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Research Article

AN OVERVIEW ON DENGUE FEVER

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Abstract

Dengue fever is the one of the rapidly expanding mosquito-borne viral disease in the world, with high mortality and morbidity rates especially in tropical and subtropical regions. The mosquito involved in the transmission of dengue is Aedes. The circulation of dengue disease is influenced by various factors such as, topography, rainfall, temperature and rapid urbanization or globalization. The clinical symptoms range from unapparent to severe forms and fatal outcomes. Dengue is a most important public health problem due its quick expansion globally and its burdens are currently unfulfilled because of absence of precise treatment, easy diagnostic method for the early phase of infection and successful and well-organized vector control system. Dengue is caused by the dengue virus (DENVs) infection and clinical manifestations include dengue fever (DF), dengue hemorrhagic fever (DHF), or dengue shock syndrome (DSS). Due to a lack of antiviral drugs and effective vaccines, several therapeutic and control strategies have been proposed. A systemic literature review was conducted according to PRISMA guidelines to select proper references to give an overview of DENV infection. Results indicate that understanding the virus characteristics and epidemiology are essential to gain the basic and clinical knowledge as well as dengue disseminated pattern and status. Different factors and mechanisms are thought to be involved in the presentation of DHF and DSS, including antibody-dependent enhancement, immune dysregulation, viral virulence, host genetic susceptibility, and pre-existing dengue antibodies. This study suggests that dissecting pathogenesis and risk factors as well as developing different types of therapeutic and control strategies against DENV infection are urgently needed.

Keywords: Dengue virus, DENV, Dengue haemorrhagic fever, Antibody-dependent.

INTRODUCTION

Dengue fever is a mosquito-borne viral infection which has a sudden onset that follows symptoms such as headache, nausea, weakness, intense muscle and joint pain, swelling of lymph nodes (lymphadenopathy), and rashes on the skin. Many symptoms of dengue fever include gingivitis and swollen palms and soles. Dengue can affect any person but appears to be more serious in immunocompromised people. Because it is caused by one of the five dengue virus serotypes, it is possible to have dengue fever multiple times. It is a life-threatening condition, and it may progress to the most critical form called dengue shock syndrome. [1]

Epidemiology

Dengue virus causes the disease and burdens in most tropical and subtropical regions of the world, mainly in the Caribbean, Central and Southeast Asia and South America. More than hundred countries are affected by dengue virus all over the world each year, and there is a high risk of infection with approximately 3.6 million people live in these countries. The epidemics of dengue virus occurs annually in Australia, Africa, Southern America, Asia. Dengue disease has been historically reported from centuries ago. In 992 AD first, compatible symptoms were noted in Chinese medical encyclopedia. In 1635, the epidemic resembled dengue in West Indies and in 1699 in Central America. It then became common in America in the 20th century. In the 20th century the viral transmission by mosquitoes was discovered.

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In 1953 the dengue viral cases were reported in the Philippines, and DHF was reported in 1956 due to infection by heterologous serotypes or secondary infections. Dengue virus disease affect humans and has become anational and international public health problem for all humansin recent years. The estimation of the World Health Organization in public health is that around 2.7–3 billion humans are actively living in the zones where dengue is transmitted by mosquitoes After World War II, the dengue become a heavy burden on public health, due to the Urbanization. From Philippines the first two outbreaks of Dengue hemorrhagic fever were reported in 1953 and 1956 which may be due to lack of public health support, unplanned urbanization, improper mosquito control measures. Other reasons for dengue outbreaks include overpopulation, a lack of fresh drinking water, air travel, and awareness of health effects. Dengue virus disease affect humans and has become a national and international public health problem for all humans in recent years. The estimation of the World Health Organization in public health is that around 2.7–3 billion humans are actively living in the zones where dengue is transmitted by mosquitoes [2].

Etiology

Dengue virus (DENV) is a single-stranded, positive-sense RNA virus in the Flaviviridae family and the Flavivirus genus. When viewed under the transmission electron micrograph, the virions appear as a bunch of black spots. Yellow fever virus, West Nile virus, St. Louis encephalitis virus, Japanese encephalitis virus, tick-borne encephalitis virus, Kya Sanur Forest disease virus, and Omsk hemorrhagic fever virus belong to this family, and majority of them is transmitted by arthropods (mosquitoes or ticks).

Table 1. Epidemology of dengue fever

Affected	2015		2016		2017		2018		2019		2020		2021#	
States/UTs	*C	D	C	D	C	D	C	D	C	D	C	D	C	D
Andhra Pradesh	3159	2	3417	2	4925	0	4011	0	5286	0	925	0	3285	0
Arunachal Pradesh	1933	1	13	0	18	0	1	0	123	0	1	0	0	0
Assam	1076	1	6157	4	5024	1	166	0	196	0	33	0	55	0
Bihar	1771	0	1912	0	1854	0	2142	0	6712	0	493	2	396	2
Chattisgarh	384	1	356	0	444	0	2674	10	722	0	57	0	854	0
Goa	293	0	150	0	235	0	335	1	992	0	376	0	1073	0
Gujarat	5590	9	8028	14	4753	6	7579	5	18219	17	1564	2	8013	2
Haryana	9921	13	2493	0	4550	0	1898	0	1207	0	1377	0	5671	0
Himachal Pradesh	19	1	322	0	452	0	4672	7	344	2	21	0	195	0
J & K	153	0	79	1	488	0	214	0	439	0	53	0	1051	4
Jharkhand	102	0	414	1	710	5	463	1	825	0	79	0	156	1
Karnataka	5077	9	6083	8	17844	10	4427	4	16986	13	3823	0	5062	5
Kerala	4075	25	7439	13	19994	37	4083	32	4652	16	4399	5	3794	1
Madhya Pradesh	2108	8	3150	12	2666	6	4506	5	4189	2	806	0	11354	0
Meghalaya	13	0	172	0	52	0	44	0	82	0	4	0	16	0
Maharashtra	4936	23	6792	33	7829	65	11011	55	14907	29	3356	10	10320	22
Manipur	52	0	51	1	193	1	14	0	359	0	37	0	44	0
Mizoram	43	0	580	0	136	0	68	0	42	0	67	0	34	0
Nagaland	21	1	142	0	357	0	369	0	8	0	1	0	0	0
Odisha	2450	2	8380	11	4158	6	5198	5	3758	4	496	0	6610	0
Punjab	14128	18	10439	15	15398	18	14980	9	10289	14	8435	22	16511	0
Rajasthan	4043	7	5292	16	8427	14	9587	10	13706	17	2023	7	10984	39
Sikkim	21	0	82	0	312	0	320	0	444	0	11	0	203	0
Tamil Nadu	4535	12	2531	5	23294	65	4486	13	8527	5	2410	0	3665	0
Tripura	40	0	102	0	127	0	100	0	114	0	24	0	31	0
Telangana	1831	2	4037	4	5369	0	4592	2	13331	7	2173	0	5983	0
Uttar Pradesh	2892	9	15033	42	3092	28	3829	4	10557	26	3715	6	21687	7
Uttrakhand	1655	1	2146	4	849	0	689	3	10622	8	76	1	641	1
West Bengal	8516	14	22865	45	37746	46			**NR	NR	5166	0	224	0
A& N Island	153	0	92	0	18	0	49	0	168	0	98	0	157	0
Chandigarh	966	1	1246	0	1125	0	301	0	286	0	265	0	889	0
Delhi	15867	60	4431	10	9271	10	7136	4	5077	0	1269	0	2794	6
D&N Haveli	1154	0	4161	2	2064	0	493	0	1491	2	248	0	383	0
Daman & Diu	165	0	89	0	59	0	163	0	625	2	71	0	219	0
Puduchery	771	0	490	2	4568	7	592	2	2030	2	633	1	752	0
Total	99913	220	129166	245	188401	325	101192	172	157315	166	39419	56	123106	90

Approximately 11,000 nucleotide bases were present in the dengue genome, which codes for a single polyprotein. It is made up of three structural protein molecules (C, prM, and E) that constitute the virus particle and seven non-structural proteins (NS1, NS2a, NS2b, NS3, NS4a, NS4b, and NS5) which are required for viral replication. The five strains of the virus (DENV-1, DENV-2, DENV-3, DENV-4, and DENV-5) are referred to as serotypes because they vary in serum reactivity (antigenicity). The main cause of dengue fever is an infected mosquito bite and besides it, it may be accidentally acquired after vertical transmission, especially in near-term pregnant women through the placenta infected blood products through organ transplantation and even after needle stick injury. [3]

Dengue transmission

Mosquito-to-human transmission: Humans are infected with the virus through bites of the infected female mosquitoes, primarily Aedes aegypti mosquito. Virus replicates in mosquito mid-gut, after feeding on the DENV infected person, before spreading to secondary tissues such as the salivary glands. The time between ingesting the virus and transmitting it to a new host is referred to as extrinsic incubation period (EIP). After an EIP of 8-10 days, mosquito becomes infective and is capable to transmit infection. A person infected with dengue infection becomes infective to the mosquitoes 6-12 hours before onset of disease, and remains infective for 3-5 days. 26 Once infected, the mosquito can transmit the virus for the rest of its life.

Human-to-Mosquito transmission

Mosquitoescan become infected with DENV from people who are infected. This can include people who have the symptomatic dengue infection, people who have yet to develop the symptomatic infection (arepresymptomatic), and people who display no sign/symptoms of illness (they are asymptomatic). Hu-man to mosquito transmission could occur up to2days before somebody shows the symptoms of ill-ness, up to 2 days after fever has resolved. The riskof the mosquito infection in the patient is related with the high viremia and fever. On the other hand, high levels of DENV specific antibodies are related with the decreased risk of the mosquito infection. 26Most individuals are viremic for around 4 to 5 days but viremia could last for about 12 days.

Other modes of the transmission

Dengue is a mosquito-borne viral disease that can also be transmitted in other ways, including:

- **From pregnant person to fetus**

An infected mother can pass the virus to her fetus during pregnancy or around the time of birth

- **Through blood products, organ donation, and transfusions**

Rare cases of transmission have been recorded in laboratory or healthcare settings.

- **Sharing needles**

This can include taking blood from a carrier and transmitting it to a healthy person.

- **Sexual contact**

Some evidence suggests that dengue can be spread through sexual contact.[3]

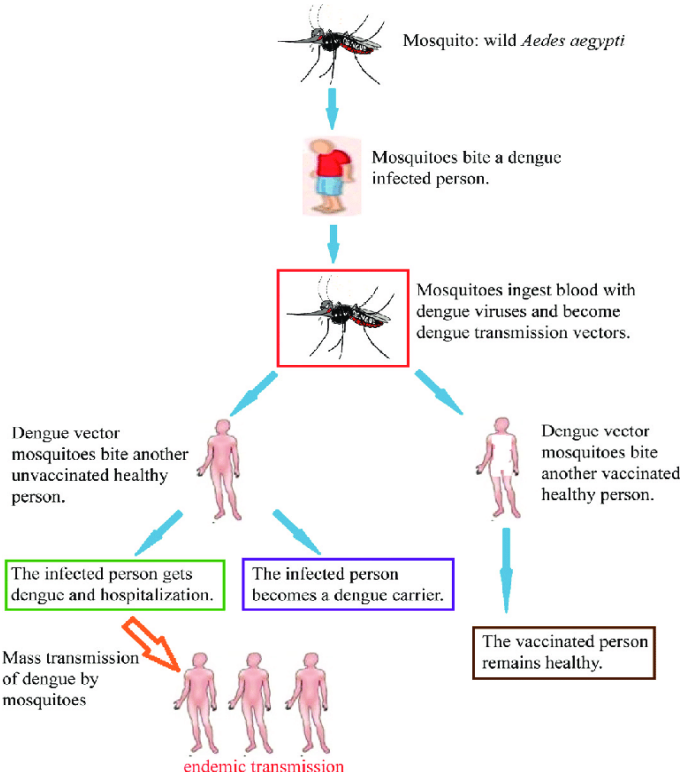

Figure 1. Dengue transmission

Pathology

Dengue virusgainsenters the host organism through the skin following an infected mosquito bite. Humoral, cellular, and innate host immune responses are implicated in the progression of the illness and the more severe clinical signs occur following the rapid clearance of the virus from the host organism. Hence, the most severe clinical presentation during the infection course does not correlate with a high viral load. Alterations in endothelial micro vascular permeability and thromboregulatory mechanisms lead to an increased loss of protein and plasma. Proposed theories suggest that endothelial cell activation caused by monocytes, T-cells, the complement system, and various inflammatory molecules mediate plasma leakage. Thrombocytopenia may be related to alterations in megakaryocytopoiesis, manifested by infection of human hematopoietic cells and compromised progenitor cell growth. This may cause platelet dysfunction, damage, or depletion, leading to significant hemorrhages. [5]

Clinical manifestation

1. **Undifferentiated fever** - most common in primary infection & difficult to differentiate from numerous other viral diseases.
2. **Dengue Fever** - seen in both primary and secondary infections, characterized by biphasic & acute-onset high-grade fever lasting for 3 days to 1week, Severe headache, lassitude, myalgia, joint pains, 50–82% report with a peculiar cutaneous rash, metallic taste, appetite loss, diarrhoea, vomiting, and stomach ache. Bleeding episodes are infrequently seen in DF, although epistaxis and gingival bleeding, substantial menstruation, petechiae/purpura, and gastrointestinal tract (GIT) hemorrhage can occur.
3. **Dengue Hemorrhagic-** Fever - seen during secondary infection and may alsoseen during primary infection in infants.

➢ Clinical parameters: Acute-onset febrile phase – high-grade fever lasting from 2 days to 1 week. Hemorrhagic episodes (at least one of the following forms): Petechiae, purpura, ecchymosis, epistaxis, gingival and mucosal bleeding, GIT or injection site, hematemesis and/or malena.

4. **Dengue shock syndrome-** DSS is defined as DHF accompanied by anunstable pulse, narrow pulse pressure cold, restlessness, clammy skin, and circumoral cyanosis. Progressively worsening shock, disseminated intravascular coagulation and multiorgan damage account for a high mortality rate associated with DSS. The shock persists for a short span of time and the patient can promptly recovers with supportive therapy. [6]

Classification

The WHO classifies DF into two groups:

1. Uncomplicated
2. Severe

Severe cases are linked to excessive hemorrhage, organ impairement, or severe plasma escape, and the remaining cases are considered uncomplicated.

DHF was further subdivided into grades I–IV.
Grade I: Only mild bruising or a positive tourniquet test
Grade II: Spontaneous bleeding into the skin and elsewhere
Grade III: Clinical sign of shock
Grade IV: Severe shock - feeble pulse, and blood pressure cannot be recorded.
Here, grades III and IV comprise DSS4.[7]

Developmental phases of dengue fever

The three phases of dengue include

➢ Febrile phase
➢ Critical phase
➢ Recovery phase

Febrile phase

- The febrile phase of DF includes a sudden high-grade fever of approximately 40oc which lasts for about two to seven days. Biphasic fever is seen in about 6% of patients, particularly in patients with DHF or severe dengue. Biphasic fever is described as the fever which sets back for at least one day and the next fever spikes which lasts for one more day. Other symptoms include myalgia, arthralgia, facial flushing, headache, sore throat, nausea, vomiting, lack of appetite, etc. Mild hepatomegaly may be present. CBC shows leukopenia, thrombocytopenia, and increasing

haematocrit. Elevation of hepatic transaminases is commonly observed in laboratory findings.

Critical phase

- Majority of patients recover fully and do not enter the critical phase of DF. However, patients that do enter the critical phase show defervescence which is the decrease in body temperature to 37 to 38oc and plasma leakage. It usually lasts for about two days. The onset of this phase is indicated by rapid fall in platelet count and can progress to shock, organ dysfunction or haemorrhage.

Recovery phase

- Sinvolves gradual drop in haematocrit, increase in white blood cells followed by platelets and recovery from other symptoms. This phase may be associated with fatigue. Some patients develop "recovery rash" and bradycardia in this phase.

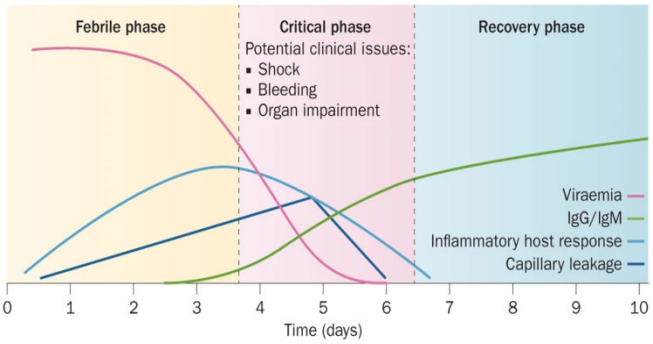

Figure 2. Developmental phases of dengue fever

Pathophysiology

The pathophysiology of DENV and the immune response of the host are not fully understood. Primary manifestations of disease include capillary leak syndrome (plasma leakage due to DHF-specific endothelial cell dysfunction), thrombocytopenia (seen in all types of DENV infection, but extreme in DHF), hemorrhagic tendencies, and leucopoenia. It is known that the major viral envelope (E) of glycoprotein in the virus helps to bind the host cells, followed by viral replication. Data suggest that monocytes are the primary target. Infected monocytes induce the production of interferon-a (IFN-a) and IFN-b. Envelope (E), precursor membrane protein (pre-M), and non-structural protein 1 (NS1) are the major DENV proteins targeted by antibodies as part of the host immune response. Studies have shown that DENV-specific CD4+ and CD8+ T lymphocytes attack infected cells and release IFN-g, tumor necrosis factor-a (TNF-a), and lymphotoxin. Primary infection induces a lifetime immunity of the individual to that particular serotype, but not to secondary infection by another serotype.[9]

Bite of Aedesaegypti
↓
The virus penetrates to the skin
↓
The virus infects and replicates inside the Langerhans cell
↓
Langerhans cells release interferons (to limit the spread of infections)
↓
Infected Langerhans cells go to the lymphatic system to make the immune system
↓
Then goes to the circulation
↓
Results in viremia high levels of virus in the blood stream
↓
Activation of immune response increase lymphocyte
↓
Decreases neutrophils and white blood cells
↓
Release of pyrogen causes fever and increased blood pressure in vessel causes rashes
↓
Causes dengue fever

Signs and symptoms

Many people experience no signs or symptoms of a dengue infection.

When symptoms do occur, they may be mistaken for other illnesses such as the fluid and usually begin four to 10 days after you are bitten by an infected mosquito.

Dengue fever causes a high fever — 104 F (40 C) — and any of the following signs and symptoms:

- Headache
- Muscle, bone or joint pain
- Nausea
- Vomiting
- Pain behind the eyes
- Swollen glands
- Rash

Many people experience no signs or symptoms of a dengue infection.

When symptoms do occur, they may be mistaken for other illnesses — such as the flu — and usually begin four to 10 days after you are bitten by an infected mosquito.

Laboratory diagnosis of dengue virus infection

Laboratory diagnosis of dengue virus infection can be made by the detection of specific virus, viral antigen, genomic sequence and/or antibodies (Guzman and Kouri, 2003). Virus isolation has been considered as the conventional diagnostic test for detecting the DENV infection. For virus isolation, samples taken from patients are cultured in various cell lines of either mammalian (BHK-21, Vero and LLCMK2 cells) or mosquito (CLA-1, AP-61, Tra-284, C6/36, AP64 cells) originor in live mosquitoes (Shu *et al.,* 2004, Colombo, 2016).

Diagnosis

In assessing a patient's condition, the following tests are recommended:

- Haematocrit
- Serum electrolytes and blood gas studies
- Platelet count, prothrombin time, partial thromboplastin time and thrombin time Liver function tests–serum aspartate aminotransferase, serum alanine

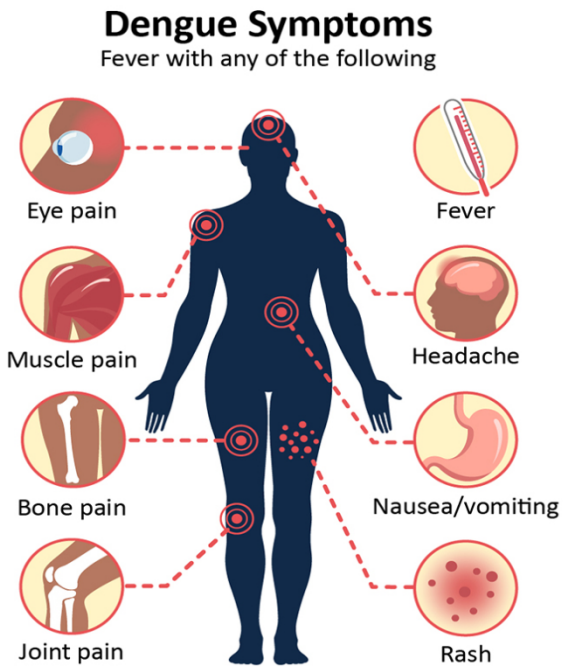

Figure 3. Signs and Symptoms of Dengue Fever

- Aminotransferases
- Renal Function tests
- Serological tests- dengue antibodies
- Serum Cholesterol & Albumen
- Chest X-Ray PA view
- Abdominal Ultrasound
- Virological Studies

Management

- **Symptomatic management:** During the febrile phase, adequate oral fluids is necessary and paracetamol is used as antipyretic. Using other non-steroidal anti-inflammatory medications should be avoided due to increased bleeding risks. The patient can be managed at home in this phase. Patients are advised to seek medical advice if they experience warning symptoms such as excessive vomiting or diarrhoea, early bleeding manifestations, etc.
- **Fluid management:** The cornerstone for the management of dengue fever is the fluid resuscitation, especially in critical phase. The goal of fluid management is to maintain the intra vascular compartment at an adequate level while preventing patient overload. This can be achieved by careful step-wise fluid administration based on clinical parameters, urine output, and degree of haemoconcentration. The first line of treatment is crystalloids (0.9% saline), colloids (dextran) is the second line of treatment. In addition to fluid management, correction of acidosis, blood sugar and calcium is also important in critical phase of dengue.
- **Blood products:** Several factors such as bone marrow suppression, peripheral destruction of platelets, platelet dysfunction, coagulopathy, and vasculopathy can cause thrombocytopenia in dengue patients. Hence platelet transfusion is required to increase the platelet counts.

Treatment

The treatment for dengue virus infection mostly involves the use of tepid sponging for fever and antipyretics for pain or fever management. No specific antiviral drug is available against dengue, but several sulphated polysaccharides extracted from seaweeds have been studied, and high antiviral activity against DENV has been observed. Two polysaccharide ride compounds from two different seaweeds, kappa/ iota/nu carrageen an G3d and the dL-galactan hybrid C2S-3, showed antiviral activity against all serotypes of DENV by interfering with virus internalization inside the host cell by inhibiting host cell receptors (heparin sulphate). Curdlan, a sulphated polysaccharide, also showed an inhibitory effect on DENV by interacting directly with the viral E protein and altering E protein structure to restrict ADE and pathogenicity of the virus in the host body. A poly sulphated fraction from the coenocytic green seaweed Caulerpa cupressoides can also inhibit DENV-1 infection pathogenicity in vitro. Ribavirin (a guanosine analog) with a combination of other nucleotide analog (brequinar, INX-08189) has been shown to inhibit nucleoside biosynthesis, thus reducing DENV activity in the host cell. Glycyrrhizin and its derivatives or modified products induce antiviral activity by affecting the secretion of interferons against DENV and inhibiting DENV protein transport and post-translational modifications. The uridine analogue 6-azauridine inhibits de novo pyrimidine synthesis and DNA synthesis and is converted intracellularly into mono-, di-, and triphosphate derivatives, which are incorporated into RNA and inhibit protein synthesis. One analog nucleoside adenosine, NITD008, has antiviral effects against DENV as well as against all other flaviviruses both in vitro and in vivo. Recently, an experimental antiviral drug, curcumin (from turmeric) and its derivatives, was assessed to determine its anti-dengue activity. Curcumin {1,7-bis (4-hydroxy-3 methoxyphenyl)-1,6-heptadiene-3,5-dione} and its analogs, such as bis-demethoxy Curcumin (CC2), acyclic analog (CC3), and cyclohexanone analog (CC5) showed efficacy in inhibiting DENV replication to prevent severe infection. A few other experimental antiviral treatments using CP26, CDDO-me, UV-4B, ivermectin, and ketotifen are in trial and are also facing great challenges in controlling dengue. [10]

Vaccination against dengue

Dengvaxia® (CYD-TDV), the first live attenuated vaccine for dengue developed by Sanofi Pasteur, and was licensed in year December 2015 and is now approved by the regulatory authorities in about 20 countries. The vaccine is intended for people living in the endemic areas, ages 9 to 45 years, who have had atleast one documented DENV infection in past. The vaccination schedule consists of 3 doses of 0.5 ml, administered at 6-month intervals. CYD-TDV is available in either a single-dose or a multidose (5-dose) vial. It is freeze-dried and reconstituted before injection with either a sterile solution of 0.4% sodium chloride for the single-dose administration or a sterile solution of 0.9% sodium chloride for the 5-dose administration. The 0.5 ml dose should be administered subcutaneously (s/c) after reconstitution. There are no adjuvants or preservatives in the CYD TDV dengue vaccine. The shelf life of CYD-TDV is 36 months when stored between 2°C to 8°C. After re constitution, vaccine must be stored at 2°C to 8°C and kept away from light. According to the WHO multi-dose vial policy, any reconstituted doses left at end of a vaccination session must be discarded in 6hours of opening/reconstitution or at end of vaccination session, whichever comes first.

Vaccination is contraindicated: in people who have a history of severe allergic reactions; Individuals suffering from a congenital or acquired immune deficiency; Individuals infected with HIV, whether symptomatic or asymptomatic; Women who are pregnant or breastfeeding; and Vaccination should be avoided in individuals suffering from moderate to severe febrile or acute illnesses.

Prevention and Control

At the present time, the primary method for control ling or preventing dengue virus transmission is to combat mosquito vectors. This is achieved by:

- **Prevention of the mosquito breeding:** Preventing the mosquitoes from accessing egg laying habitats through environmental management, and modification; Properly disposing of the solid waste, and re moving the artificial man-made habitats which can hold water; and using the proper insecticides on outdoor water storage containers.
- **Personal protection from the mosquito bites:** Personal house-hold protection measures like window screens, repellents, insecticides such as coils, and vaporizers are used; and wearing of full-sleeved shirts and full pants with socks to reduce skin expo sure to mosquitoes.
- **Community participation:** Educating the community about the dangers of mosquito-borne diseases; Collaborating with community to increase participation, and mobilization for the sustained vector control; and Sensitizing and involving community for the detection of "Aedes mosquito" breeding places, and their elimination.
- **Reactive vector control:** During outbreaks, health authorities may use emergency vector control measures such as space spraying insecticides.
- **Active mosquito, and virus surveillance:** To determine the effectiveness of the control interventions and active monitoring, and surveillance of the vector abundance, and species composition must be carried out. [11]

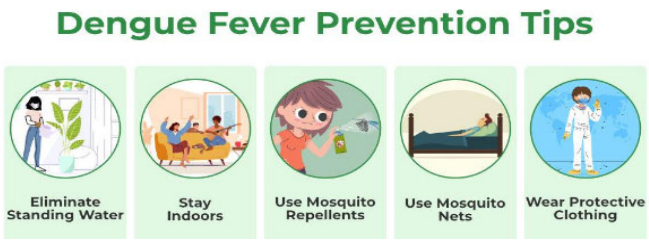

Figure 4. Prevention and control of dengue fever

Global strategy for the dengue prevention and control 2012-2020

The global strategy encourages multi-sectoral partners to coordinate and collaborate on an integrated vector management approach and long-term control measures at all levels. 36The goals are a) to reduce the dengue mortality by at least 50% by 2020; b) to reduce dengue morbidity by-at least 25% by 2020; and c) to estimate the true burden of the disease by 2015. [12]

Conclusion

Dengue fever is a terrible disease and a growing public health problem. A rapid increase in unplanned urbanization leads to more mosquito breeding sites, hence a greater number of people are exposed to Aedes Aegypti mosquitoesbite. These include semi-urban and slum areas where household water storage is normal and where solid waste disposal facilities are inadequate. The urgent need for a vaccine to minimize morbidity and mortality due to this disease has been recognized in a cost-effective manner in recent years.

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