

# A Comprehensive Review, Recent Updates and Challenges of Dengue Fever: A Resurging Tropical Disease

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Date of Submission: 04-12-2023

Date of Acceptance: 17-12-2023

## Abstract

Dengue is the most important arthropod-borne viral disease of public health significance. Compared with nine reporting countries in the 1950s, today the geographic distribution includes more than 100 countries worldwide. Many of these had not reported dengue for 20 or more years and several have no known history of the disease. According to estimates from the World Health Organisation, around 2.5 billion people are susceptible to dengue infection. Initially identified in the 1950s, it has emerged as a primary contributor to infant mortality in numerous Asian and South American nations. Travellers from the US who visit Latin America, Asia, and the Caribbean frequently come into contact with dengue, a mosquito-borne illness that is on the rise. Clinical manifestations can vary from a straightforward fever to shock or hemorrhagic fever. Numerous outcomes can occur over the clinical course, and receiving proper supportive care can significantly lower death rates. A more complex clinical course may result from repeated viral exposures.

**Keywords:** Mosquitoes, Subtropical disease, illness, flaviviruses, Vaccines

## I. INTRODUCTION

One of the most prevalent diseases spread by mosquitoes in tropical and subtropical areas, dengue virus infection can result in anywhere between 100 and 400 million cases of infection annually worldwide (WHO). The global dengue epidemic's distribution suggests that dengue infection outbreaks are occurring everywhere in the

world). A recent WHO report states that DENV is now the second most serious virus-caused illness after COVID-19 due to the rising number of infected cases in 2020. Philippines, Vietnam, India, Colombia, and Brazil were found to have the highest rates of DENV infection among these nations [1]. A major contributing factor to the global spread of diseases carried by mosquitoes is the rapid urbanization process, which can result in poorly planned infrastructure and ineffective management of vector control. According to previous reports, the DENV E protein and ZIKV E protein shared up to 50% of their homology [2]. This resulted in cross reactivity and ADE during the second infection from any flaviviruses, depending on the quantity and specificity of cross reactive antibodies produced by the immune system [3]. Additionally, a review and presentation of recent advancements in diagnostic and therapeutic approaches will be provided to offer potential solutions for addressing the cross-reaction problem. Indeed, until specific, sensitive diagnostic markers and vaccines or therapeutic agents that are sensitive and effective in treating DENV infection are developed, the search for new therapeutic agents and diagnostic markers will never stop [4,5].

## DIFFERENT TYPES OF DENGUE FEVER AND THEIR SYMPTOMS:-

### THE DENGUE VIRUS SEROTYPES –

Dengue virus serotypes include Dengue virus serotype 1 (DENV-1), Dengue virus serotype 2 (DENV-2), Dengue virus serotype 3 (DENV-3), and Dengue virus serotype 4 (DENV-4). Infection with one serotype does not confer immunity to the others,

and subsequent infections with different serotypes can result in more severe forms of dengue [6].

### 1. Dengue Virus Serotype 1 (DENV-1)

DENV-1 is one of the four variants of the dengue virus. Infections with DENV-1 can result in dengue fever, a debilitating illness characterized by symptoms such as high fever, severe headache, pain behind the eyes, joint and muscle pain, rash, and mild bleeding. While many cases of dengue fever are relatively mild, severe forms of the disease can occur, leading to complications such as dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS)[7,8].

### 2. Dengue Virus Serotype 2 (DENV-2)

DENV-2 is another serotype of the dengue virus. Similar to DENV-1, infections with DENV-2 can cause dengue fever and may lead to complications in some cases. The symptoms of dengue fever can range from mild to severe, and severe cases require prompt medical attention. It's important to note that individuals infected with DENV-2 are not immune to the other serotypes, and subsequent infections

with different serotypes can result in more severe symptoms [9,10].

### 3. Dengue Virus Serotype 3 (DENV-3)

DENV-3 is one of the four serotypes responsible for dengue fever. Infections with DENV-3 can manifest with symptoms similar to other serotypes, including high fever, severe headache, joint and muscle pain, and rash. Dengue is transmitted to humans primarily through the bites of infected mosquitoes, emphasizing the importance of mosquito control measures in preventing the spread of the virus[11].

### 4. Dengue Virus Serotype 4 (DENV-4)

Completing the quartet of dengue virus serotypes is DENV-4. Infection with DENV-4 can result in dengue fever, with symptoms that may include high fever, severe headache, pain behind the eyes, joint and muscle pain, and rash. The diversity of symptoms makes the diagnosis of dengue challenging, and healthcare providers often rely on laboratory tests to confirm the presence of the virus[12].

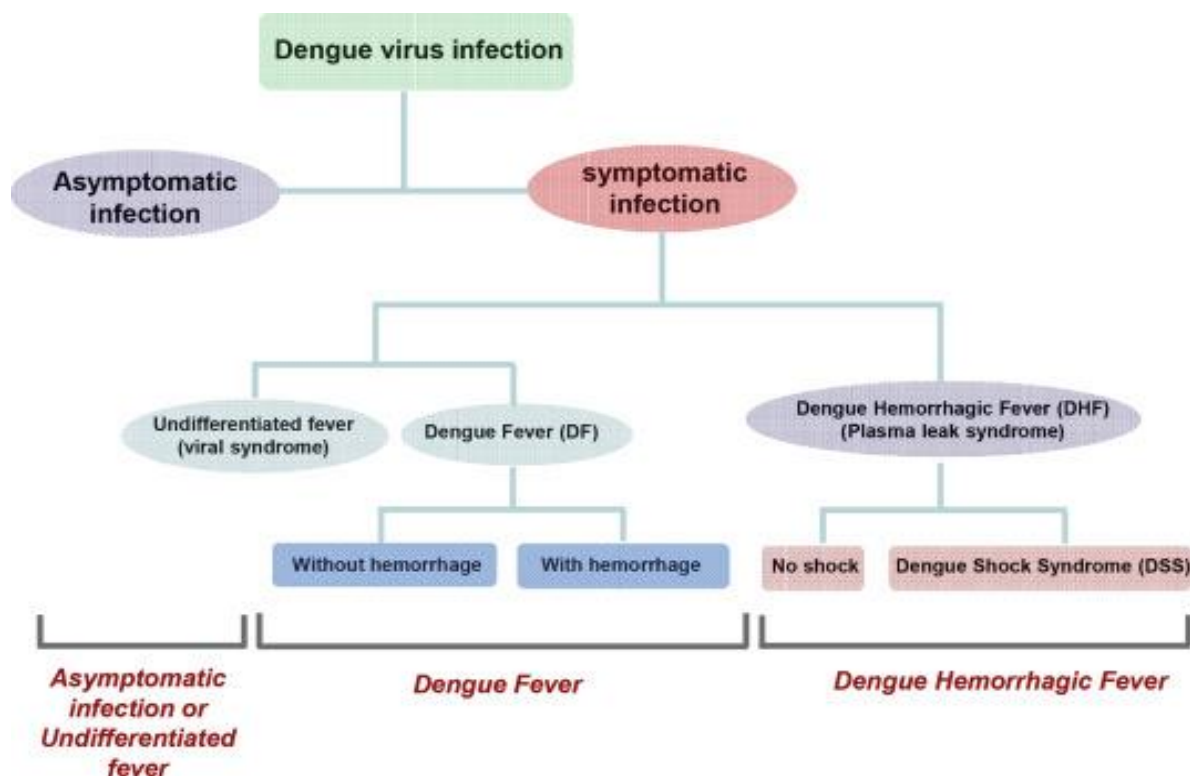


Figure 1. Flow chart of the classification of dengue infection and clinical presentation.

Table 1. The clinical symptoms of dengue infection [13].

S.No.	TYPES	DISCRIPTION	SYMPTOMS	DURATION
1.	Dengue fever	Viral infection caused by DENV Transmitted through the bite of the infected aedes Mosquito.	“Flu-like” syndrome, Retro-orbital pain Fever Rash Intense headache Intense joint and muscle pain Nausea	2-7 days
2;	Dengue Hemorrhagic Fever (DHF)	Also called severe dengue , DHF mainly observed in Children and infants.	Plasma leakage, Pleural effusion, bleeding, Raise in hematocrit levels, Restlessness Abdominal pain, Vomiting Sudden drop in temperature	After 3-5 days of fever
3.	Dengue Hemorrhagic Fever in Pregnancy (DHFP)	DHFP seen in pregnant women than non-pregnant women DHFP is more likely infected in 3 <sup>rd</sup> trimester.	Death of the unborn baby low ,Low birth weight Premature birth, Headache, eyepain.	After 3-5 days of fever
4.	Dengue shock syndromes (DSS)	DSS develops after Dengue hemorrhagic fever It is caused by abnormal and increased host immune responses	Hypotension, Decrease in platelet count leads to leakage of plasma subsequent shock. Fluid accumulation with respiratory distress Critical bleeding , Organ impairment, Cardiorespiratory failure and cardiac arrest.	After 3-5 days of fever

## Dengue Symptoms

Fever with any of the following

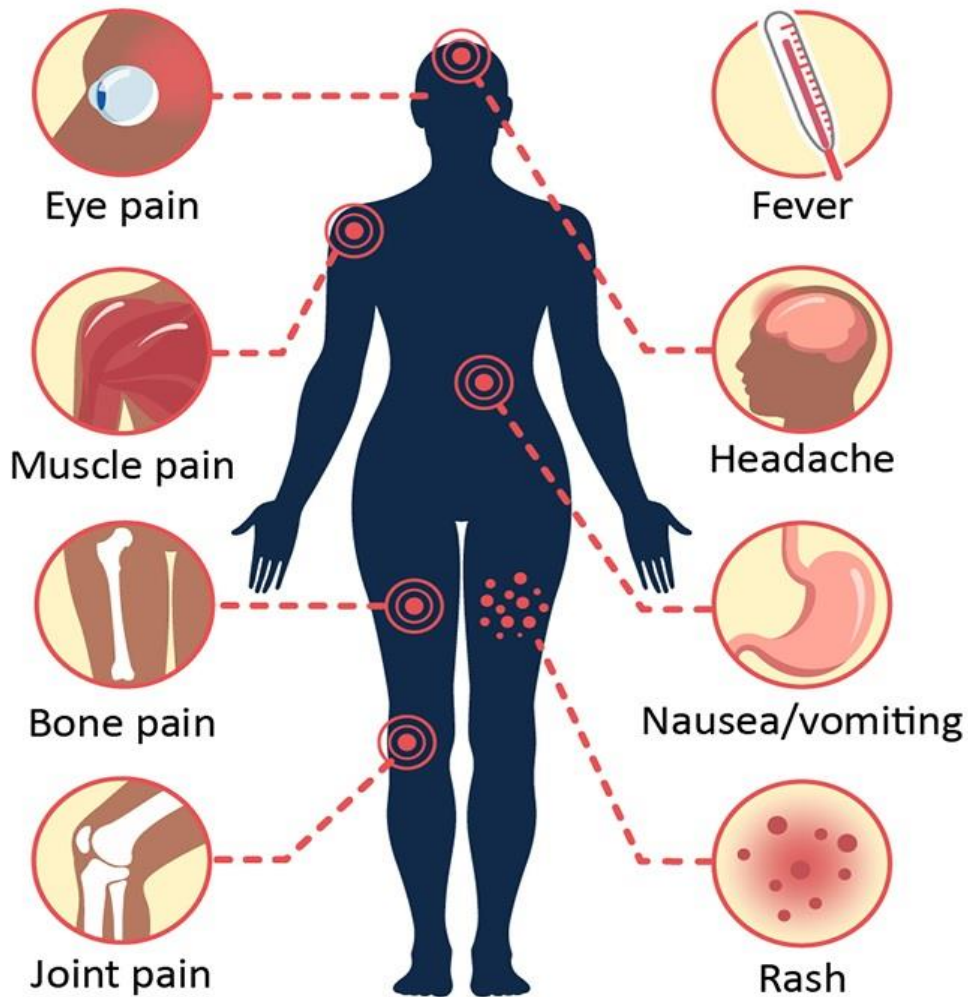


Figure 2: Pictorial depiction of the symptoms of dengue fever

### ETIOLOGY

➤ One of the four dengue viruses is the source of dengue fever (DENV). The bite of an infected mosquito is the means by which humans contract these viruses. The two most prevalent mosquito species that transmit dengue fever are *Aedes aegypti* and *Aedes albopictus*.

➤ The transmission cycle involves the virus circulating between mosquitoes and humans. When a mosquito bites an infected person, it becomes a vector capable of transmitting the virus to

uninfected individuals during subsequent bites[14].

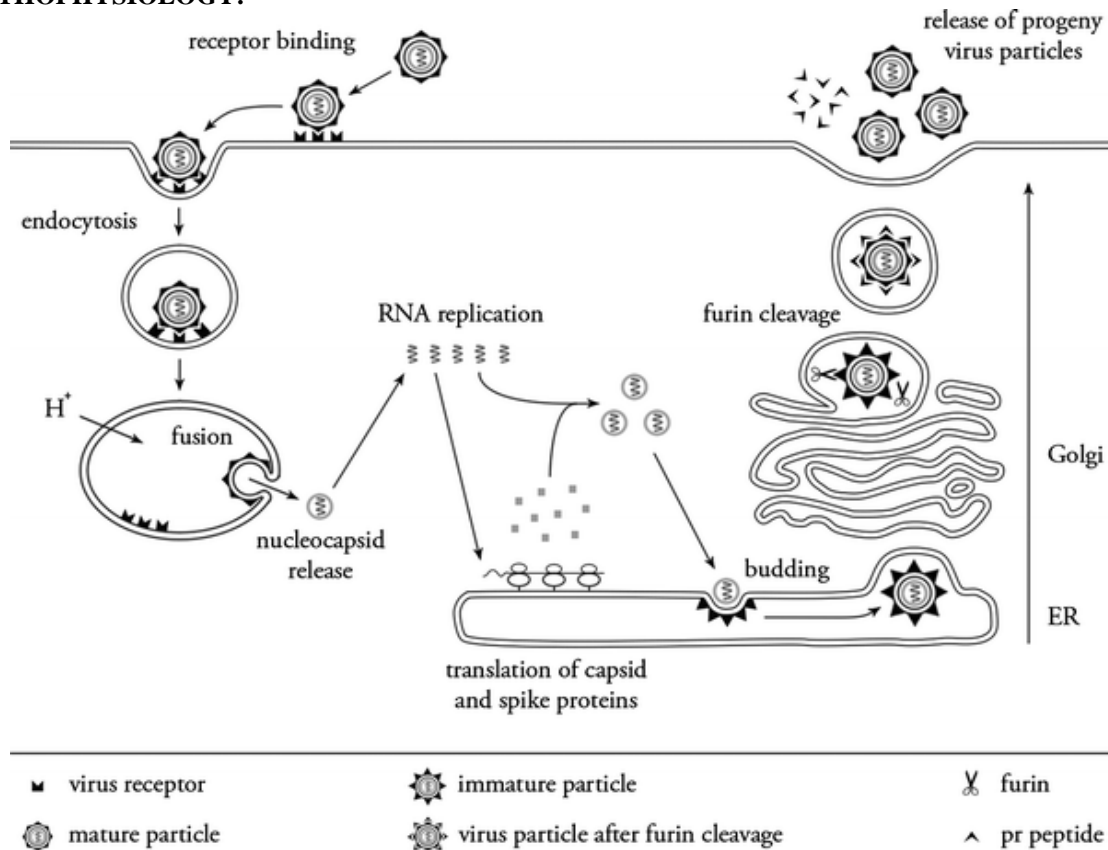
➤ Southeast Asia, the western Pacific islands, Latin America, and Africa are just a few of the tropical and subtropical regions where these mosquitoes are commonly found. The virus first enters the bloodstream through an infected mosquito bite, targets the liver, and then spreads to other organs. There, it multiplies and impedes the liver's ability to function, building up toxins in the blood and causing fever, headache, rash, and muscle soreness. Liver failure could result from its severity

if left untreated.

- Dengue fever is caused by any one of four types of dengue viruses. You can't get dengue fever from being around an infected person. Instead, dengue fever is spread through mosquito bites.
- The two types of mosquitos that spread dengue viruses are common in and around human dwellings. When a mosquito bites a dengue virus-infected person, the virus enters the mosquito. The virus then enters the bloodstream of the person who is bitten by the infected mosquito and causes an infection.
- After you've recovered from dengue fever, you have long-term immunity to the type of virus that infected you — but not to the other three dengue fever virus types. This means you can be infected again in the future by one of the other three virus types. If you get dengue fever for the second, third, or fourth time, your chances of developing severe dengue fever increase. Dengue is caused by the dengue virus, which is transmitted to humans through the bite of infected aedesmosquitoes[15]

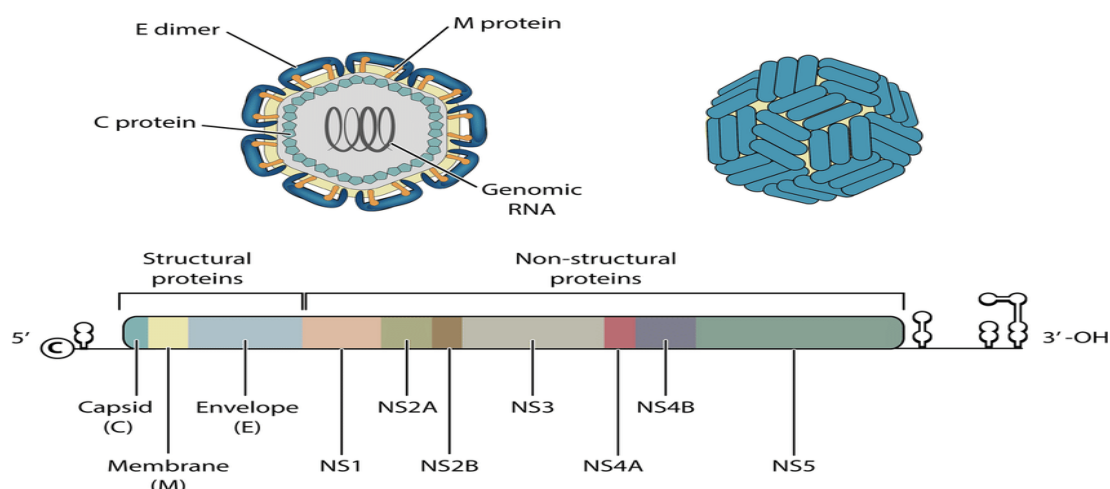
- There are four distinct serotypes of the dengue virus, and infection with own serotype does not provide immunity to the others .
- Aedesaiegypt and Aedesalbopictus mosquitoes are the primary vectors responsible for spreading dengue.
- Urbanization and population growth have led to an increase in breeding sites for aedes mosquitoes, contributing to dengue's prevalence .
- Climate factors, such as temperature and rainfall, can affect mosquito population and dengue transmission rates.
- Travel and global mobility can facilitate the spread of dengue from one region to another when infected individuals carry the virus with them
- Inadequate mosquito control measures and limited access to healthcare can exacerbate dengue outbreaks in affected areas .
- Lack of an effective vaccine for all dengue serotypes makes prevention and vector control crucial in controlling the disease[16].

**PATHOPHYSIOLOGY:-**



**Figure.3:** The Dengue virus life cycle. Details are in the text.





**Figure 4:** Schematic representation of Dengue virus genome.

One of the flaviviruses that originated in the family Flaviviridae is DENV. Dengue shock syndrome (DSS) and dengue hemorrhagic fever (DHF) are serious symptoms that can result from multiple infections with any of the four antigenically distinct DENV serotypes (DENV-1, DENV-2, DENV-3, and DENV-4) [17]. DENV is a small, icosahedral enveloped virus. Its matured enveloped structure, known as virions, is made up of seven non-structural (NS) proteins, such as NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5, and three types of structural proteins, including capsid (C), envelope (E), and membrane (M) (Clyde. Primarily the structural proteins involved in the assembly of viruses [18]. To assemble a nucleocapsid, for instance, C protein interacts with RNA. M protein, which is crucial in identifying various immune responses against various flaviviruses infections, aids in the formation of mature virus particles in E protein. According to Modis et al., it is also one of the main components of DENV that functions as a surface protein to aid in the virus's attachment and fusion on the membrane of the host cell. In addition, oligomerization of M protein can result in the formation of a structural virus particle [19]. However, the replication of the viral genome, translation, encapsidation, and appropriate folding of the viral proteins depend on non-structural proteins and cellular proteins, and these processes all take place in the cytoplasm connected to the rough endoplasmic reticulum [20].

## DIAGNOSIS OF DENGUE FEVER

### Clinical diagnosis –

➤ A blood test to look for the virus or antibodies to it can help doctors diagnose dengue infection. Inform your doctor if you become ill after

traveling or living near people who have a dengue infection. This will allow your doctor to assess the possibility that your symptoms were caused by a dengue infection. • Because the body's immune response to the virus is complex and dynamic,

➤ doctors may recommend a combination of blood tests and imaging tests to diagnose dengue fever infection. Dengue infection is difficult to diagnose without laboratory and radiology tests because the symptoms are similar to those of other diseases such as malaria at first [21, 22].

### Tests of DENGUE FEVER

➤ **Complete blood count (CBC or CBP)** -to check the platelet count, which is typical of the later stages of the illness, and to detect the decrease in hematocrit, hemoglobin, and red blood cell (RBC) count (evidence of anemia) associated with severe dengue fever blood loss[23].

➤ **Dengue Serology Test (Dengue IgG&IgM)** - to detect antibodies produced by the immune system after a person has been exposed to the virus; in both primary and secondary infections, these tests are most effective when performed at least 4 days after exposure[24].

➤ **Dengue Virus Antigen Detection (NS1)** - Dengue viral infection must be confirmed. This test is useful for detecting early dengue infection and can be performed within 1-2 days of infection [25]. In the event of severe symptoms Other blood tests and radiology imaging tests that doctors may recommend to determine the spread of dengue infection to other organs include[26].

➤ **Liver function tests (LFT)** -to detect mild elevations in serum bilirubin, elevated transaminases, and serum albumin derangements

caused by the hepatotoxic effects of the Aedes mosquito virus, which can also lead to acute liver failure with fatal outcomes [27].

➤ **Renal Function Test (RFT)** -Acute renal failure, acute tubular necrosis, hemolytic uremic syndrome, hypotension, rhabdomyolysis, proteinuria, glomerulopathy, nephrotic syndrome, or hemolysis can all be caused by an increase in serum creatinine levels [28].

➤ **ECG** -to check the heart electrical disturbances. Many patients had ECG abnormalities, primarily sinus Brady arrhythmias, ventricular asystole, sinus tachyarrhythmia's, supraventricular tachycardia (SVT), and ST- and T-wave changes caused by dengue infection's electrolyte abnormalities of potassium, calcium, and magnesium[29].

➤ **Ultrasound abdomen (USG)** -to rule out conditions such as serositis, fluid in the abdomen, gallbladder edema, pericholecystic fluid, and ascites (fluid buildup in spaces within your abdomen) caused primarily by dengue fever infection[30].

➤ **Chest X-ray** -to monitor pleural effusion (the accumulation of excess fluid between the layers of the pleura (the tissues that line the lungs and chest) and pericardial effusion (the accumulation of fluid in the saclike double-layered structure around the heart known as the pericardium) caused by dengue fever infection[31].

➤ **D-dimer** -D-dimer is a protein fragment formed when a blood clot dissolves in your body, and its level in the blood can be measured. Dengue fever infection can raise D-dimer levels in the blood, causing pain throughout the body, sharp chest pain, high fever, difficulty breathing, and changes in the skin color of your arm or leg[32].

➤ **2D echocardiography (2D Echo)** - used to assess heart muscle damage. Severe dengue fever has structural and functional effects on the heart. Cardiac complications caused by dengue virus infection range from self-limiting arrhythmias to severe myocardial infarction, which can result in hypotension, pulmonary edema, and cardiogenic shock [33].

➤ **A fibrinogen test** -to determine fibrinogen levels, Fibrinogen is a blood protein produced in the liver that aids in blood clotting. Low fibrinogen levels may make blood clotting difficult. If you have complicated dengue hemorrhagic fever and are prone to excessive bleeding, your doctor may recommend this test to check your fibrinogen levels[34].

➤ **Fibrin degradation products blood test** - to examine the FDP levels, Fibrin degradation

products (FDPs) are the substances that remain after blood clots dissolve. FDP elevations may indicate primary or secondary fibrinolysis (clot-dissolving activity) caused by dengue hemorrhagic fever [35].

## PHARMACOTHERPY OF DENGUE FEVER PHARMACOLOGICAL TREATMENT

**a.** There is no specific treatment for dengue infection. If you suspect you have dengue fever, take acetaminophen-containing pain relievers and avoid aspirin-containing medications, which may worsen bleeding. Rest, drink plenty of fluids, and consult your doctor. If you begin to feel worse within the first 24 hours after your fever has subsided, you should go to the hospital right away to be checked for complications. Fever and Pain Management:

**b.** **Acetaminophen (Paracetamol)** to reduce fever and alleviate pain [36].

**c.** **Fluid Replenishing: Intravenous Fluids:** In case of severe dehydration or shock [37].

**d.** **Blood Component Transfusion:** In severe cases with significant bleeding or a low platelet count, this procedure is used [38].

**e.** **Antipyretics and Analgesics: Use:** Because of the risk of bleeding, nonsteroidal anti-inflammatory drugs (NSAIDs) are generally avoided [39].

**f.** **Antiemetic's:** Used to treat nausea and vomiting [40].

## NON PHARMACOLOGICAL TREATMENT

There are several homeopathic remedies that are thought to be very effective in treating dengue fever, but the top five are as follows[41].

### **Perfoliatum Eupatorium**

The homeopathic remedy Eupatorium Perfoliatum is an excellent treatment for Dengue Fever. This medication is mostly prescribed to patients who have severe muscle and joint pains as well as a high fever.

### **Gelsemium**

Gelsemium is one of the most effective homeopathic remedies for Dengue Fever. It is very effective for patients who have extreme weakness and prostration. Furthermore, it is very effective for patients who have pain in the back of their heads.

### **Belladonna**

Belladonna is one of the most prescribed homeopathic remedies for Dengue Fever. It is very effective when pain is marked in the sides of head (temples). In such cases, pain is quite violent and throbbing in nature [41].

### RhusTox

RhusTox is another effective homeopathic remedy for Dengue Fever. It is usually prescribed to patients who have joint pains or general body aches because it helps to relieve pain while also treating Dengue Fever. In such cases, a person's pain is generally relieved by movement, whereas rest causes the pain to worsen. Bryonia Alba. This homeopathic medicine has been shown to be very

effective in treating Dengue Fever. The most noticeable symptom of using this medicine is the worsening of pains by even the slightest movement. However, because the precise prescription of the right medicine is dependent on the individual symptoms of the patient, it is always recommended to consult with an experienced homeopathic doctor and to avoid self-medication [41].

### PREVENTION OF DENGUE FEVER

## Dengue Fever Prevention Tips



Figure 5. Tips for Prevention of dengue fever

- Attire that covers as much of your body as possible
- If sleeping during the day, use mosquito nets, preferably nets sprayed with insect repellent window screens.
- Mosquito repellents (containing DEET, Picaridin or IR3535)
- Coils and vaporizers.
- If you get dengue, it's important to:
- Rest
- Drink plenty of liquids
- Use acetaminophen (paracetamol) for pain
- Avoid non-steroidal anti-inflammatory drugs, like ibuprofen and aspirin
- Watch for severe symptoms and contact your doctor as soon as possible if you notice any.
- In some countries, only one vaccine (Dengvaxia) has been approved and licensed. This vaccine, however, can only protect people who have a history of dengue infection. Several additional dengue vaccine candidates are under evaluation[42].

#### DO's and DON'Ts– DENGUE FEVER

#### DON'Ts –

- ✓ DO NOT USE CORTICOSTEROIDS. They are not recommended and may increase the risk of GI bleeding, hyperglycemia, and immunosuppression.
- ✓ DON'T give platelet transfusions if your platelet count is low. Platelet transfusions do not reduce the risk of severe bleeding and may instead result in fluid overload and prolonged hospitalization.
- ✓ DO NOT use half normal (0.45%) saline. Half normal saline should not be given, even as a maintenance fluid, because it leaks into third spaces and may worsen ascites and pleural effusions.
- ✓ DON'T ASSUME that IV fluids are required. First, see if the patient can take fluids orally. Use only the bare minimum of IV fluid to keep the patient well-perfused. Reduce the IV fluid rate as hemodynamic status improves or urine output increases[42].

#### DO's –

- ✓ DO notify outpatients when they should return. Teach them about the warning signs and when to look for them, as well as the critical period



that follows defervescence.

✓ DO be aware of the critical period. The critical period lasts 24-48 hours and begins with defervescence. Some patients may rapidly deteriorate during this time.

✓ DO keep a close eye on fluid intake and output, vital signs, and hemoglobin levels. Ins and outs should be measured at least once per shift, and vitals should be taken every 4 hours. During the critical period, hematocrits should be measured every 6-12 hours at a minimum.

✓ DO give PRBCs or whole blood if there is clinically significant bleeding. Transfuse blood immediately if the hematocrit drops along with unstable vital signs or if significant bleeding is visible[42].

✓ DO recognize and treat early signs of shock. Early shock is distinguished by narrowing pulse pressure (systolic minus diastolic BP approaching 20 mmHg), increased heart rate, and delayed capillary refill or cool extremities.

#### **CURRENT UPDATES ON DENGUE FEVER**

➤ January 2022, there wasn't a widely approved vaccine for dengue fever, though research and development efforts were ongoing. It's important to note that developments in the field of vaccines can occur rapidly, and information can change. Therefore, for the most current updates on dengue fever vaccines, please refer to authoritative sources such as health organizations, government health departments, and research institutions.

➤ Dengue fever is a mosquito-borne viral infection caused by the dengue virus, which is primarily transmitted by the *Aedes aegypti* mosquito. The disease is prevalent in tropical and subtropical regions, posing a significant public health challenge. Dengue fever can range from mild to severe, with severe cases leading to dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS), which can be life-threatening.

➤ Due to the lack of a specific antiviral treatment, the importance of preventive measures such as vector control and, potentially, vaccination has been emphasized. Various research initiatives and clinical trials have been conducted over the years in order to develop an effective and safe dengue vaccine[43].

#### **HISTORICAL CONTEXT:**

The search for a dengue vaccine has a long history, with research accelerating in response to the disease's growing global burden. Early attempts were hampered by the dengue virus's complexity, which has four distinct serotypes (DENV-1, DENV-

2, DENV-3, and DENV-4). Infection with one serotype confers lifelong immunity to that serotype; however, subsequent infections with different serotypes increase the risk of severe dengue [43].

#### **KEY MILESTONES of DF**

##### **1. First Dengue Vaccine (Dengvaxia):**

One of the significant milestones in dengue vaccine development was the approval of Dengvaxia (CYD-TDV) by Sanofi Pasteur. Dengvaxia, a live attenuated tetravalent vaccine, was developed to provide immunity against all four dengue serotypes. It received its first regulatory approval in Mexico in 2015. However, subsequent developments raised concerns about its safety and efficacy [44].

##### **2. Challenges with Dengvaxia:**

Dengvaxia faced challenges related to its use in individuals who had not been previously exposed to the dengue virus. In some cases, vaccination appeared to increase the risk of severe dengue in seronegative individuals. This led to a reassessment of Dengvaxia's use and highlighted the need for careful consideration of the target population and serostatus [45].

##### **3. Ongoing Research and Development:**

In the aftermath of Dengvaxia's challenges, researchers continued to explore alternative vaccine candidates. Several other vaccine candidates are in various stages of development, including those using different technological platforms such as recombinant proteins, viral vectors, and nucleic acid-based approaches [46].

#### **CURRENT VACCINE LANDSCAPE:**

##### **➤ TAK-003 (Takeda's Dengue Vaccine Candidate):**

TAK-003, a live attenuated tetravalent dengue vaccine developed by Takeda, has shown promise in clinical trials. It demonstrated efficacy against severe dengue and overall reduction in dengue cases in a Phase 3 trial. TAK-003 has received regulatory approval in some countries, and additional evaluations are underway [43].

##### **➤ National Institute of Allergy and Infectious Diseases (NIAID) TV003/TV005:**

TV003 and TV005 were developed by the National Institute of Allergy and Infectious Diseases (NIAID). Clinical trials have shown that these vaccine candidates are effective against dengue[47].

##### **➤ Other Vaccine Candidates:**

A number of other vaccine candidates are in various stages of clinical development. These include vaccines that employ various technologies, such as virus-like particles, subunit vaccines, and novel approaches to eliciting a protective immune

response.

## CONSIDERATIONS AND CHALLENGES

### ➤ Global Disease Burden

**Consideration:** Dengue fever is a major global health concern, with an estimated 390 million infections per year, approximately 96 million of which manifest clinically [48].

### ➤ Population Immunity and Epidemiological Considerations

The deployment of a dengue vaccine necessitates careful consideration of the target population as well as the local epidemiological context. Vaccination strategies must account for the variable prevalence of different serotypes in different geographical areas [49].

### ➤ Serotype Diversity and Antibody-Dependent Enhancement (ADE)

The presence of four dengue virus serotypes (DEN-1 to DEN-4) increases the risk of severe dengue due to antibody-dependent enhancement (ADE) in secondary infections with a different serotype [50].

### ➤ Long-Term Efficacy and Safety

It is critical to ensure the long-term efficacy and safety of dengue vaccines. Continuous monitoring and surveillance are required to detect any rare adverse events and to assess the duration of vaccine protection [51].

### ➤ Vector Control Challenges:

**Challenge:** *Aedes* mosquitoes, particularly *Aedes aegypti* and *Aedes albopictus*, are efficient vectors for dengue virus transmission. Vector control strategies face challenges due to urbanization, climate change, and insecticide resistance [52].

## II. CONCLUSION

In conclusion, the landscape of dengue fever vaccines is dynamic and evolving. The field has seen notable progress with the development and approval of vaccines like Dengvaxia and TAK-003. However, challenges related to vaccine safety, efficacy, and the complex nature of dengue virus interactions persist. Ongoing research and development efforts, including the exploration of new technologies, provide hope for improved and more widely applicable dengue vaccines in the future. For the most up-to-date information on dengue fever vaccines, including regulatory approvals, ongoing clinical trials, and emerging developments, it is recommended to refer to official health organizations, research institutions, and regulatory authorities. Staying informed about the latest advancements is crucial for addressing the global health impact of dengue fever and enhancing

preventive strategies.

## Acknowledgements

I am thankful to the Management, Principal and all the faculty members for providing necessary facilities to write this review article.

## Conflicts of interest None

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