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DENGUE VIRUS: EPIDEMIOLOGY, BIOLOGY AND CHALLENGES OF VACCINE DEVELOPMENT

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ABSTRACT

Dengue virus (DENV), a growing public health issue throughout the world has caused over 6.5 million laboratory confirmed cases and more than 7,800 deaths globally in 2024. DENV, belonging to the Flaviviridae family, can manifest as mild dengue fever or more severe conditions like dengue hemorrhagic fever and dengue shock syndrome. Symptoms typically include fever, headache, and muscle pain. Transmission is primarily through Aedes aegypti and Aedes albopictus mosquitoes, with climate change accelerating the spread of these vectors. The virus has five serotypes, making vaccine development particularly challenging, as immunity to one serotype does not confer protection against others. Traditional vaccines, which target the immunogenic components of pathogens, have been difficult to develop for dengue due to the complex interaction of the immune system with DENV. One key concern is antibody-dependent enhancement (ADE), in which pre-existing antibodies can potentially exacerbate the disease when a person is infected with a different serotype later on. This complicates the development of safe and effective vaccines. With Türkiye now home to Ae. albopictus and Ae. aegypti mosquitoes, the risk of dengue becoming endemic is increasing, particularly in the context of climate change. To address this threat, a One Health approach is needed, focusing on mosquito control, active surveillance of both vectors and the disease, and the development of preventive strategies. Concurrently, research into safe, effective, and widely accessible vaccines and therapeutic agents must be prioritized to combat dengue effectively and reduce its impact on public health.

Key Words: Dengue fever, Dengue virus, vaccine, antibody-dependent enhancement

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INTRODUCTION:

Dengue virus (DENV), a member of the Flaviviridae family, poses a growing public health risk globally, particularly in tropical and subtropical regions. Dengue is a vector-borne disease transmitted by Aedes aegypti and less frequently by Aedes albopictus mosquitoes carrying the DENV.[1] Climate change is identified as a pivotal factor exacerbating the spread of dengue, as shifting environmental conditions facilitate the proliferation and spread of the Aedes mosquitos. Notably, dengue has emerged as one of the most prevalent diseases globally, affecting a diverse array of regions and populations. Its pervasive nature is underscored by its continued expansion into new territories and its sustained burden on public health infrastructure.

Dengue cases have risen dramatically in recent years. According to the World Health Organization (WHO), there were 506 cases in 2000, whereas the number skyrocketed to 5.2 million cases in 2019.[2] Dengue, which was initially discovered during epidemics in Thailand and the Philippines in the 1950s, is now a major cause of hospitalization and mortality for both adults and children in many Asian and Latin American nations.[3] Over 6.5 million laboratory confirmed cases and more than 7,800 deaths were reported globally in 2024 from January to August. Dengue is not endemic in the mainland regions of the European Union (EU) and the European Economic Area (EEA), indicating that the virus is not consistently present in these areas. The majority of dengue cases are attributed to travelers who have been infected outside the mainland EU/EEA.[4,5] Nevertheless, under favorable environmental conditions and in regions where competent mosquito vectors are established, viremic travelers can trigger local transmission of the virus. This phenomenon has been documented by sporadic instances of localized dengue virus transmission since 2010.[6] Recent data from WHO underscores the escalating prevalence, notably in 2020, with notable increases observed in several countries including Bangladesh, Brazil, Ecuador, India, Indonesia, Maldives, Singapore, Sri Lanka, Sudan, and Thailand.[5] According to the WHO, around fifty to one hundred million cases of dengue occur each year (4), with half of the global population at risk. Additionally, the CDC has noted that the incidence of dengue has increased 30-fold over the past 50 years.[7]

The frequency of infections has increased due to the ease and spread of travel opportunities in the 21st century. The rising incidence of dengue is believed to be driven by factors such as international travel, the spread of new strains and mosquito vectors to various regions, climate change, population growth, overcrowded living conditions, poverty, and insufficient public health measures. Hence, a global one health approach is required to control the spread of the mosquito vectors and the transmission of the DENV.

Epidemiology of Aedes mosquitos

Mosquitoes are of public health importance when they are present in large densities or transmit disease. The spread of suburbs into natural areas has increased mosquito breeding grounds and increased their contact with humans. In cities, mosquitoes such as Ae. albopictus are in contact with humans. These invasive species are effective vectors that can spread diseases such as chikungunya and dengue fever; for example, Ae. albopictus can carry at least 22 arboviruses. The European Centre for Disease Prevention and Control published a mosquito distribution map in May and July 2024, detailing the presence of A. albopictus and A. aegypti species, which are known vectors for dengue. Surveillance data indicate that Ae. albopictus is found in the eastern Black Sea, Aegean, and Marmara regions, including Istanbul and Kocaeli. A. aegypti, on the other hand, is reported to be present in the eastern Black Sea region.[8]

Studies conducted in Turkey failed to show the presence of dengue, zika, chikungunya, or West Nile viruses within the Ae. aegypti and Ae. albopictus mosquitoes caught in Türkiye. However, viruses can enter the country through international travel and trade. Türkiye occasionally experiences cases of

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imported infections like dengue, chikungunya and zika viruses, mostly in citizens returning from abroad or travelers from other countries. To date, no locally transmitted (autochthonous) cases have been reported.[9]

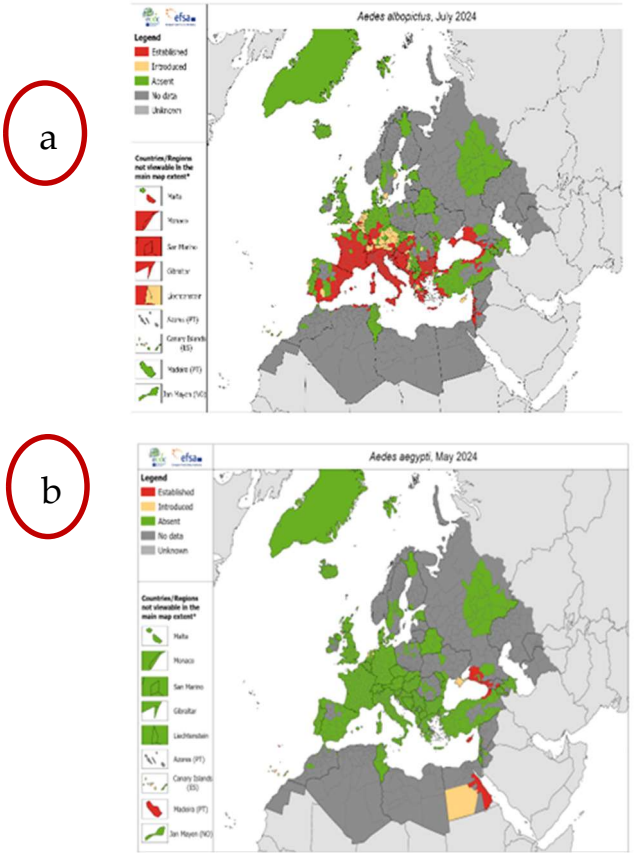

Figure 1. The maps illustrate the documented range of a. Aedes albopictus in Europe as of July 2024 and b. Aedes aegypti in Europe as of May 2024.[8]

Structure and the serotypes of the dengue virus

Arboviruses (arthropod-borne viruses), categorized based on their antigenic properties, physical structure, and replication processes, are viruses transmitted by arthropods. In addition to the most clinically important viruses belonging to the Flaviviridae family, viruses belonging to the Rhabdoviridae (Rabies virus, Vesicular stomatitis virus, Bovine ephemeral fever virus), Bunyaviridae (Hantavirus), Orthomyxoviridae (Influenza A virus), Togaviridae (Rubella virus) and Reoviridae (Rotavirus) families belong to this group.[10]

Dengue viruses are classified within the Flavivirus genus of the Flaviviridae family, sharing this taxonomic classification with other significant pathogens such as Japanese encephalitis, yellow fever, West Nile and zika viruses.[11] Structurally, DENVs are enveloped, spherical particles with an average diameter of around 500Å. Their genome consists of approximately 11 kilobases (kb) of positive-sense, single-stranded RNA (ssRNA) encoding a total of ten proteins.[11,12] DENV's genetic material, which includes seven non-structural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5) and three structural proteins (membrane (M), envelope (E), and capsid (C), is essential for controlling the virus's virulence and replication. This genomic organization is characteristic of Flaviviridae members, enabling them to encode vital components for viral assembly, replication, and evasion of host immune responses. The architecture of DENV encompasses a lipid bilayer envelope enveloping the viral nucleocapsid core, which houses the RNA genome. Structurally, DENV particles exhibit icosahedral symmetry, presenting a well-organized outer shell while harboring a less ordered nucleocapsid core, crucial for protecting and delivering the viral RNA payload.[10,14]

Dengue virus consists of four serotypes (DENV1-DENV4) according to WHO. But a new fifth serotype (DENV5) has been revealed; it was initially found in a patient's blood in Sarawak, Malaysia, in 2007.[15] Each serotype operates as a distinct infectious entity, capable of inducing the characteristic symptoms of dengue. This diversity in serotypes poses challenges for disease management and vaccine development, as immunity acquired against one serotype does not confer protection against the others. The potential of antibody-dependent aggravation, which the literature refers to as "Antibody Dependent Enhancement (ADE)" is another issue. Antibodies produced in response to an initial DENV infection can kill the virus and offer lifetime protection. Nonetheless, the DENV serotype

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experiences an early period of cross-protection in the event of heterologous infection with one of the other viral types. These antibodies are transient and do not provide neutralization but instead are cross-reactive. They form complexes with the dengue virus and bind to FcγR receptors on monocytes and macrophages. This facilitates the entry of different serotypes of the virus into these cells, resulting in enhanced viral replication. The increased viral load leads to a more severe form of dengue infection.[16]

The identification of DENV5 underscores the dynamic nature of the virus and emphasizes the importance of ongoing research efforts to understand its epidemiology, pathogenesis, and implications for public health (15). Within DENV serotypes, further stratification into various subtypes or genotypes occurs, dictated by alterations in the viral genome. This diversity in genotypes and serotypes stems from the high frequency of genetic mutations propelled by RNA polymerases. RNA polymerases lack proofreading mechanisms, leading to mutations in nearly every replication cycle of the virus. The multitude of genotypes and serotypes presents a significant obstacle in the development of effective vaccines. Immunity acquired from exposure to one serotype confers lifelong protection only against that specific serotype. Consequently, the continual evolution and diversification of DENV strains necessitate a vaccine approach capable of addressing the broad spectrum of serotypes to provide comprehensive protection against the disease.[17]

Immunopathogenesis of DENV infections

The virus enters the bloodstream after an Aedes sp. bite that is infected with DENV. Langerhans cells (epidermal dendritic cells) and keratinocytes are the initial targets of infection. These cells then go to the lymph nodes, where they make monocytes and macrophages vulnerable to infection. The virus then spreads via the lymphatic system, multiplying in a variety of cells, including blood-derived monocytes, splenic and liver macrophages, and myeloid dendritic cells.[1]

Heparan sulfate, CD14-associated lipopolysaccharide-binding proteins, Fc receptors, glycosaminoglycans (GAG), and lectin-like receptors like DC-SIGN (dendritic cell-specific intercellular adhesion molecule 3-grabbing non-integrin) enable viral attachment to the cell surface, which initiates intracellular replication. The virus subsequently uses receptor-mediated endocytosis to enter the cell. Dengue virus (DENV) enters cells via clathrin-coated vesicles. The E protein experiences conformational changes with acidification of late endosomes, facilitating the fusion of the viral and host cell membranes and the release of the nucleocapsid into the cytoplasm.[17] The endosome's acidic environment makes it easier for the virus to fuse with the membrane, releasing the nucleocapsid (NC) into the cytoplasm and enabling the RNA genome to become uncoated. The cytoskeleton then transports the viral components toward the endoplasmic reticulum (ER). A cap-dependent mechanism initiates the translation of DENV's positive-strand RNA into a polyprotein. The RNA genome replicates on the ER membrane using the positive-sense RNA as a template. The production of both positive- and negative-strand viral RNA depends on the DENV NS5 protein. It has RNA cap methylation and RNA-dependent RNA polymerase (RdRp) activity.[19] While viral capsid proteins are translated in the cytoplasm, viral E and M proteins are inserted into the ER membrane during translation. The genomic RNA is wrapped in capsid proteins in the cytoplasm once the negative-strand anti-genome RNA has produced sufficient copies of positive-sense RNA. After that, it is carried into the ER lumen, where it joins the M protein that is created when PrM is cleaved by the host. Variations in pH during virion synthesis and release affect the shape and arrangement of the E protein on the surface of the mature virion. The encapsulated virions stay in the lumen after making their way through the ER and the trans-Golgi network. As the encapsulated virions sprout from the ER into the cytoplasm, they acquire an extra outer membrane on top of the ER membrane. When the ER-derived membrane merges with the plasma membrane, mature virions are discharged into the extracellular area. This makes it possible for the freshly created virions to proliferate and infect more cells.[20,21]

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Mononuclear cells predominantly experience apoptosis after being infected, while dendritic cells that are infected but do not fully replicate the virus stimulate inflammatory and hemostatic reactions. As a result, the number of infected target cells and factors affecting viremia levels may determine the equilibrium between proinflammatory and anti-inflammatory cytokines, chemokines, and other agents, thereby defining the characteristics of the inflammatory response.[22] The dissemination of viral infection hinges upon the transfer of the virus from infected to uninfected cells, necessitating a sequence of discrete events. The viral life cycle encompasses distinct stages, including virus entry into the host organism, replication within host cells, assembly of new viral particles, and eventual release from the host cell.[18]

The innate and adaptive immune responses to DENV are pivotal for defending against infection, yet they can also trigger pathological reactions that exacerbate the disease. Therefore, creating effective and safe dengue vaccines and therapeutic treatments requires an understanding of the processes governing immune-mediated protection against pathogenesis. The production of vasoactive chemicals from intravascular and extravascular cells such as mast cells, lymphocytes, monocytes, and tissue macrophages are one of the ways the dengue virus damages the vascular endothelium. For example, it has been suggested that several substances produced by mast cells, T cells, monocytes, and macrophages increase vascular permeability. Although, DENV virus infects various cell types, the main responding cells are monocytes, macrophages and mast cells. These cells mount an important response to DENV infection by producing potent signaling molecules such as chemokines, cytokines, lipid-derived mediators and other immunological mediators.[23]

Following infection, three distinct scenarios may arise: lasting immunity against the same DENV strain, temporary protection against infection or disease from a different dengue serotype, and subsequent reinfection with an alternate dengue serotype capable of inducing severe illness.[24,25]

The third and most severe effect is ADE, a condition that may exacerbate rather than lessen the disease and is purportedly brought on by antibodies after preimmunized people with a different DENV serotype are re-infected.[21] The phenomenon of ADE manifests during a subsequent heterotypic dengue infection following primary exposure, wherein antibodies are ineffective in neutralizing the virus and instead facilitate the uptake of virus-antibody immune complexes by phagocytes. Consequently, this process can result in elevated viral loads and trigger an immunopathogenic cascade, culminating in vascular leakage and characteristic signs indicative of severe dengue.[26]

Clinical characteristics of dengue

Dengue virus infection presents in various clinical forms, primarily classified according to their prognostic implications as dengue and severe dengue. Dengue typically manifests with general symptoms such as fever, headache, and muscle pain, and is also known as break-bone fever (pertaining to the severe musculoskeletal pain) or dengue fever. Dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) are two symptoms of severe dengue. Dengue hemorrhagic fever is distinguished by heightened vascular permeability, resulting in plasma leakage, reduced platelet count, and hemorrhagic symptoms. Moreover, DSS signifies a severe manifestation of the illness, marked by a rapid drop in blood pressure leading to circulatory shock and dysfunction across multiple organs. These categorizations assist healthcare professionals in managing clinical interventions and evaluating the prognosis of individuals affected by DENV infection (14). In particular, repeated infections with distinct DENV serotypes can cause significant capillary leakage, thrombocytopenia, a sharp rise in hematocrit, bleeding signs, and a condition that worsens to shock and necessitates hospitalization. There is no specific antiviral treatment for dengue. Dengue causes an estimated 5 million hospital admissions annually, including children with DHF/DSS.[6]

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Diagnosis

The diagnosis of dengue fever involves various methods, including viral culture, serological tests for IgM and IgG antibodies, NS1 protein detection, and RT-PCR. NS1 protein allows for a quick and practical diagnosis in the early stages of infection, while PCR is more sensitive but demands greater resources and technical expertise. Serological tests may face challenges due to cross-reactivity with other flaviviruses, which can complicate diagnostic approaches, especially in individuals who have been vaccinated. Although commercial diagnostic kits are available, they often suffer from issues like low sensitivity and specificity, prompting ongoing research into improved diagnostic techniques.[27-30]

Treatment

Dengue does not presently have a particular therapy or cure. The goals of the supportive therapy options available today are to lessen symptom intensity and consequences. Fluid therapy is the cornerstone of supportive care.[10,31] Oral fluid replacement can be adequate in dengue cases; however, intravenous fluid replacement is necessary to avoid shock in cases of severe dengue.[10]

Specific therapeutic agents for dengue should possess pan-serotype activity, swiftly alleviate symptoms, and have minimal toxicity and drug interactions. However, challenges include producing antibodies protective against all serotypes and the lack of animal models mirroring human DENV pathogenesis.[26] Antiviral drug discovery approaches include those targeting host cell factors and direct-acting antivirals (DAAs) against viral components. Host-targeted approaches provide broad-spectrum efficacy but may carry toxicity risks. Conversely, DAAs directly target viral proteins with lower toxicity but higher resistance risks.[31,32] Notable antiviral targets include DENV E, C, NS2B/NS3 protease, NS5 RdRp, NS5 MTase, NS4A, and NS4B proteins. Targets for potential antiviral therapy against dengue include E, C, NS2B/NS3 protease, NS4A, NS4B, and NS5 proteins. E protein is crucial for virus attachment and fusion, making it a promising therapeutic target. NS2B/NS3 protease is essential for viral replication and infectivity. NS4A and NS4B proteins also play roles in virus replication and host cell interactions. NS5 protein is fundamental in virus replication, making its MTase and RdRp activities potential therapeutic targets. Strategies targeting these proteins offer promising avenues for dengue treatment.[32] In addition, studies investigating the anti-DENV properties of natural compounds may be important as they have a broader bioactivity and stability than synthetic drugs. Some plant compounds, such as geraniin, can inhibit DENV replication and have been shown to reduce viremia by restricting virus-cell interactions. Other phenolic compounds, such as quercetin and nordihydroguaiaretic acid, are thought to have potential anti-DENV effects through different mechanisms affecting the pathogenesis of DENV.[31,32]

Vaccination and development of vaccine formulations against DENV

The development of a vaccine against DENV is a complex and challenging task with several key components and potential impacts on public health in dengue-endemic regions. Although vaccines hold promise for dengue prevention, currently available ones may cause complications in seronegative patients and offer limited protection across all DENV serotypes. One of the primary challenges is the presence of four serotypes of DENVs, each capable of causing similar disease outcomes, including fatality. The immunological interaction between these four antigenically different serotypes is the largest obstacle. Its effectiveness depends on a vaccination that is genetically stable and equally effective against all serotypes. Vaccine-induced immunity to one dengue serotype can potentially predispose an individual to severe disease upon exposure to a different serotype, which complicates the process of developing a vaccine. The lack of dependable assay platforms to evaluate immune responses and approved animal or human models for the disease

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represent another significant obstacle. A successful dengue vaccine must be genetically stable, effective against all serotypes, affordable, and widely accessible.[33] Various approaches have been explored, including live attenuated, inactivated vaccines, DNA-based, subunit and chimeric.[27] Future dengue vaccines may incorporate nonstructural proteins from the viral backbone, aiming for more efficient dosing with fewer required doses.[34,35]

Traditional vaccination approaches often involve using the entire pathogen (either inactivated live or attenuated). However, there is growing interest in subunit vaccines that utilize only the immunogenic components of the pathogen as antigens, allowing for a more precisely controlled immunization process. While vaccines comprising whole viruses or bacteria contain numerous antigens and other microbial molecules crucial for eliciting immune responses, vaccines with fewer defined antigens may exhibit reduced reactogenicity but could also have lower immunogenicity, necessitating the incorporation of adjuvants. Employing only the immunogenic components through recombinant DNA technology can provide a more controlled and effective vaccination strategy.[36,37] It has been observed that the other proteins of the virus other than the E protein do not have functions related to the immune response developed against the virus. The E protein is the primary target of neutralizing antibodies, oversees receptor binding and fusion, and is typically involved in virus pathogenicity and binding to the host cell membrane.[10,38] The antigenic distinctiveness of DENV serotypes is based on amino acid sequence differences in the E protein EIII region. Thus, having E proteins unique to each serotype is crucial when creating an efficient recombinant vaccine formulation for four distinct serotypes.[39]

Antigen selection plays a crucial role in developing a dengue vaccine that targets specific virus strains. Selecting antigens from all four dengue virus serotypes is critical to trigger balanced and durable tetravalent immune responses.

To create a tetravalent subunit vaccine, researchers developed two vaccines based on the consensus sequences of the envelope protein's ectodomain from 3,127 DENV strains. These vaccines successfully generated specific antibodies targeting all four serotypes, highlighting the importance of carefully choosing antigens to ensure broad and effective immunity in vaccine development.[40] The failure of a tetravalent live attenuated dengue vaccine to provide adequate protection against DENV-2 highlights the complexities involved in selecting antigens that can induce broad immunity across all circulating strains. This difficulty emphasizes the need for careful antigen design to ensure cross-protection against multiple serotypes in a diverse viral population. Neutralizing antibodies against strains of all four DENV serotypes can be produced using a single DENV computationally optimized broadly reactive antigen (COBRA) E protein in both naive and dengue virus-preimmunized populations, demonstrating the influence of antigen selection on broad vaccine efficacy.[35]

Antibody-dependent enhancement poses a significant challenge in the development of vaccines targeting pathogens with diverse serotypes and currently stands as a primary obstacle in the quest for effective dengue vaccines. Antibody-dependent enhancement manifests when pathogens exacerbate disease by facilitating their entry into the body instead of conferring immunity against them. In the context of dengue, each of its four distinct serotypes possesses the capability to induce infection. Antibodies generated against one serotype may impede the production of neutralizing antibodies against another serotype. Consequently, vaccination may heighten pathogen fusion with cells without achieving the desired targeted immunity.[36] For this reason, vaccine development studies against dengue focus on subunit vaccines in which only immunogenic components are used, instead of vaccines in which the entire pathogen is used.[2,41,42]

It is inevitable to include nanotechnology and nanoparticulate carrier systems in the formulations of subunit vaccines to create a reliable and effective immune response. It has been demonstrated that dengue vaccines based on nanoparticles can effectively produce humoral and cellular immunity without the need of ADE.[39,43,44] Nanoparticles can increase antigen stability and immunogenicity, as well as potentially increase vaccine efficacy by enabling targeted delivery and slow release of antigens.[21]Strong T cell responses have been demonstrated to be induced by dengue vaccinations based on nanoparticles, high levels of neutralizing antibodies and balanced Th1/Th2 immune responses, thereby contributing to increased immunogenicity.[41,45] The current adjuvant options and the use of nanoparticles for dengue vaccine development have shown promise in enhancing vaccine efficacy by improving immunogenicity and protective efficacy. However, challenges such as the need for balanced protection against all dengue virus serotypes and the prevention of vaccine-induced enhanced severity of disease remain. The immunological mechanisms underlying adjuvant use involve the enhancement of neutralizing antibody titers and the induction of robust cellular immune responses. Although promising, more research is needed to fully understand the safety and effectiveness of nanoparticle-based dengue vaccines and novel adjuvants.

Vaccines against DENVs

Two tetravalent live attenuated dengue vaccines are currently licensed: CYD-TDV (Dengvaxia, Sanofi) and TAK-003 (Qdenga, Takeda). Both vaccines have different chimerisation and genome structure. CYD-TDV is a vaccine based on yellow fever virus and contains 4 DENV serotypes. According to clinical research, it is safe and effective for individuals who have previously had dengue infection (seropositive), but it raises the risk of severe dengue for those who have not (seronegative) due to ADE. Therefore, seropositivity testing is recommended prior to vaccination. CYD-TDV is authorized for administration in three doses to individuals aged 6 to 16 who have confirmed prior dengue infection through laboratory testing and reside in areas where dengue is endemic (46). However, since serological testing is required for the vaccine to be administered, its use in national immunization programs is limited. CYD-TDV is safe and effective in individuals with previous infection but should be used with caution in uninfected individuals. TAK-003 is a newly licensed vaccine. It is based on the DENV2 strain (TDV-2) and the other three strains (TDV-1, TDV-3 and TDV-4) were obtained recombinantly by changing the genes of TDV-2. The vaccine is licensed in the European Union for individuals aged 4 years and older, and WHO advises the administration of two doses of TAK-003, spaced at least 3 months apart, for children aged 6 to 16 years in regions with high dengue transmission rates.[47] High transmission is defined as a seroprevalence >60% at age 9 years and a mean age of peak dengue-associated hospitalizations of <16 years. Outside the 6-16 years of age, WHO also recommends that people with comorbidities at high risk of dengue complications (such as sickle cell, diabetes, hypertension, cardiovascular diseases) may receive the TAK-003 vaccine. Recently, Brazil has become the first country to incorporate TAK-003 to its national immunization program as the country is experiencing the biggest dengue epidemic in its history.[48] The studies conducted by various companies and institutions are summarized in Table 1.[49]

Conclusions

Several factors such as the globalization and rapid movement of people, climate change, increasing poverty and inequities across the world set the ground for rapid spread of Aedes mosquitos and spread of the DENVs. The greatest threat to world health in the 21st century is climate change. While extending the dengue seasons in nations where the disease is already widespread, shifting climatic conditions and an increase in the frequency of extreme weather events aid in the DENV's spread into new areas.[50] Numerous instances of dengue lead to hospital admissions, placing considerable pressure on fragile healthcare systems, especially amidst outbreaks. Meanwhile, DENVs have evolved numerous tactics to evade host immune detection many of which are not yet fully elucidated.[51]

Table 1. Summary of phase study Dengue fever vaccines

Vaccine name	Vaccine type	Vaccine assessment	Company
Dengue 1,2,3,4 vaccine	Attenuated	phase III	Butantan Institute
V181-003	Attenuated	phase II	Merck Sharp & Dohme LLC
TDENV-PIV with AS03B	Inactivated	phase II	U.S. Army Medical Research and Development Command
V181-003	Attenuated	phase II	Merck Sharp & Dohme LLC
naNO-DENGUE	Nanoparticle-based peptide	phase I	Emergex Vaccines Holding Ltd.
rDEN2/4delta 30(ME)	Attenuated	phase I	National Institute of Allergy and Infectious Diseases (NIAID)
rDEN1delta30	Attenuated	phase I	National Institute of Allergy and Infectious Diseases (NIAID)
D1ME100	Premembrane (prM) and Envelope (E) DNA Vaccine	phase I	U.S. Army Medical Research and Development Command

With the unpredictability and rising occurrence of epidemics, alongside the absence of efficient and enduring vector control methods, there exists a compelling need for a solid one health strategy to combat the vectors and the spread of the disease. Despite the availability of licensed vaccines and numerous vaccine candidates currently undergoing clinical trials, there remains a critical need for safe and efficacious vaccines and antiviral drugs.[52] Current options provide limited protection against specific serotypes of DENV and carry the potential hazard of ADE. It is extremely difficult to produce neutralizing antibodies that are equally effective against all four DENV serotypes.[53] As Türkiye is now hosting A. albopictus and A. aedes mosquitos and given the changing climate and the rapid spread of DENV across the world, there is an increasing threat for contracting endemic DENV infections. Hence, we need to develop a thorough one health approach to control the spread and growth of vector mosquitos in Türkiye, to run an active surveillance for both vectors and the disease and to develop preventive strategies to protect the lives of our communities. In the meantime, research focusing on the development of evidence-based vaccine and therapeutic agents which are safe, efficacious and readily accessible should be prioritized.

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