SM Virology

Mini Review

Advancements in Dengue Fever Research: Epidemiology, Diagnostic Approaches, and Surveillance Strategies

Ramsha Haroon[1*] and Yusra Zarlashat[2]

[1]Gomal Center of Biotechnology and Biochemistry (GCBB), Gomal University, Dera Ismail Khan, Pakistan

[2]Department of Biochemistry, Government College University Faisalabad, Faisalabad, Pakistan

Abstract

Dengue fever, a significant mosquito-borne viral disease, presents a global health challenge with an estimated 400 million infections annually. Primarily transmitted by Aedes mosquitoes, dengue is prevalent in tropical and subtropical regions, affecting approximately 2.5 to 3 billion people. This review comprehensively examines the multifaceted aspects of dengue fever, including its epidemiology, vectors, transmission dynamics, and clinical manifestations. It emphasizes the critical role of early and accurate diagnosis, evaluating various methods such as virus isolation, NS1 antigen detection, antibody assays, and molecular diagnostics like RT-PCR. The review also explores the complexities of dengue surveillance systems passive, active, sentinel, and laboratory-based and their integration with entomological data to enhance outbreak detection and response. Furthermore, it discusses vector control strategies, including the elimination of breeding sites, monitoring mosquito populations, and community engagement. By synthesizing current knowledge and identifying gaps, this review aims to provide a comprehensive understanding of dengue fever and propose future directions for improving diagnosis, surveillance, and control measures.Keywords: HIV; HBV; HCV ; Chemiluminescence ; Transfusion safety.

Keywords: Dengue fever; Aedes mosquitoes; DENV serotypes; Vector control; Tropical diseases

INTRODUCTION

Dengue fever (DF) is a significant mosquito-borne viral disease caused by one of four serotypes of the dengue virus (DENV-1 to DENV-4), which belong to the Flavivirus genus. It predominantly affects tropical and subtropical regions, with an estimated 2.5 to 3 billion people living in areas at risk of transmission. The disease is transmitted primarily by female mosquitoes of the Aedes genus, particularly Aedes aegypti and Aedes albopictus [1]. The global incidence of dengue has risen sharply since the late 20th century, with approximately 400 million infections reported annually, though many cases remain asymptomatic. The World Health Organization (WHO) has identified dengue as one of the top ten global health threats, particularly in Asia and Latin America, where it is a leading cause of hospitalization and death among children [2].

The disease's pathophysiology involves the immune response to the dengue virus. Initial infection with one serotype provides lifelong immunity to that specific strain but only partial immunity to others, allowing for the possibility of reinfection. This reinfection can lead to more severe forms of the disease due to a phenomenon known as Antibody-Dependent Enhancement (ADE), where pre-existing antibodies facilitate viral entry into cells, exacerbating the immune response [3]. The aim of this review is to evaluate and improve current strategies for diagnosing, surveilling, and controlling dengue fever. Specifically, it seeks to assess the effectiveness and limitations of existing diagnostic techniques and propose potential enhancements. The review also aims to evaluate various surveillance strategies and their integration to enhance outbreak detection and response. Additionally, it will explore current vector control measures and recommend new approaches to improve their efficacy, while also identifying key factors influencing dengue spread to guide targeted interventions and future research directions.

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THE DENGUE VIRUS: SEROTYPES AND TRANSMISSION

DENV is a significant global health concern, with four distinct serotypes identified: DENV-1, DENV-2, DENV-3, and DENV-4. Each serotype is categorized based on antigenic and genetic differences, and they co-circulate in endemic regions, primarily in tropical and subtropical areas where the primary vector, the Aedes aegypti mosquito, thrives. DENV-1, DENV-2, DENV-3, DENV-4, these serotypes are closely related but differ in their antigenic properties. Infection with one serotype provides lifelong immunity against that specific strain but only partial immunity to the others. This partial immunity can lead to increased severity upon subsequent infections with different serotypes due to a phenomenon known as ADE (Figure 1) [4].

The transmission cycle involves several key steps.

Mosquito feeding

After a female mosquito feeds on a person infected with dengue, the virus replicates within the mosquito over a period of 1 to 2 weeks (extrinsic incubation period) before it can transmit the virus to another human during subsequent feedings [5].

Breeding habits

Aedes aegypti mosquitoes are highly adapted to urban environments, breeding in stagnant water found in containers, discarded tires, and other water-holding objects around human dwellings. They are most active during the early morning and late afternoon [5].

Human-mosquito interaction

Dengue cases often cluster in households due to the close relationship between humans and mosquitoes. The movement of infected individuals and mosquitoes can rapidly spread the virus within communities [4].

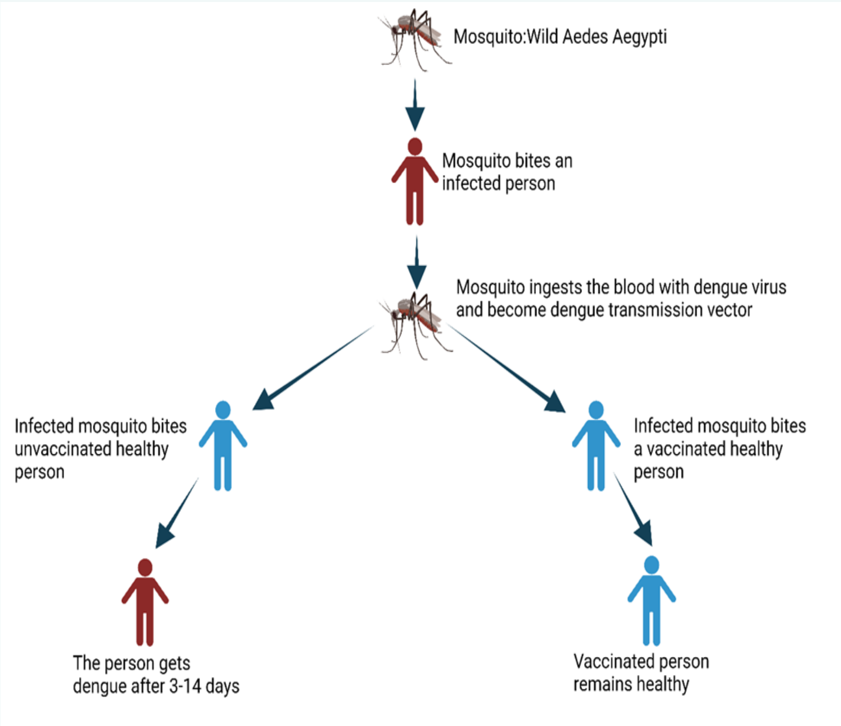

Figure 1: Dengue is primarily transmitted through the bites of infected Aedes mosquitoes, particularly Aedes aegypti and Aedes albopictus. When a mosquito bites an infected person and ingests the blood containing dengue virus then it itself becomes a transmission vector. When it bites a vaccinated healthy person it remains healthy but when it bites an unvaccinated individual gets dengue after 3;14 days.

Dengue transmission is influenced by climatic conditions. In tropical regions, transmission can occur year-round but tends to intensify during the rainy season when mosquito populations increase due to higher humidity and favorable breeding conditions. Areas with hyperendemic transmission can see infection rates ranging from 5% to 10% in the population [6].

VECTORS OF DENGUE FEVER

DF is primarily transmitted by mosquitoes of the Aedes genus. Aedes aegypti and Aedes albopictus are two primary vectors. Aedes aegypti, commonly known as the yellow fever mosquito, is a small mosquito, approximately 3-5 mm in size, characterized by its black body and white markings on its legs and thorax [7]. This species is the principal vector for dengue virus transmission. It prefers to feed on humans and is active during the daytime, making it a significant threat in urban areas where human populations are dense. The mosquito can breed in small amounts of stagnant water, which are often found in urban settings, such as flower pots, discarded tires, and containers [8]. Aedes aegypti can take multiple blood meals before laying eggs, and once infected, it can transmit the virus through its saliva during subsequent feedings. The virus can persist in the mosquito's salivary glands, allowing for effective transmission to humans [9].

Aedes albopictus also known as the Asian tiger mosquito, Aedes albopictus is another important vector for dengue. It has similar physical characteristics to Aedes aegypti but is generally more adaptable to different environments [10]. While Aedes albopictus is considered a secondary vector, it has been responsible for dengue outbreaks in various regions, including Japan, Malaysia, and Hawaii. Its vectorial capacity for dengue is lower than that of Aedes aegypti, but it can still contribute to the spread of the virus, especially in areas where both species coexist [8].

Controlling the populations of these mosquitoes is challenging due to their adaptability and the urban environments they inhabit. Traditional methods, such as insecticides, can be difficult to implement effectively in densely populated areas. Moreover, the ability of Aedes aegypti to breed in small water collections complicates eradication efforts [11].

Effective vector control strategies

Eliminating breeding sites: Regularly removing stagnant water sources where mosquitoes can breed [12].

Monitoring and surveillance: Implementing mosquito traps and ovitraps to monitor mosquito populations and dynamics [13].

Community engagement: Educating communities about the importance of mosquito control and encouraging participation in local vector control initiatives [12].

FACTORS CONTRIBUTING TO DENGUE FEVER SPREAD

Dengue fever is a mosquito-borne viral infection that poses a significant public health challenge, particularly in tropical and subtropical regions. Understanding the factors contributing to its spread is crucial for effective prevention and control measures.

Dengue is primarily transmitted by Aedes mosquitoes, particularly Aedes aegypti and Aedes albopictus. These mosquitoes thrive in urban environments and are known for their preference to bite humans. They can breed in small amounts of stagnant water, which makes common household items like flower pots, buckets, and discarded tires ideal breeding grounds [14].

Environmental conditions

The climate plays a critical role in the proliferation of dengue. Warm temperatures and high humidity levels create favorable conditions for mosquito breeding. Rainy seasons often lead to increased mosquito populations due to the accumulation of standing water, which serves as breeding sites. Studies have shown that stagnant water around homes significantly increases the risk of dengue outbreaks [15].

Urbanization

Rapid urbanization contributes to the spread of dengue by creating densely populated areas where mosquitoes can easily transmit the virus among humans. Poor infrastructure and inadequate waste management can lead to the accumulation of stagnant water, enhancing mosquito breeding opportunities [16].

Human behavior

Human activities, such as travel to endemic areas and inadequate preventive measures (like not using mosquito repellents or protective clothing), increase the risk of infection. Individuals who have previously contracted dengue are at a higher risk of developing severe forms of the disease upon subsequent infections with different virus serotypes [17].

Socioeconomic factors

Socioeconomic conditions affect the ability of communities to implement effective mosquito control measures. Areas with lower socioeconomic status may have limited access to resources for mosquito control, such as insecticides and education on preventive practices, which can exacerbate the spread of dengue [18].

Public health infrastructure

The effectiveness of public health responses, including surveillance, vector control programs, and community education, plays a vital role in managing dengue outbreaks. Regions with robust health systems are better equipped to respond to and mitigate the impacts of dengue fever [19].

Immunity and previous infections

Individuals who have had dengue fever previously may develop severe symptoms if infected again with a different serotype due to a phenomenon known as antibody-dependent enhancement. This complicates the epidemiology of dengue, as previous infections can lead to more severe outcomes upon re-exposure [20].

CLINICAL MANIFESTATIONS AND DISEASE SEVERITY

Dengue is suspected when there is a high temperature (40°C) and the following symptoms: severe headache, joint and muscle pain, swollen glands, nausea, pain behind the eyes, and vomiting [21]. Dengue symptoms typically begin 4 to 10 days after being bitten by an infected mosquito and can last for 2 to 7 days. The most common symptoms include high fever (up to 40°C or 104°F), severe headache, pain behind the eyes, muscle and joint pain, nausea, vomiting, rash, and swollen glands [22]. While most individuals experience mild symptoms, and many may remain asymptomatic, about 20% of those infected develop more severe manifestations. Severe dengue, also known as dengue hemorrhagic fever or dengue shock syndrome, is a life-threatening condition that can arise rapidly. It is characterized by severe abdominal pain, persistent vomiting, bleeding from gums or nose, blood in vomit or stools, rapid breathing, fatigue, restlessness, cold or clammy skin, weakness, and extreme thirst [15]. Severe dengue often occurs after the fever has subsided, typically within the first 24 to 48 hours, a critical phase that can lead to shock, internal bleeding, organ failure, and even death if not promptly treated. The risk of developing severe dengue increases with a second infection by a different serotype of the dengue virus. This phenomenon, known as antibody-dependent enhancement, occurs when pre-existing antibodies from a previous infection facilitate a more severe response to a new strain of the virus [23].

LIFE CYCLE OF AEDES MOSQUITOES

Female mosquitoes lay eggs on moist surfaces, often above the waterline in containers like tires, flower pots, and other artificial reservoirs. Each female can lay approximately 100 eggs per batch and may do this up to three times in her lifetime, totaling around 300 eggs [24]. The eggs can withstand dry conditions for several months and can remain viable until they are submerged in water, which triggers hatching [25].

After the eggs are covered with water, they hatch into larvae within a few days to weeks, depending on environmental conditions [26]. The larvae go through four instars (developmental stages) over about 6 to 8 days, during which they hang just below the water's surface and breathe through a respiratory siphon [25]. After completing the larval stages, the larvae transform into pupae. This stage lasts about 1 to 2 days, during which the pupae are inactive and do not feed [27].

Adult mosquitoes emerge from the pupae and typically mate within two days. Males feed on nectar, while females require blood meals to develop their eggs. The average lifespan of an adult Aedes mosquito is about two weeks, although some may live longer under optimal conditions [28].

EPIDEMIOLOGY OF DENGUE FEVER

Dengue is the most rapidly spreading mosquito-borne viral disease, with approximately 400 million infections occurring annually. An estimated 100 million cases present clinically, leading to about 22,000 deaths each year globally [29]. The disease is endemic in over 100 countries, primarily in tropical and subtropical regions. Approximately 2.5 to 3 billion people live in areas at risk of dengue transmission, with the Americas, Southeast Asia, and the Western Pacific being the most affected regions. The disease has also expanded into rural areas and new geographic locations, including parts of Europe [30].

The incidence of dengue has increased 30-fold over the last 50 years, attributed to factors such as urbanization, climate change, and globalization, which have expanded the habitat of Aedes mosquitoes. Dengue exhibits seasonal patterns, with outbreaks often peaking during the rainy season when mosquito breeding sites are abundant [31]. In the Southern Hemisphere, cases typically rise in the first half of the year, while in the Northern Hemisphere, peaks occur later. International travel plays a crucial role in the epidemiology of dengue, as viraemic travelers can introduce various dengue serotypes into non-endemic areas, prompting outbreaks. Surveillance systems help monitor these trends and provide early warnings of potential epidemics [32].

DIAGNOSIS AND SURVEILLANCE

Diagnosing dengue fever can be challenging due to its symptoms being similar to those of other viral illnesses such as chikungunya, Zika, and malaria. A combination of clinical symptoms, travel history, and laboratory tests is typically used for diagnosis. Clinically, dengue is suspected in patients presenting with sudden high fever (up to 40°C or 104°F), severe headache, pain behind the eyes, muscle and joint pain, nausea, vomiting, rash, and swollen glands. These symptoms, while indicative, are not exclusive to dengue, necessitating laboratory confirmation for an accurate diagnosis.

Laboratory diagnosis involves several methods. Virus isolation, though complex and time-consuming, can detect the dengue virus from blood samples during the early febrile phase, up to 5 days after symptom onset. NS1 antigen detection is a more rapid test that identifies the dengue virus early, even before the appearance of antibodies, and provides results within a few hours. Antibody detection is another crucial method: IgM antibodies become detectable in about 50% of patients by days 3-5 after onset, reaching 80% by day 5 and 99% by day 10. IgM levels peak around two weeks and then decline over 2-3 months. In contrast, IgG antibodies appear later, at low levels by the end of the first week, and persist for life, offering lifelong immunity to that serotype. The IgM/IgG ratio can also help differentiate between primary and secondary infections. Molecular diagnosis, particularly RT-PCR, can detect viral RNA in the early febrile phase, delivering results within 24-48 hours, though it requires specialized equipment and expertise.

Effective dengue surveillance is critical for monitoring disease trends, detecting outbreaks, and guiding prevention and control efforts. Passive surveillance involves the reporting of suspected and confirmed dengue cases by healthcare facilities to public health authorities and is the most common method. Active surveillance entails regular visits by surveillance teams to healthcare facilities to actively search for dengue cases, providing more comprehensive data but requiring more resources. Sentinel surveillance focuses on selected healthcare facilities that act as sentinels to monitor disease trends, offering representative data at a lower cost. Laboratory surveillance monitors laboratory-confirmed cases to determine circulating serotypes and identify outbreaks, necessitating a network of diagnostic laboratories. Additionally, entomological surveillance monitors Aedes mosquito populations to assess the risk of transmission, including larval and adult mosquito surveys. Integrating clinical, laboratory, and entomological data is essential for comprehensive dengue surveillance. Timely reporting and data sharing among stakeholders enable the early detection of outbreaks and inform evidence-based prevention and control strategies.

The main limitations include limited access to proficient testing regions with limited resources, the chance of antibody dependent enhancement (ADE), symptom overlap with other diseases in people who have been already infected with different dengue serotypes. Gaps in surveillance systems, climate change as well as globalization creates hurdles for the control and prevention of this outbreak. In addition to we are also facing certain problems such as vector control like insecticide resistance and removing of breeding habitat.

CONCLUSIONS AND FUTURE DIRECTIONS

Dengue fever remains a critical global health issue, particularly in tropical and subtropical regions where the Aedes mosquitoes thrive. The rapid rise in incidence over recent decades underscores the need for ongoing vigilance and effective management strategies. The disease, caused by one of four dengue virus serotypes, presents a complex challenge due to the potential for severe manifestations upon reinfection and the similarities in symptoms with other viral illnesses. Effective diagnosis combines clinical presentation with laboratory tests such as NS1 antigen detection and serological assays, alongside molecular techniques like RT-PCR. Surveillance plays a crucial role in monitoring disease trends, detecting outbreaks, and guiding public health responses. A multi-faceted approach involving passive, active, and sentinel surveillance, coupled with laboratory and entomological monitoring, is essential for a comprehensive understanding of dengue dynamics. Vector control remains a cornerstone of dengue prevention. Strategies such as eliminating breeding sites, monitoring mosquito populations, and engaging communities are vital for reducing transmission. Environmental factors, urbanization, human behavior, and socioeconomic conditions significantly influence the spread of dengue and complicate control efforts. Future directions should focus on enhancing surveillance systems and integrating new technologies to improve early detection and response. Innovations in vector control, including biological and genetic interventions, could offer new solutions to mitigate mosquito populations. Additionally, increased emphasis on community education and engagement will be crucial in fostering effective prevention practices and reducing the burden of dengue fever globally. Continued research and international collaboration are essential to address the evolving challenges posed by this significant public health threat. Future research should focus on developing more accurate and rapid diagnostic tools, enhancing vector control programs through innovative technologies, and improving the integration of entomological and epidemiological data to strengthen dengue surveillance systems.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTION STATEMENT

RH; collected data, drafted initial manuscript, and designed figure, YZ; reviewed, and revised.

REFERENCES

1. Heilman JM, De Wolff J, Beards GM, Basden BJ. Dengue fever: A wikipedia clinical review. Open Med. 2014; 8: e105-115.
2. Kothai R, Arul B. Dengue fever: An overview. Dengue Fever. 2020.
3. Khan MB, Yang ZS, Lin CY, Hsu MC, Urbina AN, Assavalapsakul W, et al. Dengue overview: An updated systemic review. J Infect Public Health. 2023; 16: 1625-1642.
4. Mangam VT, Nallam VR, Anitha A, Rama Devi P, Sanisha M. Dengue-An overview. International Journal of Pharma Research, 2018; 9.
5. Muthuraman KR, Utomo DIS, Matsuda M, Suzuki R, Park EY. Expression of dengue capsid-like particles in silkworm and display of envelope domain III of dengue virus serotype 2. Protein Expr Purif. 2024; 222: 106543.
6. Maisnam D, Billoria A, Prasad VSV, Venkataramana M. Association of dengue virus serotypes 1&2 with severe dengue having deletions in their 3′ untranslated regions (3′ UTRs). Microorganisms. 2023; 11: 666.
7. Gan SJ, Leong YQ, Barhanuddin MFHB, Wong ST, Wong SF, Mak JW, et al. Dengue fever and insecticide resistance in *Aedes* mosquitoes in Southeast Asia: A review. Parasites vectors. 2021; 14: 315.
8. Dom NC, Ahmad AH, Ishak AR, Ismail R. Assessing the risk of dengue fever based on the epidemiological, environmental and entomological variables. Procedia-Social Behavioral Sciences, 2013; 105; 183-194.
9. Man O, Kraay A, Thomas R, Trostle J, Lee GO, Robbins C, et al. Characterizing dengue transmission in rural areas: A systematic review. PLoS Negl Trop Dis. 2023; 17: e0011333.
10. Mubbashir H, Munir S, Kashif R, Nawaz HB, Abdul B, Baharullah K. Characterization of dengue virus in Aedes aegypti and aedes albopictus spp. of mosquitoes: A study in Khyber Pakhtunkhwa, Pakistan. Mol Biol Res Commun. 2018; 7: 77-82.
11. Lv RC, Zhu CQ, Wang CH, Ai LL, Lv H, Zhang B, et al Genetic diversity and population structure of Aedes aegypti after massive vector control for dengue fever prevention in Yunnan border areas. Scientific Reports. 2020; 10: 12731.
12. Diallo D, Diouf B, Gaye A, NDiaye EH, Sene NM, Dia I, et al. Dengue vectors in Africa: A review. Heliyon. 2022; 8: e09459.
13. Mwanyika GO, Mboera LEG, Rugarabamu S, Ngingo B, Sindato C, Lutwama JJ, et al. Dengue virus infection and associated risk factors in Africa: A systematic review and meta-analysis. Viruses. 2021; 13: 536.
14. Ferreira-de-Lima VH, Lima-Camara TN. Natural vertical transmission of dengue virus in aedes aegypti and aedes albopictus: A systematic review. Parasit Vectors. 2018; 11: 77.

15. Htun TP, Xiong Z, Pang J. Clinical signs and symptoms associated with WHO severe dengue classification: A systematic review and meta-analysis. Emerg Microbes Infect. 2021; 10: 1116-1128.

16. Mehmood A, Khalid Khan F, Chaudhry A, Hussain Z, Laghari MA, Shah I, et al. Risk factors associated with a dengue fever outbreak in Islamabad, Pakistan: Case-control study. JMIR Public Health Surveill. 2021; 7: e27266.

17. Kyle JL, Harris E. Global spread and persistence of dengue. Annu Rev Microbiol. 2008; 62: 71-92.

18. Khetarpal N, Khanna I. Dengue fever: Causes, complications, and vaccine strategies. J Immunol Res. 2016; 2016: 6803098.

19. Viennet E, Ritchie SA, Williams CR, Faddy HM, Harley D. Public health responses to and challenges for the control of dengue transmission in high-income countries: Four case studies. PLoS Negl Trop Dis. 2016; 10: e0004943.

20. Guzman MG, Harris E. Dengue. Lancet. 2015; 385: 453-465.

21. Peeling RW, Artsob H, Pelegrino JL, Buchy P, Cardosa MJ, Devi S, et al. Evaluation of diagnostic tests: Dengue. Nat Rev Microbiol. 2010; 8: S30-38.

22. Thomas S, Waltham MA. Dengue virus infection: Clinical manifestations and diagnosis. USA: UpToDate, 2018.

23. Guzman MG, Alvarez M, Halstead SB. 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. 2013; 158: 1445-1459.

24. Ridha MR, Marlinae L, Zubaidah T, Fadillah NA, Widjaja J, Rosadi D, et al. Control methods for invasive mosquitoes of Aedes aegypti and Aedes albopictus (Diptera: Culicidae) in Indonesia. Vet World. 2023; 16: 1952-1963.

25. Muttis E, Balsalobre A, Chuchuy A, Mangudo C, Ciota AT, Kramer LD, et al. Factors related to Aedes aegypti (Diptera: Culicidae) populations and temperature determine differences on life-history traits with regional implications in disease transmission. J Med Entomol. 2018; 55: 1105-1112.

26. Anoopkumar AN, Puthur S, Varghese P, Rebello S, Aneesh EM. Life cycle, bio-ecology and DNA barcoding of mosquitoes Aedes aegypti (Linnaeus) and Aedes albopictus (Skuse). Commun Dis, 2017; 49: 32-41.

27. Garzón MJ, Maffey L, Lizuain A, Soto D, Diaz PC, Leporace M, et al. Temperature and photoperiod effects on dormancy status and life cycle parameters in Aedes albopictus and Aedes aegypti from subtropical Argentina. Med Vet Entomol. 2021; 35: 97-105.

28. Hawkes FM, Hopkins RJ. The mosquito: An introduction. Mosquitopia, 2021; 16-31.

29. Roy SK, Bhattacharjee S. Dengue virus: Epidemiology, biology, and disease aetiology. Can J Microbiol. 2021; 67: 687-702.

30. Jayarajah U, Dissanayake U, Abeysuriya V, De Silva PK, Jayawardena P, Kulatunga A, et al. Comparing the 2009 and 1997 World Health Organization dengue case classifications in a large cohort of South Asian patients. J Infect Dev Ctries. 2020; 14: 781-787.

31. Zerfu B, Kassa T, Legesse M. Epidemiology, biology, pathogenesis, clinical manifestations, and diagnosis of dengue virus infection, and its trend in Ethiopia: A comprehensive literature review. Trop Med Health. 2023; 51: 11.

32. Zeng Z, Zhan J, Chen L, Chen H, Cheng S. Global, regional, and national dengue burden from 1990 to 2017: A systematic analysis based on the global burden of disease study 2017. EClinicalMedicine. 2021; 32: 100712.