A Mini Review on Dengue: Advances in Management, Vector Control, and Vaccination Strategies

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***Abstract*— More individuals are affected by dengue than any other vector-borne viral disease around the world. Dengue is an infectious disease, mainly transmitted by the mosquito *Aedes aegypti*, predominant in tropical and subtropical climates. Symptoms of the disease range from mild fever to severe dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS). The diagnosis process contains serological testing, nucleic acid identification, and virus isolation. Current management focuses on fluid management, monitoring for early warning signs of serious disease, and supportive care. There are still no certified vaccines or antiviral medications. Currently recommended methods for preventing dengue include controlling vectors, using insecticides, and promoting the use of personal protective equipment. This mini review points out the need for better management practices to minimize dengue fever globally and the challenges and future directions for research.**

Keywords- dengue, diagnosis, management, vaccine

I. INTRODUCTION

Dengue fever is a highly prevalent mosquito-borne disease affecting millions globally [1]. The illness has the highest worldwide morbidity rate [2]. In the past 50 years, dengue fever prevalence exploded, with over 50% of the global community living in high-risk zones across 100 nations [3]. Approximately 50 to 100 million people are infected worldwide each year [4]. The precise incidence of dengue remains unclear; however, estimates indicate that the annual number of cases ranges from 284 to 528 million, with 96 million of those classified as confirmed cases [3, 5, 6]. According to the World Health Organization, 75% of the global dengue cases in 2012 were reported in Asia [3]. During the period from 1991 to 2008, dengue epidemics took place every 3 to 5 years, gradually spreading to various regions of Sri Lanka [5, 7]. In 2009, a notable epidemic occurred, resulting in 35,008 suspected cases and 346 fatalities [4]. Dengue fever emerged as a significant public health concern from 2010 to 2016, marked by a consistent rise in the number of cases. The mortality rate is 1-5% without therapy and less than 1% with treatment [4].

Dengue is caused by the dengue virus (DENV), which belongs to the Flavivirus genus within the Flaviviridae family [1]. Flaviviruses are RNA viruses characterized by a single-stranded, positive-sense structure [8]. It is spread by mosquitoes belonging to the Aedes genus, particularly Aedes aegypti and Aedes albopictus [1]. The illness arises from infection by four related, yet distinct dengue viruses known as DENV1, DENV2, DENV3, and DENV4 [2]. The RNA genome of flaviviruses encrypts a singular polyprotein which is dismantled by both host and viral proteases, yielding seven nonstructural proteins: NS1, NS2a, NS2b, NS3, NS4a, NS4b, and NS5. Additionally, three structural proteins are present, namely the core, membrane, and envelope proteins [9]. Beginning in 2017 Sri Lankan epidemic attributed to the DENV2 serotype, on an annual basis dengue instances consistently surpassed 50,000, reaching a peak marking the highest number of cases and deaths (186,101 reported cases and 440 deaths) [7, 10]. DENV1 was the predominant serotype until mid-2016 but was replaced by DENV2 in 2017. In 2019, there were 114,240 cases recorded, with a gentle increase annually. DENV3 was identified and observed to transpire after 2019 [5, 11].

Effective management strategies are critical for managing and preventing dengue fever because they provide integrated treatments to optimize effect and achieve better outcomes. This review offers the importance of effectively managing dengue fever in reducing morbidity and mortality, preventing outbreaks, current updates about pharmacological management and vaccination strategies, and improving global health outcomes.

II. METHODOLOGY

This literature review was comprehensively conducted to analyze existing scholarly articles, research papers, and clinical trials related to dengue virus management and prevention. Primary sources were gathered from databases such as PubMed, Google Scholar, and Web of Science. Two main areas were addressed: the effectiveness of supportive care strategies in reducing morbidity and mortality, and emerging antiviral therapies. Studies on vaccine development and vector control measures were also included. Key findings were compiled to highlight trends in dengue management and pinpoint research gaps. Both qualitative and quantitative data from recent studies were used to ensure a comprehensive evaluation of the current state of dengue treatment and prevention efforts.

III. DIAGNOSTIC CHALLENGES AND CLINICAL MANIFESTATIONS

Dengue virus (DENV) is transmitted to humans primarily by Aedes mosquitoes, particularly Aedes aegypti [12]. Upon

a mosquito bite, the virus enters the bloodstream, targeting skin cells like immature Langerhans cells and keratinocytes [13]. Infected cells migrate to the lymph nodes, where monocytes and macrophages are recruited, spreading the virus throughout the lymphatic system. Various immune cells, such as myeloid dendritic cells, splenic and hepatic macrophages, and blood-derived monocytes, become infected during this primary viremia [14, 15].

Keep your text and graphic files separate until after the text has been formatted and styled. Do not use hard tabs, and limit use of hard returns to only one return at the end of a paragraph. Do not add any kind of pagination anywhere in the paper. Do not number text heads-the template will do that for you. Following a 4–10-day incubation period, DENV infection symptoms typically appear within 2–7 days [16]. While most infections are asymptomatic, DENV can cause a range of clinical symptoms, from mild flu-like dengue fever (DF) to severe conditions like dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS), which can result in hypovolemic shock [16]. DF usually lasts for 3 to 7 days and may include symptoms like headache, muscle pain, and fatigue [17]. In newborns and children, DF often manifests as a maculopapular rash, while adults may experience more severe symptoms such as fever, intense headache, joint pain, and gastrointestinal discomfort. Bleeding, such as petechiae, nosebleeds, and bleeding gums, is also common, along with laboratory indicators like leukopenia, thrombocytopenia, and elevated liver enzymes [18].

Less than 3% of individuals who are infected develop DHF. It is characterized by vascular leakage and thrombocytopenia, which is a low platelet count of ≤ 100,000 mm^3. DHF is more likely to occur in infants born to mothers who are immune to DENV [9]. In children, DHF typically presents as a rapid rise in body temperature, face flushing, and worsening symptoms after the fever subsides. If left untreated, DHF can progress to DSS, which is characterized by a rapid, weak pulse or low blood pressure, cold skin, and faintness. Without proper treatment, DSS can lead to fatal shock within 12 to 36 hours [19]. The development of DHF/DSS is believed to be influenced by a complex interaction between the virus, the host's genetics, and immune factors [20].

Diagnosing dengue based solely on clinical symptoms can be unreliable due to overlapping symptoms with other viral infections, like chikungunya and Zika [3, 21]. To confirm DENV infection, a combination of medical history, physical examination, and blood tests is crucial, especially in dengue-endemic regions [21–23]. Various tests are used depending on the stage of the infection. During the early stages (less than five days post-infection), virus isolation, RNA detection (via nucleic acid amplification tests, NAAT), or antigen detection (NS1) are used. As viremia declines after five days, serological methods are employed to detect antibodies, particularly IgM and IgG [3, 23, 24].

Three main diagnostic approaches for DENV include molecular techniques, serological tests, and direct virus detection. Molecular techniques such as NAAT, particularly RT-PCR, are highly sensitive and considered the gold standard for the early detection of viral RNA [25]. However, these methods are costly, prone to contamination, and require trained personnel [3, 22, 26]. Virus isolation is another specific method, involving the inoculation of clinical specimens onto cell cultures, but it is time-consuming and requires specialized laboratory facilities [3, 22]. The most sensitive method for virus isolation involves mosquito inoculation, although low DENV viremia levels limit its effectiveness [27, 28].

Antigen detection, specifically of the NS1 protein, is significant for early detection of DENV [22, 29]. NS1-based tests, such as ELISA and immunochromatographic assays, can detect primary and secondary infections within nine days of symptom onset. However, these tests are less sensitive during secondary infections and for certain DENV serotypes [22, 23]. Monoclonal antibody-based NS1 ELISA tests have improved serotype specificity and can differentiate between primary and secondary infections [27].

Serological tests, like ELISA and hemagglutination inhibition assays, are commonly used due to their low cost and ease of use. These tests detect IgM and IgG antibodies, with higher IgM titers indicating primary infection and higher IgG titers indicating secondary infection. The IgM: IgG ratio helps distinguish between primary and secondary infections [22, 23]. Plaque Reduction and Neutralization Tests (PRNT) are another method used to detect neutralizing antibodies, providing greater specificity by differentiating DENV antibodies from cross-reactive flavivirus antibodies [3, 21].

Various diagnostic methods are available for dengue virus detection, each with its limitations. Virus isolation is a time-consuming process that necessitates specialized facilities. Molecular techniques such as RT-PCR are costly and require skilled technicians. While antigen detection and serological tests serve as practical alternatives, they may not be as sensitive in cases of secondary infections or for specific DENV serotypes. Ultimately, a combination of diagnostic approaches is often required to confirm DENV infection [22, 23].

IV.MANAGEMENT OF DENGUE PATIENTS

A. Supportive care

At present, there are no targeted therapies available for the remedy of dengue [2]. The therapy remains mainly supportive, focusing on fluid management [30].

Dengue fever care relies heavily on fluid resuscitation, especially during the crucial period when the rate of fluid delivery matches the rate of plasma leakage [31]. Some guidelines suggest calculating a fluid quota for the critical phase, which includes both maintenance of fluid and a 50 mL/kg fluid deficit (up to 50 kg) over 48 hours [31]. Managing severe dengue requires replacing plasma lost due to increased vascular permeability, especially during the critical period [32]. Dengue fever treatment requires the administration of two categories of volume expanders: crystalloids, which are water-soluble molecules, and colloids, which consist of water-insoluble molecules, to restore lost fluids [32].

To prevent hypovolemic shock caused by plasma leakage in dengue hemorrhagic fever, vigorous intravascular volume repletion is necessary [4]. Oral rehydration may suffice in moderate instances, especially with prompt medical treatment [4]. For individuals who have already experienced fluid loss,

intravenous fluid treatment is advised, and blood transfusion is recommended for significant bleeding [4].

The fluid management of dengue-infected individuals still faces substantial problems due to the lack of reliable indicators for predicting severe disease development [33]. Patients who can take oral fluids and have no complications may be discharged home [33].

B. Pharmocological management

Currently, there are no certified medications by the Food and Drug Administration (FDA) for the treatment of dengue [3]. Clinical studies have evaluated several anti-dengue treatment drugs, including carbazochrome sodium sulfonate, which is utilized to mitigate capillary leakage, oral prednisolone, which provides anti-inflammatory effects, and statins, which are employed for their anti-DENV properties and their role in alleviating endothelial inflammation [3]. Other anti-DENV medicines, including balapiravir which is a nucleoside analog and polymerase inhibitor, and celgosivir which is a glucosidase I inhibitor, have also been explored in studies [3]. Indian research has shown that Cocculus hirsutus has potential anti-dengue efficacy in vitro and in vivo trials in mouse models and additional research is now underway [34]. Drugs licensed for other illnesses, including chloroquine, prednisolone, lovastatin, ivermectin, and ribavirin, are examined for possible anti-DENV properties. However, no benefits have been established thus far [34]. Corticosteroids have been used to treat uncommon dengue complications, which are believed to be immune-mediated rather than virus-related [35].

According to the clinical trials conducted, carbazochrome sodium sulfonate reduces the number of patients who are experiencing pleural effusion [3]. Significantly fewer people developed dengue hemorrhagic fever and vomiting after using chloroquine [3]. The study found that steroid medication during the early acute phase of dengue did not increase or prolong viremia. Furthermore, there were no notable side effects, save for a trend toward hyperglycemia in the high-dosage group [36]. The experiment found that celgosivir was typically safe and well-tolerated, but did not lower viral load or fever burden in dengue patients [36].

There are many challenges in developing an effective anti-dengue treatment. It is difficult to identify an inhibitor that is active against four dengue serotypes [3]. Creating antibodies that give equal protection against all serotypes is another challenge [3]. In addition, there is no realistic animal model that replicates human DENV pathogenesis, hindering the development of a safe and effective therapy [3].

The ideal dengue therapeutic should have pan-serotype activity, swift symptom relief, minimal toxicity, large-scale distribution, minimal adverse effects, and tolerability for adults, children, infants, pregnant women, and patients with co-morbidities [3].

V.VACCINES

The characteristics of sustained effectiveness, dependable safety, and cross-immunity against all serotypes are essential for the perfect dengue vaccine [37]. However, the advancement in dengue vaccine research is hampered by the antibody-dependent enhancement (ADE) impact after infection with different strains and the absence of appropriate animal models [37]. There have been studies conducted on five different dengue vaccine formulations; DNA vaccine, live attenuated vaccine, inactivated vaccine, recombinant subunit vaccine, and viral vectored vaccine [38]. They mainly respond by increasing the body's immune response to the dengue virus (DENV) envelope protein and non-structural protein 1 (NS1) [39, 40].

A. Live attenuated vaccines

A live attenuated vaccination is made from a live pathogen that has been designed to be less virulent or avirulent, acting as an antigen component [41]. These vaccines highlight the advantages of distributing a collection of defensive antigens while offering long-term immune protection [41]. The initial licensed tetravalent dengue vaccine is CYD-TDV (Dengvaxia®), and two second-generation vaccines, TAK-003 (DENVax) and TV003/TV005, are currently in phase 3 trials [41]. There are variations among these vaccines in terms of their backbone structure, non-structural proteins, and chimeric elements [28]. These vaccinations have been shown to trigger B-cell responses, but T-cell immune responses to dengue virus nonstructural antigens are modest [42]. The approved chimeric tetravalent vaccines have demonstrated insufficient effectiveness against hetero-serotype DENVs, probably because of an absence of cellular immunity [42, 43]. The NS1 peptide, which has a conserved wing domain, is intended to minimize pathogenic cross-reactivity while remaining immunogenic. Antibodies against the modified NS1 peptide protected mice from dengue virus, avoiding hemorrhage or death [40].

B. Inactivated vaccines

Inactivated vaccines are made from inactivated microorganisms treated with materials like formaldehyde to inhibit their infectivity [44, 45]. This vaccine is deemed safe, with a low chance of pathogen reactivation following inoculation [44, 45]. Obtaining high virus concentrations by in-vitro cell culture made the dengue inactivated vaccine unsuitable. Despite obstacles, DENV-2 was successfully reproduced at elevated levels in Vero and FRhL-2 cell cultures, resulting in pure and inactivated dengue vaccines [44, 45]. Inactivated dengue vaccines require larger immunization doses or frequency to induce virus neutralizing antibodies [46, 47]. They typically include C, M, E, and NS1 proteins as antigenic elements to enhance immune response. However, composite vaccinations provide better defense than single-type vaccines [48].

C. Recombinant subunit vaccines

Recombinant subunit vaccines use prokaryotic or eukaryotic cells to produce antigenic proteins, resulting in long-lasting immune responses for protection or therapy [48, 49]. DENV's E proteins are the key candidates for subunit vaccines [48].

D. Viral vector vaccines

Less virulence vaccinia virus, adenovirus, and alphavirus are commonly used to deliver DENV antigens [38, 50]. The first two viruses are the highest frequently employed viral vectors because of extensive research and their ability to trigger a strong immune response against their antigens.

Recombinant vaccinia virus-producing dengue type 2 virus E protein has been shown to provide substantial protection against infection [51]. The 80% greatly immune-stimulating C-terminally shortened E proteins of DENV4 and DENV2 were expressed using a safer, host-specific modified vaccinia Ankara (MVA) virus vector. The study found that modified vaccinia Ankara recombinant producing 80% of the dengue virus 2 E protein induced significant anti-E antibodies in mice, but insignificant levels in rhesus monkeys [52].

E. DNA vaccines

A DNA vaccination is a plasmid that encodes specific antigens and may be administered into the body to induce immunological responses [53]. Kochel et al. (1997) reported that BALB/c mice were intradermally vaccinated with a DNA vaccine-producing precursor membrane (prM), 92% of the E protein of DENV2, and all the mice tested optimistic for anti-dengue antibodies [53]. DNA vaccines are inexpensive, stable, also suited for large-scale manufacturing, but they lack immunogenicity. Plasmid modification with enhanced promoters, alternate transmission techniques, several dosages, and simultaneous vaccination with adjuvants might be solutions to this problem [54].

Although five alternative dengue vaccine formulations have been studied, the only currently approved dengue vaccine is Dengvaxia (CYD-TDV). However, it is only recommended for people aged 9 to 45 with a documented history of past dengue infection, as it increases the risk of severe dengue in seronegative people. Recent evidence reveals that the overall efficacy of Dengvaxia declines with time, decreasing to 61.2% after 54 months, with variable efficacy rates based on the serostatus of recipients—64.2% in dengue-immune persons and 53.5% in seronegative individuals [55]. Developing candidates, such as TAK-003 (Qdenga), have shown encouraging outcomes in clinical studies. The CDC's Advisory Committee on Immunization Practices recently reviewed its performance, noting that it effectively protects seropositive recipients against all dengue types and provides some protection for seronegative recipients against DENV-1 and DENV-2 infections, though its efficacy against DENV-3 is uncertain [55]. Considering these advances, the development of a dengue vaccine still faces significant difficulties. The dengue virus's four unique serotypes impede the development of a universally effective vaccine. Issues such as antibody-dependent enhancement (ADE) and the lack of a clear immunological correlate of protection make vaccination effectiveness studies more difficult. Furthermore, the high cost of vaccines and the necessity for serological testing before immunization limit access in endemic locations, where the economic impact of dengue is most prominent [56].

While existing dengue vaccines, especially Dengvaxia, give some amount of protection, their limits need continuous research into more effective and broadly applicable vaccinations. The continuous research into novel options such as TAK-003 provides promise for better dengue preventive techniques. However, addressing the challenges of serotype diversity, safety, and cost-effectiveness will be crucial for the successful implementation of dengue vaccination programs worldwide [57].

VI.PREVENTION AND VECTOR CONTROL

Vector control mainly targets larvae and adult mosquitoes for elimination or to alleviate hazards [15]. Vector control methods encompass the removal of breeding grounds, the application of chemical insecticides and larvicides, and the utilization of microorganisms such as bacillus thuringiensis [58]. Mosquitoes may reproduce in even small amounts of clear stagnant water, such as between the trunk and leaves of huge plants, making it challenging to eradicate them and such ecosystems are nearly tough to remove [58]. Dengue control has grown increasingly problematic due to urbanization, population expansion, greater international travel, and inadequate vector control programs in dengue-endemic countries [59].

For control of larvae, critical interventions include clearing breeding locations, community mobilization and education, management of the environment, and regulations [56]. Organic synthetic insecticides, insect growth regulators like methoprene and pyriproxyfen, and chitin synthesis inhibitors like diflubenzuron and triflumuron are chemical larvicides that have been shown to have necessary residual effects [42].

Household insecticides and repellents are used to repel adult mosquitos [60]. Insecticide-impregnated nets or curtains are a key component of community engagement in controlling mosquitos [60]. Environmental management involves enhancing water supply and storage systems, implementing measures to prevent mosquito breeding in water containers, managing solid waste, organizing community clean-up initiatives, and making necessary structural changes [61].

VII. CONCLUSION

Dengue fever remains a significant global health burden, particularly in tropical and subtropical regions where Aedes aegypti mosquitoes thrive. While the current management strategies focused on vector control, supportive care, and symptom monitoring, are effective in minimizing the disease's acute impact, they fall short of addressing the long- term challenge. Through this study, we highlight the critical need for creative methods, such as the development of effective vaccines and antiviral therapies that have yet to be realized.

REFERENCES

[1] J. M. Torres-Flores, A. Reyes-Sandoval, and M. I. Salazar, “Dengue Vaccines: An Update,” BioDrugs, vol. 36, no. 3, pp. 325–336, 2022, doi: 10.1007/s40259-022-00531-z.

[2] L. L. Hermann, S. B. Gupta, S. B. Manoff, S. Kalayanarooj, R. V. Gibbons, and B. A. G. Coller, “Advances in the understanding, management, and prevention of dengue,” J. Clin. Virol., vol. 64, pp. 153–159, 2015, doi: 10.1016/j.jcv.2014.08.031.

[3] H. Harapan, A. Michie, R. T. Sasmono, and A. Imrie, “Dengue : A Minireview,” vol. 1, pp. 1–35, 2020.

[4] V. Srinivas and V. R. Srinivas, “Dengue Fever: a Review Article,” J. Evol. Med. Dent. Sci., vol. 4, no. 29, pp. 5048–5058, 2015, doi: 10.14260/jemds/2015/736.

[5] G. N. Malavige, C. Jeewandara, A. Ghouse, G. Somathilake, and H. Tissera, “Changing epidemiology of dengue in sri lanka —challenges for the future,” PLoS Negl. Trop. Dis., vol. 15, no. 8, pp. 1–10, 2021, doi: 10.1371/journal.pntd.0009624.

[6] N. E. A. Murray, M. B. Quam, and A. Wilder-Smith, “Epidemiology of dengue: Past, present and future prospects,” Clin. Epidemiol., vol. 5, no. 1, pp. 299–309, 2013, doi: 10.2147/CLEP.S34440.

[7] H. A. Tissera et al., "Severe dengue epidemic, Sri Lanka, 2017," Emerg. Infect. Dis., vol. 26, no. 4, pp. 682–691, 2020, doi: 10.3201/eid2604.190435.

[8] M. Vouga et al., "Dengue, Zika and chikungunya during pregnancy: Pre- and post-travel advice and clinical management," J. Travel Med., vol. 26, no. 8, pp. 1–13, 2019, doi: 10.1093/jtm/taz077.

[9] A. Mathew and A. L. Rothman, "Understanding the contribution of cellular immunity to dengue disease pathogenesis," Immunol. Rev., vol. 225, no. 1, pp. 300–313, 2008, doi: 10.1111/j.1600-065X.2008.00678.x.

[10] U. Jayarajah et al., "Pattern of dengue virus infections in adult patients from Sri Lanka," Trans. R. Soc. Trop. Med. Hyg., vol. 112, no. 3, pp. 144–153, 2018, doi: 10.1093/trstmh/try034.

[11] D. Ariyaratne et al., "Epidemiological and virological factors determining dengue transmission in Sri Lanka during the COVID-19 pandemic," PLOS Glob. Public Heal., vol. 2, no. 8, p. e0000399, 2022, doi: 10.1371/journal.pgph.0000399.

[12] D. Guha-Sapir and B. Schimmer, "Dengue fever: New paradigms for a changing epidemiology," Emerg. Themes Epidemiol., vol. 2, pp. 1–10, 2005, doi: 10.1186/1742-7622-2-1.

[13] A. Y. Limon-Flores et al., "Dengue virus inoculation to human skin explants: An effective approach to assess in situ the early infection and the effects on cutaneous dendritic cells," Int. J. Exp. Pathol., vol. 86, no. 5, pp. 323–334, 2005, doi: 10.1111/j.0959-9673.2005.00445.x.

[14] A. P. Durbin et al., "Phenotyping of peripheral blood mononuclear cells during acute dengue illness demonstrates infection and increased activation of monocytes in severe cases compared to classic dengue fever," Virology, vol. 376, no. 2, pp. 429–435, 2008, doi: 10.1016/j.virol.2008.03.028.

[15] S. Blackley et al., "Primary Human Splenic Macrophages, but Not T or B Cells, Are the Principal Target Cells for Dengue Virus Infection In Vitro," J. Virol., vol. 81, no. 24, pp. 13325–13334, 2007, doi: 10.1128/jvi.01568-07.

[16] B. E. E. Martina, P. Koraka, and A. D. M. E. Osterhaus, "Dengue virus pathogenesis: An integrated view," Clin. Microbiol. Rev., vol. 22, no. 4, pp. 564–581, 2009, doi: 10.1128/CMR.00035-09.

[17] S. Kalayanarooj et al., "Early clinical and laboratory indicators of acute dengue illness," J. Infect. Dis., vol. 176, no. 2, pp. 313–321, 1997, doi: 10.1086/514047.

[18] A. O. Guilarde et al., "Dengue and dengue hemorrhagic fever among adults: Clinical outcomes related to viremia, serotypes, and antibody response," J. Infect. Dis., vol. 197, no. 6, pp. 817–824, 2008, doi: 10.1086/528805.

[19] WHO, "Dengue haemorrhagic fever Diagnosis, treatment, prevention and control," 2nd Ed. [Internet], vol. 36, no. 3, pp. 670–670, 1997, doi: 10.4269/ajtmh.1987.36.670.

[20] G. N. Malavige, N. Fernando, and G. Ogg, "Pathogenesis of Dengue viral infections," Sri Lankan J. Infect. Dis., vol. 1, no. 1, p. 2, 2011, doi: 10.4038/sljid.v1i1.2987.

[21] S. L. Beltrán-Silva, S. S. Chacón-Hernández, E. Moreno-Palacios, and J. Á. Pereyra-Molina, "Clinical and differential diagnosis: Dengue, chikungunya and Zika," Rev. Médica del Hosp. Gen. México, vol. 81, no. 3, pp. 146–153, 2018, doi: 10.1016/j.hgmx.2016.09.011.

[22] N. Raafat, S. D. Blacksell, and R. J. Maude, "A review of dengue diagnostics and implications for surveillance and control," Trans. R. Soc. Trop. Med. Hyg., vol. 113, no. 11, pp. 653–660, 2019, doi: 10.1093/trstmh/trz068.

[23] S. S. Hegde and B. R. Bhat, "Dengue detection: Advances and challenges in diagnostic technology," Biosens. Bioelectron. X, vol. 10, no. December 2021, p. 100100, 2022, doi: 10.1016/j.biosx.2021.100100.

[24] P. F. Wong, L. P. Wong, and S. AbuBakar, "Diagnosis of severe dengue: Challenges, needs and opportunities," J. Infect. Public Health, vol. 13, no. 2, pp. 193–198, 2020, doi: 10.1016/j.jiph.2019.07.012.

[25] J. Rodriguez-Manzano, P. Y. Chia, T. W. Yeo, A. Holmes, P. Georgiou, and S. Yacoub, "Improving Dengue Diagnostics and Management Through Innovative Technology," Curr. Infect. Dis. Rep., vol. 20, no. 8, 2018, doi: 10.1007/s11908-018-0633-x.

[26] B. H. Kok, H. T. Lim, C. P. Lim, N. S. Lai, C. Y. Leow, and C. H. Leow, "Dengue virus infection – a review of pathogenesis, vaccines, diagnosis and therapy," Virus Res., vol. 324, no. June 2022, p. 199018, 2023, doi: 10.1016/j.virusres.2022.199018.

[27] M. G. Guzman, M. Alvarez, and S. B. Halstead, "Secondary infection as a risk factor for dengue hemorrhagic fever/dengue shock syndrome: An historical perspective and role of antibody-dependent enhancement of infection," Arch. Virol., vol. 158, no. 7, pp. 1445–1459, 2013, doi: 10.1007/s00705-013-1645-3.

[28] S. R. Hadinegoro et al., "Efficacy and Long-Term Safety of a Dengue Vaccine in Regions of Endemic Disease," N. Engl. J. Med., vol. 373, no. 13, pp. 1195–1206, 2015, doi: 10.1056/nejmoa1506223.

[29] M. A. Kabir, H. Zilouchian, M. A. Younas, and W. Asghar, "Dengue detection: Advances in diagnostic tools from conventional technology to point of care," Biosensors, vol. 11, no. 7, pp. 1–28, 2021, doi: 10.3390/bios11070206.

[30] P. D. Kilmer, "Review Article: Review Article," Journalism, vol. 11, no. 3, pp. 369–373, 2010, doi: 10.1177/1461444810365020.

[31] S. A. Kularatne and C. Dalugama, "Dengue infection: Global importance, immunopathology and management," Clin. Med. J. R. Coll. Physicians London, vol. 22, no. 1, pp. 9–13, 2022, doi: 10.7861/clinmed.2021-0791.

[32] N. T. Hung, "Fluid management for dengue in children," Paediatr. Int. Child Health, vol. 32, no. SUPP1, pp. 39–42, 2012, doi: 10.1179/2046904712Z.00000000051.

[33] D. A. Muller, A. C. I. Depelsenaire, and P. R. Young, "Clinical and laboratory diagnosis of dengue virus infection," J. Infect. Dis., vol. 215, no. Suppl 2, pp. S89–S95, 2017, doi: 10.1093/infdis/jiw649.

[34] A. Tayal, S. K. Kabra, and R. Lodha, "Management of Dengue: An Updated Review," Indian J. Pediatr., vol. 90, no. 2, pp. 168–177, 2023, doi: 10.1007/s12098-022-04394-8.

[35] S. Rajapakse, "Corticosteroids in the treatment of dengue illness," Trans. R. Soc. Trop. Med. Hyg., vol. 103, no. 2, pp. 122–126, 2009, doi: 10.1016/j.trstmh.2008.07.022.

[36] H. Beesetti, N. Khanna, and S. Swaminathan, "Investigational drugs in early development for treating dengue infection," Expert Opin. Investig. Drugs, vol. 25, no. 9, pp. 1059–1069, 2016, doi: 10.1080/13543784.2016.1201063.

[37] A. Wilder-Smith, "Dengue vaccine development by the year 2020: challenges and prospects," Curr. Opin. Virol., vol. 43, pp. 71–78, 2020, doi: 10.1016/j.coviro.2020.09.004.

[38] L. E. Yauch and S. Shresta, Dengue virus vaccine development, 1st ed., vol. 88. Elsevier Inc., 2014.

[39] Y. Liu, J. Liu, and G. Cheng, "Vaccines and immunization strategies for dengue prevention," Emerg. Microbes Infect., vol. 5, no. 1, pp. 1–6, 2016, doi: 10.1038/emi.2016.74.

[40] Y. C. Lai et al., "Antibodies Against Modified NS1 Wing Domain Peptide Protect Against Dengue Virus Infection," Sci. Rep., vol. 7, no. 1, pp. 1–15, 2017, doi: 10.1038/s41598-017-07308-3.

[41] S. S. Whitehead, J. E. Blaney, A. P. Durbin, and B. R. Murphy, "Prospects for a dengue virus vaccine," Nat. Rev. Microbiol., vol. 5, no. 7, pp. 518–528, 2007, doi: 10.1038/nrmicro1690.

[42] K. H. Ng et al., "Persistent Dengue Infection in an Immunosuppressed Patient Reveals the Roles of Humoral and Cellular Immune Responses in Virus Clearance," Cell Host Microbe, vol. 26, no. 5, pp. 601-605.e3, 2019, doi: 10.1016/j.chom.2019.10.005.

[43] S. Sridhar et al., "Effect of Dengue Serostatus on Dengue Vaccine Safety and Efficacy," N. Engl. J. Med., vol. 379, no. 4, pp. 327–340, 2018, doi: 10.1056/nejmoa1800820.

[44] J. R. Putnak et al., "An evaluation of dengue type-2 inactivated, recombinant subunit, and live-attenuated vaccine candidates in the rhesus macaque model," Vaccine, vol. 23, no. 35, pp. 4442–4452, 2005, doi: 10.1016/j.vaccine.2005.03.042.

[45] R. Putnak et al., "Immunogenic and protective response in mice immunized with a purified, inactivated, dengue-2 virus vaccine prototype made in fetal rhesus lung cells," Am. J. Trop. Med. Hyg., vol. 55, no. 5, pp. 504–510, 1996, doi: 10.4269/ajtmh.1996.55.504.

[46] W.-Y. Tsai, A. Durbin, J.-J. Tsai, S.-C. Hsieh, S. Whitehead, and W.-K. Wang, "Complexity of Neutralizing Antibodies against Multiple Dengue Virus Serotypes after Heterotypic Immunization and Secondary Infection Revealed by In-Depth Analysis of Cross-Reactive

Antibodies," J. Virol., vol. 89, no. 14, pp. 7348–7362, 2015, doi: 10.1128/jvi.00273-15.

[47] A. K. Sundaram et al., "Comparison of purified psoralen-inactivated and formalin-inactivated dengue vaccines in mice and nonhuman primates," Vaccine, vol. 38, no. 17, pp. 3313–3320, 2020, doi: 10.1016/j.vaccine.2020.03.008.

[48] N. K. Tripathi and A. Shrivastava, "Recent Developments in Recombinant Protein–Based Dengue Vaccines," Front. Immunol., vol. 9, no. August, pp. 1–15, 2018, doi: 10.3389/fimmu.2018.01919.

[49] E. L. Pang and H. S. Loh, "Towards development of a universal dengue vaccine – How close are we?," Asian Pac. J. Trop. Med., vol. 10, no. 3, pp. 220–228, 2017, doi: 10.1016/j.apjtm.2017.03.003.

[50] S. Murrell, S. C. Wu, and M. Butler, "Review of dengue virus and the development of a vaccine," Biotechnol. Adv., vol. 29, no. 2, pp. 239–247, 2011, doi: 10.1016/j.biotechadv.2010.11.008.

[51] R. H. Men, M. Bray, and C. J. Lai, "Carboxy-terminally truncated dengue virus envelope glycoproteins expressed on the cell surface and secreted extracellularly exhibit increased immunogenicity in mice," J. Virol., vol. 65, no. 3, pp. 1400–1407, 1991, doi: 10.1128/jvi.65.3.1400-1407.1991.

[52] R. Men et al., "Immunization of rhesus monkeys with a recombinant of modified vaccinia virus Ankara expressing a truncated envelope glycoprotein of dengue type 2 virus induced resistance to dengue type 2 virus challenge," Vaccine, vol. 18, no. 27, pp. 3113–3122, 2000, doi: 10.1016/S0264-410X(00)00121-3.

[53] T. Kochel et al., "Inoculation of plasmids expressing the dengue-2 envelope gene elicit neutralizing antibodies in mice," Vaccine, vol. 15, no. 5, pp. 547–552, 1997, doi: 10.1016/S0264-410X(97)00215-6.

[54] J. R. Danko, C. G. Beckett, and K. R. Porter, "Development of dengue DNA vaccines," Vaccine, vol. 29, no. 42, pp. 7261–7266, 2011, doi: 10.1016/j.vaccine.2011.07.019.

[55] S. J. Thomas, "Is new dengue vaccine efficacy data a relief or cause for concern?," npj Vaccines, vol. 8, no. 1, 2023, doi: 10.1038/s41541-023-00658-2.

[56] Q. Jing and M. Wang, "Dengue epidemiology," J. Glob. Health, vol. 3, no. 2, pp. 37–45, 2019, doi: 10.1016/j.glohj.2019.06.002.

[57] K. Bharati and H. Jain, "Dengue Vaccines: Current Status and Future Prospects," J. Clin. Diagnostic Res., pp. 1–6, 2019, doi: 10.7860/jcdr/2019/20714.12962.

[58] S. Rajapakse, C. Rodrigo, and A. Rajapakse, "Treatment of dengue fever," Infect. Drug Resist., vol. 5, no. 1, pp. 103–112, 2012, doi: 10.2147/idr.s22613.

[59] C. Buhler, V. Winkler, S. Runge-Ranzinger, R. Boyce, and O. Horstick, "Environmental methods for dengue vector control – A systematic review and meta-analysis," PLoS Negl. Trop. Dis., vol. 13, no. 7, pp. 1–15, 2019, doi: 10.1371/journal.pntd.0007420.

[60] H. H. Yap, N. L. Chong, A. E. S. Foo, and C. Y. Lee, "AND FUTURE PROSPECTS," 1994.

[61] M. A. F. Mahmud et al., "Environmental management for dengue control: A systematic review protocol," BMJ Open, vol. 9, no. 5, pp. 1–4, 2019, doi: 10.1136/bmjopen-2018-026101.