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Review Article

Reemergence of dengue virus in Bangladesh: Current fatality and the required knowledge

*Rashed Noor**

Department of Microbiology, School of Life Sciences, Independent University, Dhaka, Bangladesh

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Abstract

The current fatality of dengue among the Bangladeshi population has drawn the interest of the public health professionals primarily to focus on the environmental, social, and clinical reasoning as well the possible remedies. This year, in 2019, the dengue situation in Bangladesh has appeared with all its dreadful effects leading to the highest death cases due to dengue virus (DENV) infection. According to the Directorate General of Health Services report, this year (2019) the number of DENV-infected people has appeared to be around five times higher (approximately 50,000 cases so far) compared with the last year, 2018 (around 10,000 cases). The present review discussed the current epidemics of dengue infection in Bangladesh as well the possible means of disease curing in terms of general preventive concepts. However, besides the precise treatment of the dengue-affected patients, the knowledge on DENV genome and on the protective immunity against such reemerging disease is essential.

Keywords: *Bangladesh, Dengue, Public health, Secondary infection*

Introduction

Current epidemics and the preventive strategies

Along with the research priorities, the pathogenesis and epidemiology of any emerging disease needs to be fully understood in order to find the way to control and eradicate that specific disease. It is already well known that the genus *Flavivirus* consists of a large number of emerging and reemerging human pathogens, including dengue virus (DENV), chikungunya virus (CHIKV), Zika virus (ZIKV), yellow fever (YFV), and West Nile (WNV) viruses and Japanese encephalitis viruses transmitted by the mosquito vectors, *Aedes aegypti* and *Aedes albopictus*. Among them, DENV is the most prevalent viral particle round the globe. Many researches on dengue infection have already been accomplished; now, it is quite clear that the dengue infection (i.e., the endemic and the sporadic local transmission of DENV) is largely influenced by the environmental factors including the geographical location, global warming and climate changes, irregular precipitation, and unplanned urbanization, triggering the distribution of the major mosquito vector *A. aegypti* [1,2]. The Eastern Mediterranean, American, South-East Asian, Western Pacific, and African regions were subjected to the endemic transmission of the virus, whereas the sporadic local transmission was known within Europe and the United States where *A. albopictus*, a secondary vector, may also prevail together with the primary vector *A. aegypti* [2].

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The location of the Southeast Asian country Bangladesh seems to be the fitting habitat for the survival of the primary dengue vector *A. aegypti* vector (in some cases *A. albopictus* too) as well as its increased transmission. In Bangladesh, DENV has really posed its serious fatal effect this year, and in connection with the previous researches, the major cause of this disease has been pointed on the environmental effects (average rainfall, humidity, and temperature) as well as the improper urbanization [3]. The gradual increase in the atmospheric temperature (thereby supporting the expansion of the habitats of the mosquito larvae and pupa) for the last couple of years, especially in the city of Dhaka, possibly led to increased frequency of dengue infection. In general, the dengue fever is pointed by the sudden onset of high fever; severe headache and pain behind the eyes; and pain in the bones, muscles, and joints. Dengue hemorrhagic fever (DHF) appears as the severe form whereby continuous bleeding and sometimes shock comes about which in turn may lead to death that is most severe and frequent among children. Bleeding usually starts after 3–5 days of dengue fever; the high fever extends for 5–6 days, which declines usually on the 3rd or 4th day before the body temperature rises again, imparting discomfort

**Address for correspondence:*
Dr. Rashed Noor,
Department of Microbiology, School of Life Sciences, Independent University, Bangladesh (IUB), Plot 16, Block B, Aftabuddin Ahmed Road, Bashundhara, Dhaka 1229, Bangladesh.
E-mail: rashednoor@iub.edu.bd

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and extreme weakness. Like chikungunya, dengue fever may spread very quickly and is very likely to affect a large number of populations, resulting in extreme fatality. According to the Institute of Epidemiology, Disease Control and Research, Bangladesh, most of the people who died of dengue this year in Bangladesh suffered from the shock syndrome and were second time infected [4]. The "Death Review Committee" of the Directorate General of Health Services (DGHS) also confirmed that most of the deaths were due to the secondary infection with a different DENV serotype [4].

Besides the knowledge on the clinical signs and symptoms as well as on the environmental factors such as global warming effect on the viral disease outbreaks, it is also important to study the viral genomics in order to completely realize the evolutionary pattern of the viruses. The detection of the possible functions and variations in the RNA sequence in DENV may be important to understand how the viral RNA structures can influence the epidemiological potential of the virus, including the pathogenesis, host adaptation, and the viral transmission between the vectors and humans. Therefore, the molecular mechanism of the DENV epidemics should be brought into focus of the current research by the physicians and the molecular biologists round the globe. The current review focused on the present condition of dengue infection in Bangladesh, the general idea on the pathogenesis mechanism of the DENV particle as well its symptoms, the protective immunity against the disease, and to some extent discussed about the genetic system of DENV augmenting its pathogenesis. The surprising role of T cell-mediated immunity in disease progression is also discussed in brief.

Pathogenesis of dengue: Possible diagnosis and symptoms

Four antigenically distinct but immunologically cross-reactive serotypes of DENV particles (DENV-1–DENV-4) are widely known so far. Infection with any of the serotypes of DENV may be long term; unfortunately, a second attack is not unlikely to the running primary infection, which results in DHF or dengue shock syndrome (DSS). DENV-3 has so far been reported to be the most pathogenic serotype; DENV-1 and DENV-2 have been noticed to be nearly similar in their pathogenic traits, whereas DENV-4 is probably the least pathogenic serotype [1,5]. Experiments considering the preseason total binding antibody levels, measured by the nonserotype-specific indirect enzyme-linked immunosorbent assay (iELISA), revealed that the "undetectable" and the "low-to-medium" levels of iELISA titers were associated with increased risk of secondary DENV infection. Moreover, followed by the primary infection, the risk of the secondary infection during the 2nd year may be similar to that of during the 1st year; in the next year and afterward, the infection risk may gradually decline [5].

Infection with DENV results in an assorted range of symptoms including mild fever to life-threatening hemorrhagic fever, neuroinflammation, and even shock. The main targets include the specific serotype detection, the cross-reactivity of antibody responses (immunoglobulin M or IgM), and detecting the viral nonstructural protein 1 (NS1 antigen through ELISA), the so-called principal infection marker [5,6]. Diagnosis of infection by the amplification of DENV genome through the reverse transcription quantitative polymerase chain reaction (RT-qPCR) is known to be restricted only for research purpose [6,7]. Dengue diagnosis by antidengue antibodies has not been that much useful because the IgM antibodies are quite likely to appear in the late stage of infection, and the high titer of IgG (typically a four-fold increase) is only a sort of demonstrative substantiation [7,8]. That is the reason why most of the clinicians principally depend on the clinical diagnosis based on the serial changes in the hematological parameters (complete blood count, CBC; hematocrit, HCT levels, etc.), which is actually not that specific. Thus, the reverse transcription loop-mediated isothermal amplification (RT-LAMP) has become suggestive of dengue diagnosis [6,9].

The primary dengue symptoms are usually noticed as headache, retro-orbital pain, arthralgia, myalgia, and appearance of rashes, whereas the secondary infection symptoms include hemorrhagic manifestations, leukopenia (decrease in white blood cells <5000 cell/mm^3 and platelet count <150,000 cell/mm^3), and an increasing HCT levels by 5%–10%. The secondary attack can be apparently understood by the continuous high fever for 2–7 days accompanied with severe and continuous pain in the abdomen; bleeding from the nose, mouth, and gums; skin bruising; frequent vomiting (sometimes with blood); liver enlargement, coal tar-like black stools, excessive thirst (dry mouth); pale and cold skin; and through restlessness or excessive sleepiness. DHF and DSS may be considered as the plasma leakage as well as the disruption in homeostasis followed by death. In the course of plasma leakage, the protein-rich fluid component of the blood seeps out of the blood vessels into the surrounding tissues, and hence, this is regarded as the trickiest situation resulting in the severe dengue. Unfortunately, the detection of plasma leakage in the secondary dengue often appears to be difficult [3,6].

Possible role of dengue virus genome on the disease epidemics

The DENV particle consists of a positive-sense single-stranded RNA molecule of approximately 11 Kb of genomic size. Although a plenty of researches showed how the RNA signals function during the flavivirus infections, their molecular mechanisms of pathogenesis are still obscure [10,11]. The 3' untranslated region (3' UTR) of DENV genome has been reported to impart the epidemiological robustness of DENV as well as their adaptation and survival in different geographical locations [11]. Indeed, the 3' UTR of the DENV genome is being thought to be responsible for the DENV evolution. A study of the organization of the DENV 3′ UTR is important because it is similar to that in the other flaviviruses (CHIKV, ZIKV, YFV, and WNV). The DENV 3′ UTR has been shown to consist of necessary elements for the replication of viral particles; it harbors the accessory RNAs (noncoding regulatory RNAs), which may play important roles in modulating the viral processes and in the control of the host antiviral responses [12,13]. Indeed, such noncoding subgenomic flaviviral RNA (sfRNA), especially

from the DENV2 serotype, may disrupt the antiviral response in the salivary gland of the Aedes mosquito vector, which, in turn, triggers the disease outbreak [7,11]. RNA structures within the proximal segment of the DENV 3′ UTR have been found to be resistant against the host nuclease activity, thereby producing an elevated level of sfRNA during infection; hence, the 3'UTRs appear to be the most important determinants of DENV fitness in human–mosquito cycles [10,13].

Indeed, DENV RNA elements (existing within the 5' and 3' UTRs and within the viral coding sequence) have long been known to play an active role in accelerating or silencing the replication of DENV [14]. Earlier, the cis-acting RNA motif, a small hairpin structure within the 3'-UTR region, has been shown to be stringently required for the DENV replication in the vector [15]. This is interesting to ponder that the viral RNA coexists both in linear and in the circular conformations (imparting flexibility to the viral genome), and such a dynamic trait of RNAs are essential for DENV replication [10,14,15]. Among all serotypes, so far, DENV1 B has been known to possess the highest replication efficiency possibly due to the capacity of its nonstructural proteins to suppress the host interferon (IFN) signaling as well as due to the relatively high enzymatic activity of the NS2B3 protease [14,16]. Thus, the DENV genome, the single-stranded RNA molecule, contains huge information that acts as signals to induce, repress, or promote the viral replication, which, in turn, may pose the dengue epidemics.

Dengue and protective immunity: Cellular and humoral immune responses

In response to DENV infection, several cytokines and chemokines are released along with the action of monocytes, macrophages, dendritic, T cells, mastocytes, the IFN regulatory factors, and different IFNs. Usually, the NS3-specific $CD8^+$ T cells from the patients with severe dengue reveal an elevated level of tumor necrosis factor over the cytokine IFN-γ in children with mild dengue [17]. In general, strong cellular ($CD4^+$ T cells, $CD8^+$ T cells, and $CD69^+$ T cells) and humoral immune responses (antibodies) are induced by the primary infection with any of the DENV serotypes. The specific prototype of immune dominance is dependent on the T cell type, the infecting DENV serotype, and on the infected person's previous history of infection [Figure 1].

Indeed, the cell-mediated immunity and the humoral responses are expected to impart long-lived protection against the same serotype [2,5,17]. On the contrary, the booster infection with a different serotype may evoke the elevated risk of developing severe dengue. Hence, the primary infection brings out the cross-reactive immunity which is actually protective; nevertheless, it may be oppositely pathogenic depending on the context of the subsequent infection [Figure 1]. Thus, both humoral and cellular immunity against DENV appear to contribute to the pathogenesis of dengue. In case of antibody (Ab)-dependent enhancement (ADE), the preexisting cross-reactive antibodies escalate the viral burden upon the successive heterotypic infection through the enhancement of Fcγ receptor-mediated cellular uptake [17,18]. Hence, there is a direct role for DENV serotype cross-reactive antibodies in severe dengue outbreak [18]. In case of the secondary DENV infection, there is the role of the cross-reactive T cells accordingly, where the activated T cells during acute infection are cross-reactive with a previously encountered serotype (s) together with a relatively low affinity for the currently infecting serotype, which, in turn, leads to the pathogenesis of the disease [Figure 1]. This is to be mentioned that, currently, there is strong support for the protective role of the cross-reactive T cells over their pathogenic role during the DENV infection [17-19]. However, more comprehensive analyses involving the precise phenotype and epitope specificity of $CD4^+$ and $CD8^+$ T cells during the acute and convalescence phases of DENV infection are required for a clear understanding of the role of T cells serving for the protective immunity or for the pathogenic immunity.

Dengue virus genome and knowledge on immunity: How does it help in designing vaccines?

It is already known that the DENV genome encodes (i) three structural proteins including capsid, the precursor membrane, and the envelope and (ii) seven nonstructural proteins including NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5 [18]. The immune genetic study on the mice model revealed that the $CD8^+$ T cell responses are specific for the nonstructural proteins including NS3, NS4B, and NS5 (in DENV serotype 1, 2, and 4) and both structural and nonstructural proteins in case of DENV3 serotype, whereas $CD4^+$ T cells choose epitopes in the capsid and the NS3 and NS5 proteins [19]. The serotype-specific T cells dominate the primary infection, whereas in case of the secondary infection, the memory T cells (recognizing the conserved epitopes) may increase together with naïve serotype [Figures 1 and 2]. Interestingly, the involvement of the microRNAs has also been reported [8]. Deducing the immunodominant T cell epitopes in each flaviviral proteome, parameters influencing the immunodominance, and understanding the extent to which each epitope induces the T cell cross-reactivity to the different serotypes are important parameters for designing the appropriate vaccine [18]. However, the only licensed DENV vaccine, Dengvaxia® (Manufacturer: Sanofi Pasteur), is known to elicit suboptimal antibody responses against all the serotypes; however, unfortunately, the vaccine-induced antibody responses are very much likely to diminish within 3–4 years after vaccination [19,20]. The application of the vaccine within Asian-Pacific and Latin American regions revealed that the children within 2–5 years of age who had never been exposed to DENV got an elevated risk for developing severe dengue upon vaccination [21].

Dengue prevention strategies in Bangladesh: The governmental legislative bodies

Approximately 3.9 billion people in 128 countries are at risk of dengue infection with around 22,000 deaths each year [6]. Like in other countries, the Aedes mosquito vectors are also known to be responsible for the transmission of the emerging and reemerging diseases such as dengue,

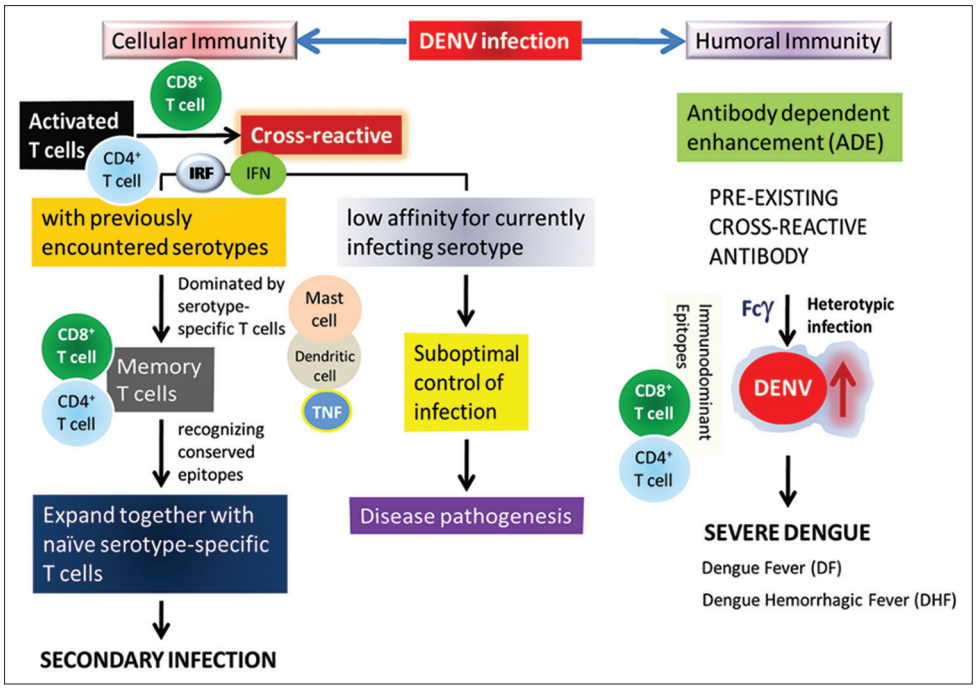

Figure 1: Immunity against DENV triggers pathogenesis. Primary infection with DENV triggers the release of several cytokines and chemokines together with the activation of cell-mediated immunity and humoral immunity. The reinfection, especially with a different serotype, induces the heightened threat of developing severe dengue (DHF). While the primary infection imparts the cross-reactive protective immunity, the secondary infection may be oppositely pathogenic. The direct role for DENV serotype cross-reactive antibodies is shown in this model during the severe dengue outbreak. Besides, the serotype-specific T cells prevails the primary infection; however, during the secondary infection, the memory T cells recognize the conserved epitopes and thereby increase together with naïve serotype, leading to the severe dengue. DENV: Dengue virus, DHF: Dengue hemorrhagic fever

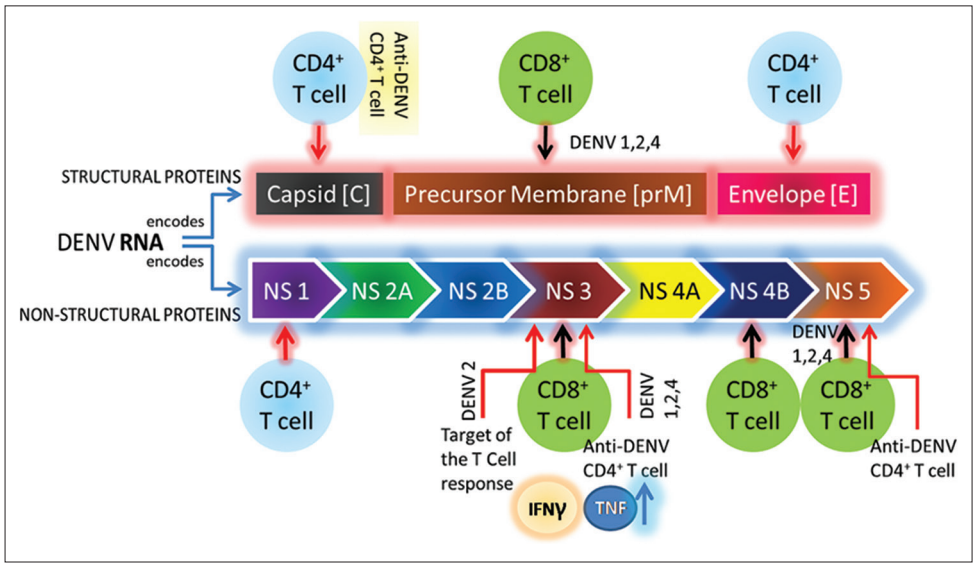

Figure 2: Model of the role DENV RNA in its pathogenesis using the mice model. DENV RNA is translated into three structural proteins and seven non-structural proteins. In the DENV serotypes 1, 2, and 4, the $CD8^+$ T cell responses have been shown to be specific for the nonstructural proteins including NS3, NS4B, and NS5. In DENV3 serotype, the $CD8^+$ T cell responses are specific both for the structural and nonstructural proteins; and the $CD4^+$ T cells are reactive against structural protein, capsid, and the nonstructural proteins, NS3 and NS5 proteins. DENV: Dengue virus

chikungunya, and Zika infection in Bangladesh [22]. Indeed, there is no defined diagnostic biomarker, particularly in those patients who have caught the secondary infection. However, because DENV infection exhibits a broad range of clinical symptoms, accurate laboratory diagnosis is vital for patient supervision. In Bangladesh, dengue management is principally based mostly on the supportive fluid therapy, together with the serological tests including nonstructural protein 1 (NS1 antigen), IgM and IgG levels, HCT levels, and platelet counts. However, recently, the application of the multiplexed adaptive reverse transcription polymerase chain reaction has been reported for the detection of not only DENV but also ZIKV and CHIKV [7].

Precise attention to DENV infection in Bangladesh was first given in 2000 when approximately 6000 patients were diagnosed with this virus. Approximately 10,000 people were infected with DENV last year, of which 26 died. Several governmental regulatory bodies, including the "Health Sector Plan in Bangladesh, 4th Health, Population and Nutrition Sector Program (HPNSP: 2017-2022)," the "Communicable Disease Control (CDC)" which is one of the functional units of the DGHS under the Ministry of Health and Family Welfare of Bangladesh, the "Integrated Vector Management strategy," and the "intensive ACSM (Advocacy, Communication and Social Mobilization)," have been working on the emerging disease awareness and control program [3]. At present, the CDC is known to operate with its seven components under its operational plan in the HPNSP whereby the Aedes mosquito-borne diseases (such as dengue, chikungunya, and Zika infections) are the subcomponents of the Malaria Elimination Control Program [3]. As a preventive measure, this year in the early March, the communicable disease wing of the DGHS conducted a survey, which revealed that a high level of larvae of *Aedes* mosquito can be found in the stagnant waters in the abandoned tires, plastic drums and buckets, flower vases, and most importantly in the open tanks of the under-construction buildings.

Bangladesh has already encountered the ZIKV infection and CHIKV infection and most importantly currently is undergoing the DENV secondary disease outbreak [22]. The average symptoms have been noticed to be nearly overlapping to those of dengue or chikungunya. Such a clinical dilemma imposes great fatality on the mass public health. Therefore, to control the DENV infection, besides the regular monitoring of the antibody titers (i.e., the IgG and IgM levels) and the platelet counts as well as the plasma leakage during the secondary infection, more emphasis should be given on some other aspects such as (a) launching the novel detection methods for the serotype-specific DENV detection; (b) gaining knowledge on the dengue viral genomics, precise serotyping, epidemiological tools, as well as accurate surveillance and protective immunity; (c) examining the sociobehavioral activities; and (d) setting the environmental indicators, as discussed in this literature are important for effective management of dengue situation in Bangladesh.

Indeed, as a highly populated and as a developing country with the resource-poor settings, Bangladesh has experienced a range of diseases including influenza, tuberculosis, enteric diseases, hepatitis virus infections, urinary tract infections, and malaria due to relative unawareness accompanied with defective disease diagnosis system [23-29]. Along with such existing diseases among which some are emerging, the onset of DENV infection together with CHIKV is really alarming. According to the WHO, the incidence of dengue has increased 30-fold over the last 50 years around the world [29]. Up to 50–100 million infections are taking place annually in over 100 endemic countries, which actually puts almost half of the world's population at risk; and very unfortunately, Bangladesh is one of those countries with an alarming risk of morbidity and mortality due to dengue. Such a situation definitely demands perfect diagnosis and control of the reemerging diseases such as DENV infection.

Recommendations: How to manage dengue infection in Bangladesh?

Besides the disciplinary control by the governmental regulatory bodies, people should be cautious of the seriousness of the DENV infection. This can be done by the social awareness programs. Actually, because there is no specific medicine to mitigate the disease, an early diagnosis is stringently helpful [30]. The aqueous extract of *Carica papaya* leaves has been found to exhibit prospective remedies against dengue fever [31]. This can even eliminate the complications including death. According to the WHO, Bangladesh, aspirin and ibuprofen must be avoided in case of dengue fever because these medicines tend to increase the bleeding frequency and also stomachache. Rather, paracetamol is suggested only on the medical advice [30]. If the signs of DHF are noticed, the patient should be immediately transferred to the hospital. The infected person should drink fluids as much as possible [30].

For a researcher conducting study on dengue infection, it is important to know that the mosquito vector *A. aegypti* gets DENV by biting the infected persons, and the first symptoms occur within 5–7 days. The mosquito usually remains indoors and in the cool and shaded places outside. The female mosquito lays eggs in water containers which breed within 10 days. Such information must be disseminated among the general people. Thus, the mass community people may be concerned of the problems of stagnant waters inside drums, jars, pots, buckets, flower vases, plant saucers, tanks, discarded bottles, tins, tires, water cooler, etc., and of the places where rainwater is stored [30,32]. All these efforts should be intensified before the transmission season especially during and after the rainy season [30]. Indeed, the vector mosquito control (i.e., its multiplication) is the utmost priority to prevent dengue outbreaks [32]. Therefore, it is strongly suggested to drain out water from the coolers, tanks, barrels, drums buckets, etc., to take out water from refrigerator drip pans regularly; to maintain the stored water containers in covered condition; and to discard the solid wastes/objects where water may be trapped (e.g., bottles, tins, tires, etc.); as well as rainfall flushing [30,33]. Another most important aspect of preventing dengue is to keeping safe from mosquito bites during the daytime. Wearing full-sleeve clothes and long dresses, massaging repellents, using mosquito coils and electric vapor mats all the day in the house or office, using mosquito nets even at the day time, and treating the curtains with insecticides could be effective remedies [30].

In fine, this year, our densely populated country, Bangladesh, is struggling with its worst outbreak of dengue fever, with almost all the hospitals and clinics full of dengue- infected patients having the symptoms such as high fever, vomiting, and joint pains. It has been deadliest year since the first recorded dengue epidemic in 2000. There is the governmental action to control the spread of this mosquito-borne disease such as the public awareness campaigns to kill the mosquito larvae. Besides, the researchers should give more emphasis on the epidemiology and genomics of DENV; and the research protocols need to be fine-tuned to diagnose the disease accurately, for the better inspection of the infected patients [34].

Conclusion

In Bangladesh, the survey data on the emerging and reemerging diseases are actually sufficient, but the major problem relies on the technical expertise on disease management, which is the most important aspect to accurately control any disease outbreak. Such expertise principally depends on the complete knowledge on the mechanism of disease progression and also on the genomic and immunologic properties of the corresponding infecting agent. Such knowledge-based attitude, especially of the relevant health professionals including the physicians and the health workers, would go a long way to regulate the disease outbreak. DENV infection has now blasted in Bangladesh mainly due to the lack of public awareness on hygiene and the home-based management of health conditions as well. As discussed in this review, the pathogenesis of dengue augmented by the blended action of the genetic components of the DENV particle accompanied with the host cell T cell-mediated immunity would be of interest to precisely characterize the disease during an outbreak.

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Conflicts of interest

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