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REVIEW

Dengue: epidemiology, diagnosis methods, treatment options, and prevention strategies

Dimple Kothari[1] · Niralee Patel[1] · Ashok Kumar Bishoyi[1]

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Abstract

Dengue is an arboviral disease caused by dengue virus, which is mostly found in tropical regions, and the number of human cases has increased dramatically since 2000, with 5.2 million cases reported in 2019, according to WHO reports, 70% of which were in Southeast Asia, the Western Pacific, and Asia. Dengue infection can result in a wide range of clinical manifestations, ranging from fever to severe dengue shock syndrome, which can be fatal, particularly in those with secondary dengue. This review of the aetiology of dengue fever examines the complex interactions between the virus and the immune system and the interaction between viral and host factors and also covers outbreaks, the severity of disease caused by different serotypes, and methods for diagnosis of dengue, such as serological tests, nucleic acid amplification tests, and ELISA assays for detecting the NS1 antigen. Current treatment options and prevention strategies, including vector control measures, environmental interventions, and insect repellents are also discussed. This review highlights the challenges involved in developing a dengue vaccine, which is complicated by the need for an efficient and balanced immune response against all genotypes of the four serotypes.

Abbreviations

RNA	Ribonucleic acid
DENV	Dengue virus
DHF	Dengue haemorrhagic fever
GOARN	Global Outbreak Alert and Response Network
SEA	Southeast Asia
DENV 1	Dengue virus 1
DENV 2	Dengue virus 2
DENV 3	Dengue virus 3
DENV 4	Dengue virus 4
PCR	Polymerase chain reaction
qRT-PCR	Quantitative reverse transcription PCR
ELISA	Enzyme-linked immunosorbent assay
HI	Hemagglutination inhibition
NT	Neutralization test
CF	Complement-fixation test
PRNT	Plaque reduction neutralization test
FDA	Food and Drug Administration
CYD-TDV	Chimeric yellow fever virus DENV tetravalent dengue vaccine
LATVs	Live-attenuated tetravalent dengue vaccine
NIH	National Institutes of Health
ADE	Antibody-dependent enhancement
CR	Complement receptor
DEG	Differentially expressed gene
SD	Severe dengue
CP	Convalescent patient
NK	Natural killer cell
ACOT	Acyl-CoA thioesterase

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✉ Niralee Patel
niraleegpatel@yahoo.co.in

Dimple Kothari
dimplekothari71298@gmail.com

Ashok Kumar Bishoyi
ashokbiotech4@gmail.com

[1] Department of Microbiology, Faculty of Science, Marwadi University, Rajkot, Gujarat 360003, India

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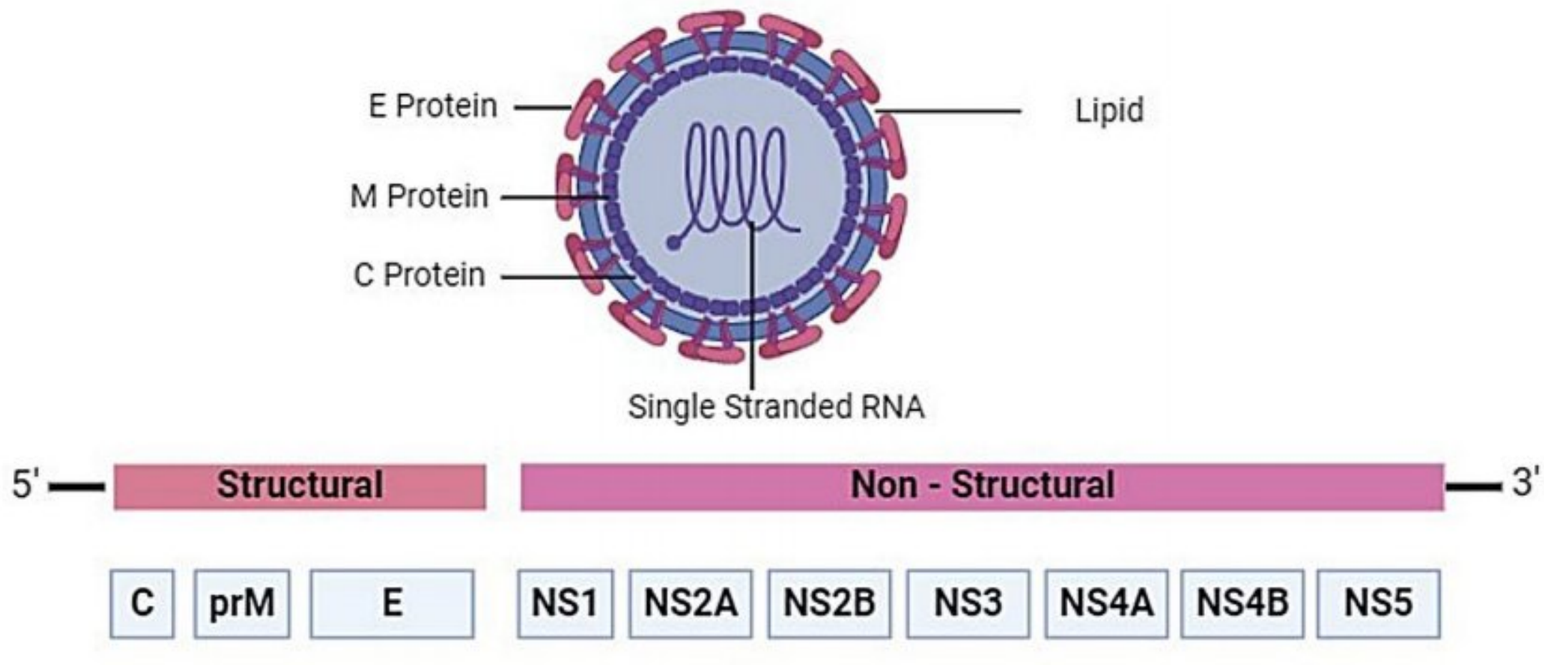
Introduction

Dengue virus (DENV) is an arthropod-borne virus that is spread by *Aedes aegypti* and *Aedes albopictus* mosquitoes in subtropical and tropical regions. *Aedes aegypti* is a peridomestic species that is mostly found in urban areas, whereas

Fig. 1 Structure of dengue virus



Aedes albopictus, whose populations are expanding rapidly, is a potential vector in rural areas [1]. Clinical features of dengue include headache, arthralgia, fever, thrombocytopenia, skin rash, leukopenia, and increased liver activity. It has become a global public health threat over the past seven decades [2]. About 50% of the global population is at risk of DENV infection, and over the past 50 years, the number of reported DENV infection cases has increased by 30-fold in both rural and urban areas across the world [3]. The risk factors for severe dengue include young age, individual genetic characteristics, and previous infection with a different dengue virus serotype [4]. In suburban and urban areas, mosquitoes breed in containers and thrive in warm, humid conditions [5].

It has been estimated that, globally, there are 390 million dengue fever cases and around 22,000 associated deaths each year [4, 6, 7]. The World Health Organization (WHO) estimates that there were 5.52 billion cases of dengue fever from 2000 to 2019 [8], with 40–50% of the population living in areas where dengue fever is common. In Asia, America, and Africa, dengue is a major disease with a prevalence of 70%, 16%, and 14%, respectively, and DENV is considered endemic in over 100 countries [5, 8].

DENV is a spherical, positive-sense, single-stranded RNA virus. Its genome is approximately 10–11 kb in length and has a capped structure, and DENV virions have a diameter of about 50 nm [9]. The structure of dengue virus and its genome are depicted in Fig. 1. The genome encodes a single polyprotein of 3.4 kDa, which is cleaved into three structural proteins (capsid, membrane precursor, and envelope) and seven non-structural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5) [10]. The single open reading frame is flanked by 5' and 3' untranslated regions ranging from 95 to 135 nt and 114 to 650 nt in length, respectively [11]. The non-structural proteins, which are not incorporated into the virion, are responsible for immune evasion and replication of the viral genome [12]. The functions and composition of both the structural and non-structural proteins are listed in Table 1.

Table 1 Functions of the structural and non-structural proteins of dengue virus

Gene/protein	Length	Function
C	100 aa	Genome encapsulation
Pre M/M	166/75 aa	Pre M/M functions as a cap-like structure that prevents the E protein from inducing premature fusion.
E	493–495 aa	E mediates viral binding and fusion. Domain III contains determinants of host range, tropism, and virulence.
NS1	46 aa	NS1 inhibits complement activation and is involved in viral replication.
NS2A	218 aa	NS2A coordinates the switching between RNA packaging and replication and is involved in antagonism of interferon production
NS2B	130 aa	NS2B is a cofactor for NS3 involved in the structural activation of the DENV serine protease.
NS3	618 aa	NS3 is a multifunctional protein with chymotrypsin-like serine protease, RNA helicase, and RNA triphosphatase (RTP/NTPase) activity that is involved in polyprotein processing and RNA replication.
NS4A	150 aa	NS4A causes membrane modifications that are essential for virus replication.
NS4B	245–249 aa	NS4B facilitates viral RNA replication by interacting directly with NS3 and hinders interferon-induced signalling.
NS5	900 aa	NS5 is a bifunctional enzyme with methyltransferase and RNA-dependent RNA polymerase activity

Virus transmission cycle

Aedes aegypti is an efficient vector of arboviruses that is highly anthropophilic and feeds multiple times before completing the oogenesis process [10]. The eggs of female mosquitoes are often deposited in tires, flower pots, or

water-filled buckets, which can serve as breeding sites for mosquitoes that facilitate the spread of the virus [13]. The transmission cycle of DENV and symptoms of dengue are depicted in Fig. 2.

Humans are the primary amplification host of DENV, which is spread by female mosquitoes when they ingest the blood of infected individuals. The virus replicates in the mid-gut of the mosquito and then spreads to secondary tissue such as the salivary gland. There is an extrinsic incubation period of 8–12 days between the time of ingestion and transmission of the virus to a new recipient [10]. During this period, virions are released in the saliva, allowing the virus to be transmitted to the human host [14].

Pathophysiology of dengue

After an infected mosquito bites the host, there is an incubation period of up to 2 weeks (commonly 5 to 7 days) before the symptoms develop. The pathogenesis of dengue is influenced by a number of viral and host factors. There are three phases to the illness: an initial phase of febrile illness, a critical phase starting about 4–5 days after the onset of fever, and a spontaneous recovery phase [15]. During the fever phase, the infected individual develops a high temperature (39 to 40°C) with symptoms such as headache, vomiting, nausea, myalgia, and joint pain. The critical phase occurs about 42–76 hours after the onset of illness [10]. Based on symptoms alone, DENV infections are difficult to differentiate from other infectious diseases such as malaria, leptospirosis, influenza, measles, typhoid, or rickettsia, or coronavirus or Zika infections [16].

DENV invades the host cell through endocytosis. Within the cell, the viral membrane fuses with the endosomal membrane to discharge the viral genetic material into the cytoplasm, where it is translated from viral RNA into 10 proteins. Virus particles are assembled on the surface of the endoplasmic reticulum and mature in the Golgi network before they are released from the cell in their infectious form [17]. The replication cycle of dengue virus is illustrated in Fig. 3.

DENV outbreaks

In the Eastern Mediterranean, the Americas, Southeast Asia, Africa, and the Western Pacific, DENV is endemic in 100–128 countries, with a large number of fatal cases [18]. WHO reported around 12 million cases of dengue illness and dengue haemorrhagic fever (DHF) in 1998, with 3448 fatal cases, resulting in fatality rates of 0.5–3.5% in Asian countries [19]. Globally, DENV infects around 400 million individuals each year, with 100 million experiencing clinical symptoms [20]. Dengue outbreaks were reported in Indonesia and Egypt already in 1779, and, in 2003, dengue fever was reported in Bangladesh, Thailand, Indonesia, India, Sri Lanka, the Maldives, Myanmar, and Timor-Leste [10, 21].

Bhutan reported its first DENV outbreak in 2004, and the Global Outbreak Alert and Response Network (GOARN) reported an outbreak in Timor-Leste with a fatality rate of about 3.55% in 2005. Nepal reported its first dengue fever case in 2006. From 2001 to 2007, 1299 people suffered from DHF, with a fatality rate of 1.2% [10]. From 2010 to 2016, approximately 1.6 million dengue cases were reported in South and North America, 49,000 of which were severe. The largest outbreak was in 2016, when 2.38 million cases

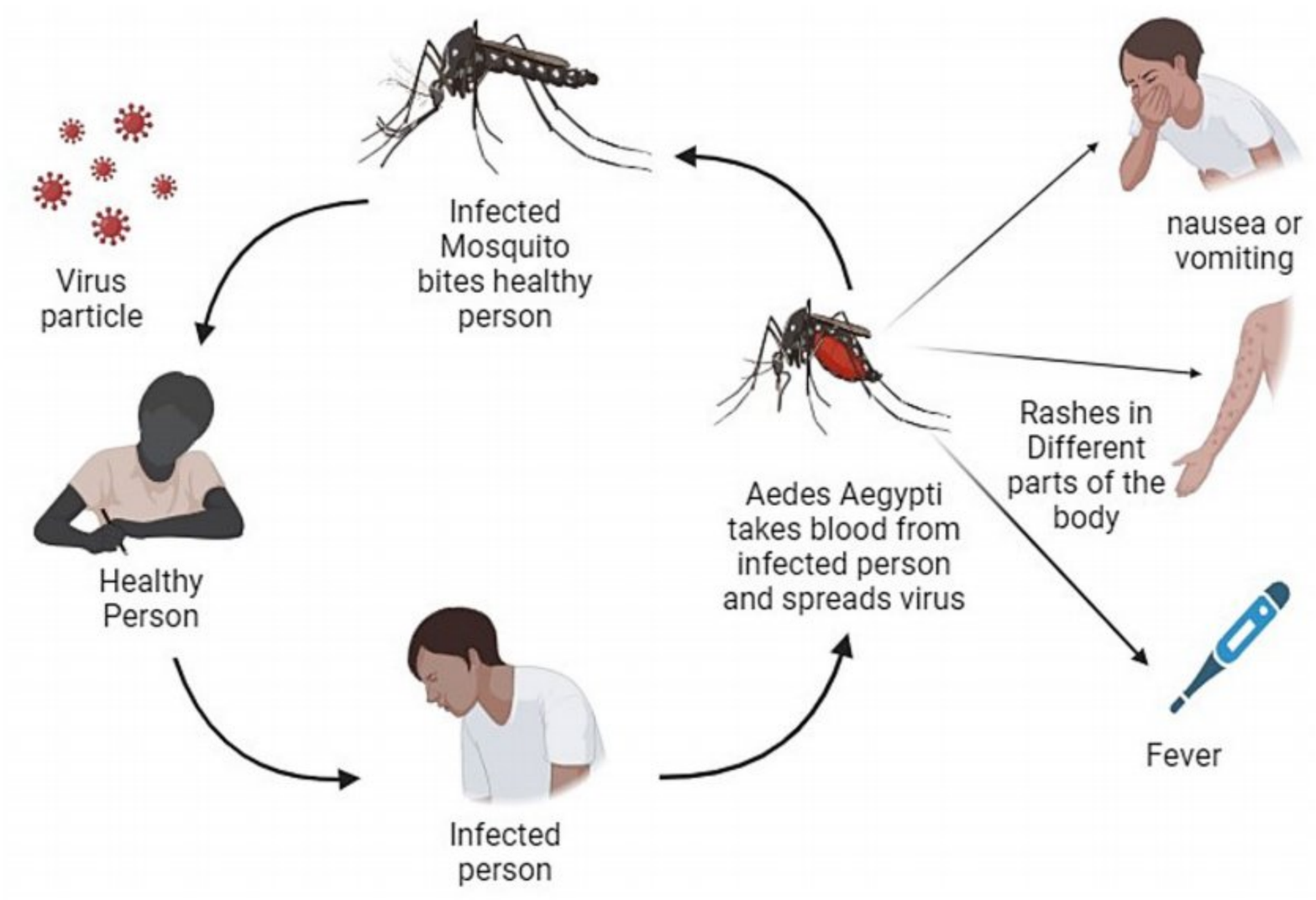


Fig. 2 Transmission cycle of DENV

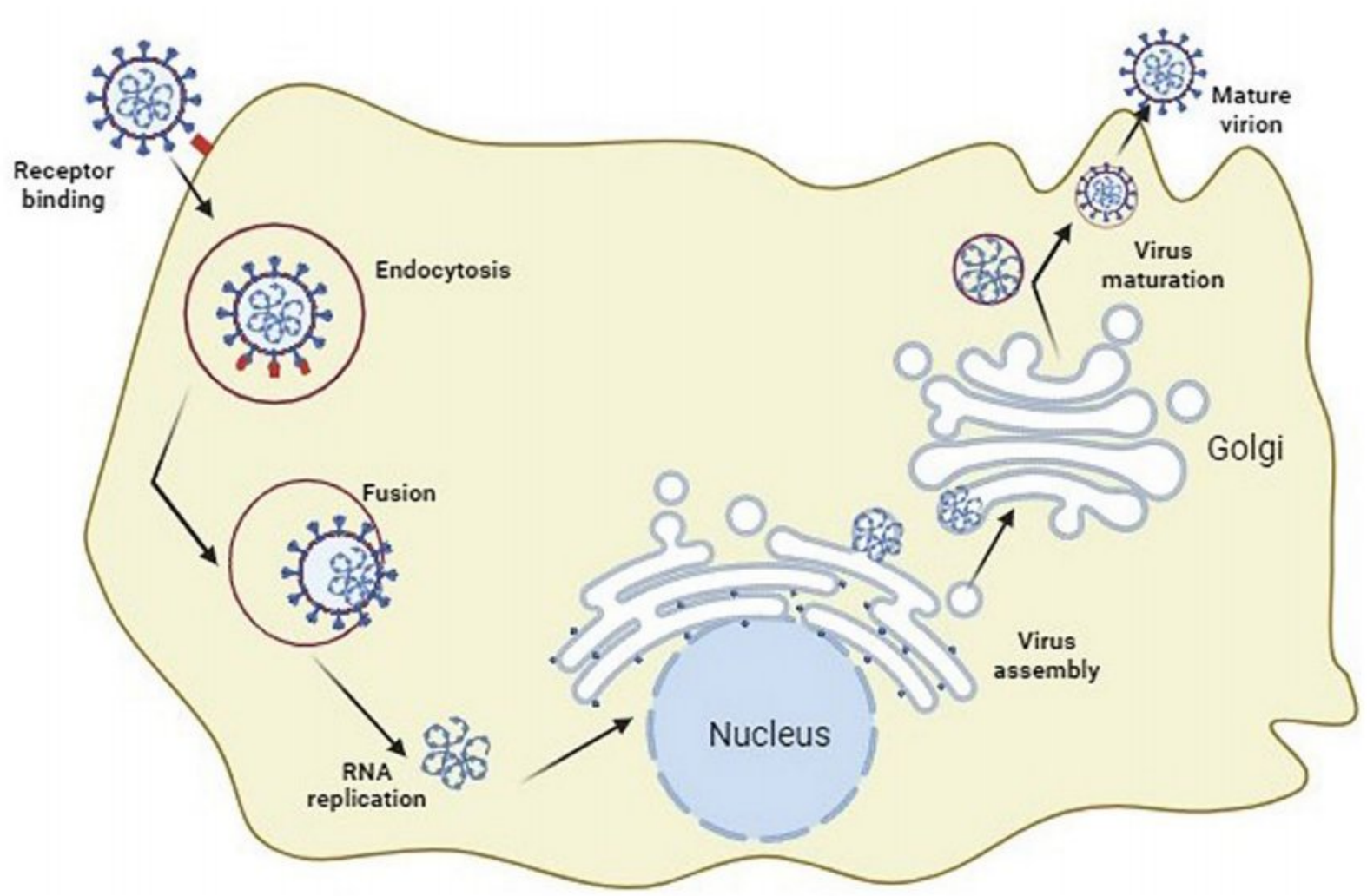


Fig. 3 The replication cycle of dengue virus

were reported. In the years 2010 to 2020, there was a large increase in the hospitalization of children between 10 and 19 years of age due to dengue in the US territory of Puerto Rico [22]. In 2014, Japan experienced its first outbreak in 70 years [23]. At that time, Brazil recorded its highest number of cases, around 1.5 million, which then increased to 3 million cases by 2019 [24]. DENV transmission has also been documented in various European countries, indicating that it is not limited to the tropics [25]. A study conducted between 1990 and 2019 found that dengue illness had increased by 85.47% worldwide during that period [26]. Afghanistan, Côte d'Ivoire, Tanzania, Benin, the Democratic Republic of the Congo, Burkina Faso, Angola, and many European countries are among the countries into which DENV has expanded recently [18, 27, 28]. According to the European Centre for Disease Prevention and Control (ECDC), more than 7.5 million dengue cases and over 3000 deaths have been reported in 73 countries. The current status of dengue is illustrated in Fig. 4.

The dengue burden is higher in South and Southeast Asian countries, including Bangladesh, India, Pakistan, Nepal, Sri Lanka, and the Maldives, with 1.3 billion cases worldwide [21, 27, 29, 30]. Data from 2015–2019 indicated a 46% increase in the number of dengue cases, from 451,442 to 658,301. However, there was a slight decrease in mortality during that period, with the number of fatal cases decreasing from 1584 to 1555 [8]. Together, China, Malaysia, Japan, Singapore, Indonesia, Korea, Myanmar, Thailand, Vietnam, Laos, the Philippines, Cambodia, and other East Asian countries account for 60% of dengue cases [31].

Status of dengue in India

In India, the capital city of Delhi has seen a concerning increase in dengue cases, but no fatalities have been reported recently. Typically, dengue cases are reported in India during July and November. However, the financial hub Mumbai has also seen a notable increase in dengue infections, and other states, including Andhra Pradesh, Tamil Nadu, Telangana, Karnataka, Maharashtra, West Bengal, and Uttarakhand, are also reporting cases. The National Vector Borne Disease Control Program (NVBDCP) has made public official data indicating that, as of August 30, 2022, India had recorded 30,627 dengue cases, 12 of which were fatal. However, in the previous year, 2021, there had been 93,245 cases, 36 of which were fatal [32].

Association of serotypes with disease severity

Dengue viruses that infect humans can be classified into four serotypes: DENV-1, DENV-2, DENV-3, and DENV-4. The existence of multiple serotypes plays an important role in the commonly observed phenomenon that secondary DENV infections often cause more-severe disease than do primary infections. This is believed to be due in part to antibody-dependent enhancement (ADE), in which serotype-specific antibodies are formed during a primary infection and confer long-lasting immunity against the infecting serotype, but, when the individual is infected later with a different serotype, the antibodies generated are unable to neutralize the virus and instead combine with it to form immune complexes that infect cells more efficiently than the virus alone.

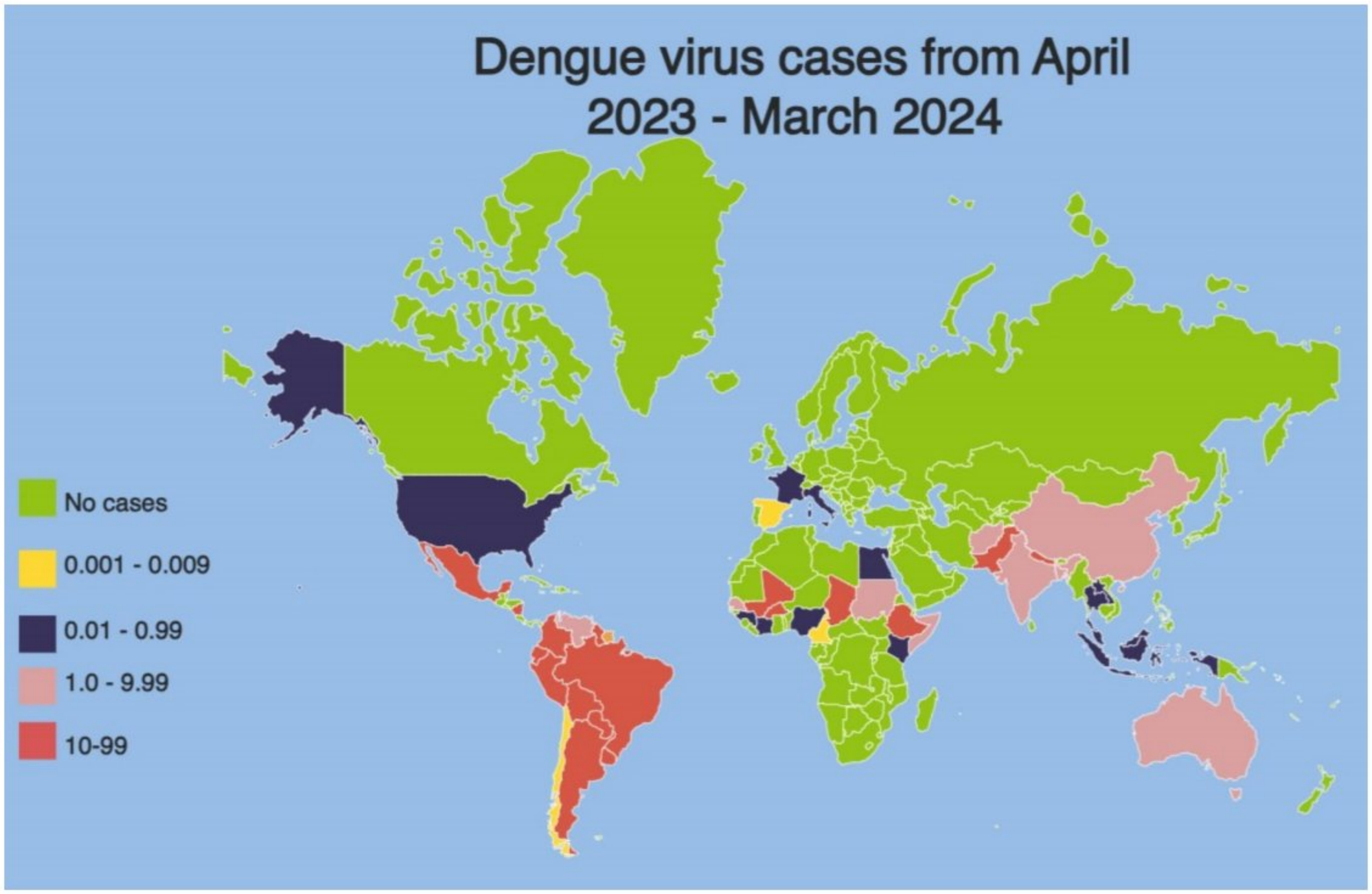


Fig. 4 Current status of dengue worldwide

During a secondary infection, experimental animals show a higher peak of virus production than during the first infection [33]. The envelope proteins of the four dengue virus serotypes differ in their amino acid sequences by about 30% [34]. Furthermore, the severity of infection also depends on which serotype caused the first infection. Anantapreecha and colleagues reported that primary infection with DENV-1 is associated with more-severe secondary infections when compared to other serotypes [35]. In a study evaluating the immunogenic effects of different dengue serotypes, it was found that the NS4A, NS4B, and E proteins of DENV-2 and DENV-3 elicited stronger cytokine responses, including TNF-α and IFN-γ responses, when compared to other serotypes [36]. On the other hand, DENV-4 was found to be less immunogenic [37].

DENV-2, which causes infections worldwide and is more commonly associated with major diseases than the other serotypes, is circulating extensively in South America [3, 38] and has been associated with an increased mortality rate in Brazil [24]. The risk of severe disease increases with the co-circulation of multiple DENV serotypes due to the potential for infection with different serotypes [39]. Several studies have provided information on the global spread of DENV-2, highlighting the need for further research on phenotypic variation, survival of strains, and adaptation of the host, which affects the epidemiology of the virus and supports its circulation in endemic regions [40]. The introduction of various serotypes and their persistence over time increases the risk of clinical re-infection with different serotypes [41].

DENV-2 is constantly changing due to its high rate of mutation and migration, resulting in the emergence of new strains. The concurrent circulation of various strains of the virus in a region can lead to a larger number of epidemic events than are caused by the other three serotypes [42–45]. There are five different genotypes of DENV-2: American or genotype I, which is prevalent in the Caribbean and South Pacific; cosmopolitan or genotype II, in Taino, the Philippines, New Guinea, and Thailand; Asian-American or genotype III, in Vietnam, Jamaica, and Thailand; Asian I and II or genotype IV, in Indonesia, the Seychelles, Burkina Faso, Sri Lanka, and Vietnam; and sylvatic or genotype V, in rural areas of Africa [46]. The distribution of these genotypes is shown in Fig. 5.

Widespread travel has contributed to the high genetic diversity of all four dengue serotypes, and this has important implications for immunity or vaccine efficacy [47–50]. The number of arbovirus infections can be reduced by

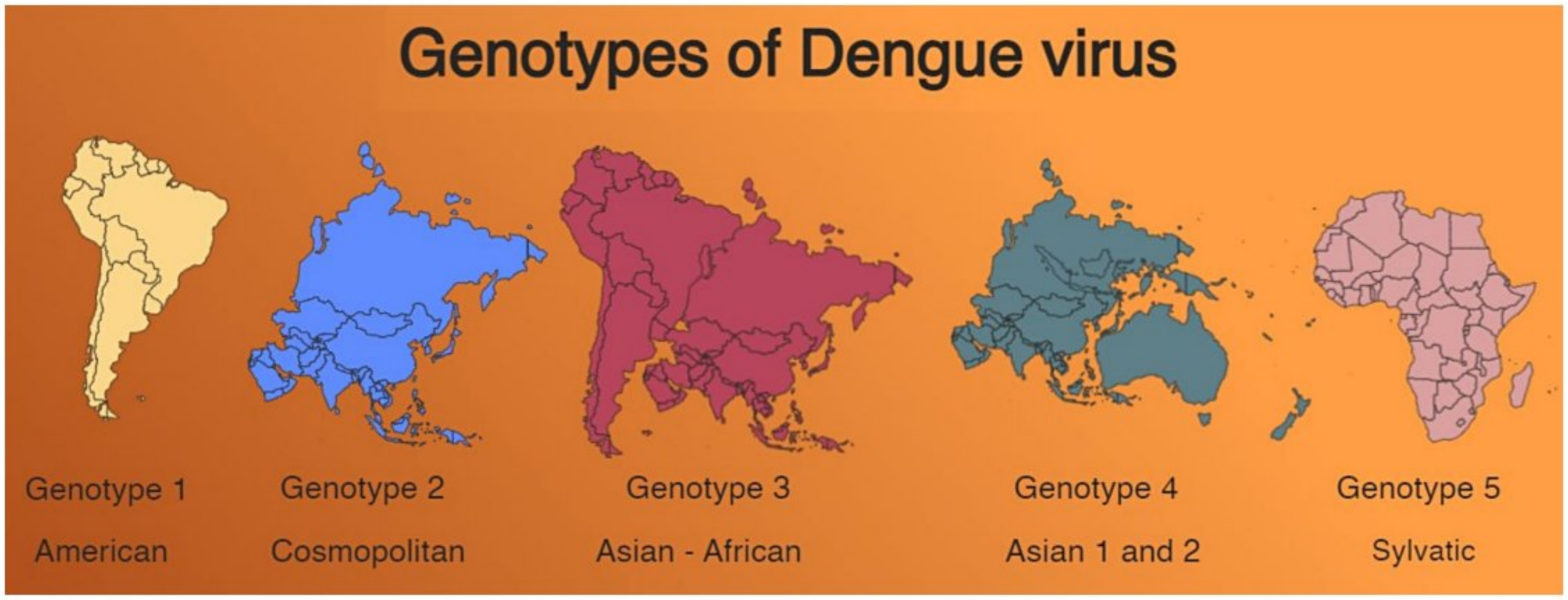


Fig. 5 Genotypes of DENV-2

monitoring their ongoing spread worldwide, investigating the possible causes of their recurrence, and conducting epidemiological surveys in endemic areas [51].

Genes and enzymes involved in dengue pathogenesis

The pathogenesis of dengue is influenced by immune responses to DENV infection. Individuals with DHF often exhibit elevated levels of circulating cytokines and chemokines, along with extensive immune activation [52, 53]. The heightened risk of severe dengue during secondary infection is partly explained by antibody-dependent enhancement (ADE) of infection and partly by the phenomenon of T-cell "original antigenic sin", in which memory B and T cells activated by the initial serotype may show reduced affinity for epitopes of the subsequent infecting serotype [54]. ADE occurs when antibodies from a previous infection bind to viral particles of a different DENV serotype in the current infection, but instead of effectively neutralising the infecting virus, these antibodies facilitate viral entry into Fc-receptor-bearing immune cells, such as monocytes and dendritic cells, thereby increasing viral replication and the overall viral burden [54, 55]. Although the complement system plays a protective role in limiting viral replication, its excessive activation can lead to more-severe disease by intensifying the inflammatory response. Initial studies showed the occurrence of extensive complement activation and a significant decrease in the levels of plasma complement proteins in DHF patients [56]. Plasma from patients with severe dengue during a secondary infection with a different serotype showed elevated levels of complement anaphylatoxins (C3a and C5a) and the terminal complement complex (sC5b-9), suggesting a link between complement activation and dengue severity [57]. These observations indicate that complement overactivation contributes to DHF pathogenesis. During the acute phase of the disease, soluble immune complexes (IC) formed by circulating DENV and DENV-specific antibodies have been detected in patients' circulation [58]. These complexes can be opsonised with complement molecules and rapidly captured by complement receptors (CR1) on red blood cells (RBCs). The complement-fixing ICs adhere to the cells until IC-bound RBCs pass through the spleen and liver, where IC is removed from the RBCs and deposited in these tissues [57]. While this mechanism is crucial for viral clearance from the circulation, DENV, in the form of an IC, potentially exploits this opportunity to infect Fc-receptor-bearing cells in the liver, potentially disseminating the infection. However, this hypothesis requires further investigation. It is worth noting that soluble IC activates complement less efficiently than large immune complexes where anti-DENV antibodies bind to dengue antigens present on DENV-infected cell surfaces [59].

Microarray technology enables the analysis of differentially expressed genes (DEGs) during dengue infection, revealing virus-host interactions and identifying biomarkers for dengue and severe dengue through genome analysis of host gene expression in peripheral blood [60]. However, the gene sets identified thus far have not demonstrated universal applicability. It is therefore useful to examine differences in gene expression signatures between four pairs of groups: (1) DF and healthy controls (CO), (2) SD and healthy CO, (3) convalescent patients (CP) and DF, and (4) CP and SD.

MICB has been identified as a crucial gene in dengue infection. This gene produces an activating ligand for natural killer cells (NK) and potentially CD8 T lymphocytes. Changes in MICB levels can affect the antiviral capabilities of NK cells, thereby increasing the risk of severe dengue (SD) [61]. MICB is upregulated in the DF vs. CO and SD

vs. CO scenarios, with a 0.9-fold change, whilst in the CP vs. DF and CP vs. SD scenarios it is downregulated, with a 0.1-fold change. Toll-like receptors (TLRs) are essential for recognising pathogens and activating inflammatory pathways during dengue infection [62]. TLR6 gene expression decreases in DF vs. CO and SD vs. CO comparisons, with fold changes of -1.325 and −1.422, respectively. In contrast, TLR7 gene expression increases by 1.3-fold in both cases. TLR7, which recognises single-stranded RNA viruses, modulates host immune responses by detecting viral uridine-containing single-strand RNAs. Among the immune-response-associated genes, enhanced expression of TNFSF13B has been observed, with a 1.27- and 1.39-fold change in DF vs. CO and SD vs. CO comparisons, respectively. Conversely, TNFRSF10B, C, and 14 showed reduced expression. TNFSF13B is linked to B cell activation and is involved in the immune response to live attenuated tetravalent dengue vaccine candidates [63]. Furthermore, TNFRSF17, which is critical for regulating humoral immunity and promoting B cell survival, showed upregulation, with 3.8- and 2.8-fold changes in SD vs. CO and DF vs. CO comparisons [37]. A group of genes encoding nuclear factors 1A, 1B, and 1C display downregulation in SD vs. CO and DF vs. CO comparisons.

Enzyme specificity and its role in differences between dengue serotypes

Enzymes play a multifaceted role in the context of dengue serotypes, influencing both viral replication and the host immune response. Each of the four DENV serotypes has a unique enzymatic profile that influences its pathogenicity and the immune response it elicits [64]. One of the key viral enzymes is the NS2B-NS3 protease, which is essential for viral replication. This enzyme complex cleaves the viral polyprotein into the functional proteins necessary for genome replication and the assembly of new virions and is therefore a potential target for antiviral drug development [65]. Inhibitors of the NS2B-NS3 protease have shown promise in preclinical studies, highlighting the potential for therapeutic interventions that could mitigate the impact of dengue fever [66]. In addition to viral enzymes, cellular enzymes also play a significant role in the host's immune response. For example, the presence of dengue virus can trigger the activation of host enzymes such as cyclooxygenases (COX) and lipoxygenases (LOX), which are involved in the inflammatory response. This inflammatory cascade can lead to symptoms associated with dengue, such as fever, pain, and, in severe cases, haemorrhagic manifestations [67]. Understanding the interactions between viral enzymes and host enzymes is crucial for developing effective treatments and vaccines, and the pattern of enzymatic activity can vary significantly among the DENV serotypes. For instance, DENV-2 has been associated with more-severe disease manifestations compared to DENV-1, partly due to differences in how these serotypes interact with the host's immune system and the role of enzymes involved in these processes [68].

The upregulation of diverse lipid species plays a crucial role in the life cycle of DENV serotype 2 (DENV2). Notably, host phospholipids and sphingolipids become more abundant during infection, some of which facilitate viral replication, while other are involved in the host response to infection [69]. These molecules originate from fatty acyl-CoAs, which are fatty acids that have undergone esterification to coenzyme A (CoA). The acyl-CoA thioesterases (ACOTs) are a family of hydrolases that regulate the intracellular equilibrium between fatty acyl-CoAs and free fatty acids (FFAs). These enzymes catalyse the hydrolysis of fatty acyl-CoA to release FFA and coenzyme A [70]. siRNA-mediated loss-of-function studies have shown that simultaneous knockdown of type I ACOTs 1 and 2 significantly enhanced the release of infectious DENV2 particles. Conversely, isolated knockdown of ACOT2 markedly reduced DENV2 protein translation, genome replication, and the release of infectious virus. Similarly, the loss of the function of ACOT7, a mitochondrial type II ACOT, has been shown to suppress DENV2 replication [70].

By identifying the specific types of enzymes involved and their mechanisms of action, new insights can be gained that might lead to innovative therapeutic approaches as well as a better understanding of dengue pathogenesis.

Diagnosis

A serological test can be used up to 7 days after symptoms start to appear to diagnose dengue fever and to determine the serotype of the virus. These tests are sufficiently sensitive to detect IgM and IgG at least four days after infection. Numerous methods for diagnosis of dengue have been described in the WHO guidelines, including serological tests, nucleic acid detection, antigen detection, and haematological tests. Although these methods can be used for rapid diagnosis in the field, they require expertise, advanced facilities, proficiency in lab work, and a considerable amount of time and effort for processing of serum samples for confirmation of positive cases [6].

The initial laboratory diagnosis of dengue is made by direct detection of viral components in serum or by serological analysis. Confirmatory tests include molecular diagnostics methods such as polymerase chain reaction (PCR) and quantitative reverse transcription PCR (qRT-PCR). The sensitivity of these methods depends on the time since the onset of disease [71]. The primary serological tests used for

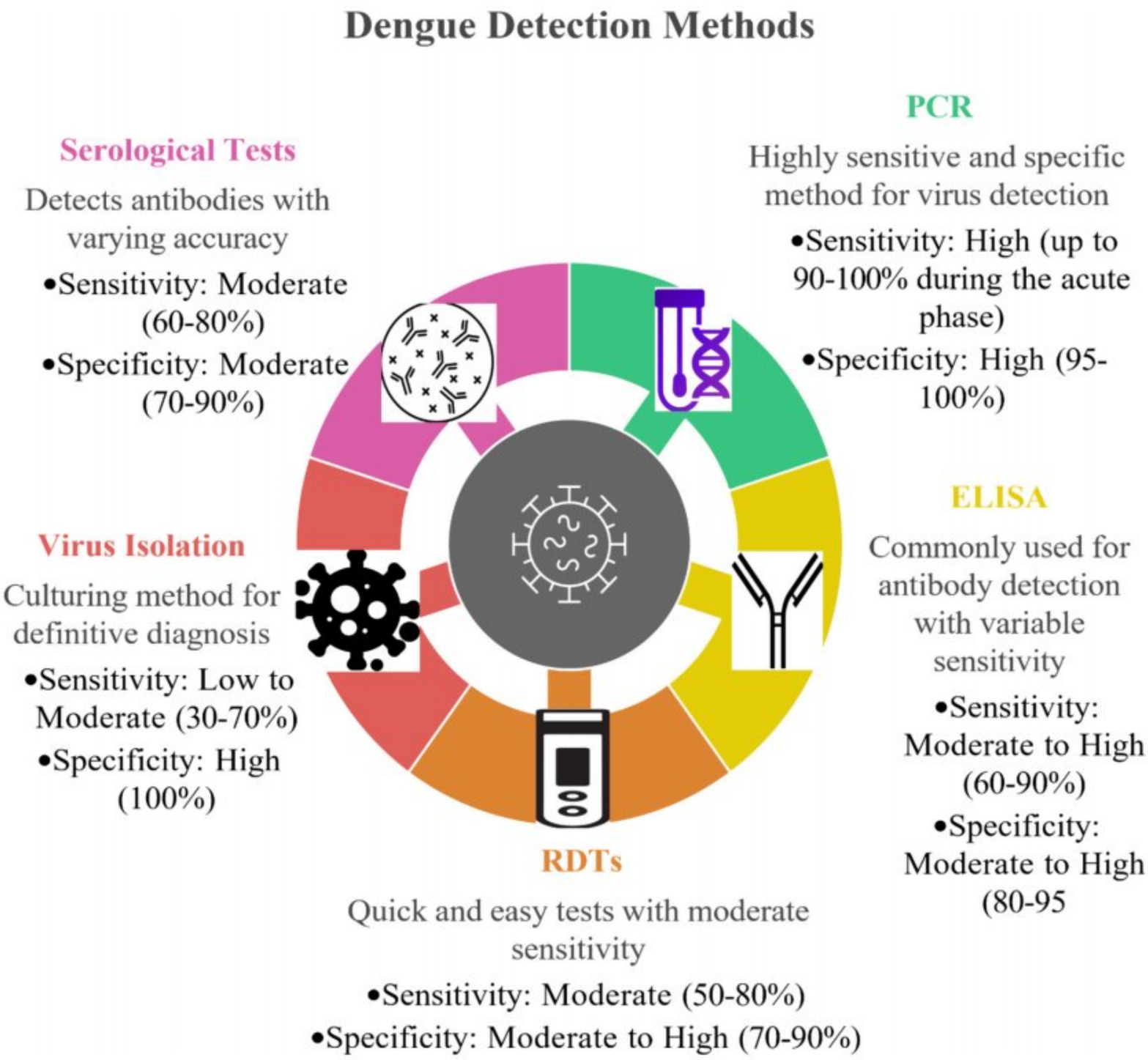


Fig. 6 Overview of diagnostic methods for detection of DENV infection

diagnosis are ELISA (enzyme-linked immunosorbent assay) hemagglutination inhibition (HI), neutralization (NT), complement fixation (CF), IgM capture ELISA (MAC-ELISA), and indirect IgG ELISA. However, these rapid diagnostic tests are not completely reliable due to the cross-reactivity of other flaviviruses [72]. Antibodies that are produced in response to infection are measured by ELISA-IgM capture and indirect IgG assays, but due to the cross-reactivity with closely related viruses, confirmatory tests such as the plaque reduction neutralization test (PRNT) are necessary. A summary of dengue diagnosis methods is shown in Fig. 6.

Serological tests

Dengue is most frequently diagnosed using serological tests for detection of IgM and IgG antibodies and HI tests, which are easy to perform, relatively inexpensive, and can be performed at room temperature. IgM can be detected around 7–10 days after the first exposure to the virus. During an acute infection, IgG levels tend to rise and then remain stable for an extended period. Complete blood cell counts are performed to test for low platelet levels, which is a common indication of late-onset dengue. Severe dengue fever is associated with blood loss, and therefore, haemoglobin, haematocrit, and red blood cell counts also need to be monitored [10].

The HI assay is dependent on the agglutination of red blood cells (RBCs) by the virus, which is mediated by the viral E protein, and allows the presence of anti-DENV antibodies in serum to be detected based on their ability to inhibit hemagglutination. However, ELISA-based techniques for detecting dengue-specific IgM and IgG have largely replaced this assay. IgM can be detected in serum about one week after the onset of fever, but the IgM ELISA has low sensitivity and specificity [73]. A recent study showed that the sensitivity and specificity of commercially available IgM kits differ greatly, depending on the quality of the antigen used [73, 74]. The plaque reduction neutralization test (PRNT) is another method for antibody detection. This assay is designed to detect neutralizing antibodies that block the infection of cultured cells. This assay has the advantage of differentiating between specific antibodies against DENV and cross-reacting antibodies against other flaviviruses [75].

Recently developed ELISA and rapid immunochromatographic (IC) assays have demonstrated the ability to identify primary and secondary DENV infections about 9 days after the onset of illness, by targeting the NS1 protein. The NS1

antigen is detectable within the first week of infection and can be used to confirm an active DENV infection [74].

A meta-analysis of 30 studies showed that the PanBio NS1 ELISA kit is 66% sensitive and 99% specific. The Platelia NS1 ELISA kit displayed a sensitivity of 74% and a specificity of 99%, which is different from the results obtained by other techniques [76]. A meta-analysis conducted by another researcher showed the IC assay to be slightly more sensitive than ELISA, achieving a sensitivity of 71% compared to 67% for ELISA [77]. NS1-based assays have been found to be especially useful for verifying DENV infections [77], but their low sensitivity makes them unreliable for initial diagnosis [78]. The first four to six days after infection are the best time to test for anti-dengue IgM antibodies. However, in secondary infections, IgM levels are sometimes too low to be detectable. Furthermore, as a result of cross-reactivity amongst flaviviruses, the specificity of IgG assays can also be reduced [73, 79].

Nucleic acid amplification tests

Nucleic acid amplification tests performed on different components of whole blood of symptomatic dengue patients demonstrate great sensitivity and specificity for the detection of DENV RNA within the first 7 days of illness [80].

Nucleic acid amplification tests are effective for diagnosing dengue within the first 7 days of infection, and viral RNA in a clinical sample can be detected within 1–2 days after infection. RT-PCR-based methods for DENV detection include one-step quantitative RT-PCR, multiplex RT-PCR [81], and nested RT-PCR [82]. The specificity of RT-PCR-based methods can vary between 80% and 100%, depending on the genome region targeted and the amplification or detection method used [6]. The multiplex RT-PCR test can be performed quickly, but it requires expensive equipment and reagents as well as skilled practitioners [6]. The single-step RT-PCR assay and species-specific RT-PCR assay have similar features [82, 83].

Molecular diagnostic assays for the detection of individual DENV serotypes are not available in many countries, especially in underdeveloped countries.

Treatment

At present, there is no specific treatment or remedy for dengue. The existing supportive treatment options aim to mitigate symptom severity and complications. Fluid therapy, especially intravenous fluid replacement in severe cases, is a crucial component of dengue management, intended to prevent shock [84]. The updated WHO guidelines offer specific details for managing dengue cases of differing severity. The U.S. Food and Drug Administration (FDA) has not yet approved any particular drugs for the treatment of dengue fever. Numerous potential anti-dengue therapeutic agents have undergone medical trials, including oral prednisolone, carbazochrome sodium sulfonate, and lovastatin [85, 86]. Trials have also explored treatments to reduce severe bleeding, particularly infusions of donated platelets or recombinant human (rh) IL-11 [87, 88]. Progress in the development of effective therapeutics has been sluggish, and there remains an unsatisfied need for a successful anti-dengue drug [5, 89]. Ideally, therapeutic drugs against dengue should be effective against all serotypes, should be fast-acting and well tolerated, and should have minimal toxicity. They should be easy to distribute, have few interactions with other medications, and be suitable for use in both children and adults, as well as in pregnant women and individuals with co-morbidities [89].

Vector control

The chief method for prevention of DENV infection is through vector control, which can be done using chemical or biological agents, such as larvicides or insecticides, or environmental interference, including the elimination of potential vector breeding sites such as containers and waste disposal areas [90]. Chemical control using insecticides is used in many regions [91], especially during dengue outbreaks [92]. Recently, novel biological control methods have been developed, including paratransgenesis, sterile insect techniques, and genetically modified vectors [91, 93–97]. Social measures to prevent human exposure to mosquitoes include the use of insect repellents, wearing sleeved clothes, and the use of mosquito nets for windows and beds [98, 99]. The majority of these approaches rely extensively on community involvement and compliance [100–102].

Vaccine

Government officials and policymakers in regions with a high incidence of dengue fever are now considering the potential benefits of using vaccination strategies for dengue prevention programs [103]. Historically, dengue vaccine development has been hampered by the need for a tetravalent vaccine that is capable of eliciting protective immunity against all four serotypes in order to prevent antibody-dependent enhancement. The first licensed vaccine, Dengvaxia (CYD-TDV), developed by Sanofi Pasteur, was found to be only partially successful due to its variable efficacy and safety in seronegative individuals, leading to very restricted usage recommendations [104]. Another recently developed dengue vaccine, CYD-TDV (chimeric yellow fever virus-DENV-tetravalent dengue vaccine), produced by Sanofi Pasteur, has been approved in numerous countries

and has undergone phase II clinical trials in Colombia, Brazil, Puerto Rico, Honduras, Mexico, Peru, Thailand, and Singapore [105–108]. TDV, previously called DENVax, is a chimeric vaccine developed by Takeda Vaccines Inc. TDV is built upon a DENV-2 a dengue-2 PDK-53 backbone and is effective against all four dengue serotypes. Recently, Takeda's TAK-003 (QDENGA) has completed phase III trials and has shown promising efficacy and safety results across diverse age groups and geographical regions [85]. TAK-003 demonstrated sustained protection against symptomatic dengue and hospitalizations for up to three years post-vaccination, with an overall efficacy rate of approximately 80%. Although it is most effective against DENV-2, it is also protective against DENV-1 and DENV-3 in both seropositive and seronegative individuals. Currently, however, its efficacy against DENV-4 has not been determined conclusively [85]. This vaccine's favourable profile positions it as a strong contender for widespread immunization programs, particularly in endemic regions [109]. Flavivirus-naive adults have been studied in two phase I studies to assess the safety and immunogenicity of TDV. No adverse effects were observed in either study. In addition, it was found that TDV induces high levels of antibodies against all four dengue serotypes in dengue-naïve adults [110, 111]. Vaccines stimulate immunity for up to four years, but their efficacy is affected by many factors, including the virus serotype as well as the age and the serostatus of the individual [112]. CYD-TDV has been shown to be protective in seropositive subjects over nine years of age. As recommended by the WHO Strategic Advisory Panel, seronegative patients should not be vaccinated with CYD-TDV, because vaccination increases the risk of severe dengue in these individuals [113].

Two live-attenuated tetravalent dengue vaccines (LATVs), TV003 and TV005, developed by the U.S. National Institutes of Health (NIH), continue to show robust immunogenicity and long-term protection in various phase II trials and have been shown to induce a better immune response than inactivated vaccines, subunit vaccines, or DNA vaccines [114]. The LATVs are more effective at inducing humoral and cellular immunity, they present viral epitopes in their native state, and they are less expensive to produce. In a randomized, double-blind trial including [115] flavivirus-naïve individuals, five tetravalent admixtures (TV001-TV005) were evaluated. The results showed an insignificant difference in the occurrence of antagonistic effects between vaccine and placebo recipients [116]. In flavivirus-naive individuals, the vaccine stimulated a trivalent antibody response in 90% of the cases, and after a single dose, seroconversion against all four DENV serotypes was observed in 45% of the subjects. The seroconversion rates were 85–100% for DENV-1, DENV-3, and DENV-4, but only 50% for DENV-2 [116].

D1ME100 is a nucleic acid vaccine developed by the Naval Medical Research Center in the United States that consists of plasmid DNA for expression of the E and prM genes [117]. DNA vaccines against DENV-1 and DENV-2 induce anti-dengue neutralizing antibody responses in primates, and the DENV-1 vaccine in particular demonstrated 80–95% protection against live virus challenge in rhesus macaques and Aotus monkeys [118].

Future dengue vaccines will need to generate a long-lasting, highly effective neutralizing antibody response against all four serotypes [5, 119]. This goal is made more challenging by the fact that DENV undergoes rapid evolution, resulting in numerous strains within each serotype, and there is considerable genetic divergence among the four serotypes, and even within each serotype. Therefore, further research on the development of a nontoxic and efficient vaccine that provides efficient cross-protection remains a global priority [119].

Conclusions and future aspects

The global burden of dengue is rising steadily, affecting over 100 countries with endemic transmission and causing significant outbreaks in various regions. DENV has four distinct serotypes that cause illness ranging from minor febrile infections to severe dengue with a fatal outcome. The pathophysiology of DENV infection is influenced by multiple viral and host factors, with severe disease frequently linked to secondary infections and the genetic traits of the host. Despite the use of laboratory tests including serological and nucleic acid amplification methods, accurate diagnosis is hindered by challenges such as cross-reactivity with other flaviviruses and the need for specialized equipment and expertise. Molecular diagnostic tests are not readily available worldwide and are expensive. Affordable and efficient kits for the detection of the individual DENV serotypes are still needed.

Although there is still a need for specific antiviral therapy for dengue, supportive care and preventive measures are available, and it is very important to manage the effects of the disease and prevent complications. Vaccination is a promising approach for preventing dengue, with several vaccines in development and some already approved for use in certain regions. A comprehensive approach to surveillance, diagnosis, treatment, and prevention is necessary to reduce the public health risk of dengue. We need to work across disciplines, regions, and sectors to mitigate its impact on global health. Climate change is projected to increase the disease burden of dengue, expand its geographical distribution, and cause more people to be exposed to the virus. While progress has been made in laboratory-based diagnosis, including

the development of point-of-care tests for detection of the viral NS1 protein and immunoglobulin M, reliable biomarkers for predicting severe disease progression are still lacking. Future research should focus on non-climatic drivers of dengue vector proliferation and factors that favor transmission in climatically suitable areas in order to improve projections and inform adaptation strategies. This research can be aligned with the sustainable development goal SDG No 3, which is to ensure healthy lives and promote well-being for all people at all ages.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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