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Original Article

The Etiological Characteristics of Hand, Foot, and Mouth Disease in Yuyao, China, 2010-2023

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Abstract

Background: We aimed to analyze the etiological composition of Hand, Foot, and Mouth Disease (HFMD) in Yuyao from 2010 to 2023, and to provide scientific decision and basis for the development of preventive and control measures for HFMD.

Methods: Employing descriptive epidemiological methods, we analyzed the etiological results of mild cases of HFMD monitored from 2010 to 2023.

Results: From 2010 to 2023, 4,294 samples from HFMD patients in Yuyao, China were analyzed, with 2,362 (55.01%) testing positive for enteroviruses. The most common serotypes were EV71 (30.57%), CA16 (25.91%), and CA6 (8.26%). There was a significant variation in positivity rates over the years, with the lowest in 2023 (22.61%) and the highest in 2012 (95.45%). EV71 was the dominant serotype before 2018, but other serotypes became more prevalent afterward, with CA6 emerging as the primary strain post-2018.HFMD cases occurred year-round, with a clear seasonal pattern peaking from April to October, especially in May. This period accounted for 81.63% of all cases. The disease affected individuals of all ages, but the majority (83.74%) were children under six. Males had a higher detection rate than females, with a significant difference between the genders.

Conclusion: Between 2010 and 2023, the composition of pathogens causing HFMD in Yuyao underwent significant changes. These observations not only deepened the understanding of the epidemic trends and etiological evolution of the disease in the area but also provided scientific support for the development of more targeted prevention and control measures.

Keywords: Hand; Foot; Mouth disease; Etiological characteristics; Enterovirus; China

Introduction

Hand, Foot, and Mouth Disease (HFMD) is a prevalent childhood illness that arise from enterovirus infections. This contagious disease typically presents with symptoms such as fever, followed by distinctive skin rashes appearing on the hands, feet, buttocks, and inside the mouth. In more severe instances, it can lead to complications including encephalitis, acute flaccid paralysis, myocarditis, and pulmonary edema, which can be life-threatening in extreme cases (1).

Enteroviruses (EV) are classified into types A, B, C, D, etc., with 116 serotypes primarily infecting humans. Currently, at least 23 serotypes are known to cause HFMD (2). Among these, Enterovirus species A (EV-A) is predominant, with more than 90% of the pathogenic strains belong-

ing to this group. EV-A encompasses 25 serotypes, including Enterovirus A71 (EV71) and Coxsackievirus A (CV-A) serotypes 2–8, 10, 12, 14, and 16 (3).

Since 1997, numerous large-scale outbreaks of hand, foot, and mouth disease (HFMD) have occurred in multiple locations across the Asia-Pacific region, particularly in South and Southeast Asia. These outbreaks have affected countries and regions including Malaysia, Taiwan, Japan, Vietnam, Singapore, Thailand, and China (4-6). The primary pathogens responsible for these epidemics have been EV71 and CV-A16. Notably, severe cases and fatalities are often associated with EV71 infections (7).

However, recent global trends have shown an emergence of Coxsackievirus group A type 6 (CA6) as a significant contributor to HFMD outbreaks, with multiple countries reporting epidemic occurrences (8, 9). In mainland China, too, there has been a gradual rise in the number of HFMD cases associated with CA6 infections (10, 11). Although a large-scale EV71 vaccination program has been implemented in China since 2016, this vaccine is only effective against EV71 and has no cross-protective effect against other serotypes such as CA6 (12, 13), which may be one of the reasons. In addition, the lack of immunity to the CA6 serotype in the population (14) and the possible mutations in the virus genome may also contribute to this situation (15).

Therefore, we aimed to conduct an in-depth analysis of the alterations in the pathogen spectrum of HFMD within our region from 2010 to 2023.

Materials and Methods

Data collection

During the period from 2010 to 2023, the laboratory of *Yuyao Center for Disease Prevention and Control* actively conducted surveillance of HFMD in strict accordance with the *'Guidelines for the Prevention and Control of Hand, Foot, and Mouth Disease (2010 edition and 2018 edition)* ' issued by the Ministry of Health of the People's Republic of China. For clinically diagnosed HFMD cases, the following sample collection principles were adhered to: at least five pharyngeal swab or fecal samples from newly-diagnosed patients should be collected each month. If the total number of cases in a month was less than five, samples should be collected from all cases. During this period, the laboratory collected a total of 4,294 samples, including 3,695 fecal samples and 599 pharyngeal swab samples. All samples were stored at -80°C to ensure sample quality and the accuracy of subsequent tests.

Sample testing

Viral nucleic acids were extracted using QIAGEN RNeasy Mini Kit (Germany), followed by fluorescent reverse transcription polymerase chain reaction (RT-PCR) nucleic acid test kit (Zhijiang, China) to detect pan-EVs, EV71 and CA16. Since 2018, further nucleic acid testing for CA6 and CA10 was started in this region for enterovirus-positive specimens. Throughout the entire detection process, all operations were strictly carried out in accordance with the instructions of the test kits. Positive and negative controls were set up in each experiment to ensure the accuracy of the test results. The test results were determined based on the amplification curves, with reference to the instructions of the test kits and the quality control of each batch. All the reactions were carried out on the fluorescence quantitative PCR instrument (Model 7500) of the American company ABI.

Statistical analysis

Categorical variables were presented as absolute numbers (percentages), with intergroup comparisons of rates and proportions performed using Pearson's chi-square test. Temporal trend analysis was conducted using the trend chi-square test, considering *P*-values <0.05 as statistically significant.To control for Type I error due to multiple testing, the Bonferroni method was applied. Confidence intervals (95% CIs) for detection rates were computed using the normal approximation method to quantify variability around point estimates.

Results

Detection situation

Between 2010 and 2023, a total of 4,294 samples from distinct HFMD patients were collected, of which 2,362 (55.01%) tested positive for enterovirus (EV) nucleic acids. Among the EV-positive specimens, the distribution of different EV serotypes was as follows: EV71 comprised 30.57%, CA16 accounted for 25.91%, CA6 constituted 8.26%, CA10 made up 0.38%, and the remaining 34.89% were attributed to other EV types. The lowest EV positivity rate was recorded in 2023 at 22.61%, while the highest positivity rate occurred in 2012, reaching 95.45%. The differences in positivity rates across different years were statistically significant ($\chi^2 = 1046.79$, $P = 0.001$, adjusted $\alpha = 0.000549$). The positive detection rate of HFMD showed a significant decreasing trend over time ($\chi^2_{trend} = 1147.01$, $P < 0.001$).Throughout the 14-year period, substantial fluctuations were observed in the prevalence of various EV strains: EV71 ranged from 0.00% to 65.38%; CA16 fluctuated between 0.00% and 39.60%; CA6 varied between 17.76% and 63.46%; CA10 dipped as low as 0.00% and reached up to 5.77%; and other unidentified EV types oscillated between 19.15% and 75.95%.In general, prior to 2018, EV71 dominated as the main serotype with a prevalence of 38.97%, particularly exerting absolute dominance between 2010 and 2012 (Table 1).

Table 1: Pathogen detection status of HFMD in Yuyao, 2010-2023

Year	No.of postive	Detection rate (%)	EV71	CA16	CA6	CA10	Others
			N (%)	N (%)	N (%)	N (%)	N (%)
2010	874	82.69	387 (44.28)	240 (27.46)	/	/	247 (28.26)
2011	130	92.20	85 (65.38)	16 (12.31)	/	/	29 (22.31)
2012	210	95.45	84 (40.00)	80 (38.10)	/	/	46 (21.90)
2013	134	70.16	31 (23.13)	11 (8.21)	/	/	92 (68.66)
2014	243	60.60	75 (30.86)	56 (23.05)	/	/	112 (46.09)
2015	83	36.56	21 (25.30)	16 (19.28)	/	/	46 (55.42)
2016	61	26.64	8 (13.11)	15 (24.59)	/	/	38 (62.30)
2017	79	30.98	16 (20.25)	3 (3.80)	/	/	60 (75.95)
Total[a]	1814	66.67	707 (38.97)	437 (24.09)	/	/	670 (36.93)
2018	149	49.17	10 (6.71)	59 (39.60)	40 (26.85)	5 (3.36)	35 (23.49)
2019	94	36.02	5 (5.32)	33 (35.11)	38 (40.43)	0 (0.00)	18 (19.15)
2020	85	34.27	0 (0.00)	2 (2.35)	45 (52.94)	1 (1.18)	37 (43.53)
2021	107	37.02	0 (0.00)	60 (56.07)	19 (17.76)	0 (0.00)	28 (26.17)
2022	61	25.21	0 (0.00)	21 (34.43)	20 (32.79)	0 (0.00)	20 (32.79)
2023	52	22.61	0 (0.00)	0 (0.00)	33 (63.46)	3 (5.77)	16 (30.77)
Total[b]	548	34.84	15 (2.74)	175 (31.93)	195 (35.58)	9 (1.64)	154 (28.10)
Total	2362	55.01	722 (30.57)	612 (25.91)	195 (8.26)	9 (0.38)	824 (34.89)

Note, Total[a]: Data summary from 2010 to 2017; Total[b]: Data summary from 2018 to 2023;/: indicates no testing performed for that pathogen in the given year

Time distribution

Statistical data from the period between 2010 and 2023 show that HFMD cases were detected in every month from January to December, with a distinct seasonal distribution concentrating primarily in the months from April through October. May emerged as the peak month for detecting positive cases. The number of positive HFMD cases during the April to October period accounted for 81.63% of the annual total, and the differences in monthly detection rates were statistically significant (χ^2 = 144.86, *P*=0.000, adjusted α =0.000758) (Fig. 1). Different pathogenic types exhibited varying dominant distribution months: EV71 was most prevalent from April to September, while CA16 demonstrated its advantage mainly between February and July. CA6 showed a peak dominance in October. In contrast, other enteroviruses maintained relatively high detection rates throughout the entire year.

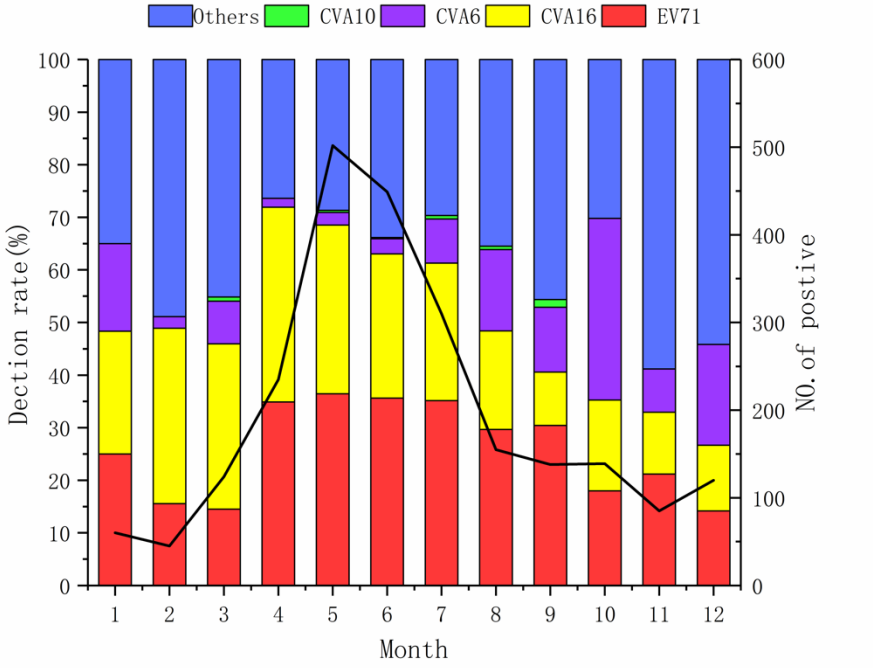

Fig. 1: Time distribution of HFMD outbreaks in Yuyao, 2010-2023

Age distribution

Among all the HFMD cases identified in Yuyao, the oldest affected individual was 59 years old, while the youngest patient was merely 1 month old. The incidence rate of HFMD in children below the age of six constituted a relatively high proportion of the total cases, amounting to 1978 out of 2362 cases, which translates to 83.74% (Table 2). There were significant differences in the positive detection rates of the different age groups (χ^2=624.29, *P*=0.000, adjusted α = 0.0024). Among different age groups, the incidence of EV71 is highest among children aged 2 to 3 years. On the other hand, CA16 is most commonly found in children aged 4 to 5 years, and CA6 has its highest proportion in children who are 6 years old or above.Additionally, other EV strains tend to predominate in infants under the age of 1 year.

Table 2: Age distribution of HFMD Cases in Yuyao, 2010-2023

Age	No. of postive	Detection rate (%)	EV71	CA16	CA6	CA10	Others
			N (%)	N (%)	N (%)	N (%)	N (%)
<1	153	75.74	57 (37.25)	29 (18.95)	3 (1.96)	0 (0.00)	64 (41.83)
1-2	408	77.57	140 (34.31)	75 (18.38)	15 (3.68)	1 (0.25)	177 (43.38)
2-3	398	68.27	165 (41.46)	111 (27.89)	16 (4.02)	3 (0.75)	103 (25.88)
3-4	486	66.94	126 (25.93)	140 (28.81)	39 (8.02)	2 (0.41)	179 (36.83)
4-5	329	60.70	94 (28.57)	111 (33.74)	22 (6.69)	2 (0.61)	100 (30.4)
5-6	204	56.82	59 (28.92)	52 (25.49)	22 (10.78)	0 (0.00)	71 (34.8)
≥6	384	28.32	81 (21.09)	94 (24.48)	78 (20.31)	1 (0.26)	130 (33.85)
Total	2362	55.01	722 (30.57)	612 (25.91)	195 (8.26)	9 (0.38)	824 (34.89)

Gender distribution

The results of the different gender groups showed that the positive detection rate was higher in males than in females, with a male to female sex ratio of 1.49:1, and the difference in the positive detection rate between the different gender groups was statistically significant (χ^2=33.54, P<0.05) (Table 3). Examination of annual data from 2010 to 2023 showed considerable fluctuations in the gender ratio of positive detections, ranging from a low of 1.02:1 to a high of 4.08:1. Despite these variations, the overall trend remained consistent, with the number of positive cases consistently higher in males than in females throughout the study period.

Table 3: Gender distribution of HFMD Cases in *Yuyao*, 2010-2023

Gender	No.of postive	Detection rate (%)	EV71	CA16	CA6	CA10	Others
			N (%)	N (%)	N (%)	N (%)	N (%)
Male	1415	58.91	430 (30.39)	368 (26.01)	122 (8.62)	6 (0.42)	489 (34.56)
Female	947	50.05	292 (30.83)	244 (25.77)	73 (7.71)	3 (0.32)	335 (35.37)
Total	2362	55.01	722 (30.57)	612 (25.91)	195 (8.26)	9 (0.38)	824 (34.89)

Discussion

HFMD is a common infectious disease among children, characterized by its rapid transmission and strong epidemic potential. The transmission factors of HFMD are complex with diverse transmission routes, capable of causing extensive outbreaks within a short period. From 2010 to 2023, the average positive detection rate of pathogens of HFMD in Yuyao was 55.01%. Over time, this detection rate showed an overall downward trend, decreasing from 95.45% in

2012 to 22.61% in 2023. This trend is consistent with the research findings in some cities in China (16, 17). As for the reasons behind this decline, one possible explanation is that a substantial number of susceptible individuals were previously infected, resulting in the establishment of a certain level of herd immunity within the population (18). Another contributing factor may be the widespread implementation of EV71 vaccination. Research based on transmission dynamics models has demonstrated that concentrated, large-scale EV71 vaccination not only significantly reduced the incidence of hand, foot, and mouth disease (HFMD) caused by EV71 infection but also decreased the number of HFMD cases attributable to non-EV71 pathogens (19). Notably, there was a significant rebound in the positive detection rate in 2018. Whether this change is attributed to alterations in serotype distribution or the impact of climate remains to be further investigated.

In terms of pathogen types, other enteroviruses predominantly accounted for the cases. Notably, since its inclusion in routine surveillance in 2018, enterovirus CA6 has consistently maintained a high epidemic activity. The underlying mechanisms of its persistent prevalence may be closely associated with frequent viral genomic recombination and antigenic variation: Studies have demonstrated that the VP1 capsid protein-coding region of CA6 exhibits a remarkable mutation rate at amino acid sites due to sustained directional immune selection pressure from host defenses. This adaptive evolution likely enhances its capacity to evade immune clearance (20). In contrast, CA16 displays cyclical epidemic fluctuations, whereas the detection rate of EV71 has shown a progressive downward trend over time.

Significantly, after the introduction of the EV71 vaccine into the market, its positive detection rate sharply decreased, reaching zero detections from 2020 to 2023, which aligns with the research conducted by Wang MeiFen and others (21, 22). This phenomenon could be attributed to the prior EV71 epidemic, the formation of immune barriers in susceptible populations through vaccination, as well as the improved clinical management and implementation of intervention measures against EV71 in recent years in China. Research has shown (23)that following the release of the EV71 vaccine, there has been an increase in severe and fatal cases caused by other enteroviruses, suggesting that daily monitoring practices for HFMD should be adaptively adjusted according to the actual situation on the ground. Currently, the inactivated EV71 vaccine used domestically can only prevent HFMD caused by EV71 infection and does not match the prevailing strains of pathogens in the HFMD pathogen spectrum in Yuyao. Therefore, the development of a multivalent vaccine capable of preventing infections caused by EV71, CA16, and CA6 viruses is urgently needed.

In Yuyao, the occurrence of HFMD demonstrates a broad temporal distribution, showing characteristics of persistent cases throughout the year; however, there is a distinct seasonal pattern, with a peak in case numbers primarily concentrated between April and October. Within this period, pathogens such as CA16, EV71, and CA6 serve as the main dominant causative agents, leading to infections at varying times throughout the year, which aligns with reports found in relevant research studies (24-26). It is noteworthy that these dominant pathogens each exhibit specific high-incidence months, alternately driving epidemic trends across different years. The fluctuation in serotypes of HFMD infections and variations in population immunity might be associated with the cyclical nature of the disease's prevalence (27). During the period from April to October each year, as nurseries, kindergartens, and schools start their semesters, the increase in population mobility, expansion of activity ranges, and greater frequency of group activities make this period a crucial time for the rise in the incidence of hand, foot, and mouth disease (HFMD). Especially in densely populated nurseries, kindergartens, and educational institutions, the risk of disease outbreaks significantly increases. Previous studies have shown that there is a positive correlation between population density and the incidence of HFMD, which provides favorable conditions for the rapid spread of the virus (28, 29). Moreover, the seasonal occurrence of HFMD is

further influenced by meteorological factors (30), as high temperatures and humidity provide conducive conditions for the proliferation and survival of pathogens. Chen's study on climatic factors in Zhejiang Province highlighted significant associations between environmental conditions and enterovirus transmission. Notably, temperature demonstrated an inverted U-shaped relationship with CVA16 and EV71 incidence: CVA16 risk peaked at 18°C (11–25°C range) under >77% humidity, while EV71 reached maximum risk at 21°C (11–32°C range) under similar conditions. Other enteroviruses exhibited elevated risks at temperatures >11°C and humidity >76% (30).

The analysis of the demographic distribution of HFMD reveals a significant concentration of cases among children aged six and under, a phenomenon tightly tied to the unique physiological and behavioral traits of this age bracket. Young children, by nature, are notably energetic and curious, often exposing themselves to a greater variety of pathogens during their interactions with the environment and other individuals. Moreover, they commonly have yet to fully cultivate sound hygiene practices, which might lead to infrequent handwashing or touching their mouths and noses following contact with contaminated items, thereby elevating their susceptibility to infections. Furthermore, the immune systems of children below six years are still undergoing development, leaving them relatively weaker in terms of defending against viruses compared to adults and older children with more mature immune defenses. As such, the incidence rate of HFMD decreases in tandem with the child's aging process and the progressive fortification of their immune system (31). Consequently, in both preventative and control strategies for HFMD, there is a pressing need to focus on safeguarding the health and well-being of this specific age category. Implementing rigorous health education programs, boosting vaccination coverage, and enacting efficacious public health interventions can effectively mitigate the occurrence of HFMD within this population.

Regarding gender disparities, the statistics indicate that the incidence rate for males (58.91%) is marginally higher than for females (50.05%). This difference might possibly be associated with attributes such as men's tendency towards more extroverted and active behavior, broader scopes of activity, and a higher likelihood of encountering infected persons or contaminated objects (32). The root causes of such gender differences likely involve intricate interactions between a variety of social and biological factors, and further investigation is needed to uncover the exact reasons for this disparity.

This study provides critical insights into the evolving epidemiology of HFMD in Yuyao, highlighting the substantial impact of EV71 vaccination on pathogen dynamics and the emergence of non-EV71 strains like CA6. The findings underscore the urgent need for multivalent vaccines and adaptive surveillance strategies to address shifting transmission patterns. However, the study has limitations. The relatively small sample size in certain years may reduce the statistical power of trend analyses, potentially introducing variability in detection rates. Additionally, the focus on laboratory-confirmed cases could underestimate the true prevalence due to undiagnosed mild infections. Future studies with larger, population-based samples and standardized diagnostic methods are needed to validate these observations and refine prevention strategies.

Conclusion

This 14-year study on HFMD in Yuyao found fluctuating dominance among enterovirus serotypes, with EV71 initially prevailing and later replaced by CA6. The disease exhibited a year-round presence but saw a pronounced seasonal peak from spring through autumn, peaking in May. Predominantly affecting young children, HFMD posed risks across all ages, with males having a higher infection rate. The shifting pathogenetic trends illuminated the changing epidemic dynamics and etiology of HFMD in Yuyao,

emphasizing the need for targeted, strategic disease control measures.

Journalism 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

The authors declare that there is no conflict of interest.

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