RESEARCH ARTICLE

Emerging Hand Foot Mouth Disease in Bangladeshi Children- First Report of Rapid Appraisal on Pocket Outbreak: Clinico-epidemiological Perspective Implicating Public Health Emergency [version 1; peer review: 1 approved with reservations]

Md. Azraf Hossain Khan¹, Kazi Selim Anwar², A. K. M. Muraduzzaman³, Md. Abid Hossain Mollah^{4,5}, S. M. Akhter-ul-Alam¹, Kazi Munisul Islam⁶, Sheikh Ariful Hoque⁷, Md. Nazrul Islam¹, Md. Ahasan Ali⁸

¹Department of Dermatology and Venerology, Pabna Medical College and General Hospital, Hemayetpur, Pabna, Bangladesh

²Institute of Epidemiology, Disease Control and Research (IEDCR), Dhaka, 1212, Bangladesh

³Department of Virology, Institute of Epidemiology, Disease Control and Research (IEDCR), Dhaka, 1212, Bangladesh

⁴Department of Pediatrics, Institute of Research & Rehabilitation in Diabetes, Endocrine and Metabolic Disorders (BIRDEM), Dhaka, Bangladesh

⁵International Center for Diarrheal Diseases Research, Bangladesh (icddr,b), Dhaka, 1200, Bangladesh

⁶Infectious Disease Division, Centre for Advanced Research in Sciences (CARS), University of Dhaka, Dhaka, Bangladesh

⁷Tissue Culture Laboratory, Centre for Advanced Research in Sciences, Institute of Public Health (IPH), Dhaka, Bangladesh

⁸Microbiology Section, Institute of Public Health, Dhaka, Bangladesh

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Abstract

Background: Hand, foot and mouth disease (HFMD) is a common contagious disease among children under 5 years, particularly in the Asia-Pacific-region. We report a localized outbreak of childhood HFMD for the first time from Bangladesh, diagnosed only based on clinical features due to gross lack of in laboratory-diagnostic facilities.

Methods: Following the World Health Organization's case-definition, we conducted a rapid-appraisal of HFMD among 143 children attending Pabna Medical College and General Hospital with fever, mouth ulcers and rash. Data were collected between September and November 2017 using a preset syndromic approach and stringent differential diagnostic-protocols.

Results: The mean age of children was 2.9±2.3 years. Age did not differ with sex (P=0.98), first sibling being more likely to (62%) belong to middle-income families. Younger children (<5 years) were more

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1. **H Rogier van Doorn** , Oxford University
 Clinical Research Unit, Hanoi, Vietnam
 University of Oxford, Oxford, UK

likely to suffer with moderate-to-high (38.5°C) fever ($P<0.04$), painful oral ulcers ($P<0.03$) and painful/itchy rash ($P<0.01$). Sex did not differ with other symptoms, but boys had less painful oral ulcers than girls ($P<0.04$). Fever (63%) and chicken-pox-like-rash (62%) was observed more in mid-October to mid-November than September to mid-October ($P<0.01$ and $P<0.03$, respectively). No differences in symptoms (fever, oral ulcers and extremity rash) were observed with precipitation, nor with ambient temperature. Children <5 years (85%) had quicker recovery (within 5 days) than those ≥ 5 years (69%), ($P<0.04$), with marginal differences in sex ($P<0.05$).

Conclusions: Our findings highlight the potential usefulness in diagnosing HFMD based on clinical parameters, although stringent differential diagnosis remains indispensable. It is particularly applicable for resource-constrained countries who lack appropriate virology laboratory equipment. Since no specific treatment or effective vaccination is available for this disease, supportive therapy and preventive measures remain the primary methods to circumvent transmission augmented by climate-related factors. Standardized virology laboratory warrants appropriate diagnosis and globally representative multivalent vaccine is deemed essential towards preventing HFMD.

Keywords

Emerging Childhood-HFMD, Bangladesh, Rapid-Appraisal, Pocket-Outbreak

2. **Md. Azizul Haque**, Rajshahi Medical College
Hospital, Rajshahi, Bangladesh

Any reports and responses or comments on the article can be found at the end of the article.

Corresponding author: Kazi Selim Anwar (kselim2256@gmail.com)

Author roles: **Hossain Khan MA:** Conceptualization, Data Curation, Funding Acquisition, Methodology, Project Administration, Resources, Supervision, Visualization, Writing – Review & Editing; **Anwar KS:** Conceptualization, Data Curation, Formal Analysis, Methodology, Project Administration, Resources, Software, Supervision, Validation, Visualization, Writing – Original Draft Preparation; **Muraduzzaman AKM:** Conceptualization, Data Curation, Formal Analysis, Methodology, Supervision, Validation, Writing – Original Draft Preparation; **Hossain Mollah MA:** Formal Analysis, Resources, Supervision, Visualization, Writing – Review & Editing; **Akhter-ul-Alam SM:** Data Curation, Project Administration, Resources, Supervision, Visualization; **Munisul Islam K:** Data Curation, Formal Analysis, Methodology, Resources, Software, Writing – Review & Editing; **Hoque SA:** Formal Analysis, Methodology, Resources, Software, Supervision, Writing – Review & Editing; **Nazrul Islam M:** Data Curation, Project Administration, Resources, Supervision, Visualization; **Ali MA:** Data Curation, Formal Analysis, Project Administration, Resources, Software, Validation, Writing – Review & Editing

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Introduction

Of all commonly occurring febrile illness and rash syndromes¹, hand, foot and mouth disease (HFMD) remains the most among young children^{2,3}. Although this viral infection remains largely contagious^{4,5}, it is self-limiting and benign. Severe cases occur red with a low incidence (3.2% to 8.5%) and fatalities are rare^{6–8}. Starting in the West during the mid-1970's^{1,2} HFMD emerged in the Asia-Pacific region in mid-1990s^{9–11} heralding as a major public health hazards^{2,10}. Epidemiologically, it follows a 2–3 years cyclical pattern¹¹ but may break out anytime⁹ as has occurred in India (Orissa¹² and Calcutta¹³), bordering with Bangladesh.

With the complaints of mild-to-moderate fever ($\geq 38.5^{\circ}\text{C}$ ⁸; 101.3°F) childhood HFMD, characteristically manifest with body rashes^{1,4}, mostly of the knees and buttocks^{4,14}, augmented by painful oral/buccal ulcers and blisters. Papulo-vesicular rash in the extremities consequently forms pustules⁶. Most children recover/heal within 7–10 days^{5,8,9}. Of the few complications, neuro-respiratory syndromes⁴ (encephalitis, aseptic meningitis and acute flaccid paralysis)^{3,4} occur mainly in younger children; these are rare but seldom fatal^{9,15}. Children are mostly affected by neurotropic viruses like enterovirus (EV71)^{2,16} and coxsackievirus (CA-6, A-10, A-16)^{5,7,10}. These viruses are transmitted^{15,17} through direct contact/blister-fluid, droplets, oro-fecally¹⁶ and also spread out through contaminated environment, water and food¹⁸.

Reportedly, clinical diagnosis of HFMD is usually established depending on physicians' suspicions^{13,14} as the sole diagnostic modality¹². The diagnosis is primarily based on history of illness, disease-onset, presenting clinical-features^{1,6,19} and, socio-demographic profile^{12,14,20}. Small erythematous maculopapular lesion (1–5 mm) enlarge (3–15 mm) and progress to vesicular eruptions with a prominent erythematous halo^{13,21}. It is essential to perform stringent differential diagnosis (DD) to distinguish HFMD from a group of diseases. DD includes chickenpox, scabies, measles, erythema multiforme, herpangina, herpetic gingivitis, drug eruption and others^{4,14,17,22}. Laboratory diagnosis is usually not essential^{12,19,23}, and has been described by the World Health Organization (WHO) as optional¹. Conversely, the sophisticated laboratory tests used for definitive diagnosis (virus isolation, molecular analysis, PCR, genotyping)^{1,13,24} are not available in most resource-constrained countries^{3,12,13} like Bangladesh.

Since there is no specific treatment^{4,19,22,25} for HFMD, care largely remains palliative¹⁹ with antipyretics/analgesics and antihistamines. Topical anesthetics are rarely used for oral ulcers for soothing and comfort. Povidone-iodine used as a mouth wash/topical application that can relieve pain. Since no effective vaccine against HFMD-viruses is available^{1,2,7}, preventive measures remain the primary method of circumventing HFMD transmission to break infection-chains (droplets, oral-fecal route, and direct contact)^{2,18}. Effective prevention requires personal hygiene, hand washing²⁶ and a pollution-free environment¹² including food and water^{18,27}. Meteorological variations in precipitation^{8,9} and ambient temperature^{20,28} often impact on HFMD occurrences⁵ in the Asia-Pacific region^{5,9,10,15,17}, along with

atmospheric pressure and the relatively higher humidity in summer and early autumn¹⁸.

Extracts from extensive reviews, when compared with our intensive observations on upsurge of unusual febrile, rash-associated childhood illnesses between July and August 2017, were indicative of HFMD. A rapid appraisal was therefore, designed as a short-term standardized-surveillance¹. Following a pre-set case-definition and syndromic approach (according to the WHO HFMD guidelines¹), similar to a study conducted in Thailand²⁹ a strategic plan was adopted to conduct this comprehensive study from September to November 2017.

Methods

Set up, patients and research design

Utilizing a pre-set syndromic approach based on case-definition following the WHO's HFMD guidelines¹ this rapid appraisal (descriptive study) was conducted among 143 children attending Pabna Medical College and General Hospital (PMC-GH) from its catchment areas between September and November, 2017. PMC-GH is a 250-bed secondary care hospital serving a targeted population of nearly 2.81 million from its 2,371.5 km²³⁰ catchment area situated in a small poverty-stricken north-western flood-prone plain land on the Ganges Delta basin in Bangladesh.

Research instruments used

Clinical diagnostic tool. Prepared based on syndromic case-definition following the WHO's HFMD guidelines¹, similar to a prior study conducted in Thailand²⁹. Most of the contents of this tool have been shown in Figure 4 (4 A), showing the algorithm of Clinical diagnosis of HFMD¹.

Clinical case management protocol. This was prepared incorporating a history of disease, onset, chief complaints and duration of illness, clinical diagnosis and therapeutic intervention. We ascertained clinical outcome by through post-treatment follow-up in the outpatient department of PMC-GH or through cellphone-based enquiry. We performed the clinical diagnosis following WHO guidelines¹, predominantly based on three main signs/symptoms: fever, oral ulcers and rash in extremities. Fever was graded into moderate-to high (38.5°C) and none-to-low ($37\text{--}38.4^{\circ}\text{C}$), oral ulcers were grouped into three stages- more painful, less painful and painless; and, rashes in extremities into three types: painful and itchy, painless and itchy; and painful but not itchy.

Pain assessment/scoring

Since pain remains subjective in younger children in expressing pain intensity properly, we arbitrarily categorized the pain intensity based on following clinical grounds:

- i. Nullifying any history of past disease/disorders that may confound the current pain status
- ii. Facial expression of a child having body rash and/or oral ulcer on touch/other sensitizations
- iii. Impression and/or opinion of child's parent/guardian in respective cases

- iv. Finally, clinician's judgements based on disease history and presented signs/symptoms

Therapeutic index

A therapeutic index was prepared to treat childhood HFMD cases following standard therapeutic plan consisting of: antipyretic/analgesics, antihistamines, anesthetic-cream for topical applications. These aforementioned three clinical diagnostic tools (moderate-to-high fever, painful oral ulcers and painful rash in extremities) have been prepared adopting the WHO clinical management and public health response for HFMD¹ with a little modifications to suit our short-term comprehensive study (Figure 4 (4 A)).

Epidemiological tool

This tool consisted of socio-demographic variables and household (HH) income. We categorized the income of children's family following World Bank Data Help Desk 2016³¹ as follows:

- Low-income group: HH/families earning a monthly income of ≤6,946 BDT
- Lower-mid income group: HH/families earning a monthly income of 6,947–27,336 BDT
- Upper-mid-income group: HH/families earning a monthly income of 27,337–84,564 BDT
- High-income group: HH/families earning a monthly income of ≥84,564 BD

We calculated income scale using the USD rate: 1US \$ = 84.31 BDT as of 11 June 2018.

Records on seasonal data on local weather/climate (average temperature and rain precipitation) were collected from Pabna Meteorology Dept., Bangladesh over the period of September through November 2017. In Bangladesh, early autumn runs from September to mid-October, followed by late autumn/fall from mid-October to mid-November. All tools were pre-tested for this rapid-appraisal (small-scale disease surveillance)^{1,2}.

Data analysis

Crosschecked data were subjected to Pearson's chi-squared test, Fisher's exact test and Spearman correlation analysis using SPSS for Windows v.21, taking $P < 0.05$ as indicating statistical significance (at 95% CI).

Inclusion criteria/patient enrolment

Any child, irrespective of age and sex, attending PMC-GH between September and November 2017 with suspected HFMD (meeting WHO's¹ recommended criteria) were included in this study. Suspected cases having other serious disease/comorbidities were excluded, although patients were referred to concerned department for proper clinical management.

Ethical considerations

Following standard procedure of ethical issues³², written informed consent was obtained from the parents of children with suspected HFMD prior to enrolment. We detailed the parents/guardian of all children on the purpose and procedures of this

study. We also informed the parents on the lack of risk of harm/damage involved in procedures and did not collect body fluids or other biological samples. We informed the parents that they could remove their child at any stage of the study. Complete privacy and anonymity of clinical data was ensured, including its protected use research purposes only. This study had prior approval through the Ethical Committee of Pabna Medical College and General Hospital, Government of the Peoples' Republic of Bangladesh (Memo No. 1577, dated: 26/08/2017).

Results

Demographic information

The mean ($\pm$ SD) age of the 143 children was 2.9 ± 2.3 years; 80 (56%) were boys and 63 (44%) were girls. Of the total, 70% were under 5 years old. Age did not differ with sex ($P = 0.98$). Data on HH structure yielded an average size of children's family as 5.5 ± 6.9 persons/per HH. Of them, 62% having only one (no siblings) and 38% two (first sibling) children, (Table 1).

Following Word Bank, (2016) standard³¹ family/HH income-group evidenced that majority families (85%) belonged to middle-income HH/families (34% belonged to upper-middle and 51% to lower-middle income-groups living with a modest HH budget). The rest (14.7%) belonged to low-income groups lived with a tight HH-budget. Notably, children from mid-income-HHs contracted significantly more HFMD which was more among the first siblings ($P < 0.01$), (Table 1).

Assessment of symptoms

Child's age was significantly associated with three major clinical signs/symptoms. Younger children (under 5 years old) suffered more (74/91, 81%) with moderate-to-high fever than older children (17/91, 19%; $p < .04$). Similarly, painful oral ulcers (82/111, 74%) and painful itchy rash in extremities (92/116, 79%) were more common in younger than older children ($p < 0.03$ and $p < 0.01$, respectively). Notably, characteristics of skin rash in extremities of younger children's were more predominantly papulo-vesicular (59/68, 87%) than chickenpox-like (43/75, 57%), ($P < 0.01$). However, sex did not differ with other signs/symptoms except oral ulcers: boys had less painful ulcers (23/32, 72%) than girls (9/32, 28%), ($P < 0.04$), (Table 2).

None of the three major signs/symptoms of HFMD (fever, oral-ulcers/blisters and extremity rash) was associated with seasonal variations except fever and characteristics of rash. Moderate-to high fever (57/91, 63%) was observed more in fall/late-autumn (mid-October through mid-November) than in early autumn (September through mid-October), yielding 37% of cases (34/91), ($p < 0.01$). Similarly, papulo-vascular rashes were more common in fall (42/68, 62%) than in early autumn (26/68, 38%) ($P < 0.03$; Table 3).

The three major sign/symptoms among these HFMD contracted children were more prevalent on days where 0.0 mm precipitation was recorded. Rain had no significant impact on any of the three major sign/symptoms, unlike on dry days with no rainfall (0.0 mm). Similarly, all major sign/symptoms prevailed more in hot and humid days when the ambient

Table 1. Socio-demographic characteristics and household income of child's family attending the Pabna Medical College and General Hospital with the complaints of hand, foot and mouth disease (n=143 cases).

Variable	Groups	N (%)
Age	2 months–3 years	78 (54.5)
	3.1–5 Years	32 (22.4)
	>5.1 Years	33 (23.1)
Sex	Male	80 (55.9)
	Female	63 (44.1)
Age vs. sex		
χ^2	p=0.98	
Likelihood ratio	p=0.98	
Spearman's correlation	p >0.87	
Siblings	Child 1	89 (62.2)
	Child 2+	54 (37.8)
Household income*	Low income	21 (14.7)
	Low-mid-income	73 (51.0)
	Upper-mid-income	49 (34.3)
	High income	0
Sibling number vs. household income		
χ^2	p <0.01	
Likelihood ratio	p =0.01	
Spearman's correlation	p<0.01	

*Following World Bank Data Help Desk, 2016³³

Table 2. Composite table showing association of HFMD clinical features with age and sex.

Variables	Clinical manifestation							
	Body temperature		Oral ulcers		Rash in extremities		Rash characteristics	
	≥38.5°C (n=91)	37–38.4°C; (n=52)	Painful (n=111)	Painless/less-painful (n=32)	Painful/itchy (n=116)	Painless/less painful (n= 27)	Chicken pox-like (n= 75)	Papulovesicular (n= 68)
Child's age								
<3 years (n=78)	57	21	54	24	70	08	32	46
≥3 but <5 years (n=32)	17	15	28	4	22	10	19	13
≥5 years (n=33)	17	16	29	4	24	09	24	09
χ^2	P<0.04		P<0.03		P<0.01		P<0.01	
Spearman's correlation	P<0.01		P=0.01		P <0.01		P<0.01	
Sex								
Male (n=80)	52	28	57	23	68	12	44	36
Female (n=63)	39	24	54	9	48	15	31	32
Fisher's exact test	P>0.73 (2-sided); P>0.42 (1-sided)		P>0.04 (2-sided); P>0.03 (1-sided)		P>0.20 (2-sided); P>0.13(1-sided)		P>0.51 (2-sided); P>0.30(1-sided)	
Spearman's correlation	P>0.71		P<0.04		P<0.18		P<0.49	

*Mean ± SD = 2.9±2.3.

Table 3. Composite table showing association of HFMD clinical features with season/local climate.

Variables	Clinical manifestation							
	Body temperature		Oral ulcers ^s		Rash in extremities ^s		Rash characteristics	
	38.5°C (n=91)	37–38.4° C (n=52)	Painful (n=111)	Painless/less-painful (n=32)	Painful (n=116)	Painless/less painful (n=27)	Chicken pox like (n=75)	Papulo-vesicular (n=68)
Seasons								
September-mid-October (n=42)	34	8	33	9	36	6	16	26
Mid-October-mid-November (n=101)	57	44	78	23	80	21	59	42
Fisher's exact test	P<0.01 (2-sided) & <0.01 (1-sided)		p>1.0 (2-sided) & 0.53 (1-sided)		p>0.48 (2-sided) & 0.26 (1-sided)		p>0.03 (2-sided) & 0<0.02 (1-side)	
Spearman's correlation test	p< 0.01		p>0.86		p>0.37		p<0.03	
Average rainfall on admittance								
0.0 mm (n= 107)	67	40	85	22	86	21	56	51
01.7 mm (n= 22)	15	7	17	5	19	3	9	13
>20.1 mm (n= 14)	9	5	9	5	11	3	10	4
χ ² -Chi-square test	p =0.88		p>0.44		p <0.78		p <0.20	
Spearman's correlation test	p >0.70		p =0.32		p <0.76		p <0.77	
Ambient temperature on admittance								
24.4–29.9°C (n= 22) ^a	11	11	20	2	16	6	14	8
≥30°C (n=121) ^b	80	41	91	30	100	21	61	60
Fisher's exact test	p>0.16 (2-sided) and 0.12 (1-sided)		p>0.16 (2-sided) & >0.08 (1-sided)		p>0.37 (2-sided) & 0.21(1-sided)		p>0.35 (2-sided) & 0.18 (1-sided)	
Spearman's correlation test	p< 0.15		p>0.11		p>0.28		p>0.26	

^a Comparatively lower temperature: Arbitrarily set cut-off values of lower temperature (on average). ^b Comparatively higher temperature: Arbitrarily set cut-off values of higher temperature (on average)

temperature was recorded at ≥30°C (up to a maximum of 36.2°C), with no significant difference among three major sign/symptoms (Table 3).

Findings of post-treatment clinical outcome was associated with age. More younger children (<5 years) recovered in <5 days (63/74, 85%) than older peers (≥5 years) (47/69, 69%) who were more likely to recover in >5 days) (P<0.05). However, clinical disease/outcome was not associated with children's sex, although boys were more likely to suffer with the illness for 6–7 days, whereas girls tended to recover within 5 days. However, this was only marginally significant (P<0.05; Table 4).

Dataset 1. Complete raw data from each child assessed as part of this study

<http://dx.doi.org/10.5256/f1000research.15170.d211038>³⁴

Discussion

Basis of this rapid appraisal on HFMD outbreak

We conducted an extensive review on HFMD in the latest literature. Clinico-epidemiological insight from these articles

augmented by our careful observations and intensive appraisal on WHO's "Clinical management and public health response for HFMD"¹ enabled us to establish a primary clinical diagnosis of childhood HFMD on an unusual events of febrile-rash cases (M.A.H.K., unpublished observations, June–July 2017). Concurrent agreement from similar reports attested our HFMD diagnosis among those febrile illness and rash syndrome cases in children as correct^{1–3}. Gauging the potential of a sudden upsurge in childhood HFMD cases (during July 2017) attending PMC-GH from its catchment area made us aware that we faced an upcoming localized outbreak. A strategic plan was thus urgently adopted to conduct this rapid appraisal (short-term standardized surveillance)¹ on childhood HFMD utilizing a pre-set case-definition/syndromic approach based on the WHO's HFMD guidelines¹. This study is comparable with a study conducted in Thailand²⁹.

The main objective of this descriptive study (rapid appraisal) was to create awareness on childhood HFMD as a newly emerged disease in Bangladesh and tended to stir-up country's public health emergency squad in getting alert to combat similar upcoming-HFMD outbreaks. In conducting this study,

Table 4. Composite table showing association of HFMD clinical features with season/local climate.

Variables	Post-treatment clinical outcome of childhood HFMD like-disease	
	Cured in >5 days (n=69)	Cured in <5 days (n=74)
Age of children (Mean= 2.9 ± 2.3 years)		
<1–3 years (n=78)	32	46
3.1–5 years (n=32)	15	17
5.1–10 years (n=33)	22	11
Chi-square (χ^2) test:	p < .04	
Correlations	p < .02	
Sex		
Male (n= 80)	44	36
Female (n=63)	25	38
Fisher's exact test	p <0.09 (2-sided), p<0.05 (1-sided)	
Pearson's correlation	p < .07	

we were also able to assess the clinical skill, diagnostic potential and epidemiological insight of PMC-GH team along with instant local support, which will also prove helpful. The findings of our study will help to show how skillfully the clinicians at the mid-level secondary-care hospitals remain capable in combating localized HFMD outbreaks quite confidently. They accomplished it utilizing own resources and work force, without seeking additional assistance. Credit goes to concerned physicians (dermatologist and/or pediatricians) in establishing correct diagnosis of childhood-HFMD based on strong yet rational suspicions, as reported by others^{12,13,23} along with institution of supportive therapy. Every issue was addressed and resolved successfully despite huge constraints in manpower, funding and gross lack in diagnostic facilities, though laboratory-test is reportedly not essential, often^{14,19,25}.

Potentials and dynamics of HFMD outbreaks

HFMD has emerged as a major public health problem in recent years^{2,10}. HFMD was first recognized in the Western world^{1,2} during the mid-1970s². It was then spread out in the Asia-Pacific region since the mid-1990s^{3,6,9}, mostly in four countries (Malaysia, Taiwan, China and Singapore)^{3,6,9,11}. HFMD outbreaks were also reported in the Indian districts of Orissa¹² and Calcutta¹³, bordering with Bangladesh. It is therefore strange that no data or published reports exist in Bangladesh yet then, as Prabir *et al.* commented rightly and in-time²³. Despite epidemiological forecasts that HFMD outbreaks occur in a 2–3-year cyclical pattern¹¹, two large epidemics broke out in 2 consecutively years: one in Malaysia during 1997 and the other in Taiwan, the following year⁹.

All these facts and figures, including epidemiological hunches and variabilities support our strong speculation of this localized outbreak of HFMD in Pabna that we could combat boldly. Based on such experience, we do suspect that HFMD might

have emerged in Bangladesh earlier, but, swept on unnoticed. HFMD often remains ‘underestimated’ due to its benign nature and self-limiting clinical features^{6,8}. These facts led us to suspect that latent HFMD cases or small localized outbreaks might remained under-reported or un-reported (Kazi Selim Anwar and Md. Abid Hossain Mollah, personal observation, June 2017).

Clinico-epidemiological perspectives

Using observations of clinical course, disease progression, short-term suffering and disease outcome confirms that childhood-HFMD remains a benign and self-limiting disease, observations that are consistent with several other studies^{6–8}. We attest that HFMD can be diagnosed accurately once there is a strong suspicion^{13,14}. The presenting signs and symptoms can be the sole diagnostic modality, too¹². We diagnosed these HFMD cases based on a patient's history, onset and the presented clinical features^{6,19}. In addition, we considered the patient's socio-demographic characteristics^{12,14}, and a positive history of similar sign/symptoms in child's family, nursery and/or in schools^{12,14}. However, our data does not agree to such higher incidences of severe disease (8.5%) that was reported from Vietnam⁸, rather it goes in favor of ‘no’ or ‘rare fatalities’ contrarily^{5,6}.

Our data yielded a significant association between age groups and three major clinical signs/symptoms. Moderate-to-high fever, painful oral ulcers and itchy-painful rashes were directly proportional to younger children which was consistent with several other findings^{4–6,8,9}. Moderate-to-high fever remains an important, but not mandatory or principal sign of HFMD, as the WHO's guidelines for clinical and public health response indicate¹, in agreement with our findings. Oral and/or axillary temperature in 64% of cases revealed a moderate fever (38.5°C), ranging mostly between 37.5°C and 38.2°C; the rest (36%) had no or a low-grade fever (ranging between 37.0 to 38.4°C).

This variation in body temperature led us to postulate that fever itself can never be considered as the sole symptom in confirming HFMD diagnosis. Our observation on ‘fever’ though remain consistent with several authors, such as Van Pham *et al.*⁸, and other studies reported high patient body temperatures in HFMD-cases^{5,9}.

The most important characteristic symptoms for HFMD remains papulo-vesicular rash, often manifesting as painful chicken-pox-like rashes. We observed that this papulo-vesicular rash (Figure 3) was painful in 60% of cases and was less painful/painless in 40% of cases. Since pain remains subjective in younger children in expressing pain intensity, we categorized HFMD based on no recent history of pain status, facial expression of child having body rash/oral ulcer on touch/other sensitizations and impression of child’s mother and the clinician’s rational judgements. Our findings on rashes and its types in patients with childhood HFMD remain consistent with other reports^{1,4}, particularly its distributions in knees or buttocks^{1,2,7,13,14,17}. We observed itchy rashes in child’s extremities, forming small pustules that were filled with turbid fluid (Figure 1) and in some cases it consequently crusted off⁵ after 3–4 days. These rash symptoms remain consistent with several prior reports^{1,4,13,14}.

Figure 1. Multiple vesicular lesions containing turbid fluid seen in right knee of 4-year old girl.

Most of the children under 5 years (78%) suffering from HFMD had characteristic oral ulcers and/or painful blisters in tongue/mouth (Figure 2), symptoms cited in several reports^{1,4,7,14,16,17}. However, we found less painful/painless oral ulcers/blisters in 22% HFMD cases. Although the exact reason for these less pain/painless oral ulcers remain unclear, we postulate that it could be due to a varied perception and/or different tolerability level by those children. Of course, being unwilling to mention or disclose about their tolerable/bearable little pain feeling shy or even being scared of cannot be ruled-out, either. Some of these children may have taken analgesics at home before coming to hospital, which they did not disclose despite repeated questioning. Notably, we did not find any sign/symptom that significantly differed with sex of children except oral ulcers. More boys had less painful ulcers than girls ($P < 0.04$). Our findings that revealed a sex differences for some specific clinical sign/symptom remain unique, though findings from a study in India reported an overall male-female ratio of 21:17¹³.

Differential Diagnosis of HFMD

We performed a thorough DD to make the clinical diagnosis of HFMD as perfect as practicable. We performed the DD to differentiate HFMD from closely similar diseases, like

Figure 2. An oral ulcer on tongue with surrounding erythema of a 5-year old boy.

Figure 3. Papulo-vesicular lesions surrounded by erythematous zones on the left palm of a 1.5-year-old boy.

varicella/chicken-pox, scabies, measles, erythema multiforme, herpangina, herpetic gingivitis, drug eruptions, as several reports have mentioned^{1,6-8,22}. Mosquito bite was also included in the DD as it was reported in a recent study in India, underlining this simple yet valuable DD-point¹³. Particular attention in the DD was paid to the characteristics of skin lesions where macules and papules quickly evolve into vesicles. Characteristically, the lesions in these children occurred on their palms, soles, and buttocks²². We observed vesicles in majority of these children that ruptured with the formation of erosions and crusts. However, Sharma *et al.* observed in Indian patients that it starts with small (1–5 mm) erythematous maculopapular lesions that rapidly enlarged to 3–15 mm lesions, progressing to vesicular eruption with prominent erythematous halo^{13,14}. We observed this common dermatological phenomenon in some of our studied children with HFMD. Nonetheless, our observation remains similar to that of Bhumes *et al.* from India that oral lesions begins as erythematous macules and then evolved into vesicles (measuring 2–3 mm) on an erythematous base²¹.

Laboratory diagnosis for HFMD

Laboratory diagnosis is usually not essential^{12,23} to confirm a readily diagnosed HFMD case based on rational judgement of existing clinical features. Even, lab diagnosis often remains unnecessary¹⁹. Laboratory tests, such as serotyping, molecular, PCR and genotyping³ and virus culture^{1,13,24}, may not be feasible, available and more importantly not affordable in resource-constrained countries^{12,13} like Bangladesh, particularly in hard-to-reach/remote areas. Although few studies report high WBC count or blood glucose, as associated with HFMD severity^{13-19,23,24}, it remains scarcely seen in recent literature.

Adopted from WHO: A guide to Clinical management and public health response for Hand, Foot & Mouth Disease.¹(WHO, 2011)

Figure 4. Decision tree for the clinical diagnosis and management of hand, foot and mouth disease.

Furthermore, rise in blood glucose level may be due to other viral diseases rather than HFMD, and may well remain confounded by a wide range of infections and/or inflammatory processes. Moreover, in some pediatric cases, it may not be practically possible to collect intravenous blood from younger children, who possess thin veins, particularly at the primary care health centers in grass-root level. Children often become too agitated when attempts are made to draw blood, as we observed, with their parents distressed, and the children non-compliant and non-cooperative. However, we observed this was more an issue among less-educated and low-income group families.

Latest literature shows that virological diagnosis remains the main diagnostic tool. Of the four species in the family of Picornaviridae (groups EV-A, B, C and D) that cause HFMD in children, chiefly remain EV 71 and coxsackie-virus A-6, A-10 and A16^{3,7,8,10,24}. More crucial is that these viruses are transmitted rapidly^{15,17} through direct contact, respiratory droplets, via feces/blister-fluid and contaminated environment¹⁸.

Specific treatment for HFMD viruses

There is no specific treatment^{22,25} or pharmacological intervention⁴ available for HFMD yet. Since it largely remain supportive^{19,25} we prepared a standardized therapeutic index involving our clinical experts that we followed as therapeutic measure among childhood cases of HFMD in this study. It consisted of: i) antipyretic/analgesics, ii) antihistamines, and iii) anesthetics drugs (oral gel or ointment). Skin lesions in those cases (observed in only two cases) healed within 3–4 days; we did not prescribe any acyclovir due to the highly reported adverse effects (nephropathy and neurotoxicity). Since oral acyclovir is poorly absorbed, we prescribed it as an exception in recommended dosage of oral syrup (20 mg/kg body-weight) for 5 days only in eight severe cases (mean age, 2.4 years). However, children with profuse skin-lesions with severe pain responded dramatically, with early recoveries. Reasons for this mechanism or the basis of its pathogenicity and the pharmaco-dynamics of acyclovir are not fully understood, which necessitates further investigation.

Vaccination of HFMD

Though no effective vaccine available yet against HFMD-viruses^{1,2,7}. Scientists have been attempting to develop a vaccine against HFMD in Malaysia (since 2010)³³, in China (since 2012)³⁵, and in Taiwan (since 2014)^{36,37}. Cai *et al.* demonstrated how active immunization with an experimental inactivated CA16 vaccine can confer full protection- which provided a solid foundation for developing inactivated whole-virus vaccines against CA16 infection in humans³⁵. Similarly, Chih-Wei Lin *et al.*³⁶ found some 'prospect and challenges' with critical bottlenecks in the development of multivalent HFMD vaccines. They demonstrated how combined vaccine would reduce number of injections simplifying WHO's ongoing child immunization schedule to protect against several viruses, like H5N1, EV71 and JEV at the same time³⁶. Yican Cui *et al.* attempted to develop a combined bivalent-vaccine comprising EV71 and A16 to give balanced protective immunity³⁷. There is also evidence for the further development of multivalent vaccines for broader protection against HFMD³⁷.

Due to a lack of available vaccines against viruses that cause HFMD^{15,17,18}, preventive measures remain the primary way of circumventing HFMD. Prevention methods includes good personal hygiene, proper hand washing²⁶ pollution free environment^{12,18}, sewage²⁷, and germ-free water and food¹⁸. Although avoiding person-to-person contact² through isolation remain justified, it may often not be practical in unprivileged low-income communities and/or resource-constrained healthcare settings like Bangladesh. It is imperative to increase mass awareness among such communities more.

Clinical outcome

In agreement with other studies^{4,6}, our data also revealed that younger children (<5 years old) recovered more quickly (in <5 days) than their elder peers (>5 years old) who recovered in 6–7 days (>5 days) ($P < 0.05$). There was a marginal significant difference in sexes, since boys had seemingly quicker recovery than peer girls did ($P < 0.05$). Nevertheless, according to latest literature, most childhood HFMD-cases resolve themselves within 7–10 days^{5,8,9}. These findings remain consistent with that of other reports from Asia-Pacific countries^{4–8}, including India^{12,13,14,18}.

Complications

Complications of childhood HFMD remain few, although younger children may develop them more often^{7,17,21}. We found three cases (2.09 %) of such complications (mild-to-moderate severity) who we had to pay a special attention to. The first case (a 4-year-old girl) was a case of pneumonia, who we treated with IV antibiotics and discharged following recovery after 2 days. The second one was an admitted case of pyoderma (a 5-year-old boy), who received appropriate antibiotics and was discharged on after 3 days. We diagnosed a third case of a 1.5-year-old girl with a case of post-HFMD Onychomadesis³⁸, who had clinically diagnosed HFMD 25 days before, who had shedding of skin on her right little finger since last few days. On repeated observations (weekly) her nail resumed in original position after 3 weeks of her development of a nail problem without any medication. This scenario remains comparative to a report from South Korea³⁸. However, the mechanisms of Onychomadesis and its association with HFMD is not yet fully understood as literature shows³⁸ and that, some viruses are responsible for onychomadesis as a temporal variation.

Although CA16 and EV71² are mostly associated with neuro-respiratory syndromes^{1,4}, we did not observe serious complications, nor encountered any death in the children with HFMD, a finding that remain consistent with several reports^{5,6,9,15}.

HFMD cases and local weather/climate

Several studies carried out in the Asia-Pacific region reported an association of HFMD cases with a wide range of meteorological findings (weather, climate, ambient temperature, humidity, rain, etc.)^{5–10,15,17,18}. Meteorological factors reportedly remain associated with HFMD outbreaks in Asia-Pacific regions^{5,17}, like Singapore^{9,15}, China¹⁰ and Hong Kong²⁰. The rainy season⁸ and short-term variations in temperature^{20,28} had an impact on HFMD occurrence⁵ in this region. This includes atmospheric

pressure, relative humidity and rain precipitation⁹ as well which peaks in summer and early autumn¹⁸. We conducted this study during autumn, that runs in Bangladesh from early September through November in two phases: early autumn from September to mid-October, while its next phase (late autumn/fall) from mid-October to November.

One limitation is that we could not conduct a proper meteorological study as reported from some Asian countries^{9,10,15,20}. As a small part of our study, we only tried to find out briefly if local weather has any impact on HFMD just to acquire a preliminary idea in this aspect. However, the literature did not reveal any such study/report detailing the symptom-specific association of HFMD with seasons, as we have tried to. Some of our overall findings remain comparable with that of others^{5,6,9,10}. Our data from the rapid appraisal of short-term surveillance demonstrated certain seasonal characteristics of local weather were associated with HFMD, like fever and rash characteristics. Moderate-to high fever (63%) was observed more often in fall/late-autumn (mid-October to November) than in early autumn (September to mid-October), yielding 37% cases ($P < 0.01$). A similar result was obtained for papulo-vascular rashes, which predominantly occurred in fall (62%) rather than in early autumn (38%), ($P < 0.03$).

However, our data did not support an impact of rainfall/precipitation or ambient temperature on any of the three major signs/symptoms we have evaluated. We observed that childhood HFMD cases occurred mostly in dry weather with no rainfall (0.0 mm). Similarly, the three major symptoms of HFMD were more likely to be observed during hot/humid days, with no difference in disease severity. These findings on climatic factors or locally prevailed weather did not corroborate with the findings of others^{5,9,10}.

Socio-demographic characteristics and Household economy of victim's families

One of the other unique strength of our study was to dig out an association of socio-demographic and/or HH economy of children's families with that of childhood HFMD. The age group of victimized children (mean $\pm$ SD, 2.9 ± 2.3 years) remained similar to several reports^{1,2,7,8,14–21}. However; the age of children did not differ significantly with sex. The HH structure revealed an average size of children's family containing 5.5 ± 0.7 persons/HH, 62% of who were the first child and 38% were the second children. The HH income scale/grades, following the World Bank standard family/HH income-groups³¹, highlighted that the majority of families (85%) belonged to middle-income HHs living on a modest budget. While 34.3% had upper-mid incomes, 51% had lower-mid levels of income. However, 14.7% belonged to the low-income group, who were to live on a very tight HH budgets. Notably, but logically (based on ecology, environment, health care facilities, etc.) HFMD infection was observed more among first siblings and from families significantly associated with living on tight/low HH-budget than in second sibling ($P < 0.01$). This finding should be noteworthy as one of our unique findings associating among family size, child's-sibs and HH-budget/family-economy. These findings might have several multifaceted reasons, but our postulation go in favor

of gross inadequacy in health care expenditure by individual families, the distance of PMC-GH from respective HHs and of course, total family income as one of the major concerns. Although such socio-economic parameters and public health issues demand to be explored further, some studies highlighted that the occurrence of HFMD is associated with patients' personal hygiene, post-defecation hand-washing, water and sanitation²⁶. Surrounding environment, like food and drinking water¹⁸, including the contaminated sewage water²⁷ also have a particular role in transmitting HFMD viruses amidst surrounding communities.

Insights on principal findings

- Our clinico-epidemiological observation indicates childhood-HFMD has emerged in Bangladesh.
- Some outbreaks in Calcutta indicate that HFMD emerged in Bangladesh earlier.
- The physicians' rationally judged clinical suspicion (signs/symptoms) can establish a correct diagnosis.
- Stringent differential diagnosis remain indispensable to exclude similar fever- or rash-causing illness.
- Laboratory diagnosis seems unessential, particularly during HFMD outbreak situations when proper laboratory-diagnosis (virus culture, serology, molecular analysis) is not readily available.
- We experienced that early forecasting may aid in combating HFMD outbreaks in catchment areas to curb complications more successfully.
- Small-scale/localized outbreaks can be combated utilizing existing health-care/hospital set up/facilities.
- No specific treatment for HFMD exists, although supportive therapy can treat cases of HFMD in a week.
- It is imperative to increase mass awareness to stop transmission of HFMD viruses (air/droplet, environment).
- Personal hygiene, hand washing and a pollution-free environment are mainstays of HFMD prevention

Conclusion

We could diagnose cases of childhood HFMD successfully based on clinical signs/symptoms only and all cases recovered well within a week. Stringent differential diagnosis on similar rash and/or fever diseases/syndromes were deemed indispensable. The local climate may influence HFMD. Time consuming and costly laboratory diagnosis (virological/molecular) is not essential in resource-constrained settings, particularly during outbreak situations. No specific treatments or effective vaccinations exist for this often-underestimated disease yet. Supportive therapy and strict preventive measures is able to circumvent/destroy EV or CA viruses to combat ongoing HFMD-outbreaks/threats.

Recommendations

Development of a globally representative multivalent HFMD vaccine remains necessary, particularly in countries where HFMD widespread, before it becomes pandemic. Both the

government health services and meteorology departments should work together since climate is shown to be an early indicator of potential HFMD outbreaks. Our findings warrant that the countrywide public health emergency operations teams be more alert towards the effective prevention and control of HFMD in resource-constrained countries like Bangladesh. The governments of such countries should come up with a well-designed, sustainable strategic plan to combat upcoming HFMD outbreaks, in close-cooperation with national and global NGOs and UN organs to prevent its pandemic threat in the near future.

Data availability

Dataset 1. Complete raw data from each child assessed as part of this study. DOI: [10.5256/f1000research.15170.d211038](https://doi.org/10.5256/f1000research.15170.d211038)³⁴.

Consent

Written informed consent was obtained from the parents/guardians of each child for the publication of this report and the images contained within it.

Author information

Md. Azraf Hossain Khan is currently at Department of Dermatology and Venereology, Rajshahi Medical College Hospital,

Bangladesh. Kazi Selim Anwar is currently at Faculty, Department of Infectious Diseases, School of Medicine, International University of Health & Welfare (IUHW), Japan.

Competing interests

No competing interests were disclosed.

Grant information

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H Rogier van Doorn

¹ Oxford University Clinical Research Unit, Hanoi, Vietnam

² Centre for Tropical Medicine and Global Health, Nuffield Department of Clinical Medicine, University of Oxford, Oxford, UK

The authors describe the results from a prospective observational study of children attending a single hospital in Bangladesh using WHO diagnostic criteria. If this is the first time HFMD has been described from Bangladesh, this is of major relevance locally and regionally.

I recommend the authors to use the STROBE guidelines/checkbox to verify whether all required data are included.

The main findings are that a number of cases of HFMD among young children was described from one hospital in Bangladesh, the symptom and age distribution are relatively similar to what is known from the region. Healthcare workers should be aware of this illness, its prevention and treatment and warning signs of severe illness.

I have made some comments and suggestions below, the most important being to shorten and bring more focus on the current data in the discussion.

Specific comments:

- Add this sentence on the aetiology, to replace the sentence in the second paragraph of the introduction: "HFMD is caused by several serotypes of Enterovirus A, the most common being Enterovirus A71 (EV-A71) and Coxsackievirus A16 (CV-A16) and more recently also CV-A6 and CV-A10. EV-A71 is associated with a higher proportion of severe illness."
- Please add the exact case definition that was used to enrol children.
- 143 children were included, how many children were eligible during the period of enrolment? How many were not enrolled because of exclusion criteria or otherwise, how many didn't consent?
- Can an epidemiological curve be added?
- Any further information on cases in the region, nearby hospitals?
- Were any warning signs detected during the study?
- Because of the epidemiology of HFMD, the preferred age stratification would be 0-6, 6-12,

- 12-24, 24-60 and >60 months or similar (e.g. Xing et al¹)
- It is common to study the effects of precipitation allowing for a lag period of few days (incubation period)
 - Reviews on the epidemiology, mortality and long-term outcome of HFMD have been published recently. These can be referenced in the discussion for clarity.
 - The discussion deals with a broad spectrum of general topics. This is appropriate for a report to be circulated among local healthcare workers, but not for the current scientific publication. I would suggest to focus on the data from the current study for the discussion here, to broadly describe the findings and if there were any striking differences with what has been described from the region. The authors should not overinterpret the data from this relatively small sample size to look for potential associations.
 - In the third paragraph of the discussion the authors state that outbreaks occurred in 1997 and 1998, despite forecasts. The referenced forecasts were derived from timeseries from Malaysia from 1998-2006 and could not have predicted the 1997-8 outbreaks. There are syndromic and serotype specific timeseries from Japan dating back to the 1980s that may have forecasted these, but to my knowledge no major HFMD outbreaks had occurred in Malaysia and Taiwan prior to these.
 - In the laboratory diagnosis section, it is important to realise that diagnosis of EV-A71 as the main pathogen is important as it is associated with a higher proportion of severe illness.

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Is the work clearly and accurately presented and does it cite the current literature?

Partly

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

I cannot comment. A qualified statistician is required.

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Clinical Microbiology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 19 Oct 2018

Kazi Selim Anwar, Institute of Epidemiology, Disease Control and Research, Dhaka, Bangladesh

Comment specific response from the authors:

The authors thankfully appreciate the reviewer-1 for **approving** the paper with reservations and thank for the kind review and comments.

The followings remains the comment specific response from the authors:

Comment-1: The authors describe results from a prospective observational study of children attending a single hospital in Bangladesh using WHO diagnostic criteria. If this is the first time HFMD has been described from Bangladesh, this is of major relevance locally and regionally.

Reply-1: Yes, this observational study in our hospital remains the first report on HFMD from Bangladesh. We, therefore, thank you sincerely, for such an important comment.... "it remains of major relevance locally and regionally".

Comment-2: I recommend the authors to use STROBE guideline/checkbox to verify if all required data included

Reply-2: Yes, agreed. We have uploaded **STROBE** guideline to verify our data in revised version.

Comment-3: The main findings that a number of cases of HFMD in young children was described from one hospital in Bangladesh, symptom & age distribution are relatively similar to what is known from the region.

Reply-3: Yes, we are glad to see your valuable comment that HFMD symptoms in younger children remain relatively similar with that of other reports from South/SE- Asian region.

Comment-4: Healthcare workers should be aware of this illness, its prevention and treatment and warning signs of severe illness

Reply-4: Yes, we appreciate your comment that healthcare workers must be aware of HFMD its prevention & treatment, particularly on warning signs of severe illness. Mentioned in 8th bullet point of "Insights on principal findings".

Comment-5: I have made some comments and suggestions below, the most important being to shorten and bring more focus on the current data in the discussion.

Reply-5: Yes, agreeing to your most suggestion, shortened the discussion part focusing on current data-that really makes sense. Shortened discussion part as suggested

Comment-6: Add this sentence on the aetiology, to replace the sentence in 2nd para-graph of introduction"HFMD is caused by several serotypes.... with a higher proportion of

severe illness."

Reply-6: We thankfully agreed to replace it in the 2nd paragraph of introduction.. HFMD is caused by several serotypes of enterovirus A, the most common being enterovirus A71 (EV A71) and coxsackievirus A16 (CV-A16) and more recently, also (CV A-6, and CV A-10). EV-A71 is associated with a higher proportion of severe illnesses "

Comment-7: Please add the exact case definition that was used to enroll children

Reply-7: Though it is mentioned in Fig.4, we have reemphasized the WHO recommended exact case definition of HFMD: having i) fever or history of fever, ii) papulovesicular rash on hand & foot iii) with or without oral ulcers.

Added this case definition in 2nd line of method and in clinical diagnostic tool, as well.

Comment 8: 143 children were included how many were eligible during enrolment period? How many were not enrolled because of exclusion criteria or otherwise, how many didn't consent?

Reply-8: Since it was an outbreak situation, we had to enroll all 143 children attending our hospital from Sept. to Nov., 2017 with suspected HFMD cases (who met WHO criteria). Guardians of all children provided written consent to enroll.

Comment 9: Can an epidemiological curve be added?

Reply-9: Well yes, but we have described almost all epidemiological features in tables.

Comment 10: Any further information on cases in the region, nearby hospitals?

Reply-10: No. We explored to determine that among surrounding families, nurseries or kindergarten/primary schools, but none revealed any positive information.

Comment 11: Were any warning signs detected during the study

Reply 11: No, not as such. Of the 3 complications that we observed, only girl had onychomadesis, 1 child had pneumonia and the other had pyoderma. These may well be regarded as 'cautionary', if not 'warning' signs.

Comment 12: Because of the epidemiology of HFMD, the preferred age stratification would be 0-6, 6-12, 12-24, 24-60 and >60 months or similar (Xing et al¹)

Reply 12: Yes. But during that pocket outbreak our hospital team categorized the HFMD victimized children into two groups of <5 and >5 years only. Since 77% of them fell under <5 years it was further categorized into <3 years & 3.1 to <5 years. This age-stratification was done to fit aged-matched cases facilitating analysis.

Reply 13: It is common to study the effects of precipitation allowing for a lag period of few days (incubation period)

Reply 13: Yes. But we could not do that due to paying more attention in tackling/combating the on-going emergency of that pocket outbreak.

Comment 14: Reviews on the epidemiology, mortality and long-term outcome of HFMD have been published recently. These can be referenced in the discussion for clarity.

Reply 14: Well, yes. But we have described some of those in our discussion already.

Comment 15: The discussion deals with a broad spectrum of general topics. This is appropriate for a report to be circulated among local healthcare workers, but not for the current scientific publication.

I would suggest to focus on the data from the current study for the discussion here, to broadly describe the findings and if there were any striking differences with what has been described from the region. The authors should not overinterpret the data from this relatively small sample size to look for potential associations.

Reply 15: Thanks for the good suggestions. We have shortened the discussion part, focused on our data from our current study and tried to describe the striking findings only that yielded some regional differences. And we also tried to avoid over-interpreting our data (relatively small sample size).

Comment 16: In the third paragraph of the discussion the authors state that outbreaks occurred in 1997 and 1998, despite forecasts. The referenced forecasts were derived from time series from Malaysia from 1998-2006 and could not have predicted the 1997-8 outbreaks. There are syndromic and serotype specific time series from Japan dating back to the 1980s that may have forecasted these, but to my knowledge no major HFMD outbreaks had occurred in Malaysia & Taiwan prior to these.

Reply 16: Thanks for pointing it out rightly. After cross checking on the contents of this sentence we have removed the following sentences 'Despite epidemiological forecasts that HFMD outbreaks occur in a 2-3-year cyclical pattern two large epidemics broke out in 2 consecutively years: one in Malaysia during 1997 and the other in Taiwan, the following year.' Corrected this part as edited in the 2nd paragraph of 'Potentials & dynamics of HFMD outbreak'.

Comment 17: In the laboratory diagnosis section, it is important to realise that diagnosis of EV-A71 as the main pathogen is important as it is associated with a higher proportion of severe illness.

Reply 17: Yes. Good point. We have added this point in lab diagnosis sect giving importance to diagnose EV-A71 as the main pathogen causing proportionately more severe cases of HFMD. It was reflected in 3rd paragraph of laboratory diagnosis, properly.

Finally the authors thank the reviewer-1 for his kind comments and suggestions once again.

Competing Interests: No competing interests were disclosed.

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