



Dengue overview: An updated systemic review



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ABSTRACT

Dengue is caused by the dengue virus (DENVs) infection and clinical manifestations include dengue fever (DF), dengue hemorrhagic fever (DHF), or dengue shock syndrome (DSS). Due to a lack of antiviral drugs and effective vaccines, several therapeutic and control strategies have been proposed. A systemic literature review was conducted according to PRISMA guidelines to select proper references to give an overview of DENV infection. Results indicate that understanding the virus characteristics and epidemiology are essential to gain the basic and clinical knowledge as well as dengue disseminated pattern and status. Different factors and mechanisms are thought to be involved in the presentation of DHF and DSS, including antibody-dependent enhancement, immune dysregulation, viral virulence, host genetic susceptibility, and preexisting dengue antibodies. This study suggests that dissecting pathogenesis and risk factors as well as developing different types of therapeutic and control strategies against DENV infection are urgently needed.

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Contents

| | |
|---|------|
| Introduction | 1626 |
| Methods | 1626 |
| Results..... | 1626 |
| Dengue virus..... | 1626 |
| Epidemiology of dengue..... | 1628 |
| Dengue virus vectors and their distribution | 1629 |
| Clinical manifestations | 1629 |
| Risks and mechanism correlated dengue severity | 1630 |
| Antibody-dependent enhancement | 1630 |
| Viral factor..... | 1630 |
| Host factors | 1630 |
| Diagnosis..... | 1631 |
| Acute phase diagnosis | 1631 |
| Convalescent phase diagnosis | 1632 |
| Current challenges and future prospects for dengue diagnostic tests | 1632 |
| Dengue treatment..... | 1632 |
| Options for treating dengue illness by natural medicine | 1632 |

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| | |
|--|------|
| Dengue vaccine | 1632 |
| Advantages and disadvantages analysis of dengue vaccines | 1633 |
| Control strategies | 1635 |
| Community-based control programs | 1635 |
| Biological controls | 1635 |
| Chemical controls | 1636 |
| Discussion | 1636 |
| Conclusion | 1637 |
| Funding | 1637 |
| CRediT authorship contribution statement | 1637 |
| Declaration of Competing Interest | 1638 |
| Acknowledgments | 1638 |
| References | 1638 |

Introduction

Dengue virus (DENV) belongs to the *Flaviviridae* family, which includes more than 70 major human disease-causing pathogens affecting mostly inter-tropical regions, where 3.9 billion people live [1]. It is an arboviral disease that is mostly transmitted to humans by the bite of mosquitoes, especially those of the *Aedes* genus, primarily by *Aedes (Stegomyia) aegypti* (Linnaeus, 1762) and in some rare cases by *Aedes (Stegomyia) albopictus* (Skuse) [2]. Dengue virus has four serotypes including DENV-1, DENV-2, DENV-3, and DENV-4 and all serotypes can cause human infection [3]. The primary DENV infection may be asymptomatic or results in mild fever, but if it becomes severe, it can cause coagulopathy, increased vascular fragility, and increased permeability; this condition is called dengue hemorrhagic fever (DHF), and after that, it may progress to hypovolemic shock, which is called dengue shock syndrome (DSS). These two diseases are life-threatening and be potentially fatal [4]. Most DF diseases are self-limited with a low mortality (< 1%) when detected early and provided with proper medical care. Some patients might develop severe diseases (including DHF/DSS) with a mortality rate around 2%– 5% after receiving treatment; when left untreated, the mortality rate is as high as 20% [5,6].

Epidemiological survey indicates that DENV infection is spread to approximately two-fifths of the world's population, infecting nearly 390 million people annually, resulting in 500,000 hospitalizations and 20,000 deaths. It is mostly distributed in the Eastern Mediterranean, Southeast Asia, Africa, the Western Pacific, and South America [7]. Approximately 2.5 billion people are at threat of contracting dengue, and the cases which are reported are 100 million of dengue fever each year, up to 500,000 go on to develop the infection's potentially fatal DHF or DSS. The majority of DHF and DSS cases are brought on by a subsequent viral infection with a different serotype or secondary infection. Currently, the reasons and mechanisms that lead to dengue severity and pathogenicity are not fully understood. The present knowledge indicates that several factors involved in virology and host immune system are correlated with DHF/DSS occurrence. In addition, the climate change also plays an important role in *Aedes* mosquitos' distribution, subsequently having impact on DENV transmission. Combined, this information indicates that dengue incidence and development of severe dengue syndromes are complicated. In this study, we conducted a systemic review to address the current knowledge and information regarding dengue pathogenesis, diagnosis, treatment and prevention to give an overview and updated information.

Methods

In this study, we analyzed the information from literatures regarding clinical manifestation, pathogenesis, diagnosis, treatment, prevention and control of DF/DHF. The literature review was performed following the PRISMA guidelines to select eligible articles

[8]. References were selected from several database including PubMed, Web of Science and Google Scholar. Search results was limited to articles published in the English language. The paper selection period spanned literature from 1980 to 2023, and the keyword search encompassed Dengue, Dengue virus, Serotype, Dengue fever, Dengue Hemorrhagic fever, Dengue Shock Syndrome, Clinical manifestation, Epidemiology, Treatment, Vaccines, and Control strategy. The selected articles were reviewed to assess their relevance, case numbers and quality of methodology (Fig. 1). Two independent reviewers assessed the level of data quality from these selected literatures. In this study, literature with a small sample size was excluded, defined as any study involving fewer than 100 participants diagnosed with dengue virus infection. Disagreements were resolved by joint discussion and consensus. Ethics approval and informed consent were not required for this study.

Results

Dengue virus

Dengue virus is a single-strand positive-sense RNA genome consisting of 11 kb in length [9]. The single predictable polyprotein is translated by the genome that is used by the virus-encoded protein into seven non-structural proteins and three structural proteins, which are defined as follows: Non-structural gene 1 (NS1) Non-structural gene 2 A (NS2A) and Nonstructural gene 2B (NS2b) Non-structural gene 3 (NS3) Non-structural gene 4 A (NS4A) Non-structural gene 4b (NS4b) Non-structural gene 5 (NS5) and the structural proteins, including capsid protein (CP), envelope protein (EP), and membrane protein (MP). Some of the noncoding regions (NTR) are also present on the 3' end of the genome [10,11] (Fig. 2). The structural protein plays a dynamic role in the structure of viral proteins, and the non-structural protein plays a vital role in virus entry, replication, assembly, and pathogenesis in the host, where they cause disease and pathogenesis [12].

This dengue is structured in an icosahedral shape and has an envelope formed by a layer of protein at its outer core. The icosahedral core is forty to fifty nanometers in diameter and has a C-protein viral genome. The core is surrounded by two well-known proteins, membrane (M) and envelope Proteins (E), which create the lipid envelope [13]. In addition, non-structure proteins play essential roles in regulation of DENV replication such as immunological regulation, inducing vascular leakage, assisting vRNA synthesis and dengue polyprotein cleavage. The functions and size of each non-structural gene of the dengue virus are discussed in the Table 1 below.

Regarding DENV infection and replication, there are numerous mammalian cell receptors reported to be mediated DENV attachment and entry such as DC-SIGN/l-SIGN [18,19], heparan sulfate [20], mannose receptor [21], HSP70/HSP90 [22], laminin receptor [23], dopamine receptor [24,25] etc. In the early phase of DENV

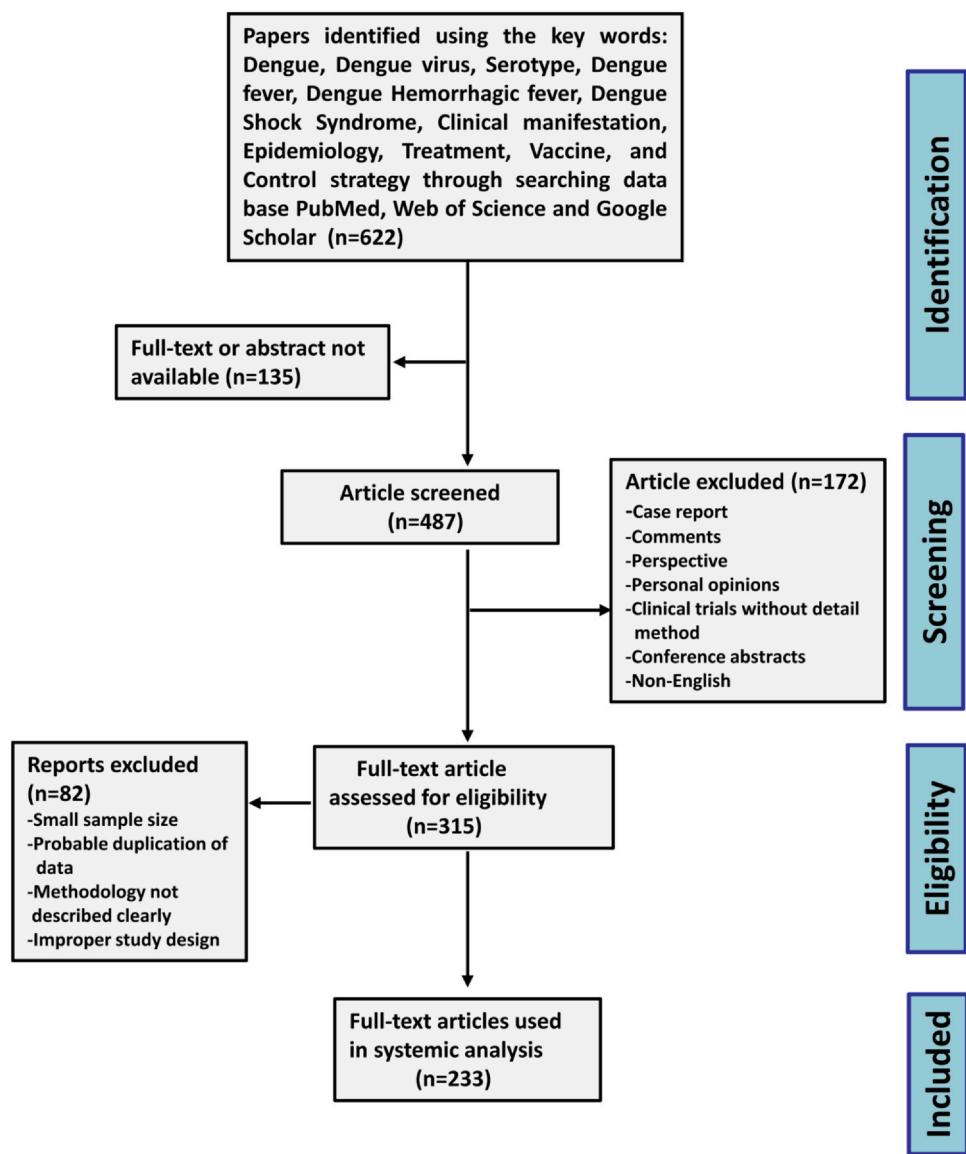


Fig. 1. The flowchart of paper selected in this study.

replication, virus particles would attach to the receptors and further enter the cell via the clathrin-mediated endocytosis pathway. The virus merges with the endosomal membrane once it has reached the interior of the cell and is then released into the cytoplasm. When the virus particle splits apart, the viral genome is released. The viral genome is replicated after the translation of the viral RNA (vRNA) into a single polypeptide, which is then divided into ten proteins.

When structural proteins and freshly synthesized RNA protrude from the endoplasmic reticulum (ER), virus assembly takes place on its surface. The trans-Golgi network (TGN) is the place where the immature viral particles mature and change into their infectious form [26]. At that point, the fully developed viruses are expelled from the cell and are free to infect additional cells and a detailed representation of the DENV life cycle shown in Fig. 3.

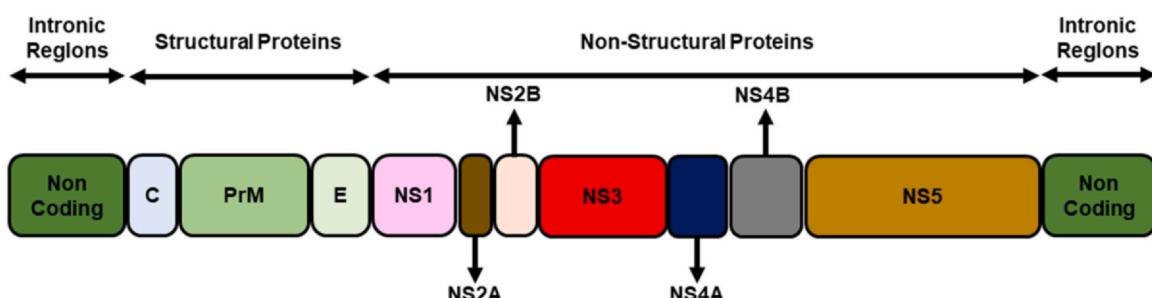
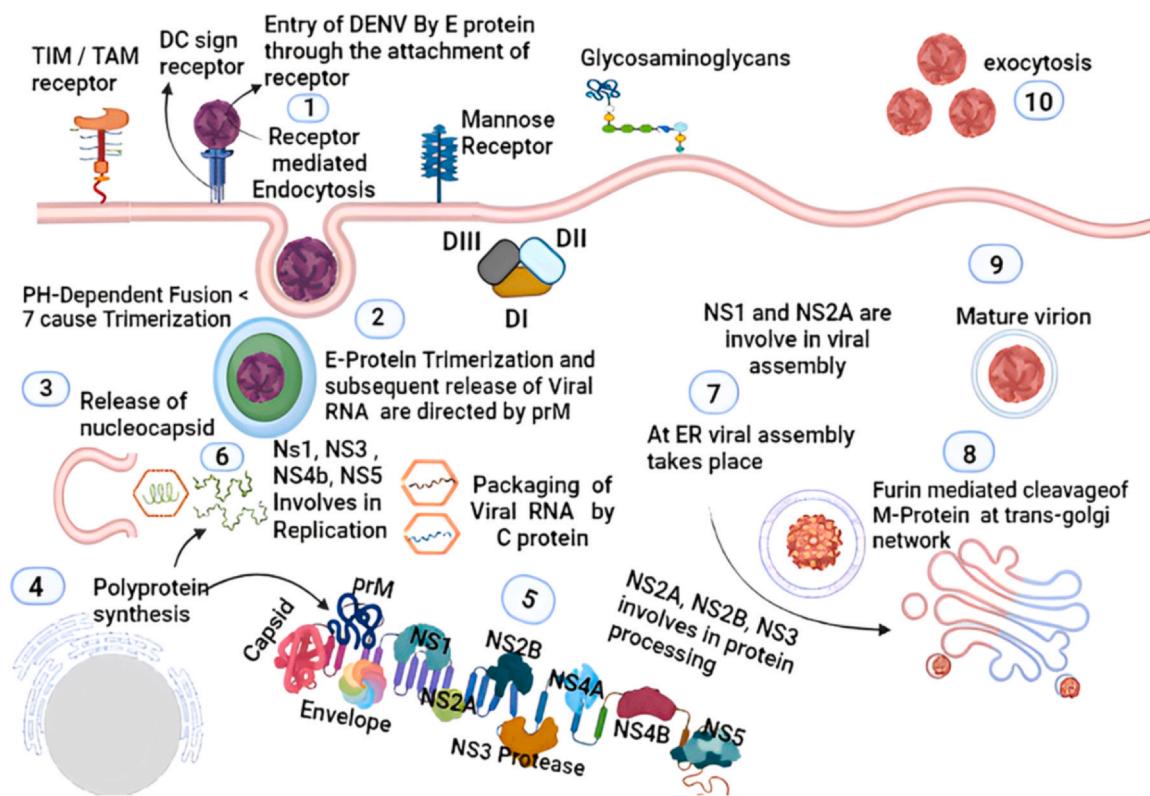


Fig. 2. Genomic structure of dengue virus (created in Biorender).

Table 1

Dengue non-structural proteins and their Functions.

| Non-Structural Protein of dengue | Size (kDa) | Features of NS proteins | Main Function | References |
|-----------------------------------|------------|---|--|------------|
| Non-Structural protein 1 (NS1) | 46 | Can be associated Endoplasmic reticulum attached membrane associated or secreted (sNS1) | Early viral RNA replication involves sNS1.sNS1 Implicated in vascular leakage by the activation of innate immune system. | [13–15] |
| Non-Structural protein 2 A (NS2A) | 22 | Integral membrane protein that is hydrophobic | NS2B is a protein that plays a role in RNA replication. | [16] |
| Non-Structural protein 2B (NS2B) | 14 | Protein that is small and hydrophobic. | Co-factor for the NS3 enzyme | [16] |
| Non-Structural protein 3 (NS3) | 69 | Several catalytic domains in a multifunctional protein | During RNA synthesis, it is involved in nucleoside triphosphates and catalytic domains helicase activities. | [17] |
| Non- Structural protein 4 (NS4A) | 16 | Integral membrane protein that is hydrophobic | It's necessary for replication vesicles to develop. | [17] |
| Non- Structural protein 4B (NS4B) | 30 | It's necessary for replication vesicles to develop. | NS5 inhibits IFN and IFN signaling. | [17] |
| Non-Structural protein 5 (NS5) | 105 | The largest and most well-preserved | *Dengue virus protein involved in the production of RNA *Involved in the IFN blockage system. | [17] |

**Fig. 3.** Dengue virus life cycle. DENV infects and replicates involving several steps, including virus attachment, receptor mediated endocytosis, virus uncoating, viral protein generation, vRNA replication, virus assembly and release.

Epidemiology of dengue

Dengue virus causes the disease and burdens in most tropical and subtropical regions of the world, mainly in the Caribbean, Central and Southeast Asia and South America [27]. More than hundred countries are affected by dengue virus all over the world each year, and there is a high risk of infection with approximately 3.6 million people live in these countries [7]. The epidemics of dengue virus occurs annually in Australia, Africa, Southern America, Asia. Dengue disease has been historically reported from centuries ago. In 992 AD first, compatible symptoms were noted in Chinese medical encyclopedia. In 1635, the epidemic resembled dengue in West Indies and in 1699 in Central America. It then became common in America in the 20th century. In the 20th century the viral transmission by mosquitoes was

discovered [28]. In 1953 the dengue viral cases were reported in the Philippines, and DHF was reported in 1956 due to infection by heterologous serotypes or secondary infections [27,29]. After World War II, the dengue become a heavy burden on public health, due to the Urbanization [20]. From Philippines the first two outbreaks of Dengue hemorrhagic fever were reported in 1953 and 1956 which may be due to lack of public health support, unplanned urbanization, improper mosquito control measures [17]. Other reasons for dengue outbreaks include overpopulation, a lack of fresh drinking water, air travel, and awareness of health effects [1]. Dengue virus disease affect humans and has become a national and international public health problem for all humans in recent years. The estimation of the World Health Organization in public health is that around 2.7–3 billion humans are actively living in the zones where dengue is transmitted by mosquitoes

[30]. Despite the fact that there is a risk of infection in 129 nations where 70% of the burden of dengue exists in Asia [7].

As previously mentioned, dengue is primarily transmitted by mosquitoes, causing disease in tropical and sub-tropical regions. Antibody prevalence data and serotype distribution provide insights into the population-level risk and guide public health decision-making. The emergence of different dengue serotypes can be traced back to historical records. DENV-1 was first reported in 1943 in French Polynesia and Japan, followed by Hawaii in 1944 and 1945. DENV-2 was first reported in 1944 in Papua New Guinea and Indonesia, followed by the Philippines in 1954 and 1956, respectively. Malaysia and Thailand have reported many consecutive years of DENV-2 occurrence since the early 1960s, Indonesia since the early 1970s, and China, India, the Philippines, Sri Lanka, and Singapore since the 1980s. The Philippines and Thailand were the first countries to report DENV3 in 1953. Since 1962, reports of DENV-3 have been made in Asia annually. In 1953, DENV-4 was first discovered in Thailand and the Philippines. Since then, DENV-4 has been reported yearly in the region, most frequently in Thailand, where DENV-4 reporting peaked between 1999 and 2002. Since 1978, Sri Lanka has also reported DENV-4 almost annually. Periods of more frequent reporting have occurred in the Indochina region, as well as Indonesia, India, Myanmar, and French Polynesia, despite the fact that reporting by nation has not been as consistent as for other DENV types [31]. The distribution of the serotypes varies in different countries, but Serotype-2 has been reported as the predominant serotype in recent years in some countries, including Pakistan, Sri Lanka, Indonesia, India, Thailand, Germany, and France, followed by serotypes 1 and 3. Serotype 4 is significantly lower than all other serotypes [32–36]. In another study in America, they reported DENV-1 and DENV-4 as the predominant serotypes in America from 2010 to 2020 [37]. However, due to the widespread impact of the COVID-19 pandemic, the documentation of dengue cases and their subsequent effects in the following year, 2020, remains limited.

Over the past 20 years, the number of dengue cases reported by WHO, 505,430 cases in 2000 to over 2.4 million in 2010, and 5.2 million in 2019 [38]. The number of reported deaths increased from 960 in 2000–4032 in 2015, mostly affecting younger age groups. In 2020 and 2021, both the overall number of cases and the number of reported deaths appeared to be declining [30]. The data is still incomplete, and the COVID-19 pandemic may have made it more difficult to report cases in some nations [38]. In 2019 the Dengue affected several countries including Bangladesh, the Philippines, Afghanistan, Malaysia, Thailand, Pakistan, Singapore, and Vietnam, as well as in the American region. The highest pandemic occurred in 2019 in countries including the Philippines (420,000), Vietnam (320,000), and Malaysia (131,000) [30]. During that time, there were 101,000 cases in Bangladesh, Malaysia (131,000), Philippines (420,000), Vietnam (320,000) in Asia and 3.1 million cases of DENV in the Americas [30]. In 2020, dengue again affected many countries globally, including Cook Island, Brazil, Bangladesh, Yemen, Thailand, Iran, Sri Lanka, Singapore, Nepal, the Maldives, Indonesia, India, and Ecuador [30]. In 2021, dengue did the same as 2020 and affects different countries, including the Reunion Islands, Peru, Paraguay, Kenya, Fiji, Colombia, Cook's Island, the Philippines, Vietnam, India, and Brazil [30]. More recently, European Center for Disease Prevention and Control reported dengue outbreak after COVID-19 pandemic period. They reported from January 2022–31 December 2022, 4110,465 cases of DENV and 4099 deaths. The majority of the cases were reported from Brazil (2363,490) Vietnam (367,729), the Philippines (220,705), Indonesia (125,888) and India (110,473). And the majority of the deaths were reported from Indonesia (1082), Brazil (991), the Philippines (722), Vietnam (140), and India (86) [30]. A potential reason may be due to these countries having less restrictive visa requirements for personal or business traveling.

The above information covered the basic characteristics of DENVs and their epidemiological analysis in relation to dengue disease and serotype distribution. In the following section, we will delve into the discussion of dengue virus vectors and their distribution.

Dengue virus vectors and their distribution

Ae. aegypti and *Ae. albopictus* are the most important vectors of the dengue and yellow-fever viruses. Both took advantage of trade developments to spread throughout the tropics from their native area. *Ae. aegypti* primarily feeds on people during the day and engages in indoor resting behavior. It is typically found in urban areas and breeds in artificial water containers like plastic storage bins and rubber tires. Although it exhibits strong anthropophagic behavior, *Ae. albopictus* prefers to rest outside and is an opportunistic feeder. Climate variables like temperature, rainfall, and relative humidity have a significant impact on the presence and population size of these arthropod vectors [39]. The fact that *Ae. aegypti* is distributed in the tropical regions and *Ae. Albopictus* from tropical to temperate regions shows that the geographical distribution of these two species differ along the north-south gradients [40]. Sub-Saharan African, Caribbean, and Oceanian nations were discovered to exhibit a wide range of suitability, whereas the majority of European, North American, and Northern Asian countries were discovered to exhibit a small or nonexistent range of suitability. Italy, Greece, and Croatia were discovered to have a wide range of suitability within Europe. Other nations in South America like Brazil, Colombia, and Venezuela, also offered a significantly wider range of suitable regions [41]. In Taiwan, regions located below the Tropic of Cancer are inhabited by both *Ae. aegypti* and *Ae. albopictus* mosquitoes, while regions above the Tropic of Cancer are exclusively populated by *Ae. albopictus* [42–44]. Although both mosquito species serve as vectors for dengue transmission, *Ae. aegypti* is widely recognized as the primary vector responsible for dengue spread in many countries [30].

Having explored the epidemiology and vector distribution of dengue, our focus now shifts to the detailed discussion of the clinical manifestations caused by the dengue virus, which will be presented in the subsequent section.

Clinical manifestations

Around 80% of primary DENVs infection do not present symptoms with only less than 20% infected individuals displaying clinical manifestations. Dengue fever is characterized by severe headache, mild fever, rashes, muscle and joint pain, nausea, and vomiting [1]. The DHF is characterized by high temperature, megalohepatitis, hemorrhagic phenomena, shock, and often cardiovascular disturbances. DHF was initially reported to primarily affect children under the age of 15; however, subsequent studies have indicated its occurrence in adults as well [45–48].

DENV infection triggers an acute febrile disease [49,50]. Some studies indicate that the DENV NS1 is present in large amounts in the patient's serum, both extracellularly as a soluble unknown lipoprotein and also on the surface of the cell [51–54]. The high levels of these proteins may correlate with the disease severity and contribute to the pathogenesis of DHF in the host [55]. A single-serotype infection might result in permanent immunity to that serotype and can provide short-term cross-protection against other serotypes. However, it has been reported that heterotypic secondary DENV infection has high chance to lead to severe dengue, including DHF and DSS [29,56]. In order to prevent viral replication in infected cells or mitigate the effects of particular inflammatory mediators on target cells, there is a tremendous need for innovative therapeutic agents and vaccines. The contribution of genetics to resistance to DHF and DSS is also something that has to be clarified [57]. Furthermore, some clinical symptom and other non-communicable

diseases were recently reported to correlate with dengue severity, such as hypertension and diabetes [58–62]. In order to provide a more detailed analysis of the occurrence of DHF/DSS and the factors associated with dengue severity, the next section will focus on discussing the potential risk factors and mechanisms that are correlated with these conditions.

Risks and mechanism correlated dengue severity

Antibody-dependent enhancement

Infants and those with secondary DENV infections are the groups most frequently affected by severe dengue [63]. The most frequently mentioned explanation for this phenomenon is disease-dependent antibody enhancement (ADE). When an immune response produces antibodies that recognize and attach to pathogens but are unable to stop infection, this is known as antibody-dependent enhancement (ADE) [64]. As a result, the pathogen can enter cells and worsen the immune response because these antibodies behave as a "Trojan horse". ADE was initially demonstrated to be correlated with dengue severity in infants who had their first infection with DENV and subsequently displayed DHF. As we know, mothers can transmit IgG antibodies to their newborn children (including anti-dengue IgG). When the newborns get infected by another serotype of DENV via Aedes mosquito's bite severe manifestations were observed, proposing that the original anti-dengue IgG did not have viral neutralizing capabilities instead possessing enhancing abilities [65]. Increased viral entrance into host cells, particularly dendritic cells and macrophages, is made possible by this virus-antibody complex [64]. When ADE is present, the virus infection and propagation increased which would further trigger a higher amount of multiple cytokine productions by immune cells, which is called the cytokine storm and ultimately ends in a more serious illness. Katzelnick et al. previously examined data from a long-term study of Nicaraguan children exposed to dengue virus[64]. They confirmed that dengue ADE occurs at a specific range of antibody concentrations- low levels of antibody did not enhance disease, intermediate levels exacerbated disease, and high antibody titers protected against severe disease [64], discussed in Fig. 4. In addition, dengue ADE currently can be observed in certain mouse model [66] and rhesus monkeys [67].

Primary DENV infection results in the activation of adaptive immune responses (both T and B cells), and DENV-specific T cells could be activated and clonally expanded to combat infection. Upon termination of primary infection, memory DENV-specific T and B cells are formed and are retained with a higher frequency compared to other naïve cells. This immune response could last a lifetime. In a secondary infection with the same serotype of DENV infection (homotypic infection), the virus will induce a memory response that activates highly specific T and B cell responses. However, when a secondary challenge with a different serotype of DENV (heterotypic infection) is presented, the primary antibodies lack neutralization capabilities but could cross-react with heterotypic DENVs and trigger Fc_γ receptor-mediated antibody dependent enhancement (ADE) as well as expand the memory T cell pool, which has low specificity for this different serotype of DENV and poor viral clearance[68–70].

Viral factor

There may be variances in pathogenicity between strains and serotypes, and viral titer correlates with the severity of the disease [71]. Dengue NS1 is a hexameric protein that is secreted into the bloodstream. It is found as a dimer on the cell surface and as a monomer inside cells. RNA replication and complement immune evasion are two of the many roles that NS1 plays during the viral life cycle. In the past few years, key roles for the protein NS1 in the pathogenesis of severe dengue disease have been revealed. These roles include the protein's direct interaction with the vascular

endothelium and its ability to cause the release of vasoactive cytokines from immune cells, both of which cause endothelial hyper permeability and vascular leak [72]. In addition plasma levels of the virion-associated envelope protein domain III (EIII) as a virulence factor for endothelial damage [73]. As to virulence, hypotheses have emerged from clinical, epidemiological, associative, and entomological studies that initially characterized variances in DENV virulence. According to this hypothesis, the development of DHF/DSS could be attributed to infection by a particularly virulent serotype or strain within the spectrum of virus serotypes. During past decades, DENV1–4 serotypes have been reported to be potentially associated with DHF/DSS epidemics in different countries [74–76]. For example, in Southeast Asia and the Americas, the initial epidemics of DHF in these regions were associated with DENV-2 [45,77–79]. Raymond Cologna et al. previously studied the infection and growth indicating that DENV-2 viruses causing DHF epidemics (Southeast Asian genotype) can outcompete viruses that cause DF only (American genotype), suggesting that this DENV-2 strain leads to more hemorrhagic dengue epidemics [80]. Based on the information above, it is suggested that mechanisms inducing DENV virulence are complicated which are correlated with several factors, such as new clades, subgenotypes, characteristics of genome variants and virus-host immune interaction.

Host factors

Several host factors were reported to correlate dengue severity. When a virus, the host, and the host immune system interact to cause the severe disease in 2–4% of people with secondary infection, DHF results from a very complex mechanism [81]. Host genetic factors are equally as significant in the pathogenesis of DENV infection as the various viral factors. Human Leucocyte Antigen (HLA) is one of the host genetic factors that contributes to DENV pathogenesis [82]. The significance of pre-existing primed memory HLA Class-I restricted cross-reactive T cells has been suggested by the observation that many HLA Class-I alleles are associated with severe dengue in secondary infections. On the other hand, DENV infection and disease severity have been shown to be protected by HLA class-II, particularly by DRB1 alleles [83]. The risk of DHF is doubled in people with the TGF-1-509 CC genotype, according to a study by Chen et al. in Taiwan [84]. Having the CTLA-4 + 49 G allele along with other risk factors increased the risk even more [82]. Perez et al., reported that tumor necrosis factor-α, transforming growth factor-β1, and interleukin-10 gene polymorphisms were correlated with protection or susceptibility to DHF[85]. Further, recently several reports indicated that the increased levels of host vascular endothelial growth factor (VEGF), granulocyte-macrophage colony-stimulating factor(GMSF), granulocyte colony-stimulating factor, transforming growth factor beta(TGF-β), and hepatocyte growth factor(HGF) as well as reduced levels of platelet-derived growth factor(PDGF) and epidermal growth factor (EGF) were observed in severe dengue [86–90].

The association between the balance of type 1 and type 2 host immunity and dengue disease severity has been proposed [91,92]. It has been observed that a type 1 dominant immune response is associated with DF, while a type 2 immune response is linked to the severe dengue (such as DHF) [91]. Furthermore, mast cell products and high levels of type 2 cytokines are also found to be associated with severe dengue disease [91,93,94]. A recent study by Fonseka et al. indicated that group 2 innate lymphoid cells (ILC2) are activated by epithelial cytokines and mast cell-derived lipid mediators, resulting in the production of type-2 cytokines [68]. During acute DENV infection, activation of ILC2 was observed, and the presence of a compromised type I-IFN signature was associated with severe dengue disease. The study also revealed that circulating ILC2 are permissive to DENV infection, especially when activated by prostaglandin D2 (PGD2). Furthermore, supernatants from activated ILC2 enhanced monocyte infection in a GM-CSF and mannose-dependent

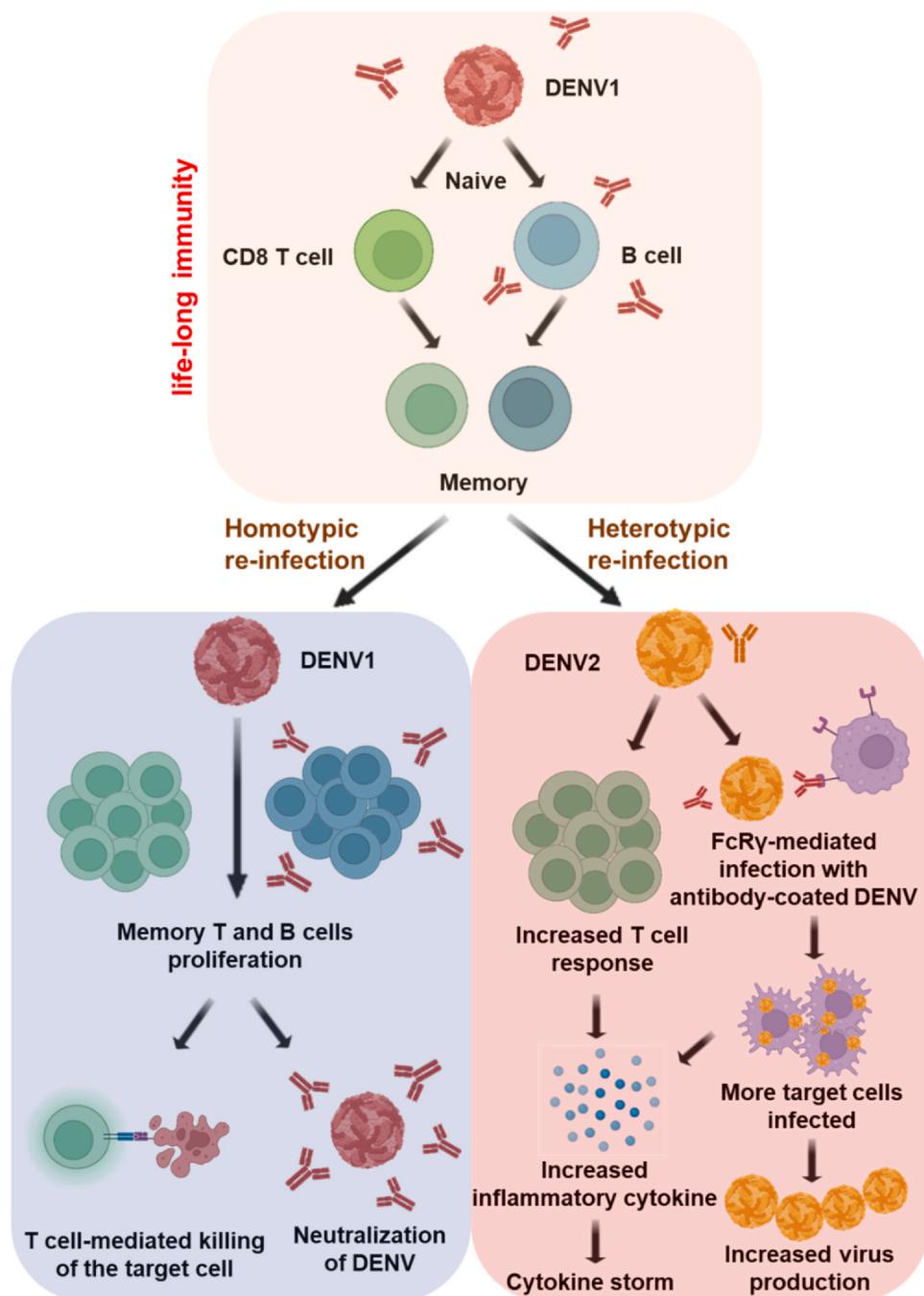


Fig. 4. Primary and secondary homotypic and heterotypic DENV infection.

manner. These findings suggest that DENV exploits innate type 2 pathways to evade early control of viral replication and facilitate viral dissemination [68].

Following the exploration of various risk factors and mechanisms associated with dengue severity, the subsequent section will delve into the current diagnostic methods employing serological or molecular assays for detecting DENV infection in clinical.

Diagnosis

Clinical diagnosis of dengue can be difficult, depending on where a patient is in the infection process. Depending on where you live, there may be a number of disease-causing pathogens or disease states that can mimic the disease spectrum caused by dengue infection. Dengue

fever can be presented in the early stages of clinical disease as a mild, undifferentiated "flu-like" fever with symptoms similar to those of other diseases such as influenza, measles, Zika, chikungunya, yellow fever, and malaria [95]. Some patients who have low immunity can go quickly from mild disease to severe condition and even death, so early laboratory diagnosis for DENV is beneficial and may be life-saving for those who have low immunity [96]. Here, we discussed the dengue disease in acute and convalescent phase.

Acute phase diagnosis

The acute phase of dengue is defined as the first 1–7 days after symptom onset. DENV is typically present in blood or blood-derived fluids such as serum or plasma during this period. Molecular tests like RT-PCR can detect DENV RNA [97]. The non-structural protein

NS1 is a protein found in dengue viruses that can be detected using commercial tests including Immunochromatographic tests (ICT). A negative molecular or NS1 test result is not conclusive [98]. Any serum sample collected from symptomatic patients during the first 1–7 days of illness should be tested for Nucleic Acid Amplification Test (NAAT) or NS1 antigen and specific IgM antibodies. Performing both molecular and IgM antibody tests (or NS1 antigen and dengue IgM antibodies) can detect more cases than either test alone [99,100]. Another test, IgM antibody capture Enzyme-linked immunosorbent assay (MAC-ELISA), can be used for the qualitative detection of IgM antibodies which are specifically against dengue 1–4 types of envelope proteins. So, if any type of antigen is present in the sample it could bind to the IgM antibodies, using for the diagnosis of the early phase of DENV infection [100].

Convalescent phase diagnosis

The convalescent phase of dengue is the time frame that begins more than 7 days after the onset of symptoms. IgG antibodies should be identified at higher levels even though IgM antibodies are often still present during the convalescent phase [100]. In cases of dengue infection, the IgM antibodies become detectable on days 3–5 of sickness and last for 2–3 months, whereas the IgG antibodies develop by the fourteenth day and last a lifetime. IgG levels grow in secondary infection within 1–2 days of the onset of symptoms, together with IgM antibodies [101]. In the convalescent phase, IgG antibody capture Enzyme-linked immunosorbent assay (GAC-ELISA) is used for the late phase of DENV detection. GAC-ELISA could detect the IgG antibodies not only 7–10 days after the onset of symptoms but also over a period of 10 months or more [97].

Current challenges and future prospects for dengue diagnostic tests

The diagnostic methods and procedures for the detection of dengue viral infection have significantly improved over the past ten years. However, given the distinctiveness of the DENV and the range of diseases that can be contracted after infection, some issues still call for further research [102]. The NS1 biomarker can currently be found using the dengue diagnostic, but the biomarker levels vary. These proteins are expressed by some people, albeit in small amounts. Some crucial biomarkers, such as those related to intravascular leakage, rise in severe dengue; if we can spot these biomarkers rising, medical professionals can act right away [103]. The development of a single assay to verify dengue infection is challenging due to the disease's complex pathogenesis and clinical characteristics. Sensitivity could be increased by combining several of the available clinical diagnostic tests. To distinguish dengue from other flaviviruses and/or other tropical infectious diseases, numerous efforts are being made to develop multiplexed point of care testing (POC) tests (such as microfluidic diagnostic devices) covering multiple infectious agents and multiple parameters per pathogen [104].

While early and prompt diagnosis is crucial for the control of dengue disease, it is also essential to focus on the treatment of DENV infection in order to reduce disease severity and mortality. Therefore, the next section will provide detailed information on the current stage of treatment options for dengue.

Dengue treatment

There is no specific antiviral treatment for dengue disease. The World Health Organization (WHO) nominated the development of tetravalent DENV vaccine on top priority bases for the most money gaining tactic to dengue deterrence [105,106]. Usually, dengue fever resolves on its own. Fluid replenishment, analgesics as supportive care, and bed rest are typically enough [107]. There is no known drug that can be used to treat this condition, nevertheless fever can be treated with acetaminophen. Careful management of severe dengue

is necessary. For flexible management considerations and proactive care of bleeding, Methylprednisolone was demonstrated in a single dose, but it is not recommended by WHO and CDC, due to risk factors for developing immunosuppression, hyperglycemia and gastrointestinal bleeding [108,109]. When treating dengue shock, there is no mortality benefits [110].

Options for treating dengue illness by natural medicine

Natural medicines have antiviral, larvicidal, and mosquitocidal properties, as well as the ability to repel mosquitoes, which makes them active against *Ae. aegypti*. Below are some of the most significant natural treatments.

- 1) Eupatorium perfoliatum, often known as boneset, is a widely accessible plant that is crucial in the treatment of dengue fever. The best way to consume it is as tea [110,111].
- 2) Boesenbergia rotunda (Temu kunci): The roots are often ground into a paste that is applied topically. Muscular discomfort and nausea, which are very distressing for those who have this illness, are lessened by using the herb [110,112].
- 3) Kaempferia parviflora: The leaves and stem are used as an herbal virus cure. According to studies, a bioactive component in Kaempferia parviflora directly inactivates DEN 2 [110,113].
- 4) Carica papaya: The juice from the leaves is used to raise platelet levels [110,114].
- 5) Solanum villosum: Berry extract is reported to possess larvicidal activity against *Ae. aegypti* [110,115].
- 6) Combretum collinum: Extract of shoot bark possess larvicidal against *Ae. aegypti* [110,116].
- 7) Delonix elata: Leaf and seed extracts are reported to exert larvicidal and ovicidal activities against *Ae. aegypti* and *A. stephensi* [110,117].

Dengue vaccine

Due to the lack of potent antiviral treatments for dengue, prompt and supportive management with volume replacement, especially in patients with severe dengue is the keystone for preventing severe disease and death. Vaccines and antiviral medications are the two main ways to control viral diseases. The complexity of the four serotypes (DENV-1–4) and the potential role of antibody-dependent enhancement in severe dengue have both hampered the development of a DENV vaccine [110,118,119]. In 1940, it was first established that flaviviruses have certain antigens which mediate complement fixation(CF) [120]. After the identification of these proteins by flaviviruses, it was described that envelope protein and NS1 proteins with CF were linked to neutralization [121]. The E protein mediates the first stage of infection, the viral particle attachment and internalization, the E protein is typically treated as the primary strategies against the Flavivirus infection, including dengue [122]. Despite E protein being a good candidate for vaccine creation, a severe side effect causes by non-specific immunoglobulins interacting with the protein and causing ADE has been demonstrated and some alternative strategies were developed [123]. Accordingly, several novel strategies in vaccine development have been proposed via using different viral antigens or recombinant virus candidates to induce the immune response mainly targeting NS1, premembrane (prM) and envelope (E) proteins. The E protein targeted vaccines include Live attenuated vaccine (CYD-TDV), subunit vaccine (V180, cED III), Inactivated vaccine (PIV), DNA Vaccine (TVDV), Viral vector vaccines (CAdVax-Den) (Fig. 5). These all vaccine candidates are still under research and clinical trial evaluation [124–127].

In addition to prM and E based vaccines, consideration for NS1 as immunogens have been proposed and validated. It is known that high levels of NS1 proteins in plasma correlates with disease severity and hemorrhage and recovered patients were observed to have high titer of anti-NS1 antibodies. Many, advantages were reported to use

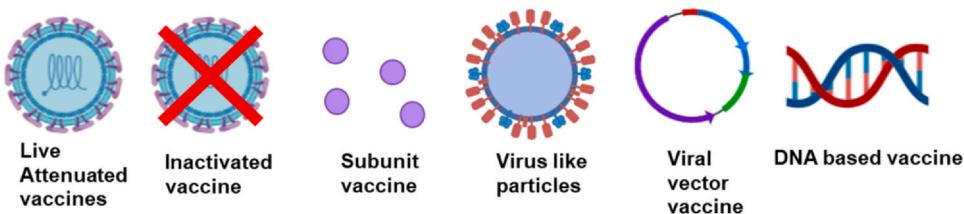


Fig. 5. Current types of dengue vaccines. There are several types of dengue vaccines under development, including live attenuated vaccines, inactivated vaccines, subunit vaccines, virus-like particles, nucleic acid-based vaccines, and viral vector vaccines.

NS1 as vaccine immunogens including higher conservation among all four serotypes, lower risk of inducing antibodies against E protein and ADE phenomenon [128]. Despite NS1 vaccination could induce potent humoral responses against DENV infection. According to the reports, NS1 antibodies can also recognize host factor by molecular mimicry, which can lead to tissue damage and impaired physiological process [129]. NS1 based vaccine strategies including, Subunit vaccine strategies (DENV NS1 vaccines), DNA Vaccines strategies (pNS1-tPA vaccine), Vector vaccine candidates (Baculovirus-expressed NS1), Attenuated vaccine candidates (DENVax), which are under research and clinical trials [130–132]. Currently some vaccines are under the pre-clinical research phase including Virus like particle vaccine strategies (DSV4, VEE-VRP) and Viral vector vaccine strategies (MV-DEN) [133,134].

Advantages and disadvantages analysis of dengue vaccines

We have provided a brief introduction of current dengue vaccines, their immunogenic candidates, and various types. This section will delve into the advantages and disadvantages associated with these vaccines.

Live attenuated vaccines (LAVs) are composed of weakened living pathogens to make them less virulent. They offer the benefits of delivering a range of protective antigens and inducing long-lasting immune protection [135]. LAVs are considered cost-effective and promising in the development of a DENV vaccine, with significant replication in Vero cell culture and antibody levels comparable to wild-type virus infection in non-human primates [136]. However, despite their efficacy in protecting against severe disease in dengue-positive individuals, concerns have been raised about LAVs. Seronegative individuals might face an increased risk of severe dengue disease and higher chances of hospitalization. Additionally, the preparation of LAVs poses challenges, such as attenuating viral toxicity, ensuring genetic stability, preventing reversion, and managing interference in multicomponent LAVs [122,137–140].

Inactivated vaccines are composed of antigenic material from a pathogen (e.g., virus or bacterium) rendered inactive while still capable of providing protection against the live pathogen [141]. A DENV2 inactivated vaccine demonstrated effectiveness in rhesus monkeys through formalin inactivation and sucrose centrifugal purification [141,142]. These vaccines provide two key advantages: enhanced safety, as they cannot revert to a more harmful form, and a balanced antibody response induced by each serotype in a multivalent inactivated virus vaccine [138,143,144]. Nonetheless, these vaccines have some limitations. They lack immunity to non-structural proteins, as they solely contain structural proteins of DENV. Seronegative subjects require adjuvants for optimal immunogenicity, leading to increased cost and reactogenicity. Furthermore, multiple booster doses are necessary for long-term immunity, and high production costs arise due to DENV's inability to grow to high titers in tissue culture cells [138,143,144].

Recombinant subunit vaccines contain antigenic proteins produced by prokaryotic or eukaryotic cells, promoting durable protective/therapeutic immune responses [145]. While expressing recombinant dengue proteins in *E. coli* is relatively straightforward,

challenges such as endotoxin contamination and improper protein folding may arise [146]. Alternatively, using bacteria like *Neisseria meningitidis* or the baculovirus system has been proposed to generate DENV subunit vaccines [147,148]. Despite these challenges, subunit vaccines excel in inducing balanced immune responses against all four DENV serotypes, minimizing the ADE effect. However, subunit vaccines are generally more expensive to manufacture than LAVs. Moreover, their inability to replicate within the host might limit the duration of immune responses, potentially requiring additional doses [138,143,145,149].

Viral vector vaccines use various vectors, such as vaccinia virus, adenovirus, and alphavirus, to deliver DENV antigens for vaccine development [150]. Some challenges have been encountered when expressing certain DENV4 proteins in the Cidofovir-resistant vaccinia (WR) strain [151]. To enhance effectiveness, recombinant vaccinia viruses expressing DENV E protein have been developed [152]. Adenoviral vectors offer advantages like easy gene manipulation, detection of gene replication defects, and high protein expression. In mice, a replication-defective adenovirus expressing DENV2 E protein successfully induced DENV2 antibodies and specific T cell immunity [153]. Alphavirus-vectored dengue vaccines show promise, with virus replicon particles (VRP) effectively expressing antigens and inducing protective antibodies in monkeys and mice against DENV1 and DENV2, respectively [154,155]. Adenoviral vectors stand out among other viral vectored vaccines due to their ease of genetic manipulation, ability to detect gene replication defects, and high antigen expression. Viral vectored vaccines remain a potent method to elicit cellular immunity and hold potential for stronger humoral responses. However, one challenge of this approach is that people may previously have been exposed to the virus vector and raise an immune response against it, reducing the effectiveness of the vaccine [138,143,156].

The DNA vaccine is a plasmid encoding specific antigens, designed to stimulate immune responses when injected *in vivo* [157]. For example, intradermal vaccination of BALB/c mice with a DNA vaccine expressing prM and 92% of DENV2 E protein induced anti-dengue antibodies in all mice [157]. Comparatively, ME100, a DNA vaccine expressing prM and 100% of E protein, showed more efficient antibody production than E80 (80% of E protein) in mice [158]. DNA vaccines fusing DENV2 prM/E with the immunostimulatory CpG motif provided protective immunity against DENV2 and improved the neutralizing antibody response, surpassing the standard DENV2 prM/E DNA vaccine [159]. Furthermore, a DENV2 DNA vaccine expressing a recombinant protein containing DENV2 EDIII and *E. coli* maltose-binding protein (MBP) elicited neutralizing antibodies in mice [160]. Guiding proteins targeting the immune system were employed to enhance protectivity in DNA vaccine development. Despite their stability, cost-effectiveness, and suitability for mass production, DNA vaccines face challenges in achieving high immunogenicity. Overcoming these challenges may involve implementing highly efficient promoters through plasmid modification, exploring alternative delivery strategies, co-immunization with adjuvants, and incorporating immunostimulatory motifs. These approaches could address limitations related to

Table 2
Different types of Vaccine strategies for vaccine development.

| Vaccine Type | Vaccine Name | Target Antigen | Strategy | Advantages | Disadvantages | References |
|---------------------------|---|--|---|---|--|---|
| Live Attenuated | Dengvaxia (CYD-TDV) (FDA Approved) TV003/TV005 | prM & E | Replacing the 1–4 genes with prM/E gene of the YF17D virus. | They provide the advantages of delivering a wide range of protective antigens and inducing long-lasting immune protection. LAVs are considered cost-effective and promising for developing a DENV vaccine, with significant replication in Vero cell culture and antibody levels comparable to wild-type virus infection in non-human primates. | Seronegative individuals are susceptible to an augmented risk of severe dengue disease, leading to increased hospitalization rates. Furthermore, the development of Live Attenuated Vaccines (LAVs) entails several intricacies, such as mitigating viral toxicity, ensuring genetic stability, preventing reversion to pathogenicity, and addressing interference issues in multicomponent LAVs. ^a | [168,169] [137,138,143] |
| | DENVax | Live Virus | Attenuation of DENV1, DENV3, DENV4, and a chimeric DENV2/DENV4 truncating 3 nucleotides in the 30 UTR Substituting DENV1, DENV3, DENV4 coding sequence for the DENV2 PDK-53 attenuated vaccine. | Misfolding NS1 interfering with the host ribophorin 1 protein found in the reticulum, which then results in improper NS1 glycosylation. | They lack immunity to non-structural proteins since they only contain structural proteins of DENV. Seronegative subjects need adjuvants to achieve optimal immunogenicity, which increases cost and reactogenicity. Additionally, long-term immunity requires multiple booster doses, and high production costs result from DENV's inability to grow to high titers in tissue culture cells. | [161,174] [138,143] |
| Inactivated virus vaccine | PIV | Inactive Virus | Tetraivalent purified formalin-inactivated virus and dengue purified formalin inactivated virus (DPIV/TPIV). | These vaccines provide two key benefits: enhanced safety, as they cannot revert to a more harmful form, and a balanced antibody response through each serotype in a multivalent inactivated virus vaccine. | Subunit vaccines are generally more expensive to manufacture than LAVs. Moreover, their inability to replicate within the host might limit the duration of immune responses, potentially requiring additional doses. | [175,176] [137,145,149] [177,178] |
| Subunit Vaccines | V180 | 80% E | A truncated, recombinant protein that contains DEN-80E. | Subunit vaccines excels in inducing balanced immune responses against all four DENV serotypes, minimizing the ADE effect. | The recent experience with DNA vaccines has brought to light certain disadvantages, such as the necessity for multiple doses, experimental adjuvants, immunostimulatory motifs, and specialized injection equipment. | [180] [138,143] [161][181] |
| | DENV NS1 | NS1 | DENV 2 NS1 Subunit purified protein | | | |
| | CED III | Consensus envelope domain II (CED III) | DENV 2 NS1 Subunit purified protein different adjuvants are fused to a staphylococcal A protein as an adjuvant E. coli recombinant envelope domain III (ED III) | | | |
| DNA vaccine | pNS1-tPA | t-PA signal fused DENV 2 NS1 plasmid | | | | |
| | TVDV | prM& E | Vector of a recombinant plasmid encoding | | | |
| Vector vaccine | CAdVax-Den | prM& E | Two divalent complex dengue vaccines, CAdVax-Den1-2 or CAdVax-Den3 and 4, were created using a recombinant replication-defective adenovirus vector (CAdVax-Den3-4) | Dengue DNA vaccines offer high stability, cost-effectiveness, and suitability for mass production. They induce moderate immune responses, are non-replicating and non-infectious, and allow rapid customization for specific dengue virus serotype. | The recent experience with DNA vaccines has brought to light certain disadvantages, such as the necessity for multiple doses, experimental adjuvants, immunostimulatory motifs, and specialized injection equipment. | [180] [138,143,182] |
| | Baculovirus-expressed NS1 MV-DEN | NS1 | Recombinant DENV2 or 4 NS1 expressed from the Baculovirus-insect cell system | These vaccines remain effective in eliciting cellular immunity and have the potential to induce stronger humoral responses. | One challenge associated with this vaccine is that some individuals may have had prior exposure to the virus vector. As a result, they might mount an immune response against it, potentially leading to a reduction in the vaccine's effectiveness. | [183,184] [133] |
| Virus like particles | DSV4 | NS1 | Envelope protein domain III (ED3) | | | |

(continued on next page)

| Vaccine Type | Vaccine Name | Target Antigen | Strategy | Advantages | Disadvantages | References |
|--------------|--------------|---|----------|------------|---------------|------------|
| VEE-VRP | prM& E | The prM and E antigens of all four viral strains are expressed by the Venezuelan equine encephalitis (VEE) virus replicon particle (VRP), which demonstrated a quick and effective seroconversion rate in mice and NHP. | | | | [185] |

experimental adjuvants, specialized injection equipment, and multiple doses [161–163].

Viral-like particles (VLPs) provide an alternative approach for DENV vaccine development. These recombinant particles structurally resemble wild-type viruses but lack viral genetic material, making them non-infectious and unable to replicate. VLPs are assembled through the expression of recombinant prM and E proteins [164]. They hold promise for inducing antibodies that target critical epitopes for viral neutralization, but research on VLPs generated by prM/E-based DNA vaccines is limited [162,165]. VLP vaccine candidates offer advantages such as reduced reactogenicity and suitability for immune-compromised individuals. They can also promote a balanced immune response in tetravalent formulations. However, potential disadvantages include a less comprehensive, potent, and durable immune response, potentially leading to antibody-dependent enhancement (ADE). Adjuvants may be required to enhance their efficacy [165–167].

In summary, the current DENV vaccine strategies, including the major types and their respective advantages and disadvantages, are summarized in Table 2.

Control strategies

In addition to understanding the essential aspects of dengue, such as epidemiology, risk factors, clinical manifestations, diagnosis, and treatment, it is crucial to focus on effective control measures for dengue vectors and disease dissemination. Currently, various control strategies have been proposed to address this issue. The upcoming sections will discuss the current control plans and programs implemented for dengue.

Community-based control programs

The main aim and purpose of this program is to control and exterminate the active breeding sites which divide the people of a community into different groups based on their education level and knowledge about the disease [27]. These programs have shown a lot of effectiveness and have helped reduce mosquito populations in some countries, which play a vital role in the prevention of the DENV [186]. These programs need to provide education and knowledge about the vector and the disease as well as bring awareness in the community to identify preventive measures for the community [29]. However, despite the implementation of community-based control programs in most dengue-affected countries, the effectiveness of these programs in controlling dengue infection is still limited. This limitation can be attributed to various factors, including variations in country size, human population, available resources, and the methods and plans employed across different countries [187,188].

Biological controls

The control and prevention of DENV vectors to eliminate and reduce the vector population depends on biological control methods and plans. Conservative control plans are not effective against this mosquito-borne vector, which bites almost constantly during the day. So new strategies are required for the control of the mosquito vector's population. The genetically modified mosquitos are used as the major strategies in the biological control plans, we have studied in a previous literature that sterile insect techniques (SIT) have been used effectively for several years in the protection of mosquito vectors in several countries [189]. The main function of SIT is to harm the health of male insects by preventing them from breeding with females and reducing their breeding ability [29,190].

A group of bacteria found in the reproductive tissues of arthropods which is called Wolbachia. They are involved in different types of mechanisms for employing of reproduction of their hosts containing pathogenesis, feminization and reproductive incompatibility and they are transmitted to the host through cytoplasm of eggs [191,192].

Wolbachia is used as a biological control for mosquito vector against DENV and many other arboviral disease, which is an alternative strategy for the control of Mosquito vector [193]. Some countries have used male Wolbachia-carrying Ae. aegypti (Wolbachia-Aedes) mosquitoes to reduce the dengue mosquito population [194]. Wolbachia causes cytoplasmic incompatibility (CI), which impairs the development and cause embryo death after mating with uninfected females. Hoffmann et al. reported that Wolbachia infection does not affect the male Ae. aegypti's ability to compete. The body size effect also suggests that Wolbachia males raised in laboratories may have an advantage due to their superior nutrition and larger size during a field release episode. This highlights its possible use for disease control and may encourage Wolbachia spread via CI in wild mosquito populations [194]. A research team from Australia described the intracellular bacterium Wolbachia introduction into natural Ae. aegypti mosquito populations, they interfere with pathogen transmission and influence key life history traits such as lifespan [195–197]. According to other studies, Wolbachia reduces dengue transmission by two factors: vector competence and mosquito population density [196,198].

Ae. aegypti can also be genetically altered and used to eradicate other mosquitoes in a community. This strategy was firstly conducted by Oxitec, a UK-based, US-owned biotechnology company that develops genetically modified insects. Their second-generation Friendly™ OX5034 genetically modified (GM) male Ae. aegypti mosquitoes carry a gene (tTAV-OX5034) that is inherited by their offspring, enabling the male offspring to survive while suppressing the survival of female offspring. Through consistent releases of the OX5034 GM male mosquitoes during the mosquito season, the absence of female mosquitoes emerging in the release area leads to a decline in the population of Ae. Mosquitoes [199,200]. The OX5034 GM Ae. Aegypti mosquito has been approved for release in Florida and Texas by the US Environment protection Agency (EPA). Due to the EPA Approval local mosquitoes control programs are now able to assess the impact of GM mosquitoes on Ae. aegypti mosquito population reduction in areas where they have been released thanks to an EPA authorization. In a lab self limiting genes and a marker genes are used to create OX5034 GM mosquitoes in large numbers. Researchers can recognise these GM mosquitoes in the wild due to a fluorescent marker gene that glows in a special red light and act as self limiting gene that prevent female mosquito offspring from developing into adult mosquitoes. A GM is exposed to GM mosquito eggs that contains self limiting gene. When they hatch, grow up, and reach adulthood, they are ready to mate with wild females. The offspring receive the genes, and the female offsprings will die before reaching adulthood. The neighborhood's Ae. aegypti mosquito population should decline as a result [201].

Chemical controls

The use of chemical control has been seen over the last several decades for the control of mosquito vectors, which works very effectively. However by using it long-term, they have many disadvantages, like the negative impact on the environment and the resistance of vectors to the chemicals they contain, as well as the fact that plants extract containing insecticide [202]. While scientists have made advancements in developing environment friendly ingredients derived from plant extracts to control these vectors, these plant extracts still demonstrate remarkable efficacy against Ae. aegypti. The different types of insect growth regulators (IGRs) that are produced from other chemical compounds also have the efficacy of inhibiting development and growth in different types of insects, including the changes in the developing stages and the subsequent killing of insects before they reach the adult stage to prevent the spread of disease. The effective IGRs employed for larval control of Ae. aegypti include spinosad, cyromazine, and methoprene [29,203,204]. Additionally, several other IGRs have been utilized to inhibit the growth of target vectors. To reduce the adult mosquito

population, various insecticides, known as adulticides, are utilized. These substances can be applied through aircraft or truck-mounted sprayers on the ground. Commonly used synthetic pyrethroid insecticides for adult mosquito control include prallethrin, etofenprox, pyrethrins, permethrin, resmethrin, and sumithrin, along with organophosphate insecticides such as malathion and naled by various state and local organizations[205–207].

Discussion

In a recent decade, dengue has caused several outbreaks in some Asian and Latin American countries and its vector-Ae. aegypti and Ae. Albopictus were reported to expand their habitat area [208]. One of influencing factors is the climate change. Therefore, several control programs have been proposed to control DENV transmission. Prompt and accurate diagnosis is also important to early detection of DENV infection which is beneficial for dengue transmission and disease control in clinical. In addition, severe disease progression caused by DENV infection currently remains unpredictable which leads to the essentiality to find the key biomarkers for prediction of severe dengue occurrence. In this review, we discussed dengue pathogenesis, treatment strategies, and control measures.

Our results indicate that the factors induced dengue severity are complicated and many factors from host or virus are involved. Therefore, development of new diagnostic assay or platform are demanded to detect virus antigen or specific antibody in the early or late phase after infection, respectively. Furthermore, vector control plan is required to efficiently block dengue transmission cycle. Our study indicated that the pathogenesis of DENV is more complex due to both host and viral factors, however, the detail mechanisms remain elusive. Several factors, such as, cytokines, viral NS1 protein, neutralizing or enhancing antibodies and HLA types etc. are currently considered to be correlate with dengue severity development. Our results indicated that TNF- α , TGF- β 1, and IL-10 gene polymorphisms were correlated with protection or susceptibility to DHF and the higher levels of VEGF, GMSF, GCSF, TGF- β , and HGF as well as lower levels of PDGF and EGF were observed in severe dengue patients. Partial similar findings were reported in the other studies, indicating that TNF- α , TGF- β , IFN- γ , IL-7, IL-8 and IL-10, involved in the progression of severe dengue [209–211]. More recently, Puc et al., indicated that IL-10 was a potential diagnostic marker for DF whereas CD121b demonstrated to be predictive of the severe dengue development [212]. This information suggests that elevated certain cytokines such as TNF- α , TGF- β and IL-10 might correlate DENV infection and DHF syndrome development. Nevertheless, different study groups pointed out different cytokine as the predictive for dengue severity. The bias existed in these studies might be resulted of size of study population, difference of mean age and studying areas with different races.

Regarding diagnosis of DENV infection, the current most conducted in clinical is to detect viral NS1 protein due to higher amounts of dengue NS1 proteins would be secreted out during the early phase of infection. It is known that NS proteins are responsible for viral replication and host immune evasion and NS1 is detectable in the serum and other body fluids immediately at the onset of symptoms, even before the appearance of IgM antibodies[213–215]. The exact roles of NS1 are not well understood. NS1 is dimeric in early stages of infection and secreted in hexameric form in later stages. DENV NS1 antigen tests can be as sensitive as molecular tests during the first 0–7 days of symptoms. After day 7, NS1 tests are not recommended. Furthermore, NS1 positive test result is only indicative of a dengue infection but does not provide serotype information [216]. In addition, dengue MAC-ELISA for detection of anti-dengue virus IgM antibody is also recommended for early diagnosis of DENV infection. Because during DENV infections, IgM antibodies can be detected within 3–5 days following the onset of fever. Due to high similarity of flavivirus NS1, MAC-ELISA with sufficient sensitivity to detect low DENV IgM antibody titers and also could be specific to discriminate DENV infection in areas where multiple flaviviruses and

other pathogens cocirculate [217]. Mahapatra et al. reported that early diagnosis of dengue could be mainly by NS1 antigen detection whereas IgM ELISA is a better tool during the later stage of infection. Dengue RT-PCR is more effective in IgM negative samples [218]. Similarly, another study reported that only NS1 antigen could be used to test during the first two days of fever. MAC ELISA begins to show positive by the third day of illness and gradually its positivity increases [219]. Combined, we suggest that NS1 antigen test remains a good tool for early diagnosis compared to MAC ELISA. An alternative choice could be considered using combined testing with a nucleic acid amplification test (NAAT) and MAC-ELISA which could provide a diagnostic result during the first 1–7 days of illness. It is worthy of developing novel detection assay for NS1 detection, such as biosensor platform.

As we mentioned, there is still a lack of dengue specific antiviral drugs at current status. In some developing countries, the natural herbal products would be used for dengue treatments such as *eupatorium perfoliatum*, *boesenbergia rotunda* etc. However, the old drug repurposing strategies have been reported to be potentially useful against DENV infection. Drug repurposing, also known as research into clinically approved drugs for new indications, can significantly speed up the development of antiviral medications. For example, a previous report indicated that Prochlorperazine (PCZ), a dopamine D2 receptor (D2R) antagonist demonstrated an antiviral effect against DENV infection via blocking D2R mediated viral binding and viral entry [220]. The other example is Phenothiazines, a pharmacological diverse compound with a wide range of properties that make them as great candidates for drug repurposing. By screening libraries of therapeutically approved compounds, three phenothiazines (prochlorperazine, trifluoperazine, and fluphenazine) were found to be potent inhibitors toward flavivirus, including HCV and DENV [221,222]. Another old drug, such as quinine [223] or Ribavirin [224–226] was reported to inhibit DENV infection. Some other candidates previously reported to use for flavivirus treatment (including valparoic acid, sirolimus, resveratrol, vorinostat, and Y-27632) were also reported to work on dengue treatment [227]. We therefore suggest that development of novel antiviral drug as well as repurposing of current old drugs are important strategies for dengue prophylactic and therapeutic application.

We described that the FDA-approved vaccine “Dengvaxia” a live attenuated vaccine has some limitations, which is only effective for children from 9 to 16 years of age and can cause severe dengue in the children under 9 years old who has not been infected by DENV previously [228]. Dengvaxia was also reported not safe for the women with pregnancy with outcomes of vertical transmission from mother with viremia to baby and also at the time of breast-feeding [229]. This vaccine is reserved for individuals with an established prior infection, mechanisms involved in vaccine functionality are secondary and often two-fold. However, why this vaccine requires a prior infection and then could reach full protectivity against 4 serotypes of DENVs, remain not fully understood. A previous study hypothesized that an immunodominance effect might occur when varying frequencies of T-cell responses from a primary DENV infection alter the response to secondary infections according to serotype [230]. Dorigatti et al. also reported that previous exposure to the yellow fever virus may have been a contributing factor in children who produced higher DENV titers due to their ability to bypass what would normally be a heightened cellular requirement in response to the yellow fever component of Dengvaxia and instead to generate specific immune response against envelope proteins [231]. Combined, these studies indicate that Dengvaxia induces only mild antibody cross-reactivity toward heterotypic DENVs. The effectiveness of DENV-neutralizing antibodies and vaccines varies based on initial serostatus, the emergence of specific cross-reactive components, and the development of protective responses. For children residing in dengue-endemic areas and individuals traveling to such regions, the administration of Dengvaxia can be considered as a standardized tool, given the observed benefits. Regarding the control

measures, our results indicate different control measures for DENV transmission in different ways. At earlier period, the insecticide-based vector control programs had adequate efficacy and effect on the environment, but they have not been continued for a long time. Several strategies have been identified to control the transmission of DENV through focusing on the vectors. The strains of the bacterium Wolbachia were introduced to the *Ae. aegypti* mosquito population, which exhibited significantly diminished vector competence. But Wolbachia has some adverse effects, like negative ecological change, reduced mosquito management effectiveness, lower standards of public health, and adverse socio-cultural and economic impacts [232]. Currently, Wolbachia offers an intriguing new possibility for the biocontrol of arboviral diseases, including dengue [198]. But the challenge is how it will affect high-transmission areas. More recently, the genetic modified (GM) mosquitoes were authorized to be conducted in US via release of male *Ae. aegypti* mosquitoes genetically modified to prevent reproduction. The genetically engineered males carry a gene that passes to their offspring and kills female progeny in early larval stages. Male offspring won't die but instead will become carriers of the gene and pass it to future generations. As more females die, the *Ae. aegypti* population should decline. While GM mosquitoes offer an alternative approach to vector control, there are concerns about potential unquantifiable risks that may lack sufficient oversight in natural ecosystems. It is possible that these GM mosquitoes could carry or inadvertently develop unknown pathogens that could pose risks to human health [233]. We suggest that Wolbachia, vaccines, GM mosquitoes and other control measures can together decrease the transmission of DENV and protect people from DENV in both high- and low-transmission areas.

Conclusion

In this study, we provide an updated overview of dengue. We offer the basic and latest information in various aspects of dengue including clinical manifestation, mechanism of the disease, current treatment, control, and prevention of DENV. Our results indicate that understanding the DF/DHF pathogenesis, risk factors, and different types of therapeutic and control strategies used for the treatment of DENV are necessary. Dengue fever is currently a global public health threat that requires effective licensed vaccines, vector control measures, and early diagnostic tests to prevent the burden of this disease.

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CRediT authorship contribution statement

Muhammad Bilal Khan and Sheng-Fan Wang discussed the concept and designed the manuscript. Zih-Syuan Yang, Chih-Yen Lin, Ming-Cheng Hsu, Wen-Hung Wang and Wanchai Assavalapsakul assisted in paper selection and manuscript preparation. Aspiro Nayim Urbina provided assistance with language editing and data analysis. Yen-Hsu Chen and Sheng-Fan Wang made critical revisions and gave suggestions of the manuscript. All authors read and approved the final manuscript.

Declaration of Competing Interest

We have no conflict of interest to declare.

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