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Research Article

Dengue Fever: A Rare Perspective and Emerging Strategies for Sustainable Global Control

Priyanka Malaiyappan[1], Esther Deva Ramya[2], Vettrivel Arul[3], Gokulraj Ganesan[4]

[1]Medical Officer, Manam Healthcare Hospital, Tirupur, Tamil Nadu, India
[2]Professor & Head, Department of Homoeopathic Repertory and Case Taking, Vinayaka Mission's Homoeopathic Medical College & Hospital, Vinayaka Mission's Research Foundation (DU), Tamil Nadu, India
[3]Assistant Professor, Department of Community Medicine, Research Methodology & Biostatistics, Vinayaka Mission's Homoeopathic Medical College & Hospital, Vinayaka Mission's Research Foundation (DU), Tamil Nadu, India
[4]Assistant Professor, Department of Surgery, Excel Homoeopathy Medical College, Dr M.G.R Medical University, Tamil Nadu, Chennai, India
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I N F O

Corresponding Author:
Vettrivel Arul, Department of Community Medicine, Research Methodology & Biostatistics, Vinayaka Mission's Homoeopathic Medical College & Hospital, Vinayaka Mission's Research Foundation (DU), Tamil Nadu, India
E-mail Id:
Veldoc4565@gmail.com
Orcid Id:
https://orcid.org/0000-0002-2319-726X
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A B S T R A C T

Dengue fever remains one of the most pressing global public health challenges, driven by its increasing incidence, expanding geographical reach, and complex clinical manifestations. This review synthesises current knowledge on dengue's epidemiology, transmission dynamics, and clinical spectrum, highlighting the roles of Aedes mosquitoes, environmental factors, and socioeconomic determinants in shaping disease patterns. We explore the immune-mediated mechanisms underlying severe dengue as well as emerging insights into epigenetic modifications that affect both acute and long-term outcomes. The multifaceted impact of dengue is further underscored by its occupational, maternal, and neonatal health complications, which contribute substantially to the economic and healthcare burdens in endemic regions. Innovative therapeutic strategies, including the development of monoclonal antibodies and novel vaccines, alongside integrated vector control and early warning systems, are advancing the fight against dengue. Future research directions and policy recommendations emphasises the need for affordable diagnostics, refined prognostic biomarkers, improved surveillance, and climate-adapted public health interventions to mitigate dengue's spread and severity. Urban planning, though underexplored, has transformative potential in mitigating dengue through mosquito-resistant infrastructure and climate-adaptive strategies. Future efforts must integrate interdisciplinary solutions focusing on innovative therapeutics, targeted prevention, and strengthened healthcare systems to combat dengue effectively and address its evolving challenges in both endemic and emerging regions.

Keywords: Dengue Fever, Vector-Borne Disease, Global Health, Emerging Therapeutics

Introduction

Dengue fever is a viral illness transmitted primarily by mosquitoes, which has surfaced as a pressing global public health issue, especially in tropical and subtropical regions.1 The main vectors for the transmission of the dengue virus (DENV), a member of the Flaviviridae family, are Aedes aegypti and Aedes albopictus mosquitoes. DENV exists in four antigenically distinct serotypes—DENV-1, DENV-2, DENV-3, and DENV-4. Infection with any one serotype offers lifelong immunity to that specific type but grants only temporary cross-protection against the remaining serotypes.[2] This mechanism underpins the risk of severe disease following sequential infections with different serotypes, playing a central role in the development of severe dengue.[3] Over the past few decades, the global incidence of dengue has risen substantially. The World Health Organisation (WHO) estimates that approximately 390 million dengue infections occur worldwide each year.[1] Several interlinked factors are driving this surge, including climate change, rapid urbanisation, increased global travel, and insufficient vector control strategies.[4–6] Currently, dengue is endemic in more than 100 countries, with frequent outbreaks reported across Central and South America, Southeast Asia, and, more recently, emerging epidemic cycles in parts of Africa and North America.[7] This geographical expansion underscores the growing danger posed by dengue and emphasises the pressing need for comprehensive prevention and control measures.[8] Clinically, dengue infection manifests across a broad spectrum, from asymptomatic or mild dengue fever (DF) to more serious forms such as dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS).[9] Typical features of DF include high fever, intense headache, muscle and joint pains (myalgia and arthralgia), and a characteristic skin rash.1 Early and accurate diagnosis, along with timely clinical intervention, plays a critical role in minimising the progression to severe disease. A minority (approximately 5–10%) of symptomatic individuals develop severe dengue, marked by vascular leakage that can result in circulatory collapse and potentially death. Constant monitoring of vital signs and clinical progression allows healthcare providers to identify high-risk patients and initiate supportive interventions such as fluid resuscitation and organ support. As dengue continues to expand into new regions due to climate change, it places increasing strain on healthcare systems globally.[10] Considering the mounting global impact of dengue, robust and integrated control strategies are urgently needed. These include targeted vector control, comprehensive disease surveillance, and the development of effective vaccines. Environmental management to eliminate mosquito breeding habitats is a cornerstone strategy for controlling vector populations.[11] Moreover, reliable and timely surveillance systems are vital for detecting disease trends and mounting a rapid response to outbreaks.[8] Vaccine development has long been a priority in dengue research. Several vaccine candidates are in various stages of clinical evaluation, with some already being deployed in endemic areas.[3] The deployment of effective vaccines has the potential to substantially reduce disease burden, particularly where transmission is high.[12] However, challenges such as ensuring equitable vaccine distribution and determining optimal immunisation strategies remain significant.[13] Concurrent research is focusing on deepening the understanding of dengue pathogenesis, improving diagnostic methodologies, and discovering new therapeutic avenues. These research efforts are instrumental in shaping more effective approaches to control and ultimately eliminate dengue as a major public health threat.[14] Additionally, predictive models incorporating climate-related data are enhancing early warning systems, allowing for more proactive and timely interventions.[15] This review synthesises the current understanding of dengue's occupational, socioeconomic, maternal-neonatal, and therapeutic implications; highlights global preventive strategies; and outlines emerging policy recommendations and future research directions crucial for tackling this escalating public health concern.

Epidemiology and Global Distribution

Dengue remains widely prevalent across tropical regions, with local patterns of dengue virus transmission heavily influenced by factors such as rainfall, ambient temperature, urban expansion, and the geographical presence of the primary mosquito vector, Aedes aegypti. Currently, sustained endemic transmission of dengue is reported in regions including the Eastern Mediterranean, the Americas, South-East Asia, the Western Pacific, and Africa. Meanwhile, sporadic and localised outbreaks have also emerged in parts of Europe and the United States, primarily due to the introduction of the virus into susceptible environments.[16] As a rapidly emerging mosquito-borne viral disease, dengue is transmitted among humans primarily by Aedes species, which are also responsible for the spread of other arboviruses like chikungunya and Zika. The distribution and intensity of dengue outbreaks are shaped by environmental and socio-demographic variables such as geography, rainfall patterns, temperature shifts, and accelerated urbanisation or population movements. These factors have led to increased transmission, greater incidence of cases, and the emergence of hyperendemic regions where more severe disease manifestations are frequently observed.[17] Dengue is currently considered the fastest-growing mosquito-borne viral infection in the world, associated with significant morbidity and mortality. Over recent decades, extensive progress has been made in understanding its epidemiology, encompassing aspects such as disease burden, transmission dynamics, risk factors, and preventive strategies. Notably, dengue has continued to spread to new territories, including

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higher latitude zones, and a fifth serotype, DENV-5, has been recently identified, further complicating control efforts.[18] Each year, an estimated 50 to 100 million people are infected with the dengue virus, imposing a substantial economic burden on healthcare systems and affected households. Global dengue outbreaks between 1990 and 2015 provided a detail of epidemiological trends, clinical manifestations, serotype prevalence, and contributing risk factors.[19] Despite its global significance, the true public health burden of dengue remains uncertain. Recent studies employing cartographic modelling have attempted to address this gap by mapping dengue's global, regional, and national burden. These efforts suggest that dengue may cause up to 390 million infections annually, over three times higher than earlier WHO estimates.[20] Over time, dengue epidemiology has undergone substantial transformation, with expanding geographic spread, increasing transmission intensity, and heightened disease severity in previously endemic zones. These shifts are documented in multiple studies, offering improved insights into the evolving distribution of dengue.[4] Dengue is now recognised as the most critical mosquito-borne viral disease worldwide. Historical accounts suggest symptoms resembling dengue date as far back as the Chin Dynasty (265–420 AD). In the past fifty years, the virus and its mosquito vectors have proliferated across most tropical and subtropical regions. This geographic expansion has paralleled dramatic rises in incidence, repeated outbreaks, and the establishment of hyperendemicity, all of which have contributed to more severe disease outcomes.[7] Globally, around 2.5 billion individuals are estimated to be at risk of dengue infection. With the advent of climate change, the epidemic potential of dengue is expected to rise. Temperature increases may enhance the replication rate of the virus and boost the survival and activity of mosquito vectors. Analyses of past and present transmission patterns indicate that climate change could significantly alter the future global distribution of dengue.[21] These evolving epidemiological patterns highlight the urgent need for region-specific data, climate-integrated surveillance systems, and proactive vector control strategies to mitigate future outbreaks and reduce the global burden of dengue.

Transmission Dynamics and Influencing Factors

The Aedes aegypti mosquito serves as the principal vector for dengue virus (DENV) transmission and is also responsible for the spread of other arboviruses, including chikungunya, Zika, and yellow fever. Over the past five decades, Aedes mosquitoes have exhibited remarkable geographic expansion, now being reported in 129 countries and adapting effectively to urban ecosystems, making them one of the most invasive mosquito species globally.[22] Aedes albopictus, while considered a secondary vector for dengue, has demonstrated a strong adaptability to temperate climates and continues to spread rapidly across multiple continents.[23] In contrast, Aedes aegypti remains more prevalent in tropical and subtropical environments, resulting in a global distribution pattern where both vectors complement each other's ecological places.[24] Climatic conditions play a critical role in modulating the transmission dynamics of DENV. Environmental parameters such as temperature and humidity influence the mosquito life cycle, affecting key aspects such as development rate, adult lifespan, and viral replication within the vector. Warmer temperatures tend to accelerate mosquito maturation and enhance viral replication, while humidity directly impacts survival rates and breeding site persistence.[25] Beyond climate, landscape-related and socioeconomic factors, including land use, vegetation coverage, degree of urbanisation, population density, and household income, have been identified as significant determinants of Aedes mosquito distribution.[26] Another important but less frequently discussed mechanism in dengue persistence is vertical transmission, where infected female Aedes mosquitoes pass the virus to their progeny through transovarial transmission. This mechanism is especially relevant during interepidemic periods, allowing DENV to be maintained in mosquito populations even in the absence of active human-to-mosquito transmission cycles.[23] Climate change is increasingly recognised as a powerful driver of vector-borne disease transmission. Rising global temperatures and shifting rainfall patterns contribute to extended breeding seasons, wider mosquito ranges, and increased vectorial capacity, thereby facilitating higher rates of dengue transmission. Additionally, global travel and migration continue to amplify the risk of DENV introduction into non-endemic regions, further complicating containment efforts.[27] As global environmental and societal changes continue to reshape mosquito ecology and virus transmission, a proactive, multidisciplinary approach combining entomology, climatology, urban planning, and public health is essential to estimate risks and guide future interventions. Strengthening community engagement, investing in sustainable vector control innovations, and aligning public health policies with climate adaptation strategies will be crucial in disrupting the complex transmission cycles of dengue.

Mechanisms of Infection and Immune Response

The immune-related pathogenesis of dengue is primarily driven by mechanisms such as antibody-dependent enhancement (ADE), T-cell dysregulation, and the excessive release of pro-inflammatory cytokines collectively contributing to the development of severe disease, especially during secondary infections with a different serotype.[28] The human innate immune system, particularly monocytes, macrophages, and dendritic cells, plays a critical role in the early response to infection. These cells act as primary antigen-presenting cells and are essential for shaping long-

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term immune memory.[29] In individuals previously infected with one dengue serotype, cross-reactive antibodies may bind to a new, heterologous serotype without effectively neutralising it. Instead, these antibodies can assist the virus in entering immune cells that carry Fc receptors. This facilitates increased viral replication within the host, resulting in high viral loads and an amplified immune response, which can lead to a cytokine storm, a surge in inflammatory mediators that increases the risk of plasma leakage and vascular damage.[30] There are four antigenically distinct DENV serotypes (DENV-1 to DENV-4). While infection with one serotype confers lifelong immunity to that particular type, it does not protect against subsequent infections with other serotypes. In fact, second or third infections increase the risk of dengue haemorrhagic fever due to ADE. This phenomenon allows non-neutralising antibodies to promote viral entry into immune cells, triggering excessive inflammation and worsening the clinical course, including neurological complications and multi-organ dysfunction. A key feature of severe dengue is endothelial dysfunction, which causes increased vascular permeability and can lead to life-threatening complications such as shock and encephalopathy. Elevated levels of inflammatory cytokines, especially tumour necrosis factor-alpha (TNF-α), are known to disrupt the endothelial barrier during the critical phase of illness. Additionally, the non-structural protein 1 (NS1) of the dengue virus can directly damage the endothelial glycocalyx layer (EGL), a protective barrier of the blood vessels. The breakdown of this layer is associated with clotting abnormalities, white blood cell accumulation, and fluid leakage factors that contribute significantly to disease severity.[31] As understanding of dengue immunopathogenesis evolves, it becomes increasingly clear that effective interventions must go beyond viral suppression to also address immune modulation and endothelial protection. Further focusing on host-virus interactions, immune evasion strategies, and molecular markers of disease severity will be instrumental in shaping next-generation vaccines and targeted therapies.

Clinical Spectrum: From Typical Symptoms to Rare Complications

Dengue virus (DENV) infection presents with a wide range of clinical manifestations, from mild febrile illness to severe, life-threatening complications. The spectrum includes uncomplicated dengue fever (DF), dengue haemorrhagic fever (DHF), and dengue shock syndrome (DSS). In recent years, neurological complications such as encephalopathy have been increasingly documented. Initially believed to be secondary to systemic complications like liver failure, shock, and coagulopathy, there is growing evidence supporting dengue virus neurotropism, indicating that some cases may involve direct viral encephalitis.[32] The typical incubation period for dengue is 5–7 days, after which the illness progresses through three distinct phases: febrile, critical, and recovery. Early symptoms are often non-specific, requiring high clinical suspicion. Early recognition of shock and timely supportive treatment, particularly intravenous fluid therapy, significantly reduces the risk of death in severe dengue to less than 0.5%. Common laboratory findings in dengue patients include leukopenia, thrombocytopenia, hyponatraemia, and elevated liver enzymes such as AST and ALT, while erythrocyte sedimentation rate (ESR) typically remains normal. Immunologically, infection with one DENV serotype grants lifelong immunity to that serotype but only temporary cross-protection against others, increasing the risk of more severe outcomes with subsequent infections33 recovery. The febrile phase is marked by the sudden onset of high-grade fever (up to 40 °C), typically lasting 2 to 7 days, and may exhibit saddleback or biphasic fever patterns in around 6% of cases, particularly in those with dengue haemorrhagic fever (DHF) or severe dengue. This phase presents with symptoms such as facial flushing, skin erythema, myalgia, arthralgia, headache, sore throat, conjunctival injection, anorexia, nausea, and vomiting. Skin manifestations include a blanchable macular rash within 1–2 days of fever onset and a possible secondary maculopapular rash later. Heightened capillary permeability characterises this stage, lasting 1–2 days, and is typically followed by a rapid decline in platelet count, rising haematocrit levels, and leukopenia before the onset of warning signs. If not managed, the disease may progress into the critical phase, where complications such as shock, organ dysfunction, haemorrhage, or disseminated intravascular coagulation may arise. The recovery phase then follows, lasting about 2 to 3 days, during which extravascular fluid is gradually reabsorbed and bradycardia may occur. Some patients may develop expanded dengue syndrome, a severe variant involving multiple organ systems, including neurological (e.g., febrile seizures, encephalitis, intracranial bleeding), gastrointestinal (e.g., hepatitis, pancreatitis), cardiovascular (e.g., myocarditis, pericarditis), respiratory (e.g., ARDS), and renal (e.g., acute kidney injury) complications, often associated with profound shock.[34] With the growing complexity of dengue presentations and the emergence of atypical forms, especially in co-infection or immunocompromised states, it is vital for clinicians to remain alert to the evolving clinical spectrum. Enhanced clinical awareness, early intervention, and supportive care are the cornerstones to reducing dengue-related morbidity and mortality in both endemic and newly affected regions.

Epigenetic Insights and Long-Term Effects of Dengue

Dengue virus (DENV) infection leads to a variety of epigenetic changes, especially through alterations in microRNA (miRNA) expression, which significantly influence host immune responses and support viral replication. For example, DENV

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infection increases the expression of miR-146a, which suppresses the production of interferon-beta (IFN-β) by targeting tumour necrosis factor receptor-associated factor 6 (TRAF6), helping the virus escape immune detection.[35] Additionally, miR-927 regulates genes involved in diverse cellular processes such as post-translational modifications (SUMO), protein translation (eIF-2B), innate immunity (NKIRAS), exocytosis (EXOC-2), endocytosis (APM1), and cytoskeletal structure (FLN). Among these, FLN was found to be a direct target of miR-927, as confirmed by a dual-luciferase reporter assay, and its expression was significantly affected by both overexpression and inhibition of miR-927. Since FLN also influences the Toll signalling pathway, its regulation by miR-927 alters the expression of key antimicrobial peptides like Cecropins A and G and Defensin D.[36] Beyond miRNAs, DENV directly interacts with host histone proteins, affecting nucleosome assembly and gene transcription. The viral capsid protein binds to histones H2A, H2B, H3, and H4, which may disrupt host DNA transcription and further enhance viral replication.[37] These molecular changes can lead to long-term consequences in infected individuals. Over half of the patients with previous dengue or dengue haemorrhagic fever report lingering symptoms that are thought to be linked to immune imbalances, including changes in autoimmune markers and FcγRIIa gene polymorphisms.[38] Experimental models have shown that miRNAs-15/16 are elevated during DENV-4 infection in liver cells, which activate apoptosis via caspase pathways, indicating their role in virus-induced cell death.[39] In Aedes mosquito vectors, DENV infection also alters miRNA expression post-transcriptionally, impacting immune-related genes and possibly modifying transmission potential.[40] As a result, researchers are exploring the potential of targeting these epigenetic pathways for treatment. Histone deacetylase inhibitors (HDACi) like valproic acid have been shown to reduce pro-inflammatory cytokine release in DENV-infected macrophages, pointing to a possible method of controlling the hyperinflammatory state in severe cases.[37] Furthermore, DNA methylation inhibitors are being considered as potential tools to reverse stress- or virus-induced epigenetic modifications.[41] DENV induces complex epigenetic modifications that influence both the immediate immune response and long-term clinical outcomes. A deeper understanding of these molecular interactions not only enhances our knowledge of dengue pathogenesis but also enhances innovative treatment strategies focused on epigenetic regulation for better control of disease severity and post-infection recovery.

Environmental Challenges in Dengue Transmission

Dengue fever, a rapidly spreading mosquito-borne viral illness, has resurged worldwide due to environmental disruptions such as climate change, deforestation, and urban expansion. Rising global temperatures and altered rainfall patterns have widened the habitat range of Aedes mosquitoes—the primary vectors for dengue—allowing transmission in areas previously unaffected. According to The Lancet, over half of the global population is now at risk, with 100–400 million infections occurring annually. This surge is largely driven by climate variability, increased global mobility, and urbanisation.[42] Environmental modifications like deforestation and climate change have also been closely linked to increased dengue incidence, emphasising the influence of ecological factors on disease patterns.[43] Air pollution further complicates the transmission landscape. Higher levels of air pollutants, especially particulate matter (PM2.5, PM10) and carbon monoxide (CO), have shown a positive association with increased dengue cases, possibly due to their effects on mosquito behaviour or human immune response.[44] Low concentrations of PM10 and PM2.5, in combination with the number of precipitation days, were predictive of monthly dengue case numbers, reinforcing the complex interconnection between air quality and disease dynamics.[45] Mosquito behaviour has been observed to undergo various changes when they come into contact with individuals carrying pathogens. although more evidence is needed.[46] Furthermore, as climate change continues to intensify, the infectious potential of dengue is expected to grow. A systematic review concluded that climatic factors, particularly temperature, rainfall, and humidity, play a key role in modulating dengue transmission.[5] Altogether, the rising incidence of dengue underscores the urgent need for integrated public health interventions that not only focus on mosquito control but also consider broader environmental, climatic, and socio-ecological dynamics. Strengthening climate-resilient health systems and advancing research on long-term effects, including possible cancer risks, are essential to managing the future burden of dengue.

Occupational and Socioeconomic Impact of Dengue

Dengue fever imposes significant occupational and socioeconomic burdens, especially in endemic regions, as individuals with outdoor occupations face higher risks of contracting vector-borne diseases.[47] The economic impact is profound, with a systematic analysis in India estimating around 53 million symptomatic cases in 2016 and an economic burden of approximately US$5.71 billion48, while in Brazil, treatment costs for dengue cases from 2000 to 2015 approached USD 159 million, placing a substantial strain on public health resources.[49] Furthermore, a multi-country study in Vietnam, Thailand, and Colombia showed that socioeconomic factors such as education and income levels greatly influence disease severity, perception, and healthcare-seeking behaviour, thus affecting the overall disease burden.[50] Occupational risks are projected to

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increase dramatically; analyses predict that by 2030, over 10% of workers in key industries in countries like the USA, China, Japan, and Germany could be at risk, with rates exceeding 70% in India and Brazil, potentially disrupting industrial activities.[51] Addressing these challenges will require comprehensive strategies that combine effective vector control, workplace interventions, and robust policy measures to mitigate the economic and health impacts.[47] Such measures are crucial to safeguard both public health and economic stability in regions vulnerable to dengue outbreaks.

Maternal And Neonatal Health Risks of Dengue

Dengue virus (DENV) infection during pregnancy is linked to significantly higher risks of adverse maternal and neonatal outcomes compared to uninfected pregnant women. Studies report that pregnant women with dengue face increased risks of maternal mortality, stillbirth, and neonatal deaths, with pooled prevalence rates of dengue shock syndrome and preterm birth reaching 14.9% and 14%, respectively.[52] Some analyses have observed a maternal mortality rate as high as 15.9% among infected mothers, compounded by risks such as preterm labour and postpartum haemorrhage that contribute to considerable morbidity for both the mother and baby. These alarming outcomes underscore the urgent need for vigorous vector control strategies in affected regions.[53] Additionally, a systematic review and meta-analysis examining the association between maternal DENV infection and adverse birth outcomes found that, although there were higher rates of preterm birth and low birth weight, the associations were not statistically significant.[54] Neonatal dengue often remains underdiagnosed due to its clinical resemblance to sepsis; case reports emphasise the need for a high index of suspicion in infants born to febrile mothers—even when maternal serology is negative—with the severity of neonatal illness correlating with the severity of maternal disease.[55] These findings highlight the critical need for enhanced monitoring and management of pregnant women in dengue-endemic areas. Strengthening prenatal care, improving diagnostic vigilance, and implementing robust vector control measures are essential to mitigate the risks and safeguard the health of both mothers and their infants, ultimately contributing to improved maternal and neonatal outcomes.

Innovative Therapeutic Approaches and Vaccine Development

Dengue fever, a significant global health concern, has driven the development of novel therapeutic strategies that include monoclonal antibodies (mAbs) and region-specific vaccines. For instance, the human monoclonal antibody 9C7 can bind all four dengue virus (DENV) serotypes by recognising a conformational epitope on the envelope protein, which neutralises the virus in vitro and protects mouse models from lethal challenges. To address the risk of antibody-dependent enhancement (ADE), where suboptimal antibodies increase viral entry into host cells, modifications such as LALA mutations or deletions have been introduced into 9C7's Fc region.[56] Advances in antibody discovery have facilitated the development of therapeutic mAbs against emerging arbovirus infections, including DENV, with several candidates demonstrating protective effects in animal models; however, challenges like ADE require these antibodies to be carefully designed and evaluated to ensure both safety and efficacy.[57] In India, which bears a large portion of the global dengue burden, vaccine development has gained momentum with both indigenous candidates and those licensed from abroad undergoing clinical trials to meet the region's specific needs.[58] Furthermore, innovative approaches are also being explored through the design of a tetravalent subunit multi-epitope vaccine that targets conserved sequences across structural and non-structural proteins from each serotype,[59] with computational models suggesting potential efficacy although experimental validation is still pending.[60] Complementing these strategies, vector control interventions such as the release of Wolbachia-infected Aedes aegypti mosquitoes have been shown to reduce dengue incidence by 57% in field trials conducted in Singapore, demonstrating the value of biological control methods as a support to vaccination efforts.[61] These advancements underscore a multifaceted approach to combating dengue, integrating therapeutic antibodies, tailored vaccine development, and innovative vector control strategies to address the diverse challenges posed by the disease across different regions.

Integrated Prevention and Management Strategies

Dengue fever continues to pose significant public health challenges globally, prompting the adoption of innovative prevention and management strategies. Vector control remains a cornerstone in these efforts, where traditional methods such as eliminating mosquito breeding sites and using insecticides are now augmented by biological interventions. For instance, introducing larvivorous fish like Poecilia reticulata into water containers has effectively reduced mosquito larvae populations,[62] while the Wolbachia method of releasing mosquitoes infected with the Wolbachia bacterium has led to a 60% decline in dengue cases in areas like Niterói, Brazil.63 Chemical interventions using insecticides such as organophosphorus compounds and pyrethroids continue to play a role in adult mosquito control, although emerging insecticide resistance necessitates careful application and the search for alternative measures.[62] Additionally, simple household-level interventions, such as covering water storage containers with untreated fine net screens, have significantly reduced mosquito breeding.[64] Efforts to control dengue have also

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shifted toward vaccine development as early vector control techniques proved less effective or even harmful over time. Researchers are now targeting key viral proteins like the envelope (E) protein and the non-structural NS1 protein. This has led to the development of various vaccine types, including live attenuated, recombinant subunit, inactivated virus, viral vectored, DNA, and mRNA vaccines, with innovative approaches such as recombinant DNA plasmids aimed at enhancing vaccine efficacy, as well as strategies to disrupt the DENV life cycle within mosquitoes.[65] In clinical management, treatment remains largely supportive with a focus on hydration and symptomatic relief. However, emerging therapeutic strategies are exploring direct antivirals to reduce viral replication and host-targeted drugs to mitigate inflammation and vascular damage, thereby reducing dengue-related morbidities.66 Integrated One Health strategies, which recognise the interconnectedness of human, animal, and environmental health, emphasise that effective dengue management requires a multifaceted approach, including vector control, environmental management, and active community engagement. Continuous monitoring and evaluation of these interventions are essential to adapt to changing local conditions and emerging challenges.[67] These latest strategies for dengue involve a combination of traditional vector control methods, innovative biological interventions, vaccination efforts, and supportive clinical management. Ongoing research and integrated approaches are crucial to address the evolving challenges posed by dengue globally.

The World Health Organisation's (WHO) guidelines outline a structured method for diagnosing, classifying,

Table 1.Guidelines for Dengue Case Management Based on WHO Recommendations

Step	Category	Criteria / Features	Recommended Actions
Assessment	Presumptive Diagnosis	Lives/travel to endemic area. Fever + ≥2 of: anorexia/nausea, rash, aches/pains, leukopenia, positive tourniquet test, warning signs. Lab-confirmed dengue (especially if plasma leakage suspected).	Proceed to classification
Classification	Group A	No warning signs AND: Able to drink, urinate regularly, no coexisting conditions. Access to health care	Tests: FBC, HCT Treatment: Oral fluids, rest, paracetamol (≤4g/day adults) Monitoring: Daily—WBC, fever resolution, warning signs Discharge: If stable, with written instructions
	Group B	Warning signs OR co-existing conditions (infancy, pregnancy, elderly, diabetes, renal failure, living alone)	Tests: FBC, HCT Treatment: Oral or IV fluids (0.9% saline/Ringer's) Monitoring: Vitals, HCT, WBC, platelets, urine output, temperature Fluid Therapy: Adjust fluids based on clinical and lab response Reassess HCT: Rising = plasma leakage; Decreasing = bleeding
	Group C	Severe dengue: Severe plasma leakage with shock or fluid accumulation with respiratory distress. Severe bleeding: Severe organ involvement	Tests: FBC, HCT, organ function Treatment: Compensated shock: 5–10 ml/kg/hr crystalloids, then reduce gradually Unstable: Repeat bolus, titrate based on HCT response Hypotensive shock: 20 ml/kg bolus crystalloids/colloids, adjust by response If HCT ↓ and unstable: Suspect bleeding → blood transfusion Hemorrhagic complications: 5–10 ml/kg RBC or 10–20 ml/kg fresh blood

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Clinical Course	Phases of Illness	Days 1–3 (Febrile): High fever, viremia. Days 4–6 (Critical): Defervescence, risk of plasma leakage, shock, bleeding, organ impairment. Days 7–10 (Recovery): Reabsorption, fluid overload	Monitor temperature, HCT, platelet trends, organ status. Adjust fluids cautiously in critical phase to prevent overload in recovery. Look out for clinical deterioration as warning sign for severe dengue progression.
Monitoring	All Groups	HCT, WBC, platelets, Vitals (pulse pressure, capillary refill), Urine output, Fluid balance	Group A: Home monitoring with return instructions. Group B & C: In-hospital monitoring, escalation based on response

and managing dengue cases, starting with presumptive diagnosis based on clinical symptoms and exposure to endemic areas. Cases are categoried into three groups to ensure appropriate care: Group A includes patients with mild symptoms managed at home with supportive care; Group B involves cases displaying warning signs such as abdominal pain or dehydration, requiring hospital-based treatment and further tests; and Group C comprises severe cases, including complications like plasma leakage or organ impairment, necessitating intensive care and specialised monitoring. This classification system optimises patient outcomes by tailoring treatment approaches to disease severity, as elaborated in Table 1.[68]

Future Research Directions and Policy Recommendations

Dengue fever remains a major global health concern, prompting the need for targeted research and informed policy interventions. One key research direction is the development of affordable and accurate diagnostic tools. Promising, lower-cost molecular techniques and affordable NS1 assays are under development, as current commercial assays are often variable in quality and too expensive for widespread public use. Combining NS1 detection with anti-DENV IgM antibody tests shows promise for early diagnosis, but these assays need further refinement for use in low- and middle-income settings.[69] Another important focus is the identification of prognostic biomarkers for severe dengue. While clinical symptoms remain the primary method for predicting severe disease, researchers are now investigating innate immunity gene expression, specific cytokines, and markers of T and B cell activation. These efforts aim to develop validated assays to improve triage and treatment outcomes for patients at high risk.[69] Enhancing surveillance systems and outbreak responses is also critical. Strengthening passive surveillance through improved laboratory support, sentinel reporting, and staff motivation can provide a more accurate baseline for outbreak alerts. In addition, integrating electronic event-based surveillance and monitoring changes in dengue serotypes could lead to better risk assessment tools.[70] Effective vector control strategies remain central to dengue management. Traditional approaches such as using organophosphate larvicides are now being questioned due to efficacy concerns and potential health risks. Alternative methods—including biological control using natural predators of Aedes larvae, genetically modified mosquitoes, and community-based source reduction programmes—have shown potential to reduce mosquito populations and dengue transmission.[71] The integration of vaccination with vector control is another promising strategy. Introducing dengue vaccines must be complemented by community-driven efforts to reduce mosquito breeding sites and improve overall case management, ensuring that vaccination is part of a broader, integrated dengue control framework.[72] Addressing major gaps in our understanding of severe dengue epidemiology is essential. Consistent case definitions and a better grasp of the demographic, virological, immunological, genetic, and clinical factors are needed to understand who is at highest risk of developing severe dengue.[73] Developing early warning systems is also a priority. An evidence-based handbook has been created to bridge research with policy and practice, supporting contingency planning and early warning during dengue epidemics by pinpointing key decision-making processes.[74] Finally, advancing vaccine development remains a top research priority. Although several vaccine candidates, such as Sanofi Pasteur's Dengvaxia, Takeda's Qdenga, and the NIH's TV003, have shown varying degrees of effectiveness and safety, the inherent immunological challenges posed by the four DENV serotypes require ongoing investigation and optimisation of vaccine strategies.[75]

These research directions and policy recommendations underscore the need for a multifaceted approach to dengue management. Combining affordable diagnostics, biomarker research, strengthened surveillance, innovative vector control, integrated vaccination efforts, and robust early warning systems will be essential for adapting to the evolving challenges of dengue. Such comprehensive strategies not only promise to reduce disease burden but also help build resilient health systems that can better protect vulnerable populations worldwide.

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Conclusion

Dengue fever poses a significant global health challenge with rising incidence, geographical spread, and complex presentations demanding urgent action. Factors like climate change, urbanisation, and inadequate vector control intensify the issue, necessitating proactive interventions. Advances in vaccines, vector control, and predictive modelling show promise, though equitable access remains a hurdle. Rare complications offer insights for targeted therapies and diagnostics. On a molecular level, epigenetic changes induced by dengue may predispose recovered patients to autoimmune and inflammatory disorders, raising concerns about intergenerational effects in endemic regions. Urban planning and architectural innovation in mitigating dengue remain inadequately discussed. Incorporating mosquito-repelling building materials or community-scale infrastructure to disrupt breeding cycles could be transformative but has yet to be systematically integrated into prevention strategies. Climate-adaptive architectural solutions aligned with epidemiological trends could provide sustainable approaches. These underexplored dimensions highlight the need for interdisciplinary strategies to redefine dengue control and unlock innovative pathways to address its global impact effectively.

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