DOI: 10.55522/jmpas.V13I3.6448 ISSN NO. 2320 – 7418

International peer reviewed open access journal

Journal of Medical Pharmaceutical and Allied Sciences

Journal homepage: www.jmpas.com CODEN: JMPACO

Review article

A review of dengue transmission and dengue therapy among people

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Received - 17-04-2024, **Revised -** 17-05-2024**, Accepted** - 12-06-2024 **(DD -MM-YYYY)**

Refer This Article
Tran Trong Duong, Tran Thai Phuc, Park Sung Jong, Vu Hai Nam, 2024. A review of dengue transmission and dengue therapy among people. Journal of medical pharmaceutical and allied sciences. V 13 - I 3, Pages- 6623 – 6630. Doi: https://doi.org/10.55522/jmpas.V13I3.6448.

ABSTRACT

Dengue fever is a significant threat to global health, caused by the dengue virus and transmitted mainly by Aedes mosquitoes. It is crucial to understand the transmission dynamics of the virus to develop effective control and prevention strategies. Epidemiological studies have provided valuable insights into outbreaks' spread patterns, risk factors, and nature. These are essential for targeted interventions such as vector control, reducing human-mosquito contact, and community-based preventive measures. At the same time, there is a pressing need to develop effective therapies to alleviate the disease burden and reduce mortality associated with dengue outbreaks. Current therapeutic research focuses on antiviral treatments, supportive care strategies, and vaccine development to combat the diverse clinical manifestations of dengue. To address the multifaceted challenges of dengue, there must be a concerted effort toward developing robust preventive measures, innovative therapies, and enhanced diagnostic tools. A comprehensive understanding of its transmission dynamics coupled with effective therapeutic interventions is pivotal in pursuing dengue control and mitigation, as it poses a formidable global health challenge.

Keywords: Dengue fever, Transmission dynamics, Therapy development, Epidemiology, Vector control, Public health, Global health threat.

INTRODUCTION

Global estimates indicate that there are approximately 50 million to 200 million cases of dengue infections on an annual basis, resulting in over 20,000 deaths related to dengue. The World Health Organization (WHO) has identified dengue as the most significant mosquito- borne viral disease globally, owing to its extensive geographic prevalence and the associated disease burden. Disability-adjusted life year (DALY) estimates exhibit some variability, but a 2009 assessment suggested that 700,000 DALYs are lost annually due to dengue on a global scale. The reported cases of dengue in 2011 demonstrate its widespread presence across the globe. Tropical and subtropical regions, inhabited by up to 3.6 billion people, are at risk of dengue virus transmission [10], [13].

Dengue is attributed to the dengue virus, a mosquito-borne pathogen classified within the Flaviviridae family. The primary vehicle for the transmission of dengue is the Aedes aegypti mosquito, which transmits the virus to humans via its bite. The dengue virus has achieved extensive distribution across tropical and subtropical zones worldwide, thereby contributing to the global prevalence of the disease [4].

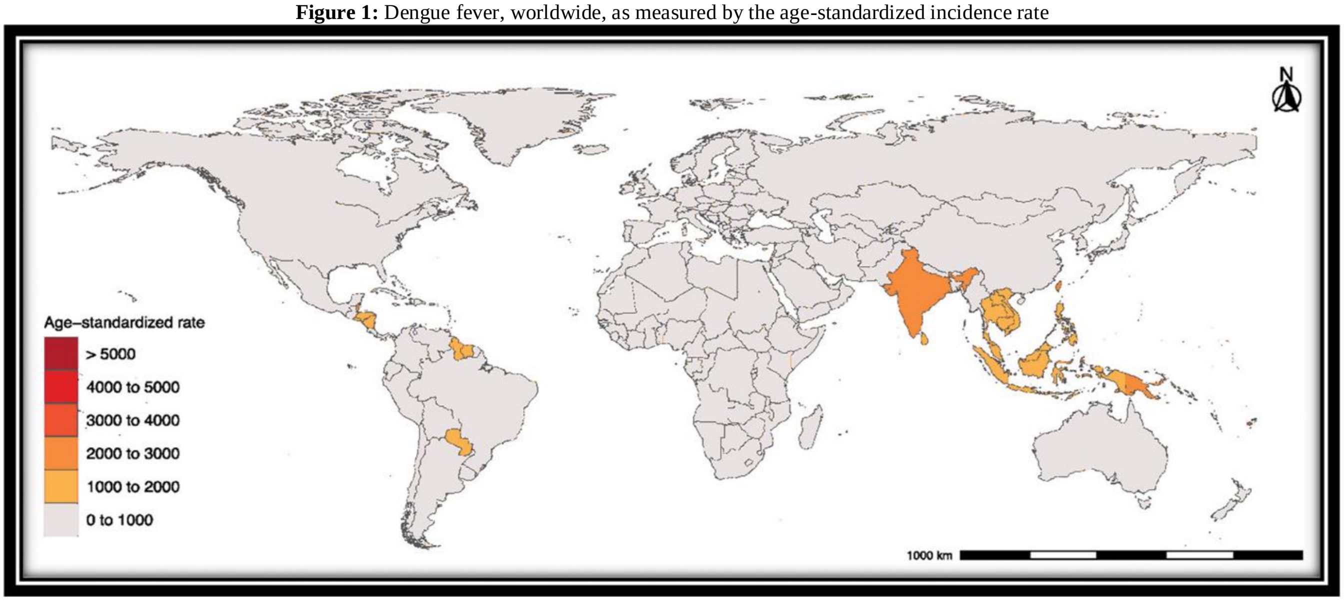
The primary mosquito vector for dengue, Aedes aegypti, is thought to have originated from either Africa or Asia and disseminated through shipping vessels in the 1800s. Dengue, a mosquito-borne viral illness, boasts a lengthy history, with symptoms traceable as far back as the Chin Dynasty between 265 420 AD. The disease underwent additional expansion during World War II when troops dispersed inland, and advancements in modern transportation further facilitated its dissemination. The expansion of dengue is expected to increase due to factors such as climate change, globalization, travel, and viral evolution. Dengue is a complex disease with a wide range of symptoms, which can often be mistaken for other tropical diseases that cause fever [5].

This fever is frequently accompanied by symptoms such as muscle and joint pain, loss of appetite, sore throat, headaches, and a skin rash. The majority of individuals with dengue undergo a self-limiting clinical course, indicating that the disease does not progress to severe forms like dengue hemorrhagic fever (DHF) or dengue shock syndrome (DSS). The risk of developing severe dengue is believed to be heightened in cases of secondary dengue infections or exposure to particularly virulent viral strains.

In severe instances, dengue can give rise to complications such as a low platelet count (thrombocytopenia) and heightened permeability of blood vessels, potentially leading to hemorrhage and shock. As of now, there is no vaccine or specific antiviral therapy specifically designed for the treatment of dengue [6].

The Americas bear an estimated annual cost of dengue amounting to US$2.1 billion, with approximately 60% of this cost attributed to indirect factors such as productivity losses. In Southeast Asia, the economic burden associated with dengue in studied nations is estimated to be around US$950 million annually, with approximately 52% of the costs stemming from productivity loss [7].

Figure 1: Dengue fever, worldwide, as measured by the age-standardized incidence rate



Importance of Understanding Transmission Dynamics and Therapy Development

Comprehending the transmission dynamics and developing therapeutic strategies for dengue is imperative for effective disease control and management. Dengue fever, resulting from the dengue virus, impacts millions globally, especially in tropical and subtropical regions. To successfully control and manage dengue, it is vital to possess a comprehensive understanding of its transmission dynamics. This entails the examination of factors influencing virus spread, including mosquito behavior, human mobility patterns, and environmental conditions.

The Factors thatIinfluence Dengue Transmission are

Mosquito vectors play a crucial role in understanding transmission dynamics. The disease is transmitted through the bite of infected Aedes mosquitoes, primarily Aedes aegypti. Aedes mosquitoes are well-suited for urban environments and are notable for their capacity to breed in small water containers, posing challenges for effective elimination.

- Dengue transmission takes place when infected mosquitoes bite humans, subsequently transmitting the virus to others through subsequent bites.
- The comprehension of human movement patterns, including travel and migration, is valuable in predicting the spread of dengue across diverse geographical areas.[8]

Therapy Development for Dengue

- Vector control campaigns
- Public awareness programs
- Development of dengue vaccines
- Antiviral drugs are being investigated as potential therapeutic options
- Fluid replacement therapy
- Community participation in source reduction activities, such as eliminating stagnant water sources, can also contribute to mosquito control efforts.

Dengue Transmission

Dengue fever stands as a substantial global health threat, primarily transmitted through the bites of Aedes mosquitoes, specifically Aedes aegypti and Aedes albopictus.

Aedes aegypti, particularly prevalent in urban areas, serves as the principal vector for dengue transmission. Adapted to human environments, this mosquito species thrives in close proximity to human habitation. Aedes aegypti's efficiency in transmitting the dengue virus is attributed to its feeding behavior, involving multiple blood meals from different individuals within a single gonotrophic cycle.

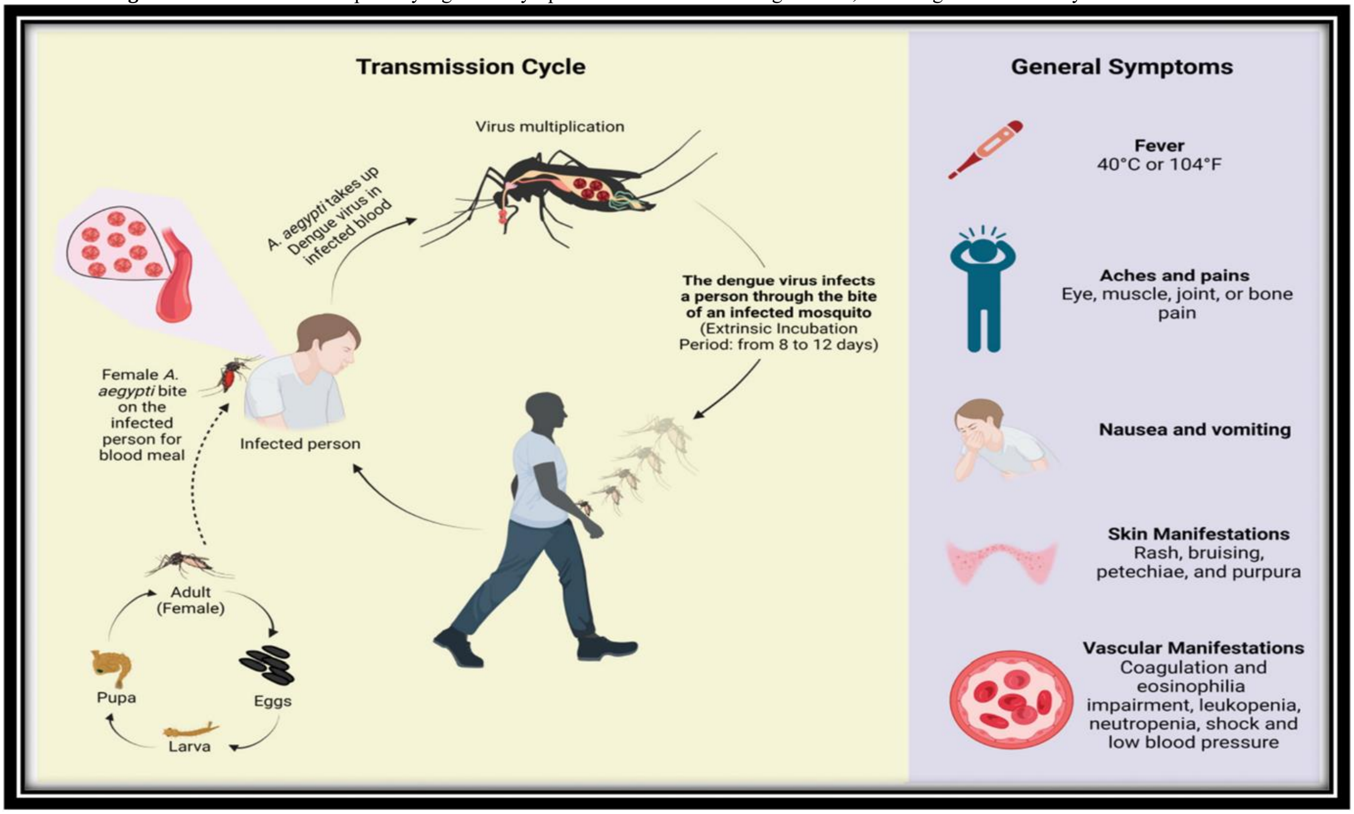
Aedes albopictus, also known as the Asian tiger mosquito, is another significant dengue vector. It exhibits adaptability to a variety of environments, surviving in both urban and rural areas. While less efficient in dengue virus transmission compared to Aedes aegypti, Aedes albopictus can still play a noteworthy role in transmission, especially where it is the predominant mosquito species.

The transmission of dengue occurs when female Aedes mosquitoes become infected with the virus by feeding on an infected individual during the viremic stage of the disease. The virus then replicates within the mosquito's body, spreading to other tissues, including the salivary glands. Subsequent mosquito bites can transmit the virus to susceptible individuals [9].

Efforts to control Aedes mosquitoes and prevent dengue transmission involve diverse strategies, including source reduction aiming to eliminate or modify mosquito breeding sites, such as removing standing water containers and implementing proper waste management practices. Insecticide-treated bed nets and indoor residual spraying are effective measures for reducing mosquito populations and preventing bites.

Community engagement and public awareness campaigns play a pivotal role in promoting personal protective measures, including wearing long sleeves and using mosquito repellents, contributing to comprehensive dengue prevention and control.

Figure 2: A rundown of the primary signs and symptoms associated with dengue fever, including the disease's cycle of transmission



Mosquito-Human-Mosquito Cycle

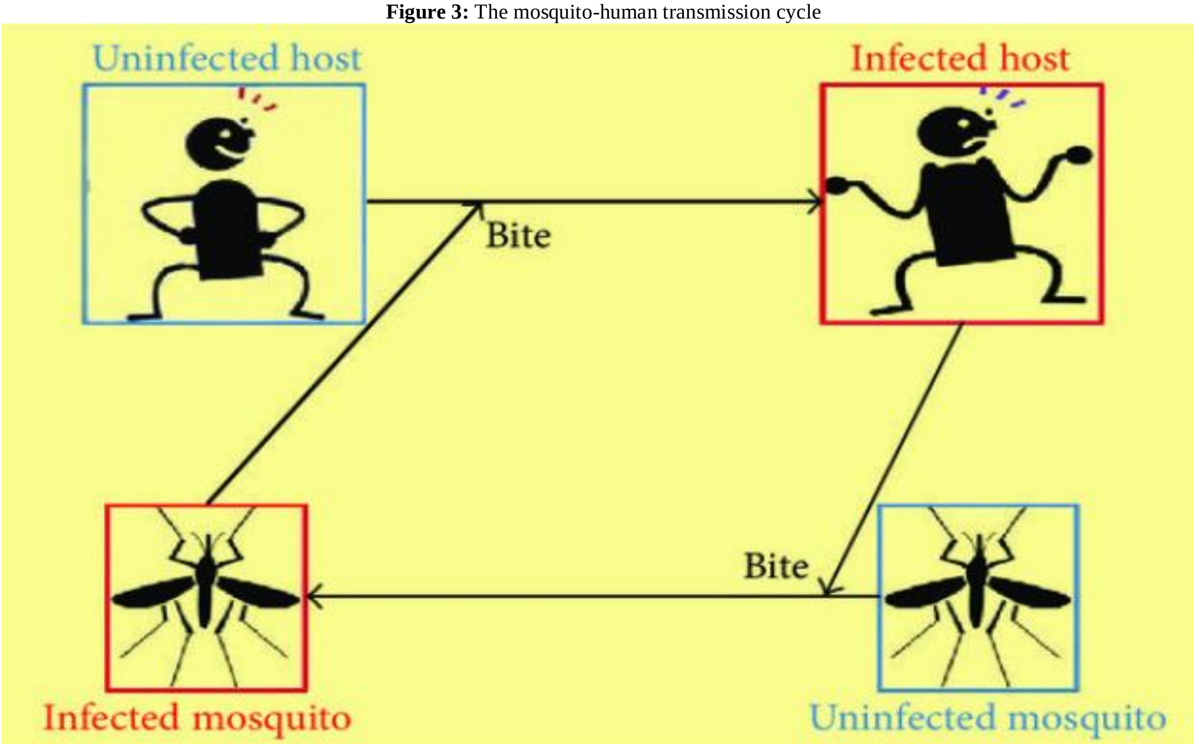
The mosquito-human-mosquito cycle is a pivotal aspect of dengue transmission, involving the transfer of the dengue virus between infected human hosts and Aedes mosquito vectors, ultimately leading to transmission to susceptible individuals. The cycle initiates when a female Aedes mosquito feeds on an infected human during the viremic stage, allowing the virus to replicate and spread within the mosquito. After an incubation period, the mosquito becomes infectious and can transmit the virus to a new human during subsequent blood meals, perpetuating the cycle. The newly infected individual becomes a potential source of infection for other Aedes mosquitoes.

Key factors contributing to the mosquito-human-mosquito cycle include the biting behavior of Aedes mosquitoes, which prefer daytime biting with peak activity during early morning and late afternoon. This behavior heightens the risk of human-mosquito contact and subsequent dengue transmission. Another critical factor is the viremic stage of dengue infection, during which individuals have elevated virus levels in their blood, making them highly infectious to Aedes mosquitoes [10].

Efforts to interrupt this cycle involve various strategies such as vector control, aiming to reduce mosquito populations and prevent human-mosquito contact. This can be achieved through source reduction, which eliminates or modifies mosquito breeding sites, as well as the use of insecticide-treated bed nets and indoor residual spraying. Vaccination is another approach, with promising candidates under development and in clinical trials. Vaccination plays a crucial role in preventing dengue infections, reducing disease burden, and contributing to herd immunity.

Early diagnosis facilitates timely control measures, including targeted vector control campaigns and public awareness programs. Prompt treatment can also lessen the duration and severity of symptoms, potentially reducing the risk of further transmission. A comprehensive approach combining vector control, vaccination, early diagnosis, and treatment is essential for effective dengue control and prevention [11].

Figure 3: The mosquito-human transmission cycle



Factors Influencing Transmission

Factors that influence the transmission of dengue, factors include climate, urbanization, and human behavior, among others. Understanding how these factors contribute to dengue transmission is-

Climate

Climate is a key factor in dengue transmission. The Aedes mosquito vector thrives in warm and humid environments, with optimal temperatures for mosquito growth and reproduction ranging from 25 to 30°C. Changes in climate patterns, such as increased temperatures and rainfall, can lead to increased mosquito populations and higher rates of dengue transmission [12].

Urbanization

Urbanization is another important factor in dengue transmission. Aedes mosquitoes are well- adapted to urban environments and prefer to breed in artificial water containers, such as discarded tires, flower pots, and water storage containers. Rapid urbanization and population growth can lead to increased opportunities for mosquito breeding and human-mosquito contact, increasing the risk of dengue transmission.

Human Behaviour

Human behavior is a crucial factor in dengue transmission. The movement of infected individuals can facilitate the spread of the virus across different geographical areas. Travel and migration patterns can also contribute to the introduction of new dengue serotypes into susceptible populations, increasing the risk of severe disease outcomes. Human behavior can also influence mosquito breeding habitats, such as through improper waste management practices and the storage of water containers.

Socioeconomic

Other factors that influence dengue transmission include socioeconomic status and access to healthcare. Low-income communities are often at higher risk of dengue due to factors such as inadequate housing conditions and limited access to healthcare services. Lack of access to healthcare can lead to delayed diagnosis and treatment of dengue cases, increasing the risk of severe disease outcomes [13], [15].

Geographical Distribution and Outbreaks

Dengue is a major public health concern, with an estimated 390 million infections and 20,000 deaths occurring annually. It is a mosquito-borne viral disease that is endemic in many tropical and subtropical regions of the world. The disease is caused by four serotypes of the dengue virus (DENV-1 to DENV-4) and is transmitted primarily by Aedes mosquitoes, particularly Aedes aegypti and Aedes albopictus.

Dengue is endemic in over 100 countries, with the majority of cases

Geographical Distribution

Occurring in Southeast Asia, the Western Pacific, and the Americas. The disease has also spread to new regions in recent years, including parts of Europe and Africa. The disease is primarily found in tropical and subtropical regions, with the highest burden of cases occurring in Southeast Asia, the Western Pacific, and the Americas [16]. In Southeast Asia, countries such as Thailand, Vietnam, and the Philippines experience a high incidence of dengue. These countries have suitable climatic conditions and dense populations, providing an ideal environment for the Aedes mosquitoes that transmit the virus. The Western Pacific region, which includes countries like Malaysia, Indonesia, and the Pacific Islands, also has a significant dengue burden. In the Americas, dengue is endemic in many countries, particularly in the Caribbean and Central and South America. Countries like Brazil, Mexico, and Colombia report a high number of dengue cases each year. Africa has traditionally been considered a low-risk region for dengue. However, recent outbreaks have been reported in countries like Burkina Faso, Senegal, and Kenya. In Europe, localized outbreaks have occurred in countries such as France and Croatia, mainly as a result of imported cases from endemic regions. Similarly, in the Middle East, countries like Saudi Arabia and Yemen have reported sporadic cases of dengue [17], [18].

Outbreaks

Large-scale outbreaks have occurred in many regions of the world, including Asia, the Americas, and Africa. One of the largest dengue outbreaks on record occurred in Brazil in 2019, with over 2 million cases reported. The outbreak was attributed to a combination of factors, including a high number of susceptible individuals, favorable climatic conditions for mosquito breeding, and inadequate vector control measures [19].

In Southeast Asia, dengue outbreaks occur regularly, with several countries reporting high numbers of cases annually. In 2019, the Philippines declared a national dengue epidemic following a sharp increase in cases. Other countries in the region, such as Thailand and Vietnam, also experience regular dengue outbreaks [20].

In the Americas, dengue is endemic in many countries, particularly in the Caribbean and Central and South America. Large-scale outbreaks have occurred in several countries, including Brazil, Mexico, and Colombia. In 2019, Honduras declared a state of emergency following a surge in dengue cases [21].

In Africa, dengue is an emerging public health threat. While the disease has traditionally been considered rare in Africa, recent outbreaks have been reported in several countries, including Burkina Faso and Senegal. The introduction of new dengue serotypes into susceptible populations is a particular concern in Africa due to the lack of immunity among the population [22].

Pathogenesis

Viral characteristics

The Dengue virus (DENV) exhibits specific characteristics that impact its pathogenesis and interactions with the host immune system.

DENV is an enveloped virus with a single-stranded RNA genome, belonging to the Flaviviridae family and classified into four distinct serotypes (DENV-1 to DENV-4). While these serotypes share a high genetic similarity, they possess distinct antigenic properties [23].

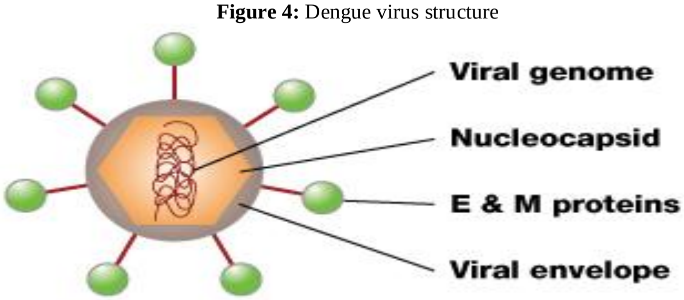
Upon infection, DENV targets host cells, particularly immune cells like monocytes, macrophages, and dendritic cells. Within these cells, the virus undergoes replication, resulting in the production of viral proteins and the release of viral particles.

The host immune response plays a pivotal role in controlling DENV infection. Innate immune cells recognize the virus through pattern recognition receptors (PRRs), triggering the production of interferons (IFNs) and pro-inflammatory cytokines. These cytokines, in turn, activate the adaptive immune response [24].

The adaptive immune response involves the activation of T cells and B cells. CD8+ cytotoxic T lymphocytes (CTLs) within the T cell response play a critical role in eliminating virus- infected cells. B cells produce antibodies that can neutralize the virus and enhance its clearance.

Despite its protective role, the immune response to DENV can also contribute to disease pathogenesis. In some instances, the immune response becomes dysregulated, leading to an exaggerated inflammatory response and increased vascular permeability. This dysregulation can result in plasma leakage, organ damage, and the development of severe dengue [25].

Figure 4: Dengue virus structure



The dengue virus has a roughly spherical shape. Inside the virus is the nucleocapsid, which is made of the viral genome and C proteins. The nucleocapsid is surrounded by a membrane called the viral envelope, a lipid bilayer that is taken from the host. Embedded in the viral envelope are E and M proteins that span through the lipid bilayer. These proteins form a protective outer layer that controls the entry of the virus into human cells.

Clinical Manifestations

The clinical manifestations of dengue can vary widely, ranging from asymptomatic or mild illness to severe forms of the disease. The majority of dengue infections are asymptomatic or result in a self-limiting febrile illness known as dengue fever (DF). DF is characterized by symptoms such as high fever, headache, muscle and joint pain, and rash.

Dengue infection can progress to more severe forms, including dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS). These severe forms of dengue are characterized by plasma leakage, bleeding tendencies, organ impairment, and in the case of DSS, shock.

Early recognition and proper management of dengue are essential to prevent complications and reduce mortality. Treatment primarily focuses on supportive care, such as fluid replacement to maintain hydration and close monitoring of vital signs. In severe cases, hospitalization and intensive care may be required [26].

Diagnostic Methods

The diagnosis of dengue involves the use of various methods to identify the presence of the dengue virus or detect the immune response against it.

Diagnosis

The initial diagnosis of dengue is often based on clinical symptoms and physical examination. Fever, headache, muscle and joint pain, rash, and other characteristic symptoms are considered in conjunction with the patient's travel history or known local dengue activity [27].

Laboratory Tests

Enzyme-Linked Immunosorbent Assay (ELISA)

This serological test detects dengue-specific antibodies in the blood. It can help confirm a recent or past dengue infection.

Polymerase Chain Reaction (PCR)

This molecular test detects the presence of viral genetic material (RNA) in the blood. PCR is useful for early diagnosis and can differentiate between dengue serotypes.

NS1 Antigen Test

This rapid diagnostic test detects the NS1 protein produced by the dengue virus. It is commonly used in the early stages of infection.

Haematological Tests

- **Complete Blood Count (CBC)**

Dengue infection often causes a decrease in platelet count (thrombocytopenia) and white blood cell count (leukopenia). Monitoring these changZes can aid in diagnosis.

- **Tourniquet Test**

This test involves inflating a blood pressure cuff to examine small red spots (petechiae) that appear when the cuff is released. It can indicate vascular fragility, a common feature of dengue infection.

- **Serotyping**

Determining the specific dengue serotype involved in an infection is important for surveillance and outbreak management. It is typically done through specialized laboratory tests [28], [29].

Dengue Therapy and Management

Dengue therapy and management primarily focus on supportive care to manage symptoms and prevent complications. Prevention measures such as vector control and personal protection are crucial in reducing the burden of the disease. Vaccines are available and can protect against all four dengue serotypes but should be used in conjunction with other prevention measures. Early recognition and appropriate management are essential in preventing complications and improving outcomes for individuals with dengue there is currently no specific antiviral therapy for dengue, and treatment primarily focuses on supportive care to manage symptoms and prevent complications [30].

Fluid Replacement

Fluid replacement is a crucial aspect of managing dengue, particularly in severe cases or cases of dengue shock syndrome (DSS). The primary goal is to ensure adequate hydration and prevent complications associated with plasma leakage and dehydration. In mild cases of dengue, oral rehydration therapy (ORT) is typically sufficient. This involves the consumption of oral rehydration solutions containing a balanced mixture of water, salts, and sugars. ORT aids in restoring electrolyte balance and preventing dehydration. However, in severe cases involving significant plasma leakage or shock, intravenous (IV) fluid replacement becomes necessary. IV fluids are administered directly into the bloodstream to rapidly restore fluid volume and maintain blood pressure. The choice and quantity of IV fluids depend on the individual's condition and the severity of the disease. Isotonic crystalloid solutions, such as normal saline or Ringer's lactate, are commonly employed for fluid replacement. These solutions maintain a balanced concentration of electrolytes that closely resemble the body's fluids. Close monitoring of the patient is essential throughout the management process. Maintaining adequate hydration is critical, particularly in severe cases where plasma leakage and dehydration may occur. While ORT is recommended for mild cases, severe cases may require the administration of intravenous fluids to ensure a prompt and effective response to fluid imbalances.

For Fever: Antipyretics such as **paracetamol**

Acetaminophen are commonly used to manage fever and relieve pain. Non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin and ibuprofen should be avoided, as they can increase the risk of bleeding.

Laboratory Tests

Laboratory tests play an important role in the diagnosis and management of dengue. Several laboratory tests are available to detect the presence of the dengue virus or assess the immune response against it.

Enzyme-Linked Immunosorbent Assay (ELISA)

ELISA is a serological test that detects dengue-specific antibodies in the blood. It can help confirm a recent or past dengue infection. ELISA is commonly used in outbreak investigations and surveillance.

Polymerase Chain Reaction (PCR)

PCR is a molecular test that detects the presence of viral genetic material (RNA) in the blood. PCR is useful for early diagnosis and can differentiate between dengue serotypes. It is also used to monitor viral load during the course of the disease.

NS1 Antigen Test

The NS1 antigen test is a rapid diagnostic test that detects the NS1 protein produced by the dengue virus. It is commonly used in the early stages of infection and has high sensitivity and specificity.

Complete Blood Count (CBC)

CBC is a hematological test that measures the number of red blood cells, white blood cells, and platelets in the blood. Dengue infection often causes a decrease in platelet count (thrombocytopenia) and white blood cell count (leukopenia). Monitoring these changes can aid in diagnosis and guide fluid management.

Tourniquet Test

The tourniquet test involves inflating a blood pressure cuff to examine small red spots (petechiae) that appear when the cuff is released. It can indicate vascular fragility, a common feature of dengue infection.

Serotyping

Determining the specific dengue serotype involved in an infection is important for surveillance and outbreak management. It is typically done through specialized laboratory tests. Such as complete blood count (CBC) and haematocrit (HCT) can help assess the severity of the disease and guide fluid management.

Blood Transfusion

In severe cases of dengue, blood transfusions may be necessary to replace lost blood volume or correct bleeding tendencies.

Hospitalization

Hospitalization may be necessary for individuals with severe dengue or those at risk of complications. Intensive care may be required for individuals with dengue shock syndrome (DSS) or severe bleeding.

Limitations of Current Therapies and Vaccines

Despite the progress made in dengue prevention and control, current therapies and vaccines have limitations. Here are some limitations.

Limited Efficacy

The effectiveness of current dengue vaccines varies depending on the vaccine type and the population being vaccinated. The first licensed dengue vaccine, Dengvaxia, has shown variable efficacy in different populations and age groups.

Lack of Specific Antiviral Therapy

There is no specific antiviral therapy for dengue, and supportive care remains the mainstay of treatment.

Risk of Vaccine-Induced Enhancement

There is a potential risk of vaccine- induced disease enhancement, where prior exposure to one dengue serotype may increase the risk of severe disease upon subsequent exposure to a different serotype.

CONCLUSION

This review has provided a comprehensive overview of Dengue transmission and therapy, shedding light on the multifaceted nature of this global health challenge. Dengue continues to exert a significant toll on communities worldwide, with its complex interplay of viral dynamics, clinical manifestations, and challenges in therapeutic intervention. The exploration of Dengue transmission highlighted the pivotal role of Aedes mosquitoes and the intricate relationship between environmental factors and the spread of the virus. Current therapeutic approaches primarily focus on supportive care, and antiviral drugs are still in the early stages of development. The limitations in Dengue therapy underscore the urgent need for research and innovation to identify more effective treatment modalities. Vector control measures, another crucial aspect of Dengue prevention, face obstacles such as insecticide resistance and the need for sustained community engagement.

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