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"CLINICAL CHARACTERISTICS & OBSERVATION OF DENGUE FEVER: A STUDY IN TERTIARY CARE HOSPITAL, DHAKA, BANGLADESH"

Mohammad Moniruzzaman Bhuiyan[1*], Nadira Dilruba Hoque[2], Mahfuza Nasrin[3], Md. Ibrahim Khalil[4] and Nasrin Akhter[5]

[1]Assistant Professor, Dept. of Pediatrics, Sir Salimullah Medical College (SSMC) & Mitford Hospital, Dhaka, Bangladesh.

[2]Assistant Professor, Dept. of Pediatrics, Sir Salimullah Medical College (SSMC) & Mitford Hospital, Dhaka, Bangladesh.

[3]Associate Professor, Dept. of Microbiology, Uttara Adhunik Medical College, Dhaka, Bangladesh.

[4]Assistant Professor, Dept. of Pediatrics, Sir Salimullah Medical College (SSMC) & Mitford Hospital, Dhaka, Bangladesh.

[5]Assistant Professor (Psychiatry), Mugda Medical College, Dhaka, Bangladesh.

***Corresponding Author: Mohammad Moniruzzaman Bhuiyan**

Assistant Professor, Dept. of Pediatrics, Sir Salimullah Medical College (SSMC) & Mitford Hospital, Dhaka, Bangladesh.

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ABSTRACT

Introduction: Incidence of dengue infection has increased around the world in recent decades and has become a major internationalpublic health concern. Early diagnosis is essential and clinical suspicion is based on the frequency of symptoms in the population. The exact clinical profile is important for management and prognosis. This study is an attempt to describe the salient clinical as well as laboratory findings of serologically confirmed hospitalized cases of dengue fever. **Materials and Methods:** A hospital-based prospective study was undertaken in the outdoor patients Department of Pediatrics in Tertiary Care Hospital, Dhaka, Bangladesh to assess the clinical profile & observation of dengue infection in hospitalized patients. NS1 antigen and IgM dengue antibody-positive cases were included. These patients were admitted with fever, myalgia, headache, vomiting, abdominal pain or bleeding manifestations. NS1 antigen and IgM dengue antibody was estimated using capture ELISA. The diagnosis of dengue fever, dengue hemorrhagic fever and dengue shock syndrome was based on the WHO (World Health Organization) criteria. **Results:** The study was enrolled 101 patients of suspected dengue fever of whom 51 (50.49%) were serologically confirmed to have dengue infection. 28 (55.0%) patients were males and 23 (45.0%) were females. 38 (37.62%) patients had classic dengue fever while 12 (11.88%) fulfilled the criteria of dengue hemorrhagic fever. Of those patients with dengue hemorrhagic fever, 6 patients had developed dengue shock syndrome. **Conclusion:** Dengue presents as a highly unspecific illness and is hardly recognized as a clinical entity by primary health carephysicians. Dengue infection can have potentially fatal consequences, and to date, vector control methods to prevent the spread of the virus have been unsuccessful. Although there are promising vaccine candidates in development, further studies are required for a greater understanding of the humoral immune responses to Dengue infection and observation disease pathogenesis.

KEYWORDS: Dengue, Dengue Shock Syndrome, Dengue Hemorrhagic Fever.

I INTRODUCTION

Incidence of dengue infection has increased around the world in recent decades and has become a major international public health concern. It is estimated that worldwide nearly 2.5 billion people continue to live at risk of contracting the infection while 50 million cases and 24,000 deaths tend to occur in 100 endemic countries every year.[1] In Bangladesh, epidemics are becoming more frequent. Involvement of younger age group and increase in the frequency of epidemics are indicators of higher incidence of infection.[2, 3] Dengue was first reported in 1780, when Benjamin Rush described this condition as "break bone fever". Dengue is a mosquito-borne viral illness caused by one of the four serotypes of the dengue virus (DENV; (DENV-1 to DENV-4) belonging to the family Flaviviridae. The virus serotypes are closely related but antigenically distinct. Dengue infections can result in a wide spectrum of disease severity ranging from an influenza-like illness (dengue fever; DF) to the life-threatening dengue hemorrhagic fever (DHF)/dengue shock syndrome (DSS), which, if left untreated, areassociated with mortality as high as 20%.[4-6] Early diagnosis is essential and clinical suspicion is based on the frequency of symptoms in the population.The first confirmed report of dengue infection in Bangladesh dates back to 1960s, and

since then more and more new states have been reporting the disease which mostly strikes in epidemic proportions often inflicting heavy morbidity and mortality.[7] Several fatal forms of the disease i.e., DHF, DSS have been reported in Bangladesh from time to time in different parts of Bangladesh. During all these epidemics infection occurred in active childrens in the age group of 16–60 years.[12,13] The common signs and symptoms observed were fever, headache, myalgia, arthralgia and bleeding manifestations have also been observed.The exact clinical profile is important for management and prognosis. This study is an attempt to describe the salient clinical as well as laboratory findings of serologically confirmed hospitalized cases of dengue fever.

II HISTORICAL BACKGROUND

Isolation and detection of dengue virus date back to World War II. Further characterization led to postulation of dengue virus as an agent involved in various past outbreaks exhibiting dengue-like symptoms. Dengue-like disease is illustrated in ancient Chinese manuscripts dating back to 992 and also tothe 1600s in the West Indies.[30] The first detailed account of dengue shock syndrome (DSS) was recorded by Benjamin Rush in 1780 when an outbreak was reported in Philadelphia among people living near the Delaware River.[31] North America saw similar disease patterns in the 18th and 19th centuries along the Atlantic coast, on the Caribbean Islands, and also in the Mississippi basin.[30] Ae. aegypti mosquito as a vector of dengue virus was first discovered. However, it absolutely was solely in 1943-44 that the trendy chapter of infectious disease analysis started. This was when for the first time dengue virus was cultured and later isolated from suckling mice brain.[32,33] Dengue virus belongs to the Arbovirus group of viruses that are transmitted through insect vectors. Virions are 40-50 nm in diameter and spherical in shape with 11kb single-stranded RNA containing asingle open reading frame. Dengue virus consists of ten proteins, three of which are structural and seven nonstructural, and it has has four serotypes, namely DENV1, DENV2, DENV3 and DENV4. The Indian landmass is especially tormented by DENV2 and DENV3 serotypes. DENV1 and DENV4 were identified by studying neutralizing antibodies in the blood of volunteers in 1973[12] while DENV1 and DENV2 were isolated as a consequence of the failure of viral strains to cross-protect human volunteers.[35] All four virus serotypes cause similar ill health, however severe and fatal harm unwellness is a lot of usually related to DENV2 and DENV3 infections. DEN2 type (genotype IV) and DEN3 (genotype III) are the most commonly isolated genotypes.[36,37]

III MATERIALS AND METHODS

Settings: A hospital-based prospective study was undertaken in the outdoor patients Department of Pediatrics in Tertiary Care Hospital, Dhaka, Bangladesh to assess the clinical profile & observation of dengue infection in hospitalized patients.

Study design: Prospective cross-sectional study.

Study period: Four months spread among one seasons (July-October 2019).

Inclusion criteria

a) Dengue patients admitted in medical and adolescent wards of Tertiary Care Hospital, Dhaka, Bangladesh.
b) Patients of all age groups, showing a temperature of >38.5oC for >24 hours, and clinically diagnosed as having dengue fever.

Exclusion criteria

a) Denguecases with definite source of infection (e.g. respiratory or urinary tract infection, meningitis).
b) History of bleeding tendency since birth.
c) Immuno compromised patients.

Sample Size: Number of patients included in the study was 101.

All Data Collection and Analysis: A hospital-based prospective study was undertaken in the Department of Pediatrics in Tertiary Care Hospital, Dhaka, Bangladesh to assess the clinical profile & observation of dengue infection in hospitalized patients. NS1 antigen and IgM dengue antibody-positive cases were included. These patients were admitted with fever, myalgia, headache, vomiting, abdominal pain or bleeding manifestations. NS1 antigen and IgM dengue antibody was estimated using capture ELISA. The diagnosis of dengue fever, dengue hemorrhagic fever and dengue shock syndrome was based on the WHO (World Health Organization) criteria.Only those patients were included in the study with classical features of dengue – fever with chills, body ache, headache, rash, bleeding manifestations and thrombocytopenia and had a positive ELISA test. Patients who had malaria and enteric fever were excluded from the study. Detailed history and clinical examinations were done. Hematological profiles and biochemical investigations were done at the time of admission and were followed by daily (or bi-daily) investigations as required until discharge. Signs of plasma leakage were assessed by chest radiograph and abdominal ultrasonography. Specific investigations were performed in patients who presented with neurological involvement (cerebrospinal fluid analysis, neuroimaging, electro diagnostic studies or muscle biopsy) or hepatic failure (viral markers, peripheral smear and serology for plasmodium falciparum, typhoid fever and leptospirosis). The study enrolled 101 patients of suspected dengue fever of whom 73 (34.93%) were serologically confirmed to have dengue infection. Statistical analysis was performed by Chi -Square test done by using the Statistical Package "SPPS" for Social Sciences, with $p<0.05$ taken as statistically significant.

Disease and Treatment

In 1997 the WHO classified clinical cases of dengue into three different subgroups based on the disease symptoms: dengue fever (DF); dengue hemorrhagic fever (DHF); and dengue shock syndrome (DSS).[32,44] Since overlap between these manifestations had been observed in 2009 this definition was revised as dengue with or without warning sign and severe dengue.[32] It is acknowledged by clinicians that the illness presents as a spectrum of disease instead of distinct phases. While the revised scheme is more sensitive to the diagnosis of severe dengue, and facilitates triage and case management, issues remain with its applicability, some experts considering that a more specific definition of warning signs is required. This calls for research into the diagnostic value of these warning signs on patient outcomes and the cost-effectiveness of the new classification system to ascertain if the updated classification requires yet further modification, perhaps to include elements of both systems.[45] Currently, there are no antiviral medications to target DENV so treatment of each patient is supportive, i.e. provided to alleviate their disease symptoms only.[46] The main goal of clinical management is to restrict or reverse increased vascular permeability, a hallmark of severe dengue, that leads to leakage of plasma into pleural and peritoneal cavities and shock.[46] In the absence of a cure, therefore, effective prevention, control and early management strategies are important to combat the disease and to reduce both the incidence and mortality rate arising from dengue. Implementation of effective mosquito control and surveillance strategies are critically required for more accurate early prediction and better preparation for outbreaks, as well as to directly reduce local transmission of DENV.[44,47-49] An efficacious vaccine is not currently available, but under development, and would also be beneficial as a prophylactic means to curb dengue incidence and mortality rate.[50,51]

Classification and Reporting of Dengue Cases

The WHO 1997 dengue classification system requires four essential criteria to be met for consideration as severe disease. Without any one of the four criteria, dengue patients will be classified as DF, although they might have already developed shock. This means that this classification system was not sensitive enough to include some cases of severe dengue.[32] Hence, not only did this result in inaccurate reporting but led to an avoidable potentially life-threatening situation for each misdiagnosed patient. This prompted the WHO (World Health Organization) within 12 years to revise its dengue classification system.[32] This was an apparent attempt to achieve better case management and to reduce mortality. However, in the decade since its introduction there is no evidence that switching to the 2009 classification system has had an effect in reduce mortality from dengue.[32] In part as a consequence, the mortality rate is unacceptably high in many developing countries, including Indonesia. Ignoring the update of the system, the 1997 classification is still used to report dengue in this country, where only DHF and DSS are diagnosed. Reporting dengue in Indonesia is mandatory within 72 hours after diagnosis. Severe secondary infection could explain the increase in CFR.[20] A possible reason is that nowadays, with different serotypes circulating in the population, DENV has become more pathogenic.[73] If the virulence of DENV remains stable, the CFR should be constant over time.[73]

Signs and Symptoms of Clinical Infection

Further to a person being bitten by an infectious mosquito the incubation period of dengue prior to onset of illness is around 3-7 days.[74] There are a variety of common symptoms of dengue infection, including fever, headache, rash and myalgia.[53,75] Most clinical symptoms of severe dengue only manifest at late stage infection.[47] Severe plasma leakage is determined by shock (DSS) or fluid accumulation with respiratory distress and ascites. Severe bleeding and significant damage to major organs are often involved,[32] affecting the liver (aspartate transaminase (AST) or alanine transaminase (ALT) >1000 U/L detected), heart and central nervous system.[76] In Indonesia, predictors of severity are neither standardized nor used consistently. Clinicians assess for warning signs and symptoms for clinical case management, including spontaneous bleeding, plasma leakage (presence of ascites and pleural effusion), hepatomegaly, abdominal painhaemoconcentration, thrombocytopenia, and sharp increase of AST or ALT levels.[75]

Diagnostic Tests

Diagnosis of dengue infection in the acute phase is important primarily for clinical care, but also facilitates the timely implementation of control measures and outbreak surveillance. Currently, two types of detection method are used to diagnose dengue if infection is suspected, namely direct and indirect tests.[77] Direct testing includes virus isolation[73] and real-time RT-PCR assay[78-80] of different DENV serotypes, and so can provide a differential diagnosis. This type of method is limited in its use due to the short duration and low titre of the viraemia in the peripheral blood of an infected person, up to 7 days after the onset of symptoms.[81] Indirect (serological) testing can be used to attain a rapid diagnosis, as early as the first day of fever, and involves detection in patient serum of developing immunoglobulin (Ig) M and IgG antibodies to DENV non-structural protein-1 (NS-1) [44]. These methods include ELISA, for which there is now a commercially available kit, and immune chromatography.[81-82] Except for a few private institutions public and private hospitals in Indonesia do not yet perform dengue serotype surveillance.[8] Therefore, the great majority of dengue diagnoses are made purely by evaluation of clinical criteria using the outdated WHO (World Health Organization) 1997 classification system and supported by a basic haematological screen,[9] including thrombocyte, leukocyte and haematocrit counts.[83] Not all Indonesian health services can utilize IgM/IgG and

NS-1 rapid tests as diagnostic tools due to the relative expense of the immunological reagents and a lack of medical laboratory expertise that is required to run each of these methods.

Vector Locations, Behaviours and Breeding

A recent detailed longitudinal study found that the most common mosquito species trapped in Indonesia from which DENV could be isolated was Ae. aegypti (90.9%), while Ae. albopictus contributed only 9.1% of virus-positive samples.Ae. aegypti inhabits urban communities, living in close proximity to humans and resulting in more frequent bites[84] compared to Ae. albopictus which prefers more peri-urban and rural environments, which are thus less populated.[85] Both Ae. aegypti and Ae. albopictus may breed in water-holding vessels, including tyres, pots, tins and glass containers.[72,74] Dengue is particularly common in densely populated urban regions of Indonesia,[66] where the co-existence of people and Ae. aegypti provides conditions that are conducive to a high rate of transmission. This is a significant problem in a country where more than half the inhabitants reside in metropolitan area. Rapid urbanization, as has occurred in the capital city in recent years, is associated with poor housing quality, limited safe water supply and restricted access to waste management. These encourage mosquito breeding and are significant contributing factors to the rising dengue incidencerate in Indonesia and other tropical low-income countries that are similarly experiencing accelerated population growth.[75] Moreover, a tropical climate and humid environment are conditions conducive to Aedes mosquito transmission of DENV.[36,84]

Mosquito Prevention and Control

Estimates of mosquito abundance, including measurable correlates such as egg production and numbers of childrens caught in baited traps, are valuable indicators of the adequacy of disease prevention and control in any given location. [1] There are also several ways to eliminate places where the peri-domestic Ae. aegypti prefers to lay eggs in and surrounding homes.[86-88] In low-income tropical countries where dengue is a public health threat mosquito control is an ongoing necessity, especially in urban areas of high endemicity such as Jakarta,[14] in order to reduce the presence of the Aedes vector and thereby to lower the rate of DENV transmission. This can be achieved by effective environmental management, including draining mosquito-breeding containers.[86] Larvicide treatment of pooled water is important to suppress the growth of mosquito populations and thus to reduce the risk of a sudden dengue outbreak.[89] Fogging, the technique of spraying a fine aerosol of fast-acting insecticide, is also used but is only effective for killing children mosquitoes in enclosed spaces such as household rooms and basements.[90] The limitations to control of Aedes mosquito populations include financial constraints, insecticide resistance and insufficient community involvement.[91,92] The prolonged use of chemicals insecticides has led to widespread development of mosquito resistance,[93,94] while its indirect effects on community health and the environment are for debate.[90] Likewise, larvicides, including the commonly used organophosphate temephos (marketed by BASF as Abate®), are toxic to marine wildlife in which they accumulate, and at high doses can cause nausea and dizziness in people. Moreover, it was reported that temephos did not reduce mosquitoes long-term.[90]

IV RESULTS

The study was enrolled 101 patients of suspected dengue fever of whom 51 (50.49%) were serologically confirmed to have dengue infection. 28 (55.0%) patients were malesand 23 (45.0%) were females. 38 (37.62%) patients had classic dengue fever while 12 (11.88%) fulfilled the criteria of dengue hemorrhagic fever. Of those patients with dengue hemorrhagic fever, 6 patients had developed dengue shock syndrome.Most of dengue cases occurred during the month of June to September depicts the role of rainy season on clustering of cases. Maximum number of cases 51 cases (68.49%) was in the children age groups as seen in Table1. As seen in Table 2 fever was present in all cases and is the most common symptom followed by headache, myalgia, vomiting etc. Hemorrhagic manifestations were seen that included petechiae, ecchymosis, gum bleeding, hematuria, malena, hematemesis and epistaxis. Most common complicationswere hepatic dysfunction, renal failure, multi organ failure, encephalopathy and ARDS.

Table 1: Age distribution of patients with Dengue fever (n=51).

Age	Male	Female	Total
(Years)	n=31	n=20	51
1-5 Yrs.	12	07	19
5-10 Yrs.	11	08	19
10-15 Yrs.	08	05	13
Total	31	20	51

Among 51 suspected dengue cases 39 (76.5%) caseswere serologically dengue positive. Therefore, 12 (23.5%) serologically dengue negative cases were excluded from the study. Among the 39 serologically dengue positive patients 18 (46.1 %) were NS1 antigen positive, 13 (33.3%) IgM antibodies and 8(20.6%) both IgM and IgG antibodies positive. The distribution of the serologically dengue positive patients out of 51 clinically suspected cases were shown in [Table 1].

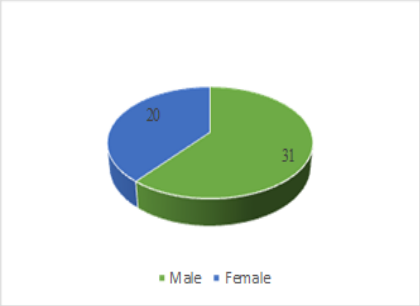

Figure-1: Sex distribution of Patients.

Table 2: Symptoms and complications of dengue fever (n=51).

Symptoms	Patients (N=51)
Fever	37
Headache	27
Myalgia	19
Vomiting	21
Breathlessness	15
Abdomen pain	13
Bleeding tendency	11
Skin rash	7
Complications	
Hepatic dysfunction	24
Renal failure	19
Encephalopathy	8
Multi organ failure	5
ARDS	2

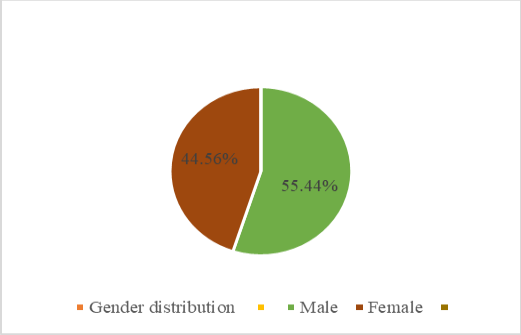

Figure-2: Geographical distribution of the male and female patient.

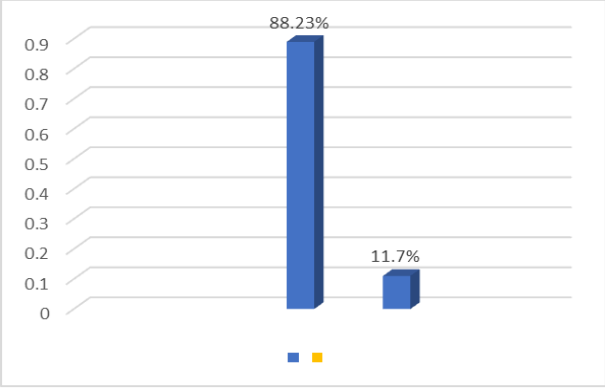

Figure-3: Geographical distribution of the urban and rural patient.

Table 3: Distribution of the serologically dengue positive patients (n=51).

	Number	Percentage
Total serology positive	39	76.5
Total serology negative	12	23.5
Serological test	Positive	Percentage
NS1 Ag	18	46.1
IgM	13	33.3
Both IgM and IgG	8	20.6

Among the study patients 28(55.44 %) were male and 23(44.56%) were female [Figure-2]; 45 (88.23%) from urban and 6 (11.77%) rural area [Figure-3]. The age of the children range from 1 year to 18 years with a mean age of 6.66 ±3.69 years. The age distribution of the patients are shown in [Table 2]. Deranged liver operate in dandy fever infection is a results of the direct impact of the virus on liver cells or the unregulated host response against the virus. Headache was conjointly seen less often compared to different studies. This has conjointly been documented in our study.

V DISCUSSION

Dengue is a very important emerging disease of the tropical and sub-tropical regions. The identification is by clinical features but they can present with varied manifestation.[13,14]This study describes the clinical profile, laboratory features and outcome of DF/DHF/DSS in children patients.The male to female ratio in this study was 2.04:1 respectively. The study revealed that majority of the cases was in the younger age group 51 cases (50.49%). The clinical profile of dengue revealed that fever was the most common presenting symptom (100%). Similar studies in past have also substantiated fever as being themost common presenting symptom. Abdominal pain and vomiting were due to the liver injury caused by the dengue virus. Other infections that cause fever andgastrointestinal symptoms such as typhoid, leptospirosis, and enteroviral infections are common in India and may often lead to a delay in the diagnosis of dengue.Complications observed in present study were hepatic dysfunction, renal failure, encephalopathy, multi organ failure, and ARDS. Deranged liver operate in dandy fever infection is a results of the direct impact of the virus on liver cells or the unregulated host response against the virus. Fulminant hepatic failure occursbecause of acute severe hepatitis and massive necrosis of the liver, causing hepatic encephalopathy and even death.[15] An exclusive study on dengue shock syndrome conducted in Mumbai in 2003 reported hepatomegaly (97.4%), altered sensorium (58%), diarrhoea (50%), rash (42%), and cough (38%) in a significant number of cases Headache was conjointly seen less often compared to different studies. This has conjointly been documented in our study. Most of the patients presented with dengue fever while dengue hemorrhagic fever and dengue shock syndrome were a minority group. Similar findings have also been reported from ruralMaharashtra. Hemorrhagic manifestations included petechiae, ecchymosis, gum

bleeding, hematuria, malena, hematemesis and epistaxis. Early clinical features of dengue infection are variable among patients, and initial symptoms are often non-specific; therefore, specific laboratory tests are necessary for an accurate diagnosis.[2,16] According to the US Centers for Disease Control and Prevention (CDC) and the WHO (World Health Organization) dengue guidelines,[2] the clinical features of DF and DHF are sudden onset of fever, severe headache, myalgias and arthralgias, leucopoenia, thrombocytopenia, and hemorrhagic manifestations. It occasionally produces shock and haemorrhage, leading to death. Classic DF symptoms include fever, headache, retro-orbital pain, myalgias and arthralgias nausea, vomiting, and often a rash. Some DF patients develop the more serious form of the disease DHF with symptoms that include a decline in fever and presentation of hemorrhagic manifestations, such as microscopic hematuria, bleeding gums, epistaxis, hematemesis, melina, and ecchymosis. DHF patients develop thrombocytopenia and hemoconcentration; the latter is due to an increase in the concentration of blood cells resulting from the leakage of plasma from the bloodstream. These patients may progress into DSS, which can lead to profound shock and death if not treated. Advance clinical symptoms of DSS include severe abdominal pain, protracted vomiting, and anotable change in temperature from fever to hypothermia.[5] According to previous studies, there is a steady increase in the number of dengue patients over the past few years was noted. This is due to the rapid urbanization with unplanned construction activities and poor sanitation facilities contributing fertile breeding grounds for mosquitoes. Due to an increase in the alertness among medical fraternity following the initial epidemic and the availability of diagnostic tools in the hospital have contributed to the increased detection of cases.[17] A gradual increase in cases was noticed during rainy season. Pre-monsoon increase in the number of cases was noted in the months of March and April due to the stagnation of water, after a few bouts of pre-monsoon rainfall which facilitate vector breeding. These findings highlight that preventive measures against dengue infection should be taken during water stagnation periods after the initial bouts of rainfall and at the end of monsoon. In this study, DENV1 and DENV3 infections were observed but not DENV4 in 2016 and 2017. In addition, DENV1 and DENV3 coinfections were detected in 18.5% cases in the year 2012, with higher tendency for hemorrhagic manifestations. Previous studies have shown that DENV2 and DENV3 serotypes were associated with haemorrhagic manifestations whereas Chandrakantaet. Concurrent infections may present the possibility of recombination between viruses leading to the emergence of more virulent strains, underscoring the need for continued surveillance and serotyping.

VI CONCLUSION

Dengue is one amongst the key causes of dedifferentiated fever. It presents as an extremely broad wellness and is hardly recognized as a clinical entity by primary health care physicians. This study support additional studies on applying intervention measures to boost the diagnostic accuracy and exactness at the first tending level in dandy fever endemic regions. This study highlights the practician the importance of break bone fever to clinicians within the areas of medical specialty, manifestations, complications and outcome of the wellness. Dengue fever infection will have probably fatal consequences, and up to now, vector management strategies to forestall unfold of the virus are unsuccessful. Though there are promising immunizing agent candidates in development, additional studies are needed for a larger understanding of the body substance immune responses to dengue fever break bone fever infectious wellness infection and disease pathological process.

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