Dengue Virus: Infection, Immunological Response, and Vaccine Development

Nariman Sindi[1*]

[1]*Department of Medical Laboratory Technology, Faculty of Applied Medical Sciences,*
King Abdulaziz University, Jeddah, Saudi Arabia.

Author's contribution

The sole author designed, analysed, interpreted and prepared the manuscript.

ABSTRACT

In the tropics and subtropics climates worldwide, the dengue virus (DENV) is the most common of arboviruses and a significant public health threat. The severe disease usually occurs during the primary infection, but more serious cases begin after the second instance of infection with a different serotype. Humans' innate immune system is composed of monocytes, macrophages, and dendritic cells, and they are capable of mounting rapid inflammatory responses. These cells are also called primary antigen-presenting cells, and they are essential for the formation of the immune system's long-term memory mechanisms. Through scientific advances, valuable knowledge into the pathogenesis of more serious diseases, and new methods to the production of dengue vaccines and antiviral drugs have been provided. We summarized details in the current literature review, including references, abstracts, and full text of journal articles. So that, we tried to review all available studies that projected existing awareness about the immune response to the dengue virus and the current status of the vaccine. Such information was selected and extracted from the PubMed, Web of Science, and Google Scholar databases for published data from 2000 to 2020 using relevant keywords containing a combination of terms, including dengue fever, epidemiology, clinical manifestation, immune response, and vaccine.

_____

Corresponding author: E-mail: nsindi@kau.edu.sa;

1. INTRODUCTION

Dengue virus (DENV) is a single-stranded RNA virus in the genus *Flavivirus*. It consists of four serotypes strongly linked but antigenically different. In more than 125 tropical and subtropical countries worldwide, the virus is widespread [1,2].

The most prevalent DENV transmission method is through the *Aedes* mosquitoes. The predominant vector of DENV is *Aedes aegypti*, a highly domesticated mosquito, but DENV Transmission may also be maintained by *Aedes albopictus* [3]. Few studies of other transmission routes, such as blood or bone marrow transfusion and solid organ transplantation [4].

Even though dengue is a well-known illness, there are variations in its clinical manifestations. In most cases, the DENV-associated condition varies from asymptomatic to acute febrile self-limiting disease. Case definitions for DENV infection are Dengue fever (DF), Dengue hemorrhagic fever (DHF), and dengue shock syndrome (DSS), which were provided by the World Health Organization (WHO) [5]. Increased dengue infection shows damage to organs such as the brain, liver, heart, or kidneys, a relevant and significant feature that has been reported in some cases, but that has been very hard to connect to the virus given the variable severity of these complications. As a result of these complications, the WHO has included organ injury in the recommendations for severe dengue cases [6]. For example, neurological effects may appear during or after acute infection, may be intermittent or permanent [7], and may involve both the central [8] and peripheral nervous systems [9].

For DENV infection, the three main immune cells are monocytes, macrophages, and dendritic cells (DCs). These cells are the significant phagocytic cells responsible for identifying and eliminating invasive pathogens in the innate immune system. They are antigen-presenting cells (APCs) that are important for adaptive cellular immunity to be initiated, expanded, and polarized. DENV targeting these cells can have a profound effect on immune modulation [10].

Dengue also takes a heavy economic burden on impacted nations' health care services. For the past sixty years, the battle for a good vaccine for dengue has been underway, but any successful cure or vaccine remains uncertain. Vaccination must be safe and less cost-effective. Several approaches were used to create the goal vaccines [11,12].

In this article, we tried to review all available studies that projected existing awareness about the immune response to the dengue virus and the vaccine's current status.

1.1 Study Design

The revised details on the Dengue virus immune response and vaccines were summarized in this literature review. Such information was selected and extracted from the PubMed, Web of Science, and Google Scholar databases for published data from 2000 to 2020 using relevant keywords including dengue fever, epidemiology, clinical manifestation, immune response, and vaccine.

1.2 Clinical Disease and Epidemiology

1.2.1 Epidemiology

Dengue is becoming a public health concern in recent years, as the cumulative prevalence has grown dramatically in the past 20 years, and no suitable antiviral medications are easily accessible [13].

The epidemiological model assesses how about 390 million individuals living in 128 countries in endemic or epidemic regions get the most common form of arbovirus infection each year [14,15]. Around 60 million symptomatic DF cases will rise per year, leading to ten to twenty thousand deaths [16]. Last two decades, the dengue rate recorded to WHO rises from 505,430 in 2000, over 2.4 million in 2010, and 4.2 million in 2019 [17]. Reported cases of death from 960 to 4032 increased from 2000 to 2015 [18].

In 2020, dengue continued to affect several countries of Southeast Asia, with reports of increases in the numbers of cases in the Philippines, Malaysia, Vietnam,and Banglash [19], and Yemen[20], [21]. High number of cases were reported in Bangladesh (101,000), Malaysia (131,000) Philippines (420,000), Vietnam (320,000) in Asia [19]. The highest number of cases of dengue ever recorded worldwide was in 2019. All areas were affected, and dengue transmission was reported for the first time in Afghanistan [22]. About 3.1 million cases have been registered in the American region alone, with more than 25,000 identified as severe [23].

The incidence of dengue infections spread by two species of *Aedes* mosquitoes is affected by

climate change. For their growth, survival, and feeding behavior, dengue and other arbovirus vectors, including chikungunya, Zika virus, and yellow fever, rely on temperature and precipitation [24]. Dengue transmission is highly temperature-sensitive, affecting generation time, the period from one vector-to-human transmission cycle to the beginning of a new cycle [25]. The epidemic possibility is defined by vectorial capacity. Global vector potential for the transmission of the dengue fever virus was recorded as the highest on record in the 2018 *Lancet* climate Countdown survey, rising to 9·1 percent for *Aedes Aegypti* and 11.1 percent for *Aedes Albopictus*, more than the baseline of the 1950s [26]. The most up-to-date maps reveal that these *Aedes* species are present on all continents, including North America and Europe [27]. Latest studies suggest *Aedes Albopictus* is widespread in Europe due to its rapid growth in the last few years [28]. Eggs of different mosquito types. The *albopictus* mosquito has been observed both north and south of the European continent [29], and the mosquito vector is expected to spread ever farther across Europe [30], as well as into uncolonized regions of China [31].

1.2.2 Clinical disease

The Dengue virus achieves entrance through the skin into the host organism after an infected bite of the mosquito. The disease's development includes humoral, cellular, and innate host immune responses and the more serious clinical signs arise after the rapid clearance of the virus from the host organism. Therefore, the most serious clinical appearance during the infection is not associated with a high viral load [32]. The WHO framework categorizes infections with the symptomatic dengue virus into an undifferentiated fever, DF syndrome, and DHF (Fig. 1) [33].

1.2.3 Classic dengue fever

DF is a severe flu-like illness affecting people of all age groups (infants, children, adolescents, and adults) [34]. Fever, headache, retro-orbital pain, generalized skin rash, myalgia, and arthralgia are the classical manifestation of moderate DF type. The first symptom of DF may be skin lesions, which can be effective in creating the diagnosis. The rash is common in DF, with an occurrence recorded in some> 80% studies and maybe evanescent and polymorphic in appearance in some studies [35]. It is possible to predict a full recovery from dengue fever, while certain dengue infections lead to atypical severe disease without DHF or DSS symptoms [35,36].

1.2.4 Dengue hemorrhagic fever and Dengue shock syndrome

During a secondary infection with dengue, DHF is also seen. It may also occur in infants via a primary infection due to maternally achieved dengue antibodies [37,38]. DHF is associated with high acute onset fever and constitutional signs and facial erythema, describing the onset of febrile disease [39]. DHF is graded into four grades by the WHO. DHF Grades I and II are relatively moderate non-shock events, while shock events are more extreme and accompanied by grades III and IV [40]. Hypovolemic shock due to excessive plasma leakage may occur in some infected individuals [41]. The life-threatening DSS develops at or shortly after grade III fever reduction and is defined by a damp and clammy face with a weak pulse or hypotension. The pulse and blood pressure are untraceable in the deep shock stage (grade IV), causing death within 12 to 36 hours of shock onset [42]. Viraemia in DHF and DSS is typically 10-100 times greater than in classic dengue fever [43].

1.3 The Structure of the Dengue Virus

Dengue fever virus is part of the Flaviviridae family of viruses, the same family of viruses as yellow fever, West Nile fever, Japanese encephalitis, and tick-borne encephalitis [44]. The DENV genome is single-stranded RNA (11 kb long). Three structural proteins and seven nonstructural (NS) proteins are present in the spherical enveloped virus, including NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5. The infectious virion has a diameter of about 50 nm and contains the Capsid (C), Membrane (prM), Envelope (E) and RNA genome (Fig. 2) [45]. The protein on the surface of the mature virion, but also below the E protein [46,47].

The replication of RNA viruses, which depend primarily on infected cells' cytoplasm, is NS proteins' responsibility. In this, the fundamental enzymatic behavior of several NS proteins is involved. The NS1 is located on the E. In viral RNA replication, it plays an important role. In the early stages of infection, NS1 is dimeric and is secreted at later stages in the hexameric form [49]. NS3 and NS5 are better characterized from NS proteins, all of which have enzymatic activity

necessary for viral replication [50]. NS5 is essential for RNA virus synthesis and has the fully necessary methyltransferase activity for RNA 5' capping and 2'-O-methylation viruses. NS3 is also important for the synthesis and capping of RNA viruses [51–53].

E glycoprotein (55 kDa) is important for viral attachment and cell entry because it is the antiviral goal for neutralizing and enhancing antibodies. The E protein is composed of three distinct domains (DI, DII, and DIII). Domain I is in the center, II has an internal fusion loop that is implicated in the dimerization and domain III involved in binding to cell receptors (Fig. 3) [54,55]. The E protein is a major component of DENV vaccines due to its role as an immunogen.

Still, cross-reactive E protein, NS1, and NS3 antibodies are developed against all other serotypes after secondary infection, rendering serotype-specific detection more complicated for secondary or multiple infections [28]. Infectious viruses and NS1-encoded viruses are found in the blood during the acute phase, and high-level early viremia and NS1-encoded antigenemia have been linked with more serious clinical presentations [43,57,58]. The identification of NS1 is also the basis for clinical assessment [31].

The clinical pictures ranging from asymptomatic, moderate febrile disease, classical DF to more serious DHF and DSS disease [59–61]. Recent reporting on dengue in children showed that secondary DENV-2, relative to other serotypes, infection, is more likely to cause serious illnesses [43,62]. In comparison, primary cases of DENV-1 were more explicit, while primary cases of DENV-2 and DENV-3 were usually more silent [63].

1.4 Immunological Response to Dengue Virus

1.4.1 Innate immune response

1.4.1.1 Innate immune cells for dengue virus infection

There has been a growing interest in understanding the cellular pathways that DENV uses to reach the host cell (Fig. 4). Langerhans cells (LCs), dermal cells, and dendritic cells (DCs) have been suggested as the key targets for DENV infection at the mosquito bite site [64,65].

The DCs play a significant role in the innate and adaptive immune response. They are distributed as partly undifferentiated immune cells in all body tissues, preferentially located at sites where a pathogen can access [66]. Also, these cells send signals to recruit natural killer (NK) cells via tumor necrosis factor (TNF)-α leading to granzyme, perforin, and INFγ secretion [67]. In this regard, Cerny et al. recommended that DCs in human skin are likely to be significant targets for in vivo DENV infection. This suggestion was based on discovering intradermal DENV-2 injection into mice or human skin from normal donors *In Vitro,* resulting in extremely aggressive antigen-presenting cell migration. These data demonstrated that DENV infects and activates LCs differently and that infected cell types lead independently to inflammation and adaptive response [68].

Human NK cells, representing 10-15% of all circulating lymphocytes, are bone marrow-derived lymphocytes that share a common progenitor with T-cells. The primary lymphoid population involved in innate immunity constitutes NK cells. Virally infected cells and activated resident macrophages are quickly recruited into infected organs and tissues through chemoattractant stimuli [69]. To restrict viral replication during the early stages of DENV infection and thus reduce corresponding pathogenesis, early activation of NK cells and type-I INF-dependent immunity may be necessary. Cytokines that reduce inflammation and tissue injury are also produced by NK cells [70,71]. In a DENV-infected mouse model, early activation of NK cells and B-lymphocytes could be significant for primary DENV infection clearance [70].

Moreover, viral antigens were observed in DENV-infected cells such as Kupffer cells, alveolar macrophages, endothelial cells, lymphocytes, and monocytes [73]. This viral load constitutes a significant risk factor for serious disease progression. The infection of these cells essentially impairs hemostatic and immune responses to DENV. Infected cells die primarily via apoptosis and, to a lesser degree, via necrosis. Necrosis tends to trigger toxic agents that cause the mechanisms of fibrinolysis and coagulation. Depending on the degree of inflammation of bone marrow stromal cells and interleukin levels such as IL-6, IL-8, IL-10, and IL-18, hemopoiesis is inhibited, resulting in decreased blood thrombogenicity. Platelets are closely aligned with endothelial cells and retain

vascular integrity, requiring an average number of functioning platelets. High blood virus load and probable viral tropism of endothelial cells, severe thrombocytopenia, and platelet dysfunction may contribute to serious capillary fragility, clinically described as petechiae, simple bruising, and gastrointestinal mucosal bleeding identified by DHF [74].

Many innate immune response cells are granulocytes that retain mediators, including particular inflammatory proteins and cytokines [75]. The most abundant leukocytes in the blood are neutrophils, which are an essential element of innate immunity. Chemotaxis is induced by epithelial cells, and resident macrophages, which secreted chemokines like IL-8 and other cytokines such as TNF-alpha and IFN-β. These neutrophils generate TNF-alpha that can act against viral infections and create cationic peptides cysteine, defined as defensins. [76]. Little information is available regarding the role of these cells during viral infection. The circulating levels of neutrophilic elastase and lactoferrin in children with DENV infection were evaluated in early work described by Juffrie et al. They found a significant rise in IL-8, which is significantly related to neutrophil degranulation [77]. Blood examination of patients suffered from DHF also revealed a slightly earlier rise (5–6 days) in the number of immature neutrophils but a later increase (10–12 days) in the number of mature neutrophils. These data indicated that neutrophils could promote the stimulation of complement, coagulation, and fibrinolytic system, creating an aberrant immune activation [78]. Recent research revealed that DENV could form neutrophil extracellular traps (NETs) *In Vitro* [79]. A study conducted found that the amount of neutrophil elastase is higher in people afflicted with DENV. Patients with DHF had slightly higher elastase activity levels compared to patients without DHF, which meant that inflammation could be related to the more severe form [80]. Opasawatchai et al. have recently studied the genotype and functional reactions of neutrophils in DENV patients. The findings exhibited that neutrophils upregulate CD66b expression during acute DENV infection and generate a more vigorous respiratory reaction. In cells isolated from DENV-infected patients during the acute process of infection, drastic decondensation of nuclei, an early event in NET growth, has also been markedly increased. The *in vitro* incubation of the DENV-2 virus within the NETs significantly decreased infectivity. In the serum of patients with DHF, but not uncomplicated DF, elevated amounts of NET components were found. Also, the levels of pro-inflammatory cytokines were elevated relative to those in DF patients. They indicated that during DENV infection, NETs may perform a dual function and neutrophils are participated in immunological responses [81].

1.4.1.2 The Complement system

The complement system is also one of the immune response to the infection. It is composed of over 30 different soluble and cell surface proteins, and the complement system is an essential component of innate immune responses to different pathogens. It is triggered by classical, lectin, and alternative pathways and controlling viral infections by different mechanisms, including virion or infected cell lysis, anaphylatoxin production, and T and B cell response [82]. Recent research by Avirutnan et al. is starting to focus attention on the dual function of the complement system in DENV infection defense and pathogenesis [83]. Anti-DENV antibodies could cause supplementation on the surface of infected endothelial cells in an in vitro study [84]. In a prospective study, NS1 could activate complement proteins correlated with disease severity [85]. In another prospective study, complement factors were high in DHF patients than in DF patients [86]. The association between NS1 activity and complement activation or altered complement activation regulation in dengue pathogenesis was recorded in these studies [85,86].

1.4.1.3 Innate immune pathways for dengue virus detection

Immune cells are the first to respond to infection by a pattern recognition receptor (PRR) [87,88]. When DENV is internalized in cells, dsRNA intermediates are produced throughout viral genome replication [89]. Crucially, PRRs generated by different susceptible cell types in the skin can detect this crucial step of the DENV replication cycle [90]. PRR recognition may enable the development of cytokines and chemokines that cause an antiviral condition to occur. Type 1 interferon (IFN) responses are caused by activating these PRR [91,92]. Activation of TLR-3 contributes to the activation of transcriptional interferon regulatory factors IRF-3and IRF-7. This results in transcriptional upregulation of type I (alpha and β) INF [93–95]. However, the IFN plays a key role in complex innate and adaptive immune processes, including tolerance to viral entry, promotion of T-

cell immune response, and successful antibody class-switching responses [96].

1.5 Adaptive Immune Response

Infection clearance is linked to humoral and cellular adaptive immune responses to DENV infection and plays a significant role in protecting against re-infection. It is also considered to play a key role in decreasing the severity of the disease seen in patients with DHF or DSS [48].

A series of events targeted at healing and pathogen removal is provoked by stimulation of macrophages and mast cells at pathogen entrance areas. These lead to inflammatory mediators release, alteration of tight endothelial junctions, and adhesion molecules. Allow the recruiting of other innate immune cells to the site and the activation of neighboring resident tissue cells to respond to the threat (Fig. 5) [97-99].

1.5.1 B cells and antibody responses

During infection with DENV, B cells have been seen to play a significant role, demonstrated by the latest findings of a substantially high number of plasmablast/plasma cells that occur during the acute phase [101]. In order to cause B cell proliferation and differentiation into effector plasma cells or long-lived memory B cells, activation of B cells by dengue-specific B cell receptor (BCR) has been clarified [102].

In the adaptive immune system, B cells play an important role in the secretion of antigen-specific antibodies that shield and react to invading pathogens. Activated B cells contribute to the development of immunoglobulins (IgM, IgG, and IgA) unique to viruses, most of which attach to the viral envelope protein and neutralize virions, thereby blocking them from reaching target cells. IgE will stimulate innate immune cells via the high-affinity crystallizable fragment (Fc) epsilon receptor, which is displayed at significant concentrations on mast cells and elevated on activated DCs [103].

The main DENV infection has a reasonably normal immune response, via an initial IgM followed by an IgG response to dengue antigens. An increased IgG with a reduced IgM is observed during secondary infection. [104]. Plasma cells and titers of DENV-specific antibodies rise in the blood within days after infection. Using human serum-deprived from IgM, it was shown that the IgG reaction already accounted for ~50 % of the neutralizing potential of DENV-specific immune serum at 4–7 days after the onset of fever. In comparison to other viral infections, such as HIV, which may cause hypergammaglobulinemia, only a small rise in the activation of polyclonal B cells was found [105]. In addition, the DENV-specific B cells in primary infection are extremely serotype-specific [106].

The main targets of antibodies produced during primary and secondary DENV infections are the E, prM, and NS1 proteins. Antibodies to E and prM have been shown by antibody-dependent enhancement (ADE) to improve infection of Fc receptor-bearing cells in vitro, and this has been hypothesized to lead to in vivo pathogenesis [107].

Numerous mechanisms can deter infection, including preventing binding, inhibiting the virus fusion with the endosomal vacuole, which prevents the release of viral RNA, and complementary lysis of the antibody-coated virus [108,109]. In animal studies, the antibody-mediated defense has been successfully confirmed by the active transmission of antibodies to envelop proteins [110,111].

1.5.2 Adaptive T cell responses

The cell-mediated adaptive immune response consists of CD4+ and CD8+ T cells to enable B cells to activate and destroy virally infected host cells [112]. While T cells play an important role in the battle against viral infections, both harmful and defensive actions of T cells in the sense of DENV infection have been recorded [65,113–115].

CD8+ T cell targets NS3 proteins, then Capsid, NS5 and NS4A/B proteins. In comparison, CD4 T cell targets mainly Capsid, accompanied by proteins such as E, NS3, NS2A/B, and NS5 [115].

Dendritic cells link innate and adaptive immune responses. *In vitro*, infected DCs stimulate T cell IFN-γ production [116–118]. Others revealed that DENV-infected DCs mediated the immediate propagation of naive CD4+T cells but stayed nonpolarized in the role of the effector. Down regulation of the production of IFN-alpha/β-stimulated genes [119]. Both types of T cells play a defensive role in murine models towards DENV infection, avoiding serious illness and promoting viral clearing [120–123].

Another subset of CD4 T cells is called follicular T helper cells (Tfh), which allows T cells to support and activate B cells [124]. Protective

functions in human infectious diseases and vaccines have been identified with Tfh cells [125–127]. They supply B cells with many types of T cell assistance, like stimuli encouraging survival, chemoattraction, proliferation, division of plasma cells, hypermutation, and recombination of class switches. They are important and have an evident responsibility to protective immunity against pathogens [128].

For infected APCs, tissue-resident CD8+ T cells roam the skin and can produce instant adaptive immunity. Cytotoxic cells CD8 and CD4 + T produce cytotoxic molecules including granzymes and perforins that can destroy virus-infected cells through pathways based on MHC I and MHC II. By generating inflammatory cytokines such as IFN-γ and TNF-alpha, T helper (Th1) cells mediate and encourage antiviral immune responses, while regulatory CD4+T cells inhibit inflammation induced by immune response by generating cytokines like IL-10 and transforming growth factor (TGF)-β. DENV-specific germinal center B cells are aided by Tfh cells and are important for efficient germinal center reactions, facilitating high-affinity antibodies, memory B cells, and long-lived plasma cells [112].

Studies in both the murine and humans established defensive HLA alleles associated with strong T cell responses [129].

1.6 Dengue Virus Vaccine

With many dengue cases worldwide, vaccine production has a promising prospect to control the disease, especially to protect children from infection. Dengue has four distinct serotypes; the affected person has long-term immunity against a subsequent infection with a related DENV serotype following regeneration of one serotype. However, subsequent DENV infection with a different serotype is associated with ADE, a mechanism that leads to the manifestation of DHF [107,130]. Therefore, vaccine production should promote long-lasting immunity and simultaneously defend against all four DENV serotypes. A list of vaccine candidates is summarized in Table 1.

Multiple candidates for tetravalent vaccines are being created. That includes live-attenuated vaccines, inactivated whole-virus vaccines, protein-based vaccines, chimeric vaccines, and synthetic particle-like mRNA virus vaccines [131].

Four serotypes form the dengue serocomplex, each of which consists of multiple genotypes [132]. The four serotypes share genetic homology of 65-75 % with one another and are antigenically different. This high level of pathogen sequence heterogeneity, characteristically correlated with RNA viruses, presents special vaccine production obstacles [113].

1.6.1 Live attenuated vaccines (LAV)

Live attenuated (LAV) vaccinations appear to replicate natural infection by inducing humoral and cellular responses that elicit long-lasting immunity. LAVs comprise a weaker version of a live virus [133].

Serial dilutions have been used to attenuate DENV by culturing with primary dog kidney (PDK) cells, accompanied by a final passage with fetal rhesus lung cells. The monkeys are used to test applicants for vaccines and screen them. The DENV-2, -3, and -4 vaccines showed a mild reaction. DENV-1 attenuated, leading to fever and rash in 40 % of trial patients [134].

Just 30 percent overall effectiveness was demonstrated by a live-attenuated tetravalent chimeric yellow fever dengue vaccine (CYD23), showing partial (60-80 percent) defense against three out of four DENV serotypes. Despite three subsequent immunizations and high neutralization titers, no defense against DENV2 infection against all four serotypes was observed [135].

The optimal dengue vaccine should be given in single doses, give protection against all serotypes, provide long-term protection with no side effects [136]. Actually, in around 20 dengue-endemic countries in Asia, Latin America, Oceania and Europe, there is only one vaccine approved for the protection against dengue. This LVA recombinant tetravalent vaccine is the Dengvaxia (CYD-TDV) established by Sanofi Pasteur [41]. Phase III experiments revealed the vaccine's effectiveness that relied on age, serostatus, and serotype and revealed a benefit at the population level. This vaccine is only approved for individuals between the ages of 9 and 45 years of age who live in an infected area. This vaccine is also not available to the people most at risk of developing severe dengue-related symptoms. Unfortunately, the vaccine has less protection against serotypes 1 and 2 than serotypes 3 and 4 [137,138].

Table 1. Dengue vaccine candidates [136,147,150,165]

Candidate vaccine name and Vaccine type	Manufacturer/Developer	Collaborator	Method	Trial Phase
CYD-TDV LVA and recombinant	Dengvaxia®	Sanofi Pasteur	DENV-1–4 prM/E (based on a yellow fever vaccine 17D backbone	Licensed
Tetravalent LVA	Walter Reed Army Institute of Research (WRAIR), USA	GlaxoSmithKline (GSK)	Tissue culture-passaged in PDK cells	Phase II
LVA	Mahidol University, Thailand	Sanofi Pasteur	Tissue culture-passaged in PDK cells	Phase II
TV003 TV005 LVA and recombinant	National Institute for Allergy and Infectious Diseases (NIAID)	Butantan Institute	DENV-1,3,4 whole genome, DENV-2 prM/E (DENV-2 in DENV-4 backbone)	Phase III
TAK 003 LVA and chimeric	Pharmaceutical Company (Tokyo, Japan)	Takeda	genes of DENV1, 3, 4 expressed on the backbone of the DENV2 genome (prM and E).	Phase III
LVA tetravalent chimeric	Center for Disease Control (CDC), USA	Inviragen	Tissue culture-passaged DENV2 backbone and prM/E from DENV1–4	Phase II
DNA Monovalent (DENV-1)	(Vical, Boulder, CO, USA)	Navy Medical Research Center	DENV-1	Phase I
Tetravalent DNA vaccine (TVDV)	(Vical, Boulder, CO, USA)	Navy Medical Research Center	DENV-1–4 prM/E with Vaxfectin®	Phase I
TDENV-PIV Inactivated virus	WRAIR	GSK/ Fiocruz	DENV-1–4 whole genome	Phase II
Inactivated monovalent vaccine	WRAIR	GSK	Purified, inactivated DENV1	Phase 1
Inactivated tetravalent vaccine	WRAIR	GSK	Purified, inactivated DENV1–4	Phase 1

1.6.2 Chimeric live attenuated vaccines

The most developed vaccine is the chimeric vaccine for dengue/yellow fever since its genetic backbone incorporates one of the DENV serotypes with the yellow fever E and prM genes. It was shown that this vaccine was attenuated, reliable, healthy and significantly improbable to be transmitted by arthropod vectors [139]. Chimer Ivax-Dengue (Sanofi Pasteur) produces dengue-only antibodies [140].

Another chimeric live vaccine was the PDK-53 DEN-2 vaccine. In primary PDK, this virus has been amplified by passage. The DENV-2 genes are replaced by those of DENV-1, 3, and 4. In the United States and Colombia, step 1 safety trials are ongoing. The three attenuating mutations are found outside the structural protein genes and tend to be very stable. If delivered to mice and monkeys, the tetravalent vaccine is developed by merging four chimeric dengue viruses [141,142].

Phase III trials are currently in progress on two live-attenuated dengue vaccines. Takeda is developing one such live-attenuated dengue vaccine. The DENVax vaccine formed of attenuated DENV-2 (DEN2-PDK-53), whereas three chimeric DENV-1, DENV-3 and DENV-4 are incorporated into the backbone of DEN2-PDK-53. Therefore, the distinction from Dengvaxia is the presence of NS proteins attributable to the backbone of DENV2. In phase one and two clinical trials, this vaccine performed well with high neutralizing antibody titers in non-human primates and humans [143].

The National Institutes of Health (NIH) developed the other tetravalent live-attenuated dengue vaccine. It is undergoing trials in Brazil, but even other pharmaceutical manufacturers have produced vaccines based on the same principle. The vaccine comprises three full-length DENV serotypes amplified by one or multiple NS3 deletions, while the fourth is a chimeric virus wherein the DENV 2 prM and E replaces NS3 in the DENV-4 [144]. This vaccine behaved well during the phase I and II trials and was effective [145].

1.6.3 Inactivated vaccines

The method of purified formalin-inactivated whole virus vaccine is a promising vehicle for the production of a vaccine for tetravalent dengue, but findings have been less than satisfactory. It

has been shown that formaldehyde treatment induces intermolecular cross-links between proteins that contribute to altered conformation changes and antigenic epitopes [145,146]. WRAIR has manufactured a purified, inactivated DENV-2 vaccine [147].

1.6.4 DNA vaccines

Vector-based vaccines using DNA technology have been exposed to animal research recently. A DNA vaccine is a plasmid that contains one or more unique antigens encoding genes that can be inserted in vivo to express antigens and activate immune responses. BALB/c mice were vaccinated intradermally with a DNA vaccine expressing prM and E protein of DENV2 [148]. The effectiveness of three non-replicating DENV2 vaccines in rhesus monkeys alone or conjunction has been tested by scientists [149]. DNA vaccines are safe, simple to prepare, low-cost and ideal for commercial production, lacking increased immunogenicity. The approaches to address this problem can also be plasmid alteration with highly effective promoters, alternate distribution mechanisms, multiple doses, and co-immunization with adjuvants [150].

1.7 Efficacy of the Dengue Vaccine

CYD-TDV has been approved in many countries. The approvement is based on a vaccine effectiveness of 56 to 61 percent against virologically verified dengue among children in Asia and Latin America [151,152]. In a phase 3 large-scale randomized clinical trial of TAK-003 vaccine involving children from 4 to 16 years living in Latin America and Asia, Biswal et al. recently tested the efficacy, safety, and immunogenicity of two doses of TAK-003. They confirmed that TAK-003 was successful towards symptomatic [153].

In a massive, multicounty trial, an experimental dengue vaccine has shown positive early results, but crucial concerns remain about its efficacy and safety. For example, it is also uncertain if the vaccine that had an 80.2 percent effectiveness in the study could increase the seriousness of the disease in some patients, as occurred with a dengue vaccine given to 1 million children in the Philippines before the issue became apparent in 2017 [154].

In selected highly endemic areas, the Philippines were the first country to implement Dengvaxia on a wide scale, targeting around 1 million children

aged 9–10 years. An excess risk of hospitalization for dengue and extreme dengue was identified in November 2017 in vaccine subjects who did not have a prior dengue infection at the time of vaccination. Sanofi revealed a recent discovery that when given to people not previously exposed to dengue, their new dengue vaccine presents a risk [155]**.** From 2012-2015, dengue reports were very high, overflowing hospital emergency rooms and resembling a' war zone'. There was a 65% growth in the number of dengue cases in the Philippines between 2014 and 2015. At the end of 2015, there were 200,415 confirmed dengue cases and 598 deaths, compared with 121,000 cases recorded in 2014 [156]. The news on the safety issues of dengue vaccines led to substantial public outrage, with lack of faith in vaccines spreading to standard childhood vaccines [157].

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread steadily across the world since December 2019. The strength and rate of transmission of SARS-CoV-2 has contributed to major incidence and death, placing tremendous strain on public health services around the world and on the global economy. The development of SARS-CoV-2 vaccines and therapeutics is therefore a top priority and a very active area [158]. Important points should be learned from the long and complex process of producing a vaccine against dengue. First, apart from neutralizing action, we know that it is important to thoroughly analyze the titers of antibodies caused by any vaccine. Like observed in both DENV infection [159] and SARS-CoV-2 infection[160], low neutralizing antibodies titers induced infection not protection. Secondly, population genetic analysis of 103 corona virus -2 genomes found that corona virus-2 developed into two main forms L and S form on the basis of gene mutations [161]. In human populations, over six human coronaviruses are prevalent, and even more are prevalent in wild animal species. To date, it is unknown if the ongoing mutation and recombination of SARS-CoV-2 could give rise to other SARS-CoV-2 serotypes, or even to another novel coronavirus. Vaccine candidates that can offer protection against divergent coronaviruses would also be desirable. Last, clinical evidence found that the efficiency and effectiveness of dengue vaccines could be impaired by serotype, baseline serostatus, and age [152,162]. These findings advised that applicants for SARS-CoV-2 vaccines should be carefully tested in a number of animal models in order to validate their protection and effectiveness and that participants in the human sample should represent different communities. This is further emphasized by the varying seriousness of SARS-CoV-2 based on age and sex at greater risk of serious illness during primary infection [163].
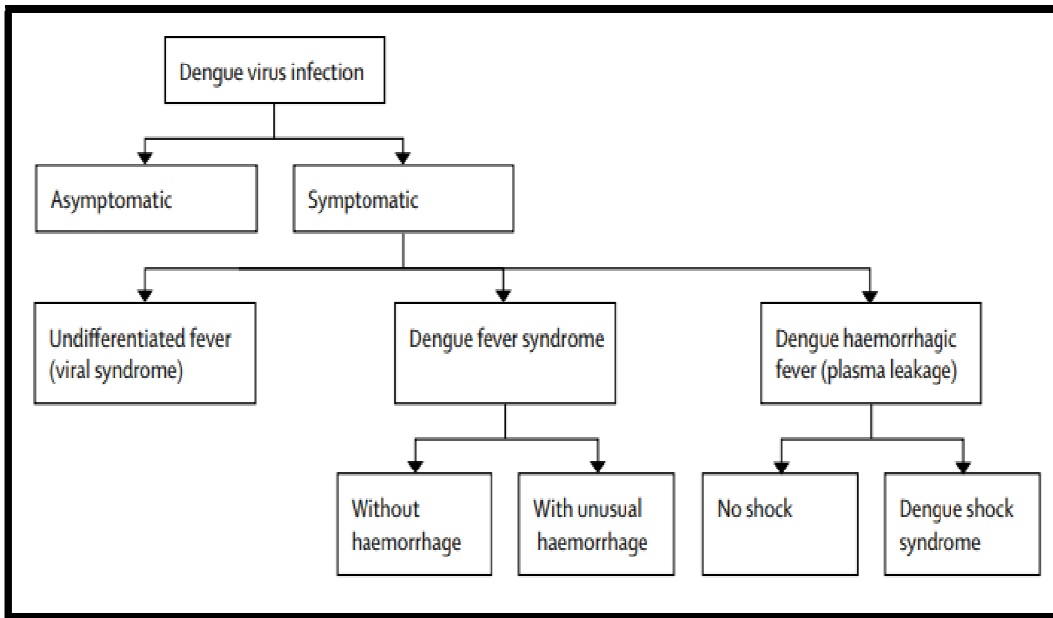

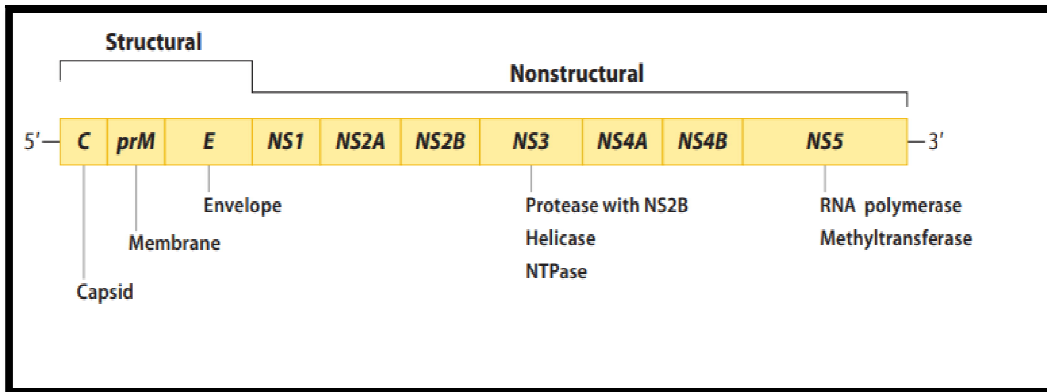**Fig. 1. WHO classification of symptomatic dengue infection [33]**

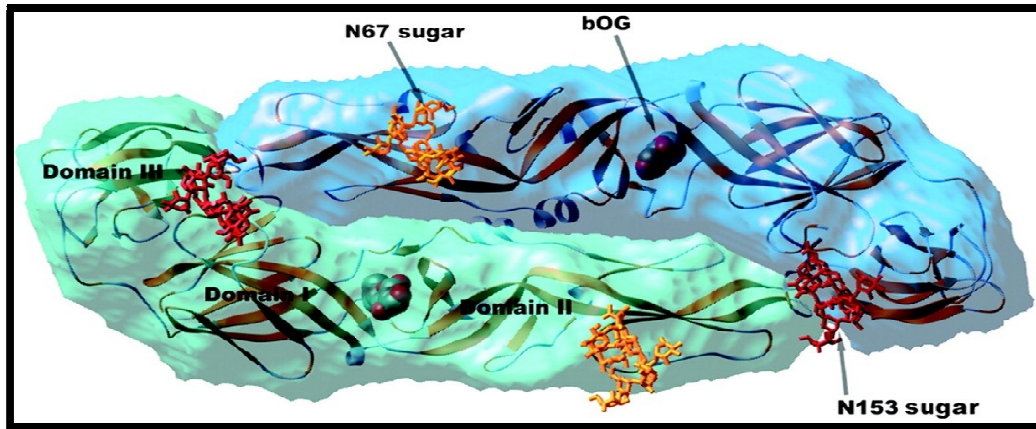**Fig. 2. The coding region of the DENV genome [48]**

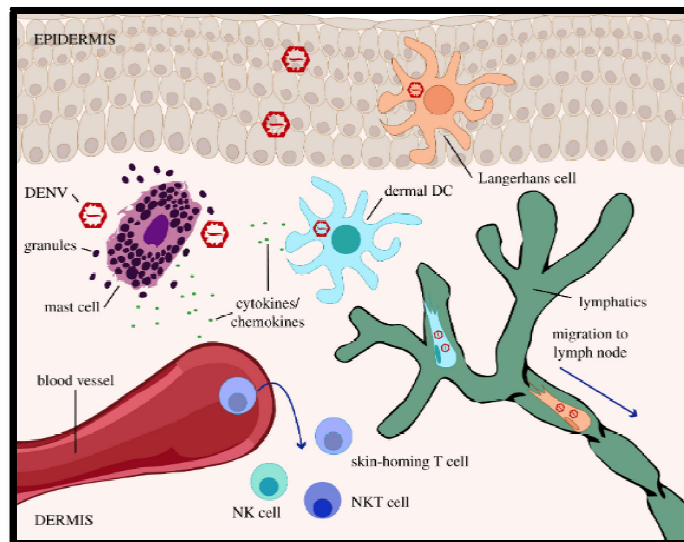**Fig. 3. The domains established within the E glycoprotein [56]**

Fig. 4. The diagram shows a network of types of immune cells that locate DENV at the entrance site [72]
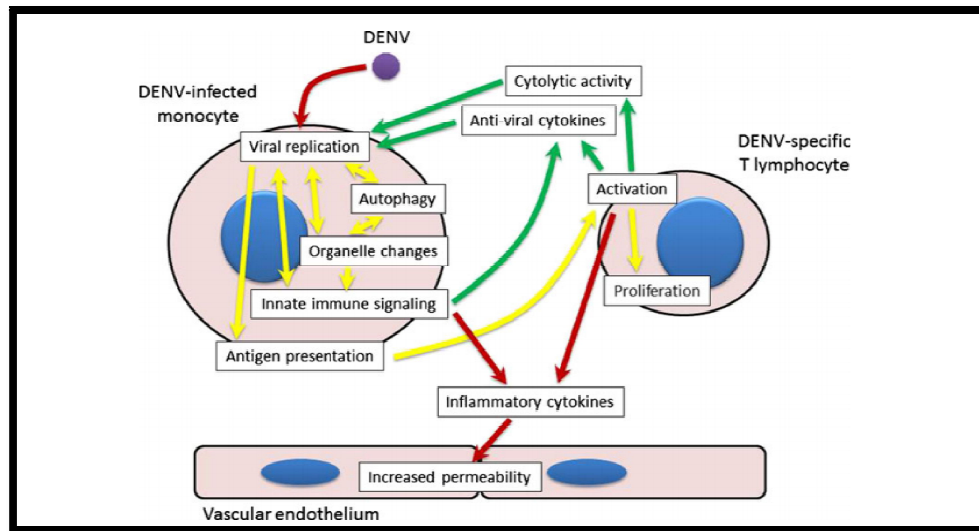
Fig. 5. Innate and adaptive immune responses to dengue virus [100]

2. FUTURE PROSPECTS

In the future, DENV research will most probably remain a challenging and exciting area. Future directions for the prevention and treatment of dengue infection are mosquito (vector) spread, dengue vaccine production, and antiviral drugs.

The need to develop a dengue vaccine has highly acquired significance due to the progressive transmission and rising incidence of dengue infection. There is a need for a safe, reliable, and economical tetravalent dengue vaccine for global public health. One approved vaccine is Dengvaxia by Sanofi-Pasteur. The administration of the vaccine has been widely debated by various parties [41].

The current antiviral study has focused on discovering novel compounds targeting the replication and innate immune evasion proteins responsible for DENV. The NS4b targeting compound inhibits all four serotypes *in vitro* RNA synthesis. There are several possible targets of NS2B/NS3 protease that decrease infectivity. Also, complement-mediated lysis was induced by a monoclonal antibody against NS1 *in vitro* and had defensive effects in vivo. Scrupulous efforts aim to produce antiviral medications that can be used to stabilize DF and prevent life-threatening events [164].

Mosquito (vector) spread management achieved by holding in standing water guppies (*Poecilia reticulata*) or copepods (*doridicola agilis*) and

infecting the mosquito population with bacteria of the genus *Wolbachia* [31].

3. CONCLUSION

Dengue has grown as a major public health issue that affects survival, affecting about 2.5 billion people in more than 100 countries. The doctor should be aware of this disease's different clinical symptoms and ensure that the treatment procedure is timely and sufficient. The doctor should also be aware of the immune repose to the dengue virus infection mechanism and involved cells. Greater knowledge of this immune response may help to solve the dengue prevention and eradication puzzle. Future directions to fight this awful disease are directed at mosquito surveillance, vaccine production, and antiviral drug regimen techniques.

4. LIMITATION OF THE STUDY

This literature review did not involve projects for university study and theses from students regarding this research's limitations. Also, not all cells of the immune system involved in the immune response have not been covered.

CONSENT AND ETHICAL APPROVAL

As per international standard or university standard guideline participant consent and ethical approval has been collected and preserved by the authors.

COMPETING INTERESTS

Author has declared that no competing interests exist.

REFERENCES

1. Mathew A, Rothman AL. Understanding the contribution of cellular immunity to dengue disease pathogenesis. Immunol Rev. 2008;225(1):300–313.
2. Morrison AC, Zielinski-Gutierrez E, Scott TW, Rosenberg R. Defining challenges and proposing solutions for control of the virus vector Aedes aegypti. PLoS Med. 2008;5(3):68.
3. Effler PV, et al. Dengue fever, hawaii, 2001–2002, Emerg Infect Dis. 2005; 11(5): 742.
4. FLS, Tan DL, Loh SK, Prabhakaran K. Dengue haemorrhagic fever after living donor renal transplantation. Nephrol. Dial. Transplant. 2005;20(2):447–448.
5. Organization WH, Dengue haemorrhagic fever: Diagnosis, treatment, prevention and control. World Health Organization; 1997.
6. Organization WH, SP for Research, T. in T. Diseases, WHOD. of C. of N T Diseases, WHO. Epidemic, and P. Alert, Dengue: Guidelines for diagnosis, treatment, prevention and control. World Health Organizationl; 2009.
7. Bopeththa B, Ralapanawa U. Post encephalitic parkinsonism following dengue viral infection. BMC Res Notes. 2017;10(1):655.
8. Ng DHL, Sadarangani SP. Locked in a cage'—A case of dengue virus 4 encephalitis. Public Library of Science San Francisco, CA USA; 2017.
9. de Oliveira Mota MT, et al. Transverse myelitis as an unusual complication of dengue fever. Am J Trop Med Hyg. 2017;96(2):380–381.
10. Sun P, Kochel TJ. The battle between infection and host immune responses of dengue virus and its implication in dengue disease pathogenesis. Sci World J; 2013.
11. Yauch LE, Shresta S. Dengue virus vaccine development. in Advances in virus research. 2014;88:315–372. Elsevier.
12. Thomas A, et al. Dimerization of dengue virus E subunits impacts antibody function and domain focus. J Virol. 2020;94:18.
13. Tremblay N, Freppel W, Sow AA, Chatel-Chaix L. The interplay between dengue virus and the human innate immune system: A game of hide and seek. Vaccines. 2019;7(4):145.
14. Brady OJ, et al. Refining the global spatial limits of dengue virus transmission by evidence-based consensus. PLoS Negl Trop Dis. 2012;6(8):1760.
15. Bhatt S, et al. The global distribution and burden of dengue. Nature. 2013; 496(7446):504–507.
16. Stanaway JD, et al. The global burden of dengue: An analysis from the global burden of disease study 2013. Lancet Infect Dis. 2016;16(6):712–723.
17. Organization WH. Global strategy for dengue prevention and control 2012-2020. WHO; 2012.
18. Guo C, et al. Global epidemiology of dengue outbreaks in 1990–2015: A systematic review and meta-analysis. Front Cell Infect Microbiol. 2017;7:317.
19. Dyer O. Dengue: Philippines declares national epidemic as cases surge across South East Asia. BMJ Br Med J. 2019;366.
20. Alghazali KA, et al. Dengue outbreak during ongoing civil war, Taiz, Yemen. Emerg Infect Dis. 2019;25(7):1397.
21. Alghazali KA, et al. Dengue fever among febrile patients in Taiz City, Yemen during the 2016 war: Clinical manifestations, risk factors, and patients knowledge, attitudes, and practices toward the disease. One Heal. 2020;9:100119.
22. MN Sahak. Dengue fever as an emerging disease in Afghanistan: Epidemiology of the first reported cases. Int J Infect Dis. 2020;99:23–27.
23. Gubler DJ, Trent DW. Emergence of epidemic dengue/dengue hemorrhagic fever as a public health problem in the Americas. Infect Agents Dis. 1993;2(6):383–393.
24. Siraj AS et al. Temperature modulates dengue virus epidemic growth rates through its effects on reproduction numbers and generation intervals. PLoS Negl Trop Dis. 2017;11(7):0005797.
25. Rocklöv J, Tozan Y. Climate change and the rising infectiousness of dengue. Emerg Top Life Sci. 2019;3(2):133–142.
26. Watts N, et al. The 2018 report of the Lancet Countdown on health and climate change: shaping the health of nations for centuries to come. Lancet. 2018;392(10163):2479–2514.
27. Kraemer MUG, et al.The global distribution of the arbovirus vectors Aedes aegypti and Ae. Albopictus. Elife. 2015;4:08347.

28. Gossner CM, Ducheyne E, Schaffner F. Increased risk for autochthonous vector-borne infections transmitted by Aedes albopictus in continental Europe, Euro Surveill. 2018;23(24):1800268.

29. Metelmann S, Caminade C, Jones AE, Medlock JM, Baylis M, Morse AP. The UK's suitability for Aedes albopictus in current and future climates. J R Soc Interface. 2019;16(152):20180761.

30. Zeller H, Marrama L, Sudre B, Van Bortel W, Warns-Petit E. Mosquito-borne disease surveillance by the European Centre for Disease Prevention and Control. Clin Microbiol Infect. 2013;19(8):693–698.

31. Simmons CP, Farrar JJ, Van Vinh Chau N, B Wills. Dengue. N Engl J Med. 2012; 366(15):1423–1432,

32. Whitehorn J, Simmons CP. The pathogenesis of dengue. Vaccine. 2011; 29(42):7221–7228.

33. Deen JL, et al. The WHO dengue classification and case definitions: Time for a reassessment. Lancet. 2006;368(9530): 170–173.

34. Thomas EA, John M, Bhatia A. Cutaneous manifestations of dengue viral infection in Punjab (north India). Int J Dermatol. 2007;46(7):715–719.

35. Huang HW, Tseng HC, Lee CH, Chuang HY, Lin SH. Clinical significance of skin rash in dengue fever: A focus on discomfort, complications, and disease outcome. Asian Pac J Trop Med. 2016;9(7):713–718.

36. Itoda I, et al. Clinical features of 62 imported cases of dengue fever in Japan. Am J Trop Med Hyg.2006;75(3):470–474.

37. Capeding RZ, et al. The incidence, characteristics, and presentation of dengue virus infections during infancy. Am J Trop Med Hyg. 2010;82(2):330–336.

38. SB Halstead et al. Dengue hemorrhagic fever in infants: research opportunities ignored. Emerg Infect Dis. 2002;8(12):1474.

39. Narayanan M, Aravind MA, Thilothammal N, Prema R, Sargunam CSR, N. Ramamurty. Dengue fever epidemic in Chennai-a study of clinical profile and outcome. Indian Pediatr. 2002; 39(11):1027–1033.

40. Kalayanarooj S. Clinical manifestations and management of dengue/DHF/DSS. Trop Med Health. 2011;1112080193.

41. Wang WH, et al. Dengue Hemorrhagic Fever-A Systemic Literature Review of Current Perspectives on Pathogenesis, Prevention and Control. J Microbiol Immunol Infect; 2020.

42. Noisakran S, Perng GC. Alternate hypothesis on the pathogenesis of dengue hemorrhagic fever (DHF)/dengue shock syndrome (DSS) in dengue virus infection. Exp Biol Med. 2008;233(4):401–408.

43. Vaughn DW, et al. Dengue viremia titer, antibody response pattern, and virus serotype correlate with disease severity. J Infect Dis. 2000;181(1):2–9.

44. Solomon T, Mallewa M. Dengue and other emerging flaviviruses. J Infect. 2001;42(2):104–115.

45. Knipe DM, Howley PM. Fundamental Virology., no. Ed. 4. Lippincott Williams & Wilkins; 2001.

46. Zhang Y et al. Structures of immature flavivirus particles. EMBO J. 2003;22(11):2604–2613.

47. Zhang W, et al. Visualization of membrane protein domains by cryo-electron microscopy of dengue virus. Nat Struct Mol Biol. 2003;10(11):907–912.

48. Murphy BR, Whitehead SS. Immune response to dengue virus and prospects for a vaccine. Annu Rev Immunol. 2011;29:587–619.

49. Scaturro P, Cortese M, Chatel-Chaix L, Fischl W, Bartenschlager R. Dengue virus non-structural protein 1 modulates infectious particle production via interaction with the structural proteins. PLoS Pathog. 2015;11(11):1005277.

50. Uno N, Ross TM. Dengue virus and the host innate immune response. Emerg Microbes Infect. 2018;7(1):1–11.

51. Neufeldt CJ, Cortese M, Acosta EG, Bartenschlager R. Rewiring cellular networks by members of the Flaviviridae family. Nat Rev Microbiol. 2018;16(3):125.

52. Mazeaud C, Freppel W, Chatel-Chaix L. The multiples fates of the Flavivirus RNA genome during pathogenesis. Front Genet. 2018;9:595.

53. Apte-Sengupta S, Sirohi D, Kuhn RJ. Coupling of replication and assembly in flaviviruses. Curr Opin Virol. 2014;9:134–142.

54. SM. Lok et al. Binding of a neutralizing antibody to dengue virus alters the arrangement of surface glycoproteins. Nat Struct Mol Biol. 2008;15(3):312–317.

55. Liu CC, Lee SC, Butler M, Wu SC. High genetic stability of dengue virus propagated in MRC-5 cells as compared to

the virus propagated in vero cells. PLoS One. 2008;3(3):1810.

56. Rey FA. Dengue virus envelope glycoprotein structure: New insight into its interactions during viral entry. Proc Natl Acad Sci. 2003;100(12).6899–6901.

57. Libraty DH, et al. Differing influences of virus burden and immune activation on disease severity in secondary dengue-3 virus infections. J Infect Dis. 2002;185(9):1213–1221.

58. Libraty DH, et al. High circulating levels of the dengue virus nonstructural protein NS1 early in dengue illness correlate with the development of dengue hemorrhagic fever. J Infect Dis. 2002;186(8):1165–1168.

59. Gubler DJ. Epidemic dengue/dengue hemorrhagic fever as a public health, social and economic problem in the 21st century. Trends Microbiol. 2002;10(2)100–103.

60. Kosasih H, et al.The epidemiology, virology and clinical findings of dengue virus infections in a cohort of Indonesian adults in Western Java. PLoS Negl Trop Dis. 2016;10(2):0004390.

61. Katzelnick LC, et al. Dynamics and determinants of the force of infection of dengue virus from 1994 to 2015 in Managua, Nicaragua. Proc Natl Acad Sci. 2018;115(42):10762–10767.

62. Balmaseda A et al. Serotype-specific differences in clinical manifestations of dengue. Am J Trop Med Hyg. 2006;74(3):449–456.

63. MG Guzman et al. Epidemiological studies on dengue virus type 3 in Playa municipality, Havana, Cuba, 2001–2002. Int J Infect Dis. 2012;16(3):198–203.

64. Navarro-Sánchez E, Desprès P, Cedillo-Barrón L. Innate immune responses to dengue virus. Arch Med Res. 2005;36(5):425–435.

65. Rothman AL. Immunity to dengue virus: a tale of original antigenic sin and tropical cytokine storms. Nat Rev Immunol. 2011;11(8):532–543.

66. Liu YJ. Dendritic cell subsets and lineages, and their functions in innate and adaptive immunity. Cell 2001;106(3):259–262.

67. Costa VV, et al. Dengue virus-infected dendritic cells, but not monocytes, activate natural killer cells through a contact-dependent mechanism involving adhesion molecules. MBio. 2017;8(4).

68. D Cerny et al. Selective susceptibility of human skin antigen presenting cells to productive dengue virus infection. PLoS Pathog. 2014;10(12):1004548–1004548.

69. Robertson MJ. Role of chemokines in the biology of natural killer cells. J Leukoc Biol. 2002;71(2):173–183.

70. Shresta S, Kyle JL, Beatty PR, Harris E. Early activation of natural killer and B cells in response to primary dengue virus infection in A/J mice. Virology. 2004;319(2):262–273.

71. Beltrán D, López-Vergès S. NK Cells during dengue disease and their recognition of dengue virus-infected cells. Front Immunol. 2014;5:192.

72. Rathore APS, St. John AL. Immune responses to dengue virus in the skin. Open Biol. 2018;8(8):180087.

73. Jessie K, Fong MY, Devi S, Lam SK, Wong KT. Localization of dengue virus in naturally infected human tissues, by immunohistochemistry and in situ hybridization. J Infect Dis. 2004;189(8):1411–1418.

74. Martina BEE, Koraka P, Osterhaus ADME. Dengue virus pathogenesis: an integrated view. Clin Microbiol Rev. 2009;22(4):564–581.

75. Alvarez Y, et al. Eicosanoids in the innate immune response: TLR and non-TLR routes. Mediators Inflamm. 2010 (2010).

76. Navarro-Sánchez E, Desprès P, Cedillo-Barrón L. Innate immune responses to dengue virus. Arch Med Res. 2005;36(5):425–435.

77. Juffrie M, et al. Inflammatory mediators in dengue virus infection in children: Interleukin-8 and its relationship to neutrophil degranulation. Infect Immun. 2000;68(2):702–707.

78. Liu CC, Huang KJ, Lin YS, Yeh TM, Liu HS, Lei HY. Transient CD4/CD8 ratio inversion and aberrant immune activation during dengue virus infection. J Med Virol. 2002;68(2):241–252.

79. Yost CC, et al.Neonatal NET-inhibitory factor and related peptides inhibit neutrophil extracellular trap formation. J Clin Invest. 2016;126(10):3783–3798.

80. Kunder M, Lakshmaiah V, M. Kutty AV. Plasma Neutrophil Elastase, α 1-Antitrypsin, α 2-Macroglobulin and Neutrophil Elastase–α 1-Antitrypsin Complex Levels in patients with Dengue Fever. Indian J Clin Biochem. 2018;33(2):218–221.

81. A Opasawatchai et al. Neutrophil activation and early features of NET formation are

associated with dengue virus infection in human. Front Immunol. 2019;9:3007.

82. Shresta S. Role of complement in dengue virus infection: protection or pathogenesis?. M Bio. 2012;3:1.

83. Avirutnan P, Hauhart RE, Marovich MA, Garred P, Atkinson JP, Diamond MS. Complement-mediated neutralization of dengue virus requires mannose-binding lectin. M Bio 2011;2(6).

84. Avirutnan P, Malasit P, Seliger B, Bhakdi S, Husmann M. Dengue virus infection of human endothelial cells leads to chemokine production, complement activation, and apoptosis. J Immunol. 1998;161(11):6338–6346.

85. Avirutnan P et al., "Vascular leakage in severe dengue virus infections: a potential role for the nonstructural viral protein NS1 and complement," J. Infect. Dis., vol. 193, no. 8, pp. 1078–1088, 2006.

86. Nascimento EJM, et al. Alternative complement pathway deregulation is correlated with dengue severity. PLoS One. 2009;4(8):6782.

87. Loo YM, Gale Jr M. Immune signaling by RIG-I-like receptors. Immunity. 2011;34(5):680–692.

88. Akira S, Takeda K. Toll-like receptor signalling. Nat Rev Immunol. 2004;4(7):499–511.

89. Lindenbach BD. The viruses and their replication. Fields Virol. 2007;1101–1152.

90. Medzhitov R, Janeway Jr C. Innate immunity. N Engl J Med. 2000;343(5):338–344.

91. Wang JP, Liu P, Latz E, Golenbock DT, Finberg RW, Libraty DH. Flavivirus activation of plasmacytoid dendritic cells delineates key elements of TLR7 signaling beyond endosomal recognition. J Immunol. 2006;177(10):7114–7121.

92. Nasirudeen AMA, Wong HH, Thien P, Xu S, Lam KP, Liu DX. RIG-I, MDA5 and TLR3 synergistically play an important role in restriction of dengue virus infection. PLoS Negl Trop Dis. 2011;5(1):926.

93. Honda K, Takaoka A, Taniguchi T. Type I inteferon gene induction by the interferon regulatory factor family of transcription factors. Immunity. 2006;25(3):349–360.

94. Schneider WM, Chevillotte MD, Rice CM. Interferon-stimulated genes: a complex web of host defenses. Annu Rev Immunol. 2014;32:513–545.

95. J Ashour et al. Mouse STAT2 restricts early dengue virus replication. Cell Host Microbe 2010;8(5):410–421.

96. Cucak H, Yrlid U, Reizis B, Kalinke U, Johansson-Lindbom B. Type I interferon signaling in dendritic cells stimulates the development of lymph-node-resident T follicular helper cells. Immunity. 2009;31(3):491–501.

97. Suto H, Nakae S, Kakurai M, Sedgwick JD, Tsai M, Galli SJ. Mast cell-associated TNF promotes dendritic cell migration. J. Immunol. 2006;176(7):4102–4112.

98. Dudeck J, et al. Engulfment of mast cell secretory granules on skin inflammation boosts dendritic cell migration and priming efficiency. J Allergy Clin Immunol. 2019;143(5):1849–1864.

99. Jawdat DM, Rowden G, Marshall JS. Mast cells have a pivotal role in TNF-independent lymph node hypertrophy and the mobilization of Langerhans cells in response to bacterial peptidoglycan. J Immunol. 2006;177(3):1755–1762.

100. Rothman AL, Medin CL, Friberg H, Currier JR. Immunopathogenesis versus Protection in Dengue Virus Infections. Curr Trop Med Reports. 2014;1(1):13–20.

101. Zompi S, Montoya M, Pohl MO, Balmaseda A, Harris E. Dominant cross-reactive B cell response during secondary acute dengue virus infection in humans. PLoS Negl Trop Dis. 2012;6(3):1568.

102. Pattanapanyasat K, et al. B cell subset alteration and the expression of tissue homing molecules in dengue infected patients. J Biomed Sci. 2018;25(1):1–11.

103. King CA, Wegman AD, Endy TP. Mobilization and Activation of the Innate Immune Response to Dengue Virus. Front Cell Infect Microbiol. 2020;10:574417.

104. Koraka P, et al. Kinetics of dengue virus-specific serum immunoglobulin classes and subclasses correlate with clinical outcome of infection. J Clin Microbiol. 2001;39(12):4332–4338.

105. Balakrishnan T, et al. Dengue virus activates polyreactive, natural IgG B cells after primary and secondary infection. PLoS One. 2011;6(12):29430.

106. Mathew A, et al. B-cell responses during primary and secondary dengue virus infections in humans. J Infect Dis. vol. 2011;204(10):1514–1522.

107. Ubol S, Phuklia W, Kalayanarooj S, Modhiran N. Mechanisms of immune evasion induced by a complex of dengue virus and preexisting enhancing anti-bodies. J Infect Dis. 2010;201(6):923–935.

108. Moi ML, Takasaki T, Kurane I. Human antibody response to dengue virus: Implications for dengue vaccine design. Trop Med Health. 2016;44(1):1.

109. Ly MHP, et al. Dengue virus infection-enhancement activity in neutralizing antibodies of healthy adults before dengue season as determined by using FcγR-expressing cells. BMC Infect Dis. 2018;18(1):31.

110. AP Goncalvez, Engle RE, Claire MS, Purcell RH, Lai CJ. Monoclonal antibody-mediated enhancement of dengue virus infection in vitro and in vivo and strategies for prevention. Proc Natl Acad Sci. 2007;104(22):9422–9427.

111. Simmons M, Putnak R, Sun P, Burgess T, Marasco WA. Antibody Prophylaxis Against Dengue Virus 2 Infection in Non-Human Primates. Am J Trop Med Hyg. 2016;95(5):1148–1156.

112. Tian Y, Grifoni A, Sette A, Weiskopf D. Human T cell response to dengue virus infection. Front Immunol. 2019;10:2125.

113. Weiskopf D, Sette A. T-cell immunity to infection with dengue virus in humans. Front. Immunol. 2014;5:93.

114. Screaton G, Mongkolsapaya J, Yacoub S, Roberts C. New insights into the immunopathology and control of dengue virus infection. Nat Rev Immunol. 2015;15(12):745–759.

115. Tian Y, Sette A, Weiskopf D. Cytotoxic CD4 T cells: Differentiation, function and application to dengue virus infection. Front Immunol. 2016;7:531.

116. Palmer DR, et al. Differential effects of dengue virus on infected and bystander dendritic cells. J Virol. 2005;79(4):2432–2439.

117. Dejnirattisai W, et al. A complex interplay among virus, dendritic cells, T cells, and cytokines in dengue virus infections. J Immunol. 2008;181(9):5865–5874.

118. Sun et al P. CD40 ligand enhances dengue viral infection of dendritic cells: a possible mechanism for T cell-mediated immunopathology. J Immunol. 2006; 177(9):6497–6503,

119. Chase AJ, Medina FA, Muñoz-Jordán JL. Impairment of CD4+ T cell polarization by dengue virus–infected dendritic cells. J Infect Dis. 2011;203(12):1763–1774.

120. Zellweger RM, Eddy WE, Tang WW, Miller R, Shresta S. CD8+ T cells prevent antigen-induced antibody-dependent enhancement of dengue disease in mice. J Immunol. 2014;193(8):4117–4124.

121. Elong Ngono A, and Shresta S. Immune response to dengue and Zika. Annu Rev Immunol. 2018;36:279–308.

122. Zellweger RM, Prestwood TR, Shresta S. Enhanced infection of liver sinusoidal endothelial cells in a mouse model of antibody-induced severe dengue disease. Cell Host Microbe. 2010;7(2):128–139.

123. Yauch LE, et al. A protective role for dengue virus-specific CD8+ T cells. J Immunol. 2009;182(8):4865–4873.

124. S Crotty. T follicular helper cell differentiation, function, and roles in disease, Immunity. 2014;41(4):529–542.

125. Wang P, et al. Oncometabolite D-2-hydroxyglutarate inhibits ALKBH DNA repair enzymes and sensitizes IDH mutant cells to alkylating agents. Cell Rep. 2015;13(11):2353–2361.

126. Locci M, et al. Human circulating PD-1+ CXCR3− CXCR5+ memory Tfh cells are highly functional and correlate with broadly neutralizing HIV antibody responses. Immunity. 2013;39(4)758–769.

127. Havenar-Daughton C, et al. Direct probing of germinal center responses reveals immunological features and bottlenecks for neutralizing antibody responses to HIV Env trimer. Cell Rep. 2016;17(9):2195–2209.

128. Crotty S, et al. A brief history of T cell help to B cells. Nat Rev Immunol. 2015; 15(3):185–189.

129. Stephens HAF, et al. HLA-A and-B allele associations with secondary dengue virus infections correlate with disease severity and the infecting viral serotype in ethnic Thais. Tissue Antigens. 2002;60(4):309–318.

130. Huang X, et al. Antibody-dependent enhancement of dengue virus infection inhibits RLR-mediated Type-I IFN-independent signalling through upregulation of cellular autophagy. Sci Rep. 2016;6(1):1–13.

131. Fahimi H, Mohammadipour M, Kashani HH, Parvini F, Sadeghizadeh M. Dengue viruses and promising envelope protein domain III-based vaccines. Appl Microbiol Biotechnol. 2018;102(7):2977–2996.

132. Allicock OM, et al. Phylogeography and population dynamics of dengue viruses in the Americas. Mol Biol Evol. 2012;29(6):1533–1543.

133. Murrell S, Wu SC, Butler M. Review of dengue virus and the development of a

vaccine. Biotechnol Adv. 2011;29(2): 239–247.

134. Sun W, et al. Vaccination of human volunteers with monovalent and tetravalent live-attenuated dengue vaccine candidates. Am J Trop Med Hyg. 2003;69(6):24–31.

135. Sabchareon A, et al. Protective efficacy of the recombinant, live-attenuated, CYD tetravalent dengue vaccine in Thai schoolchildren: a randomised, controlled phase 2b trial. Lancet. 2012;380(9853):1559–1567.

136. Whitehead SS, Blaney JE, Durbin AP, Murphy BR. Prospects for a dengue virus vaccine. Nat Rev Microbiol. 2007;5(7):518–528.

137. Hadinegoro SR, et al. Efficacy and long-term safety of a dengue vaccine in regions of endemic disease. N Engl J Med. vol. 2015;373(13):1195–1206.

138. Malisheni M, Khaiboullina SF, Rizvanov AA, Takah N, Murewanhema G, Bates M. Clinical efficacy, safety, and immunogenicity of a live attenuated tetravalent dengue vaccine (CYD-TDV) in children: a systematic review with meta-analysis. Front Immunol. 2017;8:863.

139. McGee CE, et al. Recombinant chimeric virus with wild-type dengue 4 virus premembrane and envelope and virulent yellow fever virus Asibi backbone sequences is dramatically attenuated in nonhuman primates. J Infect Dis. vol. 2008;197(5):693–697.

140. Monath TP. Dengue and yellow fever—challenges for the development and use of vaccines. N Engl J Med. 2007;357(22): 2222–2225.

141. Huang CYH, Butrapet S, Tsuchiya KR, Bhamarapravati N, Gubler DJ, Kinney RM. Dengue 2 PDK-53 virus as a chimeric carrier for tetravalent dengue vaccine development. J Virol. 2003;77(21): 11436–11447.

142. Rabablert J, Wasi C, Kinney R, Kasisith J, Pitidhammabhorn D, Ubol S. Attenuating characteristics of DEN-2 PDK53 in flavivirus-naive peripheral blood mononuclear cells. Vaccine. 2007;25(19): 3896–3905.

143. Osorio JE, Wallace D, Stinchcomb DT. A recombinant, chimeric tetravalent dengue vaccine candidate based on a dengue virus serotype 2 backbone. Expert Rev Vaccines. 2016;15(4):497–508.

144. Kirkpatrick BD, et al. Robust and balanced immune responses to all 4 dengue virus serotypes following administration of a single dose of a live attenuated tetravalent dengue vaccine to healthy, flavivirus-naive adults. J Infect Dis. 2015;212(5):702–710.

145. Whitehead SS. Development of TV003/TV005, a single dose, highly immunogenic live attenuated dengue vaccine; what makes this vaccine different from the Sanofi-Pasteur CYD^TM vaccine? Expert Rev Vaccines. 2016;15(4):509–517.

146. Schmidt AC, et al. Phase 1 randomized study of a tetravalent dengue purified inactivated vaccine in healthy adults in the United States. Am J Trop Med Hyg. 2017; 96(6):1325–1337.

147. Putnak JR, et al. An evaluation of dengue type-2 inactivated, recombinant subunit, and live-attenuated vaccine candidates in the rhesus macaque model. Vaccine. 2005;23(35):4442–4452.

148. Kochel T, et al. Inoculation of plasmids expressing the dengue-2 envelope gene elicit neutralizing antibodies in mice. Vaccine. 1997;15(5):547–552.

149. Simmons M, Porter KR, Hayes CG, Vaughn DW, Putnak R. Characterization of antibody responses to combinations of a dengue virus type 2 DNA vaccine and two dengue virus type 2 protein vaccines in rhesus macaques. J Virol. 2006;80(19): 9577–9585.

150. Danko JR, Beckett CG, Porter KR. Development of dengue DNA vaccines. Vaccine. 2011;29(42):7261–7266.

151. Villar LÁ, et al. Safety and immunogenicity of a recombinant tetravalent dengue vaccine in 9–16 year olds: A randomized, controlled, phase II trial in Latin America. Pediatr Infect Dis J. 2013;32(10): 1102–1109.

152. Capeding MR, et al. Clinical efficacy and safety of a novel tetravalent dengue vaccine in healthy children in Asia: a phase 3, randomised, observer-masked, placebo-controlled trial. Lancet. 2014;384(9951): 1358–1365.

153. Biswal S, et al. Efficacy of a tetravalent dengue vaccine in healthy children and adolescents. N Engl J Med. 2019;381(21): 2009–2019.

154. Wilder-Smith A, Flasche S, Smith PG. Vaccine-attributable severe dengue in the Philippines. Lancet. 2019;394(10215): 2151–2152.

155. Pasteur S. Sanofi updates information on dengue vaccine; 2017.

156. R Herriman. Philippines reports more than 200,000 dengue cases in 2015. Outbreak News Today; 2016.

157. Larson HJ, Hartigan-Go K, de Figueiredo A. Vaccine confidence plummets in the Philippines following dengue vaccine scare: why it matters to pandemic preparedness. Hum Vaccin Immunother. 2019;15(3):625–627.

158. Graham BS. Rapid COVID-19 vaccine development. Science (80-.). 2020; 368(6494):945–946.

159. Kliks SC, Nimmanitya S, Nisalak A, Burke DS. Evidence that maternal dengue antibodies are important in the development of dengue hemorrhagic fever in infants. Am J Trop Med Hyg. 1988;38(2): 411–419.

160. Melendi GA, et al. C5 modulates airway hyperreactivity and pulmonary eosinophilia during enhanced respiratory syncytial virus disease by decreasing C3a receptor expression. J Virol. 2007;81(2):991–999.

161. Tang X, et al. On the origin and continuing evolution of SARS-CoV-2. Natl Sci Rev. 2020;7(6):1012–1023.

162. Villar L, et al. Efficacy of a tetravalent dengue vaccine in children in Latin America. N Engl J Med. 2015;372(2): 113–123.

163. Petrilli CM, et al. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: Prospective cohort study. Bmj. 2020;369.

164. Noble CG, et al. Strategies for development of dengue virus inhibitors. Antiviral Res. 2010;85(3):450–462.

165. Wichmann O, et al. Live-attenuated tetravalent dengue vaccines: the needs and challenges of post-licensure evaluation of vaccine safety and effectiveness. Vaccine. 2017;35(42): 5535–5542.

Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sdiarticle4.com/review-history/65418