

Double trouble: A review of dengue virus co-infections and their impact on disease severity

Sujitha S, Murugesan R*

Department of Zoology, Annai Vailankanni Arts and Science College (Affiliated to Bharathidasan University), Thanjavur, Tamil Nadu, India

Abstract

Dengue virus infection, a major global health threat, rarely exists in isolation. Co-infections with other prevalent pathogens, particularly in tropical and subtropical regions, present a significant challenge to diagnosis, treatment, and patient outcomes. This review delves into the complex interplay between DENV and other common co-infecting agents, examining the epidemiological overlap, clinical presentations, immunological interactions, and potential for synergistic effects on disease severity. We highlight the current understanding of how co-infections modulate DENV pathogenesis, emphasizing the need for improved diagnostic tools, integrated surveillance strategies, and tailored treatment approaches to effectively address this growing public health concern.

Keywords: Dengue virus, co-infection, epidemiology, pathogenesis, clinical manifestations, diagnostics

Introduction

Dengue fever, a mosquito-borne viral illness, affects millions annually, with a significant burden in tropical and subtropical regions [1]. The World Health Organization estimates that approximately 390 million dengue infections occur each year, with 96 million manifesting clinically [2]. While DENV infection alone can manifest with a wide range of clinical presentations, from mild fever to life-threatening complications like dengue hemorrhagic fever

and dengue shock syndrome, the presence of co-infections adds another layer of complexity [3]. Co-circulating pathogens, including other arboviruses (e.g., Zika, chikungunya), respiratory viruses (e.g., influenza), bacterial infections (e.g., leptospirosis, typhoid fever), and parasitic infections (e.g., malaria), can interact with DENV, potentially altering disease progression and severity [4, 5] (Figure 1).

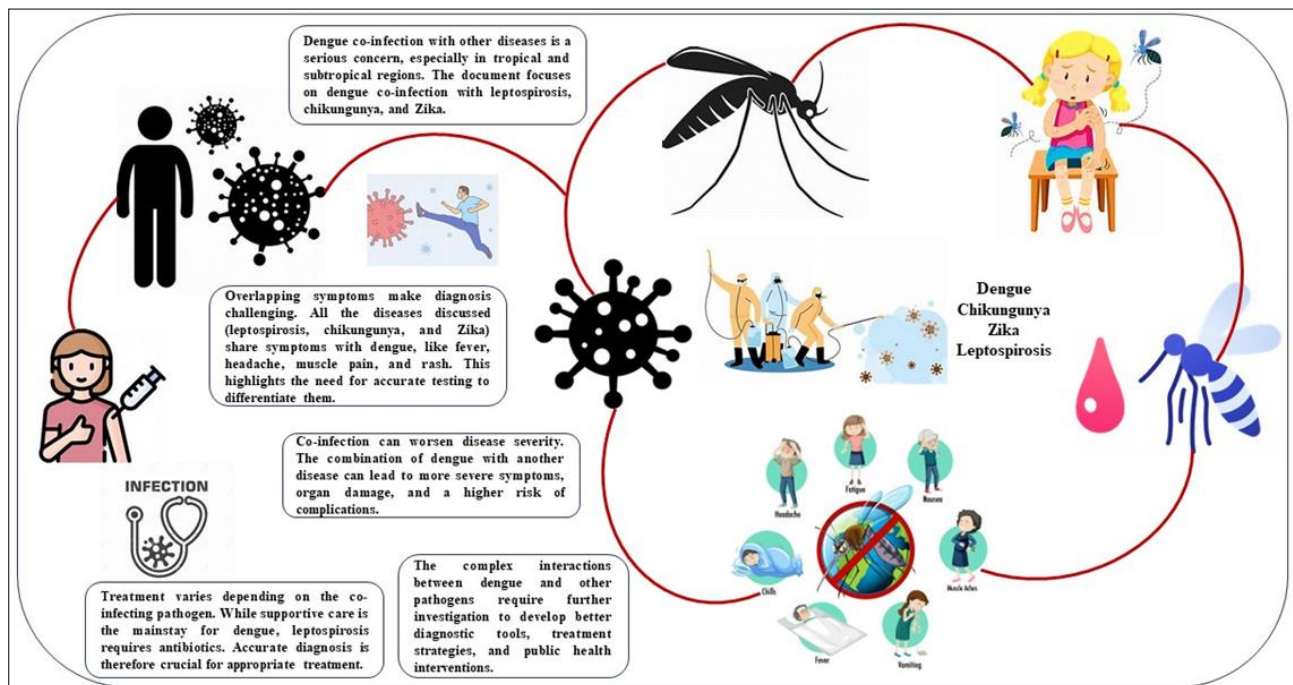


Fig 1: Dengue virus co-Infections and their impact on disease severity

This review aims to provide a comprehensive overview of DENV co-infections, focusing on:

Epidemiological Overlap: Identifying regions and populations at increased risk of co-infections based on overlapping transmission cycles and risk factors.

Clinical Manifestations: Discussing the challenges of differentiating DENV co-infections from single infections based on clinical presentation, emphasizing atypical presentations and potential for misdiagnosis.

Immunological Interactions: Exploring how co-infecting pathogens might modulate the host immune response to DENV, including potential for immune enhancement, suppression, or dysregulation.

Disease Severity: Examining the evidence for synergistic effects of co-infections on DENV severity, focusing on increased risk of severe dengue, organ dysfunction, and mortality.

Diagnosis and Treatment Challenges: Highlighting the need for accurate and timely diagnosis of co-infections, as well as the complexities of managing co-infected patients, considering potential drug interactions and tailored treatment strategies.

Dengue Virus: An Overview

Before delving into the complexities of co-infections, it's crucial to understand the virology, transmission, and pathogenesis of DENV.

1. Virology and Transmission

DENV, a member of the *Flaviviridae* family, is a single-stranded RNA virus with four distinct serotypes (DENV-1, DENV-2, DENV-3, and DENV-4). Infection with one serotype provides lifelong immunity to that specific serotype, but subsequent infection with a different serotype can lead to more severe disease due to antibody-dependent enhancement [6]. DENV is primarily transmitted to humans through the bite of infected female *Aedes* mosquitoes, primarily *Aedes aegypti* and *Aedes albopictus*. These mosquitoes thrive in tropical and subtropical climates, breeding in stagnant water sources commonly found in urban and semi-urban environments [7].

2. Pathogenesis and Clinical Manifestations

Following the bite of an infected mosquito, DENV replicates in macrophages and dendritic cells, spreading to lymph nodes and then to other tissues. The incubation period typically ranges from 4 to 10 days, after which individuals may experience a wide range of symptoms [8], including:

- **Dengue Fever:** Characterized by high fever, headache, muscle and joint pain, rash, nausea, and vomiting. Most cases are self-limiting, resolving within a week [9].
- **Dengue Hemorrhagic Fever:** A more severe form characterized by plasma leakage, thrombocytopenia (low platelet count), and hemorrhagic manifestations (e.g., bleeding gums, bruising).
- **Dengue Shock Syndrome:** The most severe form, characterized by profound shock, organ failure, and a high risk of mortality [10].

The pathogenesis of severe dengue is complex and not fully understood, but it involves a combination of viral factors (e.g., viral load, serotype) and host factors (e.g., pre-existing immunity, genetic predisposition).

Common Dengue Virus Co-infections

DENV co-infections pose a significant public health challenge, particularly in regions where multiple pathogens co-circulate. This section delves into specific co-infections,

discussing their epidemiological overlap, clinical presentations, and potential impact on disease severity [11, 12, 13, 14].

1. Dengue and Malaria

a. Epidemiological Overlap

Dengue and malaria share a striking epidemiological overlap, with both diseases being prevalent in tropical and subtropical regions. This overlap is driven by several factors:

Geographic Distribution: Both DENV and malaria parasites are transmitted by mosquito vectors that thrive in warm, humid climates. Consequently, countries in Southeast Asia, South Asia, Africa, and Latin America experience a significant burden of both diseases [15].

Vector Ecology: While DENV is primarily transmitted by *Aedes* mosquitoes, malaria is transmitted by *Anopheles* mosquitoes. Interestingly, both mosquito genera often share breeding habitats, particularly in urban and peri-urban areas with poor water management. This co-existence of vectors increases the likelihood of individuals being exposed to both pathogens [16].

Seasonal Transmission: Both dengue and malaria exhibit seasonal transmission patterns, often peaking during and after the rainy season when mosquito populations are highest. This temporal overlap further increases the risk of co-infection [17].

b. Clinical Manifestations and Diagnostic Challenges

The clinical presentations of dengue and malaria can be remarkably similar, making diagnosis challenging, especially in resource-limited settings where laboratory testing may be limited [18]. Both diseases can present with:

Fever: High-grade fever is a hallmark of both dengue and malaria.

Headache: Both infections can cause severe headaches.

Muscle and Joint Pain: Myalgia and arthralgia are common symptoms of both diseases.

Thrombocytopenia: Low platelet count is a common laboratory finding in both dengue and malaria.

This significant overlap in clinical features often leads to misdiagnosis, with dengue being mistaken for malaria and vice versa. Misdiagnosis can have serious consequences, as it can delay appropriate treatment and potentially worsen outcomes. For instance, antimalarial drugs are ineffective against DENV and may even increase the risk of bleeding complications in dengue patients [19].

c. Impact on Disease Severity

The impact of dengue-malaria co-infection on disease severity is complex and not fully understood. Some studies suggest that co-infection may lead to more severe disease, while others have reported conflicting results [20].

Potential for Synergistic Effects: Co-infection could potentially lead to a more severe clinical course due to several mechanisms:

Immune Modulation: Malaria infection can suppress the immune system, potentially making individuals more susceptible to severe dengue.

Increased Inflammation: Both dengue and malaria can trigger a strong inflammatory response. Co-infection could lead to an exaggerated inflammatory response, contributing to severe manifestations like plasma leakage and shock.

Organ Dysfunction: Both infections can affect multiple organ systems. Co-infection could increase the risk of organ damage, particularly in the liver, kidneys, and lungs.

Conflicting Evidence: Some studies have reported higher rates of severe dengue, longer hospital stays, and increased mortality in patients with dengue-malaria co-infection. However, other studies have found no significant difference in disease severity between co-infected patients and those with single infections ^[21].

d. Diagnosis and Management

Accurate and timely diagnosis is crucial for managing dengue-malaria co-infection.

Laboratory Diagnosis

Microscopy: Examination of blood smears under a microscope remains the gold standard for malaria diagnosis.

Rapid Diagnostic Tests: RDTs for malaria are available and provide rapid results, but their sensitivity can vary depending on the parasite species and density.

Molecular Tests: Polymerase chain reaction tests can detect both DENV and malaria parasites with high sensitivity and specificity.

Serological Tests: Tests detecting DENV and malaria antibodies can be helpful in confirming past infections.

Malaria Treatment: Prompt treatment with appropriate antimalarial drugs is essential for malaria.

Dengue Management: Supportive care, including fluid management, is crucial for dengue. There is no specific antiviral treatment for dengue.

2. Dengue and Leptospirosis

a. Epidemiological Overlap

Dengue and leptospirosis, both climate-sensitive diseases, often co-occur in regions experiencing heavy rainfall and flooding. This overlap is driven by:

Shared Risk Factors: Both infections are associated with exposure to contaminated water. Flooding can create breeding grounds for mosquitoes and facilitate the spread of leptospire, bacteria that can infect humans through contact with water or soil contaminated with animal urine ^[22].

Occupational Hazards: Individuals working in agriculture, sanitation, or other occupations involving contact with animals or contaminated water are at increased risk of both infections ^[23].

b. Clinical Manifestations and Diagnostic Challenges

Differentiating dengue from leptospirosis can be clinically challenging due to overlapping symptoms, including:

Fever: Both infections typically present with high fever.

Headache: Severe headache is common in both diseases.

Muscle Pain: Myalgia, particularly in the calves, is a hallmark of leptospirosis but can also occur in dengue.

Conjunctival Suffusion: Redness of the eyes, a characteristic feature of leptospirosis, can also be seen in some dengue cases.

However, some clinical features can help distinguish the two infections:

Rash: While a rash is common in dengue, it is typically absent in leptospirosis. **Jaundice:** Yellowing of the skin and eyes (jaundice) is more common in leptospirosis, indicating liver involvement.

Hemorrhagic Manifestations: While both infections can cause bleeding, severe hemorrhagic manifestations are more characteristic of severe dengue.

c. Impact on Disease Severity

Co-infection with dengue and leptospirosis can lead to more severe disease and increased risk of complications.

Increased Organ Damage: Both infections can affect multiple organs, including the liver, kidneys, and lungs. Co-infection can exacerbate organ dysfunction, leading to a higher risk of organ failure.

Increased Bleeding Risk: Leptospirosis can cause abnormalities in blood clotting factors. Co-infection with dengue could increase the risk of severe bleeding, particularly in patients who develop dengue hemorrhagic fever.

d. Diagnosis and Management

Laboratory Diagnosis: Leptospirosis Testing: Serological tests, such as the microscopic agglutination test, are commonly used to diagnose leptospirosis.

Dengue Testing: As previously mentioned, molecular and serological tests can confirm dengue infection.

Antibiotic Therapy: Leptospirosis is treatable with antibiotics, such as penicillin or doxycycline. Early initiation of antibiotics is crucial for improving outcomes.

Dengue Management: Supportive care remains the mainstay of dengue management.

3. Dengue and Chikungunya

a. Epidemiological Overlap

Dengue and chikungunya, both transmitted by *Aedes* mosquitoes, often co-circulate in the same geographic areas, leading to a high risk of co-infection.

Shared Vector: Both viruses are primarily transmitted by *Aedes aegypti* and *Aedes albopictus* mosquitoes.

Similar Geographic Distribution: Dengue and chikungunya are prevalent in tropical and subtropical regions worldwide, particularly in Southeast Asia, Africa, and the Americas.

b. Clinical Manifestations and Diagnostic Challenges

Dengue and chikungunya share several clinical features, making diagnosis challenging:

Fever: Both infections typically present with high fever.

Joint Pain: Severe joint pain (arthralgia) is a hallmark of both diseases.

Headache: Headache is common in both infections.

Rash: Both dengue and chikungunya can cause a rash. However, some distinguishing features can aid in diagnosis:

Type of Joint Pain: Chikungunya typically causes more debilitating joint pain, often affecting multiple joints symmetrically.

Persistence of Joint Pain: Joint pain in chikungunya can persist for weeks, months, or even years after the acute infection, while dengue-associated joint pain usually resolves within a few days.

4. Impact on Disease Severity

The impact of dengue-chikungunya co-infection on disease severity is not fully elucidated, and more research is needed.

a. Potential for Immune Interaction: Co-infection could potentially alter the immune response to either virus, leading to unpredictable outcomes.

b. Increased Morbidity: Co-infection might increase the overall morbidity due to the combined effects of both viruses.

a. Diagnosis and Management

Laboratory Diagnosis:

Molecular Tests: PCR tests can detect both DENV and chikungunya virus RNA in blood samples.

Serological Tests: Tests detecting antibodies to both viruses can aid in diagnosis.

Supportive Care: Both dengue and chikungunya are viral infections, and treatment primarily involves supportive care, including pain relief and fluid management.

5. Dengue and Zika

a. Epidemiological Overlap

Dengue and Zika viruses share a similar geographic distribution and are transmitted by the same mosquito vectors, leading to a significant overlap in transmission.

Shared Vector: Both viruses are primarily transmitted by *Aedes aegypti* and *Aedes albopictus* mosquitoes.

Geographic Co-circulation: Dengue and Zika viruses co-circulate in many tropical and subtropical regions, particularly in the Americas, Southeast Asia, and the Pacific Islands.

b. Clinical Manifestations and Diagnostic Challenges

Distinguishing dengue from Zika can be challenging due to overlapping symptoms:

Fever: Both infections typically present with mild fever.

Rash: Maculopapular rash is common in both dengue and Zika.

Joint Pain: Arthralgia, particularly in small joints of the hands and feet, is common in both infections.

Conjunctivitis: Redness of the eyes (conjunctivitis) can occur in both dengue and Zika.

However, some clinical features can help differentiate the two infections:

Severity of Symptoms: Zika infection is often milder than dengue, with many cases being asymptomatic or causing only mild symptoms.

Presence of Guillain-Barré Syndrome: Zika virus infection has been linked to an increased risk of Guillain-Barré syndrome, a rare neurological disorder, while dengue is not.

Congenital Zika Syndrome: Zika virus infection during pregnancy can cause congenital Zika syndrome, a pattern of birth defects in infants, while dengue does not pose a similar risk.

c. Impact on Disease Severity

The impact of dengue-Zika co-infection on disease severity is not fully understood.

Potential for Immune Enhancement: Some studies suggest that prior dengue infection might enhance Zika virus replication, potentially leading to more severe Zika disease.

d. Diagnosis and Management

Laboratory Diagnosis:

Molecular Tests: PCR tests can detect both DENV and Zika virus RNA in blood or urine samples.

Serological Tests: Tests detecting antibodies to both viruses can aid in diagnosis, but cross-reactivity between dengue and Zika antibodies can complicate interpretation.

Supportive Care: Both dengue and Zika are viral infections, and treatment primarily involves supportive care, including rest, fluids, and pain relief.

Conclusion

The co-circulation of dengue virus with other pathogens, particularly in tropical and subtropical regions, poses significant challenges for diagnosis, treatment, and disease control. The overlapping clinical presentations, potential for misdiagnosis, and the possibility of synergistic effects on disease severity underscore the need for accurate and timely diagnosis, appropriate management strategies, and integrated surveillance systems. Further research is crucial to better understand the complex interactions between dengue virus and other co-circulating pathogens, which will ultimately inform public health interventions and improve patient outcomes in endemic areas.

Credit Authorship Contribution Statement

Sugumar Sujitha: Writing – original draft.

Rengarajan Murugesan: Writing – review & editing, Supervision, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

No data was used for the research described in the article.

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