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Global Burden and Management of Dengue Virus Infection: Current Insights and Future Directions

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Abstract

Dengue virus (DENV) is a globally significant arthropod-bome virus belonging to the *Flaviviridae* family and the genus *Flavivirus*. DENV is an enveloped, positive-sense single-stranded RNA virus with a roughly spherical shape and diameter of approximately 50 nm. Dengue virus is primarily transmitted to humans through bites of infected female mosquitoes belonging to the *Aedes* genus. The virus has an incubation period of approximately 8 -12 days with its pathogenesis involving initial infection of the immune cells followed by systemic viral spread with severe disease resulting from immune-mediated mechanisms like cytokine forms antibody-dependent enhancement and endothelial dysfunction. The infection causes dengue fever and dengue shock syndrome which is usually characterized by increased vascular permeability, thrombocytopenia, vomiting, rash, organ failure, and death if left untreated. Dengue virus is widely distributed geographically whereby affects children and adolescents under the age of 15 years and a few adults, it also affects the male gender more than females due to behavioural factors, under occupation it affects outdoor workers especially farmers, construction workers and military personnel. DENV can be detected using clinical examinations, and laboratory diagnosis such as RT-PCR, and ELISA to detect the viral antibodies. Treatment of the virus involves the use of supportive therapy such as NSAIDs, adequate intake and use of antiviral drugs. Vectors control and vaccination can be used to prevent the outbreak of this virus. With coordinated efforts at local, national, and international levels, the burden of the dengue virus can be significantly reduced, improving health outcomes and saving lives worldwide.

Keywords: Dengue virus, Flavivirus, Pathogenesis, Diagnosis, Prevention, Treatment

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1. Introduction

Dengue virus (DENV) is a globally significant arthropod-borne virus belonging to the *Flaviviridae* family and the *Flavivirus* genus (Acioli-Santos, 2008). It is transmitted primarily by the bites of infected *Aedes* mosquitoes, especially *Aedes aegypti* and *Aedes albopictus*, which thrive in tropical and subtropical climates. Due to favorable environmental conditions and increasing urbanization, dengue has become endemic in more than 100 countries, affecting millions of people annually and posing serious public health challenges (Guzman et al., 2016).

There are four distinct serotypes of dengue virus: DENV-1, DENV-2, DENV-3, and DENV-4. These serotypes are antigenically unique but genetically related and are classified based on neutralization assays (Halstead, 2007). Infection with one serotype provides lifelong immunity to that specific serotype but only partial and temporary cross-immunity to others. This phenomenon

contributes to the risk of severe disease during subsequent infections with heterologous serotypes, a mechanism often linked to antibody-dependent enhancement (ADE) (Rothman, 2011).

The clinical spectrum of dengue infection varies widely, ranging from asymptomatic or mild illness to severe and potentially fatal conditions. The most common clinical presentation is dengue fever (DF), characterized by sudden onset of high fever, severe headache, retro-orbital pain, myalgia, arthralgia, rash, and mild hemorrhagic manifestations such as petechiae, epistaxis, and gingival bleeding (Acioli-Santos, 2008). Dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) represent the severe forms of the disease, marked by increased vascular permeability, plasma leakage, coagulopathy, thrombocytopenia, and in extreme cases, circulatory failure and death (WHO, 2009).

The global incidence of dengue has increased dramatically over recent decades. It is estimated that approximately 50 million infections occur annually, with over 2.5 billion people at risk of infection worldwide (Bhatt et al., 2013). The burden is particularly high in Southeast Asia, the Western Pacific, the Americas, and parts of Africa. In Asia, children under 15 years old are disproportionately affected by severe dengue, whereas in the Americas, adults tend to show higher rates of infection but with generally milder clinical outcomes (Halstead, 2007; Shepard et al., 2011).

Transmission dynamics of dengue virus are closely linked to the ecology of *Aedes* mosquitoes, which breed in artificial water containers commonly found in urban environments. The biting behavior of these mosquitoes, which tend to feed during daylight hours, complicates vector control efforts. Additionally, factors such as global travel, urban crowding, climate change, and inadequate vector control programs have contributed to the expansion of dengue's geographical range and epidemic potential (Guzman et al., 2016).

Currently, there is no specific antiviral treatment for dengue infection. Clinical management primarily focuses on early recognition and supportive care, including careful fluid management to prevent shock and other complications (WHO, 2009). Efforts to prevent dengue rely heavily on vector control strategies such as eliminating mosquito breeding sites, using insecticides, and promoting community engagement and personal protective measures like bed nets and repellents (Bhatt et al., 2013).

Vaccine development has made progress, with the first dengue vaccine, Dengvaxia (CYD-TDV), licensed in several countries. However, its use is limited by safety concerns in seronegative individuals and variable efficacy across serotypes (Sridhar et al., 2018). New vaccine candidates and antiviral agents are under development, highlighting the need for continued research to improve disease control.

Dengue virus remains a major global health threat, with complex epidemiology and clinical manifestations. Continued efforts in vector control, surveillance, clinical management, and vaccine development are critical to reducing the global burden of dengue.

1.1 History of Dengue Virus

Dengue virus (DENV) has a long and complex history, with evidence suggesting it has been affecting humans for centuries. The earliest clinical descriptions resembling dengue-like illness date back to the late 18th century. One of the first well-documented outbreaks was recorded in 1779–1780, occurring simultaneously in Asia, Africa, and North America, marking a significant spread of the disease across continents (Halstead, 2007; Simmons et al., 2012).

The name "dengue" is believed to have originated from the Swahili phrase "Ka-dinga pepo," meaning "cramp-like seizure caused by an evil spirit," reflecting the severe joint and muscle pains characteristic of the disease (Gubler, 1998). Throughout the 19th and early 20th centuries, dengue was often confused with other febrile illnesses such as chikungunya and influenza due to overlapping clinical symptoms and limited diagnostic tools.

Major dengue epidemics began to be documented as urbanization and global travel increased. In the early 20th century, dengue outbreaks became more frequent and severe, notably in Asia and the Americas. The spread of *Aedes aegypti*, the primary mosquito vector, was accelerated by expanding urban centers and improvements in transportation networks, which facilitated the global dissemination of the virus (Guzman and Harris, 2015).

The 20th century also saw significant advances in understanding the virology and epidemiology of dengue. In 1907, scientists successfully isolated dengue virus, which paved the way for experimental research on its transmission and pathogenesis (Halstead, 2007). Further classification of the virus into four antigenically distinct serotypes (DENV-1 to DENV-4) was accomplished in the mid-20th century, enabling better diagnostic and surveillance techniques (Kuno, 1997).

The emergence of severe dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) was first recognized during epidemics in the 1950s in the Philippines and Thailand, which marked a turning point in public health concerns regarding the disease (Gubler,

1998). These severe manifestations were later linked to secondary infections with different serotypes and immune mechanisms such as antibody-dependent enhancement (Halstead, 2007).

In recent decades, dengue has expanded both in geographical distribution and in disease burden. It is now endemic in over 100 countries, with tropical and subtropical regions facing recurrent epidemics affecting millions of people each year (Bhatt et al., 2013). This expansion is driven by factors such as urbanization, globalization, climate change, and inadequate vector control, which continue to challenge public health systems worldwide.

Efforts to combat dengue began in earnest in the late 20th and early 21st centuries, focusing on vector control, improved diagnostics, clinical management, and vaccine development. The first licensed dengue vaccine, Dengvaxia, was approved in 2015, though challenges remain regarding its safety and efficacy (Sridhar et al., 2018).

2. Viral Structure and Genome of Dengue Virus

Dengue virus (DENV) is a member of the genus *Flavivirus* within the family *Flaviviridae*. It is an enveloped, positive-sense single-stranded RNA virus with a roughly spherical shape and a diameter of approximately 50 nm (Mukhopadhyay et al., 2005). The virus particle (Figs. 1 & 2), or virion, exhibits an icosahedral symmetry and is composed of three structural proteins: the capsid (C), precursor membrane (prM), and envelope (E) proteins, as well as the viral RNA genome enclosed within.

Viral Genome

DENV's genome comprises a single-stranded positive-sense RNA of approximately 10.7 kilobases (kb). It contains a single open reading frame (ORF) flanked by untranslated regions (UTRs) at the 5' and 3' ends, which regulate translation and replication. The ORF encodes a polyprotein that is co- and post-translationally cleaved into three structural proteins (C, prM/M, E) and seven nonstructural proteins (NS1, N S2A, NS2B, NS3, NS4A, NS4B, NS5) that are essential for viral replication and assembly (Kuhn et al., 2002).

Capsid (C) Protein

The capsid protein is a small, highly basic protein that associates with the viral RNA to form the nucleocapsid core inside the virion. It plays a key role in packaging the viral genome and initiating viral assembly. The C protein oligomerizes to encapsulate the RNA, providing protection during transmission between host cells (Ma et al., 2004).

Envelope (E) Protein

The envelope protein is the major surface glycoprotein and is critical for viral attachment, entry, and fusion with host cells. It is arranged on the viral surface as 90 homodimers organized in a smooth, herringbone pattern on the mature virion, giving it icosahedral symmetry (Kuhn et al., 2002). The E protein mediates receptor binding and membrane fusion via pH-dependent conformational changes inside the host endosome, facilitating viral genome release into the cytoplasm (Modis et al., 2003).

Structurally, the E protein contains three distinct domains: DI (central domain), DII (dimerization and fusion domain), and DIII (putative receptor-binding domain). Domain III is implicated in binding to host cell receptors, while domain II contains the fusion loop essential for membrane fusion (Rey et al., 1995).

Precursor Membrane (prM) Protein

The prM protein is synthesized as a precursor to the mature M protein and plays a critical role in virus assembly and maturation. In immature virions, prM forms heterodimers with E protein, preventing premature fusion during viral egress (Zhang et al., 2003). During maturation in the trans-Golgi network, prM is cleaved by host furin proteases to form the M protein, which remains associated with the viral envelope and stabilizes the mature virion (Yu et al., 2008).

Lipid Envelope

The viral envelope is derived from the host cell's endoplasmic reticulum membrane and consists of a lipid bilayer embedded with the E and M proteins. This lipid envelope surrounds the nucleocapsid and is essential for infectivity, mediating interactions with host membranes during viral entry and exit (Mukhopadhyay et al., 2005).

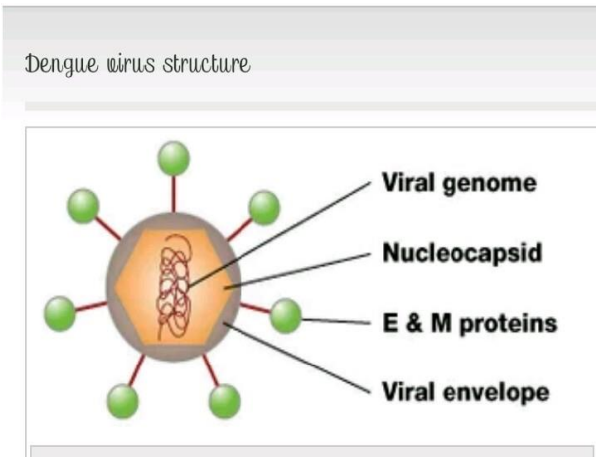

Figure 1: Structure of Dengue Virus
Source: Mukhopadhyay et al. (2005)

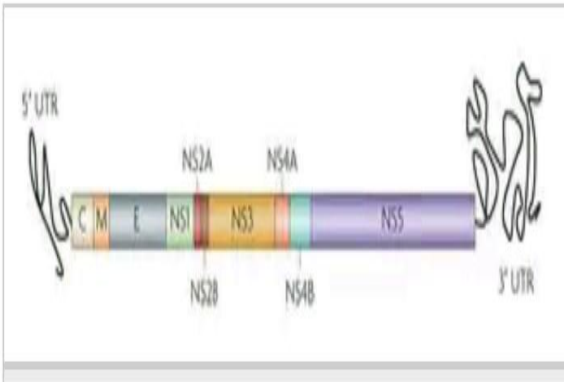

Figure 2: Genome structure of Dengue virus
Source: Kuhn et al. (2002).

2.1 Classification of Dengue Virus

Order	Unassigned
Family	*Flaviviridae*
Subfamily	Unassigned
Genus	*Flavivirus*
Species	*Dengue virus*
Vernacular Name	Dengue fever

2.2 Structural and Non-Structural Proteins of Dengue Virus and Their Functions

Dengue virus (DENV), a member of the *Flaviviridae* family, encodes a single polyprotein that is post-translationally cleaved into three structural and seven non-structural proteins (Table 1). These proteins play essential roles in viral replication, assembly, immune evasion, and pathogenesis.

Table 1: Structural and Non-structural proteins with their functions

Protein	Type	Main Function(s)
C	Structural	RNA genome encapsidation, nucleocapsid formation
prM/M	Structural	Chaperone for E protein, maturation of virions
E	Structural	Host receptor binding, membrane fusion, antigenicity
NS1	Non-Structural	RNA replication, immune modulation, secreted glycoprotein
NS2A	Non-Structural	RNA replication, virus assembly, immune modulation
NS2B	Non-Structural	Cofactor for NS3 protease activity
NS3	Non-Structural	Protease and helicase activities
NS4A	Non-Structural	Membrane remodeling for replication complex formation
NS4B	Non-Structural	Replication complex formation, immune evasion
NS5	Non-Structural	RNA polymerase, RNA capping and methylation

Source: Yu et al. (2008)

2.3 Virulent Genes of Dengue Virus

Dengue virus (DENV), comprising four distinct serotypes (DENV-1 to DENV-4), exhibits considerable genetic diversity, which plays a critical role in its virulence, epidemiology, and disease severity. Understanding the viral genes and mechanisms contributing to virulence is essential for unraveling the complex pathogenesis of severe dengue diseases, such as dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS).

One of the most widely discussed mechanisms behind severe dengue manifestations is Antibody-Dependent Enhancement (ADE). ADE suggests that non-neutralizing antibodies generated from a previous dengue infection can facilitate increased viral entry into host cells during a secondary infection with a heterologous serotype, thereby exacerbating disease severity. While this model has dominated the understanding of severe dengue pathogenesis, the evidence supporting ADE in humans remains indirect and controversial (Endy et al., 2004). The complexity of ADE highlights that the interaction between viral genetics and host immune response is not fully understood and may involve additional factors beyond antibody facilitation.

Epidemiological observations further challenge the ADE-centric model. Not all secondary dengue infections lead to DHF or DSS, and intriguingly, cases of tertiary and quaternary dengue infections have been reported without necessarily resulting in severe disease (Halstead et al., 2007). This indicates that other viral or host factors contribute significantly to disease outcome and suggests that dengue virulence cannot be solely attributed to secondary immune enhancement mechanisms.

At the genetic level, the four DENV serotypes diverge approximately 30% across their entire polyprotein sequence, reflecting significant variation in their genetic makeup (Westaway et al., 1997). Moreover, within each serotype, distinct genotypes or phylogenetic subtypes exist, which show different geographic distributions and

varying pathogenic potential. These genetic variations affect viral fitness, replication efficiency, immune evasion capabilities, and ultimately virulence in infected hosts.

Studies have indicated that specific mutations in structural and non-structural genes of DENV may influence viral replication and immune modulation, thus impacting virulence. For example, variations in the envelope (E) protein gene can alter viral binding affinity to host receptors or affect antibody neutralization, while changes in non-structural genes such as NS1 and NS5 may influence immune evasion and replication fidelity (Messer et al., 2003; Lin et al., 2004).

3. Mode of Transmission

Dengue virus (DENV) is primarily transmitted to humans through the bites of infected female mosquitoes belonging to the *Aedes* genus, particularly *Aedes aegypti* and *Aedes albopictus*. These mosquitoes are the main vectors responsible for spreading the virus in tropical and subtropical regions worldwide (Guzman and Harris, 2015). The transmission cycle begins when a mosquito bites a viremic person—that is, actively carrying the virus in their bloodstream. The virus then infects the mosquito's midgut, replicates, and disseminates to the salivary glands, making the mosquito infectious after an incubation period of approximately 8 to 12 days (Soo et al., 2016).

Once infectious, the mosquito can transmit DENV to other humans during subsequent blood meals. The mosquito remains infected for life, continually spreading the virus (Kyle and Harris, 2008). Importantly, dengue virus is not transmitted directly from person to person; human-to-human transmission occurs only via the mosquito vector (Center for Health Protection, 2012).

In endemic areas, the transmission cycle is maintained between mosquitoes and human hosts. Occasionally, non-human primates may act as reservoirs in sylvatic cycles, but the urban cycle involving humans and *Aedes aegypti* mosquitoes is responsible for the majority of dengue outbreaks (Vasilakis and Weaver, 2008). Environmental factors such as temperature, humidity, and rainfall significantly affect mosquito population dynamics and viral replication rates, influencing transmission intensity (Mordecai et al., 2017).

Vector control strategies aimed at reducing *Aedes* mosquito populations or preventing mosquito bites—such as eliminating breeding sites, insecticide use, and personal protective measures—remain central to interrupting dengue transmission (World Health Organization, 2023).

3.1 Viral Replication

The replication of the Dengue virus (DENV), a positive-sense single-stranded RNA virus belonging to the *Flaviviridae* family, occurs within host cells following a well-organized and multistep process. The virus utilizes host cellular machinery for entry, replication, assembly, and release, which is critical for understanding both its pathogenesis and the development of antiviral strategies.

1. Virus Attachment and Entry

Dengue virus initiates infection by binding to specific receptors on the host cell surface, primarily dendritic cells, monocytes, and endothelial cells. The viral envelope proteins, particularly the E (envelope) protein, mediate attachment to cell surface receptors such as DC-SIGN (Dendritic Cell-Specific Intercellular adhesion molecule-3-Grabbing Non-integrin) and mannose receptors. After attachment, the virus enters the cell via **clathrin-mediated endocytosis** (Perera-Lecoin et al., 2013; Iheukwumere *et al*., 2025a).

2. Fusion and Uncoating

Following internalization into endosomes, the acidic environment triggers a conformational change in the E protein, resulting in **fusion of the viral envelope with the endosomal membrane**. This process releases the viral RNA genome into the cytoplasm (Iheukwumere *et al*., 2025b).

3. Translation and Polyprotein Processing

Once in the cytoplasm, the viral RNA acts directly as messenger RNA (mRNA) and is translated by host ribosomes into a single long polyprotein. This polyprotein is then **cleaved by both viral and host proteases** into structural proteins (C, prM, E) and non-structural proteins (NS1 to NS5), each playing distinct roles in the viral life cycle (Lindenbach & Rice, 2003; Iheukwumere *et al*., 2025c).

4. Genome Replication

Replication occurs in membrane-bound replication complexes formed on the endoplasmic reticulum. The **non-structural proteins (especially NS3 and NS5)** play a key role in RNA synthesis. The viral RNA-dependent RNA polymerase (NS5) synthesizes a complementary negative-sense RNA template, which is then used to produce more positive-sense genomic RNA (Iheukwumere *et al*., 2025d).

5. Assembly and Maturation

Newly synthesized viral RNA is encapsidated by capsid proteins (C), and the nucleocapsid is enveloped by ER-derived membranes containing the prM and E proteins. The immature virions bud into the ER and are transported through the Golgi apparatus, where the prM protein is cleaved by **host furin protease**, converting immature virions into mature infectious particles (Zhang et al., 2003; Iheukwumere *et al*., 2025e).

6. Virus Release
Mature virions are transported to the cell surface in vesicles and released by **exocytosis**. These infectious particles can then go on to infect new cells, perpetuating the cycle (Iheukwumere *et al*., 2025f).

3.2 Pathogenesis
Dengue virus (DENV), a member of the *Flaviviridae* family and genus *Flavivirus*, causes a wide spectrum of disease in humans, ranging from asymptomatic infection and mild febrile illness to severe and potentially fatal conditions such as Dengue Hemorrhagic Fever (DHF) and Dengue Shock Syndrome (DSS). The pathogenesis of dengue is complex and multifactorial, involving viral, host immune, and genetic factors that together contribute to disease severity and outcome.

1. Viral Entry and Initial Infection
DENV is transmitted to humans via the bite of an infected female *Aedes* mosquito, primarily *Aedes aegypti*. After entering the bloodstream through the skin, the virus primarily targets **dendritic cells, monocytes, macrophages**, and **endothelial cells**. These cells serve as initial sites of viral replication (Wu et al., 2000; Iheukwumere *et al*., 2024a). Infected cells migrate to lymph nodes, leading to dissemination of the virus and viremia.

2. Viremia and Dissemination
The virus spreads systemically via the bloodstream, infecting a variety of immune and non-immune cells. High levels of viremia correspond with the febrile phase of the illness. During this period, patients may present with dengue fever (DF), characterized by **fever, headache, muscle and joint pain, rash, and mild bleeding manifestations (**Iheukwumere *et al*., 2024b).

3. Immune Response and Immunopathogenesis
The host immune response plays a dual role in controlling viral replication and contributing to disease severity:

Innate Immunity
Early production of **interferons (IFNs), cytokines, and chemokines** helps limit viral replication. However, an exaggerated innate immune response can lead to **cytokine storm**, contributing to vascular leakage and shock (Green & Rothman, 2006; Iheukwumere *et al*., 2024c).

Adaptive Immunity
T and B cells become activated, producing antibodies and cytotoxic responses. However, in secondary infections with a different DENV serotype, **non-neutralizing antibodies** from a previous infection may enhance viral entry into Fc receptor-bearing cells — a phenomenon known as **antibody-dependent enhancement (ADE)** (Halstead, 2003; Iheukwumere *et al*., 2024d). ADE increases viral replication and contributes to severe disease manifestations.

4. Endothelial Dysfunction and Plasma Leakage
A hallmark of severe dengue (DHF/DSS) is **increased vascular permeability**, leading to **plasma leakage**, hemoconcentration, and shock. This is thought to be mediated by the immune response, including **cytokines such as TNF-α, IL-6, IL-8, and IFN-γ**, and **complement activation**. Endothelial cells, while not always directly infected, are disrupted by immune mediators (Martina et al., 2009; Iheukwumere *et al*., 2024e).

5. Hemorrhagic Manifestations and Coagulopathy
Thrombocytopenia (low platelet count), impaired coagulation, and increased fibrinolysis contribute to the bleeding tendencies seen in DHF. Dengue virus affects **megakaryocyte development and platelet function**, and immune complexes may lead to **platelet destruction**. Liver involvement can further impair coagulation factor synthesis (Iheukwumere *et al*., 2024f).

6. Dengue Shock Syndrome (DSS)
When plasma leakage becomes severe, it leads to **hypovolemic shock** and multi-organ failure. DSS is a life-threatening condition requiring urgent fluid resuscitation. It commonly occurs in children in endemic regions, especially during secondary infections (Iheukwumere *et al*., 2025g).

7. Recovery and Long-Term Immunity
With supportive care, many patients recover fully. Long-term immunity is **serotype-specific**, meaning infection with one DENV serotype provides lifelong protection against that serotype but not against others. Subsequent infections with a different serotype increase the risk of severe disease due to ADE (Iheukwumere *et al*., 2025h).

3.3 Disease associated with dengue virus
Dengue virus (DENV) infection causes **dengue fever (DF)**, a widespread mosquito-borne viral illness prevalent in tropical and subtropical regions. Dengue fever presents with a range of clinical manifestations, from asymptomatic infection to severe and potentially fatal disease (Guzman and Harris, 2015).

The classical form, dengue fever, is characterized by an abrupt onset of high fever, severe headache, retro-orbital pain, muscle and joint pains (often called “breakbone fever”), rash, and mild bleeding manifestations such as petechiae or gum bleeding (WHO, 2023). The illness typically lasts 2–7 days and is self-limiting, but symptoms can be debilitating and lead to significant morbidity.

More severe forms of the disease are **dengue hemorrhagic fever (DHF)** and **dengue shock syndrome (DSS)**. DHF is characterized by increased vascular permeability, thrombocytopenia (low platelet count), hemorrhagic manifestations, and plasma leakage. DSS represents the most critical phase, marked by severe plasma leakage leading to hypovolemic shock, organ failure, and death if untreated (Halstead, 2007). These severe forms are more commonly associated with secondary infections by a different DENV serotype, a phenomenon explained in part by antibody-dependent enhancement (ADE), although the exact mechanisms are complex and still under investigation (Endy et al., 2004).
Dengue poses a significant public health challenge, with an estimated 50–100 million infections occurring globally each year, and approximately 500,000 cases of severe dengue requiring hospitalization (Bhatt et al., 2013). Children are particularly vulnerable to severe disease in endemic regions, especially in Asia, whereas in the Americas, severe dengue is increasingly reported among adults (Guzman and Harris, 2015).
Early recognition and supportive care, including fluid management, are crucial for reducing dengue-related mortality. Currently, no specific antiviral treatment exists, but dengue vaccines and vector control strategies are important components of disease prevention (WHO, 2023).

3.4 Clinical Manifestation

Dengue virus infection presents a wide clinical spectrum ranging from asymptomatic or mild illness to severe, potentially fatal disease. The clinical manifestations depend on factors such as the infecting serotype, host immune status, age, and presence of comorbidities.

1. Asymptomatic Infection

Many dengue virus infections remain asymptomatic, especially during primary infections. These individuals show no clinical signs but can still contribute to transmission cycles (Guzman and Harris, 2015).

2. Dengue Fever (DF)

Dengue fever is the most common clinical manifestation and typically presents after an incubation period of 4–10 days post-infection (Fig. 3). The illness usually lasts 2 to 7 days and includes:

- Sudden onset of high fever (up to 40°C/104°F)
- Severe headache, often retro-orbital (behind the eyes)
- Myalgia (muscle pain) and arthralgia (joint pain), often severe enough to cause the nickname “breakbone fever”
- Nausea, vomiting, and abdominal pain
- Maculopapular or petechial rash (Fig. 4), often appearing 3–5 days after fever onset
- Mild hemorrhagic manifestations such as petechiae, epistaxis (nosebleeds), and gum bleeding
- Fatigue and prostration lasting for several days to weeks

Most patients recover without complications; however, some may progress to more severe forms (WHO, 2023).

3. Dengue Hemorrhagic Fever (DHF)

DHF is a severe form of dengue characterized by increased vascular permeability, plasma leakage, and bleeding tendencies. It usually develops after the initial febrile phase, often between the third and seventh day of illness as the fever subsides. Clinical features include:

- Persistent vomiting and abdominal pain
- Mucosal bleeding (e.g., gums, gastrointestinal tract)
- Positive tourniquet test indicating capillary fragility
- Thrombocytopenia (platelet count $<100{,}000/mm^3$)
- Hemoconcentration due to plasma leakage (hematocrit increase of 20% or more)
- Pleural effusion and ascites due to plasma leakage into body cavities
- Hepatomegaly and liver tenderness

Early recognition and management are crucial to prevent progression (Halstead, 2007).

4. Dengue Shock Syndrome (DSS)

DSS represents the most severe manifestation of dengue infection and results from severe plasma leakage leading to hypovolemic shock. It is a medical emergency characterized by:

- Rapid and weak pulse, narrow pulse pressure (<20 mmHg)
- Cold, clammy skin and restlessness or lethargy
- Hypotension and signs of poor perfusion
- Organ dysfunction (e.g., liver failure, encephalopathy)
- Potential fatality without prompt treatment

DSS usually develops within 24–48 hours after the defervescence phase and requires immediate intensive supportive care including fluid resuscitation (WHO, 2023).

5. Other Manifestations

- **Neurological complications:** Though rare, dengue can cause encephalitis, meningitis, or Guillain-Barré syndrome.
- **Hepatic involvement:** Mild to moderate elevation of liver enzymes is common, with rare cases of fulminant hepatitis.
- **Cardiac manifestations:** Myocarditis and arrhythmias have been reported occasionally.

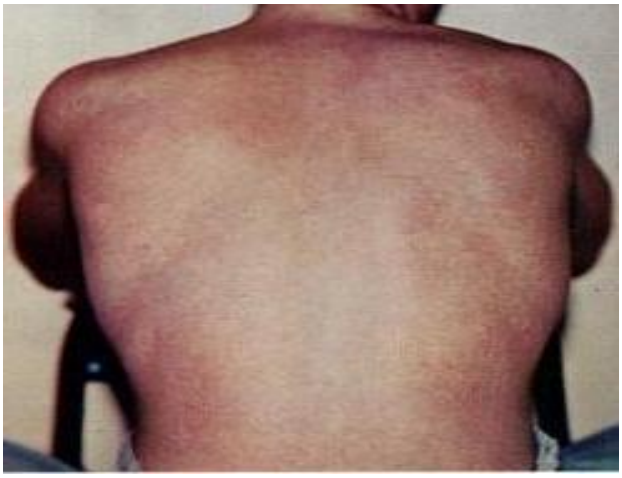

Figure 3: Patient with dengue virus rash
Source: World Health Organization, (2023)

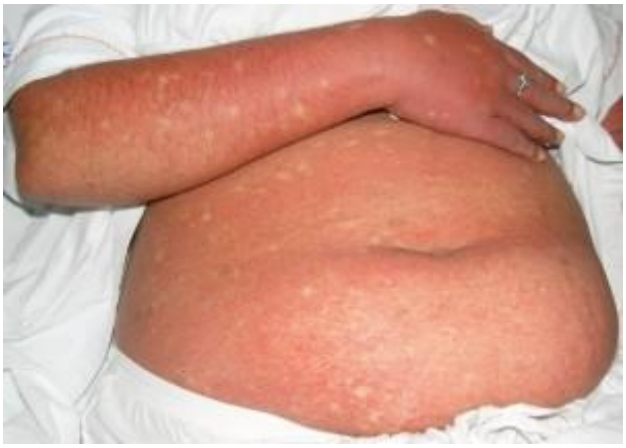

Figure 4: Patient suffering from petechiae
Source: World Health Organization, (2023)

4. Distribution of the Disease

Dengue virus (DENV) is a globally significant arbovirus responsible for dengue fever, with a broad and expanding geographical distribution primarily concentrated in tropical and subtropical regions. The distribution of dengue virus closely follows the habitats of its primary vectors, *Aedes aegypti* and *Aedes albopictus* mosquitoes, which thrive in warm, humid climates.

1. Temporal (Time) Distribution

Dengue virus transmission shows distinct temporal patterns, often linked to climatic and environmental factors.

- **Seasonality:** Dengue cases typically peak during and after the rainy season in endemic areas, when mosquito breeding sites proliferate due to increased water accumulation. For example, in Southeast Asia, dengue incidence rises from June to November, coinciding with the monsoon season (Gubler, 2011).
- **Epidemic cycles:** Outbreaks often occur in multi-year cycles, ranging from 3 to 5 years, influenced by the dynamics of herd immunity and viral serotype circulation (Kyle & Harris, 2008).
- **Long-term trends:** The overall global incidence of dengue has increased sharply over the past 50 years, associated with urbanization and globalization (Bhatt et al., 2013).

2. Age Distribution

The age distribution of dengue cases varies by region and epidemiological context:

- **Children and Adolescents:** In hyperendemic areas like Southeast Asia, dengue predominantly affects children under 15 years old, with severe forms such as dengue hemorrhagic fever (DHF) more common in this age group (World Health Organization [WHO], 2009).
- **Adults:** In the Americas and parts of South Asia, dengue infection is more frequent among adults, though recent years have seen increasing incidence among younger populations as well (Sharp et al., 2015).
- **Age-related severity:** Severity and mortality risk may be higher in younger children and the elderly due to differences in immune response and comorbidities (Halstead, 2007).

3. Sex Distribution

Sex differences in dengue infection rates and outcomes have been observed, though they vary by setting:

- **Incidence:** Many studies report a slightly higher incidence in males than females, possibly due to behavioral factors increasing exposure risk, such as outdoor activities (Aguilar et al., 2015).
- **Severity:** Some evidence suggests males may experience more severe dengue manifestations, but this is inconsistent and may relate to genetic and hormonal influences on immune responses (Sangkaew et al., 2021).
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4. Occupation Distribution

Occupation influences dengue risk through varying degrees of mosquito exposure:

- **Outdoor Workers:** People working outdoors or in environments conducive to mosquito breeding, such as agricultural workers, construction workers, and military personnel, have increased exposure risk (Manrique-Saide et al., 2015).
- **Urban Residents:** Individuals in urban occupations are also at risk due to the

peridomestic nature of *Aedes aegypti*, which thrives in human-made containers and habitats.

- **Indoor Exposure:** Some occupations with indoor work can have lower risk, but *Aedes aegypti* is a day-biting mosquito that frequently enters homes, so indoor transmission is still significant (Gubler, 2011)..

5. Place (Geographical and Environmental Distribution)

- **Urban vs. Rural:** Dengue is predominantly an urban and peri-urban disease due to the preference of *Aedes aegypti* for human-made breeding sites. However, rural outbreaks also occur, especially with *Aedes albopictus* acting as a secondary vector (Guzman & Harris, 2015).
- **Climate Zones:** Endemic in tropical and subtropical regions globally (Fig. 5). Transmission rarely occurs in temperate zones except during warm months or in localized outbreaks (Messina et al., 2014).
- **Microenvironment:** Within cities, dengue incidence varies between neighborhoods based on housing density, water storage practices, and vector control efforts (Erlanger et al., 2008).

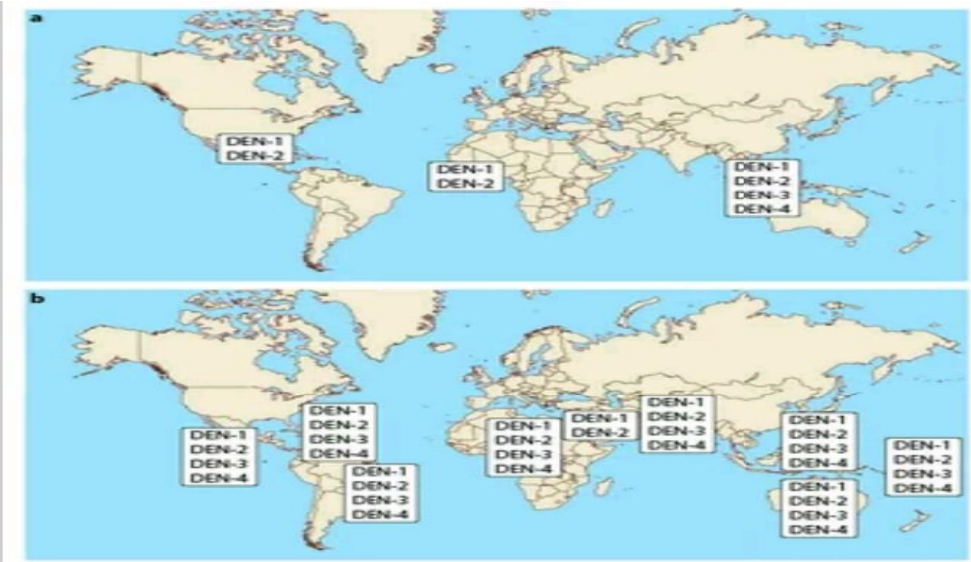

Figure 5: Distribution of the virus
Source: Gubler, (2011)

4.1 Diagnosis

Dengue virus (DENV) infection presents a significant public health challenge in tropical and subtropical regions of the world. It is transmitted by Aedes mosquitoes, primarily *Aedes aegypti*, and can result in a wide range of clinical manifestations—from mild febrile illness to severe complications such as dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS). Accurate and timely diagnosis is critical for appropriate clinical management, reducing fatality rates, and implementing effective vector control measures. Diagnostic methods for DENV include clinical assessment, direct detection of the virus or its components, and serological testing for host immune responses.

Clinical Diagnosis

The initial diagnosis of dengue is often clinical, especially in endemic areas during outbreaks. Dengue fever is typically suspected when a patient presents with acute febrile illness accompanied by symptoms such as retro-orbital pain, headache, myalgia, arthralgia, nausea, vomiting, rash, and sometimes mild hemorrhagic signs like petechiae or gingival bleeding. However, the clinical symptoms of dengue are nonspecific and may overlap with other tropical diseases like malaria, chikungunya, and leptospirosis (World Health Organization [WHO], 2009). For this reason, clinical diagnosis is often used as a preliminary screening tool, and laboratory confirmation is required for a definitive diagnosis.

Laboratory Diagnosis

Laboratory diagnostic methods for dengue are broadly categorized into direct and indirect approaches. Direct methods focus on detecting the virus or its components, while indirect methods involve identifying the host's immune response.

Direct Detection Methods

One of the most definitive direct methods is the reverse transcriptase polymerase chain reaction (RT-PCR), which is used to detect viral RNA in the blood. This method is most effective during the acute phase of infection, typically within the first five days of illness.

RT-PCR not only confirms the presence of the virus but can also identify the specific serotype, which is essential for epidemiological surveillance and outbreak response (Guzman and Harris, 2015; Iheukwumere *et al*., 2025i). Another widely used diagnostic tool is the detection of the nonstructural protein 1 (NS1) antigen. NS1 is a highly conserved glycoprotein secreted by all DENV serotypes and is detectable from the first day of fever up to the seventh day. NS1 antigen detection is available in the form of enzyme-linked immunosorbent assays (ELISAs) and rapid diagnostic tests (RDTs). These tests offer quick results, are easy to perform, and are particularly useful in settings with limited resources (Dussart et al., 2006).

Though less commonly used, virus isolation remains a gold standard for DENV diagnosis in research settings. It involves culturing the virus in mosquito cell lines or suckling mice, which requires specialized laboratory facilities and is time-consuming (Peeling et al., 2010).

Indirect Detection Methods (Serology)

Serological tests are based on the detection of dengue-specific antibodies. Immunoglobulin M (IgM) antibodies typically appear by the fifth day of illness and are indicative of a recent infection. IgG antibodies emerge later and indicate either a past infection or a secondary dengue infection. IgM-capture ELISA and IgG ELISA are the most commonly used serological tests. These assays are particularly useful for diagnosing dengue in the post-viremic phase when viral RNA and NS1 antigen may no longer be detectable (Priyamvada et al., 2016).
One limitation of serological testing is cross-reactivity with other flaviviruses such as Zika virus, which can lead to false-positive results. In such cases, more specific tests like the plaque reduction neutralization test (PRNT) may be required to confirm the diagnosis and determine the infecting serotype (Peeling et al., 2010; Iheukwumere *et al*., 2025j).

Combined Diagnostic Approach

A combined diagnostic strategy based on the stage of illness is recommended for effective detection of DENV. During the early phase (0–5 days), RT-PCR and NS1 antigen tests are preferred. For patients presenting after the fifth day of illness, IgM and IgG ELISA become more relevant. This stage-specific approach enhances diagnostic accuracy and facilitates timely patient management (WHO, 2009).

Point-of-Care Testing

Rapid diagnostic tests (RDTs) for NS1 and IgM/IgG have become increasingly popular, especially in low-resource settings. These tests provide results in under 30 minutes, require minimal equipment, and can be administered by non-specialized personnel. Despite their convenience, the sensitivity and specificity of RDTs can vary significantly depending on the manufacturer and local epidemiological conditions (Blacksell et al., 2011).

Differential Diagnosis

Due to the overlapping symptoms with other arboviral and bacterial infections, dengue must be distinguished from diseases such as chikungunya, Zika virus infection, typhoid fever, leptospirosis, and even COVID-19. Hence, laboratory confirmation is vital not only for accurate diagnosis but also for guiding public health interventions and clinical treatment strategies.

4.2 Treatment and Prevention

Dengue virus (DENV) infection poses a significant global health threat, particularly in tropical and subtropical regions where *Aedes aegypti* mosquitoes thrive. Despite its high morbidity and potential for severe complications such as dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS), dengue still lacks a specific antiviral treatment. As such, management primarily relies on supportive care, while prevention hinges on mosquito control, community awareness, and vaccination efforts.

4.2.1 Treatment of Dengue Virus Infection

Currently, there is no specific antiviral therapy approved for dengue virus. Treatment is largely supportive and aimed at managing symptoms, maintaining fluid balance, and preventing complications, particularly in severe cases.

Supportive Therapy

For mild dengue fever cases, treatment consists of rest, adequate fluid intake, and the use of antipyretics such as paracetamol to manage fever and pain. Non-steroidal anti-inflammatory drugs (NSAIDs), especially aspirin, are contraindicated because of their potential to worsen bleeding tendencies (WHO, 2009).

In moderate to severe dengue cases, especially those progressing to DHF or DSS, prompt hospitalization is crucial. The cornerstone of treatment is careful fluid management. Intravenous fluid therapy helps restore circulating volume and prevent shock due to plasma leakage. Electrolyte balance and hematocrit levels must be closely monitored, and in some cases, blood transfusions are required to manage severe bleeding (Gubler, 2002).

Management of Severe Dengue

Severe dengue is characterized by plasma leakage, severe bleeding, or organ impairment. These patients require close monitoring in an intensive care unit (ICU). The timely administration of colloids or crystalloids to manage shock is critical. Oxygen therapy and treatment of metabolic acidosis or coagulopathy may also be necessary. The use of corticosteroids is generally not

recommended due to lack of evidence for efficacy and potential adverse effects (Martina, Koraka, & Osterhaus, 2009).

4.2.2 Prevention of Dengue Virus Infection

Due to the absence of effective antiviral treatment, prevention is the most effective strategy for dengue control. Preventive measures fall into two major categories: vector control and vaccination.

Vector Control

Since *Aedes aegypti* mosquitoes are the primary vectors for dengue transmission, vector control remains the cornerstone of dengue prevention. Strategies include:

- **Eliminating Breeding Sites**: The most effective measure is the destruction or modification of mosquito breeding grounds such as stagnant water containers, flower pots, and discarded tires.
- **Insecticide Use**: Application of larvicides (e.g., temephos) and adulticides (e.g., pyrethroids) can reduce mosquito populations, though resistance is a growing concern.
- **Biological Control**: Some areas have employed the use of mosquito predators like larvivorous fish or bacteria such as *Bacillus thuringiensis israelensis* (Bti) to reduce larval populations (Guzman et al., 2016).
- **Personal Protection**: Individuals are encouraged to wear long-sleeved clothing, use mosquito repellents, and install mosquito nets or screens in their homes.

Community participation and intersectoral collaboration are essential for sustainable vector control. Public education campaigns on identifying and eliminating breeding sites have shown positive results in reducing dengue incidence.

Vaccination

A promising addition to dengue prevention is vaccination. The first dengue vaccine to be licensed was **CYD-TDV (Dengvaxia®)**, developed by Sanofi Pasteur. This live attenuated tetravalent vaccine has been shown to reduce the risk of severe disease and hospitalization in individuals with prior dengue exposure. However, it is not recommended for seronegative individuals due to the risk of severe dengue upon subsequent infection (World Health Organization, 2018).

More recently, other dengue vaccine candidates such as **TAK-003 (QDENGA™)** by Takeda and **TV003/TV005** developed by the U.S. National Institutes of Health (NIH) have shown encouraging results in clinical trials. TAK-003 has demonstrated high efficacy across multiple serotypes, including DENV-2, which is historically more virulent (Tricou et al., 2020).

Integrated Prevention Strategies

Combining vector control with vaccination, early diagnosis, and community engagement offers the best chance to reduce the burden of dengue. National and regional programs must incorporate surveillance systems, health education, and environmental management to ensure comprehensive prevention.

5. Conclusion

Dengue virus remains a significant global health threat, particularly in tropical and subtropical regions where *Aedes* mosquitoes thrive. The virus is responsible for a wide spectrum of diseases, ranging from mild dengue fever to life-threatening complications like dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS). Despite ongoing research, there is still no specific antiviral treatment, and current management is primarily supportive. The most effective strategies for combating dengue involve a combination of early diagnosis, efficient clinical management, robust vector control, and the use of vaccines where appropriate. Public health education, environmental sanitation, and global surveillance are essential to reduce transmission and prevent outbreaks. Continued investment in vaccine development, diagnostic innovations, and integrated mosquito management programs is crucial. With coordinated efforts at local, national, and international levels, the burden of the dengue virus can be significantly reduced, improving health outcomes and saving lives worldwide.

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