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Dengue Fever and Novel Detection Methods Based on Biosensors

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A B S T R A C T

Dengue fever, a mosquito-borne viral infection, poses a significant global health threat, and early diagnosis is crucial for effective disease management. Human infection typically occurs through infected *Aedes* mosquitoes, such as *Aedes aegypti* or *Aedes albopictus*. The disease spectrum ranges from asymptomatic infection and mild febrile illness (dengue fever) to more severe conditions, such as dengue hemorrhagic fever and dengue shock syndrome. Dengue fever is characterized by severe headache, high fever, skin rash, muscle and joint pain, nausea, and vomiting. Dengue hemorrhagic fever is marked by high fever, an enlarged liver, hemorrhagic phenomena, shock, and often cardiovascular disorders. Dengue fever is transmitted through urban (human transmission cycle) and sylvatic (animal transmission cycle) cycles. The demand for early detection of this virus has increased to control the spread of infectious diseases and protect humankind from its harmful effects. Various methods can be employed for the laboratory diagnosis of this virus to detect the virus itself, viral nucleic acids, antibodies, or antigens, or a combination of these approaches. Recently, biosensors have emerged as a potential tool for detecting and quantifying viruses, offering fast detection, relative cost-effectiveness, and high sensitivity and selectivity compared to conventional diagnostic methods such as immunological and molecular techniques. Most biosensors employ electrochemical detection techniques with transducers, owing to their easy construction, low cost, ease of use, and portability.

Keywords: *Dengue Fever, Aedes Mosquito, Clinical Symptoms, Diagnosis, Electrochemical Biosensor, Viral Disease.*

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1 Introduction

Arboviruses (arthropod-borne viruses) are a diverse group of viruses that exhibit a unique mode of transmission between arthropod vectors and vertebrate hosts. They are classified based on antigenic relationships, morphology, and replication mechanisms (1). Viral families that include arboviruses are *Togaviridae, Flaviviridae, Bunyaviridae, Rhabdoviridae, Orthomyxoviridae, and Reoviridae.* Five human epidemic arboviruses have emerged in both hemispheres in recent decades: dengue virus, Zika virus, West Nile virus, yellow fever virus, and chikungunya virus. The first four viruses belong to the genus *Flavivirus*, while the chikungunya virus belongs to the genus *Alphavirus*. Among these viruses, dengue, chikungunya, and Zika are the most significant epidemiologically. It is estimated that approximately 3.9 billion people living in over 120 countries are at risk of infection with one of these three major arboviruses (2).

Dengue fever is a debilitating disease caused by mosquito bites, with a spectrum of symptoms ranging from asymptomatic infection to severe infection with multi-organ dysfunction. The term "dengue" is derived from the Swahili phrase "Ka-Dinga Pepo," meaning "cramp-like seizure." The first clinically recognized dengue epidemics occurred almost simultaneously in Asia, Africa, and North America in the 1780s. In 1787, Benjamin Rush coined the term "break-bone fever" for this disease due to reports of muscle and joint pain during the 1780 Philadelphia epidemic (3).

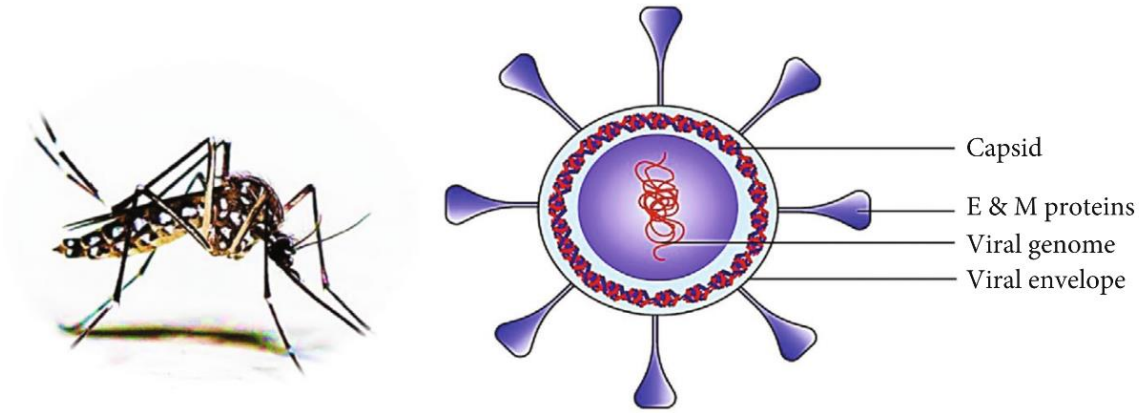

Figure 1. A schematic diagram of a spherical dengue virus enveloped by various structural proteins and an *Aedes* mosquito (4). (Source: https://onlinelibrary.wiley.com/doi/10.1155/2021/4224816).

The spectrum of the disease varies from asymptomatic infection and mild febrile illness (dengue) to more severe manifestations such as dengue hemorrhagic fever and dengue shock syndrome. Until 2008, dengue was classified into dengue, dengue hemorrhagic fever, and dengue shock syndrome based on the World Health Organization's (WHO) 1997 classification criteria. In 2009, the WHO revised the case classification system, categorizing symptomatic cases into dengue without warning signs, dengue with warning signs, and severe dengue. Dengue hemorrhagic fever, resulting from multiple dengue virus infections, was first proposed for patients in the Philippines in 1956 (5).

The transmission of the dengue virus likely originated from sylvatic cycles involving susceptible non-human primates and *Aedes* mosquitoes in Asian forests. Sylvatic transmission cycles have also been described in African forests, but there is no evidence for such cycles in the Americas. Sylvatic dengue virus transmission can occur in rural and urban areas as emerging areas. Due to the adaptation of the sylvatic virus to human hosts and previous instances of severe clinical manifestations, this virus has the potential to sustain natural horizontal transmission between humans through *Aedes aegypti* and *Aedes albopictus* mosquitoes. Humans are the primary reservoir hosts for maintaining urban dengue epidemic cycles. Although it is generally believed that non-human animal reservoir hosts exist for *Aedes* mosquito-borne flaviviruses like Zika virus and yellow fever virus, there is insufficient evidence to support this for urban dengue transmission. Zika virus was initially discovered in a monkey in Uganda. In South America, non-human primates, such as monkeys, are recognized as reservoirs for the yellow fever virus due to their high susceptibility. Among the non-human mammals involved with the dengue fever virus, monkeys and orangutans are notable. (6).

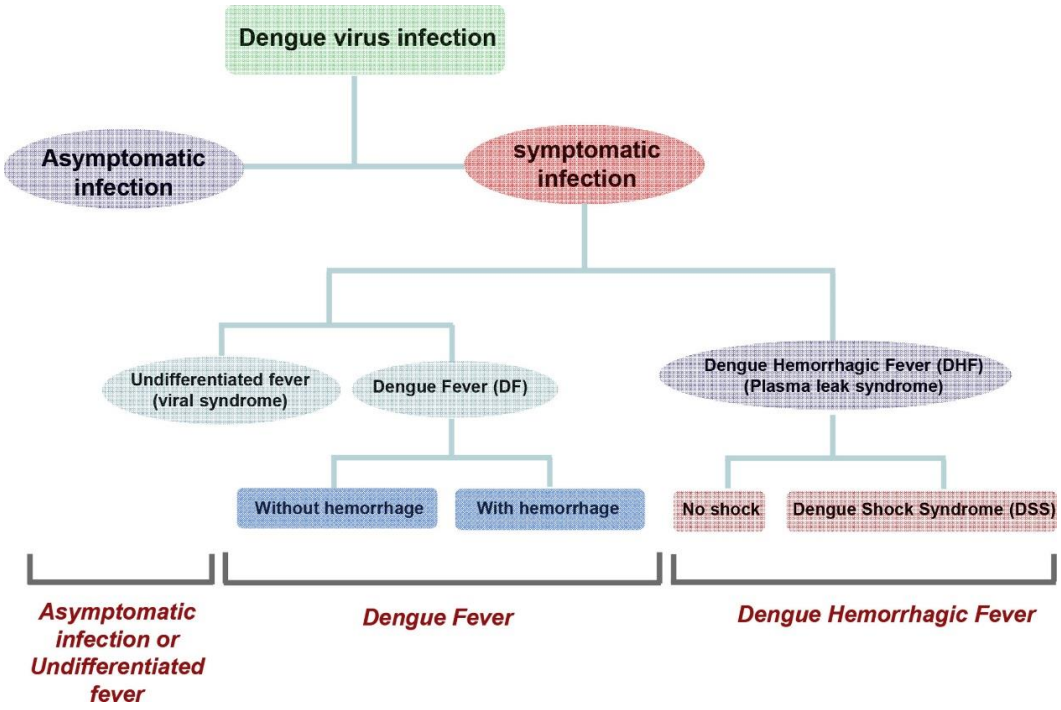

Figure 2. Flowchart of dengue fever infection classification and clinical symptoms (5). (Source: https://www.sciencedirect.com/science/article/pii/S1684118220300670).

Gwee et al. (2021) introduced a meta-analysis method to detect dengue positivity in various animals: bats (10.1%), non-human primates (27.3%), birds (11%), cattle (4.1%), dogs (1.6%), horses (5.1%), pigs (34.1%), rodents (3.5%), kangaroos (13%), and other small animals (7.3%). Most serologically positive dengue fever cases indicate potential enzootic transmission. Acute infection is rare among animals, except for bats. Further research is needed to understand the role of animals as potential reservoirs in dengue transmission (7). Aldana et al. (2021) developed a meta-analysis method to report the presence of dengue fever in various animals based on serological methods: bats (10%), primates (29%), birds (8%), sheep (1%), horses (11%), cows (0%), pigs (49%), rodents (2%), and buffaloes (7%). According to molecular methods, bats had a seroprevalence of 6%. This study confirms the presence of the dengue virus in a wide range of animal species, suggesting potential implications as possible reservoirs and increasing the likelihood of zoonotic transmission (8).

Dengue infection is a major public health problem reported in the Americas, Africa, Southeast Asia, Europe, the Western Pacific, and the Eastern Mediterranean regions. This arboviral disease is endemic in more than 100 countries, with about 390 million people infected, exhibiting varying symptoms. Approximately 70% of infections occur in Asia. Although previously limited to tropical or subtropical regions, dengue has now spread to Mediterranean climates. It is a significant cause of economic burden, particularly in Southeast Asia and the Indian subcontinent. The World Health Organization estimates that around 2.5 billion people currently live in dengue-affected areas (9). In 2015, 3.8 billion people were at risk, with projections indicating this number could exceed 6.1 billion by 2080, mainly due to population growth in endemic areas. As of April 30, 2024, over 7.6 million dengue cases have been reported to the World Health Organization, including 3.4 million confirmed cases, more than 16,000 severe cases, and over 3,000 deaths (10). Chen et al. (20204) at Harvard University used a macroeconomic model to calculate the economic burden of dengue in 141 countries and regions. The study estimated that dengue fever would cost the global economy $306 billion (INT$, at constant 2017 prices) between 2020 and 2050 (11).

2 Structure of the Dengue Virus

The dengue virus is responsible for a wide range of dengue fever diseases worldwide and has four major serotypes: DENV-1, DENV-2, DENV-3, and DENV-4. A fifth serotype (DENV-5) was identified through isolation and genetic sequence analysis in Sarawak, Malaysia, in October 2013. The mature dengue virus, characterized by a smooth surface, is approximately 50 nm in diameter, while

the immature virus has a prickly surface and a diameter of 60 nm. This virus is a positive single-stranded RNA virus with a capsular coat. It contains three structural proteins encoded by the virus: nucleocapsid or core protein (C), membrane-associated protein (M), and envelope glycoprotein (E), along with seven non-structural proteins (NS). The structural proteins are components of the dengue virus, while the non-structural proteins are involved in RNA replication (12).

The nucleocapsid protein is a 120 kDa homodimeric protein composed of 100 amino acids, including 26 basic amino acids and 3 acidic amino acids. Protein C is essential for nucleocapsid formation in the early stages of dengue virus assembly, while protein M plays a crucial role in the organization and maturation of the dengue virus particle (13). Protein E consists of three domains (domains I to III), with domain III responsible for receptor binding activity. Protein E is essential for virus attachment and fusion with the host cell membrane. NS1 is a 45 kDa N-linked glycoprotein involved in the RNA replication complex. NS2A is an approximately 22 kDa protein also involved in the replication complex, while NS2B is a 14 kDa membrane-associated protein. Another NS protein, NS3 (618 amino acids), possesses multiple enzymatic functions, such as RNA helicase and RTPase/NTPase activity. NS4A and NS4B, with molecular weights of 16 kDa and 27 kDa, respectively, are integral membrane proteins that induce membrane alterations important for dengue virus replication. Protein NS5 (104 kDa) is the dengue virus methyltransferase-polymerase and has RNA-dependent RNA polymerase activity (14).

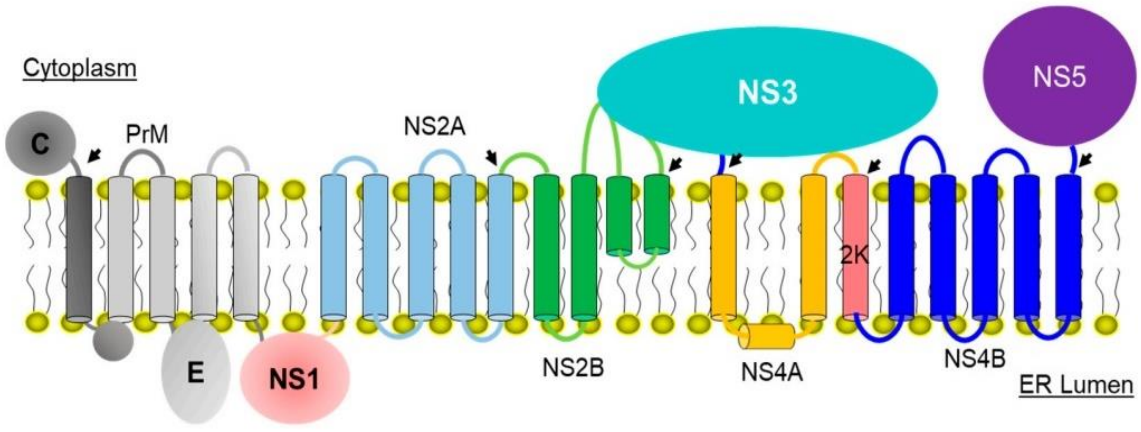

Figure 3. Organization and topology of the membrane proteins of dengue fever (12). **(Source: https://www.mdpi.com/2077-0375/12/2/231).**

3 Life cycle of dengue virus

Humans are typically infected with the dengue fever virus through the bites of infected *Aedes* mosquitoes, such as *Aedes aegypti* or *Aedes albopictus*. Dengue virus targets dendritic cells (DCs) and macrophages on the first day of infection. The virus's life cycle encompasses several processes: viral entry and attachment, fusion of the viral membrane and endosome, nucleocapsid release, protein synthesis and processing, RNA replication, nucleocapsid formation, viral assembly, viral maturation, and finally, the release of mature dengue virus particles. To attach to the host cell, the dengue virus E protein interacts with cellular factors on the target cell, such as dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin (DC-SIGN), mannose receptor, heparan sulfate, and others. Subsequently, the dengue virus enters the target cell through clathrin-dependent endocytosis. The low pH in the endosomal compartment facilitates fusion between the dengue virus and the endosomal membrane. This acidic environment aids in releasing the RNA genome from the nucleocapsid into the cytoplasm, where it undergoes protein processing and replication. Initially, the RNA genome functions as mRNA and is translated to produce viral proteins (4).

RNA genome replication occurs within a virus-induced intracellular membrane-associated replication complex composed of viral RNA, viral proteins, and host cell factors. This complex, formed on the endoplasmic reticulum membrane, also helps to protect replication products from recognition by the host's innate immune system. After

nucleocapsid formation, the dengue virus particle begins to assemble, budding as an immature dengue virus particle into the lumen of the endoplasmic reticulum. During the secretion pathway within the trans-Golgi network (TGN), the maturation of the dengue virus requires the cleavage of pre-membrane/membrane (prM/M) to M protein by the action of furin-like serine proteases resulting in the virus being in its mature and infectious form. To prevent the premature fusion of the DENV membrane with the host cell before the viral particle is released from the infected cell, the pr peptide encloses the hydrophobic fusion loop by continuing to bind with the E dimers after cleavage. Finally, the pr peptide detaches from the surface of the viral particles once the mature DENV is released into the extracellular space (15).

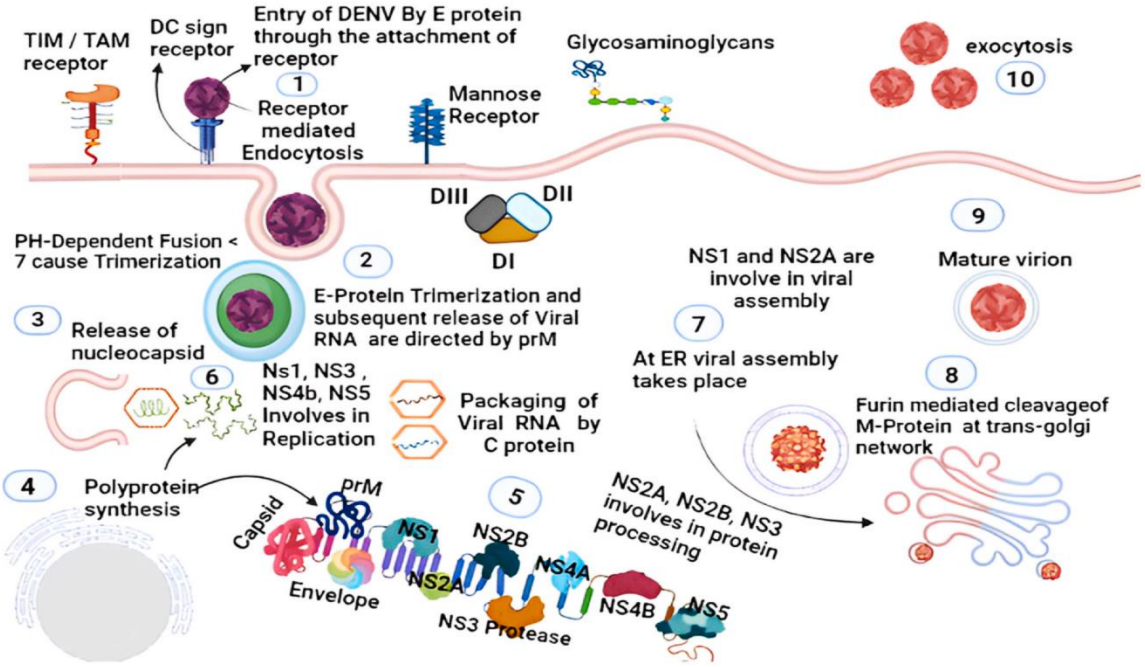

Figure 4. The life cycle of the dengue virus involves several steps for infection and replication in host cells, including attachment, receptor-dependent endocytosis, non-enveloped virus, viral protein production, viral RNA replication, virus assembly, and release (16). **(Source: https://www.sciencedirect.com/science/article/pii/S1876034123002587).**

4 Dengue virus transmission

Dengue is transmitted through two cycles: the urban (human transmission) cycle and the sylvatic (animal transmission) cycle. These cycles differ both ecologically and evolutionarily. The urban transmission cycle occurs in 128 countries, primarily involving *Aedes aegypti* and *Aedes albopictus* mosquitoes as vectors. In contrast, the sylvatic transmission cycle takes place in the sylvatic environments of Southeast Asia and West Africa, with *Aedes luteocephalus*, *Aedes furcifer*, and *Aedes taylori* mosquitoes as the main vectors. *Aedes aegypti* was introduced to the Americas during the slave trade in the 1600s and spread around the world with the expansion of the shipping industry. In urban environments, dengue transmission occurs between humans, while in sylvatic areas, transmission occurs between non-human primates with occasional transmission to human populations. Transovarial transmission (vertical transmission of dengue from female mosquitoes to their eggs) is essential for maintaining both human and sylvatic transmission cycles during dry seasons or periods between epidemics. Therefore, eradicating dengue is challenging due to the complexity of its transmission. Non-vector transmission routes, such as blood transfusion, bone marrow transplantation, and intrauterine and perinatal transmission, have also been reported (17).

Aedes mosquitoes live in close proximity to humans, feeding on their blood, resting in their homes, and laying eggs in artificial water containers. The average lifespan of a female mosquito is about one week, though some can live for up to two weeks or longer. Female mosquitoes become infected when they take a blood meal from a person during the acute febrile phase of the disease. During the extrinsic incubation period, the virus initially infects the midgut cells, then replicates in various tissues of the mosquito, and

ultimately infects the salivary glands within 5 to 12 days (typically 8 to 10 days). This process is influenced by environmental temperature, virus type, and mosquito competence. Once the salivary glands are infected, the mosquito becomes capable of transmitting the virus to another individual during subsequent blood meals. The mosquito remains infected for life and can transmit the virus to any person it bites or attempts to bite. The time between infection and the onset of disease in humans (intrinsic incubation period) ranges from 3 to 14 days, with an average of 4 to 7 days. Increased globalization, including rapid travel and trade, has significantly contributed to the spread of dengue (18).

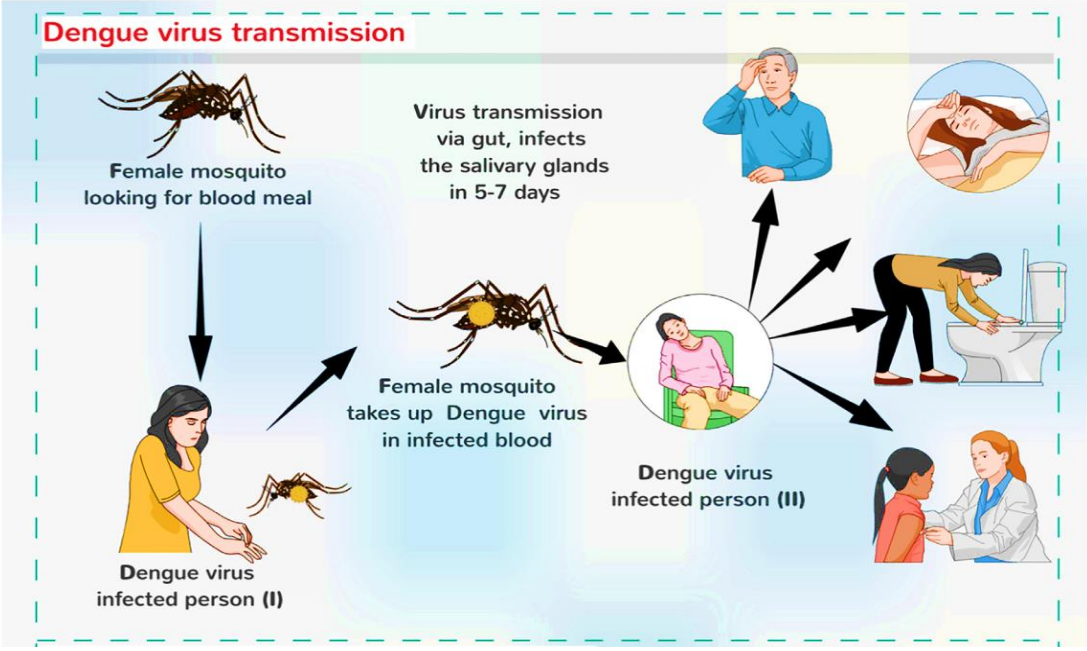

Figure 5. The method of dengue virus transmission (19). (Source: https://www.sciencedirect.com/science/article/pii/S1319562X21003910).

5 Clinical manifestations

Approximately 80% of primary dengue infections are asymptomatic, with fewer than 20% of infected individuals presenting with clinical symptoms. When symptoms do occur, dengue is characterized by severe headache, mild fever, skin rash, muscle and joint pain, nausea, and vomiting. Dengue hemorrhagic fever, a more severe manifestation of the disease, is marked by high fever, liver enlargement, bleeding phenomena, shock, and often cardiovascular disorders. Initially, it was thought that dengue hemorrhagic fever primarily affected children under 15 years of age. However, subsequent studies have shown that this condition can also affect adults (20).

Dengue virus infection causes an acute febrile illness. Some studies have shown that the dengue virus NS1 protein is present in high amounts in the patient's serum, both extracellularly as an unknown soluble lipoprotein and on the cell surface. Elevated levels of this protein may be associated with disease severity and contribute to the pathogenesis of dengue hemorrhagic fever. Infection with one dengue serotype can provide lifelong immunity to that specific serotype and offer short-term protection against other serotypes. However, secondary infection with a different dengue virus serotype is highly likely to result in severe dengue, including dengue hemorrhagic fever and dengue shock syndrome. To prevent viral replication in infected cells and mitigate the effects of specific inflammatory mediators, and there is a pressing need for innovative therapeutic agents and vaccines. Additionally, the role of genetics in resistance to dengue hemorrhagic fever and dengue shock syndrome requires further investigation. Recent reports also indicate that certain clinical symptoms, as well as non-communicable diseases like hypertension and diabetes, are associated with the severity of dengue (21).

6 Conventional methods for dengue virus detection

In areas where dengue fever is endemic or epidemic, particularly in tropical and subtropical regions such as Ethiopia, infected patients often seek medical care (22). In Ethiopia and across Africa, these febrile illnesses can be caused by various infectious pathogens, complicating the control and response to epidemics like malaria, Ebola, and COVID-19. Diagnostic tests for dengue vary in type, cost, and speed, but accurate and rapid diagnosis is crucial for effective clinical care. Laboratory diagnosis can involve detecting the virus, viral nucleic acid, antibodies, antigens, or a combination of these methods. The virus can be detected in plasma, serum, circulating blood cells, and other tissues. During the early stages of the disease, antigen and nucleic acid detection are usually sufficient for diagnosis. After the acute phase, serological tests are employed. The antibody response to dengue infection varies based on the host's immune status. Various laboratory diagnostic techniques have been developed to aid in disease control and patient management (23).

- **Virus isolation**

To isolate the virus, a blood sample is generally obtained five to six days after the onset of symptoms during the acute phase. This sample can be analyzed to detect viral RNA and NS1 antigen via reverse transcription polymerase chain reaction (RT-PCR). Furthermore, the isolated viruses can be identified using indirect immunofluorescence with monoclonal antibodies targeting all five dengue serotypes (24).

- **Molecular detection using reverse transcription polymerase chain reaction (RT-PCR)**

In this approach, particular primers are employed to identify the genes encoding the M and C proteins of the dengue virus. A common sequence found in all five dengue virus serotypes facilitates genome replication. During the second amplification step, unique primers are used to distinguish between each serotype. The resulting cDNA is analyzed using 1% agarose gel electrophoresis and then digitized. Real-time RT-PCR allows for the simultaneous analysis of multiple samples and provides quantitative and qualitative assessments. Conventional RT-PCR has demonstrated significant value in the early detection of dengue virus (25).

- **Detection of antigen**

The NS1 protein is abundant as a hexamer in all five dengue virus serotypes. The NS1 antigen is used as a marker for the early diagnosis of the disease (days 1 to 14). The enzyme-linked immunosorbent assay (ELISA) can detect NS1 quickly and with accuracy comparable to RT-PCR. However, ELISA cannot differentiate between the different dengue virus serotypes. Infection can affect the sensitivity of the test. The NS1 test provides greater accuracy during the acute phase of the disease (26).

- **Serological tests**

In addition to urine, saliva, blood on filter paper, and serum can be used to detect immunoglobulin M (IgM) and G (IgG) if samples are collected within five days or more after the onset of fever. Serum samples can be tested in either a single dilution or multiple dilutions. Most of the antigens used for this test are derived from the dengue virus coat protein (27).

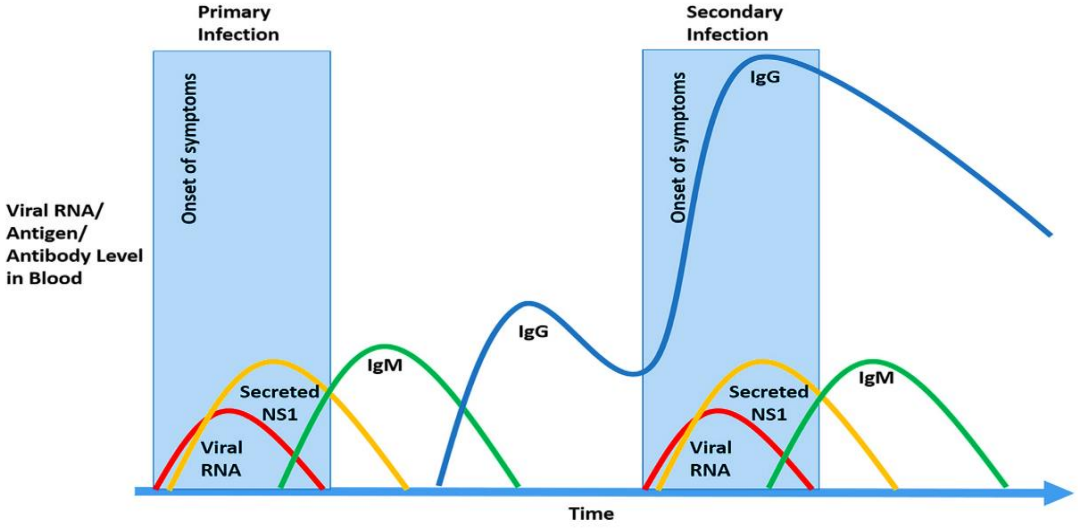

Figure 6. Schematic plots illustrating the levels of dengue virus, NS1 protein, and anti-dengue IgM and IgG antibodies in the blood during primary and secondary dengue infections over time (28). (Source: https://journals.asm.org/doi/10.1128/jcm.00707-17).

Among existing conventional methods, virus isolation is limited due to its time-consuming nature, high cost, and complex laboratory equipment requirements. In contrast, reverse transcription polymerase chain reaction (RT-PCR) can detect dengue virus RNA in the early stages of infection. This method is rapid and sensitive, although requires technical skill and a well-equipped laboratory (29). As a result, serology-based tests are currently the most popular and widely used methods because they are relatively inexpensive, sensitive, fast, and utilize reagents with a long shelf life. Among serological tests, dengue NS1 ELISA is a useful alternative to polymerase chain reaction (PCR) during the acute phase of dengue, while dengue-specific IgM ELISA is effective during convalescence. Although conventional techniques are highly sensitive, they have several drawbacks, including being time-consuming, incompatible with real-time diagnosis, requiring skilled personnel, and needing bulky and expensive equipment. On the other hand, immunochromatographic rapid diagnostic tests (RDTs) for detecting NS1 antigen and IgM antibody are suitable alternatives to ELISA-based testing. They are user-friendly, do not require equipment, and offer very short test times. However, the lack of sensitivity in rapid diagnostic tests poses a significant challenge (30).

7 Diagnosis based on new methods

The development of biosensing assays can address the limitations of ELISA and rapid diagnostic tests, as biosensing technology offers comparable or even superior sensitivity to ELISA while incorporating the portability and miniaturization features of rapid diagnostic tests. Additionally, this technology is user-friendly, cost-effective (requiring fewer reagents and consuming less energy), and allows for continuous monitoring with minimal sample preparation. Various transducers and target analytes have been employed developing of sensitive, rapid, and quantitative dengue virus biosensors. However, many of these tests aren't proper for resource-limited areas, despite dengue fever being predominantly found the same regions. (31).Consequently, there is an urgent need to develop high-sensitivity point-of-care (POC) diagnostic platforms for resource-constrained areas that are affordability, sensitivity, specificity, user-friendliness, rapid and reliable performance, equipment-free operation, and deliverability to those in need (ASSURED). Recently, various advanced sensing technologies have been developed for the rapid and low-cost diagnosis of dengue fever, utilizing principles such as fluorescence, colorimetry, or impedance detection. These sensor-based tests require smaller sample amounts. Their high sensitivity, specificity, and portability make them suitable alternatives to common laboratory tests for initial diagnosis. Additionally, multiple test reports indicate these sensors can play a crucial role in the diagnosis and differentiation of dengue fever from other flaviviruses in endemic areas (32).

Singhal et al. (2017) presented an electrochemical genosensor based on a fluorine-doped tin oxide (FTO) glass plate modified with zinc oxide/platinum-palladium (ZnO/Pt-Pd) nanocomposites to detect the consensus DNA sequence of the dengue virus using methylene blue (MB) as an intermediate agent. To achieve this, probe DNA (pDNA) was immobilized on the electrode surface. This modified electrode served as a signal amplification platform for detecting target hybridized DNA (TDNA). The sensor demonstrated a dynamic linear detection range of 1×10^{-6}-100×10^{-6} M and limit of detection of 4.3×10^{-5} M (33).

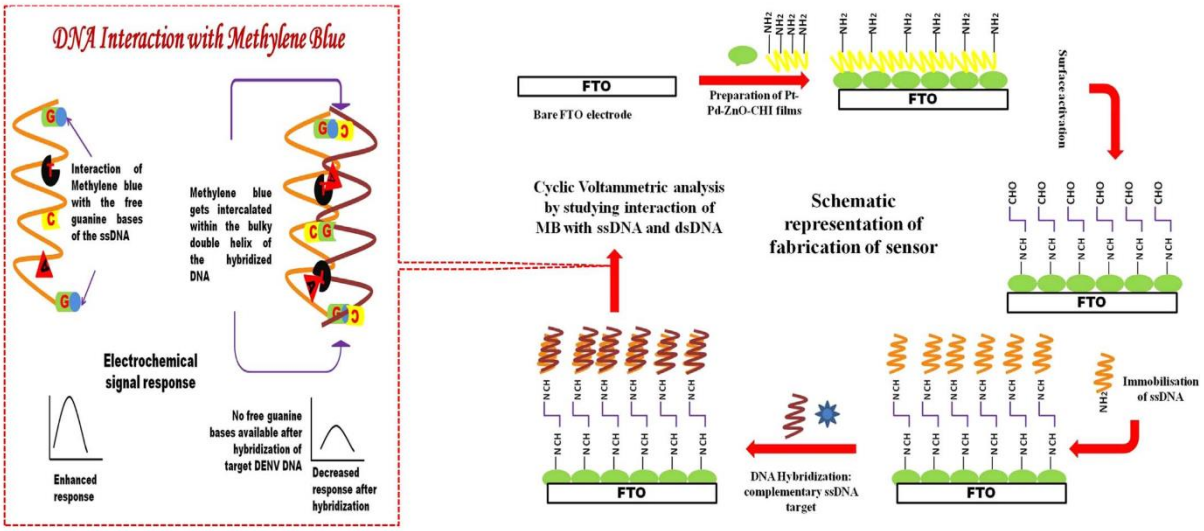

Figure 7. Schematic representation of sensor construction for detecting dengue virus DNA (33). (Source: https://www.sciencedirect.com/science/article/pii/S0956566317303640).

Nawaz et al. (2018) developed an NS1-based impedance immunosensor along with screen-printed carbon electrodes (SPCE) modified with bovine serum albumin (BSA) as a transfer substrate for the rapid analysis of dengue virus. Anti-NS1 monoclonal antibodies were immobilized on the working electrode surface. Electron transfer resistance before and after NS1 binding was monitored as a function of its concentration to perform qualitative and quantitative analyses. The impedance immunosensors detected dengue virus protein with an improved detection limit of 0.3 ng/mL and a linear range of 1-200 ng/mL (34).

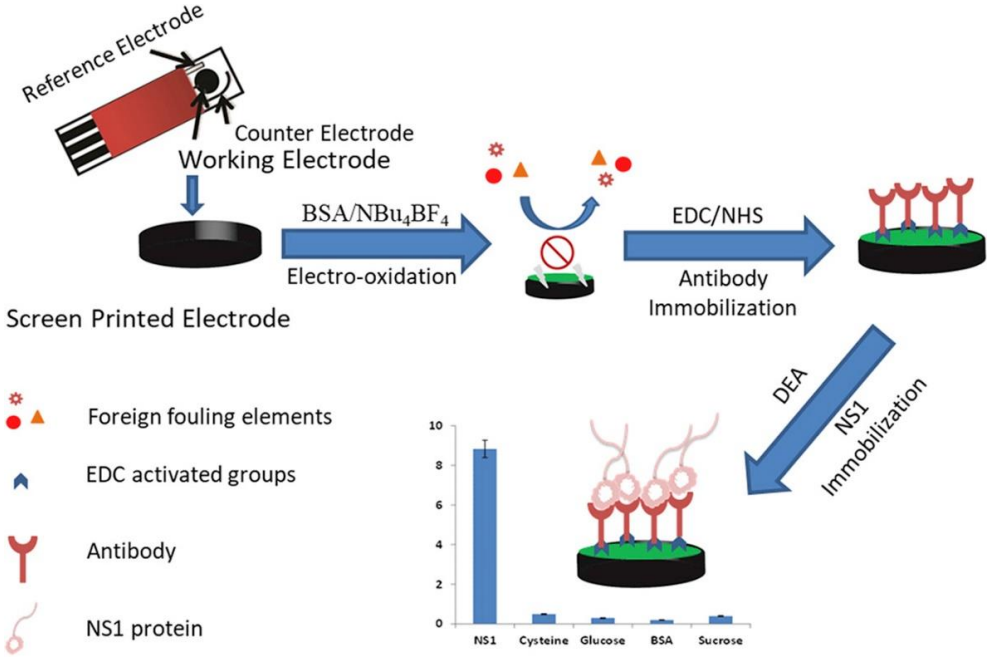

Figure 8. Graphic illustration of the fabrication protocol for an NS1-based impedance immunosensor for ultrasensitive dengue virus detection. Each step represents a progressive modification of the working electrode (34). (Source: https://www.sciencedirect.com/science/article/abs/pii/S0003267018305142).

Wu et al. (2020) showed a genosensor based on electrochemical impedance spectroscopy for the label-free and amplification-free detection of extracted dengue virus RNA nucleic acid to identify dengue virus infection. A self-assembled double layer of 6-mercaptohexanoic acid and 6-mercapto-1-hexanol was used to modify gold electrodes. The designed marker DNA (pDNA) with an NH2 end interacts with the COOH group of the self-assembled layer. This genosensor has a detection limit of 20 plaque-forming units (PFU)/mL and a linear range of 10^2-10^5 plaque-forming units (PFU)/mL (35).

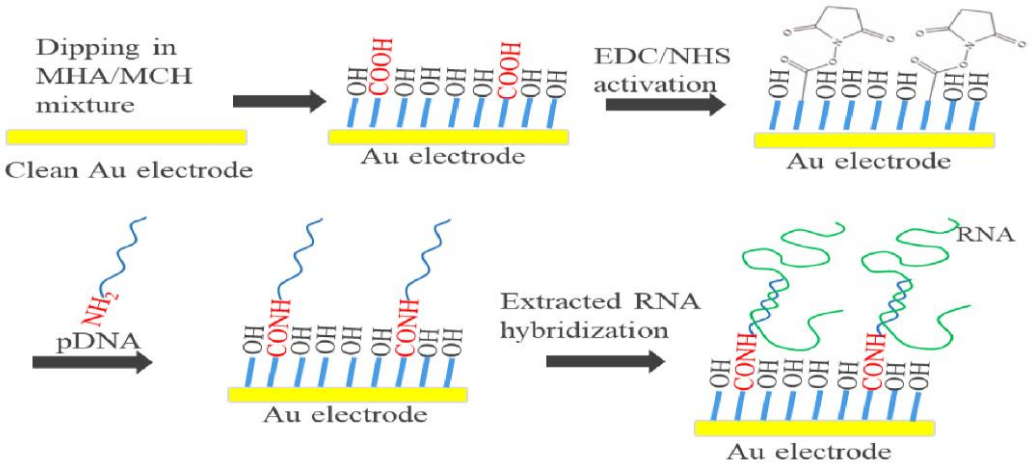

Figure 9. Cleaning and activation of the gold electrode surface, stabilization of pDNA, and hybridization of extracted RNA (35). (Source: https://www.mdpi.com/1424-8220/20/13/3728).

Siew et al. (2021) introduced a new immunosensor utilizing a graphene/titanium dioxide nanocomposite coated screen-printed carbon electrode. This immunosensor targeted dengue virus IgG antibodies using a plant-derived dengue envelope domain III protein as an antigenic probe. The developed immunosensor demonstrated high sensitivity to dengue virus IgG within a wide linear working range of 62.5-2000 ng/mL, with a detection limit of 2.8 ng/mL (36).

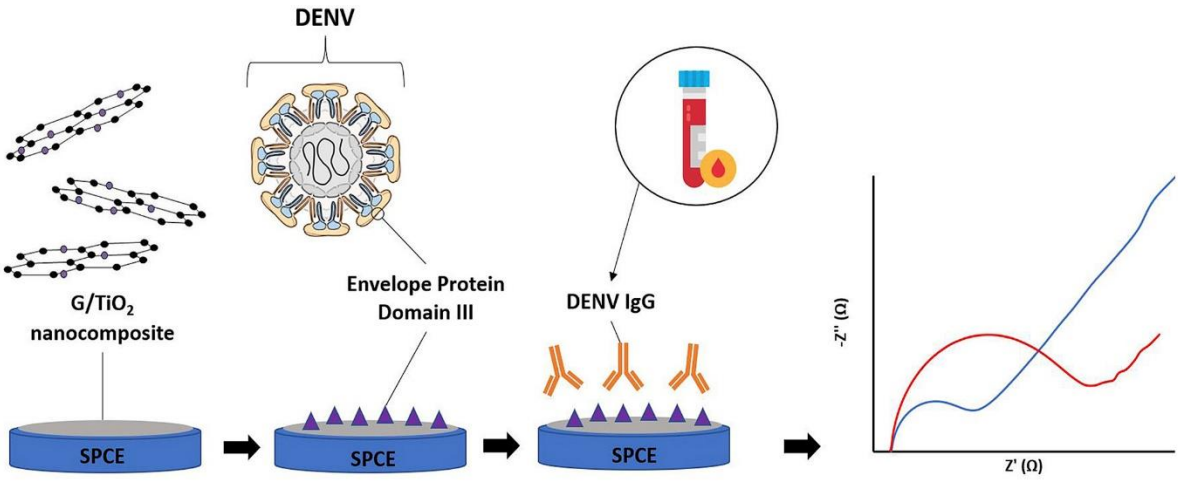

Figure 10. Schematic for the development of an electrochemical sensor using a nanocomposite-coated screen-printed carbon electrode for dengue detection (36). (Source: https://www.sciencedirect.com/science/article/abs/pii/S0956566320308800).

8 Treatment of dengue fever

Currently, there is no specific treatment or medication for dengue fever. Current treatments are supportive and aim to limit complications and severity of symptoms. One of the key treatments in dengue management is fluid therapy (37). For mild dengue fever, oral fluid replacement is generally adequate. In contrast, severe cases require intravenous fluid replacement to prevent shock. The most recent WHO guidelines provide detailed management recommendations

for various levels of dengue severity (38). No specific drug has been approved for use against dengue by the U.S. Food and Drug Administration (FDA). Several candidate therapeutic agents for dengue, targeting viral components or hosts, have been tested in clinical trials. These include carbazochrome sodium sulfonate to prevent capillary leakage, oral prednisolone as an anti-inflammatory agent, and lovastatin (statin) as both an anti-dengue virus and an anti-inflammatory agent in the endothelium. Treatments aimed at reducing severe bleeding or shortening bleeding time, such as single platelet donation or recombinant human interleukin-11, have been tested in small-scale trials. Other anti-dengue virus agents, such as chloroquine, balapiravir (a nucleoside analog and polymerase inhibitor), and celgosivir (alpha-glucosidase I inhibitor), have also been tested in trials (39).

9 Development of a dengue virus vaccine

Producing a vaccine for dengue fever has been a significant challenge due to the disease's four distinct antigenic serotypes. Primary infection with one of the dengue virus serotypes results in long-term homotypic protection. However, it also creates only short-term heterotypic protection against infections with other serotypes. Consequently, a person may experience more severe disease during a secondary heterotypic infection. The development of an effective dengue vaccine relies on the production of long-term antibody-secreting plasma cells through the formation of germinal centers (GC) in secondary lymphoid tissues, with the assistance of follicular helper T cells (Tfh) (40).

However, Dengvaxia can only be used in individuals aged 9 to 16 years who have previously been infected with dengue. (41). To date, only one vaccine, Dengvaxia (Sanofi Pasteur, Marcy-l'Étoile, France), has been licensed for use in several countries. This vaccine is a live chimeric, attenuated tetravalent vaccine containing a non-structural viral backbone derived from yellow fever 17D, combined with pre-membrane (prM) and envelope (E) genes from all four dengue virus (DENV) serotypes. Other candidate vaccines are currently undergoing various phases of clinical trials, from phase I to phase III. Candidate vaccines in phase III clinical trials include TV003/TV005 (NCT01506570) and TDV/DENVax/TAK003 (NCT02302066). The vaccine candidate TDEN-LAV (NCT01702857) is still in phase II trials, while TDEN-PIV (NCT01666652) and D1ME100/TVDV (NCT00290147) are in phase I trials. V180 (DEN-80E) (NCT01477580) has completed phase I trials (42).

10 Conclusion

Dengue fever is considered one of the most dangerous diseases affecting humans. Dengue virus infection can either be asymptomatic or present symptoms that resemble those of other viral illnesses. Consequently, early detection of this virus is crucial for monitoring disease transmission and maintaining public health. In recent decades, bio-sensing methods have played a major role in the accurate and precise detection of the dengue virus. These diagnostic platforms have the potential to enhance disease outcomes by reducing mortality risk and improving diagnostic and therapeutic procedures for critically ill patients, especially in resource-limited countries. Despite recent progress, significant obstacles remain in the commercialization of dengue biosensors due to the complex challenges associated with clinical samples and biosensors. Clinical samples often need extra preparation, such as RNA extraction, before they can be utilized in gene sensors, which complicates the use of biosensors for point-of-care testing. Integrating essential biosensor components including detection agents, sample pretreatment, transducers, and detection methods into a fully automated and portable system is a critical step toward development and commercialization. For dengue diagnosis, a biosensor could potentially replace conventional tests if it can match the speed and simplicity of rapid detection tests while maintaining the specificity of ELISA.

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Conflict of Interest

The authors declared no conflicts of interest.

Author Contributions

Every author contributed to the original idea, study design, writing, and editing of the manuscript, and the final draft was approved.

Data Availability Statement

The 1st author can provide the data upon reasonable request.

Ethical Considerations

This article is a review of existing research and adheres to all ethical guidelines concerning the use of texts and images.

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