Review Article

Asian Pacific Journal of Tropical Biomedicine

apjtb.org

doi: 10.4103/2221−1691.383687

Impact Factor® 1.7

Recent advances on pathogenesis, diagnosis, prevention, immunological aspects, and vectors of dengue: A review

Mahesh Chandra Sahu[1]✉, Rakesh Kumar Samantaray[1], Aditi Pal[1], Sanghamitra Pati[2]

[1]*Division of Medical Entomology, ICMR−Regional Medical Research Centre, Chandrasekharpur, Bhubaneswar−751023, Odisha, India*

[2]*ICMR−Regional Medical Research Centre, Chandrasekharpur, Bhubaneswar−751023, Odisha, India*

ABSTRACT

Dengue is a vector-borne disease caused by the dengue virus (DENV) of family Flaviviridae. Dengue fever is common in both developed and developing countries. Globally, approximately 400 million cases of dengue fever are reported annually, resulting in approximately 22 000 fatalities. Dengue cases in India have progressively increased in the last decade. In recent years, substantial progress has been made in understanding various aspects of dengue, including its pathogenesis, diagnosis, prevention strategies, immunological responses, and the role of vectors in its transmission. The transmission of a positive RNA virus occurs through *Aedes* mosquitoes, specifically *Aedes aegypti* and *Aedes albopictus*. This virus is associated with a wide spectrum of symptoms, ranging from mild undifferentiated fever to severe hemorrhagic fever and shock, posing a potential threat to human health. There are 4 types of antigenically distinct dengue serotypes (DENV-1 to DENV-4) and among them, DENV-2 is more lethal and extremely severe. To overcome the severity of dengue, Dengvaxia is administered to children 9 to 16 years old with evidence of previous dengue infection. The diagnosis of dengue is carried out by ELISA-based non-structural protein (NS1) and immunoglobulin tests. However, there are no specific biomarkers to identify severe disease progression. Climatic factors and temperature play an important role in complex interaction among host, vector, and virus to manifest the severity of dengue. There is a need for the refinement of climate-based disease forecasting models in India to effectively control the spread of dengue. The mosquito repellent should be used periodically to kill or repel the *Aedes* mosquito to prevent the spread of dengue in humans.

KEYWORDS: Dengue; *Aedes* mosquitoes; Insecticide; NS1; Immunoglobulin

1. Introduction

Mosquitoes are the vectors for transmission of viruses causing severe flu-like diseases and a potentially fatal complication known as severe dengue[1]. Over the past 50 years, dengue cases have multiplied 30 times affecting around half of the world's population. Wide spread of dengue across 100 nations with an infection rate 50 to 100 million per year places over half of the world's population at risk and achieved the endemic disease status[2]. The bites of infected *Aedes* species mosquitoes transmit the dengue virus (DENV) to humans [*Aedes* (*Ae.*) *aegypti* or *Ae. albopictus*]. These mosquito species are responsible for the global spread of the Zika and chikungunya viruses. DENV belongs to the *Flavivirus* genus and the Flaviviridae family. It is an encapsulated, single-stranded RNA virus with positive-sense polarity. DENV has a nearly spherical shape with a diameter of approximately 50 nm. It consists of three structural proteins and seven non-structural (NS) proteins that have various functional roles. Cross-reactivity assays have identified four distinct serotypes of DENV (DENV1-4) and each is associated with unique antigenic properties[3]. While most serotypes share similarities in terms of genetic diversity, transmission dynamics,

✉To whom correspondence may be addressed. E-mail: mchsahu@gmail.com

How to cite this article: Sahu MC, Samantaray RK, Pal A, Pati S. Recent advances on pathogenesis, diagnosis, prevention, immunological aspects, and vectors of dengue: A review. Asian Pac J Trop Biomed 2023; 13(8): 325-338.

Article history: Received 9 March 2023; Revision 15 June 2023; Accepted 19 July 2023; Available online 23 August 2023

and epidemic potential, DENV-4 stands out due to its significant genetic distinctiveness. DENV exhibits two morphological forms: the intracellular immature virion and the mature virion. The mature virion contains two membrane-associated protein molecules, envelope (E) and membrane (M) proteins, which generate a relatively homogeneous external surface. In contrast, the intracellular immature virion consists of the E protein and a precursor membrane (prM) protein. During maturation, the prM protein undergoes proteolytic cleavage, resulting in the production of the M protein. This maturation process involves significant rearrangement of virus-encoded surface proteins, leading to an asymmetric positioning of the virion spikes, which occurs upon acidification. The prM protein is cleaved at residue 91 by furin or furin-like protease, generating the pr peptide and M protein. The M protein contains structural elements such as an N-terminal loop, an α-helical domain known as MH, and two transmembrane spans referred to as MT1 and MT2[4]. DENV infection is transmitted to humans through two main cycles: the urban and enzootic cycles. The urban cycle involves female mosquitoes, primarily *Ae. aegypti* and to a lesser extent *Ae. albopictus*, which are commonly found in domestic or peri-domestic environments[5]. These mosquitoes become infected when they feed on an already infected individual and subsequently transmit the virus to other individuals through subsequent bites. They prefer to bite humans throughout the day and are commonly found in indoor and outdoor environments near human populations. In contrast, the enzootic cycle primarily involves non-human primates residing in sylvatic habitats and arboreal mosquitoes, specifically *Ae. taylori* and *Ae. fucifer*.

Unlike many flaviviruses, DENV has a restricted distribution within its natural host range and primarily utilizes primates as amplification and reservoir hosts[6]. The urban transmission cycles occur within urban areas, where human reservoir hosts interact with mosquitoes serving as disease vectors. The larval maturation process of mosquitoes takes place near domestic water containers. DENV transmission does not occur through direct person-to-person contact. However, infected individuals can serve as carriers of the virus, facilitating its spread between countries or regions during the viremic phase when the virus replicates in the bloodstream. In recent years, substantial progress has been made in understanding various aspects of dengue, including its pathogenesis, diagnosis, prevention strategies, immunological responses, and the role of vectors in its transmission[7]. This review aims to provide an overview of the recent advances in these areas, highlighting key findings and advancements that have contributed to our knowledge of dengue.

2. *Aedes* as a dengue vector

Arthropod-borne viruses are responsible for a significant portion of the global burden of communicable human diseases, accounting for over 100 different diseases[8]. *Aedes* is a genus of mosquitoes (Culicidae family) that was originally localized to tropical and subtropical regions but is now distributed on all continents apart from Antarctica[9]. *Aedes* mosquitoes are easily recognizable due to the distinct black-and-white markings on their bodies and legs. They are known to bite humans during the daytime and are also attracted to artificial light sources. These mosquitoes exhibit a higher frequency of biting during the morning and evening hours. *Aedes* mosquitoes belong to the Animalia kingdom, Arthropoda phylum, Insect class, Diptera order, Culicidae family, and *Aedes* genus[10].

2.1. Classification of Aedes

Johann Wilhelm Meigen termed the genus *Aedes* its name in 1818. The generic name is derived from the ancient Greek word *Aedes*, which means "odious" or "unpleasant." According to historical definitions, the genus has around 700 species[11]. *Ae. aegypti* and *Ae. albopictus* are the main vectors responsible for transmitting the DENV.

2.2. Life cycle and characteristics of Aedes mosquito

Aedes mosquitoes undergo a complete metamorphosis, including distinct stages of egg, larva, pupa, and adult, making them holometabolous insects. The duration of the adult life cycle can vary depending on environmental conditions, typically ranging from two weeks to one month[12]. Most species of *Aedes* mosquitoes exhibit non-autogeny, meaning that females require a blood meal after mating to develop their eggs. After a full-blood meal, females can lay a significant number of eggs, usually ranging from 100-200 per batch. The quantity of eggs produced is influenced by the size of the blood meal consumed.

The eggs of *Aedes* mosquitoes are laid individually on moist substrates, often in areas prone to intermittent flooding, such as tree cavities and artificial containers. They are not laid in clustered groups but rather dispersed across multiple sites. The eggs are typically found at various distances above the water surface, indicating that the female mosquito does not deposit the entire batch of eggs in a single location[13].

The larvae of mosquitoes are commonly referred to as "wrigglers" or "wigglers" due to their observable sporadic movements in water when disturbed. The *Aedes* larvae respire oxygen using a siphon located at the posterior end, which is elevated above the water surface, while the remainder of the body is suspended in a vertical position. Larvae are commonly observed in residential environments, specifically in areas such as puddles, pots, cement tanks, tree holes, tires, or any other container that contains stagnant water. The process of larval development is influenced by temperature. The larvae undergo four distinct developmental stages, known as instars, with the first three instars being relatively brief, while the fourth instar can last up to three days. The fourth instar larvae exhibit a length of approximately eight millimeters and demonstrate robust feeding

behavior. Males typically undergo pupation at an earlier stage due to their comparatively accelerated developmental rate about females. *Ae. aegypti* may stay in the larval stage for months if the surrounding temperatures are cold until there is an adequate water source. Following the fourth instar, *Aedes* larvae transition into the pupal stage[14].

Pupae, alternatively referred to as "tumblers," exhibit an absence of feeding behavior and undergo a developmental process that typically spans a duration of approximately 2 to 3 days. Adults undergo emergence by ingesting air, which leads to the expansion of the abdomen, resulting in the splitting open of the pupal case. The emergence process involves the adult emerging head first[14,15].

Aedes adults can easily differentiate from other mosquitoes based on their physical characteristics. Their entire body is striped and particularly prominent on their legs, scutellum. Additionally, *Aedes* mosquitoes have short palpi and an abdomen that is either pointed or tapered, often displaying pale bands. Adult *Ae. aegypti* and *Ae. albopictus* mosquitoes are frequently distinguished based on the presence of white scale bands located on the dorsal region of the thorax. When considering *Ae. aegypti*, the observed pattern consists of two linear segments that are encompassed by curved lines resembling the shape of a lyre on either side. On the other hand, *Ae. albopictus* exhibits a singular expansive line of white scales located centrally on the thorax[14,16].

2.3. Transmission of disease by Aedes mosquitoes

Aedes mosquitoes are known to transmit various viral diseases in tropical regions of the Americas, Africa, and Asia[17]. Among these diseases, DENV is spread by two significant species, *Ae. aegypti* and *Ae. albopictus*. Both species have distinctive features, with *Ae. aegypti* exhibiting straight lines encircled by curved lyre-shaped lines on its thorax, while *Ae. albopictus* has a single broad line of white scales in the middle (Figure 1). The adult female *Aedes* mosquito typically lives for 20-30 days and lays around 60-100 eggs after feeding on blood from animals, including humans[18–20]. *Ae. aegypti* is the primary mosquito vector for dengue, chikungunya, and Zika viruses in tropical, subtropical, and temperate areas. These mosquitoes have adapted to live near human settlements, both in urban and rural settings, leading to multiple outbreaks of these diseases in recent years. Identifying mosquito species accurately is crucial for understanding disease transmission and implementing effective control measures. However, there is a shortage of experts in mosquito taxonomy, hindering the morphological identification process. *Aedes* mosquitoes, along with *Culex* species, are responsible for transmitting various arboviruses, including flaviviruses (such as dengue, yellow fever, and West Nile viruses), alphaviruses (like chikungunya and o'nyong-nyong viruses), and bunyaviruses (such as rift valley fever virus). The prevalence of arboviral diseases, particularly dengue, chikungunya, and Zika, has led to severe epidemics in different regions over the past decade. These diseases pose significant global public health challenges. Factors such as population growth, urbanization, globalization, travel, and climate change contribute to the transmission of these infections, especially among travelers returning to temperate regions[21,22]. Furthermore, as *Aedes* vectors can exist in temperate zones, infected travelers can initiate outbreaks in areas where these viruses are not endemic[23]. The three most prevalent arboviruses dengue, chikungunya, and Zika have resulted in several severe epidemics in France Polynesia and Latin America during the past ten years. Accurate identification of adult *Aedes* mosquito species is crucial for understanding disease transmission patterns and implementing effective control strategies. This is particularly important in light of the increasing global impact of these arboviral diseases[22].

3. Epidemiology

Vector-borne diseases (VBDs) pose a significant global health burden, with more than one billion human infections and one million deaths reported annually. Among these diseases, DENV is particularly concerning, as it has the potential to infect a substantial

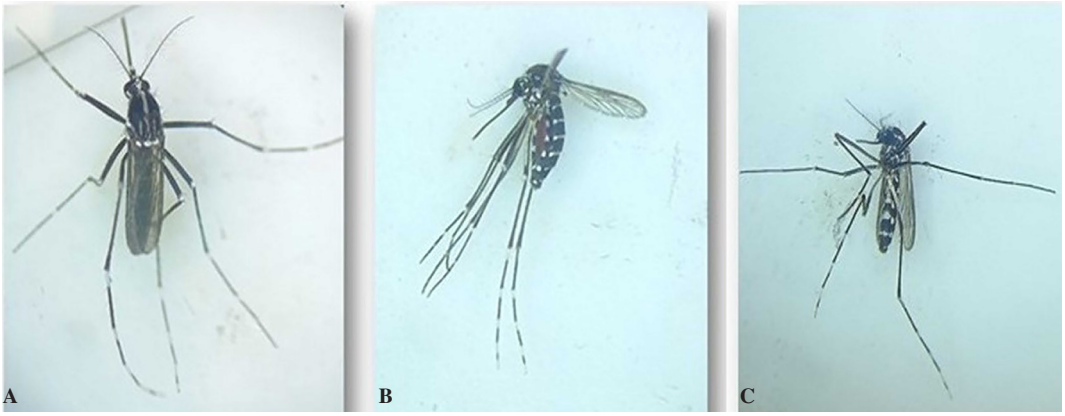

Figure 1. Dorsal side (A), lateral side (B), and ventral side (C) of *Aedes albopictus*.

portion of the global population. According to the World Health Organization, DENV can infect over 2.5 million people worldwide, which accounts for more than 40% of the global population[24,25].

Recent studies have provided estimates on the prevalence of dengue infections. It is believed that approximately 390 million dengue infections occur worldwide each year, with around 96 million of those cases manifesting symptoms. Moreover, an estimated 50 million individuals experience illness as a result of dengue infection annually. These numbers highlight the significant impact and widespread occurrence of dengue as a global health issue. Annually, it is estimated that there are approximately 390 million cases of DENV infections, resulting in over 500 000 hospitalizations and 25 000 deaths[26].

3.1. Dengue in India

The four DENV serotypes have all been prevalent in India at different times, but normally one serotype predominates during an outbreak because of the subcontinent's favorable environment. The dengue outbreak in Delhi in 1996 was mostly brought on by DENV-2 genotype IV isolates, which took the position of genotype V isolates from 1957 and 1967. In India, there were 16 000 cases and 545 fatalities during the 1996 epidemic[27]. Since 2010, the annual prevalence of dengue has increased to approximately 15 per million people in certain states. Dengue is currently widespread throughout all states and Union territories. Many states have reported recurring outbreaks during the previous three decades. In 2010, the World Health Organization reclassified the dengue outbreak in India from Category B to Category A. This suggests that the issue holds considerable implications for the field of public health. In 2016, a total of 0.13 million confirmed cases were recorded; in 2017, that number had increased to 0.19 million. The case fatality rate (deaths per 100 cases) has been maintained at 0.2% since 2015 after falling from 3.3% in 1996 due to better case management. From 2017 until the end of October 2022, a graphical representation of the total number of dengue cases registered in India and the number of people who died from the disease is presented (Figure 2)[28,29].

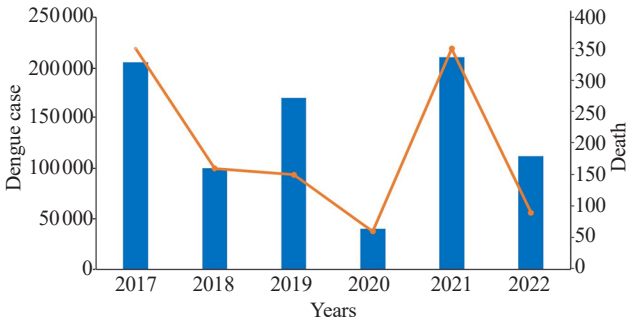

Figure 2. Dengue cases reported and death of patients by dengue from year 2017 to 2022 (till 31st October) in India.

3.2. DENV in different countries

Epidemics of dengue were recorded in East, West, and South Africa from the beginning of the 19th century. Dengue epidemics became an issue in Southeast Asian countries after World War II, partly due to urbanization[30]. There have been five significant dengue epidemics reported in African countries: Seychelles (1977-1979), Reunion Island (1977-1978), Djibouti (1992-1993), Comoros (1992-1993), and Cape Verde (2009)[31]. Since 1950, dengue epidemics have been reoccurring annually in Southeast Asian countries like the Philippines, Bangkok, Thailand, Bhutan, Brunei, Cambodia, East Timor, Indonesia, Laos, Malaysia, Myanmar, Singapore, and Vietnam[32,33]. Indonesia has the second-highest number of dengue cases between 2004 and 2010 behind Brazil. Serotype DENV-4 caused the majority of dengue incidents in Indonesia during 2009 and 2010. Dengue outbreaks can vary in intensity and occurrence from country to country and even within different regions of the same country. The first recognized dengue outbreak occurred in 1779-1780 in Asia, particularly in Indonesia, during which dengue-like symptoms were described[34].

The first documented outbreak in the Americas was reported in Cuba in 1827. Dengue outbreaks continued to be reported in Asia and the Americas throughout the 19th and 20th centuries, with varying levels of severity and geographic distribution. In the mid-20th century, the global spread of dengue became more pronounced due to increased international travel, urbanization, and the expansion of mosquito vectors[35]. In 2019, Brazil experienced a significant dengue outbreak, with over 1.5 million cases reported nationwide. In recent years, Brazil has been consistently dealing with dengue outbreaks, with varying levels of intensity. India has been facing dengue outbreaks regularly. The outbreaks usually occur during the monsoon season (June to September)[35] (Figure 3).

The number of reported cases has varied over the years. For example, in 2017, India experienced a significant outbreak, with over 180 000 cases reported. The Philippines has been a country highly affected by dengue outbreaks[36]. In 2019, the country declared a national dengue epidemic due to the high number of cases reported. Malaysia experiences dengue outbreaks almost every year, with varying severity. In recent years, Malaysia has implemented various strategies and interventions to control the spread of dengue, including community engagement and vector control measures. Thailand has a history of dengue outbreaks, particularly during the rainy season (May-October)[32]. The number of cases has varied over the years, with some years experiencing higher outbreaks than others. It is important to note that dengue outbreaks can occur in many other countries, including those in Southeast Asia, Latin America, and parts of Africa. The intensity and occurrence of outbreaks can vary depending on factors such as climate, population density, mosquito control measures, and public health interventions implemented by each country[37,38] (Figure 3).

It is important to note that the specific pathways and patterns of

Figure 3. Spreading of dengue and its outbreak in different countries.

dengue spread can vary depending on various factors, including local epidemiological situations, mosquito vector populations, surveillance capabilities, and public health interventions. Monitoring and controlling the movement of infected individuals, implementing mosquito control measures, and promoting public awareness and prevention strategies are crucial for reducing the global spread of dengue (Figure 4).

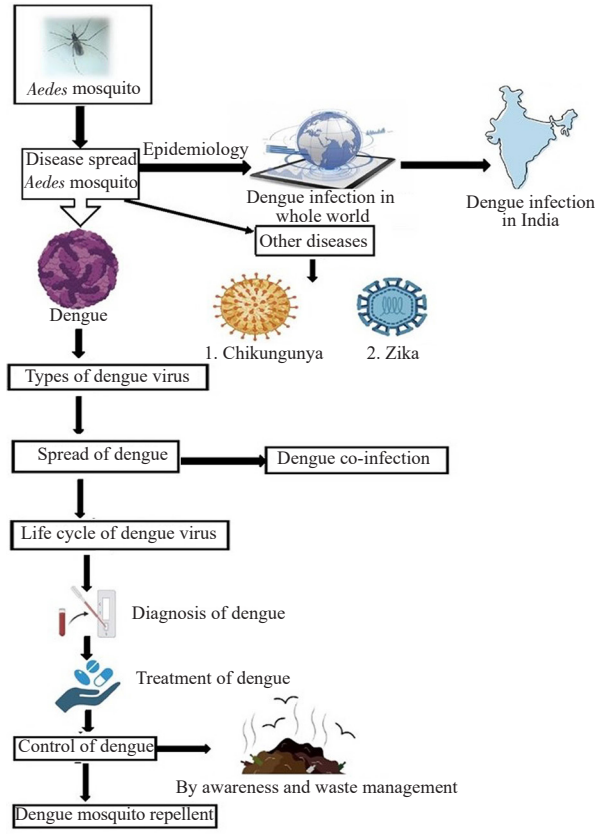

Figure 4. Spreading and control of dengue virus and their respective vectors.

4. Dengue

The most prevalent and possibly most significant arbovirus worldwide is the flavivirus known as DENV. *Aedes* mosquitoes transmit the DENV from an infected person to a healthy person[5]. In 1946, a "virus" was found to be the primary cause of dengue disease. More than 100 nations throughout Africa, Southeast Asia, the Americas, the western Pacific, and the eastern Mediterranean now have DENV endemic conditions, which originated in Africa. Although the clinical importance of apparent dengue infections has not yet been established, it is strongly believed that apparent dengue plays a significant part in maintaining dengue transmission in the absence of an epidemic. Researchers found that individuals with asymptomatic and pre-symptomatic DENV infections (low level of viremia) can infect mosquitoes through blood-feeding trials with *Ae. aegypti* mosquitoes[39]. There are four types of DENVs, and an individual can contract DENV up to four times. These four different serotypes (DENV-1, DENV-2, DENV-3, and DENV-4) are reported to circulate in the majority of endemic nations. In the blood of a patient in the Sarawak state of Malaysia, a newly found fifth serotype (DENV-5) was discovered for the first time in 2007[40,41]. The virus can cause mild dengue fever (DF), and more severe forms of the disease such as dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) when dengue infections become symptomatic. Only transient cross-protection to different serotypes is offered by primary infection, which provides lifelong serotype-specific protection. The symptoms of dengue normally appear 4-7 days (within a range of 3-14 days) after exposure, and the illness can manifest as anything from an asymptomatic infection to a serious and fatal condition (Figure 5). About one-third of infections are symptomatic, with the majority being asymptomatic or subclinical. Dengue is a term used

to describe patients who recover from a self-limited febrile illness, which is often characterized by fever, headache, retro-orbital pain, arthralgia, and myalgia. In endemic nations, children and infants bear the majority of the burden of severe dengue, which affects 1%-3% of dengue infections and has case fatality rates of between <1%-5%[41,42]. Epidemiologic research conducted in endemic areas revealed that the chance of developing a serious illness increases dramatically after contracting DENV after initial infection. However, there is a lack of agreement regarding risk factors for severe disease in travelers.

5. Types of DENV

5.1. DENV-1

The initial documentation of DENV-1 occurred in 1943 within the regions of French Polynesia and Japan, subsequently succeeded by reports originating from Hawaii in the years 1944 and 1945. Sudan holds the distinction of being the initial African nation to document the occurrence of the aforementioned event in the year 1984, and subsequent reports have been periodically documented thereafter. A large portion of the recorded incidents in the Americas can be attributed to the peak in DENV-1 reporting in 2005-2006, Pan American Health Organization[43].

5.2. DENV-2

In the 1990s, there was an upsurge in instances of more severe DHF in the Americas, probably as a result of the substitution of the American DENV-2 genotype with an imported and more virulent Asian one. DENV-2 was first identified in the Americas in 1953 in Trinidad and Tobago[44].

5.3. DENV-3

The Philippines and Thailand were the first countries to report DENV-3 in 1953. Since 1962, reports of DENV-3 have been made in Asia annually. Thailand most prominently reported DENV-3 every year between 1973 and 2010 although several Asian nations reported DENV-3 during the study period, with the most widespread reporting taking place between 1999 and 2002. The first reports in the Americas were in Puerto Rico in 1963, which continued to report DENV-3 until 1978, and then again from 1994-2008 owing to the introduction of a new DENV-3 genotype from Asia[45]. In Africa, very little DENV-3 has been documented since the initial reports in 1984-1985 in Mozambique, and incidence has generally been intermittent, except for more regular reports in Saudi Arabia between 1994 and 2009[46].

6. Transmission of dengue

DENV is primarily transmitted to humans through mosquito vectors. Mosquitoes become carriers of the virus after feeding on the blood of an infected individual. When an infected mosquito subsequently bites a healthy person, it can transmit the virus to them. It is important to note that dengue cannot be directly transmitted

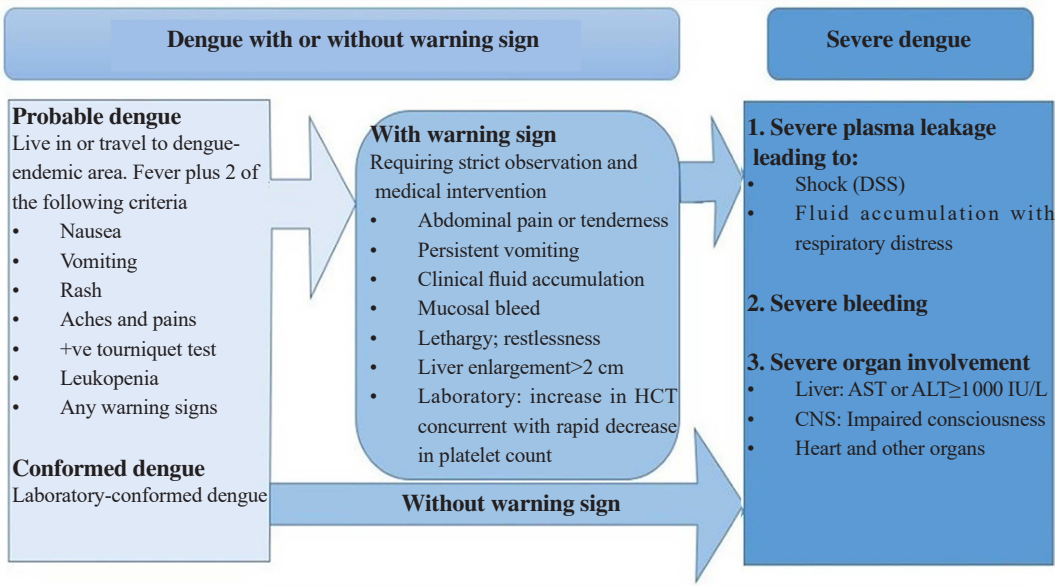

Figure 5. Classification of dengue disease progression. Criteria for dengue disease progression with and without warning signs are listed, as are the symptoms that define severe dengue. Adapted from WHO guidelines. Abbreviations: +ve, positive; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CNS, central nervous system; DSS, dengue shock syndrome; HCT, hematocrit.

from person to person, and mosquitoes are necessary for the transmission of the virus[47].

Among mosquito species, *Ae. aegypti* is the main vector responsible for dengue transmission and outbreaks. Other species such as *Ae. albopictus*, *Ae. polynesiensis*, and *Ae. scutellaris* have a limited potential to serve as dengue vectors. These mosquitoes are commonly found in and around human dwellings, as they prefer to breed near human habitation. The transmission cycle of dengue involves a human-to-mosquito-to-human pathway. After biting by an infected *Ae. aegypti* mosquito, viremia occurs, which is characterized by a high concentration of the DENV in the bloodstream. Viremia typically develops around four days after the mosquito bite and can last for up to twelve days. During the viremic phase, the person usually does not experience dengue symptoms[48] (Figure 6).

Around five days after the mosquito bite, the infected person starts showing symptoms of dengue fever, which can persist for about a week or longer. Meanwhile, the immature form of the virus ingested by the mosquito during the blood meal undergoes maturation within the mosquito's digestive tract during an incubation period of eight to twelve days. After this period, an infected mosquito can transmit the DENV to another individual when it feeds on their blood. It is worth noting that the DENV has been previously isolated from certain types of white blood cells known as polymorphonuclear leukocytes, which are believed to be phagocytic monocytes or macrophages, and non-adherent leukocytes from dengue patients[48] (Figure 7).

7. Life cycle of DENV

The DENV infection cycle initiates with the attachment of the virus to target cells through the interaction between viral surface proteins and cell surface attachment/receptor molecules (Table 1). This interaction enables the virus particle to be internalized *via* receptor-mediated endocytosis. The fusion of the viral envelope with the endosomal membrane allows the viral RNA to enter the cytoplasm. The viral genome, which is a single-strand positive sense RNA, functions as messenger RNA and is translated by the cell machinery to produce viral proteins. The genome undergoes replication, and new RNA copies are incorporated into developing viral particles. Assembly of DENV virions occurs in the endoplasmic reticulum, followed by transport through the trans-Golgi network (TGN) and secretion into the bloodstream[49].

The structure of DENV consists of a lipid envelope and two structural proteins, the M protein, and the E protein. The exterior glycoprotein shell is composed of closely packed 90 E protein head-to-tail homodimers, forming a 50-nm-diameter particle arranged in an icosahedral configuration at neutral pH and the normal temperature range in the mosquito vector. Within the late endosome of a host cell, three pH-sensing histidine residues in the *N*-terminal region of the M protein become protonated when the newly produced DENV enters. This triggers the separation of the M and E proteins, exposing the E protein fusion loop to the endosomal membrane. Interestingly, DENV-infected cells release a substantial number of developing virus particles. The interaction between viral surface proteins and cellular plasma membrane components is crucial for the recognition of viruses by target cells (Table 1)[50]. The presence and distribution of cell receptors directly impact the susceptibility of host tissues to the virus. Non-specific binding of the virus to attachment factors on the cell surface concentrates the virus and facilitates its attachment to specific receptors, which are specialized

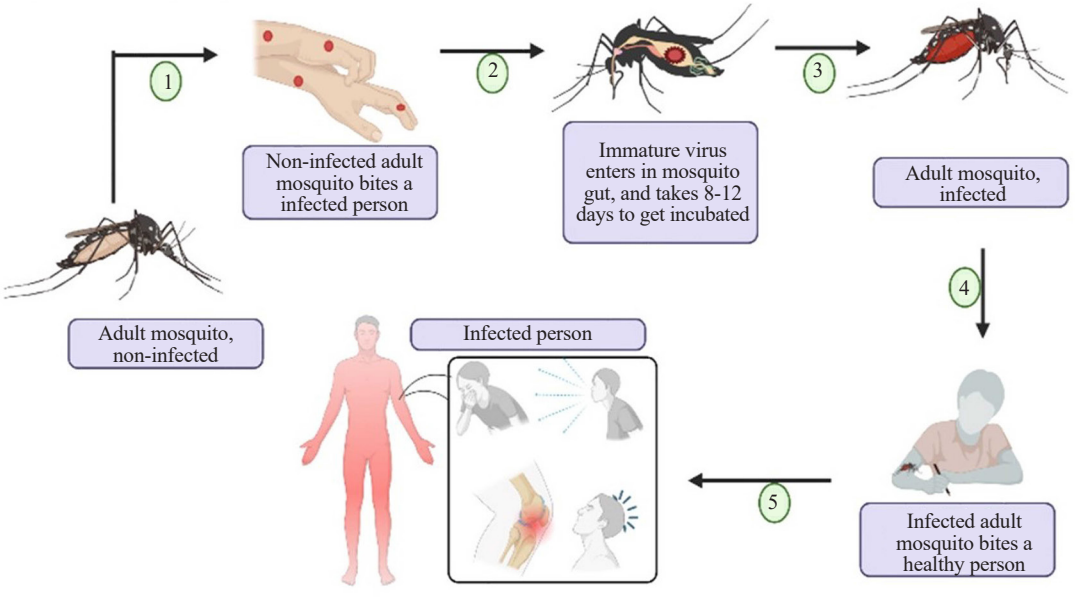

Figure 6. Transmission cycle of dengue virus from infected patient to healthy individual through *Aedes* mosquito.

molecules that promote viral entry into the target cell. The quantity and distribution of these receptors determine the sensitivity of host tissues to the virus[51]. It is important to note that these processes and interactions play a significant role in the DENV infection cycle, allowing the virus to enter and replicate within host cells[52].

8. Pathogenesis of dengue

The severity of DF can range from mild to severe, including DHF and DSS[53]. The pathogenesis of DENV infection is complex and not fully understood, involving interactions between the virus, host genes, and host immune responses. Certain factors such as comorbid conditions, gender, age, body mass index, genetic polymorphisms, and previous DENV-1 infection increase the likelihood of developing severe DHF and DSS. Severe DHF is characterized by abnormal blood coagulation, plasma leakage, and increased vascular fragility. The virus also enhances capillary permeability, resulting in fluid loss, hypovolemic shock, and organ failure in DSS[54,55].

Impaired hemostasis and plasma leakage are believed to contribute to the pathophysiological features of severe DHF. Although plasma loss and its complications have been observed in DF, it is still unclear how the virus triggers these effects. Interestingly, the severity of DENV infection peaks after the host immune system has cleared the virus rather than during the peak of viral load. The host immune response is considered a critical factor in the pathophysiology of DENV infection. Detection of DENV (-) senses RNA or NS3/ NS5 proteins in specific tissue cells may indicate active DENV replication, as these antigens are typically present during viral replication. On the other hand, the presence of other DENV antigens such as E, prM, C, and (+)-sense RNA may suggest non-specific uptake of viral RNA and antigens by cells from the environment[56].

Cells of the immune system and endothelial cells lining blood vessels play a crucial role in determining the tropism and severity of

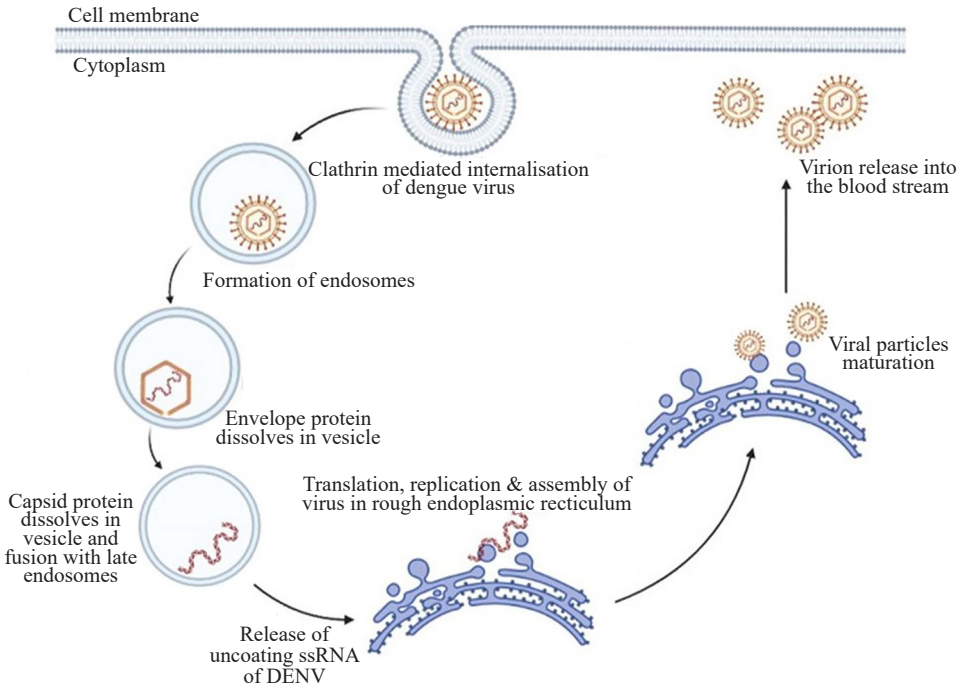

Figure 7. Dengue virus multiplication within the cell by using our cell machinery. DENV: dengue virus.

Table 1. Putative receptors for DENV in mammalian cells[49,50].

Receptor molecule	Type	Cell	Serotype
Heparan sulfate	GAG	Vero CHO K1	DENV 2
DC-SIGN	C-type lectin	Monocyte-derived dendritic cells	DENV1, 2, 3, and 4
CD14	Protein	Monocytes/macrophages	DENV 2
HSP90 HSP70	Protein	Monocyte-derived macrophages	DENV 2
Mannose receptor	Protein	Monocytes macrophages	DENV1, 2, 3, and 4
GRP78	Protein	HepG2	DENV 2
High-affinity laminin receptor	Protein	HepG2 PS Clone D	DENV1, 2, and 3
TIM-1	Protein	A549, Huh7 5.1, Vero	DENV2 and 3
Claudin-1	Protein	Huh-7, Huh 7.5	DENV 2
AXL	Protein	A549, Vero, human primary kidney, epithelial cells, human primary astrocytes	DENV 2 and/ or DENV 3

DENV pathogenesis. The infection of DENV in host cells, including macrophages, hepatocytes, and endothelial cells, significantly impacts hemostatic and immune responses. Infected cells undergo programmed cell death (apoptosis) and, to a lesser extent, necrosis, which releases toxic substances triggering coagulation and fibrinolytic systems. Hemopoiesis is inhibited, leading to reduced blood thrombogenicity, depending on the infection extent in bone marrow stromal cells and levels of cytokines like IL-6, IL-8, IL-10, and IL-18[57]. A high viral load in the bloodstream, viral tropism for endothelial cells, and impaired platelet function due to severe thrombocytopenia contribute to increased susceptibility of capillaries to rupture, leading to the development of DHF. Clinical manifestations of DHF include petechiae, easy bruising, and gastrointestinal mucosal bleeding[58].

9. Diagnosis of dengue

Infection with any of the four DENV serotypes can lead to a range of clinical outcomes, with the majority of infections being asymptomatic. However, in some cases, a moderate fever can progress to typical DHF and/or DSS. Classical DF presents as an acute illness that typically manifests 4-10 days after being bitten by an infected mosquito. Common symptoms include high fever (up to 40 ℃), severe headache, retro-orbital discomfort, malaise, intense joint and muscle pain, nausea, vomiting, and the appearance of a rash around 3-4 days after the onset of fever. Following initial infection, the individual develops immunity to that specific dengue serotype[59]. In newborns, primary infection can also lead to severe illness. DF in infants exhibits similar clinical signs during the acute febrile phase. However, during the defervescence phase, the patient's condition can rapidly deteriorate, leading to bleeding with or without vascular leakage. Symptoms may include bleeding, thrombocytopenia (platelet count <100 000/μL), ascites, pleural effusion, elevated hematocrit levels, severe abdominal pain, restlessness, vomiting, and a sudden drop in temperature accompanied by profuse sweating. Currently, there is no specific antiviral treatment for dengue, so therapy is primarily supportive. Fluid replacement is often effective in managing the symptoms of DHF and DSS[60]. Diagnosis of dengue can be challenging, as it relies on the patient's presentation and the stage of infection. Early in the illness, dengue can manifest as a mild, non-specific flu-like fever with symptoms that resemble other illnesses such as influenza, measles, Zika, chikungunya, yellow fever, and malaria. Infections with the DENV can be either asymptomatic or symptomatic. Approximately 20% of infections result in symptomatic illness, with a wide range of clinical presentations from mild to severe[7]. Fever is typically the initial symptom. The fever phase of the disease lasts between the second and seventh days and is characterized by facial flushing, generalized pain, myalgia, arthralgia, retro-orbital eye pain, photophobia, a rash called rubella form exanthema, and headaches. Sore throat, anorexia, nausea, and vomiting are also commonly observed. During this stage, a positive tourniquet test can help distinguish dengue from other infections with similar symptoms. Hemorrhagic symptoms may occur during the acute febrile phase, ranging from a positive tourniquet test and petechiae to spontaneous bleeding from the gastrointestinal tract, nose, mouth, and other mucosal sites. While virus isolation has been the traditional approach for diagnosing DENV infection, reverse-transcription polymerase chain reaction (RT-PCR) and more recently, NS1 antigen-capture enzyme-linked immunosorbent tests (ELISAs) have become increasingly utilized for faster diagnosis[61,62]. Blood samples taken from infected individuals within the first five days of fever provide the most accurate results. However, viral isolation from individuals with secondary infections is challenging due to the rapid production of cross-reactive antibodies early in the acute phase, which forms immune complexes with circulating viruses[63].

10. Co–infection with dengue

In April 2020, co-infection of SARS-CoV-2 and DENV was reported in Indonesia, marking the beginning of the pandemic. Since then, several new cases of co-infection have been identified. Given the dengue-endemic nature of many Asian countries, including those with limited resources, dengue and COVID-19 require special attention. Previously documented cases of co-infection include Reunion Island and Mayotte in France[64], with possible co-infections also observed in Asia. A study in Bangladesh found co-infection in 4 out of 20 patients, which was associated with a significant mortality rate. In India, both dengue and chikungunya diseases are increasingly prevalent. These viruses can co-circulate in regions where they are endemic. However, there have been limited investigations on DENV- chikungunya co-infection in the Punjab region of India. Among 3 160 samples collected from patients with probable dengue infection, 2 178 (68.92%) tested positive for DENV, while chikungunya IgM antibodies were detected in 127 samples (34.04%). Out of 283 samples examined for both viruses, 27 sera (9.54%) were positive for dengue and chikungunya co-infection[65].

It has been observed that dengue patients with bacterial co-infections exhibit significantly higher pulse rates, which contrasts with the finding of relative bradycardia in cases of isolated dengue fever. Furthermore, dengue patients with bacterial co-infections show a notable increase in total leukocyte count. In a study, bacteremia was detected in 5.5% of the 774 individuals diagnosed with DHF/DSS. Co-infections with organisms such as *Escherichia coli*, *Salmonella species*, *Klebsiella pneumoniae*, *Mycoplasma pneumoniae*, *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Mycobacterium tuberculosis*, *Shigella sonnei*, *Klebsiella ozaenae*, *Enterococcus faecalis*, *Rosemonas* species, *Haemophilus influenzae*, *Moraxella lacunata*,

Candida tropicalis, and herpes viruses have been reported in cases of dengue co-infection[66].

11. Some other diseases by *Aedes* mosquito

11.1. Chikungunya

Chikungunya virus (CHIKV) is an alpha-virus that is primarily transmitted by mosquitoes. It was first identified in Tanzania in 1952. In Africa, CHIKV circulates through an enzootic sylvatic cycle involving nonhuman primates, small animals, and *Aedes* mosquitoes. However, during epidemics, CHIKV can spread without the need for animal reservoirs. The virus was introduced into Asia, including India and Southeast Asia, around the 1950s, leading to significant outbreaks[67]. In 2013, the first locally transmitted case of CHIKV was reported in Saint Martin, marking its entry into the Americas. Subsequently, it rapidly spread to over 40 countries and territories across North, Central, and South America[68]. The incubation period for chikungunya is typically 2-4 days, although it can range from 1-14 days. The majority of chikungunya infections result in symptomatic illness, with more than 85% of individuals with serologic evidence of infection experiencing symptoms. The onset of chikungunya is characterized by high fever and severe symptoms, particularly debilitating arthralgia. Interestingly, the term "chikungunya" originates from a Makonde phrase that describes the stooped posture adopted by individuals suffering from severe joint pain[69].

11.2. Zika

Zika virus (ZIKV) is a flavivirus that was first identified in 1947 when it was isolated from a rhesus monkey in Uganda's Zika Forest. The first human cases were documented in 1952 in Uganda and Tanzania[70]. The incubation period for ZIKV is believed to be similar to other mosquito-borne flaviviruses. Unlike DENV and CHIKV, there is substantial evidence indicating that ZIKV can be transmitted directly from person to person. This includes horizontal transmission through sexual contact and vertical transmission from mother to fetus during pregnancy, with an estimated time range of 3-14 days. Sexual transmission has been observed in various scenarios, including male-to-female, male-to-male, and female-to-male transmission among returning travelers engaging in unprotected sexual intercourse, with male-to-female transmission being the most common. It is worth noting that sexual transmission can occur in individuals with symptomatic or asymptomatic infections. Additionally, research suggests that ZIKV can persist longer in semen compared to other bodily fluids such as cervical mucus, vaginal fluids, urine, and blood. Most ZIKV infections are asymptomatic, with serosurvey studies indicating that only around 19% of individuals infected with ZIKV report clinical symptoms[71].

12. Treatment of dengue

The primary treatment for DENV infection involves measures to manage fever, such as tepid sponging and the use of antipyretics for pain and fever control. Currently, there is no specific antiviral treatment available for dengue. However, researchers have studied sulfated polysaccharides derived from seaweeds, which have demonstrated high antiviral activity against DENV[72]. Two specific polysaccharide compounds, kappa/iota/nu carrageenan G3d, and the DL-galactan hybrid C2S-3, have shown efficacy against all DENV serotypes by blocking the virus's internalization into host cells through the interference with the host cell receptor heparin sulfate. Curdlan, another sulfated polysaccharide, has exhibited DENV suppression by directly binding to the viral E protein, modifying its structure, and reducing antibody-dependent enhancement and virus pathogenicity within the host. Additionally, a polysulfated component from the green seaweed *Caulerpa cupressoides* has been found to decrease the pathogenicity of DENV-1 infection *in vitro*[71]. Ribavirin, a guanosine analog, has shown inhibitory effects on DENV activity in host cells when used in combination with other nucleotide analogs (brequinar, INX-08189) by interfering with nucleoside synthesis[73]. Glycyrrhizin and its derivatives or modified products have been shown to inhibit DENV protein transport, post-translational modifications, and regulate interferon production. However, it is important to note that diagnostic procedures for dengue have limitations, and comprehensive testing may not be feasible in all healthcare settings. DF is recognized as a growing concern in terms of its geographic spread and severity[74].

13. Prevention and control of dengue

A live attenuated tetravalent dengue vaccine known as CYD-TDV (Dengvaxia) has received authorization in several countries, and numerous other dengue vaccine candidates are currently undergoing clinical studies[75]. Individuals returning to areas infested with *Aedes* mosquitoes should take precautions to avoid mosquito bites in order to minimize local transmission. Those experiencing symptoms should seek medical assistance promptly.

Ongoing efforts to reduce dengue transmission primarily focus on targeting the vector, employing a combination of chemical and biological methods to control *Aedes* mosquitoes, as well as managing breeding sites. Despite these efforts, the frequency of DF outbreaks continues to increase, and the endemic transmission of the disease is spreading geographically[76]. A new dengue vaccine has been approved for use in children aged 9-16 who have confirmed previous DENV infection and reside in dengue-endemic regions, including

certain U.S. territories and states. However, the vaccine is not recommended for use in visitors from the United States who are only temporarily visiting areas affected by dengue.

13.1. Activities for improving awareness

Awareness initiatives aimed at addressing VBDs have incorporated various strategies. These include:

Poster campaigns: The dissemination of posters with relevant information on VBDs to raise awareness among the community;

House-to-house awareness campaigns: Volunteers and healthcare workers visit households to educate residents about the importance of source reduction, which involves eliminating or managing mosquito breeding sites;

Distribution of notices/pamphlets/brochures: Providing informational materials to the community, such as notices, pamphlets, or brochures, to promote community engagement in efforts to reduce VBDs.

Social media campaigns: Utilizing social media platforms to disseminate information, raise awareness, and engage the community in discussions about VBD prevention and control. These initiatives aim to enhance public knowledge and participation in combating VBDs through targeted communication and community involvement[24].

13.2. Waste management

To address the issue of mosquito reproduction and associated health risks, waste management programs have been implemented. These programs aim to collect and properly dispose of waste to prevent water logging, which can serve as breeding grounds for mosquitoes. Inadequate garbage disposal has been identified as a contributing factor to this problem. Improperly discarded waste in public areas can lead to stagnant water accumulation, creating favorable conditions for mosquito breeding. This poses health risks to the community, as mosquitoes are known vectors for various diseases. By implementing effective waste management practices, such as regular waste collection, proper disposal methods, and awareness campaigns on responsible waste management, the aim is to mitigate the adverse health consequences associated with negligent waste disposal in public areas.

13.3. Dengue mosquito repellent

Essential oils derived from plant families such as Lamiaceae (mint family), Pinaceae (pine and cedar family), and Poaceae (aromatic grasses) have been widely recognized and utilized as insect repellents globally. These oils are commonly used in rural villages, where they are burned or hung in homes to deter insects. Many commercial repellents incorporate various plant essential oils for their aroma and repellent properties. Examples of these oils include peppermint, lemongrass, geraniol, pine oil, pennyroyal, cedar oil, thyme oil, and patchouli. Thyme oil, geraniol, peppermint oil, cedar oil, patchouli, and clove have demonstrated significant repellent activity against malaria, filarial, and yellow fever vectors, protecting for 60-180 min. These repellents can be applied topically or used as combustible materials to safeguard individuals or the environment from disease-carrying insects like mosquitoes. The use of repellents for personal protection is an essential component of integrated disease-vector control strategies[77].

Research has shown that liquid paraffin solutions containing lemongrass oil exhibit concentration-dependent repellency. Higher concentrations (20% and 25%) offer complete protection (100%) for up to one hour, while lower concentrations (1%-15%) provide temporary repellency. Concentrations of 10%-25% maintain significant protection (>90% repellency) for three hours. Citral, a component found in lemongrass oil, also demonstrates similar repellent effects when used at a concentration of 15% in liquid paraffin[78]. Furthermore, studies have indicated that liquid paraffin solutions of Hemizygia oil are more effective than emulsion formulations in repelling mosquitoes, even when using the same amount of oil.

14. Future perspective on dengue

Accurately predicting the future of dengue in the context of climate change is crucial for governments and public health experts to implement timely and preventive measures to protect the population from dengue outbreaks[79]. However, there are significant knowledge gaps that need to be addressed in this field. One important aspect is incorporating key socio-demographic factors such as travel patterns and demographic changes into the predictive models to obtain more precise estimates of future dengue prevalence[80]. While temperature is commonly associated with dengue transmission, it may not be the most relevant climatic factor in certain areas. Therefore, it is important to investigate other non-climatic factors that contribute to the presence of *Ae. aegypti* and *Ae. albopictus* mosquitoes, as well as the critical elements that trigger dengue transmission in these climatically favorable locations[19].

Efforts should be made to improve communication and collaboration between the research community and policymakers regarding the local drivers of dengue transmission. Coordinated initiatives are needed to facilitate frequent and effective exchanges of information to ensure that research findings are translated into actionable strategies for dengue prevention and control.

Conflict of interest statement

The authors declare that they have no conflict of interest.

Funding

This study received no extramural funding.

Authors' contributions

MCS developed the concept of the review article and contributed for writing the final version of the manuscript. Both RKS and AP prepared the images and reference settings. SP supervised the manuscript.

References

[1] Cucunawangsih, Lugito NPH. Trends of dengue disease epidemiology. *Virology* 2017; **8**. doi: 10.1177/1178122X17695836.

[2] Wilder-Smith A, Ooi EE, Vasudevan SG, Gubler DJ. Update on dengue: Epidemiology, virus evolution, antiviral drugs, and vaccine development. *Curr Infect Dis Rep* 2010; **12**: 157-164.

[3] Chaudhury S, Gromowski GD, Ripoll DR, Khavrutskii IV, Desai V, Wallqvist A. Dengue virus antibody database: Systematically linking serotype-specificity with epitope mapping in dengue virus. *PLoS Negl Trop Dis* 2017; **11**(2): e0005395.

[4] Pujar GV, Sethu AK, Bhagyalalitha M, Singh M. Dengue structural proteins as antiviral drug targets: Current status in the drug discovery & development. *Eur J Med Chem* 2021; **221**: 113527.

[5] Braack L, Gouveia de Almeida AP, Cornel AJ, Swanepoel R, De Jager C. Mosquito-borne arboviruses of African origin: Review of key viruses and vectors. *Parasit Vectors* 2018; **11**(1): 1-26.

[6] Weaver SC. Host range, amplification and arboviral disease emergence. *Arch Virol Suppl* 2005: **19**: 33-44.

[7] Wang WH, Urbina AN, Chang MR, Assavalapsakul W, Lu PL, Chen YH, et al. Dengue hemorrhagic fever–A systemic literature review of current perspectives on pathogenesis, prevention and control. *J Microbiol Immunol Infect* 2020; **53**(6): 963-978.

[8] Mayer SV, Tesh RB, Vasilakis N. The emergence of arthropod-borne viral diseases: A global prospective on dengue, chikungunya and zika fevers. *Acta Trop* 2017; **166**: 155-163.

[9] Lacour G. *Eco–physiological mechanisms and adaptive value of egg diapause in the invasive mosquito Aedes albopictus (Diptera: Culicidae)*. Belgium: Royal Belgian Institute of Natural Sciences; 2016.

[10]Abd S. Life cycle and cytogenetic study of mosquitoes (Diptera: Culicidae). Life cycle and development of Diptera. *Intech Open* 2020; **1**(7): 1-13.

[11]Huang YM. The subgenus *Stegomyia* of *Aedes* in the Afrotropical Region with keys to the species (Diptera: Culicidae). *Zootaxa* 2004; **700**(1): 1-20.

[12]Waldock J, Chandra NL, Lelieveld J, Proestos Y, Michael E, Christophides G, et al. The role of environmental variables on *Aedes albopictus* biology and chikungunya epidemiology. *Pathog Global Health* 2013; **107**(5): 224-241.

[13]Eldridge BF, Vector-Borne Disease Section Center for Infectious Diseases. *Biology and control of mosquitoes*. Sacramento: California Department of Public Health; 2008.

[14]Becker N, Petrić D, Zgomba M, Boase C, Madon MB, Dahl C, et al. Biology of mosquitoes. In: *Mosquitoes*. Springer, Cham: Fascinating Life Sciences; 2020.

[15]Snodgrass RE. The anatomical life of the mosquito. In: *Smithsonian miscellaneous collections*. Washington, USA: Smithsonian Institution; 1959, p. 1-87.

[16]Becker N, Petric D, Zgomba M, Boase C, Madon M, Dahl C, et al. *Mosquitoes and their control*. Berlin, Heidelberg: Springer; 2020.

[17]Surasiang T, Chumkiew S, Martviset P, Jamklang M. Mosquito larva distribution and natural Wolbachia infection in campus areas of Nakhon Ratchasima, Thailand. *Asian Pac J Trop Med* 2022; **15**(7): 314-321.

[18]Muktar Y, Tamerat N, Shewafera A. *Aedes aegypti* as a vector of flavivirus. *J Trop Dis* 2016; **4**(223): 2.

[19]Messina JP, Brady OJ, Pigott DM, Golding N, Kraemer MU, Scott TW, et al. The many projected futures of dengue. *Nat Rev Microbiol* 2015; **13**(4): 230-239.

[20]Das B, Ghosal S, Mohanty S. *Aedes*: What do we know about them and what can they transmit? Vectors and vector-borne zoonotic diseases. *Intech Open* 2018; **1**(11): 31.

[21]Chala B, Hamde F. Emerging and re-emerging vector-borne infectious diseases and the challenges for control: A review. *Front Public Health* 2021; **9**: 715759.

[22]Girard M, Nelson CB, Picot V, Gubler DJ. Arboviruses: A global public health threat. *Vaccine* 2020; **38**(24): 3989-3994.

[23]Rezza G. Dengue and chikungunya: Long-distance spread and outbreaks in naïve areas. *Pathog Global Health* 2014; **108**(8): 349-355.

[24]Mohd-Zaki AH, Brett J, Ismail E, L'Azou M. Epidemiology of dengue disease in Malaysia (2000-2012): A systematic literature review. *PLoS Negl Trop Dis* 2014; **8**(11): e3159.

[25]WHO. *A global brief on vector–borne diseases*. Geneva: World Health Organization; 2014.

[26]Oladipo HJ, Rabiu I, Tajudeen YA. Dengue virus and SARS-CoV-2 Co-infection dynamics: An emerging threat among African countries. *Ann Med Surg* 2022; **82**: 104398.

[27]Afreen N, Naqvi IH, Broor S, Ahmed A, Kazim SN, Dohare R, et al. Evolutionary analysis of dengue serotype 2 viruses using phylogenetic and Bayesian methods from New Delhi, India. *PLoS Negl Trop Dis* 2016; **10**(3): e0004511.

[28]Tsai CY, Lee K, Lee CH, Yang KD, Liu JW. Comparisons of dengue illness classified based on the 1997 and 2009 World Health Organization dengue classification schemes. *J Microbiol Immunol Infect* 2013; **46**(4): 271-281.

[29]Das B, Das M, Dwibedi B, Kar SK, Hazra RK. Molecular investigations of dengue virus during outbreaks in Orissa state, Eastern India from 2010 to 2011. *Infect Genet Evol* 2013; **16**: 401-410.

[30]Higuera A, Ramírez JD. Molecular epidemiology of dengue, yellow fever, Zika and Chikungunya arboviruses: An update. *Acta Trop* 2019; **190**: 99-111.

[31]Chen LH, Wilson ME. Yellow fever control: Current epidemiology and vaccination strategies. *Trop Dis Travel Med Vaccin* 2020; **6**: 1-10.

[32]Guo C, Zhou Z, Wen Z, Liu Y, Zeng C, Xiao D, et al. Global epidemiology of dengue outbreaks in 1990-2015: A systematic review and meta-analysis. *Front Cell Infect Microbiol* 2017; **7**: 317.

[33]Jing Q, Wang M. Dengue epidemiology. *Glob Health J* 2019; **3**(2): 37-45.

[34]Rogers D, Wilson A, Hay S, Graham A. The global distribution of yellow fever and dengue. *Adv Parasitol* 2006; **62**: 181-220.

[35]Junior JBS, Massad E, Lobao-Neto A, Kastner R, Oliver L, Gallagher E. Epidemiology and costs of dengue in Brazil: A systematic literature review. *Int J Infect Dis* 2022; **122**: 521-528.

[36]Kumar V, Gupta S, Khanna R. Dengue fever-a worldwide study. *J Med Pharm Allied Sci* 2021; **1**: 102-108.

[37]Slosek J. *Aedes aegypti* mosquitoes in the Americas: A review of their interactions with the human population. *Soc Sci Med* 1986; **23**(3): 249-257.

[38]Kayesh MEH, Khalil I, Kohara M, Tsukiyama-Kohara K. Increasing dengue burden and severe dengue risk in Bangladesh: An overview. *Trop Med Infect Dis* 2023; **8**(1): 32.

[39]Ten Bosch QA, Clapham HE, Lambrechts L, Duong V, Buchy P, Althouse BM, et al. Contributions from the silent majority dominate dengue virus transmission. *PLoS Pathog* 2018; **14**(5): e1006965.

[40]Roy SK, Bhattacharjee S. Dengue virus: Epidemiology, biology, and disease aetiology. *Can J Microbiol* 2021; **67**(10): 687-702.

[41]Anggriani N, Tasman H, Ndii MZ, Supriatna AK, Soewono E, Siregar E. The effect of reinfection with the same serotype on dengue transmission dynamics. *Appl Math Comput* 2019; **349**: 62-80.

[42]Mustafa M, Rasotgi V, Jain S, Gupta V. Discovery of fifth serotype of dengue virus (DENV-5): A new public health dilemma in dengue control. *Med J Armed Forces India* 2015; **71**(1): 67-70.

[43]Ramos-Castañeda J, Barreto dos Santos F, Martinez-Vega R, Galvão de Araujo JM, Joint G, Sarti E. Dengue in Latin America: Systematic review of molecular epidemiological trends. *PLoS Negl Trop Dis* 2017; **11**(1): e0005224.

[44]Dick OB, San Martín JL, Montoya RH, del Diego J, Zambrano B, Dayan GH. The history of dengue outbreaks in the Americas. *Am J Trop Med Hyg* 2012; **87**(4): 584.

[45]Vasilakis N, Weaver SC. The history and evolution of human dengue emergence. *Adv Virus Res* 2008; **72**: 1-76.

[46]Messina JP, Brady OJ, Scott TW, Zou C, Pigott DM, Duda KA, et al. Global spread of dengue virus types: mapping the 70 year history. *Trends Microbiol* 2014; **22**(3): 138-146.

[47]Pozzetto B, Memmi M, Garraud O. Is transfusion-transmitted dengue fever a potential public health threat? *World J Virol* 2015; **4**(2): 113.

[48]Carrington LB, Simmons CP. Human to mosquito transmission of dengue viruses. *Front Immunol* 2014; **5**: 290.

[49]Li L. *Structural studies of dengue virus maturation*. Purdue University; 2009.

[50]Cruz-Oliveira C, Freire JM, Conceição TM, Higa LM, Castanho MA, Da Poian AT. Receptors and routes of dengue virus entry into the host cells. *FEMS Microbiol Rev* 2015; **39**(2): 155-170.

[51]Shen WF, Galula JU, Liu JH, Liao MY, Huang CH, Wang YC, et al. Epitope resurfacing on dengue virus-like particle vaccine preparation to induce broad neutralizing antibody. *Elife* 2018; **7**: e38970.

[52]Zhang Y, Wen Z, Shi X, Liu YJ, Eriksson JE, Jiu Y. The diverse roles and dynamic rearrangement of vimentin during viral infection. *J Cell Sci* 2021; **134**(5): jcs250597.

[53]Gauri LA, Bhatnagar K, Sameja P, Nehara HR, Saini K, Dutt R, et al. Hematological indices as predictors of mortality in dengue shock syndrome: A retrospective study. *J Acute Dis* 2022; **11**(4): 150-155.

[54]Bhatt P, Sabeena SP, Varma M, Arunkumar G. Current understanding of the pathogenesis of dengue virus infection. *Curr Microbiol* 2021; **78**: 17-32.

[55]Khanam A, Gutiérrez-Barbosa H, Lyke KE, Chua JV. Immune-mediated pathogenesis in dengue virus infection. *Viruses* 2022; **14**(11): 2575.

[56]Begum F, Das S, Mukherjee D, Mal S, Ray U. Insight into the tropism of dengue virus in humans. *Viruses* 2019; **11**(12): 1136.

[57]Malavige GN, Jeewandara C, Wijewickrama A, Gunasinghe D, Mahapatuna SD, Gangani C, et al. Efficacy of rupatadine in reducing the incidence of dengue haemorrhagic fever in patients with acute dengue: A randomised, double blind, placebo-controlled trial. *PLoS Negl Trop Dis* 2022; **16**(6): e0010123.

[58]Sudarmaja IM, Swastika IK, Diarthini LPE, Prasetya IPD, Wirawan IMA. Dengue virus transovarial transmission detection in *Aedes aegypti* from dengue hemorrhagic fever patients' residences in Denpasar, Bali. *Vet World* 2022; **15**(4): 1149.

[59]De Alwis R, Williams KL, Schmid MA, Lai CY, Patel B, Smith SA, et al. Dengue viruses are enhanced by distinct populations of serotype cross-reactive antibodies in human immune sera. *PLoS Pathog* 2014; **10**(10): e1004386.

[60]Kalayanarooj S. Clinical manifestations and management of dengue/DHF/DSS. *Trop Med Health* 2011; **39**(4): S83-S87.

[61]Das B, Swain S, Patra A, Das M, Tripathy HK, Mohapatra N, et al. Development and evaluation of a single-step multiplex PCR to differentiate the aquatic stages of morphologically similar *Aedes* (subgenus: *Stegomyia*) species. *Trop Med Int Health* 2012; **17**(2): 235-243.

[62]Achee NL, Grieco JP, Vatandoost H, Seixas G, Pinto J, Ching-Ng L, et

al. Alternative strategies for mosquito-borne arbovirus control. *PLoS Negl Trop Dis* 2019; **4**(1): e0006822.

[63]de Souza Andrade A, Campos GS, Costa LFM, Monte-Alegre AF, Sardi SI. Development of monoclonal antibodies against prM of dengue virus 4. *Rev Ciênc Méd Biol* 2022; **21**(1): 40-45.

[64]Olive MM, Baldet T, Devillers J, Fite J, Paty MC, Paupy C, et al. The COVID-19 pandemic should not jeopardize dengue control. *PLoS Negl Trop Dis* 2020; **14**(9): e0008716.

[65]Kaur M, Singh K, Sidhu SK, Devi P, Kaur M, Soneja S, et al. Coinfection of chikungunya and dengue viruses: A serological study from North Western region of Punjab, India. *J Lab Phys* 2018; **10**(4): 443-447.

[66]Pandey M, Mittal H. Secondary infection in immuno-competent children with dengue: Case series. *Indian J Child Health* 2014; **1**: 74-77.

[67]Cecilia D. Current status of dengue and chikungunya in India. *WHO South-East Asia J Public Health* 2014; **3**(1): 22-27.

[68]Caminade C, McIntyre KM, Jones AE. Impact of recent and future climate change on vector-borne diseases. *Ann New York Acad Sci* 2019; **1436**(1): 157-173.

[69]Weaver SC, Osorio JE, Livengood JA, Chen R, Stinchcomb DT. Chikungunya virus and prospects for a vaccine. *Expert Rev Vaccin* 2012; **11**(9): 1087-1101.

[70]Ioos S, Mallet HP, Goffart IL, Gauthier V, Cardoso T, Herida M. Current Zika virus epidemiology and recent epidemics. *Med Mal Infect* 2014; **44**(7): 302-307.

[71]Mitchell PK, Mier-y-Teran-Romero L, Biggerstaff BJ, Delorey MJ, Aubry M, Cao-Lormeau VM, et al. Reassessing serosurvey-based estimates of the symptomatic proportion of Zika virus infections. *Am J Epidemiol* 2019; **188**(1): 206-213.

[72]Wei Q, Fu G, Wang K, Yang Q, Zhao J, Wang Y, et al. Advances in research on antiviral activities of sulfated polysaccharides from seaweeds. *Pharmaceuticals* 2022; **15**(5): 581.

[73]de Mariz e Miranda LS. The synergy between nucleotide biosynthesis inhibitors and antiviral nucleosides: New opportunities against viral infections? *Arch Pharm* 2023; **356**(1): 2200217.

[74]Guzman A, Istúriz RE. Update on the global spread of dengue. *Int J Antimicrob Agents* 2010; **36**: S40-S42.

[75]LeFevre I, Bravo L, Folschweiller N, Medina EL, Moreira Jr ED, Nordio F, et al. Bridging the immunogenicity of a tetravalent dengue vaccine (TAK-003) from children and adolescents to adults. *NPJ Vaccin* 2023; **8**(1): 75.

[76]Ebi KL, Nealon J. Dengue in a changing climate. *Environ Res* 2016; **151**: 115-123.

[77]Castillo RM, Stashenko E, Duque JE. Insecticidal and repellent activity of several plant-derived essential oils against *Aedes aegypti*. *J Am Mosq Control Assoc* 2017; **33**(1): 25-35.

[78]Hazarika H, Krishnatreyya H, Tyagi V, Islam J, Gogoi N, Goyary D, et al. The fabrication and assessment of mosquito repellent cream for outdoor protection. *Sci Rep* 2022; **12**(1): 2180.

[79]Endy TP, Yoon IK, Mammen MP. Prospective cohort studies of dengue viral transmission and severity of disease. *Dengue Virus* 2010; **1**: 1-13.

[80]Waheed I, Khalid S, Jamil Z. Predictors of complicated dengue infections in endemic region of Pakistan. *Asian Pac J Trop Med* 2022; **15**(11): 496-502.

Publisher's note