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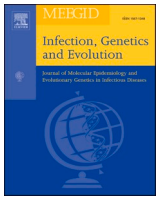

Review

Dengue virus: Etiology, epidemiology, pathobiology, and developments in diagnosis and control – A comprehensive review

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ABSTRACT

Dengue flavivirus (DENV) is the virus that causes dengue, one of the most dangerous and common viral diseases in humans that are carried by mosquitoes and can lead to fatalities. Every year, there are over 400 million cases of dengue fever worldwide, and 22,000 fatalities. It has been documented in tropical and subtropical climates in over 100 nations. Unfortunately, there is no specific treatment approach, but prevention, adequate awareness, diagnosis in the early stages of viral infection and proper medical care can reduce the mortality rate. The first licensed vaccine for dengue virus (CYD Denvaxia) was quadrivalent, but it is not approved in all countries. The primary barriers to vaccine development include inadequate animal models, inadequate etiology mechanistic studies, and adverse drug events. This study provides current knowledge and a comprehensive view of the biology, production and reproduction, transmission, pathogenesis and diagnosis, epidemiology and control measures of dengue virus.

1. Introduction

Arboviruses can infect hosts that are invertebrate or vertebrate. Because viral populations are genetically diverse, RNA viruses typically show a high degree of environmental adaptation. The creation of new harmful viruses is one effect of this flexibility. Viruses that naturally shift between hosts are thought to evolve more slowly than viruses that are host-specific (Villordo et al., 2015; Villordo et al., 2016; Nanaware et al., 2021). Based on their affiliation with a particular vector, the broad group of viruses known as flaviviruses is classified into three categories: tick-borne, mosquito-borne, and unknown (Best, 2016; Choumet and Desprès, 2015). Numerous mosquito species can transmit mosquito-borne flaviviruses, which are positive-sense single-stranded RNA viruses belonging to the Flaviviridae family of viruses. Common mosquito-borne flaviviruses that are important to human health are West Nile virus (WNV), Yellow fever virus (YFV), Dengue virus (DENV), Zika virus (ZIKV), and Japanese encephalitis virus (JEV). Human populations are now more exposed to mosquito vectors due to environmental and ecosystem changes, which raises the risk of contracting these flaviviruses (Qian and Qi, 2022; Savidis et al., 2016; Vázquez-Calvo et al., 2017). Annually, over 400 million people worldwide are infected with flaviviruses. The symptoms of flavivirus infections spread by mosquitoes can vary from a low-grade fever and arthralgia to serious damage to the liver, kidney, or brain. Neurotropic viruses that can penetrate the blood-brain barrier and infect nerve cells include WNV, JEV, and ZIKV. Visceral viruses, including YFV, infect different kinds of cells and harm the corresponding organs by causing conditions like hepatitis. Endothelial cells are susceptible to DENV infection, which may result in hemorrhagic symptoms. While some mosquito-borne flaviviruses can be vaccinated against, their effectiveness is diminished in certain populations due to restricted function and inadequate coverage in epidemic areas (Qian and Qi, 2022; Murrell et al., 2011; Redoni et al., 2020;

Abbreviations: DENV, Dengue flavivirus; WNV, West Nile virus; YFV, Yellow fever virus; ZIKV, Zika virus; JEV, Japanese encephalitis virus; DF, Dengue fever; DHF, Dengue hemorrhagic fever; DSS, Dengue shock syndrome; TGN, Trans-Golgi network; CLRs, C-type lectin receptors; Hsp70, Heat shock protein 70; ER, Endoplasmic reticulum; RER, Rough endoplasmic reticulum; IFN, Interferon; DCs, Dendritic cells'; TLRs, Toll-like receptors; RIG-I, Retinoic acid-inducible gene I; NK, Natural killer; PCR, Polymerase chain reaction; NS1, Non-structural protein 1; HI, Hemagglutination inhibition; WHO, World Health Organization; USVI, U.S. Virgin Islands; ADE, Antibody-dependent enhancement.

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Vervaeke et al., 2015). Dengue fever (DF) is caused by the dengue virus (DENV), a member of the Flaviviridae family and the most common arthropod-borne viral disease in humans. Humans are primarily infected with four DENV serotypes (DENV 1–4) through the *Aedes aegypti* mosquito. Widespread epidemics are caused by mosquito-borne DENV 1–4 serotypes, putting around 40 % of the world's population at risk of infection (Zhao et al., 2015; Mustafa et al., 2015). A variety of clinical illnesses are brought on by DENV infection, ranging from a life-threatening hemorrhagic and capillary leak condition known as dengue hemorrhagic fever/dengue shock syndrome (DHF/DSS) to an acute, self-limiting, disabling illness (DF) (Ross, 2010; Halsey et al., 2012; Haroon et al., 2019). In the twentieth century, epidemics were reported in Southeast Asia and the Pacific, which gained importance and attention with the increased spread of the dengue virus vector mosquito *Aedes aegypti*. This was associated with the circulation of four DENV serotypes and the emergence of dengue hemorrhagic fever (DHF). In the 1970s, DHF was one of the main causes of death among children in areas where DHF was present. Since then, epidemics have become more frequent and severe, covering a larger geographical area. Although major epidemics were not experienced in African regions before the 1980s, all four DENV serotypes are now present there. In tropical and subtropical nations, DENV continues to be a public health concern (Urcuqui-Inchima et al., 2010; Gossner et al., 2022; Niu et al., 2020). According to the World Health Organization, half of the world's population is at risk of contracting dengue fever (DENV), which is mostly prevalent in tropical and subtropical urban and semi-urban settings. Due to a continuing outbreak and an unanticipated surge in cases, more than five million illnesses were reported in more than 80 countries in 2023. More than 5000 DENV-related fatalities have been documented in more than 100 countries throughout five WHO regions; in 2023, Brazil, Peru, and Bolivia reported the most instances. A number of African nations, including Angola, Burkina Faso, Chad, Côte d'Ivoire, Egypt, Ethiopia, Guinea, Mali, Mauritius, Sao Tome and Principe, Senegal, and Sudan, have also recorded dengue epidemics. Public health concerns have been highlighted by the 2023 dengue case rise, which calls for concerted efforts to implement efficient preventative and control methods. The dengue outbreak in Latin America is the worst on record, and South America has reported cases sooner than anticipated. According to data from the Pan American Health Organization, the number of cases in the first 4.5 months of 2024 is 238 % greater than it was the previous year. The recent broad rise in dengue epidemics has increased interest in initiatives to manage dengue fever (Akinsulie and Idris, 2024; Kuo et al., 2024; Ly, 2024).

2. Etiology

2.1. Structure

Dengue belongs to the Flaviviridae family. Dengue virions are spherical with icosahedral symmetry, enveloped, and have a relatively smooth surface with a diameter of approximately 50 nm. They have an identifiable internal nucleocapsid core, a well-organized outer protein layer on top of a lipid layer, a sticky lipid envelope, and membrane and envelope peplomers. In addition to being the target of neutralizing antibodies, the E glycoprotein is in charge of attachment and fusion (Li and Kang, 2022; Anasir et al., 2020). The genome is a positive-sense single-stranded RNA molecule with a 5′ cap but lacking a 3′ poly-A tail, and is infectious. This genome encodes a long ORF that is translated into a polyprotein, and translation is cap-dependent, producing a polyprotein that is cleaved co- and post-translationally to form at least 10 proteins (Li and Kang, 2022). Three structural proteins—the envelope, E; membrane, M; and capsid, C—as well as seven non-structural proteins—NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5. These proteins are translated as a polyprotein that is broken down into separate proteins during maturation by the dengue NS2B/NS3 protease complex on the cytoplasmic side and the host furin and signalase proteases on the ER lumen side (Sun and Varani, 2022; Braun et al., 2020). Immature and mature spherical particles have an outer membrane derived from the ER and containing E and M proteins that form an icosahedral outer glycoprotein surface. The structural alterations in M and E proteins at varying ambient pH levels determine whether DENV is infectious or non-infectious in its mature and immature forms. The E protein undergoes structural alterations that primarily drive the transition from immature (protruding) morphology to mature (smooth) shape during transit through the trans-Golgi network (TGN). Following maturation, the infectious Pr peptide is released from the E protein into the extracellular space (pH 7.0). Viral defense and RNA replication are facilitated by NS1, which actively inhibits complement activation. NS2A and NS4B play a role in forming part of the replication complex (Fig. 1) (Braun et al., 2020; Songprakhon et al., 2020).

2.2. Host

The most prevalent virus spread by arthropods, dengue fever puts about half of the world's population at risk of illness. Dengue virus and other flaviviruses probably need a lot of host components because of their small genomes. The virus primarily infects humans, although it can also spread to non-human species. An infection may result from a bite. When a female mosquito feeds on blood from a victim of dengue fever during the first two to ten days of the illness, the virus enters the cells lining its stomach and infects them. After eight to ten days, the virus enters other tissues and travels to the salivary glands of the mosquito, where it is then secreted into its saliva [Sessions et al., 2009; Kathiriya et al., 2020).

2.3. Transmission

Over 2.5 billion people globally reside in regions where there is a high risk of contracting dengue fever, and the virus has recently moved to regions where it was either completely eradicated or nonexistent. Dengue is an arthropod-borne virus (arbovirus) that is mostly spread by *Aedes aegypti* mosquitoes, which live in urban areas (Gubler, 1998). There is currently a global resurgence of dengue fever due to the expansion of mosquito vectors and virus geographical distribution, increased disease incidence from increased frequency of epidemic transmission, and the emergence of DHF in numerous new countries. During the 1980s and 1990s, epidemic dengue transmission increased significantly (Mairiang et al., 2013). Humans contract dengue fever from female Aedes mosquitoes belonging to the subgenus Stegomyia. The most significant epidemic vector in tropical and subtropical areas is Ae. aegypti. As secondary vectors, other species like Ae. albopictus, Ae. polynesiensis, Ae. scutellaris, and Ae. niveus have proliferated (Khetarpal and Khanna, 2016).

2.4. Viral replication in mosquitoes

During natural infection, mononuclear phagocyte lineage cells such as monocytes, macrophages, and dendritic cells, including resident Langerhans cells in the skin, are primary targets for DENV infection. In insects, DENV initially infects the midgut, where it disseminates and replicates in various tissues and organs throughout the body. The wide variety of DENV-permissive cells suggests that the virus needs to attach to a universally present cell surface molecule or use several receptors to mediate infection (Lin et al., 2023). Numerous receptors have been discovered in the last ten years, suggesting that DENV can enter cells through a variety of molecules. It has been demonstrated that DENV interacts with R80, R67, and heat shock protein 70 (Hsp70) in mosquito cells. Mammalian cell receptors include heparan sulfate, Hsp90, CD14, GRP78/BiP, and a high-affinity laminin receptor (Rodenhuis-Zybert et al., 2010). Human myeloid cells and DENV particles interact through C-type lectin receptors (CLRs). The aquatic phase (larvae, pupae) and the terrestrial phase (eggs, adults) make up the eight to ten-day life cycle

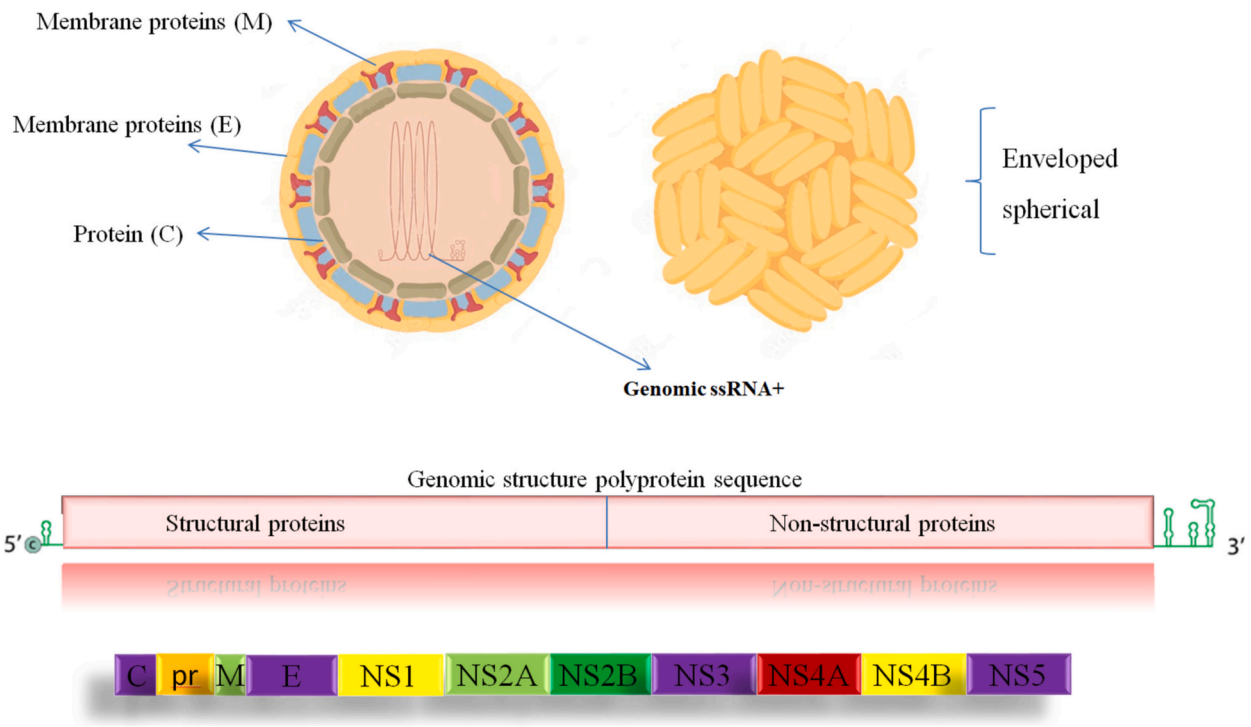

Fig. 1. Schematic images of the dengue virus genome structure.

of the Aedes mosquito at room temperature. By consuming blood from an infected individual, mosquitoes can contract the disease. The virus can spread to another person via mosquito after an incubation period of 7 to 14 days, during which it spreads from the midgut and replicates in the salivary glands. Vector management tactics have been the focus of many efforts to combat dengue fever because of the mosquito's crucial involvement in the virus's transmission cycle. Developing effective solutions for dengue transmission and replication will require a deeper comprehension of the interactions between the virus and its mosquito host (Fig. 2) (Rodenhuis-Zybert et al., 2010; Cheng et al., 2021).

2.5. Intracellular viral replication

The replication of flavivirus occurs in the cytoplasm on the membranes of the host endoplasmic reticulum (ER). Negative-sense RNA strands complement the entire length of the genome, acting as templates for positive-sense genome copies. Viral particles most likely accumulate flavivirus in the rough endoplasmic reticulum (RER), where they pick up their membranes. Viral particles eventually mature by branching off from the host cell after passing through the secretory pathway and exocytosis of the host, where they cleave prM to M (Mansfield et al., 2011). Semi-conservative and asymmetric RNA synthesis results in a tenfold increase in positive strands compared to negative strands. Metabolically labeling three types of viral RNA is possible: (1) a type of RNA that is resistant to ribonucleases and double-stranded; (2) a type of RNA that is partially resistant to ribonucleases, which is probably formed by long complementary RNA strands called replication intermediates; and (3) genomic RNA that is completely sensitive to ribonucleases (Mansfield et al., 2011; Ferrari et al., 2020). Vesicles' lumen is where RNA synthesis takes place, and the freshly created RNA genome leaves through pores that have been found and linked to the cytoplasm. The RdRp activity of the NS5 protein, NS3, additional viral NS proteins, and maybe host components that are directly engaged in RNA replication accelerate the enzymatic reaction. These proteins serve a variety of purposes during viral infection and interact with different viral and host components. Aside from NS1, NS2A, NS2B, NS4A, and NS4B, other RCs implicated in boosting viral RNA include NS1. The viral genome is

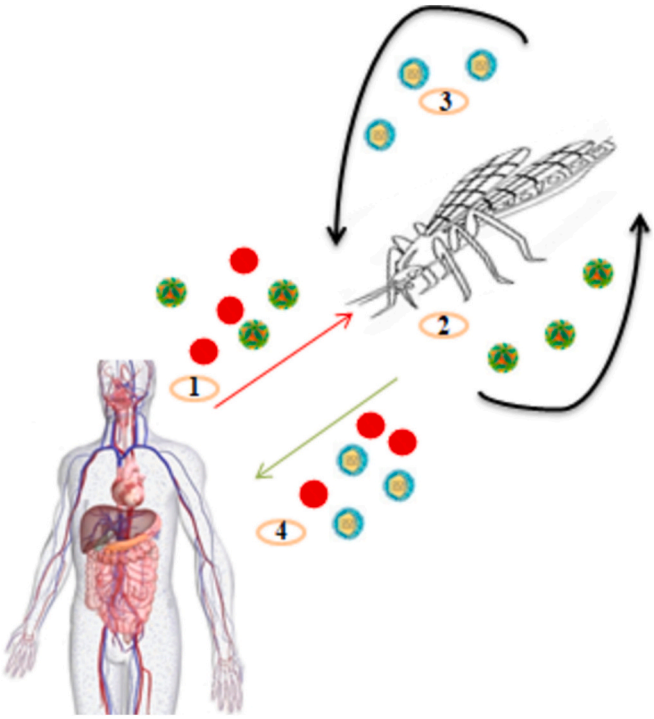

Fig. 2. Diagrams showing how the dengue virus spreads to people and how it replicates in mosquitoes: (1) the bite of the Aedes mosquito attacks humans. (2) Blood enters the mosquito's midgut and carries the dengue virus. DENV has interacted with heat shock protein 70 (Hsp70, R80, R67) in mosquito cells. (3) The virus emerges from the midgut after an incubation period of seven to fourteen days. (4) The salivary glands are where the virus reproduces, and a mosquito can infect another person.

immediately utilized as mRNA upon entrance. Cellular membranes are rearranged by protein synthesis linked to the RER to create structures known as VPs that house RCs. Translation stops when there is enough viral protein production, and RNA is transported to VPs via an unidentified method (Ferrari et al., 2020; Zerfu et al., 2023). Translation redirection to RNA synthesis may be coordinated by accumulating viral proteins or host factors produced by these proteins. Viral proteins NS4A, NS4B, and maybe NS2A are attached to the inner membrane of the VPs, but NS1 stays on the outside membrane (linked to the ER lumen). It is necessary to insert the viral polymerase NS5 and NS3 into the VPs. It's possible that host factors and NS proteins aid in the transport of RNA. NS5 primarily interacts with the 5′ end of the genome SLA promoter in order to facilitate RNA synthesis. In order to start RNA synthesis, NS5 must migrate to the 3′ end of the molecule by base pairing between the RNA ends and genome circularization (Zerfu et al., 2023; Roy and Bhattacharjee, 2021). Genomes that have just been generated leave the VPs through pores that link to the cytoplasm. These molecules can form nucleocapsids linked to capsid protein or they can be arranged with the ER, probably in CM structures, to trigger fresh rounds of viral protein translation. Protein C then packages the freshly created RNA to create a nucleocapsid. The prM and E proteins align themselves to create heterodimers with the ER lumen in the center. Following their association into trimers, the prM/E heterodimers form a curved surface network that directs virion budding as a result of these oligomeric contacts. As the immature particles created in the ER progress along the secretory pathway, prM/E heterodimers are more easily dissociated thanks to the trans-Golgi network's (TGN) somewhat acidic pH. The fusion peptide of the E protein allows the cellular endoprotease furin to cleave prM by structurally reorganizing the glycoproteins. Following furin cleavage, membrane-associated M and a "pr" peptide are produced. Mature virions are created following the pr peptide's dissociation, and they emerge from the ER to produce a fresh viral particle that can infect new cells (Fig. 3) (Lee et al., 2018).

3. DENV phylodynamic and phylogeographic analyses

Continuous evolution within circulating lineages, frequently coupled with sporadic lineage turnover, is what defines DENV evolution. A new lineage replaces an old one in this process, creating a tree topology like a ladder. Until a new, unique clade takes into account continuing instances, this pattern creates a ladderlike tree structure. Although lineage turnover can happen without any noticeable introduction, it is

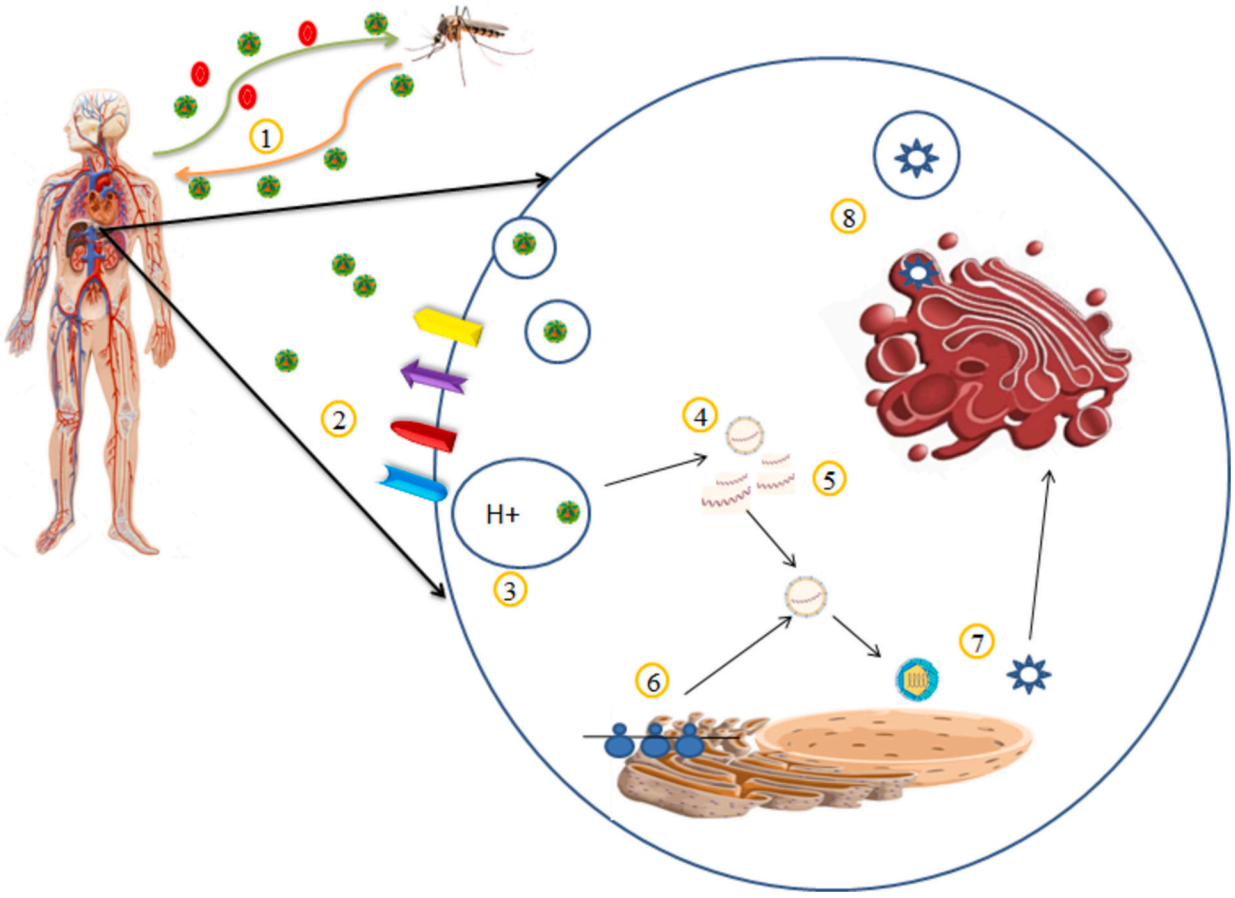

Fig. 3. Schematic illustration of dengue virus replication cycle inside human cell: (1) after successful infection, the dengue virus first invades the target cells and infects and replicates them. Target cells (monocytes (MO), macrophages (MØ), dendritic cells (DCs)). (2) Dengue virus enters the cell via receptor-mediated endocytosis using cell surface molecules via clathrin-coated vesicles. Specific receptors (heparan sulfate, Hsp90, CD14, GRP78/BiP, laminin receptor and C-type lectin receptors). (3) Acidification of late endosomes causes the E protein to reorganize structurally, which fuses the membranes of the virus and the host cell and releases the nucleocapsid into the cytoplasm. (4) The RNA genome is unencapsulated, the nucleocapsid (NC) is released into the cytoplasm, and the viral material is moved by cytoskeletal transport machinery to the endoplasm. (5) First, in a cap-dependent way, dengue virus positive strand RNA is translated into polyprotein. Positive-sense RNA serves as a template for RNA genome replication that takes place in the ER membrane. (6) During translation, viral E and M proteins are introduced into the ER membrane, but viral capsid proteins are translated in the cytoplasm. Capsid proteins encase genomic RNA in the cytoplasm, where it budded into the ER lumen to take up the M and *E*-containing coat from the ER. (7) After passing through the ER and the trans-Golgi network, enveloped virions stay in the lumen. (8) Encased virions develop an outer membrane generated from the ER after budging through the ER membrane and entering the cytoplasm. Mature virions that have been wrapped are released into the extracellular area when this ER membrane merges with the plasma membrane.

frequently linked to the introduction of viruses from other populations. Changes in dengue phenotypes, such as infectivity and severity, have been associated with major clade replacements as well as ecological and immunological variables. Major clade replacement is caused by evolutionary causes such as genetic drift, selection, or mutation that occurs in situ or through introductions. Selection can either correct or replace the less fit variants by increasing the frequency of the fittest variation or decreasing the frequency of the less fit ones. The random fixation of a variant, which causes stochastic fluctuations in variant frequencies over time, is referred to as genetic drift. Drift and selection are significant factors influencing DENV clade replacement. The phylodynamics of the invasive and diffused patterns of dengue virus serotype-1 in Guangdong, China, between 1990 and 2019 were documented in research by Lingzhai Zhao et al. (2024). In mainland China, several DENV serotypes were in circulation, especially in the provinces of Guangdong and Yunnan. Guangzhou was the predominant epicenter among 189 transmission clusters in 38 classes that belonged to 22 subtypes of DENV-1 genotypes I, IV, and V. Epidemiological studies and genome phylogeny demonstrated a distinct local sequential transmission pattern of a 5C1 (5C1-CN4) DENV-1 transmission cluster in Guangzhou between 2013 and 2015(Zhao et al., 2024; Thongsripong et al., 2023). After examining 1541 DENV-3 genomes, including two from Pará, Brazil, James Siqueira Pereira et al. (2024) determined that genotype 3III has been the most common genotype in Brazil since 2001. Within genotype 3III, the study found two major lineages, with lineage 3III_B.3.2 linked to recent instances in Brazil. There may have been several separate imports of this lineage into Brazil, since it has also been found in Cuba, the US, and Suriname. With the first introduction most likely taking place in Roraima in late 2022, the Caribbean area emerged as the main source of spread. Within Brazil, internal dispersal episodes were also detected, with noteworthy migratory pathways from São Paulo to Paraná and Roraima to Pernambuco. All of the Nicaraguan DENV-2 isolates from 2018 to 2019 formed their own clade within the Asian/American genotype, indicating that lineage swapping had a part in the phylodynamics of the virus that caused the 2019 epidemic, according to Panpim Thongsripong et al. (2023) (Pereira et al., 2024; Thongsripong et al., 2023).

4. Pathogenesis

Dengue fever is usually more common in tropical and subtropical environments around the world, often in urban and semi-urban areas. People of any age who are exposed to infected mosquitoes are susceptible to dengue fever infection. In tropical nations in Asia and South America, the rainy season offers the best conditions for the spread of dengue disease. Humans are usually infected by female Aedes mosquitoes carrying the dengue virus. Dengue fever cannot be spread by humans, but it can be transferred through blood transfusions from an infected to a healthy, uninfected individual. Both the genetics of the virus and the host, including host genetics and pre-existing immunity,

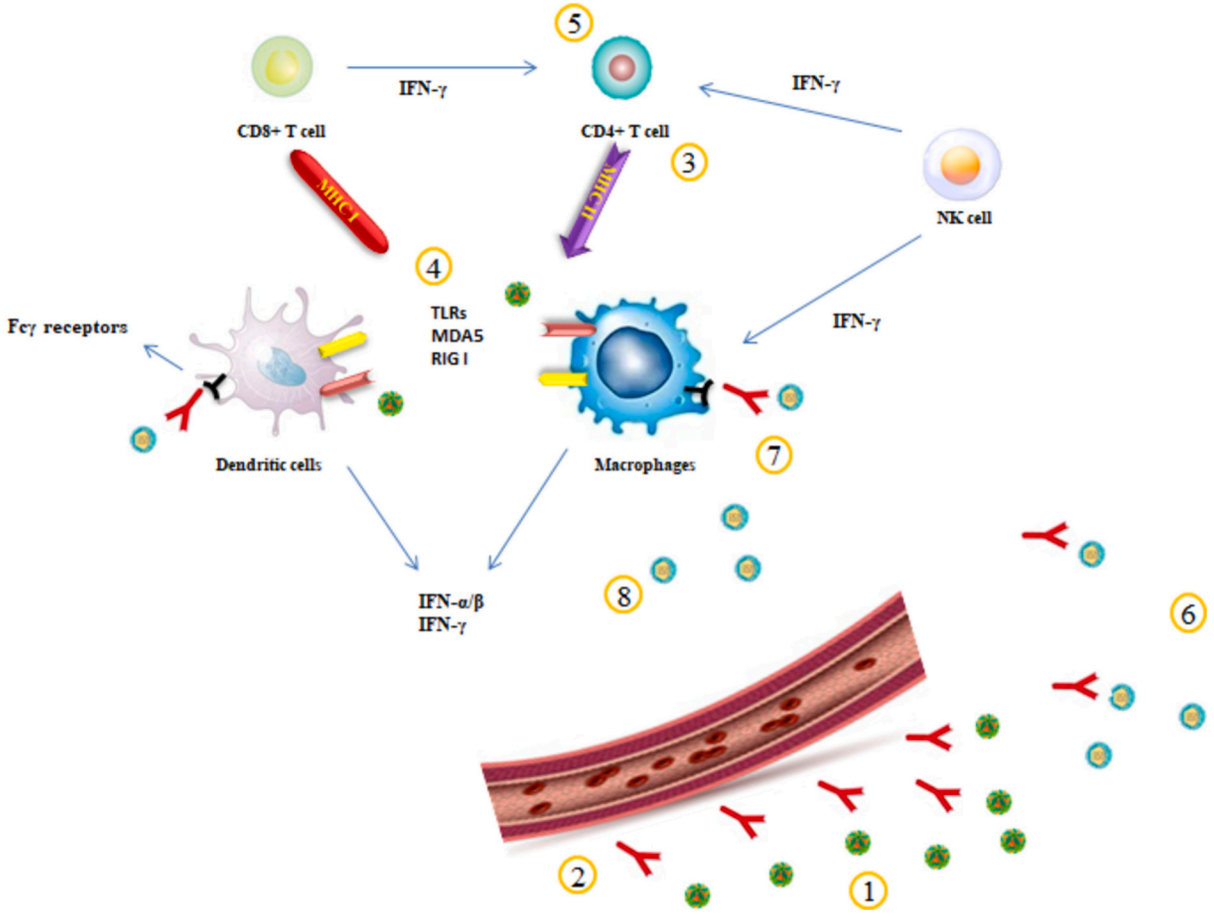

Fig. 4. Schematic illustration of dengue virus pathogenesis as well as the immune system response to dengue virus: (1) Virus attachment and entry through receptors. (2) Antibody production, which is first IgM and then IgG. (3) T cell response in dengue infection and transfer of antigen through MHC to antigen presenting cells. (4) Receiving and presenting antigens by dendritic cells, monocytes and macrophages, which leads to the production of type I IFN. (5) IFN-γ is mainly produced by NK and CD8 T cells and activates macrophages as well as CD4 T cells. (6) In the secondary heterotypic infection, antibodies against the previous dengue virus react with the heterotypic dengue virus and form an immune complex. (7) Antibody immune complexes interact with Fcg receptors expressed on macrophages or phagocytes. (8) Heterotypic dengue virus that propagates inside Fcg-expressing immune cells and further enhances viral infection.

affect viral virulence (Islam et al., 2021; Bhatt et al., 2021). Because certain DENV strains multiply more easily in humans or in mosquito vectors, they have a higher potential for spreading epidemics. Because of their quicker diffusion and shorter extrinsic incubation periods, advanced replication in mosquitoes may aid in a strain's global proliferation and success. Furthermore, certain DENV clades or genotypes may benefit selectively from cross-reactive immune responses in human populations, making it possible for strains that are resistant to host adaptive immune responses to outcompete other strains in the population (Fig. 4) (Kok et al., 2023). Some DENV strains are more suited to the environment and have a tendency to reproduce more in human hosts, which increases the risk of severe disease. The severity of a patient's illness has been linked to their viremia levels. Higher viral replication in human hosts can be attributed to three different processes, all of which strengthen target cell infection and exacerbate the cytokine cascade, hence increasing pathogenicity. (1) Higher titers are obtained when pathogenic DENV strains reproduce more quickly in human cells. (2) Pathogenic strains of DENV have the ability to elude host cross-reactive and adaptive immune responses. (3) enhanced target cell infection or enhanced virus production from infected cells are two ways that antibody-mediated infection may improve viral replication. Furthermore, with successive DENV infections, improper cross-reactive adaptive immune responses may result in more severe immunopathogenesis, or the emergence of illnesses typified by dengue shock syndrome (DSS) and dengue hemorrhagic fever (DHF) (Islam et al., 2021; Bhatt et al., 2021; Kok et al., 2023).

4.1. Clinical symptoms

Dengue fever can present itself in two ways: either as a classic form of dengue fever with additional symptoms such as fever, headache, muscle or bone pain, rash, pain behind the eyes, and petechial bleeding under the terms dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS), which can be fatal due to plasma leakage in patients, or as an undifferentiated febrile illness with maculopapular rash, especially in children, along with flu-like symptoms (Bhatt et al., 2021; Dowd et al., 2023).

4.2. Primary Dengue fever infection (febrile phase)

After being bitten by an infected mosquito, there is an incubation period of up to 2 weeks (usually 5–7 days). Following that, the patient experiences an abrupt onset of symptoms. The illness usually progresses in three stages: a feverish initial phase, a critical phase that starts four to five days after the fever first appears and may cause complications, and a spontaneous recovery phase (Kok et al., 2023; Dowd et al., 2023).

4.3. Dengue fever

The patient develops a high fever (39–40 degrees Celsius) all of a sudden, along with nonspecific symptoms like headache, myalgia, nausea, vomiting, and joint pain. Changes in taste perception, colic, constipation or diarrhea, and rarely dysuria are other typical symptoms. There may occasionally be rhinorrhea, sore throat, and cough (Islam et al., 2021; Kok et al., 2023; Khanam et al., 2022). On rare occasions, during the first few days, the fever may increase to 40–41 degrees Celsius, and children who are sensitive may get febrile convulsions. At this point in the illness, the examination may reveal face flushing, injections in the conjunctiva, and widespread erythema throughout the body. In certain instances, there may be a little maculopapular rash. Mild generalized lymph node enlargement is typical. Jaundice is uncommon, and the liver is often palpable, mushy, and somewhat painful. It rarely becomes noticeably enlarged. Splenomegaly can occasionally be seen in young newborns (Bhatt et al., 2021; Khanam et al., 2022).

4.4. Secondary infection in Dengue fever (critical phase) classic dengue fever

In classic dengue fever, body temperature varies from 39 to 40 degrees Celsius for 5 to 7 days. Dengue hemorrhagic fever is caused by the dengue virus as it methodically enters the circulation during secondary infection and damages lymph nodes and blood arteries. The latter's symptoms include bleeding from the nose, gums, and beneath the skin. On the other hand, respiratory distress appears in patients with dengue hemorrhagic fever, and severe progression can lead to dengue shock syndrome, which can result in death if untreated. Patients with chronic hemolytic illnesses, diabetes, obesity, renal failure, neonates, and the elderly need special attention. Patients with dementia may experience increasing dengue fever infections that are chronic and stay in the central nervous system (Kok et al., 2023; Dowd et al., 2023; Khanam et al., 2022).

4.5. Dengue hemorrhagic fever (DHF)

Thrombocytopenia, fever, spontaneous bleeding, and plasma leakage are the hallmarks of dengue hemorrhagic fever. For it to be identified as Dengue Hemorrhagic Fever, four clinical signs must be present. These include: (1) fever; (2) hemorrhagic episodes accompanied by at least one of the following: petechiae, ecchymosis, purpura; or bleeding from mucous membranes, gastrointestinal tract, injection sites, or other areas; (3) plasma leakage owing to increased capillary permeability; and (4) thrombocytopenia. The tourniquet test, also called the capillary fragility test, is a clinical diagnostic method to determine the patient's propensity to bleed and assess the fragility of capillary walls. Nevertheless, plasma leakage—which is indicated by an increase in hematocrit levels—must be shown in order to distinguish DHF from DF. DHF typically progresses over seven to ten days, and mortality can be lowered to less than 1 % by maintaining an adequate fluid supply. Hospitalization should only be considered for severe cases of DF and DHF [Bhatt et al., 2021; Dowd et al., 2023; Khanam et al., 2022; Prapty et al., 2023).

4.6. Dengue shock syndrome (DSS)

Dengue Shock Syndrome (DSS) is the most severe form of DHF and is characterized by the presence of all four clinical manifestations of DHF along with circulatory failure. The patient must exhibit all three signs of circulatory failure: cold skin along with altered mental status, weak pulse pressure or hypotension relative to the patient's age, and a quick and feeble pulse (Bhatt et al., 2021; Khanam et al., 2022; Chauhan et al., 2024).

4.7. Co-infections and combinations of different serotypes of DENV

Zika virus, COVID-19, Chikungunya, and West Nile virus are among the viral, parasitic, and bacterial pathogenic pathogens that can coexist with dengue fever virus infections. Co-infection rates vary greatly between nations and areas, ranging from 5 % to 30 % to 40 % to 50 %. This has made it more crucial to comprehend how co-infections affect the clinical results of diseases. Only a small number of research studies have examined the clinical consequences of co-infections, and there is little emphasis on them. Examining the traits and severity of the disease linked to co-infections will improve our comprehension of their dynamics and effects as the number of co-infections rises. Furthermore, dengue fever can coexist with parasite illnesses like malaria, particularly in tropical areas, making diagnosis and treatment more difficult and necessitating further medical attention. People should be closely watched if they are suspected of having dengue fever in order to avoid complications (Dhanoa et al., 2016; Salam et al., 2018; El-Qushayri et al., 2022; Badawi et al., 2018; Bonyah et al., 2019). Additionally, there is a higher frequency of DENV coinfections when four DENV

serotypes are circulated simultaneously in the same geographic area. In a hyperendemic area, DENV coinfections are not unusual. Patients who have co-infections appear to be more prone to more severe clinical manifestations, as indicated by a higher frequency of pleural effusion, severe thrombocytopenia, elevated creatinine levels, and warning signs. The co-infected group did not, however, seem to have more hemoconcentration or hemorrhagic symptoms. As evidenced by fewer cases of diarrhea and arthralgia/myalgia in these individuals than in mono-infected patients, co-infections may potentially change clinical presentation (Dhanoa et al., 2016; Senaratne et al., 2020).

5. Immune response

5.1. Innate immune responses in Dengue virus infection

The dengue virus interacts with two important components of the innate immune system, namely the complement pathways and type I interferon (IFN). The virus may infect people thanks to these counteracting processes, which also probably have an impact on the dendritic cells' (DCs) ability to generate and maintain successful adaptive immune responses. Additionally, the complement system improves the neutralization of flaviviruses, such as YFV, DENV, and WNV, by antibodies. Paradoxically, antibody-dependent complement activation may promote flavivirus infection in myeloid cells expressing complement receptors (Fig. 4) (Zaidi and Cedillo-Barron, 2020). In myeloid cells, complement-dependent opsonization and antibodies may promote DENV infection. Following viral infection, the type I IFN production cascade is set off by sensors that include Toll-like receptors (TLRs) and cytoplasmic receptors like retinoic acid-inducible gene I (RIG-I) and MDA5. These receptors are able to identify particular viral elements (PAMPs) and set off the cascade. During acute DENV infection, innate immune responses are likely to play a key role in determining disease outcomes, especially during the primary infection. In vitro, it has been demonstrated that IFN-α/β and IFN-γ can prevent DENV infection, but only when therapy is administered before infection. DENV multiplies at excessively high levels in mice lacking IFN-α/β and IFN-γ receptors, rendering these mice universally prone to DENV illness. This is one reason why animal models of DENV infection have highlighted the significance of IFN in protection against DENV in vivo. The IFN-mediated response to DENV infection involves both STAT1-dependent and STAT1-independent mechanisms. Research shows that whereas lower levels of IFN-γ in the setting of a severe illness may suggest an insufficient response, higher levels of IFN-α and IFN-γ in response to DENV infection are part of the protective host response. Natural killer (NK) cells are a major source of IFN-γ and are probably crucial for eliminating DENV during acute infections (Zaidi and Cedillo-Barron, 2020; Muhammad Azami et al., 2020; Sindi, 2021).

5.2. Antibody response

Dengue fever's antibody production kinetics is similar to those of many other viral illnesses, with IgM synthesis occurring first and then IgG. Dengue IgM levels during a primary DENV infection start to rise three to five days after fever onset and are nearly always detectable after fever has subsided. IgG, which is detectable for life and is thought to offer protection against reinfection with the same serotype but not against reinfection with a different serotype, replaces declining IgM levels over the course of the next two to three months. The IgM rise following a secondary infection is significantly smaller than that following a primary infection and may not occur at all. Rather, the IgG level increases faster and peaks at a higher level. Tests that differentiate between primary and secondary dengue illnesses are based on this distinction (Zaidi and Cedillo-Barron, 2020; Sindi, 2021; Waickman et al., 2022a, 2022b).

5.3. T cell response in Dengue infection

T lymphocytes identify short antigenic peptides attached to MHC class I or class II molecules' peptide-binding groove. Usually, these molecules bind to short segments of peptides that are left over when naturally occurring cell proteins break down. They may, however, obtain and deliver peptides from a reproducing pathogen while they are infected. Generally speaking, MHC class I molecules display to CD8 cytotoxic T cells peptides that are derived from intracellularly produced proteins, such a virus replicating within its host cell. On the other hand, MHC class II molecules give CD4 T cells peptides that are obtained from endocytosed antigens (Waickman et al., 2022a, 2022b; Malavige et al., 2020).

5.4. T cell response in secondary Dengue infection

T cells in Dengue Hemorrhagic Fever (DHF) produced more cytokines and showed less degranulation than T cells in Dengue Fever (DF), where T cells showed significantly higher levels of degranulation in the absence of cytokine production. Many T cells induced during secondary infection showed a weak response to the secondary infecting virus. A large number of these reactions rise, and in certain instances, peak levels correspond with the onset of severe symptoms. A possible cause of dengue hemorrhagic fever is T cell-mediated immunopathology (Zaidi and Cedillo-Barron, 2020; Malavige et al., 2020; Waickman et al., 2022a, 2022b).

6. Diagnosis of Dengue virus

Compared to T cells in Dengue Fever (DF), which produced significantly greater degranulation in the absence of cytokine production, T cells in Dengue Hemorrhagic Fever (DHF) produced more cytokines and had less degranulation. A mild reaction to the secondary infecting virus was displayed by many T cells that were generated during secondary infection. Many of these responses increase, and sometimes peak levels coincide with the onset of severe symptoms. T cell-mediated immunopathology is one potential etiology of dengue hemorrhagic fever (Roy and Bhattacharjee, 2021; Kok et al., 2023). Nucleic acid testing, antigen detection, and virus isolation can all be employed to diagnosis infection in the early stages of the illness. When the disease has reached the end of its acute phase, serology is the preferred diagnostic technique. An individual experiences a latent period lasting four to ten days after being bitten by an infected insect. Viremia appears two to three days prior to fever start and persists for five to six days following the onset. The virus can be isolated and RNA and sNS1 protein can be found during the viremia phase (Dhal et al., 2020).

6.1. Virus culture and isolation

Given that dengue infection presents symptoms similar to other febrile illnesses, laboratory confirmation of viral infection is necessary. In laboratory diagnosis, biological markers are typically targeted for dengue detection. The isolation of the virus from samples taken from suspected DENV patients and its subsequent cultivation in different cell lines is one conventional diagnostic technique for detecting DENV. Clinical samples obtained from patients are cultivated in mammalian cell lines (LLCMK2, Vero, and BHK-21) or mosquito cell lines (AP61, Tra-284, AP64, C6/36, and CLA-1 cells) (Kok et al., 2023; Dhal et al., 2020; Hegde and Bhat, 2022).

6.2. Molecular methods

Although virus isolation provides a reliable diagnosis, it is not feasible for DENV diagnosis since it is time-consuming and can take several days to complete. Due to this drawback, a polymerase chain reaction (PCR) molecular technique was developed and first referred to

as a two-step RT-PCR approach. Since viral RNA can be found early in the disease, PCR-based methods have several benefits. They are also quick, sensitive, and specific. Therefore, the diagnosis of DENV infection has been achieved through the successful application of molecular techniques including RT-PCR and nucleic acid hybridization. While PCR-based techniques are rapid and precise, their examination necessitates a laboratory setting with specialized tools and qualified staff. PCR-based techniques, however, might not always be a possibility, particularly in underdeveloped nations or areas with little resources [Kok et al., 2023; Hegde and Bhat, 2022; Lokida et al., 2020).

6.3. Antigen-capture based method

Viral proteins, like non-structural protein 1 (NS1), are ideal target biomarkers not only for identifying the virus itself but also because they are secreted from infected cells, resulting in higher levels of NS1 in the blood of infected individuals. These levels can be detected from the onset of symptoms up to nine days or more after the illness begins. Therefore, in early infections, NS1 can be identified simultaneously with viral RNA and before the antibody response develops. Another method for detecting DENV is the detection of NS1 in patients' blood using ELISA (Marques et al., 2020). Commercial NS1 tools have been developed, which has been advantageous because they are easy to use and have good sensitivity and specificity. As a result, they have become the new standard for dengue diagnosis. Rapid test strips and NS1 capture ELISAs have been commercially developed as a result of the demonstration of high amounts of NS1 secretion by quantitative-capture ELISA. Dengue diagnosis has been completely transformed by the commercial development of NS1 as a diagnostic tool, which offers straightforward, low-tech assays that are incredibly sensitive and specific (Dhal et al., 2020; Marques et al., 2020).

6.4. Serology

Dengue can be confirmed based on the host immune response, in addition to the virus or viral products. Hemagglutination inhibition (HI) tests, complement fixation tests, dot blot assays, Western blotting, plaque reduction neutralization tests, indirect immunofluorescence antibody assays, IgM and IgG antibody capture ELISAs, and complement fixation tests are some of the more effective serological diagnostics that are currently available. IgM can be detected three to five days after infection and can be found for several months. IgG, on the other hand, manifests later in the initial infection and responds quickly in subsequent infections. Additionally, determining the IgM and IgG levels in a patient's serum helps to determine if the infection is primary or secondary. For routine DENV detection, HI tests and IgM and IgG antibody capture ELISAs are the most effective serological diagnostic techniques (Cecchetto et al., 2020). For many years, the HI test has been used to diagnose dengue; while commercial kits are also available, most laboratories create their own proprietary procedures. In regions of the world where many flaviviruses are circulating (such yellow fever, Japanese encephalitis, and most recently, the Zika virus), diagnosing DENV infection by serology becomes more difficult because of cross-reactive epitopes on the flavivirus E protein that trigger cross-reactive antibody responses. In DENV serological assays, antibodies against these flaviviruses May cross-react, producing false-positive results. IgM and IgG serology should be used with NS1 antigen capture to minimize these false positives. Rapid immunochromatographic techniques and commercial ELISA for dengue NS1 antigen capture are made to be extremely specific and have no demonstrated cross-reactivity with NS1 from other

Fig. 5. Classification of laboratory tests used to detect dengue virus.

flavivirus species (Fig. 5) (Lokida et al., 2020; Marques et al., 2020; Cecchetto et al., 2020).

6.5. Rapid diagnostic tests (RDTs)

Give a fast way to identify dengue antibodies (IgM, IgG) and the dengue antigen (NS1). Diagnostics that are reasonably priced are important for tracking and identifying illnesses. Pathogen culture, Gram staining, enzyme immunoassays, ELISA, biochemical procedures, various nucleic acid amplification methods, and polymerase chain reaction (RT-PCR) are examples of traditional diagnostic methods for identifying certain infections (Pollak et al., 2023). Numerous infectious diseases have benefited greatly from these procedures in terms of diagnosis, prevention, and treatment. They do, however, have a number of disadvantages, such as the requirement for qualified personnel, complex analytical apparatus, time commitment, expense, and competence. As a result, a fresh and trustworthy diagnostic technique is required. For prompt intervention to be possible and to stop the virus from spreading across the community, rapid diagnostic testing is essential (Liu et al., 2020). This system processes complex sample handling and transfers test samples to the diagnostic center swiftly, allowing not only for quick diagnostic decision making but also minimizing potential analytical interference. Because Lateral Flow Assays (LFA) are practicable, reasonably priced, and don't require trained personnel, they could lessen the cost strain. LFAs are axis-based immunoassays, also referred to as immunochromatographic tests. The definition of an immunoassay is a biological analysis technique (Liu et al., 2020; Sukla et al., 2021). Analytes such as proteins, infectious viruses, and nucleic acids have all been tested extensively using LFA strips. A viral antigen known as NS1 is connected to viremia in the early stages of DENV infections. Given their excellent sensitivity and specificity, NS1 RDTs may be a useful substitute for other testing methods. The effectiveness of diagnostic RDTs is influenced by various factors, including the day of sample collection, main or secondary infection, and distinct DENV serotypes. When it comes to identifying NS1 and IgM biomarkers, the Q standard shows a high degree of accuracy and diagnostic capabilities. RDTs can improve dengue supervision and control programs by offering quick and precise confirmation of recent infections (Pollak et al., 2023; Sukla et al., 2021; Kabir et al., 2021).

7. Treatment

The dengue virus has made a major comeback in recent decades, resulting in extensive outbreaks over Southeast Asia, Africa, the Americas, and even portions of Europe. This virus is still endemic in more than 100 countries globally. The majority of DENV cases documented in endemic countries involve newborns and young children. There is a pressing need for an efficient antiviral combination to treat DENV infections due to the high disease load and lack of a readily available vaccination (Low et al., 2018; Diamond and Pierson, 2015; Patel et al., 2024). Finding safe and effective medications is crucial for treating DENV patients early on in order to reduce mortality after serious problems develop and stop the disease from progressing to deadly consequences (Lai et al., 2017). Due to the current dearth of effective antiviral treatments for dengue, there has been a great deal of study done on the drug discovery process. According to several theories, treating dengue with an efficient antiviral within 48 h of the onset of symptoms may quickly reduce the virus load and prevent the development of severe dengue. It might also lead to a decline in transmission and a reduction in illness consequences in DF patients. A few investigations have demonstrated that when pharmacological treatment is administered, the degree of splenomegaly and the levels of pro-inflammatory cytokines also decrease. Chloroquine and balapiravir have been used in human clinical trials on patients with acute dengue. One strategy is the creation of medications that block or alter host targets, causing the inflammatory cascade to be triggered. The intricacy of dengue pathogenesis makes it imperative to identify a set of qualities that the perfect medication for treating dengue fever (DF) should have. In conclusion, a medication must be effective against each of the four dengue serotypes (Nguyen et al., 2013). Since oral medication is the most economical to produce and distribute, it should be used for this endemic disease in developing nations. This medication should work best when taken once daily, however in cases of acute dengue, up to three doses per day may be sufficient to keep the medication's levels above the minimally effective concentration. Entry/fusion inhibitors, polyprotein translation/processing inhibitors, replication inhibitors, and viral maturation/packaging inhibitors are the four viral mechanisms that antivirals can target (Schmidt et al., 2012; Beltramello et al., 2010). In order to produce their antiviral effects, directly acting antiviral medications interact extensively with viral proteins. Research on DENV antivirals has up until now concentrated on NS and structural proteins. The E protein, which is essential for viral cell entrance, is the structural protein that has been researched the most as an antiviral target (Boldescu et al., 2017). Viruses disrupt several cellular processes in order to provide an environment that is conducive to their replication. Finding substances that obstruct these biological processes is therefore a viable antiviral tactic. Host-directed medications have the advantage of possibly causing less resistance, which could increase their effectiveness. Numerous host-directed antivirals that target distinct phases of the viral replication cycle have been uncovered by recent studies. α-glucosidase is the most researched cellular target because it helps proteins fold and mature properly. Furthermore, a number of research works detail the suppression of cellular inosine monophosphate dehydrogenase, an essential enzyme involved in nucleotide synthesis and, by extension, viral replication (Botta et al., 2018; Kaufmann et al., 2018).

8. Epidemiology

Globally, dengue fever is a noteworthy arboviral illness. It affects almost 50 % of the world's population and is endemic in more than 100 nations. Over the past 30 years, its load has significantly expanded. In the 1780s, DF epidemics were concurrently detected in North America, Asia, and Africa. Despite being endemic in the Americas, the disease is recorded in numerous nations in the WHO regions of Africa, the Americas, the Eastern Mediterranean, Asia, Australia, and the Western Pacific (Zerfu et al., 2023). The most affected regions are the Americas, South Asia, and the Western Pacific; around 70 % of infections occur in Asia (Chen et al., 2023). Less than 1 % of people with DENV infection die naturally. However, it usually varies from 1 % to 5 % in the absence of appropriate management, care, and clinical control. The World Health Organization (WHO) reports that the substantial rise in DENV infection incidence over the past few decades has put half of the world's population at danger. Every year, between 100 and 400 million people globally contract DENV (Zohra et al., 2024). The most afflicted areas are the Americas, South Asia, and the Western Pacific, with Asia accounting for almost 70 % of illnesses (Zerfu et al., 2023). Less than 1 % of people who contract DENV will die naturally. But normally it's between 1 % and 5 % in the absence of appropriate care, supervision, and management. The World Health Organization (WHO) states that because DENV infections have become much more common in recent decades, half of the world's population is currently at danger. Between 100 and 400 million people globally contract DENV each year. There have been reports of dengue epidemics in Zanzibar, Burkina Faso, Mauritania, Djibouti, Mozambique, Côte d'Ivoire, and Senegal that are linked to different serotypes. All known serotypes of dengue virus have been found in Africa overall (Shrestha et al., 2022).

8.1. Dengue in Africa

Using newly sequenced dengue virus genomes of African origin that are publicly available, representing all four serotypes, we performed a molecular epidemiological reconstruction based on our research to infer

the most likely temporal and spatial transmission pathways of each DENV serotype from their ancestral regions into and out of Africa. According to our findings, serotypes DENV1–DENV3 were repeatedly transmitted into Africa from Southeast Asia over the 20th century. The earliest known evidence points to DENV2's and DENV1's introduction into West Africa from Southeast Asia in the early and mid-1940s, respectively. This research also suggests that DENV4 and DENV1, which are most likely from Southeast Asia, were first introduced into West Africa in the middle of the 1940s (Mwanyika et al., 2021). It also seems that DENV3 originated in Southeast Asia, and it was established in Africa later in the 1960s. However, there is also evidence of the importation of DENV1 and DENV2 from the Americas into West Africa due to the resurgence of DENV in the Americas when the PAHO mosquito control program was discontinued in the middle of the 20th century. The results additionally reveal the intra- and inter-regional spread of all four DENV serotypes throughout Africa, resulting in a significant degree of geographic overlap between them. Notably, DENV has infiltrated Central Africa from both East and West Africa; however, there is no evidence to suggest that the connection is reversed. With the exception of DENV4, all of the DENV serotypes that we have found corroborate the theory that they have been introduced into Africa several times, mainly from Southeast Asia and then into adjacent regions of the continent (Mwanyika et al., 2021; Alfsnes et al., 2021). The 2023 study by Prince Gyasi et al. examined the epidemiology of dengue fever in the West African subregion, emphasizing the possibility of an epidemic and the necessity of research and surveillance to put effective control measures in place. The analysis found 58 human prevalence studies with 35,748 participants from 8 countries, the bulk of which were from Burkina Faso and Nigeria. Between 0.02 % and 93 %, the average prevalence was 20.97 % for both the acute and general prevalence categories of DENV infection. With a prevalence range of 0.02–93 %, the bulk of research was carried out on acutely febrile individuals. Four of the five nations with published reports—Cape Verde, Senegal, Burkina Faso, and Senegal—reported *Aedes aegypti* infected with DENV (Gyasi et al., 2023).

8.2. Dengue in Asia

The ratio of laboratory-confirmed dengue infections varies significantly among the SAARC countries; Nepal has the lowest ratio and Pakistan has the highest. With a significant increase in heterogeneity based on the nation and the study period, the total combined ratio of confirmed cases among suspected cases was 30.7 %. This suggests that infection frequencies, severity, and outcomes differ. When compared to the composite ratio of autochthonous dengue infections in Europe (0.7 %), this prevalence is significantly greater. Ganeshkumar et al. (2018) stated that the overall ratio of dengue infections in India was 38.3 % in their systematic review (Ganeshkumar et al., 2018; Shrestha et al., 2022). The first dengue outbreak including serotypes DEN-1 and DEN-2 was documented in Pakistan in 1994 and resulted in thousands of cases. Serotype DEN-3 was the focus of the second outbreak in Karachi in 2005, which observed a sharp rise in cases of severe DHF. In 2011, there was a significant epidemic in Lahore, Punjab, with over 50,000 cases reported. In 2013, there was a massive outbreak in the region of Khyber Pakhtunkhwa. In Pakistan, mosquito vectors have plenty of places to reproduce, including open irrigation canals, vast agricultural regions, constructed water reservoirs for many uses, rich fauna, and flooding caused by high rainfall (Zohra et al., 2024). In Nepal, the number of dengue cases has increased over time, with a total of 17,992 dengue cases reported from 68 districts in 2019. Compared to the incidence in 2016, the incidence reported in 2018 was nearly five times higher and over 140 times higher in 2019. Studies indicate that dengue infection rates are rising and spreading from lowland areas to higher altitudes (Rijal et al., 2021). There is evidence that dengue viruses (DENV) have been present in Sri Lanka since the 1960s. The first dengue infection outbreak was documented in 1965, the same year when DENV-2 reemerged and caused 440 fatalities. Despite the fact that there were 51,659 fewer cases reported in 2018 than there were in 2017, there was a rebound in 2019 with 105,049 cases reported (Malavige et al., 2021).

8.3. Dengue in the United States

Dengue fever mostly affects tourists visiting the country, as well as local disease outbreaks that happen occasionally in states across the country and endemic epidemics in U.S. territory like Puerto Rico, American Samoa, and the U.S. Virgin Islands (USVI). Between 2010 and 2020, there was a significant dengue outbreak in U.S. territory, with over 30,000 confirmed and probable cases reported. The majority of cases and hospitalizations occurred in people under the age of 20, with minors between the ages of 10 and 19 having the greatest rates. Puerto Rico reported the majority of cases (96.6 %) and was the only area to report deaths from dengue. While American Samoa only reported cases from 2017 to 2018, over a brief period (2012−2013) it experienced high dengue rates, this jurisdiction had the highest yearly incidence of 10.2 cases per 1000 inhabitants in 2017 (Ryff, 2023). Dengue fever cases in South America have been detected earlier than anticipated in 2024, and this year's outbreak is the worst in Latin America. In the first four and a half months of 2024, the number of cases is 437 % greater than the five-year average for Latin America and 238 % higher than the previous year. In regions of northern Argentina and southern Brazil where DENV was not previously a significant issue, the pandemic has expanded. Out of the 46 nations in the Americas, Brazil, Argentina, and Paraguay had the most dengue cases this year. As of late March 2024, more than 400 patients in Puerto Rico were admitted to intensive care units due to dengue fever. Puerto Rico and other Latin American nations have seen more instances of dengue fever than in the past. Over 1000 people have died from dengue fever in Latin America, including Brazil, Peru, and Honduras, with a cumulative incidence of 833 cases per 100,000 people and 7,861,445 suspected cases (Ly, 2024).

8.4. Dengue in Europe

Particularly in Southern Europe, the current climate in Europe is conducive to the local spread of dengue disease. These prerequisites include the existence of appropriate vectors (Aedes spp.), a population of sick people, and climate conditions that are conducive to viral development within the vector and vector survival. Europe is home to both of the two main dengue vectors, *Aedes aegypti* and *Aedes albopictus*. In contrast to *Aedes aegypti*, *Aedes albopictus* is presently found throughout Europe (Brem et al., 2024). These mosquitoes have established themselves in Southern Europe, especially in Italy, southern France, eastern Spain, and the eastern Adriatic coast. They are now slowly spreading into northern latitudes. In terms of autochthonous cases, 65 cases in France and 1 case in Spain were among the 66 reported cases in Europe in 2022. 76 instances in Italy, 43 cases in France, and 3 cases in Spain made up the total of 122 cases documented in Europe in 2023. In 2023, there has been a spike in cases in Italy and a fall in instances in France, whilst the number of cases in Spain seems to be steady. Four provinces in Italy had cases: Lodi, Latina, Rome, and Anzio, with 37, 2, 36, and 1 case each. There was no evidence of a link between the epidemics. Cases were dispersed around Paris and its environs, as well as the French Mediterranean coast. In 2022, two cases were discovered in Corsica. Autochthonous cases are observed in Murcia, Madrid, the Balearic Islands, and throughout the Mediterranean coast of Spain. Two autochthonous instances were documented in Ibiza in 2023 (Frasca et al., 2024).

9. Prevention and control strategies

9.1. Three types of dengue prevention and control methods may be distinguished: chemical, biological, and physical control

In order to prevent and control dengue, physical control entails surveillance to determine risk, assess programs, and give prompt actions. Vectors' behavioral characteristics are essential for identifying and lowering their population density. Community-based control initiatives raise awareness and educate the public about mosquito breeding grounds. Genetic techniques like paratransgenesis, which use genetically altered symbiotic bacteria to colonize the vector population and reduce disease transmission, are part of biological control. In order to reduce vector density and spread vector-borne illnesses in urban areas, the Sterile Insect Technique (SIT) releases male mosquitoes that have been laboratory-sterilized. Insecticides, which have been used for decades in chemical control, can have adverse effects on the environment and have caused resistance in the target vector population. By preventing growth and development, insect growth regulators (IGRs) cause alterations that kill the insect before it reaches adulthood. IGRs, which have been used to combat viral infections carried by *A. aegypti*, include diflubenzuron, endotoxins, and methoprene (Rather et al., 2017; Wang et al., 2020; Pang et al., 2017; Abidemi and Aziz, 2020).

9.2. Dengue vaccine

Dengue virus poses a global health threat, with approximately 390 million dengue infections occurring annually. This rapid spread is attributed to transportation and travel worldwide, increased urbanization, and climate changes that support the proliferation of Aedes mosquitoes. Currently, there are no efficient vaccines available to prevent dengue fever. In this study, we report a brief summary of recent advancements in dengue vaccine development (Wang et al., 2020; Kuo et al., 2018). Cross-immunity across distinct serotypes produces antibodies that aid in viral invasion rather than neutralizing virions. The term "antibody-dependent enhancement" (ADE) describes this hypothesis. In addition to signaling greater viral entry, antiviral responses, both innate and adaptive, are aided by ADE, which promotes viral replication. There is currently no specific antiviral treatment for dengue; instead, supportive care is the mainstay of treatment. In theory, immunization is the best way to avoid contracting dengue fever (Kuo et al., 2018; Katzelnick et al., 2017). Stable efficacy, dependable safety, and cross-protective qualities for all four serotypes are desirable qualities in a dengue vaccine. Nevertheless, the development of dengue vaccines is hampered by the impact of ADE during infections with other serotypes and the absence of appropriate animal models. Investigations have been conducted on five different forms of dengue vaccines: DNA vaccines, recombinant subunit vaccines, live-modified vaccinations, and inactivated vaccines (Halstead et al., 2010; Wilder-Smith, 2020). The development and application of a secure and reliable dengue vaccine may considerably contribute to lowering the incidence of dengue illness worldwide. A few decades later, the first dengue vaccine received a license. Sanofi Pasteur created the Dengvaxia® chimeric live-modified yellow fever/dengue vaccine, which has received approval in a number of nations, including Mexico, Thailand, Brazil, El Salvador, and Costa Rica. The efficacy of two more vaccine candidates, DENVax and TV003/TV005, has been investigated in Asia and Latin America (Hadinegoro et al., 2015; Aguiar et al., 2016). The four dengue virus serotypes (DENV) constituted a threat to control and provided impetus for vaccine research in 2019, as they resulted in 56 million cases of illness and 5000–40,000 deaths over a range of tropical and subtropical countries. The molecular and immunological characteristics of DENV in humans inevitably impact the outcomes of clinical studies for dengue vaccines. Infection with any DENV serotype in the first place usually causes mild to moderate feverish symptoms that last for a short while in people who have never been infected. Lifelong defense against reinfection with the same immunological DENV serotype is offered by these initial infections. A large portion of the severe dengue disease spectrum seen worldwide is caused by secondary infections. Rarely can severe dengue fever develop during the third or fourth DENV infection. The immunological state that protects against secondary infections plays a role in the development of dengue vaccines (Yang et al., 2021; Halstead et al., 2002). Live-modified dengue virus vaccines are a type of vaccine that protects against dengue fever. These vaccines contain a weakened form of the dengue virus that can stimulate an immune response without causing severe disease. Currently, some live-modified dengue vaccines available include Dengvaxia TV, Dengvaxia® (CYD-TDV), Tetravax (TV003/TV005), TAK-003, TDEN F17/F19 vaccine, Dengue with host range (HR) mutation, KD382, DENVax, and Butantan-DV (Ng et al., 2016; Wilder-Smith, 2024; Wharton-Smith et al., 2019; Kallás et al., 2024; Prompetchara et al., 2020; Huang et al., 2021). Vaccines against the inactivated or dead dengue virus can stimulate the immune system but cannot spread illness. Inactivated vaccines are usually administered in multiple doses. Some inactivated or killed dengue virus vaccines include TDEV PIV and purified psoralen-inactivated virus (Prompetchara et al., 2020; Huang et al., 2021; Dengue, 2009). Subunit vaccines comprise particular dengue virus proteins or components that are immunogenic and able to trigger an immune response. These vaccines can target specific proteins, such as envelope (E) proteins and non-structural proteins. Some of the most notable subunit vaccines include V180 (DEN-80E), which often requires multiple doses. Viral vector vaccines utilize harmless viruses, such as adenoviruses or chimeric viruses, to deliver dengue virus proteins and genes into the body. These viral vectors stimulate an immune response against dengue virus, such as the VEE-Dengue VRPs vaccine (Prompetchara et al., 2020; Huang et al., 2021; Flores et al., 2020). A DNA vaccine for dengue virus has been developed and is currently undergoing clinical trials. Furthermore, a tetravalent dengue DNA vaccine has been created by mixing equal parts of plasmid DNA that encodes the prM and E genes of each of the four serotypes (1, 2, 3, and 4) that VR1012 simulates. Other nucleic acid-based vaccines include D1ME100 and TVDV (Prompetchara et al., 2020; Huang et al., 2021; Kellstein and Fernandes, 2019). It is significant to remember that different countries may have different dengue vaccination policies and recommendations. Guidelines for the administration of dengue vaccinations and their incorporation into dengue preventive and control tactics are provided by the World Health Organization (WHO). The future outlook for dengue vaccine research and development is promising, with potential advancements in dengue prevention and control (Kamath and Aishwarya, 2024).

10. Conclusions

The dengue virus, which has spread rapidly throughout the world and is becoming more common every day, poses a major threat to human life. The primary barriers are the virus's very complex pathophysiology and its connection to bolstering the immune system. Although several live attenuated quadrivalent dengue vaccines are licensed and some are in the experimental stage, the goal is to develop an effective dengue vaccine. In order to comprehend host genetics and soluble proteins that affect susceptibility or level of protection against dengue virus infection, more research is necessary. Dengue virus vaccinations and diagnosis techniques need to be affordable because the majority of the nations where outbreaks occur are struggling financially. The three main methods of managing dengue vector mosquitoes are biological, chemical, and environmental. The goal of these strategies should be to reduce dengue virus transmission by concentrating on regions with high human-to-vector contact. Surveillance is a key component of preventing dengue virus outbreaks. It involves gathering the data and information required for epidemiological forecasting, ranging from genetic traits of the virus to the kind and severity of mild disease caused by primary or secondary infection linked to the circulating serotype in

epidemic areas.

Author contributions

IP, AG and AF wrote, reviewed, and edited the manuscript and Figs. HN, AG and MP wrote and reviewed the manuscript. IP, HN and AF conceptualized, wrote, reviewed, and edited the Figures and made the graphical abstract. IP, HN and MP reviewed and edited the manuscript.

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Declaration of competing interest

The authors declare no confict of interest, fnancial, or otherwise.

Data availability

This review is based on published, publicly available data, and did not involve the collection of new data.

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