Clinical Research Report

Journal of INTERNATIONAL MEDICAL RESEARCH

Journal of International Medical Research
2019, Vol. 47(6) 2615–2625

DOI: 10.1177/0300060519841974
journals.sagepub.com/home/imr
SAGE

Epidemiological study on hand, foot and mouth disease in Tongzhou District, Beijing, 2013–2017

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Abstract

Objective: To study the epidemiological characteristics of hand, foot and mouth disease (HFMD) in Tongzhou District, Beijing between 2013 and 2017.

Methods: Data on HFMD infections from 1 January 2013 to 31 December 2017 were collected from the Notifiable Infectious Diseases Reporting Information System and analysed. Serotyping of enteroviruses from samples from patients with HFMD was undertaken using reverse transcription–polymerase chain reaction.

Results: A total of 15 341 patients with HFMD were reported and 32 patients (0.2%) were classified as having severe HFMD. The annual mean incidence rate of HFMD was 219.3/100 000 of the general population. The incidence and case-severity rates of HFMD generally decreased between 2013 and 2017. In the floating migrant population, the incidence and cases-severity rates of HFMD were significantly higher than in the local population. The peak incidence and severity-case rates were at 2 years of age and $>$ 90% of patients were $\leq$5 years. *Enterovirus A71* and *Coxsackievirus A16* were the predominant pathogens in 2013–2017.

Conclusions: During the 5-year period 2013–2017, the incidence rate and case-severity rate of HFMD generally decreased in Tongzhou District, Beijing. The floating migrant population and children $\leq$5 years of age were at the highest risk of HFMD.

Keywords

Hand, foot and mouth disease, epidemiology, pathogen, enterovirus, children, infection

Date received: 9 November 2018; accepted: 14 March 2019

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Introduction

Hand, foot and mouth disease (HFMD) is an acute infectious disease caused by a group of human enteroviruses (EVs), such as *Enterovirus A71* (EV-A71), *Coxsackievirus A16* (CV-Al6) and others; and it mainly affects infants and children under 5 years old.[1,2] It is characterized by fever and a maculopapular or vesicular rash on the hands, feet, mouth or other parts of the body.[3,4] Although HFMD is a mild and self-limiting disease, and most sick infants or children can recuperate without complications, a few cases may progress to develop severe complications, such as neuronal pulmonary oedema, myocarditis and aseptic meningitis, causing fulminant cardiorespiratory failure or even death.[5,6] Since 2008, approximately 1.4 million HFMD cases have been reported and approximately 400 patients have died annually in mainland China;[7] so HFMD has become a serious public health problem in China. Since 2 May 2008, HFMD has been categorized as a class C notifiable infectious disease in China and healthcare institutions are required to report it on the Notifiable Infectious Diseases Reporting Information System (NIDRIS) within 24 h.[8] The present study analysed the epidemiological and aetiological characteristics of HFMD cases in the Tongzhou District of Beijing City from 2013 to 2017 in order to provide a scientific basis for the diagnosis, treatment, prevention and control of the disease.

Patients and methods

Data collection

This retrospective epidemiological study collected data on cases of HFMD between 1 January 2013 and 31 December 2017 from the NIDRIS according to the date of onset. The data included demographic information, pathogenic information, case classification and disease severity.

The study was approved by the Ethics Committee of Tongzhou District Centre for Disease Control (TCDC) (no. 2018003). The patient or the patient's legal guardian provided written informed consent.

Case definitions

Any patient with a maculopapular or vesicular rash on the hands, feet, mouth or other parts of the body, with or without fever, was classified as a clinically-diagnosed case.[7] Clinically-diagnosed cases with laboratory evidence of EV infection detected by reverse transcription–polymerase chain reaction (RT–PCR) were classified as a laboratory-diagnosed case. Clinically-diagnosed or laboratory-diagnosed cases with any cardiopulmonary complications and/or neurological complications were classified as a severe case.

Laboratory viral detection

A stool or throat swab sample was collected from patients in the acute phase of HFMD. Briefly, 1 g of stool or a throat swab was added to 5 ml 0.02 mM phosphate-buffered saline (pH 7.4) and vortexed for 1 min. The suspensions were centrifuged at 3000 *g* for 30 min at 4°C in an Eppendorf centrifuge (Eppendorf, Hamburg, Germany). Total RNA was extracted from the supernatant using a QIAamp Viral RNA Mini Kit (QIAGEN, Hilden, Germany) according to the manufacturer's instructions. The serotypes of EV (including EV-A71, CV-A16 and other EVs without further serotype identification) were identified using a real-time RT–PCR Kit (DAAN Gene, Guangzhou, China). Positive PCR products of other EVs were sequenced directly using an ABI 3730XL automated sequencer (Applied Biosystems, Foster City, CA, USA) and all sequences were

analysed using the Enterovirus Genotyping Tool for serotyping.[9]

Statistical analyses

All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY, USA). Data are presented as mean ± SD (range) or *n* (%) and the comparisons of proportions or rates were performed using χ^2-test. A *P*-value < 0.05 were considered statistically significant.

Results

A total of 15 341 patients of HFMD were reported in the Tongzhou District of Beijing City between 1 January 2013 and 31 December 2017. Of those patients, 9205 (60.0%) were male and 6136 (40.0%) were female (male:female ratio, 1.5:1). The annual mean incidence rate of HFMD was 219.3/100 000 of the general population (range, 132.8–355.4/100 000 of the general population) between 1 January 2013 and 31 December 2017. Thirty-two out of 15 341 patients (0.2%) were classified as having severe HFMD and none of the infected patients died. Both the incidence rate and case-severity rate of HFMD generally reduced from 2013 to 2017 (Figure 1).

Among the 15 341 patients, 90.5% (13 891 of 15 341 patients) were 0–5 years old and 71.2% (10 928 of 15 341 patients) were 0–3 years old. The median age of the patients was 2.7 years (interquartile range, 2.1–4.6 years). The peak incidence and peak case-severity rates of HFMD were both at 2 years of age (Figure 2).

As the majority of patients (90.5%) were aged 0–5 years old, the incidence of HFMD was compared among two different populations aged 0–5 years. The incidence rate (4.49%; 5926 of 131 890 population) and case-severity rate (0.35%; 21 of 5926 patients) of HFMD in a floating population composed of migrants from other areas of China who did not have local household registration status were significantly higher than in the local resident population (3.91% [7965 of 203 577 population] and 0.13% [10 of 7965 patients], respectively) ($P < 0.05$). The incidence rate of HFMD in the local resident population was observed to decrease, as were the case-severity rates of HFMD in the local resident and floating populations, but the incidence

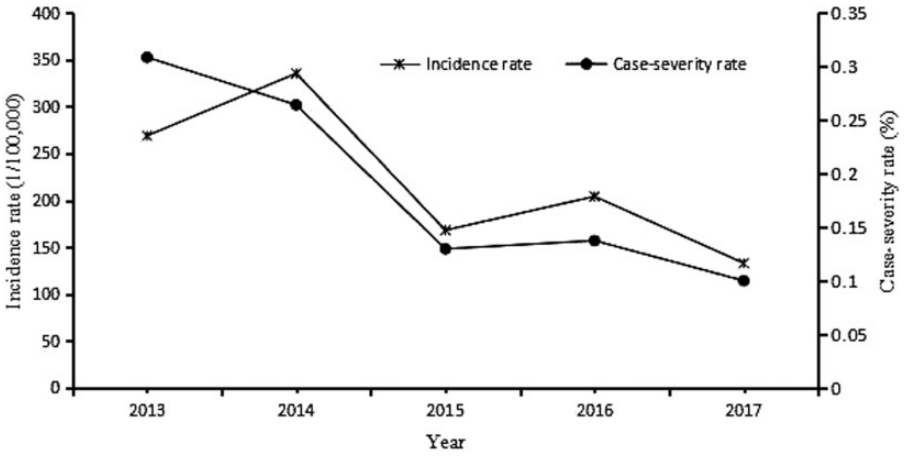

Figure 1. The incidence rate and case-severity rate of hand, foot and mouth disease reported in the Tongzhou District of Beijing City between 1 January 2013 and 31 December 2017.

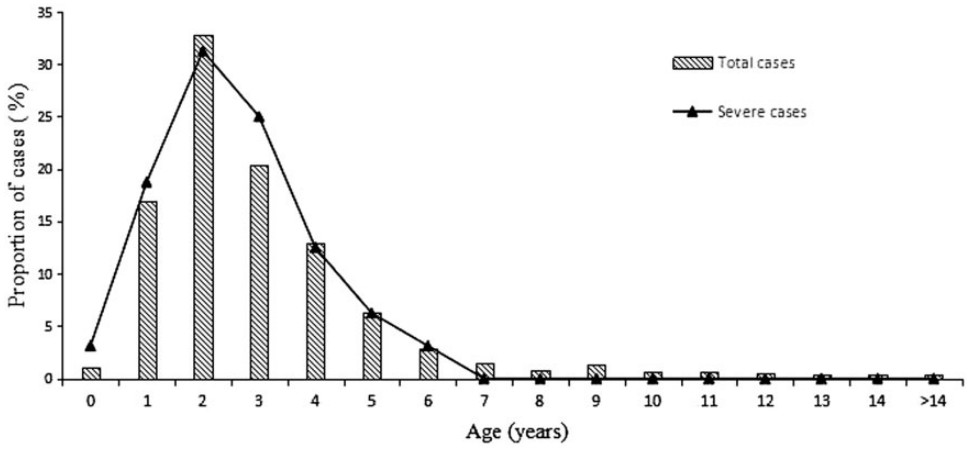

Figure 2. Age distribution of hand, foot and mouth disease reported in the Tongzhou District of Beijing City between 1 January 2013 and 31 December 2017.

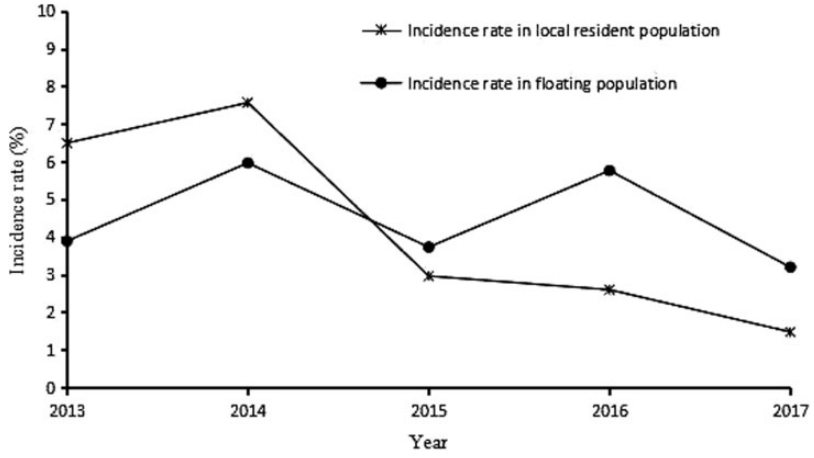

Figure 3. The incidence rates of hand, foot and mouth disease reported in two different populations, the local resident population and the floating migrant population, in the Tongzhou District of Beijing City between 1 January 2013 and 31 December 2017.

rate of HFMD in the floating population was relatively stable at approximately 4.49% (5926 of 131 890 population) across the 5-year period (Figures 3 and 4).

An analysis was undertaken based on the rural and urban populations. The incidence rate (4.99%; 5939 of 119 063 population) of HFMD in the rural population was significantly higher than in the urban population (3.68%; 7964 of 216 404 population) ($P < 0.05$). Although the cases-severity rate (0.30%; 18 of 5939 population) of HFMD in the rural population was higher than in the urban population (0.16%; 13 of 7964 population), the difference was not significant. The incidence rate of HFMD in the urban population was observed to decrease, as were the case-severity rates of

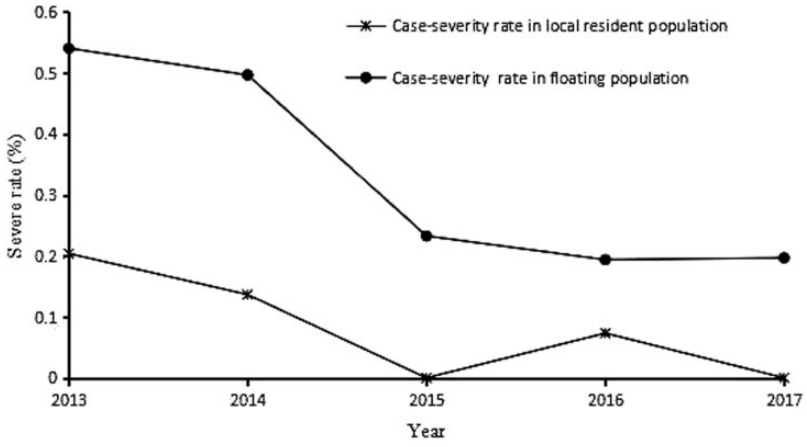

Figure 4. The case-severity rates of hand, foot and mouth disease reported in two different populations, the local resident population and the floating migrant population, in the Tongzhou District of Beijing City between 1 January 2013 and 31 December 2017.

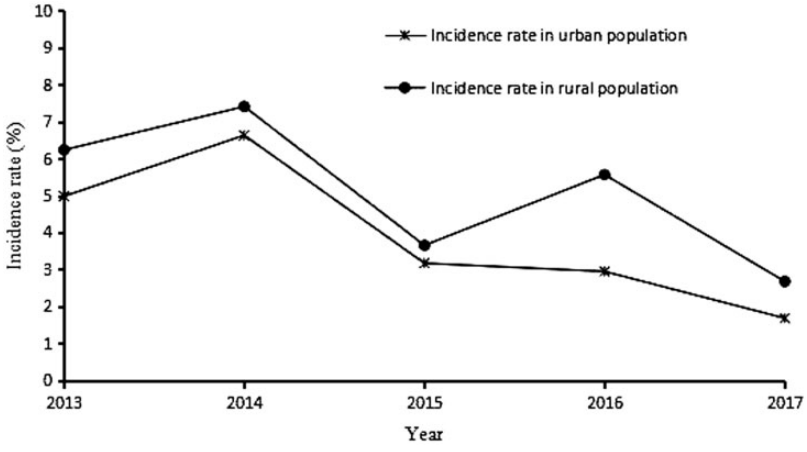

Figure 5. The incidence rates of hand, foot and mouth disease reported in two different populations, the local rural and urban populations, in the Tongzhou District of Beijing City between 1 January 2013 and 31 December 2017.

HFMD in the urban and rural populations, but the incidence rate of HFMD in the rural population fluctuated across the 5-year period (Figures 5 and 6).

Although cases of HFMD were reported every month during the 5-year period, the peak time-specific incidence was in June and July, followed by May and August, each year (Figure 7). A smaller peak occurred in October and November, and low levels of incidence occurred in December–March.

From 2013 to 2017, a total of 821 of 15 341 patients (5.35%) were classified as laboratory-diagnosed cases. The patients were predominantly infected with CV-A16 and EV-A71 in the 5-year period, followed by CV-A6 and CV-A10 (Table 1).

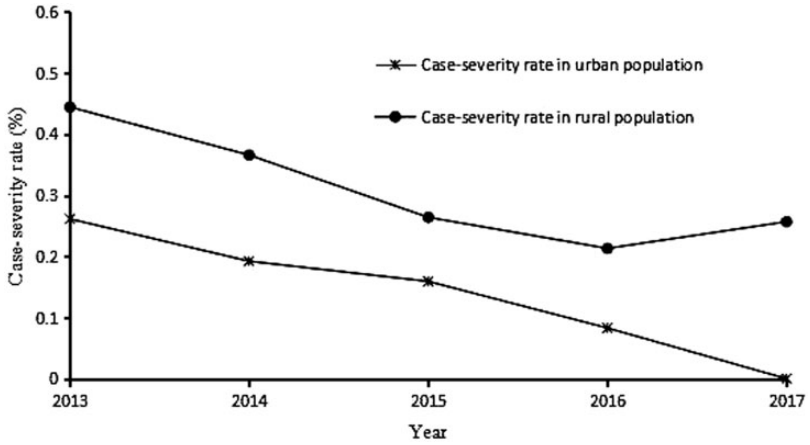

Figure 6. The case-severity rates of hand, foot and mouth disease reported in two different populations, the local rural and urban populations, in the Tongzhou District of Beijing City between 1 January 2013 and 31 December 2017.

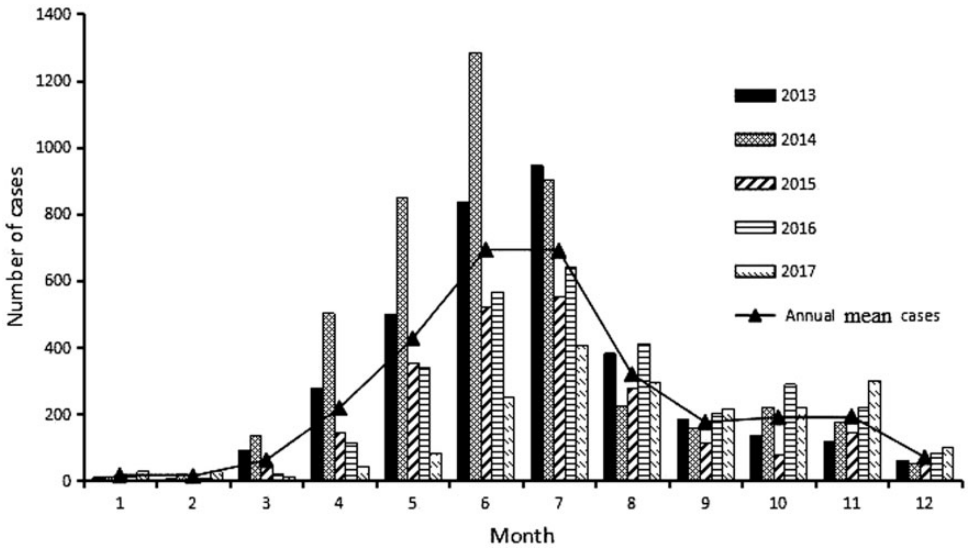

Figure 7. The monthly distribution of hand, foot and mouth disease reported in the Tongzhou District of Beijing City between 1 January 2013 and 31 December 2017.

The proportion of patients that were positive for CV-A16, EV-A71, CV-A6, CV-A10 and other EVs was 34.96% (287 of 821 patients), 30.21% (248 of 821 patients), 14.98% (123 of 821 patients), 12.18% (100 of 821 patients) and 7.67% (63 of 821 patients), respectively. In 2017, the proportion of patients infected with EV-A71 (24.77%; 54 of 218 patients) was higher than that for CV-A16 (22.48%; 49 of 218 patients). In addition, the proportion of patients infected with CV-A6 increased over time and it became the predominant serotype (31.33%; 26 of 83 patients) in 2016 and

Table 1. Serotypes of enteroviruses (EV) in patients ($n = 821$) with hand, foot and mouth disease reported in the Tongzhou District of Beijing City between 1 January 2013 and 31 December 2017.

Year	CV-A16	EV-A71	CV-A6	CV-A10	CV-A4	CV-A2	CV-A5	CV-A8	Untyped	Total
2013	86 (42.57)	56 (27.72)	25 (12.38)	25 (12.38)	3 (1.49)	3 (1.49)	1 (0.50)	2 (0.99)	1 (0.50)	202 (100.00)
2014	82 (50.31)	77 (47.24)	2 (1.23)	1 (0.61)	1 (0.61)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	163 (100.00)
2015	48 (30.97)	40 (25.81)	20 (12.90)	30 (19.35)	5 (3.23)	4 (2.58)	2 (1.29)	3 (1.94)	3 (1.94)	155 (100.00)
2016	22 (26.51)	21 (25.30)	26 (31.33)	10 (12.05)	1 (1.20)	1 (1.20)	1 (1.20)	1 (1.20)	0 (0.00)	83 (100.00)
2017	49 (22.48)	54 (24.77)	50 (22.94)	34 (15.60)	13 (5.96)	8 (3.67)	4 (1.83)	3 (1.38)	3 (1.38)	218 (100.00)
Total	287 (34.96)	248 (30.21)	123 (14.98)	100 (12.18)	23 (2.80)	16 (1.95)	8 (0.97)	9 (1.10)	7 (0.85)	821 (100.00)

Data presented as *n* of patients (%).
CV, *Coxsackievirus*.

Table 2. Serotypes of enteroviruses (EV) in patients ($n = 32$) with severe hand, foot and mouth disease reported in the Tongzhou District of Beijing City between 1 January 2013 and 31 December 2017.

Year	EV-A71	CV-A16	CV-A6	CV-A10	Total
2013	9 (81.82)	1 (9.09)	1 (9.09)	0 (0.00)	11 (100.00)
2014	10 (83.33)	0 (0.00)	1 (8.33)	1 (8.33)	12 (100.00)
2015	3 (100.00)	0 (0.00)	0 (0.00)	0 (0.00)	3 (100.00)
2016	2 (50.00)	1 (25.00)	1 (25.00)	0 (0.00)	4 (100.00)
2017	2 (100.00)	0 (0.00)	0 (0.00)	0 (0.00)	2 (100.00)
Total	26 (81.25)	2 (6.25)	3 (9.38)	1 (3.13)	32 (100.00)

Data presented as *n* of patients (%).
CV, *Coxsackievirus*.

the subdominant serotype (22.94%: 50 of 218 patients) in 2017. In 32 patients with severe HFMD, EV-A71 was the major EV serotype over the 5-year period (26 of 32 patients; 81.25%) (Table 2).

Discussion

In the present study, the annual mean incidence rate and case-severity rate of HFMD was 219.3/100 000 and 0.2%, respectively, in the Tongzhou District of Beijing City between 1 January 2013 and 31 December 2017. The annual incidence rate was higher than the national mean (120.0/100 000) level from 2008 to 2012, but the case-severity rate was lower than the national mean (1.1%).[7] The different study period and regional differences may account for the discrepancies. In this current study, 32 patients were classified as having severe HFMD and no deaths were reported. The incidence rates and case-severity rates of HFMD generally decreased from 2013 to 2017. In a previous study, the incidence rate and case-severity rate of HFMD both increased from 2006 to 2010; with 67 severe cases and three deaths.[10] The variations may be associated with improvements to the preventive and control measures carried out by the TCDC. In addition, vaccines against EV-A71-associated HFMD have been available in China since 2014.[11] As EV-A71 had been identified as the predominant pathogen in severe cases of HFMD,[12] the use of vaccines may have also accounted for the reduced incidence rate of HFMD, especially for the decreasing case-severity rate. Unfortunately, this current study did not have access to the vaccine inoculation data for these current patients. The finding that the male-to-female ratio of

patients with HFMD was 1.5:1 in this current study was consistent with the results of studies in other districts of Beijing City[13,14] and nationwide.[15]

The age distribution of patients in this current study was similar to previous studies,[14,16,17] with children ≤5 years of age being the mostly frequently affected by HFMD. In the present study, the peak incidence and peak case-severity rates of HFMD were both at 2 years of age, but in previous studies, the peak incidence occurred at 1 year of age.[17–19] However, the variation between these peaks of incidence does not necessarily demonstrate a corresponding shift in the age distribution because the difference between 1 and 2 years of age may be not significant. In addition, the median age of the reported patients in the current study (2.7 years) was lower than that of a previous study undertaken in Beijing City (3.12 years).[20]

China has the largest internal floating migrant population in the world; and in 2015, approximately 247 million Chinese were migratory, which accounted for 18% of the total population.[21] The floating population does not qualify for public health services and other assistance services in China, so they have a higher risk of infectious diseases.[22] In one study based on the stratified analysis of the population data, the incidence rate and the case-severity rate of HFMD was observed to be approximately twice as high among migrant children than local children and it was thought that the migrant young children played a central role in the transmission of HFMD in the community.[23] In the present study, both the incidence rate and case-severity rate of HFMD in the floating population were significantly higher than in the local resident population. Although the incidence rate of HFMD in the local resident population generally declined between 2013 and 2017, the incidence rate of HFMD in the floating population remained relatively stable. These results suggest that the floating population had a higher risk of HFMD compared with local residents and we recommend that prevention and control measures for HFMD should be strengthened in the floating population.

Some reports have demonstrated that the incidence rates of HFMD in urban areas is greater than in rural areas.[15,24,25] In contrast, the current results found that the rural population had significantly higher incidence rates than the urban population, which was consistent with a previous study in Tokyo.[26] Tongzhou District is a new developing area in Beijing, but the rural area has poor living conditions and poor sanitation, an ever-growing floating high-density population and poor quality of kindergartens. All of these factors may lead to a higher incidence of HFMD in the rural areas.

From the monthly distribution of HFMD data in the current study, the peak incidence was in June and July, followed by May and August, with low levels between December and March. The time patterns of HFMD in this study were similar to those observed in Northern China; however, Southern China experienced two outbreaks of HFMD that peaked in May and October each year.[7]

Previous research has suggested that EV-A71 and CV-A16 were the most prevalent pathogens for HFMD,[27–29] but the occurrence of other EVs have been increasing since 2008.[30,31] In the present study, eight serotypes of EVs were identified, including EV-A71, CV-A16, CV-A6, CV-A10, CV-A4, CV-A2, CV-A5 and CV-A8, from stool or throat swab samples from patients with HFMD. Of these, CV-A16 predominated between 2013 and 2017, followed by EV-A71, CV-A6 and CV-A10. In 2016, CV-A6 was the predominant EV; and EV-A71 predominated in 2017, followed by CV-A6. This is similar to the results of previous study undertaken

in Beijing.[20] In different geographical areas in China, the aetiological spectrum was different. For example, in Suzhou between 2008 and 2013, EV-A71 was predominant, followed by CV-A16.[32] In Shanghai, EV-A71 was the most prevalent pathogen for HFMD, followed by CV-A10, CV-A6 and CV-A16 between 2010 and 2011.[33] In some areas of China, CV-A6 has replaced EV-A71 and CV-A16 to become the most prevalent pathogenic serotype in HFMD patients.[31,34,35] Therefore, physicians will need to play close attention to HMFD infections caused by other serotypes in addition to EV-A71 and CV-A16 in the future, such as CV-A6 and CV-A10. In the present study, EV-A71 was the most prevalent serotype in 32 patients with severe HFMD, which was consistent with a previous study.[36]

This current study had several limitations. First, as HFMD is a self-limiting illness, patients may not have attended hospital, which would have made them untraceable by the surveillance system. Therefore, the number of patients with HFMD may have been underestimated. Secondly, there were relatively few laboratory-diagnosed cases in the study, which might have introduced an element of bias to the pathogen distribution of HFMD.

In conclusion, during the 5-year period 2013–2017, the incidence rate and case-severity rate of HFMD generally decreased in Tongzhou District, Beijing. The floating migrant population and children $\leq$5 years of age were at the highest risk of HFMD. The peak month-specific incidence occurred in June and July, followed by May and August. Although EV-A71 and CV-A16 were the main causative pathogens of HFMD, CV-A6 has recently been emerging as another predominant serotype.

Acknowledgements

The authors would like to thank Dr Li-Xin Chen and Dr Qiu-Hong Li (Tongzhou District Centre for Disease Control) for data extraction.

Declaration of conflicting interests

The authors declare that there are no conflicts of interest.

Funding

The study was supported by a grant from the National Natural Science Foundation of China (no. 7164240).

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References

1. World Health Organization. Western Pacific Region. *A Guide to Clinical Management and Public Health Response for Hand, Foot and Mouth Disease (HFMD)*. Geneva: WHO Press, 2011. http://www.wpro.who.int/publications/docs/GuidancefortheclinicalmanagementofHFMD.pdf
2. Liu W, Wu S, Xiong X, et al. Co-circulation and genomic recombination of coxsackievirus A16 and enterovirus 71 during a large outbreak of hand, foot, and mouth disease in Central China. *PLoS One* 2014; 9: e96051.
3. Lu B, Guo H and Lu H. Hand, foot, and mouth disease in mainland China. *Lancet Infect Dis* 2014; 14: 1041.
4. Pérez-Vélez CM, Anderson MS, Robinson CC, et al. Outbreak of neurologic enterovirus type 71 disease: a diagnostic challenge. *Clin Infect Dis* 2007; 45: 950–957.
5. Brown BA, Oberste MS, Alexander JP Jr, et al. Molecular epidemiology and evolution of enterovirus 71 strains isolated from 1970 to 1998. *J Virol* 1999; 73: 9969–9975.
6. Michos AG, Syriopoulou VP, Hadjichristodoulou C, et al. Aseptic meningitis in children: analysis of 506 cases. *PLoS One* 2007; 2: e674.
7. Xing W, Liao Q, Viboud C, et al. Hand, foot, and mouth disease in China, 2008-12: an epidemiological study. *Lancet Infect Dis* 2014; 14: 308–318.
8. Shi C, Liu J, Shi P, et al. Epidemiological characteristics and influential factors of hand, foot, and mouth disease reinfection

in Wuxi, China, 2008-2016. *BMC Infect Dis* 2018; 18: 472.
9. Kroneman A, Vennema H, Deforche K, et al. An automated genotyping tool for enteroviruses and noroviruses. *J Clin Virol* 2011; 51: 121–125.
10. Chen LX, Liu XJ, Wang BL, et al. Analysis on epidemiological features of hand, foot and mouth disease in Tongzhou District of Beijing from 2006 to 2010. *Practical Preventive Medicine* 2013; 20: 176–178 [Article in Chinese, English abstract].
11. Chen YJ, Meng FY, Mao Q, et al. Clinical evaluation for batch consistency of an inactivated enterovirus 71 vaccine in a largescale phase 3 clinical trial. *Hum Vaccin Immunother* 2014; 10: 1366–1372.
12. Zhao Y, Zhang H, Liu H, et al. Molecular characteristics of hand, foot, and mouth disease for hospitalized pediatric patients in Yunnan, China. *Medicine (Baltimore)* 2018; 97: e11610.
13. Zhang HY, Xu BL, Ning X, et al. Epidemiological characteristics of hand-foot-mouth disease in Dongcheng District of Beijing from 2013-2016. *Occup and Health* 2018; 34: 808–810 [Article in Chinese].
14. Qu QQ, LIU M and Chu YH. Epidemiological characteristics of hand, foot and mouth disease in Xicheng District of Beijing from 2012-2016. *Occup and Health* 2018; 34: 2537–2540 [Article in Chinese].
15. Zhu Q, Hao Y, Ma J, et al. Surveillance of hand, foot, and mouth disease in mainland China (2008-2009). *Biomed Environ Sci* 2011; 24: 349–356.
16. Liu BY, Luo L, Yan SY, et al. Clinical features for mild hand, foot and mouth disease in China. *PLoS One* 2015; 10: e0135503.
17. Koh WM, Bogich T, Siegel K, et al. The epidemiology of hand, foot and mouth disease in Asia: a systematic review and analysis. *Pediatr Infect Dis J* 2016; 35: e285–e300.
18. Zhang W, Huang B, She C, et al. An epidemic analysis of hand, foot, and mouth disease in Zunyi, China between 2012 and 2014. *Saudi Med J* 2015; 36: 593–598.
19. Liu MY, Liu W, Luo J, et al. Characterization of an outbreak of hand, foot, and mouth disease in Nanchang, China in 2010. *PLoS One* 2011; 6: e25287.
20. Qian H, Huo D, Wang X, et al. Detecting spatial-temporal cluster of hand foot and mouth disease in Beijing, China, 2009-2014. *BMC Infect Dis* 2016; 16: 206.
21. *Report on China's Floating Population Development 2016*. China Population Publishing House, 2016; http://www.nhc.gov.cn/rkjcyjtfzs/pgzdt/201610/57cf8a2bbafe4b4d9a7be10d10ae5ecf.shtml [Article in Chinese].
22. Hu X, Cook S and Salazar MA. Internal migration and health in China. *Lancet* 2008; 372: 1717–1719.
23. Xu Z, Shen H, Wang Z, et al. The population-based health effect of hand, foot and mouth disease in children in Shanghai. *Pediatr Infect Dis J* 2014; 33: 448–452.
24. Wang J, Hu T, Sun D, et al. Epidemiological characteristics of hand, foot, and mouth disease in Shandong, China, 2009-2016. *Sci Rep* 2017; 7: 8900.
25. Yang H, Wu J, Cheng J, et al. Is high relative humidity associated with childhood hand, foot, and mouth disease in rural and urban areas? *Public Health* 2017; 142: 201–207.
26. Urashima M, Shindo N and Okabe N. Seasonal models of herpangina and hand-foot-mouth disease to simulate annual fluctuations in urban warming in Tokyo. *Jpn J Infect Dis* 2003; 56: 48–53.
27. Ooi MH, Wong SC, Lewthwaite P, et al. Clinical features, diagnosis, and management of enterovirus 71. *Lancet Neurol* 2010; 9: 1097–1105.
28. Abzug MJ. The enteroviruses: problems in need of treatments. *J Infect* 2014; 68(Suppl 1): S108–S114.
29. He Y, Zou L, Chong MKC, et al. Genetic evolution of human enterovirus A71 subgenotype C4 in Shenzhen, China, 1998-2013. *J Infect* 2016; 72: 731–737.
30. Li Y, Bao H, Zhang X, et al. Epidemiological and genetic analysis concerning the non-enterovirus 71 and non-coxsackievirus A16 causative agents related to hand, foot and mouth disease in Anyang city, Henan Province, China, from 2011 to 2015. *J Med Virol* 2017; 89: 1749–1758.
31. Zeng H, Lu J, Zheng H, et al. The epidemiological study of coxsackievirus A6

revealing hand, foot and mouth disease epidemic patterns in Guangdong, China. *Sci Rep* 2015; 5: 10550.
32. Chen Z, Sun H, Yan Y, et al. Epidemiological profiles of hand, foot, and mouth disease, including meteorological factors, in Suzhou, China. *Arch Virol* 2015; 160: 315–321.
33. Xu M, Su L, Cao L, et al. Enterovirus genotypes causing hand foot and mouth disease in Shanghai, China: a molecular epidemiological analysis. *BMC Infect Dis* 2013,13: 489.
34. He YQ, Chen L, Xu WB, et al. Emergence, circulation, and spatiotemporal phylogenetic analysis of coxsackievirus A6- and coxsackievirus A10-associated hand, foot, and mouth disease infections from 2008 to 2012 in Shenzhen, China. *J Clin Microbiol* 2013; 51: 3560–3566.
35. Yang Q, Ding J, Cao J, et al. Epidemiological and etiological characteristics of hand, foot, and mouth disease in Wuhan, China from 2012 to 2013: outbreaks of coxsackieviruses A10. *J Med Virol* 2015; 87: 954–960.
36. Li Y, Chang Z, Wu P, et al. Emerging enteroviruses causing hand, foot and mouth disease, China, 2010-2016. *Emerg Infect Dis* 2018; 24: 1902–1906.