



RESEARCH ARTICLE

**REVISED** Emerging Hand Foot Mouth Disease in Bangladeshi Children- First Report of Rapid Appraisal on Pocket Outbreak: Clinico-epidemiological Perspective Implicating Public Health Emergency [version 3; peer review: 2 approved]

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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 lack in laboratory-diagnostic facilities.

**Methods:** Following the World Health Organization's case-definition, we conducted a rapid-appraisal of HFMD among all of the 143 children attending Pabna Medical College and General Hospital with fever, mouth ulcers and extremity 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. There was a significant difference among the age and sex of children (P=0.98), first sibling being more belonging to middle-income families (62%). Younger children (<5 years) were more 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

**Open Peer Review**

**Reviewer Status**

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

### Keywords

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

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

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**REVISED Amendments from Version 2**

To comply with both reviewer's suggestion a reference was added (Xing *et al.*, 2014) and, some information/data was included to discuss this.

The following minor errors were corrected in abstract, including a few in introduction but mostly in results section:

- The word 'gross' was removed from the 1<sup>st</sup> paragraph in abstract
- The last sentence in the 'Demographic information' section (Notably, HFMD cases.... first siblings (p <0.001)) was amended.
- The word 'papulo-vascular' is replaced with 'papulovesicular'.
- Rephrased the 1<sup>st</sup> sentence of 2<sup>nd</sup> paragraph in the 'Assessment of symptoms' section (The three major sign... recorded at 0.0 mm).
- A sentence "Time to recover from HFMD varies with age of patient" was added to the last paragraph in the 'Assessment of symptoms' section.
- The sentence "However, we neither observed such high incidences of sever disease alike from Vietnam (8.5%) 8 nor recorded any fatal case in like others reporting as 'none' or 'rare'" was removed.
- Removed the phrase "This observation led us to postulate...." from the 'Clinico-epidemiological perspectives' section, with a little modification.
- Complying with reviewer's comment, we cited 4 references in 2<sup>nd</sup> sentence of 2<sup>nd</sup> paragraph of the 'Clinico-epidemiological perspectives' section.
- We removed the 2<sup>nd</sup> sentence "Since pain remains...." from the 4<sup>th</sup> paragraph of the 'Clinico-epidemiological perspectives' section.
- The sentence "However, the exact reason ..... remain unclear." was altered.
- The 1<sup>st</sup> sentence of 2<sup>nd</sup> para was replaced as suggested in the Discussion: Lab diagnosis section.
- The 2<sup>nd</sup> paragraph of the 'Laboratory diagnosis for HFMD' section was taken out as commented.
- The 'Clinical outcome' section was a bit changed following reviewer's advice.

See referee reports

## Introduction

Of all commonly occurring febrile illness and rash syndromes<sup>1</sup>, hand, foot and mouth disease (HFMD) remains the most among young children<sup>2,3</sup>. Although this viral infection remains largely contagious<sup>4,5</sup>, it is self-limiting and benign. Severe cases reportedly occurs in lower incidences (3.2% to 8.5%) and fatalities are rare<sup>6-8</sup>. Starting in the West during the mid-1970's<sup>1,2</sup> HFMD emerged in the Asia-Pacific region in mid-1990s<sup>9-11</sup> heralding as a major public health hazards<sup>2,10</sup>. Epidemiologically, it follows a 2-3 years cyclical pattern<sup>11</sup> but may break out anytime<sup>9</sup> as has occurred in India (Orissa<sup>12</sup> and Calcutta<sup>13</sup>), bordering with Bangladesh.

With the complaints of mild-to-moderate fever ( $\geq 38.5^{\circ}\text{C}$ <sup>8</sup>;  $101.3^{\circ}\text{F}$ ) childhood HFMD, characteristically manifest with body rashes<sup>1,4</sup>, mostly of the knees and buttocks<sup>4,14</sup>, augmented by painful oral/buccal ulcers and blisters. Papulo-vesicular rash

in the extremities consequently forms pustules<sup>6</sup>. Most children recover/heal within 7-10 days<sup>5,8,9</sup>. Of the few complications, neuro-respiratory syndromes<sup>4</sup> (encephalitis, aseptic meningitis and acute flaccid paralysis)<sup>3,4</sup> occur mainly in younger children; these are rare but seldom fatal<sup>9,15</sup>. HFMD is caused by several serotypes of enterovirus A, the most common being enterovirus A71 (EV A71)<sup>2,16</sup> and coxsackievirus A16 (CV-A16) and more recently, also (CV A-6, and CV A-10)<sup>5,7,10</sup>. EV-A71 is associated with a higher proportion of severe illnesses<sup>2,16</sup>. Reportedly, these viruses are transmitted<sup>15,17</sup> through direct contact/blister-fluid, droplets, oro-fecally<sup>16</sup> and also spread out through contaminated environment, water and food<sup>18</sup>.

Reportedly, clinical diagnosis of HFMD is usually established depending on physicians' suspicions<sup>13,14</sup> as the sole diagnostic modality<sup>12</sup>. The diagnosis is primarily based on history of illness, disease-onset, presenting clinical-features<sup>1,6,19</sup> and, socio-demographic profile<sup>12,14,20</sup>. Small erythematous maculopapular lesion (1-5 mm) enlarge (3-15 mm) and progress to vesicular eruptions with a prominent erythematous halo<sup>13,21</sup>. 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<sup>4,14,17,22</sup>. Laboratory diagnosis is usually not essential<sup>12,19,23</sup>, and has been described by the World Health Organization (WHO) as optional<sup>1</sup>. Conversely, the sophisticated laboratory tests used for definitive diagnosis (virus isolation, molecular analysis, PCR, genotyping)<sup>1,13,24</sup> are not available in most resource-constrained countries<sup>3,12,13</sup> like Bangladesh.

Since there is no specific treatment<sup>4,19,22,25</sup> for HFMD, care largely remains palliative<sup>19</sup> 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 relief pain. Since no effective vaccine against HFMD-viruses is available<sup>1,2,7</sup>, preventive measures remain the primary method of circumventing HFMD transmission to break infection-chains (droplets, oral-fecal route, and direct contact)<sup>2,18</sup>. Effective prevention requires personal hygiene, hand washing<sup>26</sup> and a pollution-free environment<sup>12</sup> including food and water<sup>18,27</sup>. Meteorological variations in precipitation<sup>8,9</sup> and ambient temperature<sup>20,28</sup> often impact on HFMD occurrences<sup>5</sup> in the Asia-Pacific region<sup>5,9,10,15,17</sup>, along with atmospheric pressure and the relatively higher humidity in summer and early autumn<sup>18</sup>.

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-surveillance<sup>1</sup>. Following a pre-set case-definition and syndromic approach (according to the WHO HFMD guidelines<sup>1</sup>), similar to a study conducted in Thailand<sup>29</sup> 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 guidelines<sup>1</sup> this rapid appraisal was conducted among all the 143 children attending Pabna Medical

College and General Hospital (PMC-GH) 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 km<sup>230</sup> 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 guidelines<sup>1</sup>, similar to a prior study conducted in Thailand<sup>29</sup>. Most of the contents of this tool have been shown in Figure 4 (4 A), showing the algorithm of Clinical diagnosis of HFMD<sup>1</sup>.

**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 guidelines<sup>1</sup>, predominantly based on three main signs and/or symptoms: fever, oral ulcers and rash in extremities. Fever was graded into moderate-to high (38.5°C) and none-to-low (37-38.4°C), oral ulcers were grouped into three stages- more painful, less painful & painless; and, rashes in extremities into three types: painful and itchy, painless and itchy; and painful but not itchy.

### Pain assessment/scoring tool

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 similar disease/disorders in near past
- ii. Facial expression of a child with body rash and/or oral ulcer on touch
- iii. Impression and/or opinion of child's parent/guardian in respective cases
- iv. Finally, clinician's judgements based on history and presented signs/symptoms

### Therapeutic management guideline

A therapeutic guideline was prepared to treat childhood HFMD cases following standard therapeutic plan consisting of: antipyretic/analgesics, antihistamines, anesthetic-cream for topical applications.

### Epidemiological tool

This tool consisted of socio-demographic variables and household (HH) income. We categorized the monthly (mon) income (in Bangladeshi taka: BDT) of child's family according to World Bank (WB) Data Help Desk 2016<sup>31</sup> as follows:

- Low-income group: HH income of  $\leq$  6,946/ mon
- Lower-mid income group: HH income: 6,947–27,336/mon

- Upper-mid-income group: HH income:27,337–84,564/mon
- High-income group: HH income of  $\geq$  84,564 BD/ mon

(Calculated using USD rate: 1US \$=84.31 BDT dated 11.06.18)

### Seasonal data collection

Seasonal data on local weather/climate for average temperature and rain precipitation were collected from Pabna Meteorology Department, 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 these tools (developed or followed) were duly pre-tested for this rapid-appraisal (small-scale disease surveillance)<sup>1,2</sup>.

### 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's<sup>1</sup> recommended criteria) were included in this study. Suspected cases having other serious disease/co-morbidities were excluded, although patients were referred to concerned department for proper clinical management.

### Ethical considerations

Following standard procedure of ethical issues<sup>32</sup>, 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 $\pm$ 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 $\pm$ 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) standard<sup>31</sup> family/HH income-group evidenced that majority families (85%) belonged to middle-income HH/families (34% belonged to upper-middle

**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		
$\chi^2$		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		
$\chi^2$		p <0.01
Likelihood ratio		p =0.01
Spearman's correlation		p<0.01

\*Following World Bank Data Help Desk, 2016<sup>33</sup>

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, HFMD cases were significantly more common among children from mid-income-HHs and among 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, skin rash in extremities of younger children's were predominantly more like papulo-vesicular (59/68, 87%) than chicken pox-like (43/75, 57%) lesions (p<0.001). 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, papulovesicular rashes were more common in fall (42/68, 62%) than in early autumn (26/68, 38%) (P<0.03) (Table 3).

Findings of post-treatment clinical outcome was associated with age. Time to recover from HFMD varied with child's age. More young children (<5 years) recovered in <5 days (63/74, 85%) than older peers ( $\geq 5$  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>

### Discussion

#### Basis of this rapid appraisal on HFMD outbreak

Clinico-epidemiological insights from an extensive review on latest literature on HFMD augmented by our careful clinical observations on unusual events of febrile-rash (following

**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 <sup>2</sup>	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 <sup>s</sup>		Rash in extremities <sup>s</sup>		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)
<b>Seasons</b>								
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	
<b>Average rainfall on admittance</b>								
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 <sup>2</sup> -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	
<b>Ambient temperature on admittance</b>								
24.4–29.9°C (n= 22) <sup>a</sup>	11	11	20	2	16	6	14	8
≥30°C (n=121) <sup>b</sup>	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	

<sup>a</sup> Comparatively lower temperature: Arbitrarily set cut-off values of lower temperature (on average). <sup>b</sup> Comparatively higher temperature: Arbitrarily set cut-off values of higher temperature (on average). The three major sign/symptoms of HFMD among these children were more prevalent on those days when the rain precipitation was recorded 0.0 mm, in our outbreak areas. 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 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).

**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 ( $\chi^2$ ) 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	

WHO's "Clinical management and public health response for HFMD"<sup>1</sup>) made us enabled to establish the primary clinical diagnosis of childhood HFMD (M Azraf H Khan: Personal Observations, June–July 2017). Further, concurrent agreement from similar reports attested our diagnosis of HFMD in children, as correct<sup>1–3</sup>.

Gauging the potential of a sudden upsurge in HFMD cases in children (during July 2017) attending PMC-GH from its catchment area made us aware on an upcoming localized outbreak. A strategic plan was thus urgently adopted to conduct this rapid appraisal (short-term standardized surveillance)<sup>1</sup> on childhood HFMD utilizing a pre-set case-definition/syndromic approach based on WHO's HFMD guidelines as depicted in [Figure 4](#) (having fever or a history of fever, papulo-vesicular rash in extremities with or without oral ulcers), similar to a study conducted in Thailand<sup>29</sup>.

The principal objective of this study (rapid appraisal) was to combat the impending HFMD outbreak with a secondary aim of disseminating the existence of newly emerged disease, thus to create a mass awareness. We also aimed to stir-up the local public health emergency squad to cumulate further strength towards combating such upcoming outbreaks in future. Finally, we desired to gauge strength of administrative drive, technical knowhow and clinical skill of PMC-GH team in combating that HFMD cases based on strong yet rational suspicions, as reported by others<sup>12,13,23</sup>.

Keys to success of combatting that on-going pocket outbreak, were: **i)** Sincerity and devotion of PMC-GH team despite huge limitation in manpower and resources, **ii)** strong clinical eye suspecting HFMD as appropriate diagnosis<sup>12,13,23</sup> **iii)** instituting supportive therapy instantly, and **iv)** diagnosing HFMD despite gross lack in diagnostic facilities, though it often remains not essential in such emergencies<sup>14,19,25</sup>.

### Potentials and dynamics of HFMD outbreaks

HFMD, emerged as a major public health problem in recent years<sup>2,10</sup> was first recognized in the Western world<sup>1,2</sup> during mid-1970s<sup>2</sup>. It was then, spread out in Asia-Pacific region since mid-1990s<sup>3,6,9</sup>, mostly in Malaysia, Taiwan, China and Singapore<sup>3,6,9,11</sup>. Though a longer time series is required to ascertain EV71 outbreaks of HFMD, it generally occurs in 2-to 3-year cyclical pattern in West Pacific Region (WHO/WPRO, 2010<sup>9</sup>) as reported from Singapore, UK, Malaysia and Japan<sup>9</sup>. However, HFMD CA16 outbreak in Singapore also occurred periodically: in 2002, 2005 and 2007 but in 2006 but it was caused by EV71<sup>11</sup>. HFMD outbreaks were also reported from Orissa<sup>12</sup> and Calcutta<sup>13</sup> in India that borders with Bangladesh but strange is no published data or report exist in Bangladesh, yet (until June 2018)<sup>23</sup>. In China, incidence and mortality were reported to be the highest among 12–23 months-old children<sup>34</sup>.

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 successfully. We also postulate that HFMD might have emerged in Bangladesh earlier, but, swept on unnoticed being 'underestimated' due to its benign nature and self-limiting features<sup>6,8</sup>, or such 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). Our postulations partly remain similar to that of Xing *et al.* from China<sup>34</sup>.

### Clinico-epidemiological perspectives

Using observation (clinical course, disease progression and outcome) re-confirms other reports that childhood-HFMD remains a benign and self-limiting disease<sup>6–8</sup>. We also attest that HFMD can be diagnosed accurately on physician's strong rational suspicion<sup>13,14</sup> and presenting signs/symptoms that can aid as sole diagnostic modality<sup>12</sup>.

In addition to history, onset and presenting clinical features<sup>6,19</sup> we considered child's socio-demographic characteristics<sup>12,14</sup>, and a positive history of similar sign/symptoms in child's family, nursery/schools.

Our data yielded a significant association between age groups and three major clinical signs/symptoms. Moderate-to-high fever, painful oral ulcer and itchy-painful rash were more common in younger children- which remain consistent with other findings<sup>4-6,8,9</sup>. 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 indicate<sup>1</sup>, 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). These observations resembles with Van Pham *et al.*<sup>8</sup> though others reported high fever in HFMD-cases<sup>5,9</sup>.

Literature reveals papulo-vesicular rash as the most important characteristic symptoms for HFMD<sup>1,4,6,14</sup> often manifesting as painful chicken-pox-like rashes in 60% cases (Figure 3) though the rest 40% had it less painful or painless. Our findings on itchy rashes remain consistent with others<sup>1,4</sup>, particularly in its distributions (knees and/or buttock)<sup>1,2,7,13,14,17</sup>. Itchy rashes in child's extremities that formed small pustules were filled with turbid fluid (Figure 1) and in some cases it crusted off consequently<sup>6</sup> after 3–4 days- as other reported<sup>1,4,13,14</sup>, as well

Secondly, most of the children (78%) had characteristic oral ulcers and/or painful blisters in tongue/mouth (Figure 2), that remain similar to several reports<sup>1,4,7,14,16,17</sup>. However, the exact reason of less pain or painless oral ulcers/blisters in 22% cases in our study remain unclear. We guess it could be due to a varied perception and/or different tolerance, unwilling to mention, feeling shy or even being scared. Some of them may have taken analgesics at home prior to attending the hospital which they did not disclose despite repeated probing. Notably, sex of HFMD cases did not significantly differ with any sign/symptom except oral ulcers. More boys had it less painful than girls. Although a study in India reported an overall male-female ratio of 21:17<sup>13</sup>.

### Differential Diagnosis of HFMD

Stringently examined thorough DD was performed to differentiate HFMD from closely similar diseases, like chicken-pox/varicella, scabies, measles, erythema multiforme, herpangina, herpetic gingivitis, drug eruptions, as several reports mentioned<sup>1,6-8,22</sup>. Mosquito bite was also included as report from India, underlined it as a simple yet valuable DD-point<sup>13</sup>. Particular attention in the DD was paid on examining the characteristics of skin lesions (macules and papules quickly evolve into small vesicles manifesting on their palms, soles, and buttocks<sup>22</sup>). We observed small vesicles in majority of these children that ruptured with the formation of erosions and crusts as ascribed by Sharma *et al.* Alike his finding, we also observed those vesicles as 1–5 mm in size as erythematous maculopapular lesions that rapidly enlarged by 3–15 mm progressing to vesicular eruption with prominent erythematous halo<sup>13,14</sup> being comparable to that of a report by Bhumesh *et al.* from India<sup>21</sup>.



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



**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.

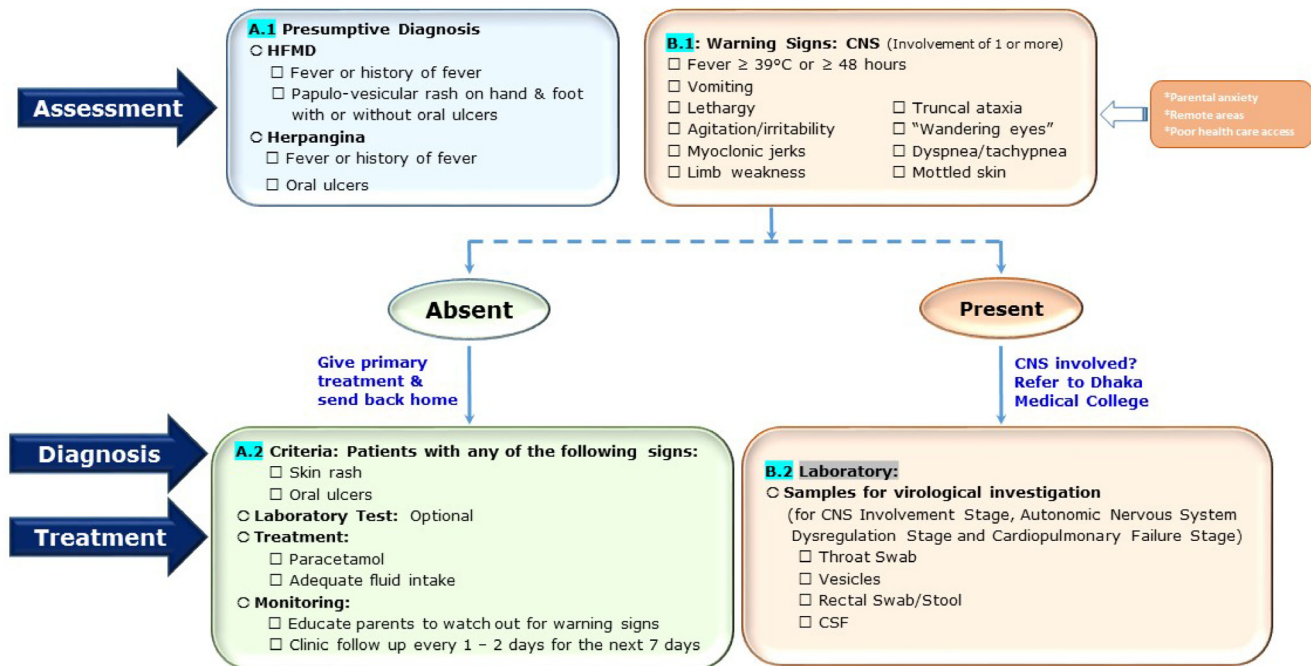
**Laboratory diagnosis for HFMD**

Laboratory diagnosis often remain unnecessary<sup>19</sup> to establish a diagnosis of HFMD. Use of WHO clinical case definition and exclusion of other similar syndromes through a stringent differential diagnosis usually remains adequate in most cases<sup>12,23</sup>. Moreover laboratory tests, such as serotyping, molecular, PCR and genotyping<sup>3</sup> and virus culture<sup>1,13,24</sup>, may not be feasible, available and more importantly not affordable in resource-constrained countries<sup>12,13</sup> like Bangladesh, particularly in hard-to-reach/remote areas. Although few studies report high WBC count or blood glucose, as associated with HFMD severity<sup>13-19,23,24</sup>, it remains scarcely seen in recent literature.

Virological assays 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, EV 71 remain the most, followed by coxsackie-virus A6, A10, A16<sup>3,7,8,10,24</sup>. All these viruses are transmitted rapidly<sup>15,17</sup> through direct contact, respiratory droplets, via feces/blister-fluid and through contaminated environment<sup>18</sup>.

**Specific treatment for HFMD viruses**

There is no specific treatment<sup>22,25</sup> or pharmacological intervention<sup>4</sup> available for HFMD yet. Since it largely remain supportive<sup>19,25</sup> we prepared a standardized therapeutic guide that was followed to take all therapeutic measures against HFMD cases. It consisted



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

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

of: i) antipyretic/analgesics, ii) antihistamines, and iii) anesthetic gel or ointment. Since, skin lesion in these cases usually got healed within 3–4 days; we did not prescribe any acyclovir due to its reported adverse effects (nephropathy & neurotoxicity). Since oral acyclovir is poorly absorbed, we had to prescribe it for 5 days only in 8 severe cases (mean age, 2.4 years), exceptionally, in recommended dosage of oral syrup (20 mg/kg body-weight). But we found them (with profuse skin-lesions with severe pain) to respond to it dramatically, with early recovery. Reasons or basis of pathogenicity or pharmacodynamics is not fully understood demanding further investigations.

### Vaccination of HFMD

Though no effective vaccine available yet against HFMD viruses<sup>1,2,7</sup> scientists have been attempting to develop it in Malaysia (since 2010)<sup>33</sup>, in China (since 2012)<sup>35</sup>, and in Taiwan (since 2014)<sup>36,37</sup>. Cai *et al.* demonstrated how active immunization with an experimental inactivated CA16 vaccine can confer full protection by developing inactivated whole-virus vaccines against CA16 infection in human<sup>35</sup>. Similarly, Chih-Wei Lin *et al.*<sup>36</sup> dissected ‘prospect & challenges’ with critical bottlenecks of developing multivalent HFMD vaccines. They demonstrated that combined vaccine will reduce number of shots that will simplify WHO’s ongoing child immunization schedule, along with protecting kids from several viruses, viz., H5N1, EV71 & JEV at the same time<sup>36</sup>. Yican Cui *et al.* attempted to develop a combined bivalent-vaccine comprising EV71 and A16 for receiving a balanced protective immunity<sup>37</sup> along with other developments in developing multivalent vaccines for broader protection for HFMD<sup>37</sup>.

### Clinical outcome

Our clinico-epidemiological data, in agreement with other reports<sup>4,6</sup> revealed that younger children (<5 years old) recovered quickly (in <5 days) than their elder peers (>5 years old) who recovered in 6–7 days (>5 days). This was similar to a report from China<sup>34</sup>, too. There was a marginal significant difference in sexes: boys had seemingly quicker recovery than girls ( $P < 0.05$ ). However, among Chinese children: boys had HFMD in 1.6 times more than the girls<sup>34</sup>. Nonetheless, latest literature attest most HFMD-cases recover within 7–10 days<sup>5,8,9</sup>. These findings remain consistent with that of others from Asia-pacific countries<sup>4–8</sup>, including India<sup>12–14,18</sup>.

### Complications

Though complications of childhood HFMD remain few, younger children may develop it more often<sup>7,17,21</sup>. In our study, three cases (2.09%) developed complications of mild to moderate severity requiring special care. The first case (a 4-year-old girl) developed pneumonia requiring I/V antibiotics & was 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 after 3 days. The 3<sup>rd</sup> case, a 1.5 year old girl having post-HFMD Onychomadesis<sup>38</sup> who were clinically diagnosed HFMD 25 days before. She had shedding of skin (right little finger) since few days. On repeated observations (weekly) her nail resumed in original position within 3 weeks without any medication. This scenario remains comparative to that of a report from South Korea<sup>38</sup>. However,

mechanisms of Onychomadesis and its association with HFMD is not yet fully understood as literature reveals<sup>38</sup> and that some viruses are responsible for onychomadesis as a temporal variation.

Although CA16 and EV71<sup>2</sup> are mostly associated with neuro-respiratory syndromes<sup>1,4</sup> we did not observe any of such severe diseases or serious complications, alike Vietnam study reporting 8.5% of severe cases<sup>8</sup>, nor we encountered any death in our HFMD cases- a finding that remain consistent with several reports<sup>5,6,9,15</sup>.

### HFMD cases and local weather/climate

Several studies carried out in the Asia-Pacific region reporting an association of HFMD cases with a wide range of meteorological findings (weather, climate, ambient temperature, humidity, rain, etc.)<sup>5–10,15,17,18</sup>. Reports on meteorological factors showing an association with HFMD outbreaks are: Singapore<sup>9,15</sup>, China<sup>10</sup> and Hong Kong<sup>20</sup>. Mostly, rainy season<sup>8</sup> and short-term temperature variations<sup>20,28</sup> had an impact on HFMD occurrence<sup>5</sup> in this region. This includes atmospheric pressure, relative humidity and rain precipitation<sup>9</sup> that peaks in summer and in autumn<sup>18</sup> partly remain similar to that of ours. We observed this pocket outbreak of HFMD among children in early autumn (September to mid-October) and in late autumn/fall (mid-October to November), 2018. Interestingly, while in North China HFMD peaks in June, it is more in May and September-October southern China<sup>28</sup>, which nearly corroborated with our findings<sup>34</sup>.

One limitation is we could not conduct a proper meteorological study as reported from some Asian countries<sup>9,10,15,20</sup>. Contrarily, we only tried to find out briefly if local weather has any impact on HFMD just to acquire a preliminary idea in this aspect. A report from China also remain alike ours that seasonal patterns were weakly associated with climate and demographic factors<sup>34</sup>.

However, the literature did not reveal any such study/report detailing the symptom-specific association of HFMD with seasons that we did, though some of our findings remain comparable with that of others<sup>5,6,9,10</sup>. Thus, data from this rapid appraisal (short-term surveillance) demonstrated certain seasonal characteristics of local weather were associated with fever and rash characteristics. Moderate-to-high fever was observed more often in fall/late-autumn (mid- October to November) than in early autumn (September to mid-October). We found similar result for rashes that predominantly occurred in fall than in early autumn. We did not observe an impact of rainfall/precipitation or ambient temperature on any of the 3 major signs/symptoms that we evaluated. We observed that childhood HFMD cases occurred mostly in dry weather with no rainfall (0.0 mm) almost equally in all three major signs/symptoms of HFMD including disease severity. These findings on local climatic factors did not corroborate with others<sup>5,9,10</sup>.

### Socio-demographic characteristics and household economy of child’s family

Another unique strength of our study was to associate socio-demographic &/or HH-economy with child’s family with HFMD. Child’s age (mean  $\pm$  SD, 2.9 $\pm$  2.3 years) group remained

similar to other reports<sup>1,2,7,8,14–21</sup> Child's age did not differ, significantly with sex. The HH structure revealed an average size of children's family as 5.5±0.7 persons/HH, 62% of who were the first kids and 38% the second ones. Following World Bank categorized family/HH income /grades<sup>31</sup> majority of children's family (85%) belonged to middle-income HHs living on a modest budget: 34.3% being in upper and 51% in lower, mid-income HHs. The rest 14.7% belonging to low-income HH are compelled to live with a very tight HH budget. Notably, a logical but unique finding, based on ecology, environment and health care utilizations, we observed HFMD cases more among first siblings than their siblings and who used to live in tight/low HH-budget. Of multifaceted reasons for this, we postulate that gross limitation in health care expenditure, distance of PMC-GH from HHs and low level of HH-income remains the major reasons. While it demands further explorations, few reports associating HFMD cases with personal hygiene and surrounding environment<sup>18,26,27</sup> remains important to stop transmitting HFMD-virus among adjacent communities.

### Prevention and control measures for HFMD

Due to a lack of available vaccines against HFMD-viruses<sup>15,17,18</sup> preventive measures remain the primary tool to circumvent HFMD-virus. Preventive methods include good personal hygiene, proper hand washing<sup>26</sup> particularly the post-defecation hand wash, pollution free environment<sup>12,18</sup> and hygienic sewage management<sup>27</sup>, ensuring germ-free drinking water and food<sup>18</sup>. Although avoid person-to-person contact<sup>2</sup> through isolation remain justified, it often may not be practical in unprivileged communities of low-income countries having resource-constrained healthcare budget like Bangladesh. But it remains imperative that mass awareness be increased both among the communities and physicians.

### Insights on principal findings

- Our clinico-epidemiological observation indicates that childhood-HFMD has emerged in Bangladesh. Earlier outbreaks in Calcutta, India (bordering with Bangladesh) remains indicative of its introduction in this country since few years but remained unreported and thus, unnoticed.
- The physicians' **strong yet** rationally judged clinical suspicion (based on signs/ symptoms) could establish a correct diagnosis, of HFMD cases.
- 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.
- Healthcare workers must remain aware on the prevention and treatment of HFMD, and, particularly on the warning signs of its severe illness.
- 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)<sup>39</sup>.

### 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.

### Grant information

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## Supplementary material

### Supplementary File 1

STROBE checklist

[Click here to access the data](#)

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## Version 3

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The introduction is currently almost entirely factually correct, but could do with editorial review of the English used. This is beyond the responsibilities of this reviewer.

Specific remaining comments:

Pain assessment: I don't understand the word 'nullifying' in the first bullet

Demographic information: without knowing the distribution of SE groups in the catchment area of the hospital, what does this information on income groups add?

Assessment of symptoms, 2<sup>nd</sup> paragraph: "None of three... except fever and rash" Rephrase this

The first two sections of the discussion can be shortened considerably, and perhaps moved to the introduction?

Laboratory diagnosis of HFMD: Diagnosis remains necessary to assess quickly whether an outbreak is EV-A71 associated, which would warrant stricter prevention and mitigation measures

The paragraphs on treatment and vaccination can be deleted. Not sure why antihistamines would be required.

HFMD cases and local weather/climate: this section is too long and speculative.

**Competing Interests:** No competing interests were disclosed.

**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.**

Reviewer Report 08 July 2019

<https://doi.org/10.5256/f1000research.21485.r50587>

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**Md. Azizul Haque**

Department of Medicine, Rajshahi Medical College (RMC), Rajshahi, Bangladesh

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Infectious disease, toxicology and rheumatology

**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.**

Author Response 11 Jul 2019

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

I, on behalf of all authors cordially thank reviewer-2 for reviewing our on-line published paper so brilliantly.

We do extend all our best wishes for reviewing our paper with so much patience and upmost care with largely valuable comments and section/topic specific valuable suggestions being seriously careful towards adding values to improve the quality of our paper.

We cordially wish that any reviewer should possess such qualities, which we believe most reviewers do have those (except few).

We also recommend that the F1000Research should take up this reviewer (the 2nd one) in their reviewing panel if can not be taken in the editorial board right now.

We wish all the bests for our 2nd reviewer, per se.

**Competing Interests:** No competing interest declared!.

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## Version 2

Reviewer Report 22 May 2019

<https://doi.org/10.5256/f1000research.18298.r48043>

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**Md. Azizul Haque**

Department of Medicine, Rajshahi Medical College (RMC), Rajshahi, Bangladesh

This is the first reported outbreak of HFMD from Bangladesh. This article will add some valuable information about distribution and burden of HFMD. Following observations has been made regarding this manuscript:

1. In abstract (background): "We report a localized outbreak of childhood HFMD for the first time from Bangladesh, diagnosed only based on clinical features due to gross lack in laboratory-diagnostic facilities." The word "gross" should be removed from this sentence.
2. In abstract (results): please clarify and rewrite this sentence "Age did not differ with sex (P=0.98)
3. In Introduction "Severe cases occur red with a low incidence (3.2% to 8.5%) and fatalities are rare", the word "red" should be replaced by "rarely"
4. In results (demographic information), the sentence "Notably, children from mid-income-HHs contracted significantly more HFMD which was more among the first siblings (P<0.01)" should be rewritten as "HFMD cases were significantly more common among children from mid-income households and in the first siblings (p <0.001)
5. In results (assessment of symptoms) in the sentence "Similarly, papulo-vascular rashes weremore common in fall..." papulovascular should be replaced with papulo-vesicular.
6. The sentence should be replaced by "The three major sign/symptoms of HFMD were more prevalent on days where 0.0 mm precipitation was recorded."
7. In the same section "Time to recover from HFMD varies with age of the patient". In the sentence "More young 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).
8. In results (Clinico-epidemiological perspectives) section, the sentence "However, we neither observed such high incidences of sever disease alike from Vietnam (8.5%) nor recorded any fatal case in like others reporting as 'none' or 'rare' looks out of context and should be removed altogether or moved to complications section. If moved to the complications section, this sentence should also be rewritten as

"In our series, we neither observed high incidence of severe disease, nor recorded any fatality." Then comparison with data from other countries may be done.

1. While discussing severe disease and death, citation from Xing et al should be included, as his group published the largest epidemiologic study to date and showed the rate of severe disease and death in patients affected by HFMD (Xing W., Liao Q., Viboud C. Hand, foot, and mouth disease in China, 2008-12: an epidemiological study<sup>1</sup>)
2. In results (Clinico-epidemiological perspectives) section, the sentence "Moderate-to-high fever, painful oral ulcer and itchy-painful rash were directly proportional to younger children which remain consistent with other findings" should be rewritten as "Moderate-to-high fever, painful oral ulcer and itchy, painful rash were more common in younger children; this finding is consistent with other studies".
3. In results (Clinico-epidemiological perspectives) section, the sentence "This observation led us to postulate variation in body temperature led us to postulate that fever itself should not be considered as the sole symptom to confirm HFMD, rather this remain consistent with Van Pham *et al*.<sup>8</sup> though others reported high fever in HFMD-cases<sup>5,9</sup>." is redundant and should be removed altogether. This is unnecessary repetition of a statement made in the same para (Moderate-to-high fever remains an important, but not mandatory or principal sign of HFMD).
4. In results (Clinico-epidemiological perspectives) section, citation is needed for the sentence "Literature reveals papulo-vesicular rash as the most important characteristic symptoms for HFMD often manifesting as painful chicken-pox-like rashes in 60% cases (Figure 3) though the rest 40% had it less painful or painless."
5. In results (Clinico-epidemiological perspectives) section, the sentence "Since pain remains subjective in younger children in expressing pain intensity, we categorized HFMD cases based on



having no history of recent pain issues, facial expression of child on slight touch on rash/oral ulcer including mother's impression plus clinician's rational judgement." is redundant and should be removed altogether. Pain assessment/scoring tool has been described in detail in the Methods section.

6. In results (Clinico-epidemiological perspectives) section, the sentence "However, the exact reason in 22% less pain or painless oral ulcers/blisters remain unclear." should be rewritten as "However, the exact reason of less pain/painless oral ulcers/blisters in 22% cases in our study remain unclear."
7. In Laboratory Diagnosis for HFMD, the sentences "Laboratory diagnosis is usually not essential<sup>12,23</sup> to confirm a readily diagnosed HFMD case based on rational judgement of existing clinical features. Even, lab diagnosis often remains unnecessary<sup>19</sup>" should be rewritten as "Laboratory diagnosis often remain unnecessary to make a diagnosis of HFMD. Use of WHO clinical case definition and exclusion of differential diagnosis is adequate in most cases."
8. Reference number 12 may be omitted as authors of that article used RT PCR for virus isolation in 7 cases.
9. The para "Furthermore, raised blood glucose level may be due to other viral diseases rather than HFMD, and may confound by other infections and/or inflammatory processes. Moreover, drawing intravenous blood from younger children possessing thin veins may be extremely difficult if not possible particularly in primary care health centers in grass-root level. Children often exhibits agitation when attempts are made to draw blood showing grossly non-compliance and non-cooperative" is redundant and should be removed.
10. In complications, the sentence "Our finding yielded three cases (2.09%) complications of mild-to-moderate severity who we had to pay particular attention to" should be rewritten as "In our study, three cases (2.09%) developed complications of mild to moderate severity requiring special care".

## References

1. Xing W, Liao Q, Viboud C, Zhang J, Sun J, Wu J, Chang Z, Liu F, Fang V, Zheng Y, Cowling B, Varma J, Farrar J, Leung G, Yu H: Hand, foot, and mouth disease in China, 2008–12: an epidemiological study. *The Lancet Infectious Diseases*. 2014; **14** (4): 308-318 [Publisher Full Text](#)

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

Yes

**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?**

Yes

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

Yes

**Are the conclusions drawn adequately supported by the results?**

Yes

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Infectious disease, toxicology and rheumatology

**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.**

Author Response 23 May 2019

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

I, on behalf of all authors whole heartedly thank the reviewer for reviewing our online published paper with so much care and attention, yet so productively and meaningfully. We, the authors, remain totally satisfied on the way the reviewer looked into every bits of our paper & in so in-depth, yet so positively.

**Comment:** Yes we agree to all of the the well-chalked & thoughtful queries, along with all his suggested points to bring some minor changes in our paper, soon.

**Final comment for the Reviewer** (*only if the F1000Research allow me to do so, please*): This is one of the best review I have had encountered ever so far (I am engaged in reviewing at least 6 globally reputed Scopus indexed journals having good impact factors).

May I, thus, recommend the F100Research group/authority to take this reviewer as one of its regular reviewers, like me, who would definitely add more significant values of International Board of Reviewers or Editorial Panel of F100Research. It would facilitate more wider scopes towards more standardized publishing, I believe, that the journal has been doing that always, of course!

Dr. Kazi Selim Anwar, in favour of all authors of this online published paper.

**Competing Interests:** No competing interests were disclosed.

Reviewer Report 04 December 2018

<https://doi.org/10.5256/f1000research.18298.r40496>

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**H Rogier van Doorn**

Oxford University Clinical Research Unit, University of Oxford, Oxford, UK

I thank the authors for addressing a number of my comments.

I still think the discussion is too long and deals with a large of number of topics that are irrelevant to the data presented, being a clinically diagnosed first-time outbreak of HFMD in Bangladesh in a single

hospital.

There is already a large body of available literature on HFMD. This manuscript adds the description of an outbreak or upsurge in Bangladesh. That is what needs to be described and interpreted / compared with other outbreaks.

There is no need in this publication for the discussion section to provide a general review on HFMD or to provide extensive general recommendations on HFMD diagnosis, treatment and prevention.

The fourth paragraph of the discussion is an interpretation for which the authors present no data, this shouldn't be in a scientific publication. Sections on laboratory diagnosis, specific treatment and vaccination are not needed in this report. The list of principal findings should also be limited to findings from THIS study.

In the introduction, rephrase the sentence on "pollution free environment". HFMD prevention is through avoiding contact with infected persons and their secretions and excretions through hygiene/hand-washing and distancing (e.g. school closure or sending sick kids home).

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

Yes

**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?**

Yes

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

Yes

**Are the conclusions drawn adequately supported by the results?**

Yes

**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.**

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Version 1

Reviewer Report 02 October 2018

<https://doi.org/10.5256/f1000research.16525.r38927>

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**H Rogier van Doorn**

Oxford University Clinical Research Unit, 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 al<sup>1</sup>)
- 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.

## References

1. Xing W, Liao Q, Viboud C, Zhang J, Sun J, Wu J, Chang Z, Liu F, Fang V, Zheng Y, Cowling B, Varma J, Farrar J, Leung G, Yu H: Hand, foot, and mouth disease in China, 2008–12: an epidemiological study. *The Lancet Infectious Diseases*. 2014; **14** (4): 308-318 [Publisher Full Text](#)

### 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 8<sup>th</sup> 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 2<sup>nd</sup> 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 2<sup>nd</sup> 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 al<sup>1</sup>)

**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 2<sup>nd</sup> 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 3<sup>rd</sup> 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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## Comments on this article

### Version 2

Author Response 05 Jun 2019

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

REVISED Amendments from Version 2/Reviewer 2:

To comply with both reviewer's suggestion a paper was added (**Ref.#39:** Xing W, Liao Q, Viboud C, Zhang J, Sun J, T Wu J, et al. Hand, foot and mouth disease in China, 2008-12: an epidemiological study. *Lancet Infect Dis* 2014; 14:308-18) and, some information/data was included to discuss.

The following minor errors were corrected in abstract, including few in introduction but mostly in results section:

- The word 'gross' was removed from the 1<sup>st</sup> paragraph in abstract, page-4.
- The 1<sup>st</sup> sentence on Page-9 (Notably, HFMD cases.... first siblings (p <0.001) was amended.
- The word 'papulovascular' is replaced with 'papulovesicular' (last sentence of 2<sup>nd</sup> para, page-10).
- Rephrased the 1<sup>st</sup> sentence of 2<sup>nd</sup> para (The three major sign... recorded at 0.0 mm), page-12.
- A sentence 'Time to recover from HFMD varies with age of patient' was added on page-12.
- The last sentence on page-14 ('However, we neither observed... or, rare') was removed.
- To comply with reviewer's opinion changed the 2<sup>nd</sup> sentence of 1<sup>st</sup> paragraph, Page-15).
- Removed the last phrase of 1<sup>st</sup> para on page-5.. "This observation led us to postulate....others. reported high fever..." with a little modification keeping ref. 5, 8-9.
- Complying with reviewer's comment, cited 4 references in 1<sup>st</sup> sentence of 2<sup>nd</sup> para, page-15.
- Removed the 2<sup>nd</sup> sentence of 2<sup>nd</sup> para on page-15 ("Since pain remains.... rational judgement)
- The 2<sup>nd</sup> sentence of 3<sup>rd</sup> par on p15 was altered a bit (However, the exact reason ..... remain unclear).
- The 1<sup>st</sup> sentence of 2<sup>nd</sup> para was replaced as suggested page-16 (discussion: Lab diagnosis).
- The 2<sup>nd</sup> paragraph of the manuscript on page-17 was taken out as commented.



- The 2<sup>nd</sup> sentence of 1<sup>st</sup> paragraph on page-18 was a bit changed following reviewer's advice. REVISED Amendments from Version 2/Reviewer 2: To comply with both reviewer's suggestion a paper was added (**Ref.#39**: Xing W, Liao Q, Viboud C, Zhang J, Sun J, T Wu J, et al. Hand, foot and mouth disease in China, 2008-12: an epidemiological study. Lancet Infect Dis 2014; 14:308-18) and, some information/data was included to discuss. The following minor errors were corrected in abstract, including few in introduction but mostly in results section:
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  - The 1<sup>st</sup> sentence on Page-9 (Notably, HFMD cases.... first siblings (p <0.001) was amended.
  - The word 'papulovascular' is replaced with 'papulovesicular' (last sentence of 2<sup>nd</sup> para, page-10).
  - Rephrased the 1<sup>st</sup> sentence of 2<sup>nd</sup> para (The three major sign... recorded at 0.0 mm), page-12.
  - A sentence 'Time to recover from HFMD varies with age of patient' was added on page-12.
  - The last sentence on page-14 ('However, we neither observed... or, rare') was removed.
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  - Complying with reviewer's comment, cited 4 references in 1<sup>st</sup> sentence of 2<sup>nd</sup> para, page-15.
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  - The 2<sup>nd</sup> sentence of 3<sup>rd</sup> par on p15 was altered a bit (However, the exact reason ..... remain unclear).
  - The 1<sup>st</sup> sentence of 2<sup>nd</sup> para was replaced as suggested page-16 (discussion: Lab diagnosis).
  - The 2<sup>nd</sup> paragraph of the manuscript on page-17 was taken out as commented.
  - The 2<sup>nd</sup> sentence of 1<sup>st</sup> paragraph on page-18 was a bit changed following reviewer's advice.

**Competing Interests:** No competing interests were disclosed.

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