divided into three regions: 1) rural area, including Pingdu District, Laixi District and Jiaozhou District; 2) urban-rural fringe area, including Chengyang District, Laoshan District, Jimo District and Huangdao District; 3) urban areas, including Shinan District, Shibei District and Licang District.

The indexes included in this study are as follows: The attack rate= The number of cases/ The overall number of exposed population in outbreaks×100%. The response time= The time of receiving report and taking measures-The onset time of the first case. The duration time= The onset time of the last case-The onset time of the first case.

Sample collection

Throat swabs were collected from at least 5 cases in one HFMD outbreak according to the guideline for the management of cluster and outbreak of HFMD. All swab samples were stored at 4 ℃ immediately after collection and quickly sent to the national network laboratory in Qingdao for aetiological indentification.

Sample testing

In the laboratory, viral RNA was extracted from the throat swabs using MagNA Pure LC total nucleic acid isolation kits in an automated nucleic acid extraction instrument (MagNA Pure LC 2.0; Hoffmann-La Roche, Switzerland) according to the manufacturer's instruction. Fluorescence reverse transcription-polymerase chain reaction (RT-PCR) nucleic acid detection kits (Jinhao, China and Zhijiang, China) were applied to detect pan-EVs, EV71, and CA16. The test results were classified into four categories: enterovirus negative, EV71 positive, CA16 positive, or other en-

terovirus positive without further serotype identification.

Statistical analysis

To analyze the epidemiological characteristic of HFMD outbreaks, we conducted descriptive analysis and correlation analysis. In the descriptive analysis, we described the epidemic situation, time, area, and population distribution of outbreaks using Excel 2010 and ArcGis 10. The chi-square (χ^2) test was used to determine the difference of categorical variables. In the correlation analysis, the Shapiro-Wilk test was used to examine the distribution of the data in the 10 years. If the data were not normally distributed, Spearman rank correlation analysis was applied to examine the correlation between the duration of outbreaks, the response time, and the number of cases. All analyses were two-sided and conducted using SPSS v.18.0 for Windows (IBM Corp., USA). $P \leq 0.05$ was considered significant.

Results

Epidemic situation of HFMD outbreaks

Overall, 116 HFMD outbreaks, which accounted for 36.94% (116/314) in all infectious disease outbreaks, occurred in Qingdao during 2009-2018 (Table 1). These HFMD outbreaks resulted in 1621 cases (including 100 severe, nonfatal cases), and 41402 exposed people. The median of cases and exposed people in these outbreaks were 14 and 116, respectively. The mean attack rate was 3.92%. The attack rate of outbreaks was higher in 2011 and 2012, reaching a maximum in 2012 with 11.54%. Then, the attack rate declined to 1.60% in 2014, which was the lowest. There were significant difference in the attack rate among 10 years ($P<0.05$). Generally, the epidemic situation of HFMD outbreaks showed a decreasing tendency in Qingdao from 2009 to 2018.

Table 1: Epidemic status of HFMD outbreaks in Qingdao, 2009-2018

Year	*No. outbreaks*	*No. cases*	*No. exposed*	*Attack rate (%)*
2009	34	525	23218	2.26
2010	21	328	4479	7.32
2011	15	255	2582	10.61
2012	11	186	1612	11.54
2013	3	36	437	8.24
2014	5	35	2193	1.60
2015	7	67	837	8.00
2016	7	68	754	9.01
2017	8	62	946	6.55
2018	5	59	4344	1.36
Total	116	1621	41402	3.92

Time, area and population distribution of HFMD outbreaks in Qingdao from 2009 to 2018

From 2009 to 2018, HFMD outbreaks were reported every year in Qingdao. The outbreaks occurred mainly from May to July with the number respectively 24, 36, and 25, which account for 73.28% among these outbreaks. Correspondingly, the cases (75.20%) were concentrated on May to July with the number respectively 435, 529, and 255. Figure 1 showed that the outbreaks presented two-peak pattern in Qingdao City from 2009 to 2018 with a primary peak in June and secondary in Nov. In addition, there were no outbreaks in Feb and Sep. The area distribution showed that HFMD outbreaks had been reported in each districts in Qingdao from 2009 to 2018 (Fig.2).

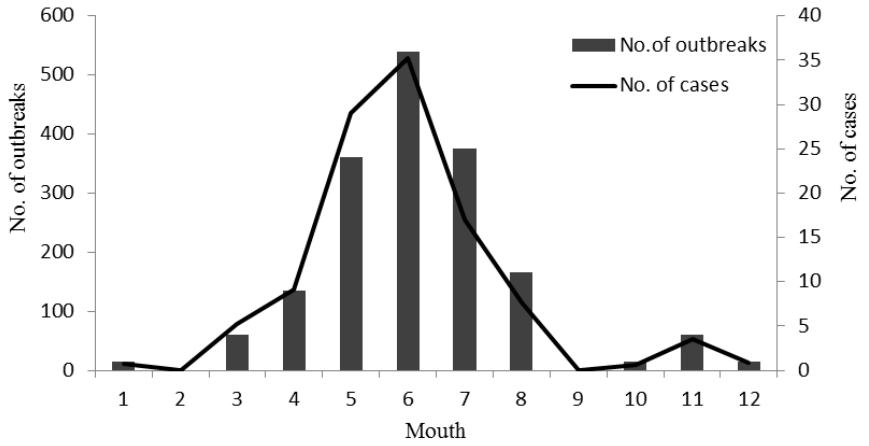

Fig. 1: Time distribution of HFMD outbreaks in Qingdao, 2009-2018

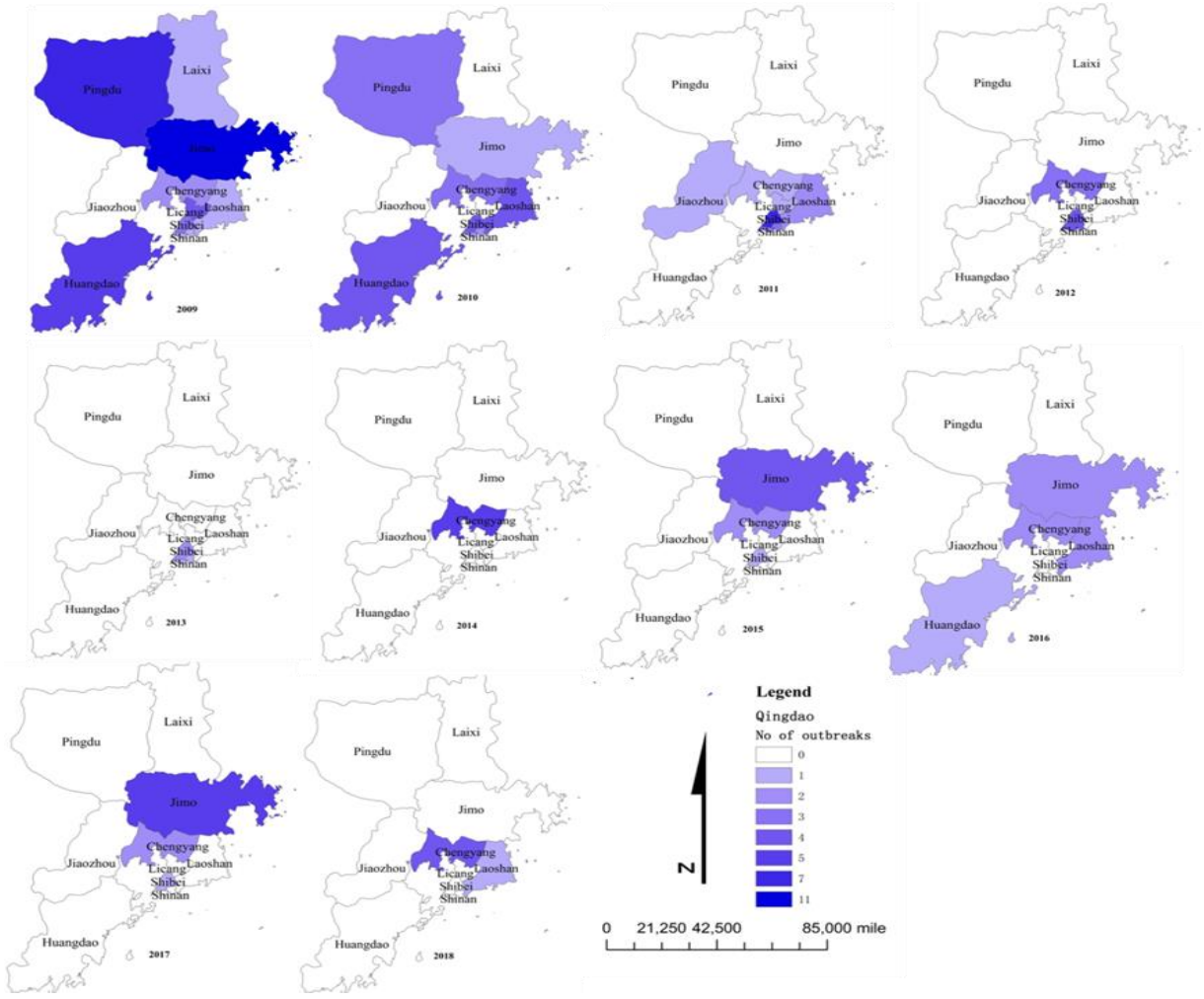

Fig. 2: Area distribution of HFMD outbreaks in Qingdao , 2009-2018

The largest numbers of outbreaks and cases were all in Jimo District in 2009 (19.83%, 10.15%). The largest cumulative numbers of outbreaks and cases respectively were in Chengyang District and

Shibei District (20.69%, 21.83%) in the ten years. From the point of the area distribution, the largest number of outbreaks occurred in urban-rural fringe area (57.00%), follow by urban areas (32.76%) and rural areas (10.34%). The change tendency of area distribution showed the pattern of rural area to urban-rural fringe area to urban areas (Fig. 2).

Among 1621 cases, the number of cases was higher in males than females (967 were male, and 668 were female), and the sex ratio between male and female cases was approximately 1.48:1(P<0.05). The attack rate in males was higher than females (P<0.05, Table 2). The age range of the cases was from 1 to 11 yr old (median: 3). According to socio-demographic information, most of the cases were nursery children (76.50%), followed by community children (23.50%).

Table 2: The attack rate of HFMD outbreaks in different sex and location in Qingdao, 2009-2018

Year	*Sex*				*Location*			
	Males		Females		Nursery		Community	
	No.	AR	No.	AR	No.	AR	No.	AR
2009	316	2.66	209	1.84	418	3.49	107	0.95
2010	199	8.68	129	5.90	308	7.07	20	16.67
2011	155	11.73	100	7.93	251	10.08	4	4.30
2012	101	12.24	85	10.80	173	14.16	13	3.33
2013	17	7.59	19	8.92	36	8.24	0	0.00
2014	22	1.96	13	1.21	0	0.00	35	1.60
2015	44	10.28	23	5.62	30	12.24	37	6.25
2016	37	9.59	31	8.42	0	0	68	9.02
2017	43	8.88	19	4.11	24	6.67	38	6.48
2018	33	1.48	26	1.23	0	0	59	1.36
Total	967	4.56	654	3.24	1240	5.94	381	1.87

No.: No. of cases; AR: Attack rate (%)

All of the outbreaks were observed in both nursery (57.76%) and community (42.24%). The attack rate of HFMD outbreaks occurred in nursery was higher than community (P<0.05, Table 2). Although the HFMD outbreaks occurred in both nursery and community in 10 years, the location distribution appeared some change tendency: the number of community outbreaks was increasing as the decreasing number of nursery outbreaks (Fig. 3).

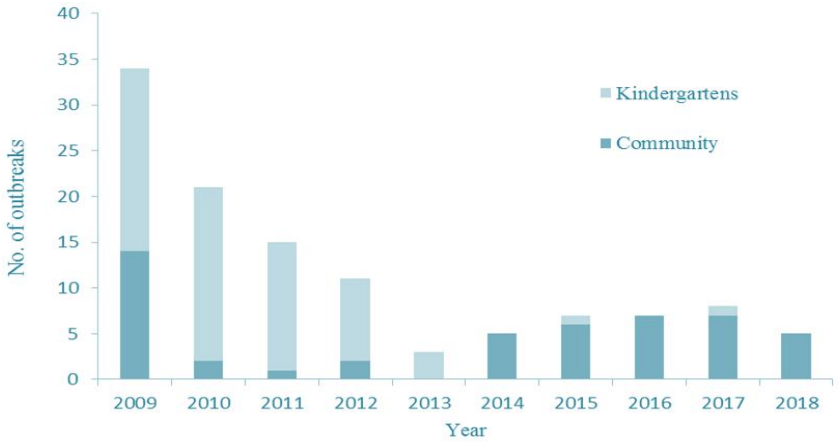

Fig. 3: Location of HFMD outbreaks in Qingdao, 2009-2018

The response times, durations of outbreaks and influence factors in Qingdao from 2009 to 2018

Among the 116 HFMD outbreaks, 97 outbreaks were reported to the China CDC within 24 h (83.62%), remaining within 1-11d (16.38%). Table 3 showed that the duration and the response time of these outbreaks ranged from 2 to 33d (median: 11d), 5 h to 21d (median: 8d), respectively. Of 67 outbreaks in nursery, 17 classes were suspended and 25 facilities were closed. All of the cases were isolated at home for at least 10 d until recovered. Through Spearman rank correlation analysis, the durations of outbreaks were significantly correlated with response times (P<0.05) and the number of cases (P<0.05).

Table 3: The correlation analysis of durations, response times and the number of cases

Influence factors	*Min*	*Max*	*Median*	*r*
Durations	2d	33d	11d	-
Response times	0.08d	11d	0.79d	0.496
No. of cases	5	47	14	0.305

r: Spearman rank correlation

Aetiological characteristics of HFMD outbreaks in Qingdao from 2009 to 2018

Overall, 187 positive specimens were detected in these outbreaks. EV71 was the major pathogens accounting for 40.64%, followed by other non-EV71/CA16 enteroviruses and CA16, accounting for 33.16%, and 26.20%, respectively. However, the predominant enteroviruses serotypes changed each year (Fig. 4). EV71 predominated from 2009 to 2011, and the percentage of other enteroviruses exhibited wave pattern: gradually increased from 2010 to 2012, and became the most frequent serotype in 2012 and 2013, then kept a low level between 2014 and 2017, presented the predominant pathogens again in 2018. CA16 became the dominating pathogens in 2014, 2015 and 2016. In addition, EV71 and CA16 co-circulation were found in four outbreaks among these positive samples.

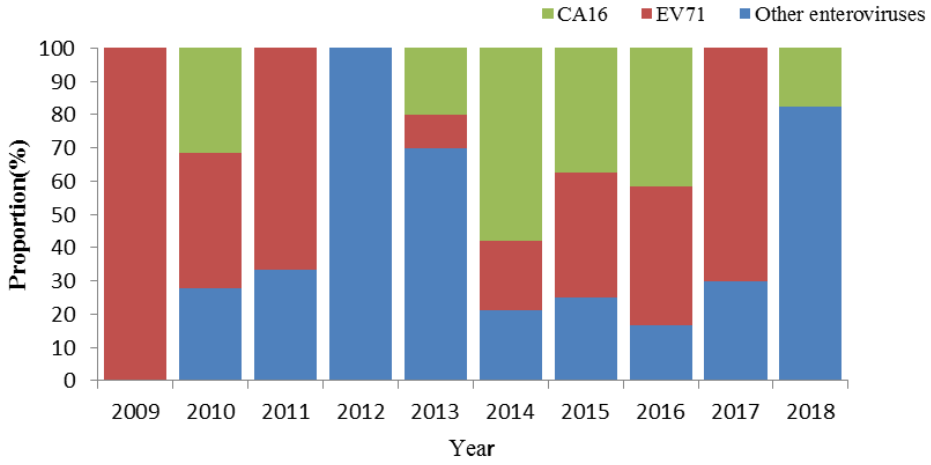

Fig. 4: Proportion of enterovirus serotypes in cases of HFMD outbreaks in Qingdao, 2009-2018

Discussion

In this study, we analyzed the epidemiological characteristics and etiological results of HFMD outbreaks in Qingdao from 2009 to 2018. The epidemic situation of the outbreaks exhibited a stable tendency with a decreasing number of outbreaks and cases. The emergency of this tendency

could be attributed to the following factors: the improvement of the surveillance to disease in CDC, the enhancement of the awareness to prevent diseases in nurseries, and the reinforcement of the concern to disease from families.

During 2009-2018, the attack rate of HFMD outbreaks appeared to the pattern of quadrennial cycle. The attack rate of HFMD outbreaks in Qingdao ranged from 1.36% in 2018 to 11.54% in 2012, with an average attack rate of 3.92%. The highest attack rate, observed in 2012, was much higher than those of Jinan, Jiaxing and Taizhou in the same year (4.03%, 2.05% and 1.13%, respectively) (20-22). However, the average attack rate was comparable with that reported in Hunan Province (3.18% during 2008-2015) (23).

HFMD is one seasonal dependent disease as the outbreaks also have seasonality (24, 25). This study showed that there were two peaks of outbreaks in Qingdao from 2009 to 2018: the primary peak was in May-July, and the secondary peak was in November. This pattern was similar to Jinan and Shanghai (26, 27). There were two kinds of peak patterns of HFMD epidemic in China: one peak in summer in northern China and two peaks in spring and autumn in southern China (13, 28-29). However, Qingdao belonged to northern city, but had two peaks of outbreak. According to related analysis, the reason of the primary outbreak peak in Qingdao might be partly attributed to climatic factors, such as temperature and humidity (30). The reason of the secondary peak might be explained by the decline of the awareness to prevent diseases and insufficient attention to the first case along with the HFMD epidemic entered a low incidence period during the season. In addition, further investigation is still needed to explain why the two-peak pattern existed.

By analyzing the area distribution, we found that HFMD outbreaks were mainly concentrated in urban-rural fringe area, followed by urban area. The number of outbreaks in rural area was much less than the other areas, which was accordance with the other studies, such as Taiwan (31). However, most studies only analyzed the difference between urban area and rural area. In our study, we added the comparison of urban-rural fringe area. By field investigation, we found that the urban-rural fringe area, with high population density and the congregation of migrant population, had terrible sanitation, tardy care, and frequently sharing public facilities, which may facilitate the transmission of EVs. The public prevention and control measures of HFMD outbreaks should be paid attention to urban-rural fringe area preferentially. Remarkably, the outbreaks pattern of "rural area to urban-rural fringe area to urban areas" emerged in Qingdao from 2009 to 2018. The emergence of this pattern may be attributed to two reasons. On the one hand, the system of HFMD prevention and control, established from 2009 and gradually improved, was based on government-leading, community-intervention and health-education cooperation. The formation of this system effectively reduced the HFMD outbreak. On the other hand, the enhancement of health conception and infrastructure in rural area resulted in the reduction of HFMD outbreaks in this area.

Gender might be a risk factor of HFMD outbreaks (30, 32,33). Consistent with these studies, more cases in outbreaks were boys than girls (male-to-female ratio, 1.45:1) in Qingdao. Owning to more active especially more outdoor activities, boys were more susceptible to contact with the contaminated environment, which could explain the male predominance in HFMD outbreaks. Therefore further professional protection should be given to boys.

Nursery as an incubation site for HFMD, was a highly susceptible location for HFMD outbreaks (34). Accordingly, HFMD outbreaks in Qingdao mainly occurred in nursery before 2013. Nevertheless, the number of outbreaks in community was dominant after 2013, which was inconsistent with other studies (34, 35). This discrepancy could be explained in two aspects. Firstly, since 2012, Shibei District had been taken as a pilot area to establish a demonstration base for HFMD prevention and control, and to carry out a series of activities for nurseries. An aggregative model, nursery (as an emphasis)-family (as a supplement)-community (as an extension)-CDC (as a

support), was formed. This model, gradually prompted in Qingdao, was greatly reduced the incidence of HFMD outbreak in nursery. Secondly, as population crowded and contacted frequently, prevention measures were different to implement, and the effect of mass prevention and control was limited in community, which was also one of the reasons for the outbreak in community. Notably, according to many laboratory results, asymptomatic healthy carriers (7.62%) (36), especially parents, served as a source of outbreak, could carry for infants. This could also increase the risk of outbreak in community. In addition, as China has introduced a "two child per family" policy, the pattern of transmission from "school to home" should also be greatly concerned. Therefore, future directions of HFMD control should concentrate on community. Based on the current situation, hygiene education should be implemented in community-based populations especially for families with children and/or children's guardians while carrying out environment disinfection, isolation of symptomatic cases, body check, and so on.

Although EV71 was the major pathogens among the HFMD outbreaks in Qingdao from 2009 to 2018, the predominant enterovirus serotypes changed each year. The proportion of other enteroviruses gradually increased. In past few years, CA6 and CA10 resulted in a large number of HFMD outbreaks in Asian-Pacific regions and Europe (35, 37). However, in our study, other enteroviruses were not further subtyped. Therefore, further molecular typing was urgently required.

By correlation analysis, the durations of outbreaks were positively correlated with response times and the number of cases. The faster the response times were, the shorter the durations and the smaller the scales of outbreaks were. Therefore, timely response was crucial to shortening the length and scale of outbreak.

Conclusion

The overall epidemic situation of the outbreaks exhibited a decreasing tendency. The characteristics of outbreaks presented two pattern, including "two-peak" pattern and "rural area to urban-rural fringe area to urban areas" pattern. Male patients were predominant in these outbreaks. To date, the locations of HFMD outbreaks in Qingdao have changed from nursery to community. Non-EV71/CA16 enteroviruses became predominant in recent years. Furthermore, the durations of outbreaks were positively correlated with response times and the number of cases. This study has shed light on the epidemiological characteristics of HFMD outbreak in Qingdao from 2009 to 2018, prove helpful for the prevention and control of HFMD outbreaks in other areas.

Ethical 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

None to declare.

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