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Dengue hemorrhagic fever: a growing global menace

Shakeela Parveen *, Zainab Riaz, Saba Saeed, Urwah Ishaque, Mehwish Sultana, Zunaira Faiz, Zainab Shafqat, Saman Shabbir, Sana Ashraf and Amna Marium

Department of Zoology, The Government Sadiq College Women University, Bahawalpur 63100, Pakistan
*Corresponding author. E-mail: drshakeela@gscwu.edu.pk

SP, 0000-0003-2486-6215

ABSTRACT

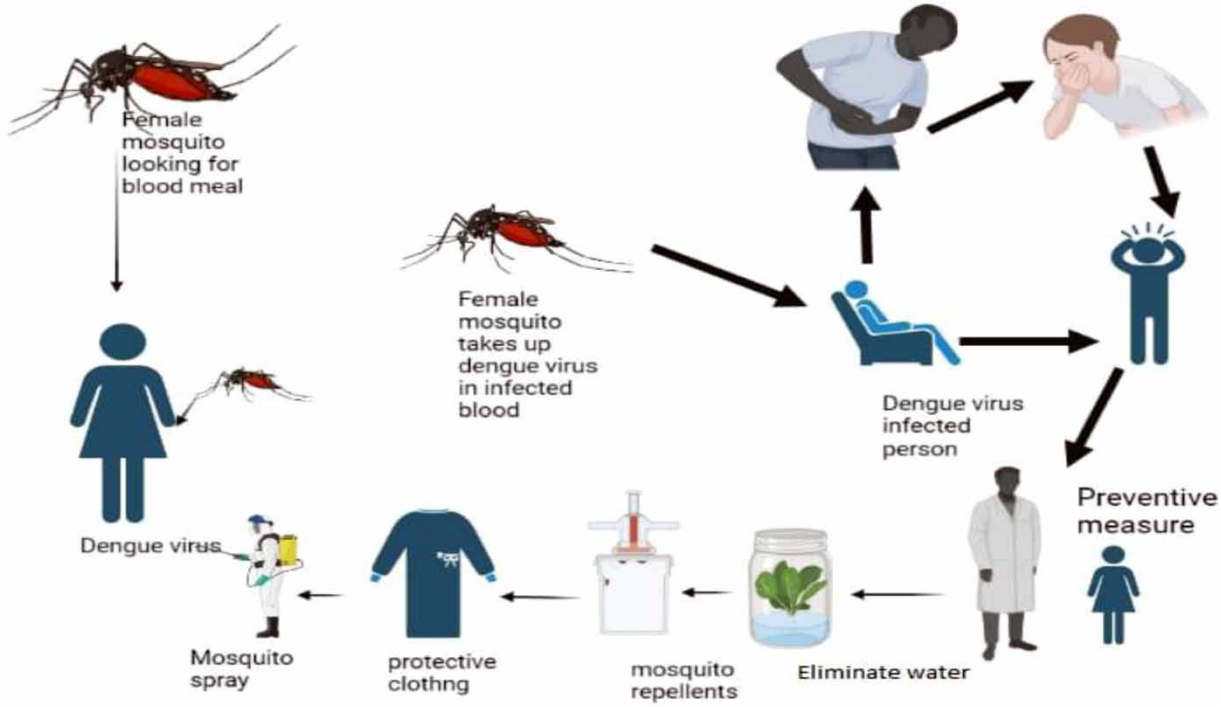
Dengue virus is an arthropod-borne virus, transmitted by *Aedes aegypti* among humans. In this review, we discussed the epidemiology of dengue hemorrhagic fever (DHF) as well as the disease's natural history, cycles of transmission, clinical diagnosis, aetiology, prevention, therapy, and management. A systematic literature search was done by databases such as PubMed and Google Scholar using search terms, 'dengue fever', 'symptoms and causes of dengue fever', 'dengue virus transmission', and 'strategies to control dengue'. We reviewed relevant literature to identify hazards related to DHF and the most recent recommendations for its management and prevention. Clinical signs and symptoms of dengue infection range from mild dengue fever (DF) to potentially lethal conditions like DHF or dengue shock syndrome (DSS). Acute-onset high fever, muscle and joint pain, myalgia, a rash on the skin, hemorrhagic episodes, and circulatory shock are among the most common symptoms. An early diagnosis is vital to lower mortality. As dengue virus infections are self-limiting, but in tropical and subtropical areas, dengue infection has become a public health concern. Hence, developing and executing long-term control policies that can reduce the global burden of DHF is a major issue for public health specialists everywhere.

Key words: aetiology, arboviruses, dengue hemorrhagic fever, epidemiology, risk factors, serotypes

HIGHLIGHTS

- Dengue hemorrhagic fever (DHF) is a significant global public health challenge affecting millions of people across the world.
- Dengue viruses spread to people through the bite of an infected *Aedes* species.
- A complex pathogen with four distinct serotypes and multiple genotypes within each serotype.
- Early diagnosis and medical intervention are critical in preventing severe outcomes.

GRAPHICAL ABSTRACT



1. INTRODUCTION

Dengue virus (DENV) is one of the most important arboviruses (arthropod-borne viruses) from a public health perspective and is known to cause dengue infection, which is mainly transmitted by *Aedes aegypti* (Mutheneni *et al.* 2017). DENV is an enveloped globular virus with icosahedral symmetry containing 11 kilobases of single-stranded RNA (Paul *et al.* 2021) that encodes an open reading frame containing three structural and seven nonstructural proteins (Uno & Ross 2018). Based on antigenic differences, four DENV serotypes with 65% genomic similarity, namely DENV-1, DENV-2, DENV-3, and DENV4, were identified in addition to DENV-5, recently discovered in Malaysia (Bashyam *et al.* 2006; Mustafa *et al.* 2015). Within each serotype, there are several genotypes (Simmons *et al.* 2012) that are phylogenetically based on sequence variation in the envelope (E) gene: DENV-1 (I–VI); DENV-2 (Asia I, Asia II, Asia/America, America, Cosmopolitan, Forest); DENV-3 (IV); DENV-4 (Asian I, Asian II, Asian/American, American, Cosmopolitan, Forest). These serotypes can elicit differential immunogenic effects by infecting different target cells, thereby eliciting a powerful cytokine response that in turn influences the severity of the disease. In addition, secondary infection with a heterologous serotype may elicit a faster immune response than primary infection due to antibody-dependent enhancement (ADE) (Bosch *et al.* 2020).

The World Health Organization (WHO) considers dengue fever (DF) as a serious hazard to public health. Climate change, accelerated population growth, and lack of medical facilities are some of the factors that have led to the rise of the DENV. There are 400 million cases of dengue each year, affecting 5 billion people, and some places have mortality rates of up to 520. More than 100 countries are affected by dengue infections, including the United States, and Europe (Lee *et al.* 2020). Symptoms of the disease may vary from mild to severe (Wang *et al.* 2020). More than half of the world's population is at risk of contracting this disease, which has increased sharply in recent years. More than 120 countries are affected by the dengue hemorrhagic virus DHF, which poses a global public health burden. In 2019, an alarming 5.2 million cases of dengue were reported (Paul *et al.* 2021). In 2022, Asia is responsible for 70 dengue cases worldwide, while 50 people are at risk worldwide (Wang *et al.* 2020). It is believed that dengue infections affect 390 million people worldwide every year and kill up to 36,000 people. 2,597,067 cases and 2,065 deaths were documented on August 24, 2022 (Armenda *et al.* 2021).

The countries with the most reported deaths are Brazil, Vietnam, and the Philippines. There have been over 2,000 new cases and over 2,000 new deaths since the last update. According to recent studies, nearly a billion people worldwide are at high risk of contracting the disease because they live in tropical and subtropical areas (Adimy *et al.* 2020). Dengue hemorrhagic fever

(DHF) affects 450,000 people each year, despite the fact that 100 million cases of classic DF are reported each year. Southeast Asia has a higher prevalence of life-threatening bleeding disorders than either Africa or America (Kayesh *et al.* 2023).

There is still a lack of a specific antiviral drug and an approved vaccine to treat and prevent DENV infection. DF and dengue hemorrhagic virus DHF remain a major public health concern worldwide. DHF has recently been reported in several dengue outbreaks and has resulted in high mortality. Clinically, DHF poses a major risk; due to the complexity of its aetiology disease causes are still unknown. In this review, we summarize and discuss the mechanisms underlying the development of DHF. We also presented the most recent views on DHF prevention and control. The pathophysiology of DHF, as well as treatments and prevention strategies, are discussed in detail in this paper. This study offers important information and perspectives on the pathogenesis of DHF as well as preventive and curative measures.

2. METHODOLOGY

2.1. Criteria for search strategy and selection

We looked through a number of databases, including Science Citation Index, Journal Citation Reports, Sci Search, Google Scholar, PubMed, Medline, SCOPUS, as well as Biological Abstracts. Access was gained to the publicly available databases. Relevant data were searched using the phrases 'dengue fever', 'dengue fever and climate change', 'dengue hemorrhagic fever (DHF), and other infectious diseases', 'risk factors and dengue fever', 'dengue fever and modeling', 'infectious diseases transmitted by vectors', 'models of vector-borne diseases', 'monitoring for the early detection of infectious diseases'.

The preliminary investigation into digital libraries uncovered a total of 120 records. Following the removal of duplicate entries, 111 records were examined to determine whether they met the criteria for eligibility. Among them, 94 were read in their entirety to determine their eligibility for the study, and 81 were selected for inclusion. The remaining 13 studies were disregarded because they were case studies, their references were inadequate, or they contained data that was already present in another study (Figure 1).

2.2. Criteria of selection

The following criteria were utilized in the selection process: (1) studies validated through a peer-reviewed process, (2) full-text research articles, (3) studies published in English, and (4) studies solely considered the map depicting the progression of dengue risk with population growth in addition to socioeconomic, demographic and epidemiological factors, serotype

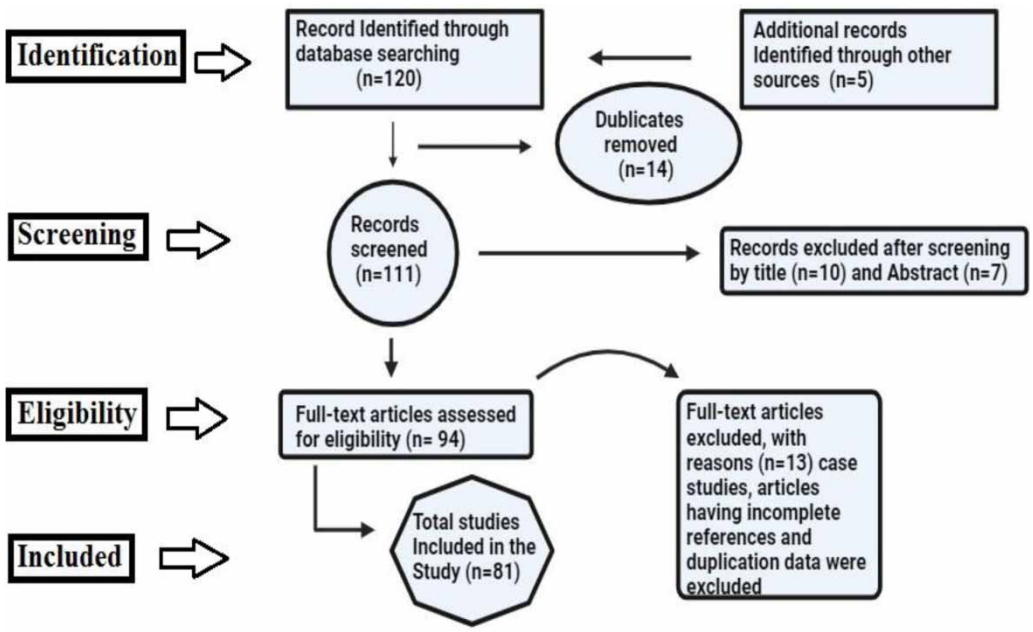


Figure 1 | Flow chart of study selection based on the inclusion and exclusion criteria. (Created with BioRender: Scientific Image and Illustration Software.)

transmission of DF by vectors, cases of DF, and its distribution. The justification behind the inclusion standards was to concentrate on the rise in population, especially in mosquito density, in addition to financial, ecological, and epidemiological as well as demographic characteristics connected with dengue transmission. Articles that did not fit the aforementioned criteria were excluded.

3. DISTRIBUTION PATTERNS OF DHF ALL OVER THE WORLD

According to WHO, DF is now a common disease in more than a 100 countries, including parts of Africa, the Western Pacific, the Americas, Southeast Asia, and the Eastern Mediterranean. The areas having the greatest influence include Southeast Asia, the Americas, and the Western Pacific, with Asia accounting for more than 70% of global disease. There is currently a high likelihood that dengue will spread throughout Europe (WHO 2022) (Figure 2).

4. SYMPTOMS OF DHF

Severe dengue is a life-threatening disease progression. Usually, 24–48 h after your fever reduces, you will start to notice acute dengue warnings. Sometimes, symptoms get worse and become life-threatening. Damaged blood vessels cause severe dengue (Hasan *et al.* 2016) and the number of clot-forming cells (platelets) in the bloodstream decreases. This can lead to shock, internal bleeding, organ failure, and even death. The warning signs of severe DF can develop quickly. You should go to the nearest ER if you have any of the symptoms or if you live in a region where the disease is widespread (Hasan *et al.* 2016). Some of the symptoms are given in Figure 3 and Table 1.

5. IMMUNOLOGICAL BASIS FOR DHF

The key steps by which DENV infection induces DHF have been a subject of controversy. DENV antibodies can influence the course of the disease in various ways. In one study, passive transmission of DENV antibodies increased viral loads in non-human primates, while a recent study showed a positive relationship between peak viral load and disease severity in humans.

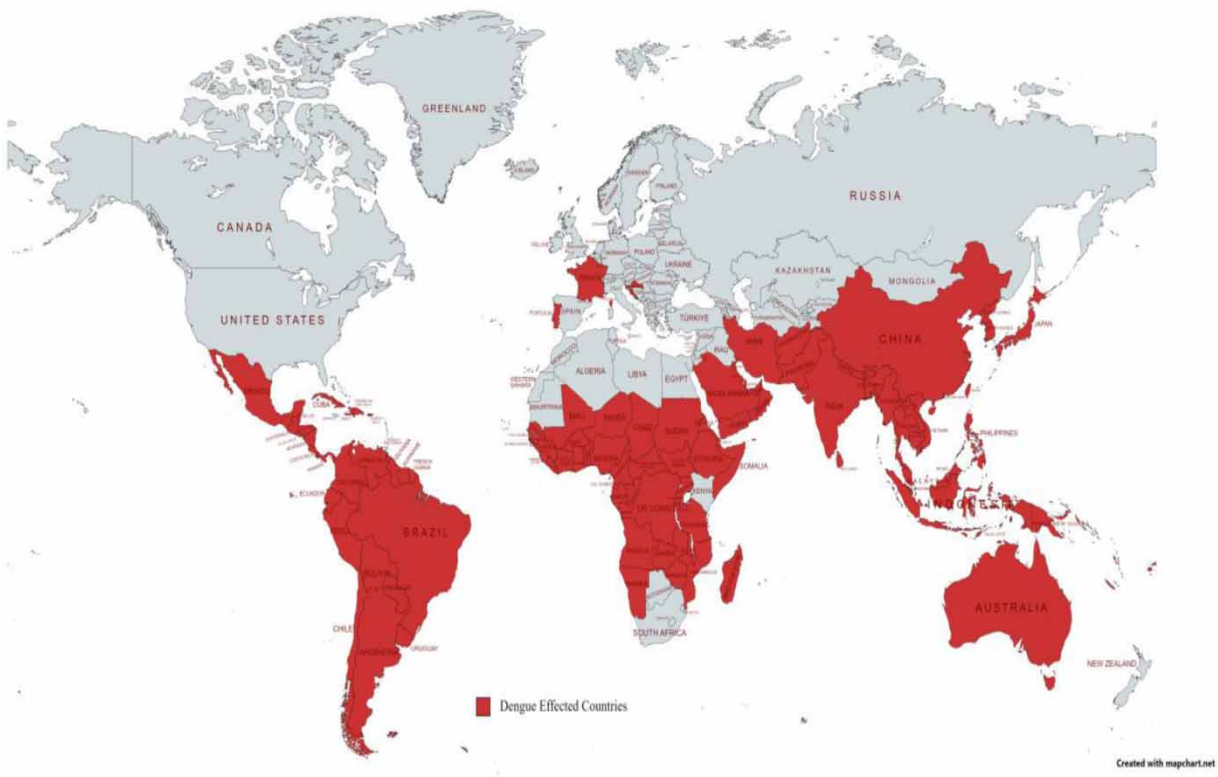


Figure 2 | The worldwide distribution of dengue fever. This map shows the countries affected in the region of Asia, Africa, Europe, and Oceania/Pacific Islands. (https://www.mapchart.net/). (Created with BioRender: Scientific Image and Illustration Software.)

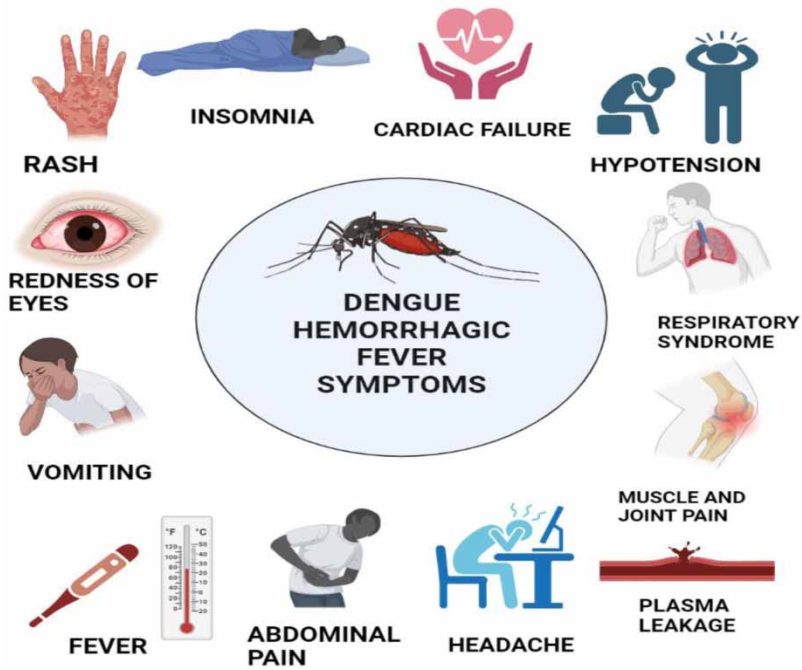


Figure 3 | Symptoms of dengue hemorrhagic fever. (Created with BioRender: Scientific Image and Illustration Software.)

Table 1 | WHO classification of dengue infections and grading of severity of dengue hemorrhagic fever (DHF)

Category	Duration	Symptoms	References
Dengue fever (DF)	2–7 days	• Rash • Fever • Intense headache • Flu-like syndrome • Nausea • Joint pain	Raza *et al.* (2020), Adane & Getawa (2021)
Dengue hemorrhagic fever (DHF)	After 3–5 days of fever	• Thrombocytopenia with <100,000 platelets/μL • Vomiting • Plasma leakage • Raise in hematocrit levels • Pleural effusion, bleeding • Abdominal pain • Sudden drop in temperature	Lee *et al.* (2020), Adane & Getawa (2021), Kosasih *et al.* (2021)
Dengue shock syndrome	After 3–5 days of fever	• Temperature reaches 37.5–38 °C • Decrease in platelet count leads to leakage of plasma subsequent shock • Multi organ damage • Progressively worsening shock • Hypotension • Cardiorespiratory failure and cardiac arrest • Fluid accumulation with respiratory distress	Villamor *et al.* (2018), Armenda *et al.* (2021)

The idea about ADE functions *in vivo* is supported by the observation that DHF persists after primary DENV infection in infants, born to DENV-immune women who subsequently acquire DENV antibodies through the placenta. Primary DENV and clinically mild secondary DENV infection suggest that other variables are also involved. In patients with severe disease, *in vivo* immune complex formation has been associated with complement activation. Cross-reactivity of

anti-E antibodies with plasminogen has been associated with bleeding in acute DENV infection, but not with DHF (Harapan *et al.* 2020). In addition, potential pathologic factors include cytokine production and cytolysis by activated T cells. Elevated levels of activation markers such as soluble TNF receptors, soluble IL-2 receptors and soluble $CD8^+$ have been associated with disease severity.

Similar associations with disease severity were found for the expression of activation markers on circulating $CD8^+$ T cells and for an increased population of DENV epitope-specific T cells. Acute DEN infection leads to increased production of several cytokines, including IFN, TNF, IL-10, and chemokines (Khanam *et al.* 2022). Although both type 1 and 2 cytokine levels are elevated in DHF, the timing of their synthesis appears to be critical as induction of type 1 cytokines occurs earlier and is associated with more severe disease. Analysis of T cell responses to DENV revealed an association between *in vitro* TNF responses to DENV antigens (Waickman *et al.* 2022).

6. VIRUSES ASSOCIATED WITH DF

Individuals are affected four times by DENV types (DENV1, DENV2, and DENV3) (WHO 2022). These four serotypes are genetically related and have a 65% genomic similarity. In October 2013, the sixth DENV-5 variant was discovered (Mustafa *et al.* 2015). A study indicated that DENV-2 and DENV-3 may induce severe illness while DENV-4 causes a mild infection; DENV-1 patients appeared to have a higher chance of developing DHF and Severe Dengue (SD) than patients with DENV-2 or DENV-3. According to a phylogenetic study, these variations may be caused by DENV-1 and DENV-2 viruses of genotypes 1 and are cosmopolitan, respectively (Yung *et al.* 2015).

Dengue viruses have significant gene mutation rates and mutation frequencies over a hundred times higher than DNA genomes. The phylogenetic analysis showed that DENV-5 and the other four serotypes shared a common ancestor. DENV1-4 follows the human cycle, while DENV-5 follows the sylvatic cycle (Mustafa *et al.* 2015).

7. DENV TRANSMISSION

7.1. Host cell infection with virus

The interaction between virus surface proteins and cellular plasma membrane elements determines whether or not target cells will recognize a virus (Islam *et al.* 2021). Currently, DENV does not have a defined receptor. The adhesion molecule of dendritic cells (DC-SIGN), the mannose receptor (MR) of macrophages, the lipopolysaccharide (LPS) receptor CD14, and stress-induced proteins, such as the heat-shock proteins 70 and 90 and the ER chaperonin GRP78, have all emerged as candidates with distinct natures in mammalian and mosquito cells. A study indicated that E protein DIII has the receptor(s) binding site (s). Based on the viral strain or serotype and the host cell, the DENV particle involves several mechanisms, such as clathrin-mediated endocytosis or clathrin-independent endocytic pathways (non-classical). The maturation of the virus particle and the identification of viral immunocomplexes by Fcγ-receptors are two additional factors that hinder viral entry (Cruz-Oliveira *et al.* 2015).

The early endosome with Rab5 is where the virion is often found to be internalized, and it either develops into or unites with the pre-existing late endosome with Rab7. The fusion of the viral envelope with the host endosomal membrane results from several conformational changes in the E protein and PrM-E. It then triggers the virus to encounter an acidic pH inside the endosome, which in turn results in viral nucleocapsid deployment in the cytosol (Raquin & Lambrechts 2017). In endoplasmic reticulum, the DENV genome is translated (ER). In the replication complex (RC), DENV genome RNA replication is carried out that comprises host cell components, viral proteins and RNA. The ER is where DENV particle assembly takes place, and virions bud into the ER as immature virus particles. After that, the trans-Golgi network is used to carry these developing virus particles (TGN). During egress, the cellular serine protease furin cleaves prM, releasing mature virus particles into the extracellular environment (Kato & Hishiki 2016) (Figure 4).

8. COMPLICATIONS ASSOCIATED WITH DHF

8.1. Neurological complications associated with DHF

Neurological disorders are those that affect not only the brain but also the spinal cord and other body nerves (Trivedi & Chakravarty 2022). New DHF guidelines and classification were announced by the WHO, and this disease now includes brain involvement (Trivedi & Chakravarty 2022). There are three different pathogenic mechanisms that explain the neurological complications of DF: (1) directly invades the central nervous system, which leads to myelitis, meningitis, and encephalitis;

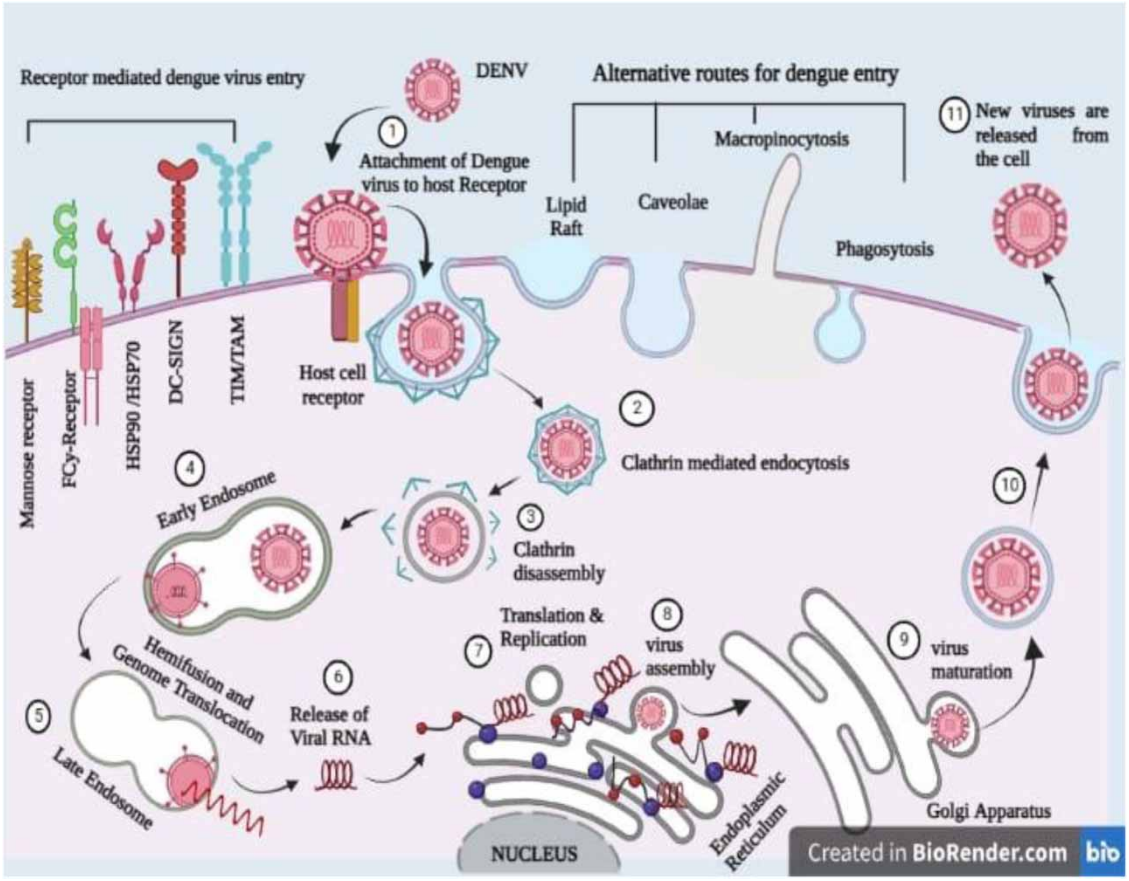


Figure 4 | Dengue virus transmission. (Created with BioRender: Scientific Image and Illustration Software.)

(2) a systemic condition that brings stroke and encephalopathy; and (3) para infection or post-infection immunomediated conditions such as optic neuritis, acute disseminated encephalomyelitis and Guillain-Barré syndrome (GBS) (Herath *et al.* 2018). Some symptoms of neurological complications include headache, confusion, seizures, hemiparesis, and even coma. In addition, MRI and CT scans both are used to determine more information about neurological complications (Weerasinghe & Medagama 2019).

The range of the neurological and neurological complications of dengue (hemorrhagic) disease is diverse. The neurotropic nature of DF has been confirmed by epidemiological and case series studies as well as in histopathological studies. The spectrum of the neurologic complications is 5.6–14.6% and they are more common within DHF, with a higher prevalence in adolescents and children (Carod-Artal *et al.* 2013). Neurological manifestations of DHF were being reported in many countries. The affected people range from the very young (3 months baby) to the very old (60 years). Some of the different neurological manifestations include myelitis, encephalitis, myositis, and GBS (Trivedi & Chakravarty 2022).

Approximately 2.5 billion people in over 100 countries have been at high risk of complications due to dengue infection. In Sri Lanka, dengue outbreaks have increased in recent decades. In 2015, a neurological complication (Encephalitis) with cerebral infection and seizure with severe headache was reported in India.

In 2017, the second case was reported in Sri Lanka, having neurological complications (cerebellar syndrome) with Gait ataxia, dysarthria, and horizontal and vertical nystagmus in DHF. In Brazil, neurological complications cases were reported, they have meningitis along with headache, fever, and vomiting and neck stiffness/rigidity (Herath *et al.* 2018). In Taiwan, the hemorrhagic stroke was reported with dysarthria, headache, vomiting, hemiparesis, and somnolence (Lardo *et al.* 2018). In Guadeloupe, neurological complication was reported, including sphincter disturbances, abrupt motor, and sensory neurons and spinal lesions at three vertebral segments (Herath *et al.* 2018). The neurological complications of DHF from 2013 to 2019 are broadly classified (Jugpal *et al.* 2017) (Table 2).

Table 2 | Neurological complications associated with dengue hemorrhagic fever

Complications	Signs and symptoms	MRI/CT scan	Treatment	References
Cerebellar syndrome	Gait ataxia, dysarthria, Horizontal, Vertical nystagmus	Brain infractions involving medulla regions and pons regions	Steroid (dexamethasone)/ Steroid therapy	Herath *et al.* (2018)
Encephalitis	Cerebral involvement indications, Seizure with severe headache	Hyperintensities in bilateral cerebral hemispheres including basal ganglia in MRI	Methyl Prednisolone	Nadarajah *et al.* (2015)
Meningitis	Headache, Fever, Vomiting, Neck stiffness/rigidity	Leptomeningeal enhancement and distention of the subarachnoid space in MRI	Antibiotics	de Oliveira *et al.* (2017); Marinho *et al.* (2017)
Disseminated encephalomyelitis	Monophasic course, Involvement of multifocal white matter, Inflammatory demyelinating	Abnormalities in the CNS white matter, with or without gray matter involvement in MRI	Intravenous dexamethasone, Immunosuppressive therapy (Plasmapheresis)	Marinho *et al.* (2017); Sulaiman *et al.* (2017)
Hemorrhagic stroke	Dysarthria, Headache, Vomiting, Hemiparesis, Somnolence	Hyperdensity at CT	Lorazepam and Diazepam & therapies	Kim *et al.* (2018), Li *et al.* (2018)
Transverse myelitis	Sphincter disturbances, Abrupt of motor, sensory neurons, spinal lesions at three vertebral segments	Medullary lesions at the thoracic and cervical levels	Steroids, High dose Methylprednisolone with antibiotic	Badat *et al.* (2018), Landais *et al.* (2019)
Ischemia stroke	Dysarthria, Hemiparesis	Acute infarct in right parietal region in MRI	Low dose aspirin, Limb physiotherapy	Li *et al.* (2018)

MRI, magnetic resonance imaging; CT, computerized tomography.

8.2. Ophthalmic complications associated with DHF

Ophthalmic complications are those complications that are related to the eyes. In the last 25 years, the geographical distribution of DHF resulted in a global revival of the disease, causing ocular infections in many tropical urban areas. Globally, 2.5 billion people were affected by these complications (Dhoot 2023). Ophthalmologists should carefully evaluate patients with dengue-related eye disease, as some patients have poor visual acuity and are treatment-resistant. Dengue ocular manifestations can occur during many stages of dengue, but are more pronounced in hemorrhagic dengue. Many cases of ocular dengue showed spontaneous improvement in vision (Somkijrungroj & Kongwattananon 2019).

There are various ophthalmic complications that affect DHF patients including myopic shift, corneal pathology, maculopathy, retinal vein occlusions, posterior uveitis, macular edema, and neuro-ophthalmic manifestations. The main symptoms are metamorphopsia, scotomata, floaters, and blurring of vision (Ng & Teoh 2015; Oliver *et al.* 2019). In 2015, many cases of ocular complication (corneal pathology) with DHF were diagnosed in many areas such as America, Western Pacific, and Southeast Asia having symptoms of lower corneal erosions and peripheral hypopyon corneal ulcer (Ng & Teoh 2015). In 2016, retinal vein constrictions were reported in Malaysia (Velaitham & Vijayasingham 2016). In 2018, the neuro-ophthalmic manifestations were reported in India as having diplopia and acute vomiting (Krishnacharya *et al.* 2018). From 2019 to 2022, posterior uveitis, macular edema and myopic shift were reported in different areas of the world (Joshi & Wadekar 2021). Tomography, optical coherence tomography, angiography, microperimetry, and near-infrared imaging have an important part in the recognition of all these problems (Somkijrungroj & Kongwattananon 2019). Ophthalmic complications reported from 2015 to 2022 are discussed in Table 3.

8.3. Lymphatic system complications

The most frequent lymphatic system complication among severe dengue infections is lymphadenopathy. Although they are uncommon, lymph node infarctions and splenic ruptures can be fatal. Another frequent sign of all dengue infection types is splenomegaly. However, it brings a deficiency in platelets and coagulation factors, causing intrasplenic hemorrhage and,

Table 3 | Ophthalmic complications associated with dengue hemorrhagic fever

Complications/Problems	Ocular signs and symptoms	Treatment	References
Myopic shift	Blurring of vision, Myopia	Timolol, pilocarpine and prednisolone eye drops	Dhoot (2023), Mi Fang *et al.* (2023)
Corneal pathology	Lower corneal erosions, Peripheral hypopyon corneal ulcer	Corticosteroid therapy	Ng & Teoh (2015)
Maculopathy	Blurred vision, Scotoma and floaters	Methylprednisolone or intravitreal triamcinolone	Latif *et al.* (2019), Oliver *et al.* (2019)
Retinal vein occlusions	Blurring of vision, Optic disc swelling, Pupillary afferent defect	Pan retinal photocoagulation and endothelial growth factor injection	Velaitham & Vijayasingham (2016)
Posterior Uveitis	Retinitis, Choroiditis, retinochoroiditis	Corticosteroid	Latif *et al.* (2019), Oliver *et al.* (2019)
Macular Edema	Blurring of vision	Intravenous methylprednisolone	Agarwal *et al.* (2019), Joshi & Wadekar (2021)
Neuro-ophthalmic manifestations	Diplopia, Acute vomiting	Botulin injections, Laser surgery	Krishnacharya *et al.* (2018)

ultimately, splenic rupture (Khan *et al.* 2022a, 2022b). A case reported fever, stiffness, chills, and sore throat. The diffuse maculopapular rash covered the entire body but secured the mucosal membranes and periorbital tissues, and was accompanied by myalgia and frequent vomiting. Upon inspection, toxic facial features, and conjunctival congestion were revealed (Chang 2021).

Along with bilaterally enlarged parotid and submandibular glands, there was also bilateral inguinal lymphadenopathy. Another study indicated vomiting, myalgia, headache, and fever. On assessment, the patient's heart rate was 112 beats per minute (bpm), normal blood pressure (BP) was 92/60 mmHg, respiratory rate was 24 breaths per minute (bpm), and oxygen saturation when breathing room air was 98% (Singh *et al.* 2018). In addition a case indicated a 5-day history of high fever accompanied by chills, vomiting, and yellowing of skin, the patient neither had a substantial medical history nor an addiction (Joob & Wiwanitkit 2020). The patient exhibited a highly icteric condition, a fever of 100°F, and bilateral subconjunctival hemorrhages. A white blood cell count automatically revealed a concentration of 20.78 with the prevalence of neutrophils and normal platelets. Blood test results revealed a hemoglobin level of 7.78 g/dL, MCV of 98.12 fl, MCH of 37.72 pg, and MCHC of 38.45 g/dL (Khan *et al.* 2019).

8.4. Cardiovascular system complications

Different cardiovascular symptoms of DF are explained with complicated pathogenesis (Figure 5). Cardiovascular manifestations in different countries along with their symptoms are given in Table 4. Several potential explanations include direct injury to cardiac myocytes and changes in the vascular endothelium membrane thus causing endothelial dysfunction due to the release of inflammatory cytokines in severe dengue (Rahim *et al.* 2022). In spite of relative bradycardia, temporary atrioventricular block, and ventricular arrhythmia, patients at one end of the clinical range are asymptomatic or only have minor heart symptoms (Rahim *et al.* 2022). A study indicated fever, malaise, and gums bleeding, with no systemic illness or not having cardiovascular disease. Peripheral white blood cell count was reported 10.7 $\times$ 10^9/L (normal range: 3.9–10.6 $\times$ 10^9/L) with 61% polymorphonuclear cells, hemoglobin was 14.5 g/dL (normal range: 12–15 g/dL), hematocrit was 42.4% (normal range: 35–45%), and platelet count was 11.0 $\times$ 10^9/L (normal range: 150–400 $\times$ 10^9/L) (Krishnan *et al.* 2016), and also revealed that the patient had DHF based on their observations of petechiae, gingival bleeding, and fever. Another case study from Brazil indicated headache, low-grade fever, arthralgia/myalgia, and lethargy (Giri *et al.* 2022). White blood cell count was 10.7 $\times$ 10^9/L (4–11 $\times$ 10^9/L) with 72% polymorphonuclear cells, hemoglobin was 14.3 g/dL (12.5–14.5 g/dL in women), hematocrit was 41.7% (35–45%), platelet count was 28.0 $\times$ 10^9/L (150–400 $\times$ 10^9/L), prothrombin time was 10.2 s (control, 10.6 s) (Yadav *et al.* 2017; Vuppali *et al.* 2018). Cabrera-Rego *et al.* carried out a study in 2021 that described the cardiovascular symptoms in 427 DVI patients. Of them, 19.7% reported cardiovascular symptoms. Specific symptoms include atrial extrasystoles (4.9%), sinus bradycardia (13.8%), ventricular systoles (4%), and 1.6% have myocarditis, while 0.2% with pericarditis. In a study by Li *et al.* (2018), 1,782 individuals with DHF were examined

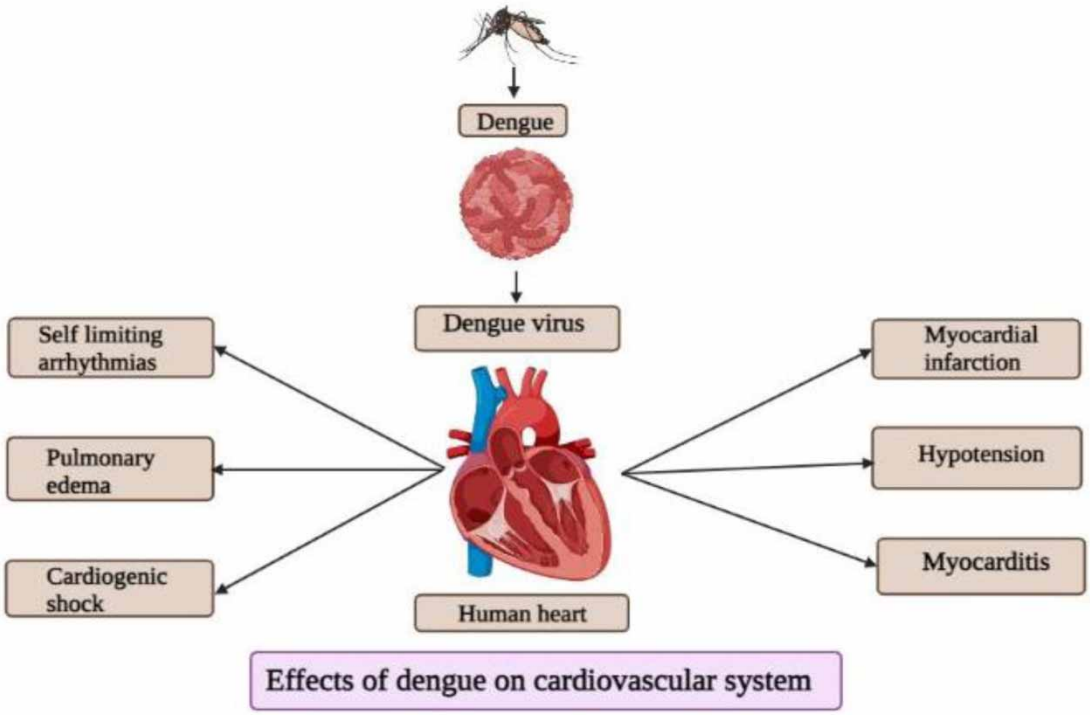


Figure 5 | Effects of dengue on the cardiovascular system. (Created with BioRender: Scientific Image and Illustration Software.)

to determine the prevalence of myocarditis using cardiac enzyme tests, ECGs, and ECHOs. 120 DHF patients between the ages of 13 and 76 years were studied (Kularatne *et al.* 2007; Aslam *et al.* 2016) and reported that 75/120 (62.5%) of the individuals had abnormal ECGs. They came to the conclusion that cardiac involvement in DHF is common and it is crucial to identify it early and differentiate it from DSS (Figure 6).

9. RISK FACTORS ASSOCIATED WITH DHF

The occurrence of dengue is contingent upon abiotic conditions that directly influence the population dynamics of mosquitoes, hence carrying significant consequences for the transmission of dengue (Yang *et al.* 2014). The epidemiology of dengue is a multifaceted phenomenon that encompasses the interactions between the host (human and mosquito), the agent (virus), and the environment (including abiotic and biotic variables). The interaction among these factors influenced the level of endemicity (Dutta *et al.* 2011; Dash *et al.* 2012).

Individuals of all age groups and genders are susceptible to potential risks and hazards (Figure 7). The presence of passively acquired dengue antibodies in neonates is a risk factor for the development of DHF. It is unlikely that dengue is the cause if the person experiences a fever that lasts for 2 weeks or more after their excursion. The migration of people from locations where the disease is common to areas where it does not facilitate the spread of dengue (Singh *et al.* 2021).

10. GLOBAL DENGUE PREVENTION AND CONTROL STRATEGY

More than 120 countries are affected by DF. In 2019, a DF case was reported. Despite the fact that 50% of the world's population is at risk for the disease, Asia is responsible for 70% of the dengue burden. According to the Global Strategy for Dengue Prevention and Control (GSPC) of the WHO, the major goal was to reduce dengue mortality to zero by 2030. For this, DF is considered a general threat and needs to be strengthened through international collaboration, preparation, prevention, and management of dengue. In June 2021, the Asian Dengue Voice and Action (ADVA) groups will celebrate World Dengue Day, International Neglected Tropics Association Day (ISNTD), and ASEAN Dengue. The International Forum underscored the critical need for successful cross-sectoral collaborations between the Ministries of Health, Environment, and Education and local private businesses. The forum collected 29,000 signatures from dengue patients in 110 countries for the United Nations WHO's World Dengue Day petitions (Srisawat *et al.* 2022).

Table 4 | Cardiovascular manifestation in different countries along their symptoms

Country	Clinical symptoms	Cardiovascular manifestation	References
China	Non-reactive	• LV dysfunction • ECG changes • Elevated cardiac enzymes	Li *et al.* (2018)
India	Dengue shock syndrome	• ECG changes • ST segment depression, • Myocarditis	Mishra *et al.* (2019)
India	Dengue hemorrhagic fever	• 3rd degree AVB	Agarwal *et al.* (2019)
India	Dengue hemorrhagic fever	• Sinus bradycardia	Krishnan *et al.* (2016)
India	Dengue shock syndrome	• Mobitz type II AV	Mishra *et al.* (2019)
Brazil	Dengue shock syndrome	• Pericardial tamponade	de Abreu *et al.* (2020)
India	Non-reactive	• Sinus bradycardia First degree AVB VPBs	Yadav *et al.* (2017)
India	Non-reactive	• Elevated troponin I • LV dysfunction • Sinus bradycardia • ST-T changes	Giri *et al.* (2022)
Sri Lanka	Dengue shock syndrome	• Pericardial effusion	Prompetchara *et al.* (2019)
India	Dengue shock syndrome	• Myocarditis • LVdysfunction	Vuppali *et al.* (2018)
India	Non-reactive	• LV dysfunction • Elevated cardiac enzymes • enzymesT wave inversion • Prolonged QTc AVB	Lakshman *et al.* (2018)
India	Non-reactive	• Sinus bradycardia • ST-T changes	Dissanayake & Seneviratne (2018)
India	Non-reactive	• Myocarditis • AF 3rd AVB 1st degree AVB	Mahmood *et al.* (2021)
India	Dengue shock syndrome	• Myocarditis • LV dysfunction • Pericardial tamponade	Agarwal *et al.* (2019)
India	Dengue shock syndrome	• Myocarditi • LV dysfunction • ST elevation • Pericardial tamponade	Biswas *et al.* (2019)
India	Dengue hemorrhagic fever/Dengue shock syndrome.	• Elevated cardiac enzymes • Myocarditis	Guzman *et al.* (2016)
Brazil	Dengue shock syndrome	• Pericardial tamponade	da Silveira *et al.* (2019)
Sri Lanka	Dengue shock syndrome	• St elevation • Myocarditis	Ahmad *et al.* (2022)
India	Dengue fever, Dengue shock syndrome, Dengue hemorrhagic fever	• ECG changes • sinus bradycardia • ST elevation • DF LV dysfunction	Simo *et al.* (2019)
India	Dengue fever, Dengue shock syndrome	• Sinus bradycardia	Khan *et al.* (2022a, 2022b)

(*Continued.*)

Table 4 | Continued

Country	Clinical symptoms	Cardiovascular manifestation	References
		• Pericardial effusion • LV dysfunction	
India	Dengue fever, Dengue shock syndrome	• ECG changes • Pericardial effusion • LV dysfunction • Elevated CK-MB	Vuppali *et al.* (2018)
Columbia	Dengue shock syndrome	• ST elevation • LV dysfunction • Global hypokinesia	Adam *et al.* (2021)
Cuba	Dengue fever Dengue shock syndrome	• ECG changes • Sinus bradycardia • VPBs 1st degree AVB • AF Pericarditis • Pericardial effusion • Myocarditis	Wei *et al.* (2022)
Taiwan	Non-reactive	• Acute heart failure • LV dysfunction	Lee *et al.* (2020)
Thailand	Dengue fever, Dengue hemorrhagic fever, Dengue shock syndrome.	• Pericardial effusion • Myocarditis • Elevated cardiac enzymes • LV dysfunction • ECG changes	Mahmood *et al.* (2021)
Pakistan	Dengue fever	• AF	Naqvi *et al.* (2021)

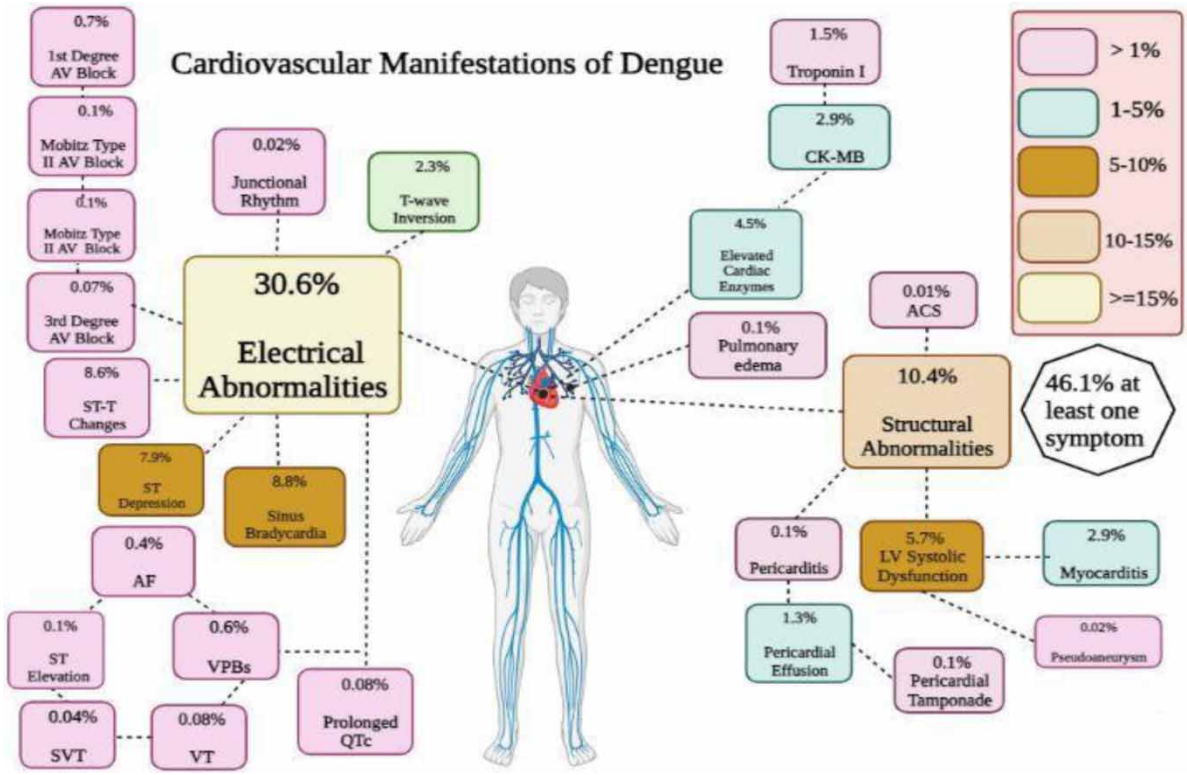


Figure 6 | Cardiovascular manifestation of dengue. (Created with BioRender: Scientific Image and Illustration Software.)

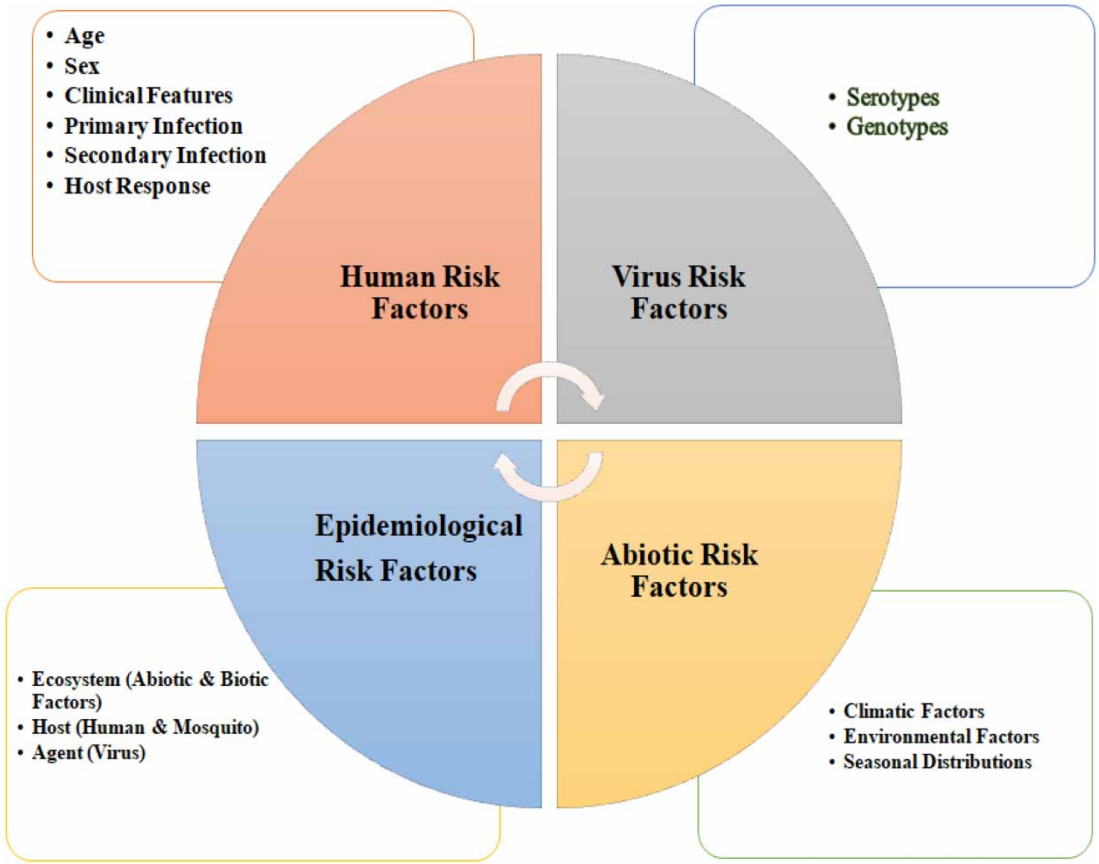


Figure 7 | Risk factors associated with dengue hemorrhagic fever (DHF). (Created with BioRender: Scientific Image and Illustration Software.)

10.1. Vaccination against DHF

At least seven DENV vaccines have been produced and are based on various platforms, including DNA, recombinant proteins, chimeric live attenuated viruses, inactivated viruses, and live attenuated viruses (Torres-Flores *et al.* 2022). They primarily work by enhancing immune responses against the E protein and non-structural protein 1 (NS1) of the DENV (Liu *et al.* 2016). The variety of DENV vaccine in phase I and II clinical trials are important. Clinical trials in phase I/II also assess how well a particular form of disease reacts to a novel therapy. Patients typically get the greatest dose of medication that did not result in adverse side effects in the phase I stage of the clinical study during phase II (Table 5). Phase III clinical studies compare a novel treatment to existing ones to see how safe and effective it is. Phase III clinical trials, for instance, could assess which patient population had higher survival rates or fewer adverse effects. The only DENV vaccine that is presently approved is Dengvaxia, however, phase III clinical studies using the TV-003/TV-005 and TAK-003 have shown encouraging outcomes (Torres-Flores *et al.* 2022) (Table 6).

Recombinant attenuated DENV vaccine candidates TV003/TV005 from the United States National Institutes of Health and TAK-003 from Takeda Inc. are now conducting clinical phase III trials, and these candidates seem to be the most close to commercialization since Dengvaxia (Park *et al.* 2022). A large-scale phase III clinical trial is now being carried out to assess the effectiveness of DENVax in dengue-endemic regions of Latin America and Asia (Torres-Flores *et al.* 2022). TDENV-PIV with AS03B is now being tested in a phase II clinical trial to find the most efficient injection (Redoni *et al.* 2020). TDENV-LAV, a tetravalent formulation of all DENV serotypes that have been attenuated in PDK and Rhesus lung cells, was investigated in a clinical phase II investigation. The results confirmed the safety of TDENV and the immunogenicity of LAVs (Wasiullah *et al.* 2022). Phase 1 clinical trials of the US NMRC's monovalent DENV-1 DNA vaccine (D1ME100) were conducted. This tetravalent DNA vaccine produced with Vaxfectin completed effectively its phase 1 trial. Tetravalent live attenuated-prime followed by tetravalent PIV boost and vice versa are heterologous regimens that

Table 5 | Dengue virus vaccine in phase II and phase I clinical trials

Vaccine type	Designation	Manufacturer	Process	Phase	References
Purified formalin-inactivated vaccine	TDENV-PIV	WRAIR, GSK	4-viral strains that have undergone formalin chemical inactivation	Phase II	Redoni *et al.* (2020)
tetravalent dengue live attenuated vaccine	TDEN-LAV	WRAIR, GSK	Contains DENV1-4 serotypes made in two different formulations F17 and F19	Phase II	Izmirly *et al.* (2020), Umair *et al.* (2023)
Recombinant Subunit Vaccines	V180	Hawaii Biotech	A recombinant truncated protein containing DEN-80E	Phase I	Rather *et al.* (2017), Deng *et al.* (2020)
DNA Vaccine	D1ME100	US NMRC	Recombinant plasmid vector encoding prM/E	Phase I	Deng *et al.* (2020), Prompetchara *et al.* (2019)
	TVDV	US NMRC	prM/E proteins from DENV1-4 are encoded via a recombinant plasmid vector.	Phase I	Deng *et al.* (2020), Prompetchara *et al.* (2019)
Heterologous prime/boost	TLAV prime/PIV boost	WRAIR	Initial immune-boost strategy	Phase I	Deng *et al.* (2020), Lin *et al.* (2021)

Table 6 | Dengue virus vaccines have been licensed or in phase III clinical trial

Vaccine type	Designation	Manufacturer	Process	Phase	Efficacy	References
Live attenuated chimeric yellow fever dengue vaccines	CYD-TDV	Sanof Pasteur	Replacing the prM/E gene of the YF17D virus with genes of the DENV1-4	Licensed	25–59%	Deng *et al.* (2020)
Live Attenuated rDEND30 Vaccines	TV003/TV005	NIAD/Butantan/Merck	Attenuation by truncating 30 nucleotides in the 30 UTR of DENV1, DENV3, DENV4, and a chimeric DENV2/DENV4	Phase III	Not yet released	Deng *et al.* (2020), Torres-Flores *et al.* (2022)
Live attenuated chimeric tetra-dengue vaccines	DENVax	Takeda/Inviragen	Replacing the coding sequences of DENV2 PDK-53 attenuated vaccine with that of DENV1, DENV3, and DENV4	Phase III	73.3–85.3%	Biswal *et al.* (2020), Deng *et al.* (2020), Torres-Flores *et al.* (2022)

are being studied in phase I trials. Phase 1 clinical trial with dose escalation and adjuvant formulation of this vaccine, designated V180, was conducted (Prompetchara *et al.* 2019).

Although various studies on vaccine production are reported there is currently no specific, effective, and safe dengue vaccine (Abidemi & Aziz 2020). Hence, reducing the mosquito population is the primary method of controlling the spread of DF. Use of personal and household protection (such as window screens, long-sleeved clothing, mosquito repellents, insecticide-treated bed nets, vaporizers and coils), administration of appropriate insecticides or predators to the outdoor water-holding containers, and open space insecticide spraying are all components of the vector control strategy. Mosquitoes adore stagnant water. They are unable to procreate and spread illness without it. The term 'water lying around' conjures up images of immobility, stillness, and stagnation. It also implied that the volume of water resting in the environment results in breeding grounds for *Ae. aegypti* mosquitoes, dengue mosquitoes, and possibly other diseases for people (McNaughton *et al.* 2018). *The Ae. aegypti* mosquitoes are drawn to the well's clear, pure water to deposit their eggs. Mosquitoes eat the microorganisms in well water. In addition, tap water contains chlorine ($Ca(OCl)_2$), a sanitizer. The capacity of mosquito eggs to hatch can be impacted by a number of active compounds found in water. When chlorine is added to water media, which has the potential to oxidize *Ae. aegypti* eggs, the hatching process may interfere (Prameswarie *et al.* 2023). We contend that this widely held belief is related to a larger logic that gave rise to the lay understanding, specifically that dengue mosquitoes are widespread

and breed in a range of environments and types of water. Numerous research has examined the effects of various control techniques, including vaccination, therapy, human self-defense, and vector controls utilizing larvicide and adulticide, on the dynamics of DHF transmission (Abidemi & Aziz 2020).

A suspected case and its 300 fatalities overwhelm the medical system in the Pakistani city of Lahore, which has a population of 496,490, where the greatest dengue epidemic happened in 2011. Incorporating interdisciplinary efforts from the Ministries of Health, Agriculture, Environment, and Horticulture, a Central Emergency Response Committee was created (Khan & Abbas 2014). Data were entered into a central patient tracking system for each confirmed case (Abdur Rehman *et al.* 2016). Technical endeavors, such as the development of online surveillance systems, global positioning systems, telephone-based surveillance systems, and a toll-free citizen hotline construction of isolation wards and highly dependent units (HDUs), provision of more beds, and hiring of medical personnel are all part of the transformation of the healthcare system (Khan & Abbas 2014; Abdur Rehman *et al.* 2016).

In 2011, dengue outbreaks were not limited to Lahore but were also common in other Punjab cities. Major public and private urban tertiary care hospitals with DF. In Sri Lanka and Thailand, healthcare personnel were trained and served as masters by a trainer (Khan & Abbas 2014). The city of Semarang in Indonesia claims a large number of dengue cases in the country. Another effective dengue prevention strategy is in Central Java. To regulate ascension, the State health department hires employees to monitor the dengue outbreak (DSWs) and enhance environmental management through community involvement, information sharing, planning, and vector control. In 2014, the DHF prevalence rate decreased by 92.4/100,000 population while the DSW was 18.14/100,000 population (Srisawat *et al.* 2022). Another type of Dengue management program called 'Tunggal Dara' is being carried out in Semarang City in cooperation with the Ministries of Education, religious hospitals, family welfare, and affairs, NGOs, and private businesses, Department of Sectors, Climatology and Meteorology, and Communities (Sayono *et al.* 2019). When comparing dengue case management, Bangkok Children's Hospital/Queen Sirikit National Institute of Children's Health (QSNICH) serves as a standard and receives high marks. Programs for dengue case management training have decreased the case fatality rate (CFR) in a number of nations. For instance, Thailand's, Timor-Leste's and Cambodia's (Kalayanarooj *et al.* 2017) (Figure 8).

Furthermore, we should create our own standards for the diagnosis, management, prevention, and treatment of dengue that the WHO or other prosperous nations may embrace. It is best to get consensus from multidisciplinary experts (Srisawat *et al.* 2022). Lessons from these effective dengue control initiatives should be used as a springboard for creating preventing dengue plans in other epidemic contexts. It is necessary to coordinate efforts across multiple sectors (health, education, environment, government, and community). An effective dengue prevention strategy leads to a fight against dengue worldwide through the use of a video conferencing system, international talks and experience sharing. Moreover, get professional advice on how to handle difficult and serious issues. The ADVA group is therefore aware of this issue. Additionally, they often host webinar series for dengue management that deliver well-informed, targeted, and customized results. Asian-wide initiatives could also have a big influence on dengue in Asia (Srisawat *et al.* 2022).

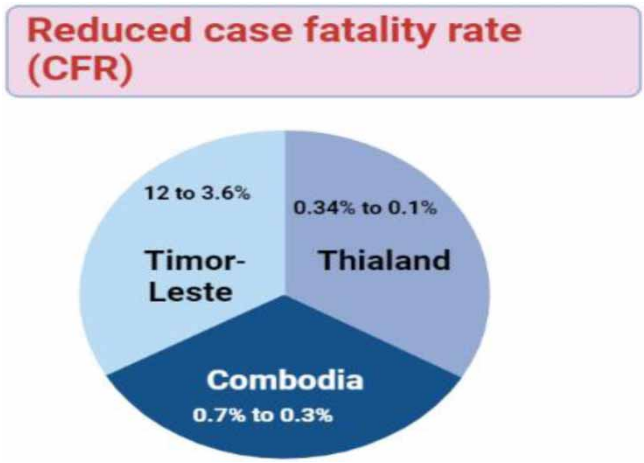


Figure 8 | The reduced case fatality rate (CPR) of dengue hemorrhagic fever. (Created with BioRender: Scientific Image and Illustration Software.)

11. CONCLUSION

DHF presents a formidable global health challenge due to the complexity of the DENV, its multi-system impact, and the absence of a specific treatment. Efforts to control DHF must encompass early diagnosis, vaccination development, and a multidisciplinary approach involving healthcare, education, and government sectors. Thus, DHF remains a pressing concern, demanding continued research and collaborative action to mitigate its impact on public health worldwide.

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DATA AVAILABILITY STATEMENT

All the relevant data is included in the paper.

CONFLICT OF INTEREST

The authors declare there is no conflict.

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