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Clinico-epidemiologic characteristics of the 2019 dengue outbreak in Bangladesh

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Background: Dengue fever shows a broad range of clinical presentations worldwide. Here we report on our clinical findings during the 2019 dengue outbreak in one of the largest tertiary care hospitals in Dhaka, the capital of Bangladesh.

Methods: A total of 747 suspected dengue cases (553 confirmed and 194 probable) were interviewed with a pro forma case record form. Statistical analyses were conducted using SPSS 20.0. Ethical clearance was obtained from the Dhaka Medical College.

Results: The mean age of the dengue cases was 27 y and approximately two-thirds were male. Positive tests for NS1 and anti-dengue immunoglobulin M antibody were present in 91.9% and 59.4% of the cases, respectively. Thrombocytopenia was present in 69% of cases and fever was present in 99.1% of cases. Gastrointestinal (GI) features, including anorexia and/or vomiting (69.4%), abdominal pain (39.8%) and diarrhoea (25.6%), were more prevalent than typical rash and pain symptoms. Hypotension was present in approximately one-quarter of patients (25.4%). Probable and confirmed dengue cases have shown similar clinical characteristics and laboratory findings.

Conclusions: The 2019 outbreak of dengue fever in Bangladesh was characterized by increased presentation with GI features. Recognition of this trend would permit early diagnosis and proper management of patients.

Keywords: Bangladesh, clinical characteristics, dengue fever, epidemiology, outbreak

Introduction

Dengue fever (DF) is an arthropod-borne viral disease transmitted by female *Aedes* mosquitoes, predominantly *Aedes aegypti* and *Aedes albopictus*.[1] Each year >100 million cases are seen worldwide and >2.5 billion individuals are at risk of contracting the disease.[2] Since 1950, dengue has emerged as a severe public health problem in Asia. Indeed, the World Health Organization estimates that 52% of the population who are at risk of dengue worldwide resides in 10 countries of Southeast Asia. Countries that are most adversely affected include Bangladesh, India, Pakistan and Sri Lanka.[3,4] In Bangladesh, the first outbreak of DF occurred in 1964, followed by sporadic outbreaks in 1977–1978 and 1996–1997.[5] In 2000, Bangladesh experienced an epidemic with 5551 cases and 93 deaths, which were well documented.[6] From 2000 to 2017, during dengue outbreaks, 40 476 cases occurred, mostly during the monsoon season (May–August). It was found in all major cities, especially in the Dhaka metropolitan area.[7,8]

The clinical manifestations of dengue infection range from mild febrile illness (i.e. DF) to severe haemorrhagic disease (i.e. dengue haemorrhagic fever) and dengue shock syndrome (DSS).[9] Patients usually present with fever, arthralgias, myalgias, retro-orbital pain, rash, subconjunctival haemorrhages, respiratory symptoms, gastrointestinal (GI) disorders, reduced platelet count and abnormal liver function tests.[10] Bangladesh experienced large epidemics of DF during 2000, 2002, 2010 and 2018. A temporal variation in the frequency of different clinical features was noted over this period. In the 2000[1] and 2002[11] outbreaks, high-grade fever with typical purpuric rash, severe body aches and thrombocytopenia[12] were the most common manifestations. In 2010[13] and 2018,[14] outbreaks with fever, GI symptoms

and bleeding manifestations with normal platelet counts followed by frequent transitions to plasma leakage syndromes leading to respiratory distress and organ dysfunction were more commonly seen and were associated with increased fatalities.[13–16] Moreover, evidence suggests that a shift in the virus serotype has also occurred over the last decade. Before 2002, dengue type 3 (DEN3) was frequently reported, and re-emergence of the same strain was observed in 2017. Subsequently a sharp rise in dengue cases was observed from the beginning of the monsoon in 2018, and with expansion of the outbreak, more dengue cases with deaths were also reported compared with the last 15 y.[17] In 2013–2016, DEN1 and DEN2 were the more predominant strains, while DEN3 and DEN4 have been more common recently.[17,18] Interestingly, co-detection of dengue serotypes in different combinations (DEN2 and DEN3 or DEN1 and DEN3 or DEN1, 2 and 3) was found in a significant number of cases.[17,18] Due to the cross-reactivity of antibodies, recent co-detection of serotypes may increase the risk of developing severe dengue infection by DEN3 and DEN4. A death review undertaken by the Institute of Epidemiology Disease Control and Research showed the presence of the DEN3 strain along with serologic evidence of previous infection.[17,19]

Since dengue is now occurring during every monsoon in Bangladesh, a better delineation of common clinical patterns should help in both the diagnosis and management of upcoming outbreaks. Thus in this study we aimed to investigate the clinico-epidemiologic characteristics of the most recent DF outbreak in Bangladesh.

Methods

Study site, study population and study participants

This cross-sectional study was conducted in the Department of Medicine, 'Dengue Corner' of the Sheikh Hasina Burn and Plastic Surgery Institute and in the Department of Paediatrics, both within the Dhaka Medical College Hospital (DMCH), one of the largest tertiary care hospitals in the capital.[20] Clinically suspected cases of dengue were initially approached for inclusion. A person living or traveling in the dengue-endemic zone with fever along with any two of the following symptoms—nausea/or vomiting, rash, aches and pains, tourniquet, leucopenia ($<4000/mm^3$) and any warning signs (abdominal pain/tenderness, persistent vomiting, clinical fluid accumulation, mucosal bleed, lethargy/restlessness, liver enlargement >2 cm, increase in haematocrit with rapid decrease in platelet count)—was considered a probable dengue case and confirmed dengue cases were defined as characteristics of the probable dengue cases along with the presence of either NS1 antigen or anti-dengue immunoglobulin M (IgM). This approach was based on the National Guideline for Clinical Management of Dengue Syndrome, Bangladesh 2018.[19] Before initiation of the study, the study protocol was reviewed and received approval from the Ethical Review Committee of Dhaka Medical College (memo no. MEU-DMC/ECC/2019/251). Informed consent was obtained before participation either from the patients or from the guardians of the patients (particularly for children). Any co-infection of dengue with other viral, protozoan or bacterial infections was excluded from this report. A detailed case record form was prepared for data collection and used throughout the data collection period. The questionnaire included three parts, covering demographic details, clinical information and relevant investigations. Age, sex, initial symptoms, underlying comorbidities, clinical findings and laboratory investigations were reviewed and recorded. Relevant investigations, including complete blood count, haematocrit, anti-dengue IgG, alanine transaminase (ALT) and aspartate transaminase (AST), and other laboratory assays were performed when relevant to the clinical presentation. A total of 793 cases were approached and 36 patients were excluded because they did not provide consent or had co-infection or critical illness. Furthermore, 10 cases were excluded due to incomplete data (>50% of variables missing information). More details are described in Figure 1. A total of 747 cases (553 confirmed and 194 probable dengue cases) were included in the final analysis.

Clinical and laboratory assay methods

Clinical data were collected from medical records and interviews with the patients or guardians of the patients. All laboratory investigations were performed in the laboratory of the DMCH. Leukopenia was defined as a total white blood cell count $<4000/mm^3$. Thrombocytopenia was defined as a total platelet count $<100\ 000/mm^3$ and elevated ALT and AST were considered when the lab value was >50 IU/L in both cases. Hyperbilirubinemia was defined as serum bilirubin >2 mg/dL. The frequency of blood tests depended on the physician's decision in individual cases. Complete blood counts were performed using automated haematology analysers (BC-5150, Mindray, Shenzhen, China), which were calibrated every 6 months for standardization of results. For detection of dengue NS1 antigen, commercially available kits (Dengue NS1 Detect Rapid Test, InBios International, Seattle, WA, USA) were used. Anti-dengue IgM and IgG were measured by enzyme-linked immunosorbent assay using a commercially available kit supplied by DRG International (Springfield, NJ, USA). Serum bilirubin, ALT and AST were estimated using a Selecta Pro M (ELITech Group, Puteaux, France). Immediate clinical examination was performed in every patient with special attention to fever, vital signs, urine output, rash, organomegaly and, when needed, organ function. All patients were followed up daily until discharge.

Statistical analyses were conducted using SPSS 20.0 software for Windows (IBM, Armonk, NY, USA). Descriptive statistics were used for continuous variables, while categorical variables were expressed as frequencies and percentages. To examine the differences between the groups, χ^2, Fisher's exact and Student's t tests were performed as appropriate. A p-value <0.05 was considered statistically significant.

Results

Of 747 patients included in the analysis, 74% were laboratory confirmed and 26% were probable dengue cases (Figure 2).

The mean age of the population was 27±31 y (range 3–85 y) and 62.7% were male, with 39.4% reporting a history of travel to an endemic zone (Table 1).

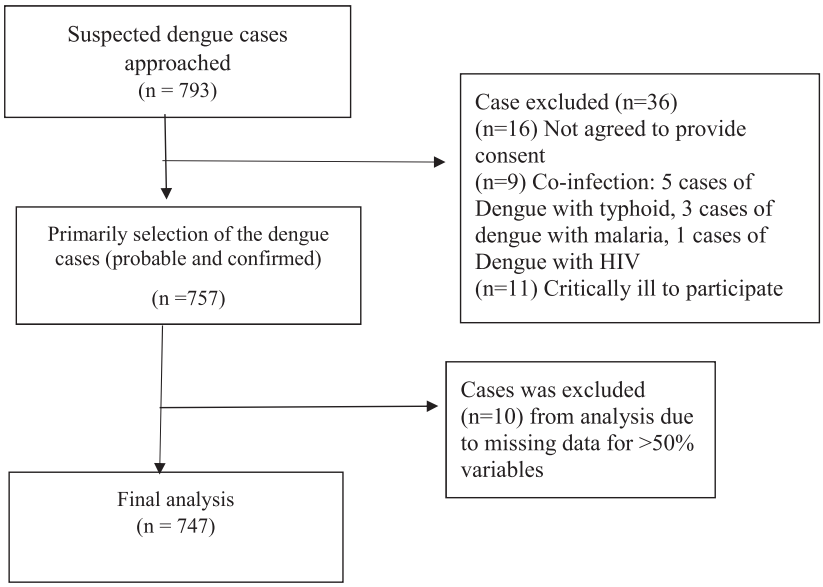

Figure 1. Flow chart of patient selection.

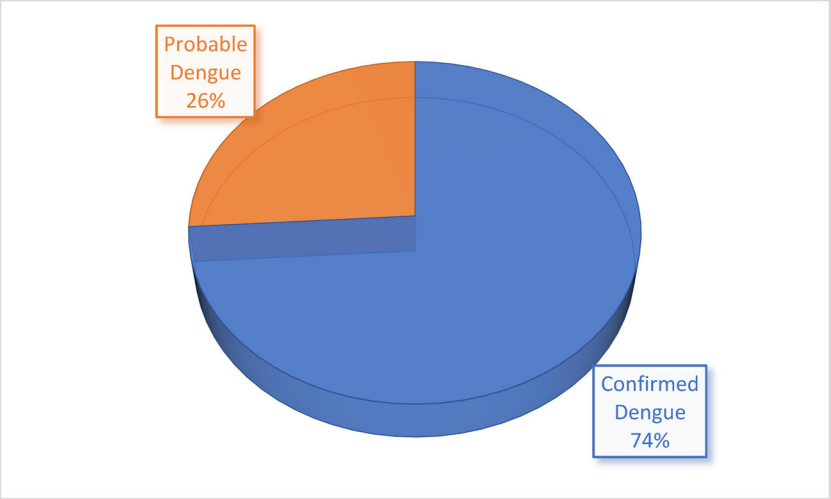

Figure 2. Proportion of laboratory confirmed and probable dengue cases (n = 747).

Fever was present in all of the probable and confirmed dengue cases. Other common symptoms were abdominal pain (84.6%), nausea/vomiting (69.2%), severe headache (61.4%) and retro-orbital pain (38.4%). The most common bleeding manifestation was melena (5.8%). Among the presenting signs, the most common were hypotension (25.4%), low pulse pressure (19.4%) and positive tourniquet test (12.9%). Skin rash was present in 4.7% of patients. Overall characteristics were statistically similar in both the probable and confirmed dengue cases, except sweating (more common in confirmed cases) and splenomegaly (more common in probable cases) ($p<0.001$ for both). The vital signs of the cohort are shown in Table 2.

Laboratory studies showed that 91.9% (n=525) of patients were positive for dengue NS1 antigen, 59.4% were positive for dengue IgM antibody and 60% were positive for dengue IgG antibody. Other investigations revealed that 69.1% had thrombocytopenia (platelet count <150 000/mm^3), 28.2% had leukopenia (<4000/mm^3), 51.7% had elevated ALT levels (>50 IU/L) and 67.9% had elevated AST levels (>50 IU/L). A similar distribution of laboratory parameters was noted in both confirmed and probable cases. More details are described in Table 3.

Discussion

Dengue syndrome has been endemic in Bangladesh since its re-emergence in 2000. During 2019, Bangladesh faced its worst outbreak, which started in Dhaka city and subsequently reached

Table 1. Demographic and relevant clinical characteristics

Characteristics	
Age (years)	Values, n (%)
<10	15 (2.6)
11–20	190 (32.4)
21–30	210 (35.8)
31–40	109 (18.6)
41–50	35 (6)
51–60	16 (2.7)
61–70	9 (1.5)
>70	3 (0.5)
Mean ± standard deviation	27.31±12.27
Sex	
Male	465 (62.7)
Female	277 (37.3)
Residence	
Rural	224 (30.5)
Urban	511 (69.5)
Occupation	
Student	145 (40.4)
Housewife	114 (31.75)
Service holder	40 (11.14)
Businessman	35 (9.74)
Hawker/street seller	8 (2.2)
Farmer	6 (1.67)
Driver	4 (1.11)
Government service	2 (0.56)
Teacher	2 (0.56)
Rickshaw puller	1 (0.27)
Unemployed	1 (0.27)
Travel to endemic zone	242 (39.4)

all parts of the country.[21] By early December 2019, >100 000 patients were admitted to the hospital for dengue fever, with 129 confirmed deaths being officially reported by the Directorate General of Health Services.[22] However, as with previous outbreaks, the final cumulative reports have yet to be completed and underreporting is highly likely to occur.

Compared with the outbreaks in the early 2000s in which the majority of patients affected were younger—either children or adolescents and young adults (5–29 y of age)[12]—the 2019 outbreak affected older people, which corresponds with studies conducted in Sri Lanka in 2018,[23] Ethiopia in 2017[24] and India in 2016.[25] This indicates that dengue, traditionally considered a disease of children, has shown an increasing shift to the adult population over the last 2 decades.[26] Lowered herd immunity and transmission outside the home are two possible explanations for the increasing involvement of adults put forward by a study in Singapore.[27] Although the pathogenesis of dengue virus is multifactorial in nature, age might act as a key modulating risk factor for primary and secondary dengue infections. In a study in Thailand, a shift of the age distribution of dengue infection towards older ages was also noted.[28] Shifting age structure from children to young adults might be a result of reductions in childhood infectious disease mortality. These immune individuals decrease the risk of dengue infection of susceptible individuals around them by providing alternative feeding sources for infectious mosquitoes. Serological testing could determine the patterns of age-specific effects of dengue infection. Many demographic changes also accompany shifts in birth rates, death rates and age structure. Control and prevention measures and changes in the distribution of serotypes or genotypes of viruses may also contribute to age shifts.

The male sex predominance found in the current cohort conforms with several previous studies.[27,29–31] Anker and Arima[30] reviewed DF epidemiologic studies from six Asian countries and noted that male dominance in adult dengue cases was consistently present. Furthermore, the authors also pointed out that the male preponderance of cases differs from DF epidemiologic characteristics in African countries, where a similar sex distribution is the rule. However, we cannot exclude the possibility that since our patients were only those referred to the hospital, the disease may still have affected sexes equally. Nevertheless, the disease manifestations may be more severe in males.

In the present study, fever was consistently present in almost all subjects. Other prominent features were nausea and/or vomiting, severe headache, anorexia, abdominal pain and retro-orbital pain. These are the common features of DF[32] and are in agreement with many other studies.[32–35] Rahman et al.[12] reported headache as the most predominant symptom, followed by myalgia/arthralgia and vomiting. In the outbreak of 2000, Aziz et al.[36] and Hanif et al.[11] found that skin rash was also a predominant feature. Alam et al.[16] examined outbreaks over 3 consecutive years (2006–2008) and found abdominal pain was the cardinal complaint after fever, with vomiting, myalgia, headache, skin rash and itching being other prominent features. Arif et al.[14] found active bleeding in the form of gum bleeding as the most common presentation with fever. However, a relatively high prevalence of GI symptoms was characteristically present in our study. It is also evident from another study that explored the clinical profile of dengue in a non-endemic zone of Bangladesh in 2019.[37]

A bleeding tendency seemed to be present among nearly one-tenth of our cohort, a finding that was also apparent in several previous studies.[36,38,39] However, during the 2002 outbreak in Bangladesh, bleeding manifestations were present in up to 72% of the study population,[1] which decreased in subsequent years.[15] The most common form of active bleeding in the current study was melena, followed by gum bleeding.

A similar picture was reported by Rafi et al.[37] during the current outbreak. Tewari et al.[32] noted gum bleeding in 15% of patients and melena in 6% of patients in a study in India during the 2013 outbreak. In a review based on outbreaks in several Southeast Asian countries, upper GI tract bleeding was the predominant form of bleeding in DF in Bangladesh.[40] Multiple factors participate in the pathogenesis of haemorrhage, including vasculopathy, platelet deficiency and coagulation dysfunction. Upper GI tract bleeding presents as melena, which indicates that nearly 6% of patients had bleeding from the upper GI tract in our study. The presence of existing GI diseases, such as gastric ulcers, duodenal ulcers, erosive gastritis and haemorrhagic gastritis, increases the risk of bleeding in dengue.[41] Given that upper GI problems are relatively common in Bangladesh,[42,43] this might explain the presence of a high frequency of GI bleeding among dengue cases. As with previous outbreaks, the present

Table 2. Clinical characteristics of confirmed and probable dengue cases[a] (N=747)

Characteristics Presenting symptoms	Confirmed dengue (n=553)[a]	Probable dengue (n=194)	p-Value[b]	Total (N=747)
Fever	553 (100)	194 (100)		747 (100)
Chill (associated with fever)	52 (9.4)	18 (9.3)	.959	70 (9.4)
Shivering (associated with fever)	20 (3.6)	4 (2.1)	.291	24 (3.2)
Sweating	123 (22.2)	20 (10.3)	<0.001	143 (19.1)
Severe headache	347 (62.7)	112 (57.7)	.217	459 (61.4)
Retro-orbital pain	216 (39.1)	70 (36.1)	.463	286 (38.3)
Eye redness	67 (12.1)	25 (12.9)	.779	92 (12.3)
Back pain	58 (10.5)	18 (9.3)	.631	76 (10.2)
Neck pain	39 (7.1)	12 (6.2)	.649	51 (6.8)
Sore throat	9 (1.6)	1 (0.5)	.246	10 (1.3)
Rash	25 (4.5)	10 (5.2)	.719	35 (4.7)
Joint pain	25 (4.5)	5 (2.6)	.236	30 (4.0)
Anorexia	210 (38.0)	66 (34.0)	.326	276 (36.9)
Nausea and/or vomiting	385 (69.6)	132 (68.0)	.682	517 (69.2)
Diarrhoea (>3 movements/day)	145 (26.2)	46 (23.7)	.491	191 (25.6)
Abdominal pain	230 (86.5)	66 (78.6)	.081	296 (84.6)
Cough	30 (5.4)	9 (4.5)	.647	39 (5.2)
Respiratory distress	25 (4.5)	9 (4.6)	.837	34 (4.6)
Convulsion	1 (0.2)	1 (0.5)	.438	2 (0.3)
Decreased urine output	13 (2.4)	2 (1.0)	.259	15 (2)
Pattern of bleeding manifestations (n=185)				
Blood in stool (melena)	30 (5.4)	13 (6.7)	.551	43 (5.8)
Gum bleeding	20 (3.6)	1 (0.5)	.025	21 (2.8)
Vaginal bleeding	10 (1.8)	0	.059	10 (1.3)
Epistaxis	9 (1.6)	0	.072	9 (1.2)
Haematuria	3 (0.5)	4 (2.1)	.059	7 (0.9)
Presenting signs[a]				
Hypotension	135 (25.0)	48 (26.7)	.656	183 (25.4)
Low pulse pressure	60 (22.1)	13 (12.4)	.032	73 (19.4)
Tourniquet test positive	12 (10.5)	7 (20.0)	.142	19 (12.8)
Rash	25 (4.5)	10 (5.2)	.719	35 (4.7)
Dehydration	31 (7.8)	7 (7.1)	.795	38 (5.1)
Anaemia	26 (6.6)	4 (4.1)	.359	30 (6.1)
Jaundice	4 (1.0)	2 (2.0)	.408	6 (1.2)
Oedema	1 (0.3)	1 (1)	.292	2 (0.4)
Pleural effusion	10 (2.5)	3 (3.2)	.724	13 (2.7)
Ascites	7 (1.8)	5 (5.2)	.063	12 (2.5)
Splenomegaly	1 (0.5)	4 (10.3)	<0.001	5 (2.1)
Hepatomegaly	3 (1.5)	2 (4.9)	.161	5 (2.0)
Vital signs, mean±standard deviation				
Heart rate (beats/min)	85.8±13.3	87.5±12.7	.150	86.2±13.1
SBP (mmHg)	96.0±14.9	96.2±15.8	.921	96.1±15.1
DBP (mmHg)	66.5±11.8	65.6±11.5	.442	66.3±11.6
Respiratory rate (per min)	18.8±4.2	19.2±3.4	.564	18.9±4.1
Temperature (°F)	99.6±1.3	99.7±1.6	.413	99.6±1.4

Data are presented as n (%) unless stated otherwise.
[a]After excluding missing values.
[b]The p-value was determined by χ^2, Fisher's exact and Student's t test as appropriate.
SBP: systolic blood pressure; DBP: diastolic blood pressure.

Table 3. Laboratory findings of the confirmed and probable dengue cases of the study[a]

Serological tests	Confirmed dengue (n=553)	Probable dengue (n=194)	p-Value[b]	Total
NS1 antigen				
Positive	525 (99.6)		<0.001	525 (91.9)
Negative	2 (0.4)	44 (100)		46 (8.1)
Dengue IgM antibody				
Positive	38 (82.6)	0	<0.001	38 (59.4)
Negative	8 (17.4)	18 (100)		26 (40.6)
Dengue IgG antibody				
Positive	19 (59.4)	17 (60.7)	0.916	36 (60)
Negative	13 (40.6)	11 (39.3)		24 (40)
Haematocrit				
High (>48%)	15 (4.4)	2 (2.2)	.344	17 (3.9)
Normal (≤48%)	329 (95.6)	89 (97.8)		435 (96.1)
Haemoglobin				
Low (<11 g/dL)	38 (11.3)	11 (12.1)	.836	49 (11.5)
Normal (≥11 g/dL)	298 (88.7)	80 (87.9)		378 (88.5)
Leukopenia				
Present (<4000/mm^3)	79 (29.0)	16 (24.6)	.476	95 (28.2)
Absent (≥4000/mm^3)	193 (71.0)	49 (75.4)		242 (71.8)
Thrombocytopenia				
Present (<150 000/mm^3)	254 (66.1)	84 (80.0)	.006	338 (69.1)
Absent (≥150 000/mm^3)	130 (33.9)	21 (20.0)		151 (30.9)
Serum bilirubin				
High (>2 mg/dL)	3 (13)	1 (14.3)	.677	4 (13.3)
Normal (≤2 mg/dL)	20 (87)	6 (85.7)		26 (86.7)
ALT				
High (>50 IU/L)	73 (50.0)	19 (59.4)	.336	92 (51.7)
Normal (≤50 IU/L)	73 (50.0)	13 (40.6)		86 (48.3)
AST				
High (>50 IU/L)	89 (67.4)	25 (69.4)	.818	114 (67.9)
Normal (≤50 IU/L)	43 (32.6)	11 (30.6)		54 (32.1)

Data presented as n (%) unless stated otherwise.
[a]The frequencies and percentages presented are after excluding missing values.
[b]The p-value was determined by χ^2 test.

study observed GI tract bleeding as a dominant presentation in the 2019 outbreak, with an increase in the frequency of diarrhoea and a decrease in the frequency of skin rash compared with that of preceding outbreaks.[44]

Hypotension was present in 25.4% of our patients. This is an indicator of plasma leakage and shows that approximately one-quarter of the patients may have had early features of hypovolemic shock. The rapidity of hypotension and shock was not observed in previous outbreaks, suggesting a shift in the clinical presentation of severe dengue. Previously DEN1 and DEN2 were the predominant serotypes;[18] thus the increased severity of the 2019 outbreak could be attributable to the DEN3 serotype, which was becoming prevalent in 2018.[8] However, this remains a possibility until a report on the prevalent serotypes during the 2019 outbreak becomes available.

DSS was present at 10% of cases in this study. In the 2000 outbreak, Rahman et al.[12] reported DSS in 0.6% of patients, and in the 2010 outbreak, Islam et al.[13] did not find any severe dengue cases. The study conducted by Rafi et al.[37] reported a prevalence of 5.9% for severe dengue cases in their study of the 2019 outbreak. Here there seems to be a shift in the epidemiologic pattern towards more severe disease in Bangladesh, which should be considered for prompt diagnosis and management of cases. However, studies related to virus mutational shifts, potential differences in vector ecosystems, changes in the environment and more precise epidemiologic characterization are needed to address the evolving nature of DF epidemics in Bangladesh. Recovery from infection provides lifelong immunity against that particular strain of virus, but subsequent infection by other strains increases the risk of DSS. The favourable climate and environment for breeding *Aedes* mosquitoes, faulty drainage systems in small and large cities and overcrowded populations might contribute to the highest frequency of dengue reinfection in our country.

A major limitation of the study involved missing data due to the inability to complete the clinical research form by hospital physicians. In addition, the overall number of children was small, likely because many of the children's consultations might have been diverted to specialized hospitals for children in the city. Additionally, serotyping of the dengue cases could not be performed, limiting the characterization of the outbreak.

However, our study was intense in that we reported a large number of cases from the endemic zone during the 2019 dengue outbreak in Bangladesh. Therefore our results will guide management strategies for future outbreaks in the country.

Conclusions

In the 2019 outbreak, the presentation of DF was characterized by an increased frequency of GI features along with fever. Melena and gum bleeding were common bleeding manifestations. These findings will be helpful in devising diagnostic and therapeutic approaches for future DF outbreaks in the country.

Authors' contributions: MJH was responsible for the conception and design of the study. MJH, MS, MRA, AB and TT were responsible for detailed outlines of the study design and data collection. MS, MASK and TT were responsible for data acquisition, literature search and associated activities. MS was responsible for data acquisition and management. TT was responsible for data analysis with assistance from the Pi Research Consultancy Center. MJH and TT wrote the first draft of the manuscript. MRA, ARB, MRI, MASK and DG reviewed the article. The final review was performed by DG and MJH approved the article.

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Competing interests: None declared.

Ethical approval: This study was approved by the Ethical Review Committee of Dhaka Medical College (memo no. MEU-DMC/ECC/2019/251). Informed consent was obtained from all participants or their guardians.

Data availability: Data and materials supporting our findings in the manuscript will be shared on request.

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