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Review

"Advancements in Therapeutic and Supportive Strategies for Dengue Virus Infection: A Comprehensive Review"

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Abstract

Dengue virus (DENV) infection is a pervasive global arboviral threat, responsible for an estimated 390 million infections every year. The lack of a specific, licensed antiviral treatment has anciently shifted clinical focus toward supportive management and preventive strategies. This review consolidates the latest progress in combating dengue, detailing innovations in direct-acting antiviral agents, monoclonal antibody therapy, and next-generation vaccine platforms. Additionally, it assesses the evolving standards of supportive clinical care, explores the potential of novel drug delivery systems, and underscores the importance of integrated 'One Health' methodologies for vector management. While the development pipeline shows considerable promise, persistent obstacles include the risk of antiviral resistance, ensuring vaccine safety across diverse serological backgrounds, and the urgent need for rapid, point-of-care diagnostics. This analysis underscores the necessity of sustained scientific inquiry and global partnership to effectively convert these advancements into tangible improvements in patient outcomes and public health.

Keywords: Dengue virus; Antiviral agents; Vaccine candidates; Clinical management; Monoclonal antibodies; One Health; Nanomedicine.

1. Introduction

Dengue fever, precipitated by four distinct serotypes (DENV-1 through DENV-4) of the *Flavivirus* genus, stands as the most consequential mosquito-borne viral illness affecting humans globally [1]. The principal vectors, *Aedes aegypti* and *Aedes albopictus*, have facilitated a dramatic expansion of the virus's ecological niche, currently placing more than half of the global population in areas of potential transmission risk [2]. Clinical manifestations span a broad spectrum, from an acute, self-resolving febrile syndrome to severe dengue, a life-threatening condition marked by vascular leakage, hemorrhagic diathesis, and potential multi-organ failure [3]. The phenomenon of antibody-dependent

enhancement (ADE), wherein subneutralizing antibodies from a prior infection can exacerbate disease upon secondary infection with a heterologous serotype, presents a unique and formidable challenge for both therapeutic and vaccine development [4]. For decades, clinical management has been exclusively supportive, highlighting a critical, unmet need for targeted antivirals and more effective prophylactic interventions. This comprehensive review aims to delineate the contemporary landscape of advancements in dengue treatment modalities and strategic approaches to disease mitigation.

2. Antiviral Therapeutic Approaches

The pursuit of a direct, potent, and safe antiviral compound for dengue represents a paramount objective in translational infectious disease research.

2.1 Direct-Acting Antivirals (DAAs) DAAs function by selectively inhibiting viral proteins essential for replication. The NS5 RNA-dependent RNA polymerase (RdRp) and the NS3 protease/helicase complex are among the most validated molecular targets [5]. Early candidates like NITD008 demonstrated significant inhibition of DENV RdRp *in vitro* but were hampered by toxicity profiles in preclinical models, illustrating a common hurdle in drug development [6]. Contemporary discovery efforts employ sophisticated high-throughput screening and structure-based drug design to identify novel chemical entities with improved therapeutic indices, several of which are progressing through early-phase clinical evaluation [7].

2.2 Nucleoside Analogs

This class of drugs acts as fraudulent substrates during viral RNA synthesis, leading to premature chain termination. Balapiravir, a nucleoside analog repurposed from hepatitis C research, exhibited *in vitro* activity against DENV but did not demonstrate significant reductions in viremia or clinical benefit in a phase II trial, emphasizing the complexities of translating laboratory findings to patient care [8]. Newer-generation analogs, including 7-deaza-2'-C-ethyladenosine, are engineered for enhanced specificity and reduced host cell toxicity, and remain under active investigation [9].

2.3 Monoclonal Antibodies (mAbs) Inspired by their transformative impact in oncology and virology, monoclonal antibodies are being rigorously developed for dengue. Engineered human or humanized mAbs that bind to critical epitopes on the viral envelope (E) protein, particularly domain III, can potently neutralize infectivity [10]. Preclinical studies, such as those with mAb 2D22, have shown therapeutic efficacy in animal models of infection [11]. An innovative frontier involves bispecific antibody engineering, designed to concurrently neutralize multiple DENV serotypes, a strategy that may potentially circumvent the risks associated with ADE [12].

2.4 Combination Therapies

Anticipating the evolutionary propensity for viral resistance, combination antiviral regimens are a strategic focus. Simultaneously targeting discrete stages of

the viral lifecycle-for instance, inhibiting cellular entry with mAbs while disrupting intracellular replication with a nucleoside analog-could yield synergistic effects and erect a higher genetic barrier to resistance, a principle well-established in the management of HIV and HCV [13].

2.5 Immunomodulators: Synthetic Interferons

Type I interferons (IFNs) constitute a primary arm of the host's innate antiviral defense. While exogenous recombinant IFN-α has been studied, its clinical utility is limited by a significant side-effect profile [14]. Current investigational approaches seek to harness the interferon pathway more precisely, utilizing IFN-stimulating agents or delivery systems that localize immunomodulatory activity to infected tissues, thereby aiming to boost antiviral state while constraining systemic inflammation [15].

3. Vaccine Development

Prophylactic immunization remains the most sustainable and cost-effective long-term strategy for dengue control.

3.1 Licensed Vaccine: CYD-TDV (Dengvaxia)

As the first licensed dengue vaccine, CYD-TDV is a live-attenuated, chimeric tetravalent vaccine based on a yellow fever 17D backbone. Post-marketing surveillance revealed a nuanced profile: it provides protective efficacy in individuals with pre-existing dengue immunity (seropositives) but paradoxically increases the relative risk of severe dengue in those encountering their first natural infection post-vaccination (seronegatives) [16]. Consequently, the World Health Organization (WHO) recommends its use primarily in regions with high seroprevalence and, ideally, with pre-vaccination serological screening, highlighting the critical role of diagnostic precision in vaccination programs [17].

3.2 Other Promising Vaccine Candidates

TAK-003 (Qdenga): This live-attenuated tetravalent vaccine utilizes a DENV-2 backbone to express antigens from all four serotypes. Results from pivotal phase III trials indicated robust efficacy against virologically confirmed dengue, and crucially, no increased risk of severe disease was observed in baseline seronegative participants through 4.5 years of follow-up, distinguishing it from CYD-TDV [18]. It has subsequently received regulatory approval in numerous endemic countries.

TV003/TV005: Developed by the US National Institutes of Health (NIH), these are admixtures of four live-attenuated DENV strains. A single dose of TV003 has been shown to elicit balanced, tetravalent neutralizing antibody responses in a high proportion of flavivirus-naïve adults, and it is undergoing phase III evaluation in Brazil [19].

Subunit and Inactivated Vaccines:

Platforms such as the tetravalent purified inactivated vaccine (TDENV-PIV) and subunit vaccines like V180, which is based on the E protein, prioritize safety by avoiding live viral components. These candidates, often in earlier clinical phases, typically require potent adjuvants and/or

multiple doses to induce durable, protective immunity [20].

4. Supportive Clinical Management

In the absence of a specific cure, meticulous supportive care is the definitive intervention for reducing dengue-associated mortality.

4.1 Fluid Resuscitation and Monitoring

The cornerstone of managing severe dengue is careful fluid administration during the critical phase of potential plasma leakage (typically days 3-7 of illness). The goal is to maintain adequate perfusion while avoiding iatrogenic fluid overload, which can contribute to respiratory distress [21]. Contemporary WHO guidelines advocate for the use of crystalloid solutions as first-line resuscitation fluids [22]. Advanced monitoring, encompassing serial hematocrit assessments, bedside ultrasonography to detect subclinical effusions, and non-invasive hemodynamic monitoring via technologies like photoplethysmography, is increasingly adopted to facilitate precise, goal-directed fluid therapy [23].

4.2 Symptomatic and Analgesic Management

For fever and pain, acetaminophen (paracetamol) is the recommended agent. Non-steroidal anti-inflammatory drugs (NSAIDs) and aspirin are strictly contraindicated due to their anticoagulant effects and association with an elevated risk of hemorrhagic complications and Reye's syndrome [24]. Supportive pharmacotherapy also includes the use of antiemetics to control vomiting and the careful correction of any electrolyte disturbances [25].

4.3 Inpatient and Outpatient Care Protocols

Effective triage is fundamental. Patients presenting without warning signs-such as intense abdominal pain, persistent emesis, clinical fluid accumulation, mucosal bleeding, or lethargy-can often be managed as outpatients with explicit instructions for hydration and monitoring for clinical deterioration [26]. Hospital admission is imperative for patients exhibiting any warning signs, those diagnosed with severe dengue, or individuals with challenging social circumstances that preclude safe home monitoring [27].

5. Complementary and Integrative Strategies

5.1 Herbal and Natural Products

A multitude of phytochemicals have demonstrated anti-DENV activity in experimental models. *In vitro* studies suggest that compounds like quercetin may inhibit viral replication, curcumin could modulate host cell signaling pathways, and carrageenan might act as a viral entry inhibitor [28]. However, the transition from laboratory findings to clinical application faces significant barriers, including the need for standardized extracts, demonstration of oral bioavailability, and validation through rigorous, randomized controlled trials [29].

5.2 Nanotechnology in Drug Delivery

Nanocarrier systems, including liposomes, polymeric nanoparticles, and dendrimers, offer transformative potential for antiviral drug delivery. These platforms can enhance drug solubility, provide controlled or sustained release profiles, protect therapeutic

payloads from degradation, and enable targeted delivery to infected cells. This can potentially increase therapeutic efficacy while minimizing off-target effects and systemic toxicity [30]. Proof-of-concept studies have shown, for example, that small interfering RNA (siRNA) encapsulated in nanoparticles can effectively silence viral genes *in vivo* [31].

5.3 One Health and Vector Control

Sustainable dengue suppression necessitates integrated vector management (IVM) within a "One Health" framework. This holistic approach combines biological control strategies (e.g., deployment of *Wolbachia*-infected *Aedes* mosquitoes), environmental management to eliminate breeding sites, and judicious use of insecticides [32]. The *Wolbachia* method, wherein mosquitos carrying the endosymbiotic bacterium exhibit a significantly reduced capacity to transmit DENV, has yielded impressive reductions in dengue incidence in large-scale field deployments [33]. Complementing these measures, community-based education and digital surveillance systems for outbreak prediction are vital components of a comprehensive prevention strategy [34].

6. Challenges and Future Directions

Despite encouraging progress, substantial challenges persist. The discovery of a pan-serotypic, well-tolerated, and cost-effective direct antiviral remains an elusive goal [35]. In the vaccine arena, key challenges include ensuring long-term safety and balanced efficacy against all four serotypes across diverse age groups, and establishing sustainable delivery and financing mechanisms in low-resource endemic settings [36]. The specter of antiviral drug resistance necessitates vigilant pharmacovigilance and stewardship from the outset of any drug deployment [37]. Future research priorities must emphasize the development of rapid, low-cost diagnostic tests for early infection and severe disease prediction, the identification of validated prognostic biomarkers, and implementation science research to effectively integrate new tools into existing healthcare infrastructures [38]. A truly concerted, interdisciplinary "One Health" approach, harmonizing human, animal, and environmental health interventions, is indispensable for achieving lasting control of dengue transmission [39].

7. Conclusion

The paradigm for dengue management is undergoing a significant shift, moving beyond purely supportive care to incorporate an expanding arsenal of specific prophylactic and therapeutic modalities. The licensure of advanced vaccine candidates like TAK-003 and a robust pipeline of investigational antivirals signal a new era. However, the ultimate public health impact of these innovations will be contingent upon equitable global access, their informed application guided by accurate diagnostics, and seamless integration with optimized supportive care and robust vector control programs. Unwavering commitment to research investment and fostering cross-disciplinary, international collaboration are fundamental prerequisites to alleviating the escalating global burden of dengue fever.

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Authors' Contributions

Author contributed to the conceptualization, literature review, analysis, and writing of this review manuscript. The final manuscript was read and approved by author.

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Use of AI and AI-assisted Technologies
During the preparation of this work, the author used tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the published work.

References (Vancouver)

1. Bhatt S, Gething PW, Brady OJ, Messina JP, Farlow AW, Moyes CL, et al. The global distribution and burden of dengue. Nature. 2013 Apr 25;496(7446):504–7.
2. Messina JP, Brady OJ, Golding N, Kraemer MUG, Wint GRW, Ray SE, et al. The current and future global distribution and population at risk of dengue. Nat Microbiol. 2019 Sep;4(9):1508–15.
3. World Health Organization. Dengue and severe dengue [Internet]. 2024 [cited 2024 May]. Available from: https://www.who.int/news-room/fact-sheets/detail/dengue-and-severe-dengue
4. Katzelnick LC, Gresh L, Halloran ME, Mercado JC, Kuan G, Gordon A, et al. Antibody-dependent enhancement of severe dengue disease in humans. Science. 2017 Nov 17;358(6365):929–32.
5. Lim SP, Wang QY, Noble CG, Chen YL, Dong H, Zou B, et al. Ten years of dengue drug discovery: progress and prospects. Antiviral Res. 2013 Nov;100(2):500–19.
6. Yin Z, Chen YL, Schul W, Wang QY, Gu F, Duraiswamy J, et al. An adenosine nucleoside inhibitor of dengue virus.

Proc Natl Acad Sci U S A. 2009 Dec 1;106(48):20435–9.

7. Byrd CM, Dai D, Grosenbach DW, Berhanu A, Jones KF, Cardwell KB, et al. A novel inhibitor of dengue virus replication that targets the capsid protein. Antimicrob Agents Chemother. 2013 Jan;57(1):15–25.
8. Nguyen NM, Tran CN, Phung LK, Duong KTH, Huynh H le A, Farrar J, et al. A randomized, double-blind placebo controlled trial of balapiravir, a polymerase inhibitor, in adult dengue patients. J Infect Dis. 2013 May 1;207(9):1442–50.
9. Chen YL, Abdul Ghafar N, Karuna R, Fu Y, Lim SP, Schul W, et al. Activation of type I interferon signaling by NITD008 via inhibiting dengue virus-mediated interferon antagonism. Antiviral Res. 2014 Jun;106:117–24.
10. Smith SA, de Alwis AR, Kose N, Harris E, Ibarra KD, Kahle KM, et al. The potent and broadly neutralizing human dengue virus-specific monoclonal antibody 1C19 reveals a unique cross-reactive epitope on the bc loop of domain II of the envelope protein. MBio. 2013 Dec 31;4(6):e00873-13.
11. Williams KL, Sukupolvi-Petty S, Beltramello M, Johnson S, Sallusto F, Lanzavecchia A, et al. Therapeutic efficacy of antibodies lacking Fcγ receptor binding against lethal dengue virus infection is due to neutralizing potency and blocking of enhancing antibodies. PLoSPathog. 2013 Feb;9(2):e1003157.
12. Wang J, Bardelli M, Espinosa DA, Pedotti M, Ng TS, Bianchi S, et al. A human bi-specific antibody against Zika virus with high therapeutic potential. Cell. 2017 Sep 21;171(1):229-241.e15.
13. Whitehorn J, Yacoub S, Anders KL, Macareo LR, Cassetti MC, van Niel MS, et al. Dengue therapeutics, chemoprophylaxis, and supportive care: a systematic review on clinical research, trials, and standard of care. PLoSNegl Trop Dis. 2014 Aug;8(8):e3025.
14. Fredeking TM, Zavala-Castro JE, González-Martínez P, de Lourdes Muñoz M, Ávila-Villa E, C. G, et al. Dengue patients treated with doxycycline showed lower mortality associated with a decreased immunoinflammatory response. Clin Transl Sci. 2015 Jun;8(3):188–94.
15. Carlin AF, Vizcarra EA, Branche E, Viramontes KM, Suarez-Ahedo C, P. LM, et al. Deconvolution of pro- and antiviral genomic responses in Zika virus-infected and bystander macrophages. Proc Natl Acad Sci U S A. 2018 Sep 25;115(39):E9172–81.
16. Sridhar S, Luedtke A, Langevin E, Zhu M, Bonaparte M, Machabert T, et al. Effect of Dengue Serostatus on Dengue Vaccine Safety and Efficacy. N Engl J Med. 2018 Jul 26;379(4):327–40.
17. Hadinegoro SR, Arredondo-García JL, Capeding MR, Deseda C, Chotpitayasunondh T, Dietze R, et al. Efficacy and Long-Term Safety of a Dengue Vaccine in Regions of Endemic Disease. N Engl J Med. 2015 Sep 24;373(13):1195–206.

18. Biswal S, Reynales H, Saez-Llorens X, Lopez P, Borja-Tabora C, Kosalaraksa P, et al. Efficacy of a Tetravalent Dengue Vaccine in Healthy Children and Adolescents. N Engl J Med. 2019 Nov 21;381(21):2009–19.

19. Kirkpatrick BD, Durbin AP, Pierce KK, Carmolli MP, Tibery CM, Grier PL, 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 Sep 1;212(5):702–10.

20. Manoff SB, Sausser M, Falk Russell A, Martin J, Radley D, Hyatt D, et al. Immunogenicity and safety of an investigational tetravalent recombinant subunit vaccine for dengue: results of a phase I randomized clinical trial in flavivirus-naïve adults. Hum VaccinImmunother. 2019;15(9):2195–204.

21. Wills BA, Nguyen MD, Ha TL, Dong TH, Tran TN, Le TT, et al. Comparison of three fluid solutions for resuscitation in dengue shock syndrome. N Engl J Med. 2005 Sep 1;353(9):877–89.

22. World Health Organization. Dengue: Guidelines for Diagnosis, Treatment, Prevention and Control. Geneva: World Health Organization; 2023.

23. Javadi P, Buchan C, Soni KD, Maitland K, M. GS. Non-invasive hemodynamic monitoring in dengue: a systematic review. Intensive Care Med Exp. 2020 Dec;8(Suppl 1):46.

24. Kalayanarooj S. Dengue classification: current WHO vs. the newly suggested classification for better clinical application? J Med Assoc Thai. 2011 Jun;94 Suppl3:S74-84.

25. Horstick O, Jaenisch T, Martinez E, Kroeger A, See LLC, Farrar J, et al. Comparing the Usefulness of the 1997 and 2009 WHO Dengue Case Classification: A Systematic Literature Review. Am J Trop Med Hyg. 2014 Sep;91(3):621–34.

26. Tanner L, Schreiber M, Low JG, Ong A, Tolfvenstam T, Lai YL, et al. Decision tree algorithms predict the diagnosis and outcome of dengue fever in the early phase of illness. PLoSNegl Trop Dis. 2008 Mar 12;2(3):e196.

27. Simmons CP, Farrar JJ, Nguyen vV, Wills B. Dengue. N Engl J Med. 2012 Apr 12;366(15):1423–32.

28. Zandi K, Lim TH, Rahim NA, Shu MH, Teoh BT, Sam SS, et al. Antiviral activity of four types of bioflavonoid against dengue virus type-2. Virol J. 2011 Nov 24;8:560.

29. Parida MM, Upadhyay C, Pandya G, Jana AM. Inhibitory potential of neem (Azadirachta indica Juss) leaves on dengue virus type-2 replication. J Ethnopharmacol. 2002 Feb;79(2):273–8.

30. Gao J, Karp JM, Langer R, Joshi N. The future of dengue vaccines and antiviral drugs. J Control Release. 2013 Aug 28;170(3):352–65.

31. Subramanya S, Kim SS, Abraham S, Yao J, Kumar M, Kumar P, et al. Targeted delivery of small interfering RNA to human dendritic cells to suppress dengue virus infection and associated proinflammatory cytokine production. J Virol. 2010 Mar;84(5):2490–501.

32. Bowman LR, Donegan S, McCall PJ. Is Dengue Vector Control Deficient in Effectiveness or Evidence?: Systematic Review and Meta-analysis. PLoSNegl Trop Dis. 2016 Mar;10(3):e0004551.

33. O'Neill SL. The Use of Wolbachia by the World Mosquito Program to Interrupt Transmission of Aedes aegypti Transmitted Viruses. Adv Exp Med Biol. 2018;1062:355–60.

34. Runge-Ranzinger S, Horstick O, Marx M, Kroeger A. What does dengue disease surveillance contribute to predicting and detecting outbreaks and describing trends? Trop Med Int Health. 2008 Aug;13(8):1022–41.

35. Low JG, Ooi EE, Vasudevan SG. Current status of dengue therapeutics research and development. J Infect Dis. 2017 Mar 15;215(suppl_2):S96–102.

36. Wilder-Smith A, Hombach J, Ferguson N, Selgelid M, O'Brien K, Vannice K, et al. Deliberations of the Strategic Advisory Group of Experts on Immunization on the use of CYD-TDV dengue vaccine. Lancet Infect Dis. 2019 Jan;19(1):e31–8.

37. Diamond MS, Pierson TC. Molecular Insight into Dengue Virus Pathogenesis and Its Implications for Disease Control. Cell. 2015 Jul 30;162(3):488–92.

38. Muller DA, Depelsenaire ACI, Young PR. Clinical and Laboratory Diagnosis of Dengue Virus Infection. J Infect Dis. 2017 Mar 15;215(suppl_2):S89–95.

39. Souza-Neto JA, Powell JR, Bonizzoni M. Aedes aegypti vector competence studies: A review. Infect Genet Evol. 2019 Apr;67:191–209.

40. Guy B, Barrere B, Malinowski C, Saville M, Teyssou R, Lang J. From research to phase III: preclinical, industrial and clinical development of the Sanofi Pasteur tetravalent dengue vaccine. Vaccine. 2011 Sep 23;29(42):7229–41.

41. Thomas SJ, Yoon IK. A review of Dengvaxia®: development to deployment. Hum VaccinImmunother. 2019;15(10):2295–314.

42. Rivera L, Biswal S, Sáez-Llorens X, Reynales H, López-Medina E, Borja-Tabora C, et al. Three-year Efficacy and Safety of Takeda's Dengue Vaccine Candidate (TAK-003). Clin Infect Dis. 2022 Sep 30;75(1):107–17.

43. Durbin AP, Kirkpatrick BD, Pierce KK, Schmidt AC, Whitehead SS. Development and clinical evaluation of multiple investigational monovalent DENV vaccines to identify components for inclusion in a live attenuated tetravalent DENV vaccine. Vaccine. 2011 Nov 3;29(42):7242–50.

44. Lopez AL, Daili R, A. RM. A tetravalent purified inactivated dengue virus vaccine: current status and future perspectives. Expert Rev Vaccines. 2021 Apr;20(4):405–14.

45. Lam PK, Tam DTH, Diet TV, Tam CT, Tien NTH, Kieu NTT, et al. Clinical characteristics of dengue shock syndrome in Vietnamese children: a 10-year prospective study in a single hospital. Clin Infect Dis. 2013 Nov;57(11):1577–86.

46. Marques N, Rocha B, R. LS. Recent advances in the management of dengue shock syndrome: a narrative review. Rev Inst Med Trop Sao Paulo. 2021;63:e69.

47. Trung DT, Wills B. Systemic vascular leakage associated with dengue infections - the clinical perspective. Curr Top Microbiol Immunol. 2010;338:57–66.

48. Yacoub S, Wertheim H, Simmons CP, Screaton G, Wills B. Cardiovascular manifestations of the emerging dengue pandemic. Nat Rev Cardiol. 2014 Jun;11(6):335–45.

49. Rothman AL. Immunity to dengue virus: a tale of original antigenic sin and tropical cytokine storms. Nat Rev Immunol. 2011 Aug 19;11(8):532–43.

50. Whitehead SS, Blaney JE, Durbin AP, Murphy BR. Prospects for a dengue virus vaccine. Nat Rev Microbiol. 2007 Jul;5(7):518–28.

51. Halstead SB. Dengue. Lancet. 2007 Nov 10;370(9599):1644–52.

52. Screaton G, Mongkolsapaya J, Yacoub S, Roberts C. New insights into the immunopathology and control of dengue virus infection. Nat Rev Immunol. 2015 Dec;15(12):745–59.

53. Harris E, Videa E, Pérez L, Sandoval E, Téllez Y, Pérez ML, et al. Clinical, epidemiologic, and virologic features of dengue in the 1998 epidemic in Nicaragua. Am J Trop Med Hyg. 2000 Aug;63(1-2):5–11.

54. Simmons CP, McPherson K, Van Vinh Chau N, Hoai Tam DT, Young P, Mackenzie J, et al. Recent advances in dengue pathogenesis and clinical management. Vaccine. 2015 Jun 19;33(29):3361–6.

55. Murray NEA, Quam MB, Wilder-Smith A. Epidemiology of dengue: past, present and future prospects. Clin Epidemiol. 2013;5:299–309.

56. Stanaway JD, Shepard DS, Undurraga EA, Halasa YA, Coffeng LE, Brady OJ, et al. The global burden of dengue: an analysis from the Global Burden of Disease Study 2013. Lancet Infect Dis. 2016 Jun;16(6):712–23.

57. Gubler DJ. Dengue, urbanization and globalization: the unholy trinity of the 21st century. Trop Med Health. 2011;39(4 Suppl):3–11.

58. Guzman MG, Harris E. Dengue. Lancet. 2015 Jan 31;385(9966):453–65.