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Dengue Fever: An Overview

Ramalingam Kothai and Balasubramanian Arul

Abstract

Dengue fever is a disease caused by a family of viruses transmitted by mosquitoes. Dengue virus (DENV), a member of the *Flaviviridae* family, causes the most widespread mosquito-borne viral infection in humans around the world today. Dengue can affect anyone but tends to be more severe in people with compromised immune systems. Dengue hemorrhagic fever is a more severe form of a viral illness. Symptoms include headache, fever, rash, and evidence of bleeding (hemorrhage) in the body. This form of dengue fever can be life-threatening and can progress to the most severe form of the illness, dengue shock syndrome. This chapter reviews the etiology, epidemiology, diagnosis, pathophysiology, transmissions, manifestations, diagnosis, treatment, and prevention of dengue.

Keywords: dengue, etiology, epidemiology, pathophysiology

1. Introduction

Dengue fever is a mosquito-borne viral infection which has a sudden onset that follows symptoms such as headache, nausea, weakness, intense muscle and joint pain, swelling of lymph nodes (lymphadenopathy), and rashes on the skin. Many symptoms of dengue fever include gingivitis, sharp pain in the eyes, and swollen palms and soles.

Dengue can affect any person but appears to be more serious in immunocompromised people. Because it is caused by one of the five dengue virus serotypes, it is possible to have dengue fever multiple times. Nonetheless, a dengue attack provides lifelong immunity to the specific viral serotype to which the patient has been exposed. This disease may also be called “breakbone fever” or “dandy fever.”

This dengue fever may become more serious and then named as dengue hemorrhagic fever and dengue shock syndrome. Dengue hemorrhagic fever is a more severe form in which hemorrhages occurs in the body. It is a life-threatening condition, and it may progress to the most critical form called dengue shock syndrome [1].

2. Etiology

Dengue virus (DENV) is a single-stranded, positive-sense RNA virus in the *Flaviviridae* family and the *Flavivirus* genus. When viewed under the transmission electron micrograph, the virions appear as a bunch of black spots. Yellow fever virus, West Nile virus, St. Louis encephalitis virus, Japanese encephalitis virus, tick-borne encephalitis virus, Kyasanur Forest disease virus, and Omsk hemorrhagic fever virus belong to this family, and majority of them is transmitted by arthropods (mosquitoes or ticks) [2].

Approximately 11,000 nucleotide bases were present in the dengue genome, which codes for a single polyprotein. It is made up of three structural protein molecules (C, prM, and E) that constitute the virus particle and seven nonstructural proteins (NS1, NS2a, NS2b, NS3, NS4a, NS4b, and NS5) which are required for viral replication [3, 4]. The five strains of the virus (DENV-1, DENV-2, DENV-3, DENV-4, and DENV-5) are referred to as serotypes because they vary in serum reactivity (antigenicity) [5].

The main cause of dengue fever is an infected mosquito bite [6], and besides it, it may be accidentally acquired after vertical transmission, especially in near-term pregnant women through the placenta [7], infected blood products [8], through organ transplantation [9], and even after needle stick injury [10].

3. Epidemiology

Awareness about the terrestrial spread and impact of dengue is relevant for assessing its relation to worldwide morbidity and mortality and knowing how to utilize the available resources for controlling the dengue globally.

Only nine countries had suffered major epidemics of dengue, before 1970. Currently it is common in most of the regions of the WHO. The Americas, South East Asia, and Western Pacific areas are the most severely affected, with Asia responsible for around 70% of the global disease burden. Throughout the recent decades, the prevalence of dengue has significantly elevated around the globe. The vast majority of cases are asymptomatic or mild and self-managed, and therefore the actual number of dengue cases is underreported. Many cases are also misdiagnosed as other febrile disorders [11].

One report indicates 390 million dengue virus infections per year, of which 96 million occur clinically (with any disease severity). The report on dengue prevalence reports that 3.9 billion people are at risk of infection with dengue viruses. Despite the risk of infection in 128 countries, 70% of the real burden is from Asia [12].

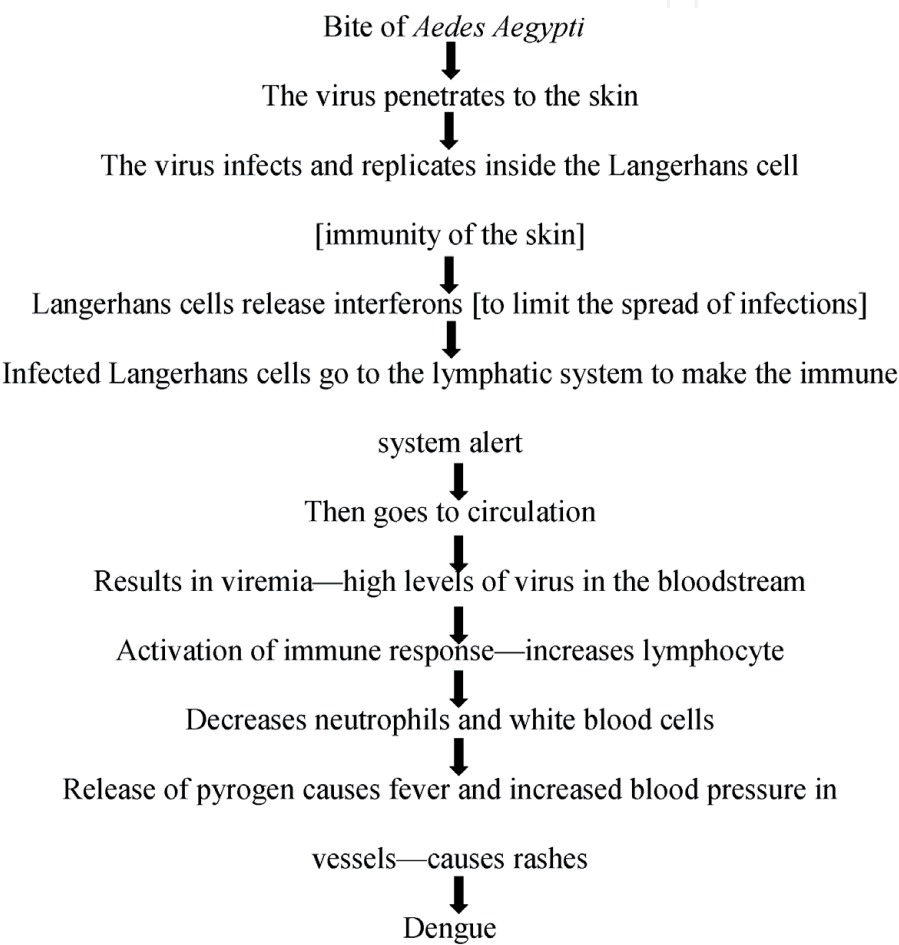
The number of dengue cases recorded to WHO has risen ~6 fold, from <0.5 million in 2010 to more than 3.34 million in 2016. The year 2016 was marked by massive dengue outbreaks worldwide. A major reduction in the number of dengue cases in the Americas was reported in 2017, from 2,177,171 cases in 2016 to 584,263 cases in 2017. It reflects a drop of 73%. Following a drop in the number of cases in 2017–2018, a sharp increase in cases is reported in 2019. Cases have increased in Australia, Cambodia, China, Lao PDR, Malaysia, the Philippines, Singapore, and Vietnam. An estimated 500,000 people with severe dengue require hospitalization every year, and an estimated 2.5% of cases are fatal each year. Nevertheless, several countries have lowered the case fatality rate to less than 1%, and internationally, there has been a decline in case of fatality between 2010 and 2016, with a significant improvement in case management through country-level capacity building. The only continent that has not witnessed dengue transmission is Antarctica.

The global burden of dengue is formidable and is a growing challenge for public health officials and policymakers. Success in addressing this growing global threat depends, in part, on strengthening the evidence base on which planning control decisions and their impact are assessed. It is hoped that this assessment of the distribution and burden of contemporary dengue risk will help to advance this objective.

4. Pathophysiology

The pathophysiology of DENV and the immune response of the host are not fully understood. Primary manifestations of disease include capillary leak

syndrome (plasma leakage due to DHF-specific endothelial cell dysfunction), thrombocytopenia (seen in all types of DENV infection, but extreme in DHF), hemorrhagic tendencies, and leukopenia. It is known that the major viral envelope (E) of glycoprotein in the virus helps to bind the host cells, followed by viral replication [13]. Data suggest that monocytes are the primary target [14]. Infected monocytes induce the production of interferon- α (IFN- α) and IFN- β [15]. Envelope (E), precursor membrane protein (pre-M), and nonstructural protein 1 (NS1) are the major DENV proteins targeted by antibodies as part of the host immune response. Studies have shown that DENV-specific CD4 $^{+}$ and CD8 $^{+}$ T lymphocytes attack infected cells and release IFN- γ , tumor necrosis factor- α (TNF- α), and lymphotoxin. Primary infection induces a lifetime immunity of the individual to that particular serotype, but not to secondary infection by another serotype.



5. Transmission

Dengue virus is the most common mosquito-borne infection in humans all over the world. It belongs to the family *Flaviviridae*, which contains more than 70 viruses [16], in which DENV is transmitted by the *Aedes aegypti* and *Aedes albopictus* mosquitoes [17].

Dengue virus is spread primarily by *Aedes* mosquitoes, in particular *Aedes aegypti*. These mosquitoes usually live between 35°N and 35°S below an altitude of 1000 m (3300 feet) [5]. They usually bite especially in the early morning and in the evening. Certain *Aedes* disease-borne species include *Aedes albopictus*, *Aedes scutellaris*, and *Aedes polynesiensis*. Human beings are the primary hosts of this virus, arousing even nonhuman primates. An infection may be obtained through a single bite. A female mosquito that consumes an infected person's blood (within a febrile, viremic span of 2 to 12 days) becomes infected with the virus in its intestine. The virus then spread

into other tissues, including the salivary glands of the mosquito, approximately after a period of 8–10 days and is subsequently released into its saliva. When it bites the other person, the virus is transmitted through its saliva to that person. The virus does not cause any harm to the mosquito [18]. *Aedes aegypti* is a main concern as it prefers to lay its eggs in containers of freshwater and stay close to humans. Infected blood products and organ donation can also cause dengue [8, 9, 19]. Even in countries like Singapore, the incidence is approximately 1.6 to 6 in 10,000 transfusions [20]. The vertical transmission (from mother to child) during pregnancy or at birth is also documented [8]. Other person-to-person forms of transmission have also been reported, but are very rare [21]. Dengue's genetic variants are regionally specific, indicating that the creation of new territories is relatively rare, despite the fact that dengue has appeared in new regions in recent decades [22].

5.1 The virus

DENV is a small single-stranded RNA virus consisting of five different serotypes (DENV-1 to DENV-5). The virus particle is spherical in shape with a diameter of 50 nm. The genome is divided into three structural proteins (capsid C prM, membrane precursor M protein, and envelope E) and seven nonstructural proteins (NS) by the host and viral proteases.

Within each serotype, distinct genotypes or lineages (viruses closely related in nucleotide sequence) have been identified, demonstrating the substantial genetic variability in dengue serotypes. However, purifying selection continues to be a dominant theme in the evolution of dengue viruses, so only viruses that are “fit” for both humans and vectors are retained. Between these, severe secondary dengue infections are often associated with “European” genotypes DENV-2 and DENV-3 [23–25]. The human hosts have established intra-host viral diversity (quasi-species).

5.2 The vectors

Different dengue virus serotypes are transmitted to humans through the bites of infected *Aedes* mosquitoes, mainly *Aedes aegypti*. This mosquito is a tropical and subtropical species widely distributed around the world, mostly between 35°N and 35°S latitudes. Such geographical limits correspond roughly to the 10°C winter isotherm. *Aedes aegypti* was located as far north as 45°N, but in warmer months, these invasions took place, and the mosquitoes did not survive the winter months. *Aedes aegypti* is also relatively uncommon over 1000 m, due to lower temperatures. The embryonic stages are found in water-filled settings, mostly in artificial containers that are closely linked to human dwellings, and often inside. Research suggests that mostly female *Aedes aegypti* may spend their lives in or around the homes where the adults emerge. It means people are spreading the virus quickly within and between populations, rather than mosquitoes. *Aedes albopictus*, *Aedes polynesiensis*, and several species of *Aedes scutellaris* were also attributed to outbreaks of the dengue [26]. Each of these species has a specific ecological, behavioral, and geographical distribution. *Aedes albopictus* has spread from Asia to Africa, Americas, and Europe in recent decades, aided particularly by international trade in used tires, where eggs are deposited as they contain rainwater. Eggs can remain viable for many months, in the absence of water.

5.3 The host

After an incubation period of 4–10 days, infection with any of the four virus serotypes can cause a wide range of illnesses, although most infections are

asymptomatic or subclinical. Primary infection is thought to cause long-term defensive immunity to serotype infections [27]. Around 2–3 months of primary infection, but without long-term cross-protective immunity, individuals suffering from infection are protected from clinical illness with a specific serotype.

Personal risk factors influence the severity of the disease and also include secondary infections (bronchial asthma, sickle cell anemia, and diabetes mellitus), age, race, and potentially chronic diseases. In particular, young children may be less able to compensate for capillary leakage than adults and are thus at a higher risk of dengue shock [5].

Seroepidemiological reports conducted in Cuba and Thailand strongly support the position of secondary heterotypic infection as a risk factor for severe dengue, although there is little evidence of serious primary infection cases [28–31]. Also, the time interval between infections and the specific viral infection sequence may be significant. For example, a higher fatality rate was observed in Cuba when DEN2 infection followed DEN-1 infection at an interval of 20 years compared to 4 years. Severe dengue is also commonly seen in infants born to dengue-infected mothers. Antibody-dependent enhancement (ADE) of the infection has been hypothesized [32] as a mechanism to explain severe dengue in the course of secondary infection and in infants with primary infections. In this model, non-neutralizing, cross-reactive antibodies produced during primary infection or acquired passively at birth bind to epitopes on the surface of the heterologous infective virus and promote the entry of the virus into Fc-bearing cells. The increased number of infected cells is expected to result in increased viral load and robust host immune response activation including inflammatory cytokines and mediators, some of which may contribute to capillary leakage. Cross-reactive memory T cells are also rapidly triggered during secondary infection, proliferate, release cytokines, and die of apoptosis in a manner that usually correlates with overall disease severity. Host genetic determinants may have an effect on the clinical outcome of infection [33], although most studies have not been able to address this problem adequately. Studies in the American region indicate that the levels of extreme dengue in individuals of African descent are lower than in other ethnic groups [34].

Recent data suggest that endothelial cell activation could mediate plasma leakage [35, 36]. Plasma leakage is believed to be associated with functional effects on endothelial cells, rather than harmful ones. Endothelial cell dysfunction may also be associated with the activation of infected monocytes and T cells, the complement system, and the production of mediators, monokines, cytokines, and soluble receptors.

Thrombocytopenia may be associated with alterations in megakaryocytopoiesis due to human hematopoietic cell infection and impaired progenitor cell growth, resulting in platelet dysfunction (activation and aggregation of platelets), increased destruction, or consumption (peripheral sequestration and consumption). Hemorrhage may result from thrombocytopenia and related platelet dysfunction or intravascular coagulation. In short, a transient and reversible imbalance of inflammatory mediators, cytokine, and chemokine occurs during severe dengue times, probably due to high early viral loads, leading to vascular endothelial cell dysfunction, hemocoagulation disorders, and then plasma leakage, shock, and bleeding.

6. Manifestations

One of three clinical forms can be used in humans, such as dengue fever (DF), dengue hemorrhagic fever (DHF), and dengue shock syndrome (DSS).

Approximately one-half of the DENV infections are asymptomatic, and some are undifferentiated (in which the patient develops fever and mild symptoms, but the source of the infection is not diagnosed as DENV). The three clinical forms of the disease vary in the severity of their symptoms, with the influenza-like DF being the least severe and the DSS being the most severe. In most cases, mild febrile DF is not fatal; however, infections that develop into DHF or DSS may be life-threatening and cause death in many cases. Patients with DHF and DSS were found to have virus titers 100- to 1000-fold higher than those with DF from the initial stage of infection [37]. Overall, DENV infection has been found to be more severe in children than adults [38].

Based on the outcome of several studies, the WHO has developed a new dengue classification. It differentiates dengue cases into cases with or without warning signs and serious cases of dengue.

Usually, signs begin to appear after an incubation period of 3–10 days [39]. The severity of clinical presentations ranges from mild symptoms to extreme life-threatening symptoms for dengue hemorrhagic fever and dengue shock syndrome [40]. Predicting the progression of mild signs to severe DHF/DSS remains a challenge due to unspecific clinical presentation and incomplete understanding of disease pathophysiology and its underlying molecular mechanisms.

The early signs of the disease are nonspecific. According to WHO, DF is characterized by febrile episodes ($\geq 40^{\circ}\text{C}$ for 2–7 days) often associated with rash, nausea, vomiting, and headache. Even though the disease affects all ages of people from infant to adulthood [41], epidemiological data showed that children tend to control this disease better than adults [42]. The severity of the above symptoms and the emergence of other symptoms, such as abdominal pain, mucosal bleeding, and lethargy and restlessness, can be seen after 3–7 days. Laboratory examination of mild dengue fever cases usually reveals elevated leukocyte counts and a small increase in hepatic aminotransferase activity. The emergence of these symptoms is a warning sign of disease progression to severe form (DHF/DSS) if therapeutic action is not undertaken. At this level, clinical intervention and continuous surveillance are necessary to prevent vascular leakage, especially in the endemic region.

Extreme dengue infection can be due to any of the four recognized DENV 1–4 serotypes. The likelihood of developing DHF/DSS is high in patients who have had dengue infection with heterogeneous serotype [43] in the past, with approximately 5–10% of patients developing extreme DHF/DSS that can be fatal unless treated promptly [44].

This type evolves at a late stage of DF, where patients will experience a defervescent process characterized by a sudden drop in body temperature. This phase is also characterized by severe bleeding, especially from the gastrointestinal tract (black, tarry stool) and thrombocytopenia ($< 50,000/\text{mm}^3$), which may affect up to 50% of DHF cases [45]. Ironically, there was a negative correlation between the frequency of DHF and the number of platelets in the blood. The exact mechanism of this association is yet to be identified. Decreased platelet counts and loss of function contribute to vascular fragility, increasing the risk of hemorrhage and plasma leakage⁵⁹. It has been proposed that DENV replicates rapidly in platelets during the acute phase of infection, as this is very important to the survival and dissemination of the virus [46]. The existence of other signs such as retro-orbital pain, maculopapular rash, petechiae, or nose or gum bleeding may help to make a definitive diagnosis of DF [47]. Subsistence in systolic pressure and hypotension can result in profound shock, known as dengue shock syndrome. Long-term DSS duration can predispose to additional complications such as severe bleeding, diffuse intravascular coagulopathy (DIC), respiratory failure, multiorgan failure, and infrequently encephalopathy leading to death [48, 49]. It was estimated that DHF-related case

fatality could exceed 15% of all cases, but proper medical treatment and symptomatic management could minimize the mortality rate to less than 1%.

Signs and symptoms depending on the stage of the disease reflect the dengue fever. People with dengue virus normally become asymptomatic (80%) or have mild symptoms such as uncomplicated fever [50, 51]. 5 % of the people have more severe illness and, in a small proportion of cases (<1%), are life-threatening and cause death despite care. The incubation period (time between exposure and onset of symptoms) ranges from 3 to 14 days, but most of the time is 4 to 7 days. Children are more likely to have atypical symptoms, often with common cold or gastroenteritis (vomiting and diarrhea)-like symptoms [52].

The characteristic symptoms of dengue are sudden fever, headache (typically behind the eyes), muscle and joint pain, and rash. The course of infection is divided into three phases: febrile, serious, and recovery. The febrile phase includes high fever, possibly over 40°C (104°F) and is associated with severe pain and headache; this period usually lasts 2–7 days. Vomiting and rash will be there along with flushed skin. In some cases, the illness is progressing to a serious stage as the fever clears. This process is characterized by major, diffuse plasma leakage usually lasting 1–2 days. Organ dysfunction and severe bleeding, usually from the gastrointestinal tract, may also occur [53]. Shock (dengue shock syndrome) and hemorrhage (dengue hemorrhagic fever) occur in less than 5% of all dengue cases. This serious phase is more common among children and young adults. The recovery phase is followed by the resorption of the leaked fluid into the bloodstream over a duration of 2–3 days. The change is often startling and can be followed by serious pruritus and bradycardia. The rash can occur, with either a maculopapular or a vasculitic appearance accompanied by desquamation. A fluid-overloaded condition can occur during this stage, in rare cases.

Dengue also affects a variety of other body systems, either in isolation or along with typical dengue symptoms. Decreased sensitivity occurs in 0.5–6% of severe cases, due to encephalitis or, indirectly, to compromised vital organs (e.g., hepatic encephalopathy). Other neurological disorders similar to dengue, such as transverse myelitis and Guillain-Barré syndrome, have been identified. Myocarditis and acute liver failure are among the most rare complications.

7. Diagnosis

Signs and symptoms of dengue fever are similar to some other illnesses, such as typhoid fever or malaria, which can sometimes hinder the likelihood of a timely and correct diagnosis. It may be diagnosed by the patient's signs and symptoms, patient's medical history, and testing blood samples (preliminary by platelet count, followed by ELISA, HI assay, and RT-PCR).

The early and precise diagnosis of dengue infection in the laboratory is of paramount importance for disease control. It was estimated that the number of cases of dengue misdiagnosed could reach a record of 50% of all cases, mainly due to a wide disparity in dengue signs and symptoms that conflict with symptoms of other viral infections, particularly for people living in or traveling to endemic areas of tropical infectious diseases. Until the antiviral vaccine is available, early and accurate diagnosis relies heavily on the prevention of serious cases and the reduction of the disease's economic burden. To date, two screening methods have been employed for early diagnosis of the disease. The first is a direct approach for the acute dengue disease phase which is focused on an antigen detection of genomic RNA from viremic patient's blood samples. The second is an indirect approach that relies on serological tests to detect dengue-related immunoglobulins by Mac-ELISA for the capture of real IgM or indirect ELISA for the capture of antiDEN IgGs.

Dengue diagnosis is usually performed clinically on the basis of recorded symptoms and physical examination, especially in endemic areas. However, early dengue fever can be difficult to differentiate from other viral infections. Tourniquet testing, which is particularly useful in environments where laboratory tests are not available, includes applying a blood pressure cuff, inflating it to the midpoint between diastolic and systolic pressure for 5 minutes, and then counting any petechial hemorrhages that occur. The higher number of petechiae makes dengue diagnosis more likely; the lower limit for diagnosis is variably specified as 10–20 petechiae per 2.5 cm² [54].

8. Treatment

There are no particular antiviral medicines for dengue, but it is necessary to maintain a proper fluid balance [55]. Treatment is dependent on the severity of the symptoms. Those who can drink and pass urine have no warning signs can be treated with daily follow-up and oral rehydration therapy at home. Those who have serious health problems, who have warning signs, or who are unable to handle daily follow-up should be admitted to the hospital for treatment. For areas with access to an intensive care unit, treatment should be given for those with extreme dengue fever. Intravenous hydration usually takes 1 or 2 days, if necessary. Fluid administration dose is titrated to 0.5–1 mL/kg per hour of urinary output, stabilizing vital signs, and normalizing hematocrit. The volume of fluid that is provided should be the smallest to achieve such markers. Bearing in mind the risk of infection, invasive medical procedures such as nasogastric intubation, intramuscular injections, and arterial punctures should be avoided. Paracetamol (acetaminophen) is used for fever and nausea, and it is important to avoid nonsteroidal anti-inflammatory drugs such as ibuprofen and acetylsalicylic acid as they may increase the risk of bleeding. For patients with compromised vital signs faced with declining hematocrit, blood transfusion should begin early, rather than waiting for the concentration of hemoglobin to decline to some predetermined “cause of transfusion” level. It is advised to deliver red blood cells or whole blood; platelets and fresh, frozen plasma are not typically recommended. Intravenous fluids are removed during the recovery phase to avoid fluid overload. When fluid overload occurs and vital signs are stable, stopping the administration of fluid can be all that is required to remove excess fluid. If the individual is outside the critical phase, a diuretic loop, such as furosemide, may be used to remove excess fluid from circulation.

9. Prevention

In December 2015, after decades of research and clinical progress, the first dengue vaccine (CYD-TDV or Dengvaxia®, by Sanofi Pasteur) was authorized [56]. Now regulatory authorities have approved it in ~20 countries.

CYD-TDV was found to be effective and safe in clinical trials in people who had past infections with the dengue virus (seropositive individuals). It does, however, bring an increased risk of severe dengue in those who undergo their first normal dengue infection after vaccination (those who were seronegative at vaccination time). It was confirmed in November 2017 by the results of an additional retrospective study analysis which determines the serostatus at the time of vaccination.

Pre-vaccination screening is the recommended strategy for countries which consider vaccination as part of their dengue control program. With this approach only individuals under evidence of past dengue infection would be vaccinated (based on an antibody test or confirmed dengue infection in the past by a verified laboratory).

Decisions on implementing a pre-vaccination screening strategy would require careful country-level evaluation, including consideration of the sensitivity and specificity of the available tests and local priorities, dengue epidemiology, country-specific hospitalization levels, and availability of both CYD-TDV and screening tests [57].

But prevention depends on the monitoring and safety of the bite of the mosquito that transmits it. The primary tool used to monitor *Aedes aegypti* is by destroying its habitats, which include standing water in urban areas (e.g., abandoned tires, ponds, irrigation ditches, and open barrels). If habitat destruction is not possible, the application of insecticides or biological control agents to standing water is another option. Reducing open water collection is the preferred and simplest method of control. Generalized spraying is often done with organophosphate or pyrethroid insecticides but is not considered successful. People can avoid mosquito bites by wearing clothes that completely cover the skin, wearing a repellent scarf, or staying in air-conditioned, screened, or nested areas. However, these approaches do not seem to be sufficiently effective, as the frequency of outbreaks in certain areas appears to be increasing, probably because urbanization is increasing the habitat of *Aedes* mosquitoes; however, the range of diseases appears to be expanding, possibly due to climate change.

10. Conclusion

Dengue fever is a terrible disease and a growing public health problem. A rapid increase in unplanned urbanization leads to more mosquito breeding sites, hence a greater number of people are exposed to *Aedes Aegypti* mosquitoes bite. These include semi-urban and slum areas where household water storage is normal and where solid waste disposal facilities are inadequate. The urgent need for a vaccine to minimize morbidity and mortality due to this disease has been recognized in a cost-effective manner in recent years.

Conflict of interest

The authors have none to declare.

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